



Association of JAK-STAT pathway related genes with lymphoma risk: results of a European case-control study (EpiLymph)

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**Association of JAK-STAT pathway related genes with
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(EpiLymph)**



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5 **European case-control study (EpiLymph)**
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Summary

Previous studies have suggested an important role of the JAK-STAT signalling pathway in tumour development. Therefore, we explored genetic variants in JAK-STAT pathway associated genes with lymphoma risk. In samples of the EpiLymph case-control study we genotyped 1536 single nucleotide polymorphisms (SNPs) using GoldenGate BeadArrayTM Technology (Illumina, San Diego, CA). Here, we report the associations between selected SNPs and haplotypes of the JAK-STAT pathway and risk of Hodgkin lymphoma (HL), B-cell lymphoma (B-NHL) and most frequent B-NHL subtypes. Among 210 relevant JAK-STAT pathway-related SNPs, polymorphisms in nine genes (*BMF*, *IFNG*, *IL12A*, *SOCS1*, *STAT1*, *STAT3*, *STAT5A*, *STAT6*, *TP63*) were significantly associated with lymphoma risk. At a study-wise significance level, we obtained a risk reduction of 28 % among carriers of the heterozygous genotype of the *STAT3* variant (rs1053023) for B-NHL. For six other variants within the *STAT3* gene we observed an inverse association with different lymphoma subtypes. A reduced risk for HL was observed for the heterozygous genotype of the *STAT6* SNP (rs324011). This is an explorative investigation to examine associations between JAK-STAT signalling related genes and lymphoma risk. The results implicate a relevant role of certain pathway-related genes in the lymphomagenesis, but still need to be approved by independent studies.

Keywords: lymphoma, susceptibility, JAK-STAT, epidemiology, association study

Introduction

Lymphomas are a heterogeneous group of malignancies originating from lymphocytes, with the main types of non-Hodgkin lymphoma and Hodgkin lymphoma (Jaffe E. S. 2001) and multiple subtypes within these categories. Strong risk factors for these lymphoid malignancies are genetic and acquired immunodeficiencies (Ekstrom Smedby, *et al* 2008),

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3 infectious agents (Hjalgrim and Engels 2008) and several occupational exposures (Cocco, *et*
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5 *al* 2010, Miligi, *et al* 2006). Apart from these, various studies (Mensah, *et al* 2007,
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7 Villeneuve, *et al* 2009, Wang, *et al* 2007, Zhang, *et al* 2007) reported an increased risk of
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9 NHL for those with a first degree relative diagnosed with a haematopoietic malignancy. This
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11 data indicates the importance of genetic predisposition for lymphoma risk (Skibola, *et al*
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13 2007), and the interplay with environmental factors as the possible etiological mechanism.
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17 The signal-transducer and activator of transcription (STAT) family consists of 7 members
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19 latently expressed in the cytoplasm and which are phosphorylated by Janus kinases (JAK)
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21 cytosolic tyrosine kinases in response to different cytokine stimuli (Schindler, *et al* 2007).
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23 They are involved in signalling cascades of various immune regulatory pathways (Egwuagu
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25 2009). Among these factors, particularly stat3 is emerging as an important player in the
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27 development of malignancies. It is constitutively activated in different cancer types (Coppo, *et*
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29 *al* 2009, Ding, *et al* 2008, Frank 2003, Hazan-Halevy, *et al* 2010, Mackenzie, *et al* 2008,
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31 Tomita, *et al* 2006), and known to promote tumourigenesis by enhancing expression of pro-
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33 survival factors such as B-cell lymphoma 2 (bcl-2), bcl-xL and myeloid cell leukaemia
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35 sequence 1 (mcl-1) (reviewed by (Hu and Ivashkiv 2009, Yu, *et al* 2009)). Also other factors
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37 of this family, such as stat 1, 5 and 6 appear to play a role in the pathogenesis of human
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39 cancers (Adamkova, *et al* 2007, Bruns and Kaplan 2006, Martini, *et al* 2008, Yu and Jove
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41 2004) and present constitutive activation in breast cancer, head and neck cancer, leukaemia
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43 and multiple myeloma (Bowman, *et al* 2000, Bromberg 2002, Yu and Jove 2004). Their
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45 prominent role in signalling pathways of well-established risk factors for cancer and their
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47 implication in various cancer types prompted us to investigate the association between genetic
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49 variants of selected genes of the JAK-STAT pathway and lymphoma risk in samples of
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51 participants to the European EpiLymph multi-centre case-control study.
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Material and Methods

Study design

A detailed description of the EpiLymph study has been published elsewhere (de Sanjose, *et al* 2006). Briefly, the EpiLymph study was carried out in six European countries (Spain, France, Germany, Italy, Ireland, and Czech Republic) from 1998 to 2004. Incident cases of lymphoid malignancies were recruited for the study and their diagnoses were categorized according to the WHO classification (Jaffe E. S. 2001). Controls were selected from the same hospitals as the cases in all centers, except in Germany and Italy where they were randomly sampled from population registries. Controls were frequency-matched to cases by age, sex, and study centre. The study included 2,348 cases and 2,462 controls. All participants were asked to donate a blood sample for DNA extraction and underwent a personal interview gathering sociodemographic information, familial and medical history, smoking and alcohol habits, a complete occupational history and details on recreational and occupational exposure to sunlight. The study was approved by the competent ethical committee in each study area, and informed consent was obtained from each study subject. The present genotyping study was restricted to EpiLymph study subjects for whom DNA was available: a total of 1,481 cases of lymphoma, including Hodgkin lymphoma (HL, $n=272$), T-cell lymphoma (T-NHL, $n=95$), and B-cell lymphoma (B-NHL, $n=1,114$), in turn including the subtypes diffuse large B-cell lymphoma (DLBCL, $n=408$), follicular lymphoma (FL, $n=200$), chronic lymphocytic leukaemia (CLL, $n=340$), marginal zone B-cell lymphoma (MZL, $n=112$), and mantle cell lymphoma (MCL, $n=54$). The corresponding EpiLymph controls ($n=1,491$) were frequency-matched by age (< 30, 30-39, 40-49, 50-59, 60-69, 70-79, ≥ 80), sex, and study centre. The German cases and controls were individually matched by gender and age (± 1 year of birth).

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3 *SNP selection*
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5 Genes and single nucleotide polymorphisms (SNPs) which have either previously been
6 associated with lymphomagenesis or have a high biological plausibility to be involved in the
7 development of lymphoid neoplasms, were selected from public databases. Tagging SNPs for
8 the selected genes and their $\pm 10\text{kb}$ flanking region were selected via pairwise SNP selection
9 with an r^2 threshold of 0.9 using Haplovew (Barrett, *et al* 2005, Carlson, *et al* 2004, de
10 Bakker, *et al* 2005) and the genotyping information for the CEU population of the HapMap
11 database (Consortium 2003) (<http://hapmap.ncbi.nlm.nih.gov>, NCBI 36 assembly, dbSNP
12 b126, phase II).

13 Only SNPs with a minor allele frequency (MAF) $\geq 5\%$ and an Illumina GoldenGate
14 Design Score of at least 0.6 were included into the oligonucleotide pooled assay (OPA).
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24 *Genotyping and sample preparation*
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33 Genotyping was performed using the Illumina™ GoldenGate assay technology (Illumina,
34 San Diego, CA). The 1,481 cases and 1,491 controls were newly plated in a 96-well format.
35 350 ng of DNA was required, with a concentration of at least 70 ng/ μl . The available DNA
36 concentration was measured using PicoGreen® (Invitrogen, Darmstadt, Germany). Samples
37 with insufficient DNA ($n=822$) were whole-genome amplified according to the
38 manufacturer's protocol for the Illustra GenomePhi V2 DNA Amplification Kit (GE
39 Healthcare, Buckinghamshire, UK). In addition, DNA extraction from blood clots was
40 performed for 312 samples using the Gentra Puregene Blood Kit (Qiagen, Hilden, Germany).
41 For quality control, three random DNA samples were placed on each plate for replication.
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55 The genotyping was carried out according to the manufacturer's protocol and as specified
56 by Fan et al. (Fan, *et al* 2006, Fan, *et al* 2003), in cooperation with the Genomics &
57 Proteomics Core Facility at the German Cancer Research Centre in Heidelberg.
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3 After generation of genotype calls with the GenCall version (5.2.0), all SNPs were
4 visually examined for individual clustering. Loci with poor performance or monomorphic
5 characteristics were excluded.
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10 Individual DNA samples with a call rate below 0.96 were removed from the dataset.
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15 *Statistical analysis*

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17 To test for deviation of genotype distribution from Hardy-Weinberg equilibrium (HWE)
18 among the controls we conducted a chi-square test. SNPs with deviation from HWE in
19 controls were excluded from further analysis. We used an adjusted *p*-value of 3×10^{-5}
20 (Bonferroni correction for 1,418 SNPs relevant after quality control). We also determined
21 whether the allelic frequency distribution differed between cases and controls.
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29 Heterogeneity of risks according to sex, age (cut-off for B-NHL: 50years, HL: 40years)
30 and study centres was tested using a chi-square test.
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36 *SNP analysis*

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38 Of the 1,536 SNPs genotyped in 1,481 cases and 1,491 controls, 97 were excluded from
39 analyses due to clustering and low call frequency, 21 due to being monomorphic in our study
40 population, and 42 because they showed a deviation from HWE (*p*-value less than 3×10^{-5})
41 among the controls. Irrespectively, a total of 109 samples were excluded on the basis of a call
42 rate less than 0.96, leading to a failure rate of 3.6 %. The failure rates for cases and controls
43 were 4.5 % (*n*=65) and 3 % (*n*=44), respectively.
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53 The associations between polymorphisms and risk of HL, T-NHL and B-NHL, as well as
54 the most frequent B-NHL subtypes, were estimated by calculating odds ratios (OR), and the
55 corresponding 95 % confidence intervals (CI) using unconditional logistic regression,
56 adjusting for age (continuous), sex and study centre, using SAS 9.2 (SAS Institute Inc. Cary,
57 NC). After quality control of the genotyping data, samples were excluded from the statistical
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analysis. To avoid loss of power in conditional logistic regression analysis, frequency matching for the whole study population using the matching variables (age, sex and study centre) was performed as was done in previous publications of the EpiLymph study (Besson, et al 2006, de Sanjose, et al 2006). Previous analysis presented similar results from conditional and unconditional logistic regression analysis of EpiLymph data (Boffetta, et al 2008). Therefore, subsequent statistical analyses were performed using unconditional logistic regression adjusted for the matching variables (de Sanjose, et al 2006).

The homozygote genotype of the most common allele was used as reference group. To increase statistical power and detect the allelic effect, we performed tests under the dominant model by combining the heterozygous and mutant genotype. We also calculated the risk association for each genotype by using the co-dominant model for the logistic regression.

The test for trend was calculated including a continuous SNP variable in the log-additive model (Breslow NE 2000). As positive association we defined an odds ratio larger than 1, whereas an inverse association was specified by an OR below 1.

Additionally, we conducted analysis for risk of HL with conditional logistic regression with complete case sets, 1:1 matched within each age-category (< 30, 30-39, 40-49, 50-59, 60-69, 70-79, ≥ 80) and by sex and study centre. As sensitivity analysis for B-NHL we conducted stratified analysis by sex and age, with cut point set at 50 years as performed by Lan et al. and Wang et al. (Lan, et al 2009, Wang, et al 2007). For HL cases the stratified analysis by age was done with a cut point of less than 40 years versus equal or older than 40 years, due to the bimodal age distribution.

As a large number of tests were performed, we had to control the family-wise error rate. The gold standard to adjust for multiple comparison is a permutation test, which is computational extensive. Since, this is a candidate gene approach based on prior knowledge of the relevance of the included genes, we selected the SNP Spectral Decomposition Approach (*simpleM* method) (Gao, et al 2008), which yields similar results as a permutation

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3 based approach (Johnson, *et al* 2010). The *simpleM* method starts with the calculation of the
4 effective number of independent SNPs, M_{eff} , for each gene, based on the underlying LD
5 structure of the genotyping data. Gene-specific M_{eff} values (${}^G M_{\text{eff}}$) were received, which were
6 added up to a study-wise M_{eff} value, ${}^{SG} M_{\text{eff}} = \sum({}^G M_{\text{eff}})$ under the assumption that the genes
7 are independent with respect to the endpoints. By applying the Bonferroni correction to the
8 number of independent tests, we obtained a study-wise significance level of $0.05 / {}^{SG} M_{\text{eff}} = 2.9$
9 $\times 10^{-4}$. Based on the distinct aetiology of the three main lymphoma subtypes (B-NHL, T-
10 NHL, and HL) (Morton, *et al* 2008), we considered the tested association between SNPs and
11 the subtypes as independent from each other and did not take them into account for the
12 multiple comparison correction.

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14 Statistical interaction was assessed for the SNPs of the most prominent genes for which
15 biological interaction was plausible based on the current knowledge of the JAK-STAT
16 pathway (Yu, *et al* 2009), by adding an interaction term in the regression model. To formally
17 test statistical interaction, the log-likelihood ratio test was applied. Furthermore, if the
18 interaction *p*-value was below 0.05 as well as for the most promising SNPs of the single SNP
19 analysis, where biological interaction was likely, we calculated risk estimates for one genetic
20 variant stratified by the genotype of the second variant included in the previous regression
21 model.

22 *Haplotype analysis*

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24 The genotyping data of the controls was transformed into Haplovew format (linkage
25 format) using the SNPtool (http://www.dkfz.de/de/molgen_epidemiology/tools/SNPtool.html)
26 to reconstruct haplotype blocks with Haplovew, using the implemented algorithm based on
27 confidence bounds by Gabriel et al. (Gabriel, *et al* 2002). The cut-off values for the haplotype
28 block generation are: MAF > 5 %, Hardy Weinberg *p*-value cut-off ≥ 0.01 and 75 % of non-
29 missing genotypes of this marker.

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2 Maximum likelihood haplotype frequency estimates were generated based on the
3 expectation-maximization (EM) algorithm implemented in the *PROC HAPLOTYPE*
4 procedure of the SAS/Genetics package (SAS 9.2). Haplotypes with a frequency < 0.05 were
5 defined as rare haplotypes and combined. The haplotype with the highest frequency was used
6 as reference.
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14 Results

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17 Descriptive Statistics

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19 Details regarding the main characteristics of the study population used for the statistical
20 analysis and the distribution of cases are presented in Table I. Briefly, 1,414 cases and 1,447
21 controls were included in the statistical analysis. The age distribution was similar among
22 cases and controls and the mean age is 55 years for both. To assess if the frequency matching
23 had worked properly, heterogeneity between cases and controls was checked by applying the
24 chi-square test, which revealed non-significant *p*-values for all three matching variables (age-
25 group: *p*=0.9; sex: *p*=0.9 and study centre: *p*=1.0). The largest lymphoma subtypes were
26 Hodgkin lymphoma (*n*=259), chronic lymphocytic leukaemia (*n*=321), and diffuse large B-
27 cell lymphoma (*n*=391).

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46 Results of Single SNP analyses

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48 Supplemental Table 1 (S1) summarizes the genes and the 210 SNPs belonging to the
49 JAK-STAT signalling pathway we studied. Eight SNPs (rs1053005, rs1053023, rs12949918,
50 rs4103200, rs6503695, rs9891119, rs9912773, rs2293158) in *STAT3* and *STAT5A* showed a
51 nominal significant association (*p*-trend < 0.01) with B-cell lymphomas combined. Five SNPs
52 (rs6581795, rs4103200, rs9912773, rs6790068, rs9681004) in interferon gamma gene
53 (*IFNG*), *STAT3*, *STAT6* and tumour protein 63 gene (*TP63*) showed a nominal sufficient
54 association with HL risk (*p*-trend < 0.05). Two of these SNPs showed a study-wise significant
55 association with HL risk (*p*-trend < 0.05). Two of these SNPs showed a study-wise significant
56 association with HL risk (*p*-trend < 0.05). Two of these SNPs showed a study-wise significant
57 association with HL risk (*p*-trend < 0.05). Two of these SNPs showed a study-wise significant
58 association with HL risk (*p*-trend < 0.05). Two of these SNPs showed a study-wise significant
59 association with HL risk (*p*-trend < 0.05). Two of these SNPs showed a study-wise significant
60 association with HL risk (*p*-trend < 0.05).

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3 association with lymphoma risk (p -value ≤ 0.0003). The heterozygous genotype of variant
4 rs1053023, located in *STAT3*, was associated with a 28 % risk reduction for B-NHL (OR_{AG} of
5 0.72, 95 % CI 0.60-0.86, p -value 0.0003). Moreover, for the *STAT6* variant, rs324011, a risk
6 reduction of 45 % was obtained for carriers of the heterozygous genotype (OR_{GA} of 0.55, 95
7 % CI 0.40-0.76, p -value 0.0003). The corresponding odds ratios and 95 % confidence
8 intervals of the most prominent SNPs are shown in Table II, as for the main B-cell lymphoma
9 subtypes in Table III.
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22 *Associations with B-NHL and subtypes*

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24 Among the 10 tagSNPs of *STAT3*, 7 SNPs (rs1053005, rs1053023, rs12949918,
25 rs4103200, rs6503695, rs9891119, rs9912773) showed a nominal statistically significant (p -
26 value <0.01) inverse association with B-NHL overall, and stayed significant at the $\alpha=0.05$
27 level for DLBCL (see Table III and S2). *STAT3* rs4103200 was related to B-NHL risk with an
28 OR_{CG/CC} of 0.78 (95 % CI 0.66-0.92) and a p -value for trend of 0.003. Similar risk reductions
29 in association with this variant were also evident for DLBCL (OR_{GC/CC} of 0.76, 95 % CI 0.60-
30 0.96); FL (OR_{GC/CC} of 0.73, 95% CI 0.54-0.99); and HL (OR_{CC} of 0.49, 95 % CI 0.27-0.90, p -
31 value for trend 0.006).
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34 Furthermore, a nominal significant association was observed for *STAT5A* – homozygous
35 mutant carriers of rs2293158 were at 32 % reduced risk of B-NHL (95 % CI 0.51-0.92, p -
36 trend 0.002). An inverse association could also be seen for the other B-NHL subtypes, but
37 with lower significance.
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40 The mutant allele of the suppressor of cytokine signalling 1 gene (*SOCS1*) variant
41 showed a nominal significant association with an increased risk for B-NHL (OR
42 rs149311_{GA/AA} 1.42, 95% CI 1.12-1.60) as well as for DLBCL (p -trend of 0.003).
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45 Two variants in Bcl-2 modifying factor gene (*BMF*) (rs3923235, rs7183977) were
46 associated with risk for DLBCL (OR rs3923235_{GG} of 0.43, 95 % CI 0.24-0.77; OR
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rs7183977_{GG} of 0.69, 95 % CI 0.46-1.02), but neither with total B-cell lymphomas nor other subentities (Table III). The GG genotype of interferon gamma receptor 1 gene (*IFNGR1*) variant (rs4896243) was positively associated with CLL risk (OR_{GG} 1.69, 95 % CI 1.19-2.40).

Associations with T-NHL

The analysis between the genetic variants and risk for T-NHL did not reveal any association with a p-value less than 0.01. However, for the *STAT5A* variant (rs2293158) we observed an inverse association with the risk of T-NHL for the GG genotype (OR_{GG} 0.18, 95 % CI 0.04-0.76) with a *p*-trend of 0.03 (see Table II). Among carriers of the interleukin 12A gene (*IL12A*) variant, for heterozygous mutants a nearly 2-fold increase in the T-NHL risk was detected (OR rs755004_{GA} 1.93, 95 % CI 1.22-3.05).

Associations with HL

Within the HL analysis we obtained one SNP with study-wide significance, and additionally 11 SNPs showed nominal significant association with HL risk. (Table II and Supplementary Table 3). HL risk was most strikingly associated with variants in *STAT6*. Here, rs324011 and rs703817 showed a 40-45 % risk reduction for HL (OR rs324011_{GA/AA} of 0.61, 95 % CI 0.45-0.82; OR rs703817_{GA/AA} of 0.62, 95 % CI 0.45-0.85). Statistical significance for the association of HL risk with both *STAT6* variants at the $\alpha = 0.01$ level was lost when only complete case sets were analyzed (Supplemental Table S3).

In addition, the conditional logistic regression analyses revealed an association of caspase 6 (*CASP6*) (rs1800627) with an increased risk (OR rs1800627_{AG/GG} of 1.75, 95 % CI 1.16-2.64, *p*-value 0.007) and *STAT4* (rs4853546) with decreased risk for HL (OR rs4853546_{GA/AA} 0.59, 95 % CI 0.40-0.85, *p*-value 0.005), respectively.

Associations within the stratified analysis

The age-stratified analysis revealed significant associations for HL with the variants of *IFNG* (rs2069718) and *STAT4* (rs7599504) as well as with *TP63* variants (rs6790068, rs9681004) among the older age-group (S5). Within the younger B-NHL cases (age < 50 y) the *CASP6* variant (rs5030552) was associated with an increased risk ($OR_{AG/GG}$ 1.94, 95 % CI 1.22-3.11, p -trend 0.003). The analysis by sex showed a decreased risk for women, who were heterozygous for the *IL7R* variant rs12516866 (OR rs12516866_{CA} 0.61, 95 % CI 0.47-0.81, p -trend 0.03) (data not shown). For the stratified analyses all herein presented p -values for heterogeneity were below 0.05.

Haplotype associations

The estimated haplotype frequencies with the most frequent haplotype taken as the reference are presented in Supplemental Table (S4). Mainly the haplotype-based associations were consistent with those of single SNP based analyses. The *STAT3* haplotype (rs4103200-rs9891119-rs9912773-rs12949918-rs17405722) with a frequency of 27 % and containing the two most significant *STAT3* SNPs, rs4103200 and rs9912773, showed a reduced risk for B-NHL (OR of 0.82, 95 % CI 0.72-0.94) and DLBCL (OR of 0.81, 95 % CI 0.67-0.98). HL risk was significantly increased for carriers of haplotypes of *BMF* (Block 1-3), *IFNG* (Block1 and 2), *STAT6* and *TP63* (see Supplemental Table 4).

Gene-gene interaction

We formally investigated interaction between different genes of the JAK-STAT pathway by comparing the genetic variants of *CASP6*, *STAT3*, *STAT1*, *IFNG* and *IL12A* between B-NHL cases and controls stratified by genotype of *BMF*, *STAT1*, *IL10*, *IFNG*, *SOCS1* and *STAT4*, respectively. Significant results are summarized in Table IV.

Interaction between the homozygous mutant carriers of *IL12A* (rs4680534) and the homozygous mutants of *STAT4* (rs517352) resulted in a nearly 3-fold increased B-NHL risk

(OR of 2.80, 95 % CI 1.30-6.05). Interaction between the *CASP6* variant (rs5030552) and two *BMF* variants (rs537455, rs16970325) showed a 57 % and 50 % increased risk, respectively. The interaction analysis of *STAT3* and *STAT1* revealed a 40 % reduced risk for carriers of the homozygous mutant of the *STAT3* variant (rs6503695) in carriers of the AA genotype of *STAT1* (OR rs6503695 of 0.60, 95 % CI 0.41-0.88). Among those of the *IL10* wildtype, carriers of the heterozygous mutant of the *STAT3* variant (rs1053023) showed decreased risk for B-NHL at the study-wise significance level (Table IV). Additionally, the heterozygous mutant of the *STAT3* SNP (rs4103200) was associated with a 29 % decreased risk for B-NHL among carriers of the *IFNG* wildtype.

Discussion

Our study identified 9 SNPs in 3 genes (*SOCS1*, *STAT3*, *STAT5A*) implicated in the JAK-STAT pathways significantly associated with risk of B-cell lymphoma, and 10 SNPs in 7 genes of this pathway (*BMF*, *CASP6*, *IFNG*, *STAT3*, *STAT4*, *STAT6*, *TP63*) associated with HL risk.

Seven SNPs in *STAT3* presented a statistically significant inverse association with B-cell lymphoma risk, and particularly with the DLBCL and FL subtypes. One of these, the rs1053023, located in haplotype block 1, showed even study-wise significance. To our knowledge this is the first time that genetic variants in *STAT3* have been associated with lymphoma risk. Stat3 is a major mediator of il6 activation (Leonard and O'Shea 1998) and it is induced by several exogenous factors, such as like lipopolysaccharid (LPS) (Samavati, *et al* 2009), cigarette smoke (Liu 2007), and infection with Hepatitis C virus (Yoshida, *et al* 2002). In normal cells stat3 activation is usually transient, whereas it is often constitutively activated in many cancers (reviewed in (Benekli, *et al* 2003, Bowman, *et al* 2000)). The transcription factor promotes tumour development and survival of tumour cells by regulating pro-survival factors, such as bcl-xL, bcl-2 and mcl-1 (reviewed (Hu and Ivashkiv 2009)). Aberrant stat3

activation has also been shown for HL (Kube, *et al* 2001), NK/T-cell lymphoma (Chiarle, *et al* 2005, Zhang, *et al* 2002, Zheng, *et al* 2002), and activated DLBCL (Ding, *et al* 2008, Lam, *et al* 2008). The interplay between STAT and nuclear factor kappa B (NFκB) pathways appears to be implicated in lymphomagenesis (Bollrath and Greten 2009, Lam, *et al* 2008, Scheeren, *et al* 2008).

Mutations in *STAT3* are a hallmark of Hyper-IgE-syndrome (HIES), a complex primary immunodeficiency (Minegishi and Karasuyama 2009) and several case reports also suggest an increased risk for certain lymphoma types and HL among HIES patients (Belada, *et al* 2010, Kashef, *et al* 2006, Minegishi 2009, Wallet, *et al* 2007). This adds to the eminent role of stat3 in immune response and the remarkable impact of its dysfunction in the aetiology of various immune diseases.

On the basis of the close functional relationship between stat3/stat1 and the cytokines il6 and il10, joint effects have been explored. For B-cell lymphoma we found evidence for statistical interaction between *STAT3* and *IL10*, as well as between *STAT3* and *STAT1*. Immunoregulatory il10 is upregulated by stat3 and is part of the stat3 feedforward loop (Yu, *et al* 2007). The opponent factor of the JAK-STAT signalling socs1, a member of the family of suppressors of cytokine signalling (Alexander 2002), was associated with increased risk for B-NHL. This is in line with recent publications indicating socs1 as tumour suppressor (Weniger, *et al* 2006), and data reporting inactivation of this gene due to mutation or hypermethylation in B-cell lymphoma entities and multiple myeloma, respectively (Galm, *et al* 2003, Mottok, *et al* 2009).

One of our most prominent results was the inverse association of *STAT5A* rs2293158 mutant genotype (GG) with risk of all main B-cell lymphoma subtypes (DLBCL, FL, CLL), as well as for T-NHL and HL. Constitutively activated stat5 in B-cell lymphoma cell lines induces the important cell cycle regulator cylinD1 (Melzner, *et al* 2005). A prominent target gene of stat5 is *BCL6*, encoding bcl-6, which regulates the expression of stat3 (Ding, *et al*

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3 2008) and is crucial for germinal centre development. Genetic variability of *BCL6* has
4 previously been associated with NHL risk (Jardin, *et al* 2007, Morton, *et al* 2009, Parekh, *et*
5 *al* 2007, Saito, *et al* 2009, Tibiletti, *et al* 2009, Zhang, *et al* 2005). Taken together, our results
6 add epidemiological evidence to the significant role of STAT genes in lymphomagenesis.
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10 Bmf binds to bcl-2 and functions as an apoptotic activator. Recent mice data suggests a
11 relevance of this factor in c-myc-driven B-cell lymphomagenesis (Frenzel, *et al* 2010) and γ
12 irradiation-induced thymic lymphoma development (Labi, *et al* 2008). In our study, variants
13 in *BMF* (rs7183977, rs3923235) were specifically associated with DLBCL risk, but not with
14 the other lymphoma subtypes. Noteworthy is the evidence for gene-gene interactions between
15 variants in *BMF* and *CASP6*, which were seen for B-cell lymphoma. This supports the
16 connection between variability in genes of apoptotic pathways and the pathogenesis of
17 lymphomas (Lan, *et al* 2009, Morton, *et al* 2009).
18
19

20 Pathogenesis of the various lymphoma subentities differs in relation to some
21 environmental (Fisher and Fisher 2004, Landgren and Caporaso 2007, Smedby, *et al* 2006,
22 Thomas, *et al* 2002) and also underlying genetic risk factors (Caporaso, *et al* 2009, El-Zein, *et*
23 *al* 2009, Skibola, *et al* 2007, Wang, *et al* 2006). In this study of the JAK-STAT pathway
24 related genes, HL risk has been associated with variants in *STAT3* (rs4103200, rs9912773),
25 *STAT6* (rs324011, rs703817) and *TP63* (rs6790068, rs9681004).
26
27

28 A hallmark of classical HL is the deregulated cytokine expression, particularly of il6 and
29 il13, which might promote the oncogenic transformation (Skinnider, *et al* 2002, Skinnider and
30 Mak 2002). These cytokines are well-known activators of the JAK-STAT pathway. Previous
31 data on HL cell lines support an important role of stat3 in the genesis of HL (Baus and
32 Pfitzner 2006, Kube, *et al* 2001, Skinnider, *et al* 2002, Skinnider and Mak 2002), and
33 inhibition of this pathway via small molecules is discussed as a therapeutic option (Holtick, *et*
34 *al* 2005, Kim, *et al* 2008, Mackenzie, *et al* 2008). Adding to this point, are observations from
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tissue microarrays, where stat3 was identified as heavily over expressed in Hodgkin and Reed Sternberg (HRS) cells (Garcia, *et al* 2003).

Carriers of the rare putatively functional variant in *STAT6* (rs324011) were at reduced risk for HL. This *STAT6* variant located in a NFkB binding site in intron2 appears to have an impact on stat6 isoform expression (Schedel, *et al* 2004, Schedel, *et al* 2009) and was previously associated with elevated serum IgE levels (Kabesch, *et al* 2006, Weidinger, *et al* 2004). Stat6 activation is a common and distinct feature of HRS cells (Skinnider and Mak 2002) and has been associated with HRS cell survival antagonistic to stat1 activity (Baus and Pfitzner 2006). Genomic imbalances detected in HRS cells revealed a frequent gain of *STAT6* (Feys, *et al* 2007, Hartmann, *et al* 2008).

We observed an 80 % increased risk for HL among homozygous carriers of the mutant allele of the *IFNG* SNP rs2069718. For this variant located in intron 3, an influence on ifng expression was reported (Pravica, *et al* 2000) and an association with the risk of SLE (OR 2.42 for CC vs TT/TC) (Kim, *et al* 2009), a reported risk factor for NHL and HL (Bernatsky, *et al* 2007, Gayed, *et al* 2009, Landgren, *et al* 2006, Mellemkjaer, *et al* 2008).

A major strength of our study is the sample size, which allowed analysis of genetic variants for lymphoma overall, as well as for the major subtypes like DLBCL, FL and CLL. However, the power to detect associations with rare subtypes such as T-NHL, MZL and MCL was limited, and the same holds true for the analysis of strata by sex and age.

Power for the detection of GxG interactions was limited in this study. However our analysis of biologically plausible interactions may put forward good candidates for replication in the framework of pooled analyses.

Another limitation of the presented study setup is the incomplete coverage of genes related to the JAK-STAT pathway. Though, we were not able to give information about the risk profile of variants in genes of the entire pathway in the context of lymphomagenesis.

Since the EpiLymph study was conducted in different European countries we checked for heterogeneity of our results across the different study centres. Among the SNPs with significant association, four variants (rs6503685, rs9912773, rs34997637, rs4853546) presented heterogeneity between study centres. Considering the high LD of the associated *STAT3* variants, their independent role in lymphoma aetiology is questionable. Thus, a more in-depth analysis of this gene is recommended to identify the functional variant(s) underlying differential risk for lymphoma associated with this region.

This exploration of the implication of JAK-STAT signalling related genes in lymphoma aetiology involved a large number of performed tests and required an adjustment for multiple comparison. Since, prior knowledge about the biological relevance of the genes was used for the selection of candidate genes, a less stringent significance threshold can be used (Hirschhorn and Altshuler 2002), as compared to GWAS. We applied the SNP Spectral Decomposition Approach (*simpleM* method) first introduced by Gao *et al.* (Gao, *et al* 2008) and applied in several recent association studies (He, *et al* 2010, Reynolds, *et al* 2010). This method takes the correlation between the different SNPs into account and calculates the effective number of independent tests for each gene.

Within the single SNP analysis two variants showed study-wise significance and support their relevance for lymphomagenesis. Furthermore, the results from the single point analyses were underlined by the haplotype analysis as well as by the GxG analysis. Nevertheless, to our knowledge there is no convenient and comprehensible solution to account for multiple comparisons due to subtype analyses. As a result, we only considered for the number of tests due to the number of analyzed SNPs.

SNPs associated with DLBCL in this study were not listed among the top 30 ranked SNPs associated with DLBCL in Skibola *et al.* (Skibola, *et al* 2009). But their analysis was based on a moderate number of DLBCL cases (n=221) and had limited power to identify variants of moderate risk. In general, there is an ongoing discussion that GWAS only identify

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3 genetic variants with a strong impact on disease development and are not able to detect those
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5 with smaller effects (Wu, *et al* 2010).
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8 Nevertheless, recent experimental and clinical data (Baran-Marszak, *et al* 2010, Baus, *et*
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10 *al* 2009, Cotto, *et al* 2010, Ding, *et al* 2008, Hazan-Halevy, *et al* 2010, Kupferman, *et al*
11
12 2009, Mackenzie, *et al* 2008, Martini, *et al* 2008, Stewart, *et al* 2009, Verma, *et al* 2010,
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14 Zhang, *et al* 2010), linking JAK-STAT pathway genes with the pathogenesis of lymphomas
15
16 provide strong biological support for the observed associations.
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19 To our knowledge, we reported for the first time inter-individual differences in
20 susceptibility to the major lymphoma subtypes in relation to variability in genes related to the
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22 JAK-STAT pathway, specifically *STAT3* (all lymphoma), *STAT6* (HL) and *STAT5A* (B-cell
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24 lymphoma). Our data adds to the growing evidence of a pivotal role of this pathway in cancer
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26 pathogenesis and other inflammation-driven phenotypes. Replication of our findings in
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28 independent studies and pooled analyses are warranted to assess subtype-specific risks and
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30 gene-gene interactions, for which statistical power in our study was limited.
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Conflict of interest

The authors declare no conflict of interest.

Table I. Selected characteristics of the final sample subset of the EpiLymph study

Characteristics	Case	Control
	patients N (%)*	subjects N (%)*
Age		
<30	147 (10)	129 (9)
30-39	147 (10)	153 (11)
40-49	175 (12)	183 (13)
50-59	269 (19)	274 (19)
60-69	390 (28)	397 (27)
≥70	286 (21)	311 (21)
Study Centre		
Spain	301 (21)	318 (22)
France	149 (11)	152 (10)
Germany	518 (37)	530 (37)
Italy	106 (7)	110 (8)
Ireland	105 (7)	102 (7)
Czech Republic	235 (17)	235 (16)
Sex		
Male	787 (56)	802 (55)
Female	627 (44)	645 (45)
Lymphoma subtype		
Hodgkin lymphoma (HL)	259 (18)	-
T-cell lymphoma (T-NHL)	90 (6)	
B-cell lymphoma (B-NHL)	1,114 (76)	-

Diffuse large B-cell lymphoma (DLBCL)	391 (28)	-
Follicular lymphoma (FL)	195 (14)	-
Chronic lymphocytic leukemia (CLL)	321 (23)	-
Mantle cell lymphoma (MCL)	48 (3)	-
Marginal zone B-cell lymphoma (MZL)	110 (8)	-
removed samples [†]	67	44
	1,481	1,491

* Percentage is based on the final population for statistical analysis

† 65 cases and 44 controls were removed due to low performance of the genotyping (call-rate below 0.96); additionally, 2 cases were excluded due to missing information on age

1
2 **Table II.** Odds ratios (OR) and 95% confidence intervals (CI) for associated SNPs of the JAK-STAT pathway with B-cell lymphoma,
3
4 T-cell lymphoma and Hodgkin lymphoma.
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Genotype	Controls*	B-NHL			T-NHL			Controls*			HL		
		N (%)	N (%)	OR [†] (95%CI)	p-value	N (%)	N (%)	OR [†] (95%CI)	p-value	N (%)	N (%)	OR [†] (95%CI)	p-value
BMF rs1540686													
AA	316 (26)	300 (28)	Reference		27 (30)	Reference		297 (26)	76 (29)	Reference			
AG	608 (51)	513 (48)	0.88 (0.72-1.07)	0.2	45 (50)	0.92 (0.56-1.53)	0.8	582 (50)	140 (54)	0.91 (0.65-1.28)	0.6		
GG	268 (22)	246 (23)	0.96 (0.76-1.22)	0.8	18 (20)	0.84 (0.45-1.56)	0.6	273 (24)	39 (15)	0.54 (0.34-0.85)	0.007		
AG/GG			0.91 (0.75-1.09)	0.3		0.90 (0.56-1.44)	0.7			0.79 (0.57-1.09)	0.2		
			p-trend	0.7		p-trend	0.6			p-trend	0.01		
BMF rs648289													
AA	357 (30)	339 (32)	Reference		31 (34)	Reference		337 (29)	84 (32)	Reference			
AG	590 (49)	497 (47)	0.88 (0.73-1.07)	0.2	43 (48)	0.91 (0.56-1.48)	0.7	569 (49)	142 (55)	0.97 (0.69-1.34)	0.8		
GG	249 (21)	230 (22)	0.97 (0.77-1.23)	0.8	16 (18)	0.79 (0.42-1.48)	0.5	250 (22)	33 (13)	0.52 (0.33-0.83)	0.006		
AG/GG			0.91 (0.76-1.09)	0.3		0.87 (0.55-1.38)	0.6			0.83 (0.61-1.14)	0.3		
			p-trend	0.7		p-trend	0.5			p-trend	0.01		
IFNG rs2069718													
GG	456 (38)	420 (40)	Reference		76 (84)	Reference		436 (38)	87 (34)	Reference			

GA	573 (48)	494 (46)	0.93 (0.77-1.11)	0.4	14 (16)	1.24 (0.68-2.27)	0.5	558 (48)	124 (48)	1.08 (0.78-1.50)	0.6
AA	164 (14)	149 (14)	0.98 (0.76-1.27)	0.9	-	-	-	159 (14)	48 (19)	1.80 (1.16-2.79)	0.009
GA/AA			0.94 (0.79-1.11)	0.5		1.17 (0.64-2.14)	0.6			1.22 (0.89-1.66)	0.2
			p-trend	0.7		p-trend	0.8			p-trend	0.02

***IFNG* rs6581795**

AA	648 (54)	577 (54)	Reference	51 (57)	Reference		619 (54)	115 (44)	Reference		
AG	464 (39)	411 (39)	1.00 (0.83-1.19)	1.0	33 (37)	0.92 (0.58-1.46)	0.7	454 (39)	120 (46)	1.47 (1.08-2.01)	0.01
GG	84 (7)	78 (7)	1.04 (0.75-1.45)	0.8	6 (7)	0.95 (0.39-2.31)	0.9	83 (7)	24 (9)	1.91 (1.10-3.29)	0.02
AG/GG			1.00 (0.85-1.19)	1.0		0.93 (0.60-1.44)	0.7			1.53 (1.14-2.06)	0.005
			p-trend	0.9		p-trend	0.8			p-trend	0.003

***IL12A* rs755004**

GG	903 (76)	802 (75)	Reference	56 (62)	Reference		876 (76)	188 (73)	Reference		
GA	272 (23)	239 (22)	0.99 (0.81-1.21)	0.9	32 (36)	1.93 (1.22-3.05)	0.005	263 (23)	66 (25)	1.08 (0.77-1.52)	0.6
AA	21 (2)	25 (2)	1.35 (0.75-2.43)	0.3	1 (1)	0.76 (0.10-5.86)	0.8	17 (1)	5 (2)	1.42 (0.47-4.30)	0.5
GA/AA			1.01 (0.84-1.23)	0.9		1.84 (1.17-2.90)	0.008			1.10 (0.79-1.54)	0.6
			p-trend	0.7		p-trend	0.02			p-trend	0.5

Table II. cont.'d

Genotype	Controls*	B-NHL			T-NHL			Controls*	HL			
		N (%)	N (%)	OR [†] (95%CI)	p-	N (%)	OR [†] (95%CI)	p-	N (%)	N (%)	OR [†] (95%CI)	p-
		value				value				value		
<i>SOCS1</i> rs149311												
GG	857 (72)	697 (65)	Reference		68 (76)	Reference		823 (71)	171 (66)	Reference		
GA	295 (25)	321 (30)	1.34 (1.11-1.62)	0.002	18 (20)	0.77 (0.45-1.32)	0.3	284 (25)	79 (31)	1.37 (0.99-1.90)	0.06	
AA	43 (4)	45 (4)	1.30 (0.85-2.01)	0.2	4 (4)	1.12 (0.39-3.27)	0.8	48 (4)	9 (3)	0.81 (0.37-1.79)	0.6	
GA/AA		1.34 (1.12-1.60)	0.002		0.81 (0.49-1.35)	0.4			1.29 (0.94-1.76)	0.1		
		p-trend	0.003		p-trend	0.6			p-trend	0.3		
<i>STAT1</i> rs34997637												
GG	709 (59)	634 (59)	Reference		64 (71)	Reference		682 (59)	158 (61)	Reference		
GA	410 (34)	374 (35)	1.02 (0.85-1.22)	0.8	24 (27)	0.63 (0.39-1.03)	0.07	397 (34)	91 (35)	0.93 (0.68-1.27)	0.7	
AA	76 (6)	57 (5)	0.84 (0.59-1.21)	0.4	2 (2)	0.28 (0.07-1.18)	0.08	76 (7)	10 (4)	0.64 (0.31-1.33)	0.2	
GA/AA		0.99 (0.84-1.17)	0.9		0.58 (0.36-0.93)	0.02			0.89 (0.66-1.20)	0.5		
		p-trend	0.6		p-trend	0.01			p-trend	0.3		
<i>STAT3</i> rs1053005												
AA	737 (62)	732 (69)	Reference		55 (61)	Reference		708 (61)	169 (65)	Reference		
AG	401 (34)	287 (27)	0.72 (0.60-0.86)	0.0004	34 (38)	1.16 (0.74-1.82)	0.5	391 (34)	83 (32)	0.89 (0.65-1.21)	0.5	

GG	57 (5)	48 (5)	0.85 (0.57-1.27)	0.4	1 (1)	0.23 (0.03-1.71)	0.1	57 (5)	7 (3)	0.54 (0.23-1.26)	0.2
AG/GG			0.73 (0.62-0.87)	0.0005		1.04 (0.67-1.63)	0.9			0.84 (0.62-1.15)	0.3
			p-trend	0.003		p-trend	0.7			p-trend	0.2
STAT3 rs1053023											
AA	737 (62)	732 (69)	Reference		55 (61)	Reference		708 (61)	169 (65)	Reference	
AG	401 (34)	286 (27)	0.72 (0.60-0.86)	0.0003	34 (38)	1.16 (0.74-1.82)	0.5	391 (34)	83 (32)	0.89 (0.65-1.21)	0.5
GG	57 (5)	49 (5)	0.87 (0.58-1.29)	0.5	1 (1)	0.23 (0.03-1.71)	0.2	57 (5)	7 (3)	0.54 (0.23-1.26)	0.2
AG/GG			0.73 (0.62-0.87)	0.0005		1.04 (0.67-1.63)	0.9			0.84 (0.62-1.15)	0.3
			p-trend	0.003		p-trend	0.7			p-trend	0.2
STAT3 rs12949918											
AA	402 (34)	403 (38)	Reference		30 (33)	Reference		387 (33)	103 (40)	Reference	
AG	574 (48)	506 (47)	0.87 (0.73-1.05)	0.2	49 (54)	1.14 (0.71-1.84)	0.6	538(47)	115 (44)	0.81 (0.59-1.11)	0.2
GG	220 (18)	158 (15)	0.72 (0.56-0.92)	0.008	10 (11)	0.61 (0.29-1.27)	0.2	231 (20)	41 (16)	0.63 (0.41-0.97)	0.03
AG/GG			0.83 (0.70-0.99)	0.03		0.99 (0.63-1.57)	0.9			0.75 (0.56-1.02)	0.07
			p-trend	0.008		p-trend	0.3			p-trend	0.03

Table II. cont.'d

Genotype	Controls*	B-NHL			T-NHL			Controls*	HL			
		N (%)	N (%)	OR [†] (95%CI)	p-	N (%)	OR [†] (95%CI)	p-	N (%)	N (%)	OR [†] (95%CI)	p-
				value								value
STAT3 rs4103200												
GG	575 (48)	577 (54)	Reference		50 (56)	Reference		556 (48)	148 (57)	Reference		
GC	506 (42)	407(38)	0.79 (0.67-0.95)	0.01	33 (37)	0.76 (0.48-1.21)	0.2	483 (42)	96 (37)	0.74 (0.54-1.00)	0.05	
CC	115 (10)	83 (8)	0.72 (0.53-0.97)	0.03	7 (8)	0.73 (0.32-1.65)	0.5	117 (10)	15 (6)	0.49 (0.27-0.90)	0.02	
GC/CC			0.78 (0.66-0.92)	0.003		0.76 (0.49-1.17)	0.2			0.69 (0.51-0.92)	0.01	
			p-trend	0.003		p-trend	0.2			p-trend	0.006	
STAT3 rs6503695												
AA	504 (42)	505 (47)	Reference		39 (43)	Reference		483 (42)	126 (49)	Reference		
AG	523 (44)	444 (42)	0.84 (0.70-1.00)	0.06	44 (49)	1.08 (0.69-1.70)	0.7	501 (43)	106 (41)	0.80 (0.59-1.10)	0.2	
GG	169 (14)	118 (11)	0.69 (0.53-0.91)	0.007	7 (8)	0.53 (0.23-1.22)	0.1	172 (15)	27 (10)	0.57 (0.35-0.92)	0.02	
AG/GG			0.81 (0.68-0.95)	0.01		0.94 (0.61-1.46)	0.8			0.74 (0.55-1.00)	0.05	
			p-trend	0.004		p-trend	0.3			p-trend	0.02	
STAT3 rs9891119												
AA	461 (39)	464 (43)	Reference		40 (44)	Reference		447 (39)	119 (46)	Reference		
AC	566 (47)	480 (45)	0.84 (0.70-1.00)	0.05	41 (46)	0.85 (0.54-1.34)	0.5	533 (46)	115 (44)	0.81 (0.59-1.10)	0.2	

CC	169 (14)	123 (12)	0.72 (0.55-0.94)	0.02	9 (10)	0.64 (0.30-1.35)	0.2	176 (15)	25 (10)	0.54 (0.32-0.88)	0.01
AC/CC			0.81 (0.68-0.96)	0.02		0.80 (0.52-1.24)	0.3			0.74 (0.55-1.00)	0.05
			p-trend	0.008		p-trend	0.2			p-trend	0.01
STAT3 rs9912773											
CC	613 (51)	606 (57)	Reference		54 (60)	Reference		588 (51)	153 (59)	Reference	
CG	485 (41)	388 (36)	0.80 (0.67-0.95)	0.01	30 (33)	0.72 (0.45-1.15)	0.2	470 (41)	96 (37)	0.78 (0.57-1.06)	0.1
GG	98 (9)	73 (7)	0.75 (0.54-1.04)	0.08	6 (7)	0.74 (0.31-1.77)	0.5	98 (8)	10 (4)	0.43 (0.21-0.87)	0.02
CG/GG			0.79 (0.67-0.94)	0.006		0.72 (0.47-1.12)	0.2			0.72 (0.54-0.97)	0.03
			p-trend	0.008		p-trend	0.2			p-trend	0.009
STAT5A rs2293158											
AA	556 (46)	561 (53)	Reference		49 (54)	Reference		547 (47)	125 (48)	Reference	
AG	513 (43)	418 (39)	0.80 (0.67-0.95)	0.01	39 (43)	0.89 (0.57-1.38)	0.6	484 (42)	114 (44)	1.07 (0.78-1.45)	0.7
GG	127 (11)	88 (8)	0.68 (0.51-0.92)	0.01	2 (2)	0.18 (0.04-0.76)	0.02	125 (11)	20 (8)	0.62 (0.36-1.08)	0.09
AG/GG			0.78 (0.66-0.92)	0.003		0.75 (0.48-1.15)	0.2			0.97 (0.72-1.30)	0.8
			p-trend	0.002		p-trend	0.03			p-trend	0.3

Table II. cont.'d

Genotype	Controls*	B-NHL			T-NHL			Controls*			HL		
		N (%)	N (%)	OR [†] (95%CI)	p-value	N (%)	N (%)	OR [†] (95%CI)	p-value	N (%)	N (%)	OR [†] (95%CI)	p-value
STAT6 rs324011													
GG	471 (39)	435 (41)	Reference			38 (42)	Reference			437 (38)	119 (46)	Reference	
GA	557 (47)	470 (44)	0.91 (0.76-1.09)	0.3		39 (43)	0.83 (0.52-1.33)	0.4		552 (48)	97 (37)	0.55 (0.40-0.76)	
AA	166 (14)	159 (15)	1.04 (0.80-1.34)	0.8		13 (14)	0.91 (0.47-1.76)	0.8		166 (14)	43 (17)	0.80 (0.52-1.23)	
GA/AA			0.94 (0.79-1.11)	0.5			0.85 (0.55-1.32)	0.5				0.61 (0.45-0.82)	
			p-trend	0.9			p-trend	0.6				p-trend	
STAT6 rs703817													
GG	310 (26)	289 (27)	Reference			23 (26)	Reference			292 (25)	87 (34)	Reference	
GA	599 (50)	525 (49)	0.94 (0.77-1.14)	0.5		47 (52)	1.00 (0.60-1.69)	1.0		578 (50)	113 (44)	0.60 (0.42-0.84)	
AA	287 (24)	247 (23)	0.92 (0.73-1.17)	0.5		20 (22)	0.90 (0.48-1.67)	0.7		286 (25)	59 (23)	0.65 (0.44-0.98)	
GA/AA			0.93 (0.77-1.12)	0.5			0.97 (0.59-1.59)	0.9				0.62 (0.45-0.85)	
			p-trend	0.5			p-trend	0.7				p-trend	
TP63 rs6790068													
AA	424 (35)	398 (37)	Reference			32 (36)	Reference			426 (37)	77 (30)	Reference	
AG	588 (49)	498 (47)	0.90 (0.75-1.08)	0.3		43 (48)	0.96 (0.59-1.54)	0.9		556 (48)	123 (47)	1.19 (0.85-1.67)	
GG	184 (15)	171 (16)	0.99 (0.77-1.27)	0.9		15 (17)	1.06 (0.56-2.02)	0.9		174 (15)	59 (23)	1.94 (1.28-2.94)	

1	AG/GG	0.92 (0.78-1.09)	0.4	0.98 (0.62-1.54)	0.9	1.37 (1.00-1.87)	0.05
2		p-trend	0.7	p-trend	0.9	p-trend	0.003
3	TP63 rs9681004						
4	AA	417 (35)	393 (37)	Reference	33 (37)	Reference	415 (36)
5	AG	588 (49)	497 (47)	0.90 (0.75-1.08)	0.2	40 (44)	0.85 (0.52-1.37)
6	GG	189 (16)	177 (17)	0.99 (0.77-1.27)	1.0	17 (19)	1.12 (0.61-2.08)
7	AG/GG		0.92 (0.77-1.09)	0.3		0.91 (0.58-1.43)	0.7
8		p-trend	0.7		p-trend	0.9	p-trend
9							0.004

* 1196 controls were taken into account for the risk analysis with the B-cell and T-cell lymphoma cases and 1153 controls were taken into account for the risk analysis with the Hodgkin lymphoma cases

† Odds ratios were adjusted for the matching variables: age (continuous), sex and study center (categorical); the common homozygote was used as reference group for each SNP
Significant *p*-values (< 0.01) are printed in bold

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2
Table III. Odds ratios (OR) and 95 % confidence intervals (CI) for associated SNPs of the JAK-STAT pathway with B-cell lymphoma subtypes:3
4
5 DLBCL, FL and CLL

Genotype	Controls*	DLBCL			FL			CLL		
		N (%)	N (%)	OR [†] (95%CI)	p-value	N (%)	OR [†] (95%CI)	p-value	N (%)	OR [†] (95%CI)
BMF rs7183977										
AA	519 (43)	199 (51)	Reference		79 (41)	Reference		138 (43)	Reference	
AG	535 (45)	155 (39)	0.75 (0.58-0.95)	0.02	87 (45)	1.07 (0.76-1.48)	0.7	155 (48)	1.09 (0.84-1.42)	0.5
GG	142 (12)	38 (10)	0.69 (0.46-1.02)	0.06	29 (15)	1.31 (0.82-2.10)	0.3	27 (8)	0.76 (0.48-1.21)	0.3
AG/GG			0.73 (0.58-0.93)	0.009		1.12 (0.82-1.53)	0.5		1.02 (0.79-1.32)	0.9
			p-trend	0.01		p-trend	0.3		p-trend	0.6
BMF rs3923235										
AA	622 (52)	230 (59)	Reference		102 (52)	Reference		171 (53)	Reference	
AG	482 (40)	148 (38)	0.82 (0.65-1.05)	0.1	76 (39)	0.97 (0.70-1.34)	0.9	133 (41)	1.00 (0.77-1.30)	1.00
GG	92 (8)	15 (4)	0.43 (0.24-0.77)	0.004	17 (9)	1.15 (0.65-2.02)	0.6	17 (5)	0.67 (0.39-1.16)	0.2
AG/GG			0.76 (0.60-0.96)	0.02		1.00 (0.74-1.36)	1.0		0.95 (0.74-1.22)	0.7
			p-trend	0.003		p-trend	0.8		p-trend	0.4
IFNGR1 rs4896243										
AA	370 (31)	113 (29)	Reference		65 (33)	Reference		81 (25)	Reference	
AG	588 (49)	172 (44)	0.93 (0.71-1.23)	0.6	92 (47)	0.90 (0.63-1.27)	0.5	149(46)	1.15 (0.85-1.56)	0.4

1	GG	238 (20)	107 (27)	1.47 (1.06-2.00)	0.02	38 (19)	0.90 (0.58-1.40)	0.7	89 (28)	1.69 (1.19-2.40)	0.003
2	AG/GG			1.09 (0.84-1.40)	0.5		0.90 (0.65-1.25)	0.5		1.30 (0.98-1.73)	0.07
3				p-trend	0.03		p-trend	0.6		p-trend	0.003

SOCs1 rs149311

11	GG	857 (72)	244 (62)	Reference		132 (68)	Reference		219 (68)	Reference	
12	GA	295 (35)	131 (34)	1.54 (1.19-1.98)	0.0009	54 (28)	1.17 (0.83-1.66)	0.4	89 (28)	1.23 (0.92-1.63)	0.2
13	AA	43 (4)	16 (4)	1.36 (0.74-2.47)	0.3	9 (5)	1.50 (0.71-3.19)	0.3	12 (4)	1.05 (0.54-2.05)	0.9
14	GA/AA			1.51 (1.19-1.93)	0.0009		1.21 (0.87-1.68)	0.3		1.20 (0.92-1.58)	0.2
15				p-trend	0.003		p-trend	0.2		p-trend	0.3

STAT3 rs1053005

24	AA	737 (62)	271 (69)	Reference		133 (68)	Reference		218 (68)	Reference	
25	AG	401 (34)	107 (27)	0.73 (0.57-0.95)	0.02	54 (28)	0.71 (0.51-1.01)	0.06	89 (28)	0.75 (0.57-0.99)	0.04
26	GG	57 (5)	15 (4)	0.77 (0.43-1.40)	0.4	8 (4)	0.79 (0.36-1.70)	0.5	14 (5)	0.81 (0.44-1.49)	0.5
27	AG/GG			0.74 (0.58-0.94)	0.02		0.72 (0.52-1.00)	0.05		0.76 (0.58-0.99)	0.04
28				p-trend	0.03		p-trend	0.08		p-trend	0.06
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Table III. cont'd.

Genotype	Controls*	DLBCL			FL			CLL			
		N (%)	N (%)	OR [†] (95%CI)	p-value	N (%)	OR [†] (95%CI)	p-value	N (%)	OR [†] (95%CI)	p-value
STAT3 rs1053023											
AA	737 (62)	271 (69)	Reference			133 (68)	Reference		218 (68)	Reference	
AG	401 (34)	107 (27)	0.73 (0.57-0.95)	0.02		54 (28)	0.71 (0.51-1.01)	0.06	89 (28)	0.75 (0.57-0.99)	0.04
GG	57 (5)	15 (4)	0.77 (0.43-1.40)	0.4		8 (4)	0.79 (0.36-1.70)	0.5	14 (4)	0.81 (0.44-1.49)	0.5
AG/GG			0.74 (0.58-0.94)	0.02			0.72 (0.52-1.00)	0.05		0.76 (0.58-0.99)	0.04
			p-trend	0.03			p-trend	0.08		p-trend	0.06
STAT3 rs12949918											
AA	402 (34)	150 (38)	Reference			77 (39)	Reference		115 (36)	Reference	
AG	574 (48)	189 (48)	0.87 (0.68-1.13)	0.3		89 (46)	0.80 (0.57-1.12)	0.2	158 (49)	0.96 (0.73-1.27)	0.8
GG	220 (18)	54 (14)	0.67 (0.47-0.95)	0.03		29 (15)	0.65 (0.41-1.04)	0.07	48 (15)	0.79 (0.54-1.16)	0.2
AG/GG			0.82 (0.64-1.04)	0.1			0.76 (0.55-1.04)	0.09		0.91 (0.70-1.19)	0.5
			p-trend	0.03			p-trend	0.06		p-trend	0.3
STAT3 rs4103200											
GG	575 (48)	216 (55)	Reference			107 (55)	Reference		172 (56)	Reference	
GC	506(42)	149 (38)	0.78 (0.61-1.00)	0.05		74 (38)	0.75 (0.54-1.04)	0.08	124 (39)	0.84 (0.64-1.09)	0.2
CC	115 (10)	28 (7)	0.68 (0.43-1.06)	0.09		14 (7)	0.62 (0.34-1.14)	0.1	25 (8)	0.74 (0.46-1.19)	0.2

GC/CC	0.76 (0.60-0.96)	0.02	0.73 (0.54-0.99)	0.04	0.82 (0.64-1.06)	0.1
	p-trend	0.02	p-trend	0.04	p-trend	0.1

STAT3 rs6503695

AA	504 (42)	184 (47)	Reference	95 (49)	Reference	153 (48)	Reference
AG	523(44)	169 (43)	0.86 (0.67-1.10)	0.2	81 (42)	0.78 (0.56-1.07)	0.1
GG	169 (14)	40 (10)	0.66 (0.45-0.98)	0.04	19 (10)	0.56 (0.33-0.95)	0.03
AG/GG			0.81 (0.64-1.02)	0.08		0.72 (0.53-0.98)	0.04
			p-trend	0.03		p-trend	0.02
							p-trend
							0.2

STAT3 rs9891119

AA	461 (39)	179 (46)	Reference	87 (45)	Reference	131 (41)	Reference
AC	566 (47)	171 (42)	0.79 (0.62-1.01)	0.07	85 (44)	0.79 (0.57-1.09)	0.2
CC	169 (14)	43 (11)	0.68 (0.47-1.00)	0.05	23 (12)	0.70 (0.43-1.16)	0.2
AC/CC			0.77 (0.61-0.97)	0.03		0.77 (0.56-1.05)	0.1
			p-trend	0.02		p-trend	0.09
							p-trend
							0.2

* 1196 controls were taken into account for the risk analysis with the B-cell lymphoma cases

† Odds Ratios were adjusted for the matching variables: age (continuous), sex and study center (categorical); the common homozygote was used as reference group for each SNP

Significant *p*-values (< 0.01) are printed in bold

Table IV. Statistical interaction between genotypes of the *BMF*, *IFNG*, *IL10*, *STAT1*, *STAT4* and *SOCS1* variants and *CASP6*, *STAT3*, *IL12*, *INFG* SNPs among B-cell lymphoma cases

No. of Controls	No. of Cases	OR* (95% CI)	p-value	No. of Controls	No. of Cases	OR* (95% CI)	p-value	No. of Controls	No. of Cases	OR* (95% CI)	p-value
BMF (rs16970325)				CASP6 (rs5030552)				IFNG (rs6581795)			
GG				GA				AA			
AA	819 (85)	658 (79)	Reference	177 (80)	167 (80)	Reference		5 (83)	18 (90)	Reference	
AG	140 (14)	169 (20)	1.50 (1.17-1.92)	0.001	43 (19)	41 (19)	1.00 (0.62-1.63)	1.0	1 (17)	2 (10)	-
GG	8 (1)	7 (1)	1.10 (0.40-3.06)	0.9	2 (1)	2 (1)	1.14 (0.15-8.41)	1.0	-	-	-
BMF (rs537455)				CASP6 (rs5030552)				IFNG (rs6581795)			
AA				AC				CC			
AA	532 (85)	458 (78)	Reference	415 (84)	322 (82)	Reference		55 (75)	62 (77)	Reference	
AG	91 (15)	123 (21)	1.57 (1.16-2.11)	0.003	76 (15)	71 (18)	1.18 (0.82-1.68)	0.4	17 (23)	18 (22)	-
GG	4(1)	6 (1)	1.74 (0.48-6.22)	0.4	5 (1)	2 (1)	0.50 (0.10-2.64)	0.4	1 (1)	1 (1)	-

1
2 STAT3 (rs4103200)
3

4 GG	308 (48)	323 (56)	Reference		228 (49)	216 (53)	Reference		39 (46)	38 (49)	Reference
6 GC	272 (42)	200 (35)	0.70 (0.55-0.89)	0.003	193 (42)	169 (41)	0.92 (0.70-1.22)	0.6	41 (49)	35 (45)	0.82 (0.42-1.56)
8 CC	68 (10)	52 (9)	0.72 (0.49-1.07)	0.1	43 (9)	26 (6)	0.65 (0.38-1.10)	0.1	4 (5)	5 (6)	1.69 (0.36-7.94)

10
11 IL10 (rs6673928)
12

13 CC CA AA

14 STAT3 (rs6503695)
15

17 AA	290 (39)	303 (47)	Reference		186 (47)	177 (47)	Reference		27 (47)	24 (50)	Reference
19 AG	351 (48)	271 (42)	0.74 (0.59-0.92)	0.008	147 (37)	151 (42)	1.07 (0.79-1.46)	0.7	24 (42)	20 (42)	0.94 (0.40-2.23)
21 GG	98 (13)	71 (11)	0.69 (0.49-0.98)	0.04	64 (16)	42 (11)	0.69 (0.44-1.07)	0.1	6 (11)	4 (8)	0.58 (0.13-2.62)

24 IL10 (rs6673928)
25

26 CC CA AA

27 STAT3 (rs4103200)
28

30 GG	335 (45)	346 (54)	Reference		208 (52)	294 (55)	Reference		31 (54)	26 (54)	Reference
32 GC	235 (45)	245 (38)	0.70 (0.56-0.88)	0.002	146 (37)	140 (38)	0.99 (0.73-1.34)	0.9	23 (40)	19 (40)	-
34 CC	69 (9)	54 (8)	0.76 (0.51-1.11)	0.2	43 (11)	26 (7)	0.63 (0.37-1.07)	0.08	3 (5)	3 (6)	-

Table IV. cont'd.

	No. of Controls	No. of Cases	OR* (95 % CI)	p-value	No. of Controls	No. of Cases	OR* (95 % CI)	p-value	No. of Controls	No. of Cases	OR* (95 % CI)	p-value	
	IL10 (rs6673928)				STAT3 (rs1053023)				STAT1 (rs13029247)				
	CC				CA				AA				
<i>IL10</i> (rs6673928)	AA	443 (60)	449 (70)	Reference	CA	249 (63)	247 (67)	Reference	AA	44 (77)	34 (71)	Reference	
STAT3 (rs1053023)	AG	257 (35)	166 (26)	0.64 (0.50-0.80)	0.0002	129 (32)	107 (29)	0.85 (0.62-1.28)	0.3	13 (23)	11 (23)	-	
	GG	38 (5)	30 (5)	0.78 (0.47-1.28)	0.3	19 (5)	16 (4)	0.87 (0.43-1.73)	0.7	-	3 (6)	-	
<i>STAT1</i> (rs13029247)	AA	AA				AG				GG			
STAT3 (rs6503695)	AA	223 (41)	242 (47)	Reference	AG	235 (45)	212 (47)	Reference	GG	46 (35)	50 (50)	Reference	
	AG	232 (43)	212 (41)	0.84 (0.65-1.09)	0.2	223 (43)	187 (42)	0.91 (0.70-1.20)	0.5	67 (51)	43 (42)	0.68 (0.38-1.23)	
	GG	90 (17)	60 (12)	0.60 (0.41-0.88)	0.008	60 (12)	50 (11)	0.91 (0.60-1.39)	0.7	19 (14)	8 (8)	0.39 (0.15-1.00)	
<i>STAT4</i> (rs1517352)	CC	CC				CA				AA			
<i>IL12A</i> (rs4680534)	CC	CC				CA				AA			

AA	173 (40)	159 (46)	Reference		249 (44)	225(42)	Reference		85 (42)	66 (37)	Reference
AG	197 (46)	148 (43)	0.84 (0.62-1.14)	0.3	242 (43)	261 (49)	1.19 (0.93-1.54)	0.2	103 (51)	88 (49)	1.11 (0.72-1.72) 0.6
GG	61 (14)	41 (12)	0.74 (0.47-1.16)	0.2	72 (13)	52 (10)	0.79 (0.53-1.18)	0.3	13 (6)	24 (13)	2.80 (1.30-6.05) 0.009

SOCS1 (rs243317)

	AA		AC		CC						
<i>IFNG (rs2069727)</i>											
AA	176 (30)	125 (23)	Reference	137 (27)	117 (27)	Reference	21 (20)	25 (26)	Reference		
AG	286 (49)	291 (55)	1.44 (1.09-1.91)	0.01	236 (47)	216 (50)	1.08 (0.79-1.47)	0.6	59 (56)	51 (54)	0.72 (0.36-1.46) 0.4
GG	124 (21)	120 (22)	1.36 (0.97-1.92)	0.07	131 (26)	106 (23)	0.89 (0.62-1.27)	0.5	26 (25)	19 (20)	0.62 (0.27-1.45) 0.3

*Odds Ratios were adjusted for the matching variables: age (continuous), sex and study center (categorical);

p-values (<0.05) are printed in bold

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For Peer Review

JAKSTAT

Gene	rs Number	SNP (NCBI)	Chr	Chr. Position	SNP Score
BMF	rs10518679	T/C	15	38169733	0.919
	rs11630670	A/G	15	38198132	0.699
	rs11634257	A/T	15	38175784	0.873
	rs11858141	T/C	15	38176975	0.819
	rs12913170	T/C	15	38163500	0.935
	rs1540686	A/G	15	38168110	0.524
	rs16970325	T/C	15	38160423	0.91
	rs16970349	A/G	15	38171424	0.872
	rs3743129	A/C	15	38171071	0.918
	rs3923235	T/C	15	38158413	0.901
	rs537455	A/C	15	38195116	0.899
	rs546220	T/G	15	38166552	0.783
	rs588739	C/G	15	38172380	0.93
	rs648289	A/G	15	38168225	1.1
	rs652196	T/C	15	38163439	0.906
	rs675173	T/C	15	38182151	0.806
	rs7183977	T/C	15	38164384	0.78
	rs998713	A/G	15	38165759	1.1
CASP6	rs1541373	T/C	4	110848343	1.1
	rs1800627	T/C	4	110833107	0.949
	rs3181345	A/G	4	110835362	0.636
	rs3212153	T/C	4	110828930	0.901
	rs5030552	A/G	4	110838455	1.1
	rs768063	A/G	4	110839905	0.972
IFNG	rs12306852	C/G	12	66849106	0.903
	rs2069716	A/G	12	66837082	0.892
	rs2069718	T/C	12	66836429	0.938
	rs2069727	A/G	12	66834490	0.9
	rs6581795	A/G	12	66846082	0.966
IFNGR1	rs12529779	A/G	6	137587799	1.1
	rs1327474	A/G	6	137582768	1.1
	rs1327475	T/C	6	137578148	1.1
	rs1854154	T/C	6	137554340	0.421
	rs3799488	T/C	6	137561473	1.1
	rs477768	C/G	6	137590330	0.75
	rs4896243	T/C	6	137556483	1.1
	rs608914	T/C	6	137588731	1.1
	rs7759040	A/T	6	137559184	0.443
	rs9402877	A/T	6	137550768	1.1
IFNGR2	rs1015873	A/C	21	33688371	1.1
	rs12626735	C/G	21	33737849	0.752
	rs16990664	T/C	21	33689817	0.756
	rs2012075	T/C	21	33718632	0.97
	rs2284553	A/G	21	33698565	1.1
	rs2834211	T/C	21	33711678	1.1
	rs2834214	T/C	21	33715576	1.1
	rs8131980	A/G	21	33731877	1.1
	rs9976971	A/G	21	33689967	1.1
	rs9978166	A/G	21	33692386	0.981
IL10	rs1554286	T/C	1	205010856	0.901
	rs17015767	C/G	1	205018021	0.982
	rs1800871	T/C	1	205013257	1.1
	rs1800872	A/C	1	205013030	0.833
	rs2222202	T/C	1	205012004	0.869
	rs3021094	A/C	1	205011575	1.1

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3		rs3024505	T/C	1	205006527
4		rs3024509	T/C	1	205009920
5		rs4390174	A/G	1	204999074
6		rs4844553	T/C	1	205000986
7		rs6673928	T/G	1	205003868
8		rs6686931	T/C	1	205022274
9		rs7548373	T/G	1	205000113
10	IL12A	rs11927521	A/G	3	161199779
11		rs2243115	T/G	3	161188974
12		rs2243131	A/C	3	161194752
13		rs2243154	A/G	3	161198936
14		rs4680534	T/C	3	161181639
15		rs485497	A/G	3	161201826
16		rs583911	A/G	3	161193084
17		rs6441282	T/G	3	161181771
18		rs6800657	A/G	3	161182066
19		rs692890	T/C	3	161182267
20		rs7372767	A/G	3	161181560
21		rs747825	T/G	3	161182213
22		rs755004	T/C	3	161183019
23		rs9811792	T/C	3	161179692
24		rs9852519	T/C	3	161203322
25	IL12B	rs10052709	C/G	5	158693055
26		rs11574790	T/C	5	158676424
27		rs1368439	T/G	5	158674592
28		rs1433048	A/G	5	158688423
29		rs2546890	A/G	5	158692478
30		rs2546893	A/G	5	158688538
31		rs2569253	T/C	5	158683571
32		rs2853694	A/C	5	158681666
33		rs3181216	A/T	5	158685556
34		rs3181225	T/C	5	158673201
35		rs4921466	T/C	5	158665350
36		rs4921468	A/G	5	158668511
37		rs6868898	T/C	5	158696998
38		rs6870828	T/C	5	158671090
39		rs7709212	T/C	5	158696755
40	IL4	rs2243248	T/G	5	132036543
41		rs2243263	C/G	5	132041198
42	IL6	rs1800797	A/G	7	22732746
43	IL7R	rs10058453	T/C	5	35916577
44		rs10063294	A/G	5	35913262
45		rs11567694	A/G	5	35893461
46		rs11567697	A/G	5	35894081
47		rs11567701	T/G	5	35895620
48		rs11567762	A/G	5	35908958
49		rs11957503	T/G	5	35918933
50		rs12516866	T/G	5	35887018
51		rs1494565	A/C	5	35883479
52		rs3777090	A/T	5	35905116
53		rs6891095	T/C	5	35902079
54	IL8RB	rs7607437	A/G	2	218716637
55	IRF4	rs1033180	T/C	6	328546
56		rs1050975	A/G	6	353012
57		rs11757491	A/G	6	357236
58		rs12211228	C/G	6	353833
59					0.966
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3		rs13208928	A/T	6	348470	0.873
4		rs1514346	A/G	6	334630	1.1
5		rs1877175	A/G	6	355493	0.795
6		rs2001508	A/C	6	349632	0.934
7		rs3778607	A/G	6	348799	0.947
8		rs3800262	A/G	6	350900	0.818
9		rs6900384	T/G	6	342937	0.975
10		rs6906608	A/C	6	356554	0.921
11		rs7768807	T/C	6	353246	0.915
12		rs9378805	A/C	6	362727	1.1
13		rs9405192	A/G	6	327537	0.956
14	JAK1	rs10789166	A/G	1	65085401	0.93
15		rs2256298	T/C	1	65103270	1.1
16		rs310211	A/G	1	65092508	1.1
17		rs7546535	T/C	1	65196508	0.924
18	SOCS1	rs149311	A/G	16	11253255	0.488
19		rs149597	C/G	16	11251443	0.865
20		rs193778	T/C	16	11258712	0.807
21		rs243317	A/C	16	11264832	0.691
22		rs408665	T/C	16	11249473	0.607
23		rs9940551	T/C	16	11247203	0.586
24	SOCS5	rs13402099	A/G	2	46800944	0.901
25		rs13412085	A/T	2	46786569	0.874
26	SOCS6	rs17082355	A/G	18	66149957	1.1
27		rs17809666	A/G	18	66134737	0.832
28		rs4891398	T/C	18	66126238	0.52
29	STAT1	rs10173099	T/C	2	191575577	0.725
30		rs10199181	A/T	2	191581798	1.1
31		rs1168	A/G	2	191538022	0.759
32		rs12468579	A/G	2	191540509	0.873
33		rs12693591	A/C	2	191568747	1.1
34		rs13029247	T/C	2	191574903	0.782
35		rs13029532	A/C	2	191584146	0.635
36		rs13035504	C/G	2	191537598	0.749
37		rs13395505	A/G	2	191546759	0.801
38		rs1400657	A/C	2	191541785	0.839
39		rs1467199	C/G	2	191588747	1.1
40		rs1547550	C/G	2	191553970	1.1
41		rs16824035	T/C	2	191545879	0.987
42		rs17749316	C/G	2	191548954	0.91
43		rs17817966	T/C	2	191590508	0.646
44		rs2066795	T/C	2	191560142	0.611
45		rs2066804	T/C	2	191550004	1.1
46		rs2280232	T/G	2	191559011	0.708
47		rs2280233	A/G	2	191558811	0.788
48		rs2280234	T/C	2	191558344	1.1
49		rs34997637	A/G	2	191567075	0.908
50		rs4327257	A/C	2	191554382	0.972
51		rs4853533	T/C	2	191545016	0.992
52		rs7562024	T/C	2	191563766	1.1
53		rs867637	T/C	2	191534627	0.884
54	STAT3	rs1053005	A/G	17	37719436	1.1
55		rs1053023	A/G	17	37719142	0.855
56		rs12949918	T/C	17	37779799	0.913
57		rs17405722	A/G	17	37796027	0.907
58		rs2293152	C/G	17	37735055	0.58

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3		rs4103200	C/G	17	37760591
4		rs6503695	T/C	17	37753059
5		rs9891119	A/C	17	37761506
6		rs9912773	C/G	17	37764060
7	STAT4	rs10168266	T/C	2	191644049
8		rs10189819	T/C	2	191716994
9		rs10931481	A/G	2	191663097
10		rs11685878	T/C	2	191717700
11		rs13020076	A/G	2	191595288
12		rs13389408	T/C	2	191641528
13		rs1517352	A/C	2	191639709
14		rs16833177	T/C	2	191595877
15		rs16833239	A/G	2	191648505
16		rs16833437	T/G	2	191727617
17		rs17769459	T/C	2	191701793
18		rs2459611	T/C	2	191647432
19		rs3024861	A/T	2	191632851
20		rs3024877	A/G	2	191613134
21		rs3024908	A/G	2	191602386
22		rs3024912	T/G	2	191601332
23		rs3024921	A/T	2	191651517
24		rs3024936	C/G	2	191603621
25		rs4571082	T/C	2	191698181
26		rs4853540	T/G	2	191625562
27		rs4853546	A/G	2	191717897
28		rs6434435	A/G	2	191662109
29		rs6752770	A/G	2	191681808
30		rs7558921	C/G	2	191596469
31		rs7574608	A/T	2	191618109
32		rs7599504	T/C	2	191684464
33		rs925847	T/C	2	191605785
34		rs932169	C/G	2	191637523
35	STAT5A	rs2293158	A/G	17	37701084
36	STAT6	rs3024971	A/C	12	55779994
37		rs3024974	T/C	12	55779012
38		rs3024979	A/T	12	55774560
39		rs324011	T/C	12	55788449
40		rs324015	A/G	12	55776367
41		rs703817	A/G	12	55776095
42	TP63	rs1464117	T/G	3	190989225
43		rs6790068	A/G	3	191090320
44		rs6790258	T/C	3	190826843
45		rs9681004	T/C	3	191093888
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JAKSTAT

Location	MAF CEU (HapMap)	Minor allele	Major allele	no. Controls
3UTR	0.1739	G	A	1447
flanking_5UTR	0.425	A	G	1447
intron	0.3	T	A	1446
intron	0.483	G	A	1447
flanking_3UTR	0.206	A	G	1447
3UTR	0.4318	G	A	1441
flanking_3UTR	0.083	A	G	1445
intron	0.052	A	G	1447
3UTR	0.458	C	A	1447
flanking_3UTR	0.292	G	A	1447
flanking_5UTR	0.217	C	A	1447
flanking_3UTR	0.367	A	C	1445
intron	0.458	C	G	1447
3UTR	0.417	G	A	1447
flanking_3UTR	0.292	A	G	1446
intron	0.217	A	G	1444
flanking_3UTR	0.317	G	A	1447
flanking_3UTR	0.4	G	A	1446
flanking_5UTR	0.375	G	A	1446
intron	0.482	G	A	1445
intron	0.083	A	G	1447
flanking_3UTR	0.2	A	G	1446
intron	0.092	G	A	1447
intron	0.067	A	G	1447
flanking_5UTR	0.195	G	C	1447
intron	0.092	G	A	1447
intron	0.381	A	G	1444
flanking_3UTR	0.415	G	A	1447
flanking_5UTR	0.337	G	A	1447
flanking_5UTR	0.192	G	A	1442
flanking_5UTR	0.424	G	A	1447
intron	0.133	A	G	1447
flanking_3UTR	0.417	A	G	1446
intron	0.0805	G	A	1447
flanking_5UTR	0.125	C	G	1444
flanking_3UTR	0.458	G	A	1447
flanking_5UTR	0.258	G	A	1444
flanking_3UTR	0.2391	T	A	1447
flanking_3UTR	0.408	T	A	1447
flanking_5UTR	0.076	C	A	1447
flanking_3UTR	-99	G	C	1447
flanking_5UTR	0.06	A	G	1447
intron	0.078	G	A	1422
intron	0.381	A	G	1421
intron	0.136	G	A	1447
intron	0.483	G	A	1447
flanking_3UTR	0.25	A	G	1447
flanking_5UTR	0.408	A	G	1447
flanking_5UTR	0.183	G	A	1447
intron	0.169	A	G	1447
flanking_5UTR	0.212	C	G	1447
flanking_5UTR	0.173	A	G	1443
flanking_5UTR	0.202	A	C	1444
intron	0.491	A	G	1443
intron	0.067	C	A	1446

JAKSTAT

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2					
3	flanking_3UTR	0.175	A	G	1447
4	intron	0.05	G	A	1447
5	flanking_3UTR	0.317	G	A	1446
6	flanking_3UTR	0.058	A	G	1447
7	flanking_3UTR	0.271	A	C	1443
8	flanking_5UTR	0.183	A	G	1447
9	flanking_3UTR	0.067	A	C	1439
10	flanking_3UTR	0.325	G	A	1443
11	flanking_5UTR	0.083	C	A	1446
12	intron	0.19	C	A	1445
13	flanking_3UTR	0.125	A	G	1447
14	flanking_5UTR	0.258	G	A	1447
15	flanking_3UTR	0.458	G	A	1446
16	intron	0.475	G	A	1446
17	flanking_5UTR	0.433	A	C	1447
18	flanking_5UTR	0.175	G	A	1446
19	flanking_5UTR	0.35	A	G	1447
20	flanking_5UTR	0.492	G	A	1447
21	flanking_5UTR	0.123	A	C	1447
22	flanking_5UTR	0.15	A	G	1447
23	flanking_5UTR	0.475	G	A	1447
24	flanking_3UTR	0.358	A	G	1447
25	flanking_5UTR	0.108	C	G	1445
26	intron	0.083	A	G	1447
27	3UTR	0.217	C	A	1447
28	intron	0.175	G	A	1447
29	flanking_5UTR	0.467	G	A	1447
30	intron	0.483	A	G	1447
31	intron	0.475	G	A	1436
32	intron	0.458	C	A	1447
33	intron	0.321	A	T	1447
34	flanking_3UTR	0.15	A	G	1447
35	flanking_3UTR	0.0625	G	A	1447
36	flanking_3UTR	0.233	A	G	1447
37	flanking_5UTR	0.342	G	A	1447
38	flanking_3UTR	0.458	G	A	1447
39	flanking_5UTR	0.367	G	A	1447
40	flanking_5UTR	0.092	C	A	1447
41	intron	0.114	G	C	1447
42	flanking_5UTR	0.481	A	G	1446
43	flanking_3UTR	0.173	G	A	1447
44	flanking_3UTR	0.408	G	A	1447
45	intron	0.233	G	A	1447
46	intron	0.075	G	A	1429
47	intron	0.345	A	C	1447
48	intron	0.117	A	G	1447
49	flanking_3UTR	0.492	C	A	1447
50	flanking_5UTR	0.379	A	C	1447
51	flanking_5UTR	-99	C	A	1446
52	intron	0.259	T	A	1447
53	intron	0.15	G	A	1447
54	flanking_3UTR	0.483	A	G	1441
55	flanking_5UTR	0.092	A	G	1447
56	3UTR	0.0526	G	A	1447
57	flanking_3UTR	-99	A	G	1447
58	3UTR	-99	C	G	1447

JAKSTAT

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2					
3	intron	0.142	A	T	1447
4	flanking_5UTR	0.15	A	G	1447
5	3UTR	0.3421	A	G	1447
6	intron	0.224	C	A	1447
7	intron	0.483	A	G	1447
8	intron	0.158	A	G	1447
9	intron	0.169	C	A	1441
10	flanking_3UTR	-99	A	C	1447
11	3UTR	0.3421	G	A	1447
12	flanking_3UTR	0.446	C	A	1447
13	flanking_5UTR	0.325	A	G	1446
14	intron	0.132	G	A	1447
15	intron	0.208	A	G	1447
16	intron	0.283	G	A	1447
17	flanking_5UTR	0.229	A	G	1431
18	flanking_3UTR	0.142	A	G	1446
19	flanking_3UTR	0.379	G	C	1445
20	flanking_5UTR	0.3	G	A	1446
21	flanking_3UTR	0.233	C	A	1447
22	flanking_3UTR	0.325	A	G	1436
23	flanking_3UTR	0.321	G	A	1447
24	intron	0.086	A	G	1446
25	intron	0.142	A	T	1447
26	flanking_3UTR	0.068	A	G	1447
27	intron	0.092	G	A	1447
28	intron	0.41	G	A	1432
29	intron	0.317	A	G	1441
30	intron	0.342	A	T	1445
31	3UTR	0.45	A	G	1446
32	flanking_3UTR	0.463	G	A	1447
33	intron	0.092	A	C	1447
34	intron	0.26	G	A	1446
35	intron	0.086	C	A	1447
36	3UTR	0.158	C	G	1446
37	intron	0.417	A	G	1447
38	flanking_3UTR	0.11	C	A	1447
39	flanking_5UTR	0.283	G	C	1447
40	intron	0.353	C	G	1439
41	intron	0.213	A	G	1446
42	intron	0.075	G	C	1447
43	flanking_5UTR	0.4792	G	A	1447
44	intron	0.079	A	G	1447
45	intron	0.3333	A	G	1447
46	intron	0.259	C	A	1447
47	intron	-99	G	A	1447
48	intron	0.358	A	G	1447
49	intron	-99	A	G	1446
50	intron	0.136	C	A	1447
51	intron	0.383	A	G	1445
52	3UTR	0.392	A	G	1447
53	3UTR	0.4792	A	G	1447
54	intron	0.158	G	A	1446
55	flanking_5UTR	0.2083	G	A	1446
56	intron	0.432	G	A	1447
57	flanking_5UTR	0.108	A	G	1447
58	intron	0.3542	G	C	1447
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JAKSTAT

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2					
3	intron	0.242	C	G	1447
4	intron	0.348	G	A	1447
5	intron	0.358	C	A	1447
6	intron	0.225	G	C	1447
7	intron	0.225	A	G	1447
8	intron	0.167	G	A	1446
9	-99	0.325	G	A	1447
10	intron	0.317	A	G	1447
11	flanking_3UTR	0.052	G	A	1422
12	intron	0.118	G	A	1447
13	intron	0.392	A	C	1446
14	flanking_3UTR	0.233	G	A	1447
15	intron	0.102	A	G	1446
16	flanking_5UTR	0.284	A	C	1447
17	intron	0.058	A	G	1447
18	intron	0.092	G	A	1447
19	intron	0.317	T	A	1447
20	intron	0.325	A	G	1447
21	flanking_3UTR	0.133	G	A	1447
22	flanking_3UTR	0.275	C	A	1447
23	intron	0.058	A	T	1447
24	intron	0.05	C	G	1447
25	intron	0.322	G	A	1447
26	intron	0.178	A	C	1444
27	intron	0.289	A	G	1447
28	intron	0.183	A	G	1447
29	intron	0.275	G	A	1447
30	flanking_3UTR	0.133	G	C	1447
31	intron	0.133	T	A	1447
32	intron	0.125	G	A	1446
33	intron	0.3	A	G	1446
34	intron	0.067	G	C	1443
35	intron	0.267	G	A	1447
36	intron	0.075	C	A	1378
37	intron	0.1	A	G	1446
38	intron	0.108	T	A	1447
39	intron	0.4	A	G	1445
40	3UTR	0.267	A	G	1447
41	3UTR	0.492	A	G	1447
42	intron	0.117	A	C	1411
43	intron	0.443	G	A	1447
44	flanking_5UTR	0.058	A	G	1447
45	intron	0.417	G	A	1444
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JAKSTAT

Chisq (controls)	HWE (controls)	Successrate (controls)	MAF	no. Cases
0.2575	0.6119	1.000	0.13	1416
0.4702	0.4929	1.000	0.47	1416
0.3314	0.5648	0.999	0.25	1416
3.5426	0.0598	1.000	0.43	1414
0.0110	0.9164	1.000	0.15	1415
0.5352	0.4644	0.996	0.49	1404
4.2181	0.0400	0.999	0.09	1416
0.0890	0.7655	1.000	0.05	1416
0.1178	0.7314	1.000	0.44	1414
0.0097	0.9217	1.000	0.28	1416
2.2905	0.1302	1.000	0.27	1415
0.4382	0.5080	0.999	0.43	1413
2.6517	0.1034	1.000	0.45	1416
0.0150	0.9024	1.000	0.46	1415
0.0166	0.8975	0.999	0.22	1414
5.4048	0.0201	0.998	0.31	1413
0.1054	0.7454	1.000	0.34	1414
1.8453	0.1743	0.999	0.39	1411
0.2162	0.6419	0.999	0.39	1416
0.7740	0.3790	0.999	0.48	1415
0.0004	0.9840	1.000	0.11	1416
0.4041	0.5250	0.999	0.13	1416
0.1115	0.7384	1.000	0.09	1415
0.5519	0.4576	1.000	0.04	1416
0.1134	0.7363	1.000	0.15	1416
1.6553	0.1982	1.000	0.07	1416
0.6954	0.4043	0.998	0.38	1411
0.4139	0.5200	1.000	0.48	1416
0.0074	0.9312	1.000	0.27	1415
1.9264	0.1652	0.997	0.23	1406
0.0265	0.8707	1.000	0.43	1415
0.7078	0.4002	1.000	0.19	1414
0.0015	0.9689	0.999	0.47	1411
0.6475	0.4210	1.000	0.13	1416
1.4438	0.2295	0.998	0.15	1412
0.0056	0.9402	1.000	0.45	1412
0.1546	0.6942	0.998	0.30	1415
0.0168	0.8968	1.000	0.25	1416
1.5125	0.2188	1.000	0.43	1413
0.7166	0.3973	1.000	0.02	1416
0.4365	0.5088	1.000	0.25	1416
0.8378	0.3600	1.000	0.02	1416
0.1907	0.6623	0.983	0.11	1398
2.2506	0.1336	0.982	0.39	1385
0.5995	0.4388	1.000	0.11	1416
8.8395	0.0029	1.000	0.45	1415
1.1816	0.2770	1.000	0.30	1414
0.0006	0.9807	1.000	0.43	1416
0.2236	0.6363	1.000	0.13	1416
0.0919	0.7618	1.000	0.19	1414
0.1418	0.7065	1.000	0.20	1416
0.0001	0.9928	0.997	0.25	1413
0.0012	0.9718	0.998	0.25	1412
0.7748	0.3787	0.997	0.44	1412
0.5379	0.4633	0.999	0.09	1415

JAKSTAT

1	0.0492	0.8245	1.000	0.15	1415
2	0.0221	0.8818	1.000	0.07	1416
3	0.1457	0.7027	0.999	0.38	1411
4	0.6945	0.4046	1.000	0.07	1415
5	0.9267	0.3357	0.997	0.21	1413
6	0.3685	0.5438	1.000	0.24	1414
7	0.3775	0.5390	0.994	0.07	1403
8	0.5909	0.4421	0.997	0.39	1414
9	3.8830	0.0488	0.999	0.12	1413
10	0.0263	0.8712	0.999	0.16	1415
11	0.2802	0.5966	1.000	0.10	1416
12	0.0040	0.9495	1.000	0.35	1416
13	0.1738	0.6767	0.999	0.48	1416
14	0.1906	0.6624	0.999	0.45	1415
15	0.0655	0.7980	1.000	0.45	1415
16	1.6613	0.1974	0.999	0.10	1411
17	0.4494	0.5026	1.000	0.30	1416
18	0.0034	0.9538	1.000	0.42	1414
19	0.0005	0.9822	1.000	0.19	1415
20	0.1345	0.7138	1.000	0.13	1414
21	0.0769	0.7816	1.000	0.44	1415
22	2.4006	0.1213	1.000	0.40	1414
23	0.0019	0.9653	0.999	0.14	1415
24	0.0134	0.9079	1.000	0.12	1415
25	1.3863	0.2390	1.000	0.18	1415
26	0.8113	0.3677	1.000	0.19	1415
27	0.0635	0.8011	1.000	0.49	1416
28	0.0160	0.8994	1.000	0.47	1416
29	4.0636	0.0438	0.992	0.47	1410
30	0.8260	0.3634	1.000	0.48	1416
31	0.0022	0.9622	1.000	0.30	1416
32	0.0028	0.9581	1.000	0.17	1416
33	0.0028	0.9580	1.000	0.11	1416
34	0.0892	0.7651	1.000	0.30	1416
35	0.5191	0.4712	1.000	0.31	1416
36	0.0283	0.8664	1.000	0.48	1413
37	0.0011	0.9732	1.000	0.34	1416
38	0.0149	0.9027	1.000	0.07	1415
39	0.0637	0.8007	1.000	0.11	1415
40	9.7921	0.0018	0.999	0.40	1416
41	1.8498	0.1738	1.000	0.33	1416
42	1.4648	0.2262	1.000	0.46	1415
43	1.4288	0.2320	1.000	0.26	1416
44	5.0211	0.0250	0.988	0.09	1396
45	5.6182	0.0178	1.000	0.28	1414
46	0.7409	0.3894	1.000	0.15	1415
47	13.7540	0.0002	1.000	0.42	1416
48	0.2661	0.6060	1.000	0.40	1416
49	0.5660	0.4518	0.999	0.41	1415
50	0.8374	0.3601	1.000	0.32	1415
51	3.0306	0.0817	1.000	0.13	1416
52	1.2720	0.2594	0.996	0.46	1412
53	0.1017	0.7498	1.000	0.07	1415
54	0.9774	0.3228	1.000	0.08	1416
55	1.1786	0.2776	1.000	0.07	1416
56	2.2220	0.1361	1.000	0.15	1415

JAKSTAT

1	0.0887	0.7658	1.000	0.08	1416
2	0.2802	0.5966	1.000	0.10	1416
3	0.0007	0.9793	1.000	0.23	1416
4	0.4139	0.5200	1.000	0.16	1416
5	1.2778	0.2583	1.000	0.50	1415
6	0.3180	0.5728	1.000	0.17	1416
7	1.5115	0.2189	0.996	0.09	1408
8	2.2220	0.1361	1.000	0.15	1416
9	0.0343	0.8530	1.000	0.25	1416
10	0.1493	0.6992	1.000	0.48	1416
11	0.5878	0.4433	0.999	0.29	1414
12	0.0981	0.7541	1.000	0.15	1415
13	2.7818	0.0953	1.000	0.26	1416
14	2.5083	0.1132	1.000	0.33	1415
15	1.8086	0.1787	0.989	0.20	1394
16	12.9654	0.0003	0.999	0.16	1414
17	3.5835	0.0584	0.999	0.48	1416
18	3.3463	0.0674	0.999	0.24	1416
19	0.0366	0.8482	1.000	0.30	1415
20	1.9473	0.1629	0.992	0.43	1400
21	1.0847	0.2976	1.000	0.42	1415
22	2.9865	0.0840	0.999	0.12	1414
23	4.2873	0.0384	1.000	0.13	1416
24	2.2122	0.1369	1.000	0.12	1416
25	0.0245	0.8755	1.000	0.07	1415
26	0.0364	0.8486	0.990	0.39	1404
27	0.2275	0.6334	0.996	0.34	1412
28	0.0645	0.7995	0.999	0.38	1416
29	0.1657	0.6839	0.999	0.46	1414
30	0.9153	0.3387	1.000	0.42	1415
31	0.5046	0.4775	1.000	0.13	1416
32	0.0074	0.9316	0.999	0.32	1415
33	1.6603	0.1976	1.000	0.09	1416
34	0.1044	0.7466	0.999	0.16	1416
35	1.3824	0.2397	1.000	0.40	1416
36	0.2333	0.6291	1.000	0.12	1416
37	1.5014	0.2205	1.000	0.24	1416
38	0.2009	0.6540	0.994	0.34	1407
39	0.1992	0.6554	0.999	0.16	1416
40	0.7849	0.3756	1.000	0.07	1416
41	1.4848	0.2230	1.000	0.44	1416
42	0.0929	0.7606	1.000	0.01	1416
43	0.1045	0.7465	1.000	0.23	1415
44	0.3026	0.5823	1.000	0.26	1415
45	0.7077	0.4002	1.000	0.47	1412
46	0.1121	0.7377	1.000	0.37	1411
47	1.8390	0.1751	0.999	0.23	1414
48	0.3070	0.5795	1.000	0.14	1416
49	0.0306	0.8612	0.999	0.37	1415
50	6.1153	0.0134	1.000	0.39	1416
51	0.0131	0.9087	1.000	0.35	1414
52	0.0300	0.8626	0.999	0.22	1416
53	0.0300	0.8626	0.999	0.22	1416
54	1.9682	0.1606	1.000	0.43	1415
55	2.1614	0.1415	1.000	0.07	1416
56	10.2408	0.0014	1.000	0.40	1414

JAKSTAT

1	0.2622	0.6086	1.000	0.31	1416
2	5.9072	0.0151	1.000	0.36	1416
3	0.0147	0.9035	1.000	0.38	1416
4	0.0209	0.8850	1.000	0.29	1416
5	0.0158	0.8999	1.000	0.19	1416
6	4.3055	0.0380	0.999	0.22	1416
7	2.6125	0.1060	1.000	0.31	1416
8	1.1677	0.2799	1.000	0.43	1412
9	0.1368	0.7114	0.983	0.08	1387
10	0.0354	0.8508	1.000	0.12	1416
11	0.7184	0.3967	0.999	0.40	1415
12	2.2635	0.1325	1.000	0.20	1416
13	2.8867	0.0893	0.999	0.08	1416
14	0.5872	0.4435	1.000	0.37	1415
15	2.7190	0.0992	1.000	0.06	1416
16	0.1292	0.7192	1.000	0.12	1416
17	0.2302	0.6314	1.000	0.27	1415
18	0.5065	0.4766	1.000	0.31	1416
19	6.0911	0.0136	1.000	0.12	1416
20	0.8629	0.3529	1.000	0.23	1415
21	0.0412	0.8391	1.000	0.05	1416
22	1.5251	0.2168	1.000	0.03	1416
23	0.1340	0.7143	1.000	0.38	1416
24	2.0522	0.1520	0.998	0.22	1413
25	0.0192	0.8899	1.000	0.38	1415
26	0.0157	0.9002	1.000	0.18	1416
27	1.4008	0.2366	1.000	0.28	1416
28	6.4526	0.0111	1.000	0.12	1415
29	1.1556	0.2824	1.000	0.07	1415
30	2.6233	0.1053	0.999	0.17	1416
31	4.3133	0.0378	0.999	0.28	1416
32	0.6664	0.4143	0.997	0.08	1414
33	2.0570	0.1515	1.000	0.32	1416
34	0.4332	0.5104	0.952	0.13	1329
35	1.4939	0.2216	0.999	0.10	1414
36	0.7452	0.3880	1.000	0.12	1415
37	0.0751	0.7841	0.999	0.38	1413
38	1.1112	0.2918	1.000	0.23	1416
39	0.0526	0.8186	1.000	0.49	1410
40	0.4006	0.5268	0.975	0.17	1394
41	0.0528	0.8182	1.000	0.40	1416
42	1.9244	0.1654	1.000	0.07	1416
43	0.0918	0.7619	0.998	0.40	1416
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JAKSTAT

Chisq (cases)	HWE (cases)	Successrate (cases)
0.0436	0.8346	1.000
1.2954	0.2550	1.000
3.0596	0.0803	1.000
0.0359	0.8498	0.999
0.1046	0.7463	0.999
0.0006	0.9812	0.992
3.6457	0.0562	1.000
0.0816	0.7751	1.000
3.9887	0.0458	0.999
0.7825	0.3764	1.000
1.9914	0.1582	0.999
0.2581	0.6114	0.998
0.1191	0.7301	1.000
0.6281	0.4280	0.999
0.8968	0.3436	0.999
0.2607	0.6097	0.998
0.0710	0.7899	0.999
0.0471	0.8282	0.996
0.7313	0.3925	1.000
0.0920	0.7616	0.999
0.3118	0.5766	1.000
1.2681	0.2601	1.000
0.7750	0.3787	0.999
0.0158	0.8999	1.000
0.3716	0.5421	1.000
0.0874	0.7674	1.000
0.0881	0.7666	0.996
3.7980	0.0513	1.000
0.0046	0.9460	0.999
0.0491	0.8247	0.993
0.3406	0.5595	0.999
1.5921	0.2070	0.999
0.3116	0.5767	0.996
1.2919	0.2557	1.000
0.4725	0.4918	0.997
3.6035	0.0577	0.997
0.2006	0.6542	0.999
1.2166	0.2700	1.000
1.3102	0.2523	0.998
0.0221	0.8818	1.000
0.2355	0.6275	1.000
0.0229	0.8796	1.000
2.2227	0.1360	0.987
4.5440	0.0330	0.978
3.3033	0.0691	1.000
3.0230	0.0821	0.999
3.3167	0.0686	0.999
2.1004	0.1473	1.000
2.4198	0.1198	1.000
0.4862	0.4856	0.999
0.3721	0.5418	1.000
0.0010	0.9754	0.998
0.0016	0.9684	0.997
0.0146	0.9040	0.997
0.0072	0.9324	0.999

JAKSTAT

1	0.1901	0.6629	0.999
2	0.3401	0.5598	1.000
3	0.0217	0.8829	0.996
4	0.0077	0.9301	0.999
5	0.3453	0.5568	0.998
6	0.6028	0.4375	0.999
7	0.2524	0.6154	0.991
8	0.0974	0.7550	0.999
9	0.1324	0.7159	0.998
10	0.1321	0.7163	0.999
11	0.1679	0.6820	1.000
12	0.5186	0.4714	1.000
13	0.0031	0.9556	1.000
14	0.1380	0.7103	0.999
15	0.0392	0.8430	0.999
16	0.6351	0.4255	0.996
17	0.9058	0.3412	1.000
18	0.0779	0.7801	0.999
19	0.3087	0.5785	0.999
20	0.3919	0.5313	0.999
21	0.0005	0.9821	0.999
22	0.6706	0.4128	0.999
23	0.1118	0.7381	0.999
24	1.2971	0.2547	0.999
25	1.0681	0.3014	0.999
26	0.4906	0.4836	0.999
27	0.4753	0.4905	1.000
28	0.1707	0.6795	1.000
29	5.0247	0.0250	0.996
30	0.3050	0.5808	1.000
31	0.2028	0.6525	1.000
32	0.1234	0.7253	1.000
33	2.5836	0.1080	1.000
34	0.8854	0.3467	1.000
35	0.0060	0.9382	1.000
36	1.2420	0.2651	0.998
37	0.0283	0.8665	1.000
38	0.5159	0.4726	0.999
39	0.8193	0.3654	0.999
40	0.9851	0.3209	1.000
41	0.9572	0.3279	1.000
42	0.1783	0.6729	0.999
43	3.4685	0.0625	1.000
44	3.6349	0.0566	0.986
45	0.9834	0.3214	0.999
46	0.4439	0.5052	0.999
47	0.7181	0.3968	1.000
48	2.4928	0.1144	1.000
49	0.0510	0.8214	0.999
50	0.6878	0.4069	0.999
51	0.0353	0.8510	1.000
52	0.0326	0.8567	0.997
53	0.6325	0.4264	0.999
54	2.0423	0.1530	1.000
55	2.7125	0.0996	1.000
56	0.9778	0.3228	0.999

JAKSTAT

5.7069	0.0169	1.000
0.0166	0.8976	1.000
0.0945	0.7585	1.000
1.8022	0.1795	1.000
0.0177	0.8941	0.999
1.7465	0.1863	1.000
0.3772	0.5391	0.994
1.5440	0.2140	1.000
0.8235	0.3641	1.000
0.7730	0.3793	1.000
1.5182	0.2179	0.999
0.7909	0.3738	0.999
1.1290	0.2880	1.000
0.1289	0.7195	0.999
3.1766	0.0747	0.984
2.0178	0.1555	0.999
1.0350	0.3090	1.000
1.3130	0.2519	1.000
0.1579	0.6911	0.999
0.7133	0.3984	0.989
0.6059	0.4363	0.999
3.2802	0.0701	0.999
1.3254	0.2496	1.000
0.2303	0.6313	1.000
1.4077	0.2354	0.999
1.5521	0.2128	0.992
0.0460	0.8301	0.997
0.0244	0.8760	1.000
0.0218	0.8826	0.999
0.0032	0.9547	0.999
0.8279	0.3629	1.000
0.0116	0.9142	0.999
0.2577	0.6117	1.000
0.1734	0.6771	1.000
0.0000	0.9962	1.000
0.0026	0.9595	1.000
0.0001	0.9909	1.000
0.0039	0.9504	0.994
0.7388	0.3900	1.000
0.5407	0.4621	1.000
0.0073	0.9319	1.000
0.1849	0.6672	1.000
0.2498	0.6172	0.999
0.0125	0.9109	0.999
0.1365	0.7117	0.997
0.4791	0.4888	0.996
0.0061	0.9378	0.999
0.2011	0.6538	1.000
0.0309	0.8605	0.999
0.2505	0.6167	1.000
0.0035	0.9528	0.999
2.5716	0.1088	1.000
3.0513	0.0807	1.000
0.0003	0.9873	0.999
0.0707	0.7903	1.000
0.0555	0.8138	0.999

JAKSTAT

3	0.8534	0.3556	1.000
4	1.3956	0.2375	1.000
5	0.0778	0.7803	1.000
6	0.4111	0.5214	1.000
7	0.0050	0.9434	1.000
8	0.0543	0.8157	1.000
9	0.0093	0.9233	1.000
10	4.5589	0.0327	0.997
11	1.4514	0.2283	0.980
12	0.3011	0.5832	1.000
13	0.7375	0.3905	0.999
14	0.0686	0.7934	1.000
15	0.8447	0.3580	1.000
16	3.8449	0.0499	0.999
17	1.5842	0.2082	1.000
18	0.2578	0.6116	1.000
19	0.7921	0.3735	0.999
20	2.9191	0.0875	1.000
21	0.2298	0.6317	1.000
22	0.2704	0.6031	0.999
23	0.1146	0.7350	1.000
24	0.2181	0.6405	1.000
25	0.0765	0.7821	1.000
26	1.9890	0.1584	0.998
27	0.5329	0.4654	0.999
28	0.1154	0.7341	1.000
29	1.7118	0.1908	1.000
30	0.2061	0.6498	0.999
31	0.8805	0.3481	0.999
32	2.5990	0.1069	1.000
33	0.0194	0.8891	1.000
34	0.0530	0.8178	0.999
35	0.0038	0.9509	1.000
36	0.0942	0.7590	0.939
37	0.6826	0.4087	0.999
38	1.7817	0.1819	0.999
39	8.2715	0.0040	0.998
40	0.4094	0.5223	1.000
41	0.9355	0.3334	0.996
42	0.1080	0.7424	0.984
43	1.1827	0.2768	1.000
44	0.0530	0.8180	1.000
45	2.5484	0.1104	1.000
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		rs324011		6	0.91	(0.76 ,1.09)	0.31504	1.04	(0.80 ,1.34)	0.78200	0.94	(0.79 ,1.11)	0.47358	0.88567
		rs324015		0	0.99	(0.83 ,1.18)	0.88528	1.38	(0.95 ,2.00)	0.09080	1.03	(0.87 ,1.22)	0.73024	0.34078
		rs703817		6	0.94	(0.77 ,1.14)	0.51925	0.92	(0.73 ,1.17)	0.50187	0.93	(0.77 ,1.12)	0.46311	0.49401
		TP63	rs1464117	56	1.13	(0.94 ,1.35)	0.20481	1.56	(0.94 ,2.59)	0.08871	1.16	(0.97 ,1.39)	0.10579	0.05622
		rs6790068		0	0.90	(0.75 ,1.08)	0.26356	0.99	(0.77 ,1.27)	0.92709	0.92	(0.78 ,1.09)	0.35480	0.66698
		rs6790258		0	1.21	(0.95 ,1.55)	0.11474	2.33	(0.58 ,9.37)	0.23224	1.24	(0.97 ,1.57)	0.08126	0.06073
		rs9681004		3	0.90	(0.75 ,1.06)	0.23798	0.99	(0.77 ,1.27)	0.95046	0.92	(0.77 ,1.09)	0.33780	0.68288

For Peer Review

		rs6790068		0	0.96	(0.59 .154)	0.85576	1.06	(0.56 .202)	0.85559	0.98	(0.62 .154)	0.93626	0.92276
		rs6790258		0	1.10	(0.58 .208)	0.77886	5.73	(0.57 .57.26)	0.13735	1.17	(0.63 .218)	0.61328	0.46202
		rs9681004		3	0.85	(0.52 .137)	0.49916	1.12	(0.61 .208)	0.71133	0.91	(0.58 .143)	0.69553	0.90000

For Peer Review

		rs6790068	0	0.96	(0.75 ,1.24)	0.77374	0.91	(0.63 ,1.30)	0.60512	0.95	(0.75 ,1.21)	0.68156
		rs6790258	0	1.08	(0.76 ,1.52)	0.67558	2.11	(0.34 ,13.12)	0.42398	1.10	(0.78 ,1.54)	0.59524
		rs9681004	3	0.92	(0.71 ,1.19)	0.52388	0.94	(0.66 ,1.34)	0.72020	0.92	(0.73 ,1.18)	0.52359

For Peer Review

1	
2	
3	(ter)
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5	
6	p-trend
7	
8	0.61182
9	0.349849
10	0.135644
11	0.870657
12	0.140916
13	0.703874
14	0.27166
15	0.788598
16	0.142129
17	0.003395
18	0.229127
19	0.369086
20	0.671501
21	0.677684
22	0.088134
23	0.081247
24	0.012073
25	0.049793
26	0.07607
27	0.819151
28	0.004491
29	0.278684
30	0.000639
31	0.072752
32	0.765728
33	0.897211
34	0.803125
35	0.999116
36	0.39276
37	0.937479
38	0.535935
39	0.543004
40	0.129812
41	0.843568
42	0.198466
43	0.030842
44	0.933834
45	0.448887
46	0.590937
47	0.55387
48	0.539941
49	0.707943
50	0.010601
51	0.481723
52	0.973341
53	0.827029
54	0.706881
55	0.475578
56	0.039241
57	0.630801
58	0.49921
59	0.627819
60	0.719253
55	0.500521
56	0.536542
57	0.657396
58	0.255659
59	0.840995
60	0.513683
55	0.431515
56	0.108268
57	0.360512
58	0.979312
59	0.608202
60	0.695523
55	0.503136
56	0.185519
57	0.714999
58	0.95213
59	0.273526
60	0.817587
55	0.718467
56	0.383466
57	0.092025
58	0.613156
59	0.358081
60	0.327154
55	0.349709
56	0.141476
57	0.724503
58	0.905873
59	0.195014
60	0.10649
55	0.014227
56	0.637812
57	0.244967
58	0.06936
59	0.064896
60	0.802329
55	0.092794
56	0.993691
57	0.662823
58	0.963116
59	0.686928
60	0.27026
55	0.22648
56	0.08631
57	0.546264
58	0.873775
59	0.164712
60	

For Peer Review

1	0.439999
2	0.471791
3	0.972195
4	0.054262
5	0.190312
6	0.38338
7	0.298238
8	0.950469
9	0.487507
10	0.514773
11	0.450938
12	0.784392
13	0.917838
14	0.266287
15	0.690072
16	0.468029
17	0.857319
18	0.963607
19	0.392586
20	0.571018
21	0.814813
22	0.815513
23	0.770769
24	0.183217
25	0.249967
26	0.575718
27	0.002734
28	0.167404
29	0.072359
30	0.609548
31	0.524629
32	0.847167
33	0.277085
34	0.259893
35	0.772847
36	0.428182
37	0.790324
38	0.229472
39	0.64124
40	0.169801
41	0.697964
42	0.967393
43	0.120866
44	0.536694
45	0.763189
46	0.782395
47	0.155362
48	0.685151
49	0.593387
50	0.599473
51	0.810252
52	0.781993
53	0.694293
54	0.938863
55	0.315964
56	0.308721
57	0.303376
58	0.485239
59	0.542427
60	0.314951
1	0.378103
2	0.517293
3	0.027291
4	0.027291
5	0.0282
6	0.915257
7	0.801747
8	0.020059
9	0.032282
10	0.021736
11	0.050584
12	0.757809
13	0.645215
14	0.137697
15	0.634629
16	0.435263
17	0.395613
18	0.157358
19	0.939157
20	0.5942
21	0.636209
22	0.812186
23	0.815596
24	0.16023
25	0.768169
26	0.847824
27	0.656992
28	0.866531
29	0.221447
30	0.497117
31	0.180312
32	0.929348
33	0.966374
34	0.051528
35	0.849691
36	0.604414
37	0.546759
38	0.783595
39	0.797968
40	0.083066
41	0.789923
42	0.037012
43	0.184451
44	0.947388
45	0.306721
46	0.454349
47	0.055484

For Peer Review

0.60435
0.52138
0.616507

For Peer Review



For Peer Review

		rs324011		6	0.79 (0.57 .1.11)	0.17330	1.05 (0.67 .1.64)	0.83926	0.85 (0.62 .1.16)	0.31165	0.767385
		rs324015		0	0.94 (0.68 .1.31)	0.73240	1.66 (0.91 .3.02)	0.10054	1.03 (0.75 .1.40)	0.86467	0.416069
		rs703817		6	0.87 (0.60 .1.25)	0.44811	0.88 (0.57 .1.35)	0.55366	0.87 (0.62 .1.23)	0.43148	0.539697
		TP63	rs1464117	56	1.46 (1.05 .2.04)	0.02499	2.49 (1.13 .5.52)	0.02399	1.54 (1.12 .2.12)	0.00844	0.00342
			rs6790068	0	0.70 (0.50 .0.98)	0.03538	0.74 (0.46 .1.19)	0.21217	0.71 (0.52 .0.97)	0.03088	0.076356
			rs6790258	0	1.40 (0.91 .2.13)	0.12229	2.65 (0.27 .26.20)	0.40329	1.42 (0.93 .2.15)	0.10167	0.087868
			rs9681004	3	0.70 (0.50 .0.98)	0.03834	0.75 (0.47 .1.20)	0.22837	0.71 (0.52 .0.98)	0.03474	0.087727

For Peer Review

		rs324011		6	0.86	(0.66 ,1.14)	0.29433	1.13	(0.77 ,1.65)	0.53841	0.92	(0.71 ,1.19)	0.52796	0.923835
		rs324015		0	0.96	(0.73 ,1.25)	0.73918	1.07	(0.59 ,1.93)	0.82191	0.97	(0.75 ,1.25)	0.80455	0.91744
		rs703817		6	1.02	(0.76 ,1.38)	0.87677	0.95	(0.66 ,1.36)	0.76460	1.00	(0.75 ,1.33)	0.99529	0.779724
		TP63	rs1464117	56	0.98	(0.74 ,1.30)	0.90770	1.43	(0.69 ,2.97)	0.33361	1.02	(0.78 ,1.34)	0.89850	0.676943
		rs6790068		0	1.02	(0.77 ,1.35)	0.88415	1.21	(0.83 ,1.74)	0.31990	1.07	(0.82 ,1.39)	0.63631	0.377747
		rs6790258		0	1.37	(0.97 ,1.94)	0.07731	4.07	(0.78 ,21.06)	0.09467	1.42	(1.01 ,2.00)	0.04373	0.02585
		rs9681004		3	1.02	(0.77 ,1.36)	0.86640	1.16	(0.80 ,1.68)	0.42787	1.06	(0.81 ,1.38)	0.67532	0.471548

For Peer Review

		rs11567762	1	1.88	(1.24	, 2.87)	0.00313	1.50	(0.44	, 5.13)	0.52020	1.85	(1.23	, 2.79)	0.00330	0.00705	
		rs11957503	0	1.08	(0.70	, 1.65)	0.73984	0.69	(0.37	, 1.28)	0.23761	0.96	(0.64	, 1.44)	0.83343	0.36444	
		rs12516866	0	0.90	(0.58	, 1.39)	0.63501	0.86	(0.47	, 1.56)	0.61042	0.89	(0.59	, 1.34)	0.57359	0.56814	
		rs1494565	2	1.04	(0.67	, 1.61)	0.85085	0.82	(0.45	, 1.49)	0.51882	0.98	(0.65	, 1.48)	0.92126	0.61636	
		rs3777090	1	1.26	(0.83	, 1.91)	0.28496	1.12	(0.57	, 2.19)	0.73836	1.23	(0.82	, 1.84)	0.31239	0.45285	
		rs6891095	0	0.64	(0.37	, 1.10)	0.10385	0.81	(0.24	, 2.75)	0.73393	0.66	(0.40	, 1.09)	0.10682	0.15229	
	IL8RB	rs7607437	10	1.50	(0.93	, 2.44)	0.09792	1.26	(0.70	, 2.30)	0.43992	1.43	(0.90	, 2.27)	0.12834	0.36155	
	IRF4	rs1033180	1	1.91	(1.18	, 3.10)	0.00887	2.15	(0.23	, 20.01)	0.50231	1.92	(1.19	, 3.09)	0.00755	0.00829	
		rs1050975	0	1.78	(1.11	, 2.84)	0.01648	-	-	-	-	1.67	(1.04	, 2.66)	0.03213	0.08109	
		rs11757491	0	0.54	(0.27	, 1.09)	0.08474	1.14	(0.14	, 9.35)	0.90290	0.57	(0.29	, 1.11)	0.09939	0.13703	
		rs12211228	1	1.52	(1.00	, 2.31)	0.05061	1.03	(0.23	, 4.52)	0.97206	1.49	(0.98	, 2.24)	0.06025	0.09771	
		rs13208928	0	0.58	(0.30	, 1.15)	0.11866	-	-	-	-	0.56	(0.29	, 1.10)	0.09207	0.07990	
		rs1514346	0	0.69	(0.40	, 1.20)	0.18665	-	-	-	-	0.66	(0.38	, 1.15)	0.14393	0.11750	
		rs1877175	0	1.18	(0.78	, 1.79)	0.42237	0.99	(0.41	, 2.41)	0.98496	1.16	(0.78	, 1.72)	0.47136	0.60184	
		rs2001508	0	1.27	(0.83	, 1.94)	0.26300	0.37	(0.05	, 2.73)	0.32669	1.19	(0.79	, 1.81)	0.40441	0.68229	
		rs3778607	1	0.74	(0.47	, 1.16)	0.18642	0.58	(0.33	, 1.02)	0.05809	0.68	(0.45	, 1.04)	0.07846	0.05239	
		rs3800262	0	1.12	(0.73	, 1.73)	0.59911	0.74	(0.17	, 3.20)	0.68920	1.09	(0.71	, 1.67)	0.68681	0.82377	
		rs6900384	14	0.77	(0.43	, 1.36)	0.36109	-	-	-	-	0.75	(0.42	, 1.32)	0.31624	0.28172	
		rs6906608	0	1.56	(1.03	, 2.36)	0.03684	1.02	(0.23	, 4.51)	0.97394	1.52	(1.01	, 2.29)	0.04485	0.07714	
		rs768807	0	1.02	(0.68	, 1.54)	0.90845	0.44	(0.13	, 1.43)	0.17032	0.94	(0.63	, 1.40)	0.76691	0.42391	
		rs9378805	0	0.78	(0.50	, 1.20)	0.25810	0.57	(0.32	, 1.03)	0.06174	0.71	(0.47	, 1.08)	0.10800	0.05655	
		rs9405192	3	1.83	(1.19	, 2.79)	0.00557	1.49	(0.75	, 2.95)	0.25231	1.76	(1.17	, 2.65)	0.00692	0.03012	
	JAK1	rs10789166	1	0.79	(0.48	, 1.29)	0.34562	0.34	(0.05	, 2.55)	0.29372	0.75	(0.46	, 1.21)	0.23498	0.17536	
		rs2256298	0	0.79	(0.52	, 1.21)	0.28037	0.63	(0.24	, 1.62)	0.33765	0.77	(0.52	, 1.15)	0.20615	0.18062	
		rs310211	1	0.76	(0.50	, 1.14)	0.18657	0.47	(0.19	, 1.11)	0.08454	0.71	(0.48	, 1.05)	0.08513	0.04628	
		rs54653535	39	0.77	(0.48	, 1.24)	0.27764	1.58	(0.68	, 3.67)	0.28765	0.87	(0.56	, 1.34)	0.51823	0.29207	
	SOC51	rs149311	3	1.45	(0.93	, 2.24)	0.07963	1.92	(0.82	, 4.49)	0.13386	1.51	(1.00	, 2.28)	0.05022	0.03830	
		rs149597	2	1.81	(1.08	, 3.03)	0.02474	1.38	(0.76	, 2.53)	0.29277	1.66	(1.01	, 2.73)	0.04524	0.30183	
		rs193778	1	1.08	(0.72	, 1.64)	0.70403	1.22	(0.53	, 2.83)	0.64336	1.10	(0.74	, 1.63)	0.63877	0.59019	
		rs243317	1	0.94	(0.62	, 1.42)	0.76847	0.56	(0.23	, 1.33)	0.18837	0.87	(0.59	, 1.29)	0.49383	0.27302	
		rs408665	28	0.93	(0.59	, 1.45)	0.74158	0.97	(0.54	, 1.75)	0.91257	0.94	(0.61	, 1.44)	0.76565	0.86189	
		rs940551	1	0.73	(0.47	, 1.12)	0.14697	0.75	(0.40	, 1.39)	0.36289	0.73	(0.49	, 1.10)	0.13312	0.20967	
	SOC55	rs13402099	3	0.85	(0.51	, 1.42)	0.54310	0.49	(0.06	, 3.73)	0.48734	0.82	(0.50	, 1.36)	0.44909	0.38706	
		rs13412085	0	0.92	(0.57	, 1.49)	0.73613	0.38	(0.05	, 2.86)	0.34768	0.87	(0.54	, 1.39)	0.56702	0.43105	
	SOC56	rs17082355	0	1.06	(0.66	, 1.71)	0.80677	1.20	(0.35	, 4.12)	0.77117	1.07	(0.68	, 1.70)	0.75830	0.72534	
		rs17809666	1	0.25	(0.09	, 0.70)	0.00814	1.59	(0.18	, 13.93)	0.67462	0.30	(0.12	, 0.76)	0.01100	0.02062	
		rs4891398	29	0.99	(0.63	, 1.56)	0.97422	1.46	(0.84	, 2.52)	0.17980	1.11	(0.73	, 1.68)	0.62123	0.25186	
	STAT1	rs10173099	10	1.09	(0.72	, 1.65)	0.69110	0.69	(0.33	, 1.44)	0.31899	1.00	(0.67	, 1.50)	0.98860	0.58139	
		rs10199181	2	0.97	(0.63	, 1.48)	0.87771	0.88	(0.47	, 1.63)	0.67969	0.95	(0.63	, 1.42)	0.78786	0.69780	
		rs1168	3	0.84	(0.53	, 1.32)	0.45055	0.99	(0.57	, 1.72)	0.97862	0.88	(0.58	, 1.35)	0.56793	0.88355	
		rs12468579	1	1.17	(0.74	, 1.83)	0.49935	0.98	(0.55	, 1.75)	0.93907	1.11	(0.72	, 1.70)	0.62774	0.94517	
		rs12693591	0	0.61	(0.36	, 1.02)	0.06003	1.95	(0.63	, 6.02)	0.24583	0.69	(0.43	, 1.12)	0.13097	0.32812	
		rs13029247	2	1.05	(0.69	, 1.58)	0.82971	0.67	(0.31	, 1.46)	0.31568	0.97	(0.65	, 1.45)	0.89374	0.53902	
		rs13029532	0	1.32	(0.80	, 2.17)	0.27939	0.85	(0.11	, 6.68)	0.87717	1.29	(0.79	, 2.10)	0.31339	0.38509	
		rs13035504	1	0.76	(0.48	, 1.20)	0.23805	0.28	(0.04	, 2.12)	0.21870	0.71	(0.45	, 1.12)	0.14457	0.09801	
		rs13395505	0	1.34	(0.86	, 2.07)	0.19248	0.81	(0.43	, 1.55)	0.53037	1.19	(0.78	, 1.81)	0.41147	0.90502	
		rs400657	0	1.18	(0.74	, 1.88)	0.48890	-	-	-	-	1.08	(0.68	, 1.73)	0.73502	0.93317	
		rs4671199	0	1.40	(0.93	, 2.10)	0.10617	0.79	(0.30	, 2.04)	0.62619	1.30	(0.88	, 1.94)	0.18850	0.45603	
		rs1547550	20	1.22	(0.80	, 1.88)	0.35489	1.40	(0.74	, 2.62)	0.29934	1.26	(0.84	, 1.89)	0.26953	0.23745	
		rs16824035	1	0.75	(0.47	, 1.19)	0.22513	0.57	(0.13	, 2.45)	0.44818	0.73	(0.47	, 1.15)	0.17808	0.16628	
		rs17749316	0	0.99	(0.54	, 1.83)	0.97868	0.00	(0.00	,	0.00	0.98817	0.96	(0.52	, 1.76)	0.89101	0.80076
		rs17817966	0	1.08	(0.69	, 1.71)	0.73178	1.10	(0.62	, 1.92)	0.74911	1.09	(0.71	, 1.67)	0.70379	0.72901	
		rs20667395	0	1.08	(0.24	, 4.80)	0.92112	-	-	-	-	1.08	(0.24	, 4.80)	0.92112	0.92112	
		rs2066804	1	1.33	(0.88	, 2.00)	0.17254	1.23	(0.50	, 3.00)	0.65245	1.32	(0.69	, 1.96)	0.17266	0.22639	
		rs2280232	1	0.69	(0.45	, 1.06)	0.09102	1.01	(0.48	, 2.12)	0.97634	0.74	(0.49	, 1.10)	0.13868	0.31304	
		rs2280233	4	0.80	(0.51	, 1.28)	0.35950	1.03	(0.60	, 1.75)	0.19754	0.87	(0.57	, 1.34)	0.53377	0.99464	
		rs2280234	5	1.25	(0.80	, 1.95)	0.32457	1.48	(0.83	, 2.66)	0.18581	1.30	(0.86	, 1.98)	0.21483	0.16394	
		rs43997637	3	1.34	(0.89	, 2.02)	0.201632	0.95	(0.39	, 2.29)	0.90876	1.28	(0.86	, 1.90)	0.22459	0.40946	
		rs4327257	0	0.68	(0.41	, 1.11)	0.12287	0.42	(0.05	, 3.16)	0.39616	0.66	(0.40	, 1.07)	0.09178	0.08309	
		rs48535333	3	1.47	(0.94	, 2.30)	0.08845	1.52	(0.83	, 2.79)	0.17569	1.48	(0.97	, 2.27)	0.06901	0.09795	
		rs5620224	0	1.38	(0.88	, 2.16)	0.15857	1.36	(0.77	, 2.42)	0.28842	1.38	(0.90	, 2.10)	0.13877	0.20470	
		rs867637	2	1.40	(0.91	, 2.16)	0.12335	1.26	(0.66	, 2.41)	0.48503	1.37	(0.91	, 2.08)	0.13292	0.24255	
		rs1053005	1	0.55	(0.34	, 0.88)	0.01307	0.68	(0.26	, 1.76)	0.42453	0.57	(0.37	, 0.88)	0.01205	0.02604	
		rs1053023	1	0.53	(0.33	, 0.85)	0.00893	0.82	(0.34	, 1.98)	0.65196	0.57	(0.37	, 0.88)	0.01205	0.03834	
		rs12949918	1	0.64	(0.42	, 0.99)	0.04252	0.53	(0.29	, 0.97)	0.03998	0.61	(0.41	, 0.91)	0.01516	0.01708	
		rs17405722	0	0.62	(0.29	, 1.31)	0.20776	2.18	(0.45	, 10.66)	0.33524	0.72	(0.37	, 1.42)	0.34590	0.56629	
		rs2293152	2	1.07	(0.68	, 1.68)	0.75663	1.39	(0.81	, 2.40)	0.23297	1.18	(0.77	, 1.73)	0.47479	0.26576	
		rs4103200	0	0.67	(0.44	,											

		rs6790068	0	0.75	(0.49 .1.17)	0.20447	0.93	(0.53 .1.65)	0.81302	0.80	(0.53 .1.20)	0.27532	0.55829
		rs6790258	0	0.86	(0.46 .1.61)	0.63937	-	-	-	0.83	(0.45 .1.57)	0.57366	0.51616
		rs9681004	3	0.81	(0.52 .1.25)	0.33368	0.98	(0.56 .1.73)	0.95295	0.85	(0.57 .1.28)	0.43655	0.74675

For Peer Review

Supplement Table2. Odds Ratios (OR) and 95% Confidence Intervals of all SNPs with BNHL and subtypes (DLBCL, FL, CLL, T-NHL, MZL and MCL), adjusted for age (continuous), sex and study center)													
Gene	db SNP ID	no. of nocalcs	Heterozygous mutant			Homozygous Mutant			Dominant Model			MCL	
			OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	p-trend	
BMF	rs10518679	0	0.68	(0.31, 1.48)	0.33126	0.00	(0.00, -)	0.98455	0.63	(0.29, 1.37)	0.23931	0.18841	
	rs11630670	0	1.16	(0.59, 2.26)	0.66460	0.73	(0.29, 1.85)	0.50248	1.03	(0.54, 1.97)	0.92134	0.61367	
	rs11634257	1	0.99	(0.54, 1.82)	0.98648	0.30	(0.04, 2.27)	0.24399	0.89	(0.49, 1.61)	0.70474	0.42564	
	rs11856141	2	1.16	(0.59, 2.28)	0.66875	1.22	(0.51, 2.90)	0.65126	1.18	(0.62, 2.23)	0.62288	0.62529	
	rs12913170	2	1.11	(0.58, 2.12)	0.75031	0.83	(0.11, 6.36)	0.85508	1.09	(0.58, 2.04)	0.79831	0.87292	
	rs1540686	22	1.58	(0.70, 3.58)	0.26869	2.26	(0.93, 5.48)	0.07059	1.79	(0.82, 3.88)	0.14396	0.06661	
	rs16970325	2	0.77	(0.34, 1.76)	0.53509	-	-	-	0.75	(0.33, 1.71)	0.49175	0.45626	
	rs16970349	0	0.85	(0.30, 2.45)	0.76380	-	-	-	0.84	(0.29, 2.40)	0.73815	0.17673	
	rs3743129	2	1.00	(0.50, 2.02)	0.99225	1.47	(0.67, 3.22)	0.33228	1.14	(0.60, 2.18)	0.68219	0.36104	
	rs3923235	0	1.19	(0.65, 2.17)	0.56655	0.53	(0.12, 2.30)	0.39453	1.08	(0.60, 1.94)	0.78940	0.82925	
	rs537455	1	1.32	(0.73, 2.40)	0.36358	0.88	(0.20, 3.88)	0.86839	1.27	(0.71, 2.28)	0.42522	0.59001	
	rs546220	5	1.33	(0.67, 2.63)	0.42057	1.42	(0.59, 3.42)	0.43215	1.35	(0.70, 2.60)	0.37059	0.38858	
	rs588739	0	1.19	(0.58, 2.41)	0.63894	1.41	(0.60, 3.28)	0.42669	1.24	(0.63, 2.44)	0.52401	0.42950	
	rs648289	1	1.41	(0.66, 3.02)	0.37030	2.02	(0.87, 4.67)	0.10027	1.59	(0.78, 3.25)	0.20398	0.09847	
	rs652196	3	0.97	(0.52, 1.79)	0.91186	0.37	(0.05, 2.81)	0.33870	0.89	(0.49, 1.62)	0.69819	0.49081	
	rs675173	6	1.26	(0.68, 2.33)	0.45813	0.75	(0.22, 2.59)	0.64688	1.17	(0.65, 2.13)	0.60143	0.19156	
	rs1839377	2	1.11	(0.61, 2.05)	0.72943	0.51	(0.15, 1.75)	0.28157	0.99	(0.55, 1.79)	0.96639	0.52716	
	rs989713	6	1.01	(0.54, 1.87)	0.98358	0.41	(0.12, 1.42)	0.15860	0.88	(0.48, 1.61)	0.67112	0.27379	
CASP6	rs1541373	1	0.55	(0.29, 1.06)	0.07472	1.27	(0.56, 2.88)	0.56209	0.69	(0.38, 1.24)	0.21178	0.83042	
	rs1800627	3	0.82	(0.40, 1.67)	0.58605	0.97	(0.44, 2.16)	0.94158	0.87	(0.45, 1.68)	0.68069	0.94414	
	rs181345	0	1.59	(0.80, 3.15)	0.18279	-	-	-	1.46	(0.74, 2.88)	0.27689	0.45513	
	rs3212153	1	0.67	(0.31, 1.47)	0.31644	1.04	(0.13, 8.13)	0.97357	0.70	(0.33, 1.47)	0.34451	0.41519	
	rs5030552	1	1.26	(0.60, 2.68)	0.54164	-	(0.00, -)	-	1.19	(0.56, 2.52)	0.65388	0.80166	
	rs68063	0	1.23	(0.42, 3.55)	0.70739	-	-	-	1.22	(0.42, 3.54)	0.70971	0.72161	
IFNG	rs12306852	0	0.68	(0.32, 1.44)	0.31484	0.94	(0.12, 7.26)	0.95001	0.70	(0.34, 1.43)	0.33098	0.38795	
	rs2069716	0	1.62	(0.78, 3.36)	0.19673	-	-	-	1.57	(0.76, 3.25)	0.22631	0.27797	
	rs2069718	8	0.65	(0.34, 1.21)	0.17454	0.77	(0.30, 1.97)	0.59213	0.67	(0.37, 1.22)	0.18839	0.32506	
	rs2069727	0	1.27	(0.59, 2.72)	0.53709	1.79	(0.78, 4.10)	0.16775	1.44	(0.70, 2.93)	0.32218	0.16273	
	rs581795	1	1.07	(0.58, 1.99)	0.82160	1.24	(0.41, 3.73)	0.69858	1.10	(0.61, 1.98)	0.75451	0.69547	
IFNGR1	rs12529779	15	1.03	(0.56, 1.90)	0.91630	0.34	(0.05, 2.60)	0.30117	0.93	(0.51, 1.70)	0.82511	0.54573	
	rs327474	1	1.41	(0.72, 2.79)	0.31917	0.81	(0.30, 2.19)	0.68280	1.25	(0.65, 2.42)	0.50637	0.93119	
	rs327475	2	0.97	(0.51, 1.84)	0.92301	0.54	(0.07, 4.08)	0.54740	0.92	(0.49, 1.73)	0.79989	0.67268	
	rs1854154	6	0.60	(0.30, 1.20)	0.15015	0.95	(0.44, 2.07)	0.90375	0.71	(0.38, 1.31)	0.27233	0.76753	
	rs3799488	0	0.64	(0.29, 1.40)	0.26470	-	-	-	0.61	(0.28, 1.33)	0.21367	0.18396	
	rs477768	8	0.66	(0.31, 1.39)	0.27561	0.93	(0.12, 7.20)	0.94098	0.68	(0.33, 1.39)	0.29064	0.34625	
	rs4896243	4	1.28	(0.63, 2.59)	0.49544	1.06	(0.43, 2.58)	0.89872	1.21	(0.62, 2.39)	0.57377	0.83492	
	rs608914	4	2.31	(1.15, 4.67)	0.01928	4.74	(1.96, 11.47)	0.00056	2.70	(1.38, 5.27)	0.00369	0.00040	
	rs759040	0	0.79	(0.42, 1.48)	0.46345	0.77	(0.18, 3.37)	0.73265	0.79	(0.43, 1.44)	0.44174	0.46555	
	rs9402877	3	0.64	(0.33, 1.25)	0.19074	0.89	(0.40, 1.97)	0.77555	0.71	(0.39, 1.30)	0.27079	0.57775	
IFNGR2	rs1015873	0	0.40	(0.05, 3.02)	0.37692	-	-	-	0.40	(0.05, 3.02)	0.37692	0.37692	
	rs2626735	0	1.78	(0.98, 3.22)	0.05741	0.53	(0.07, 4.02)	0.53580	1.63	(0.91, 2.94)	0.10268	0.29659	
	rs16990664	0	0.39	(0.05, 2.94)	0.36442	-	-	-	0.39	(0.05, 2.94)	0.36442	0.36442	
	rs2020175	45	1.17	(0.59, 2.32)	0.65170	-	-	-	1.09	(0.55, 2.15)	0.81070	0.98180	
	rs2844553	59	1.68	(0.85, 3.31)	0.13691	1.01	(0.37, 2.75)	0.97818	1.50	(0.78, 2.91)	0.22576	0.63711	
	rs2834211	0	1.09	(0.53, 2.25)	0.81525	-	-	-	1.01	(0.49, 2.07)	0.98330	0.83237	
	rs2834214	1	1.65	(0.84, 3.23)	0.14458	0.41	(0.13, 1.28)	0.12276	1.23	(0.64, 2.38)	0.53835	0.31184	
	rs1313980	2	0.81	(0.43, 1.53)	0.52255	1.31	(0.52, 3.32)	0.57086	0.90	(0.50, 1.62)	0.72856	0.93182	
	rs976971	0	1.23	(0.62, 2.45)	0.55231	0.99	(0.40, 2.46)	0.98155	1.17	(0.60, 2.26)	0.64730	0.92331	
	rs978166	0	0.43	(0.18, 1.04)	0.06129	-	-	-	0.41	(0.17, 0.97)	0.04326	0.03883	
IL10	rs1554286	2	0.85	(0.44, 1.65)	0.63599	-	-	-	0.77	(0.40, 1.48)	0.43003	0.27413	
	rs7015767	0	1.04	(0.56, 1.93)	0.91238	0.96	(0.22, 4.24)	0.95603	1.03	(0.56, 1.88)	0.93089	0.96226	
	rs1800871	9	0.91	(0.49, 1.67)	0.75095	-	-	-	0.78	(0.42, 1.44)	0.42620	0.19470	
	rs1800872	10	0.90	(0.49, 1.67)	0.74748	-	-	-	0.78	(0.42, 1.44)	0.42596	0.19568	
	rs2222202	9	1.49	(0.74, 2.97)	0.26049	0.64	(0.23, 1.75)	0.38179	1.22	(0.62, 2.40)	0.55756	0.56346	
	rs3021094	2	0.75	(0.31, 1.82)	0.52880	-	-	-	0.73	(0.30, 1.75)	0.47645	0.43676	
	rs3024505	1	0.70	(0.34, 1.45)	0.33994	0.77	(0.10, 5.94)	0.80040	0.71	(0.35, 1.42)	0.33265	0.36460	
	rs3024509	0	1.38	(0.62, 3.05)	0.42730	-	-	-	1.34	(0.61, 2.97)	0.46727	0.52765	
	rs4390174	7	1.11	(0.58, 2.12)	0.75594	1.31	(0.55, 3.14)	0.54730	1.15	(0.62, 2.13)	0.64790	0.55387	
	rs4844553	1	1.17	(0.51, 2.68)	0.71962	-	-	-	1.13	(0.49, 2.61)	0.77039	0.83550	
	rs6739328	8	1.03	(0.56, 1.92)	0.91306	0.68	(0.16, 2.98)	0.61186	0.98	(0.54, 1.79)	0.95925	0.80150	
	rs6866931	2	0.71	(0.37, 1.38)	0.31349	0.65	(0.15, 2.81)	0.56291	0.70	(0.37, 1.32)	0.27164	0.28782	
	rs748373	22	1.22	(0.53, 2.81)	0.64441	-	-	-	1.18	(0.51, 2.73)	0.69327	0.75835	
IL12A	rs1927521	6	1.18	(0.62, 2.26)	0.61339	1.11	(0.44, 2.78)	0.82161	1.17	(0.63, 2.16)	0.62763	0.72368	
	rs243115	4	0.99	(0.47, 2.11)	0.98651	-	-	-	0.92	(0.44, 1.95)	0.83368	0.68220	
	rs243131	3	1.38	(0.75, 2.55)	0.30329	0.71	(0.09, 5.55)	0.74806	1.32	(0.72, 2.41)	0.37028	0.52274	
	rs243154	0	0.55	(0.21, 1.42)	0.21506	-	-	-	0.52	(0.20, 1.35)	0.18264	0.16723	
	rs4680534	0	1.23	(0.65, 2.32)	0.52849	1.26	(0.51, 3.14)	0.61242	1.24	(0.68, 2.26)	0.49152	0.52087	
	rs4845497	1	1.37	(0.65, 2.89)	0.40922	0.94	(0.38, 2.32)	0.88773	1.22	(0.60, 2.51)	0.58274	0.88042	
	rs583911	2	0.94	(0.50, 1.79)	0.86222	0.63	(0.24, 1.63)	0.33716	0.86	(0.46, 1.59)	0.63058	0.38717	
	rs6441282	1	1.48	(0.70, 3.16)	0.30540	1.61	(0.68, 3.80)	0.27736	1.52	(0.74, 3.12)	0.25104	0.27660	
	rs6800657	6	1.58	(0.82, 3.05)	0.17110	-	-	-	1.45	(0.75, 2.78)	0.26813	0.47269	
	rs692890	0	1.55	(0.81, 2.98)	0.18541	1.96							

1		rs11567762	1	1.30	(0.69	2.46)	0.41651	0.76	(0.10	,5.85)	0.79412	1.25	(0.67	,2.32)	0.48725	0.62150	
2		rs11957503	0	1.41	(0.74	2.68)	0.29802	0.76	(0.29	,2.00)	0.5824	1.21	(0.65	,2.25)	0.53743	0.88359	
3		rs21516866	0	1.05	(0.54	,2.05)	0.88004	1.64	(0.72	,3.74)	0.23688	1.19	(0.64	,2.20)	0.58899	0.30019	
4		rs1494565	2	1.05	(0.54	,2.03)	0.87901	1.20	(0.51	,2.79)	0.67859	1.09	(0.59	,2.02)	0.78668	0.69385	
5		rs3777090	1	1.11	(0.60	,2.06)	0.72876	0.73	(0.24	,2.19)	0.57772	1.03	(0.57	,1.87)	0.91200	0.80650	
6		rs6891095	0	1.46	(0.75	,2.85)	0.26161	1.33	(0.17	,10.46)	0.78682	1.45	(0.76	,2.78)	0.25806	0.28846	
7		IL8RB	rs7607437	10	0.79	(0.40	,1.54)	0.48069	0.93	(0.42	,2.06)	0.86094	0.83	(0.45	,1.54)	0.55622	0.79651
8		IRF4	rs1033180	1	1.37	(0.64	,2.93)	0.41366	-	-	-	1.34	(0.63	,2.86)	0.44854	0.50258	
9		rs1050975	0	1.11	(0.51	,2.44)	0.79341	-	-	-	1.05	(0.48	,2.31)	0.90116	0.97491		
10		rs11757491	0	1.50	(0.70	,3.20)	0.29278	-	-	-	1.44	(0.68	,3.06)	0.34515	0.42944		
11		rs12211228	1	0.66	(0.31	,1.39)	0.27181	-	-	-	0.62	(0.30	,1.31)	0.21391	0.17753		
12		rs3208928	0	1.44	(0.67	,3.06)	0.34823	-	-	-	1.39	(0.65	,2.95)	0.39552	0.46815		
13		rs1514346	0	1.16	(0.56	,2.39)	0.68343	-	-	-	1.11	(0.54	,2.28)	0.78004	0.90454		
14		rs1877175	0	0.92	(0.49	,1.72)	0.79297	0.44	(0.06	,3.34)	0.42839	0.87	(0.47	,1.59)	0.64318	0.50265	
15		rs2001508	0	1.31	(0.70	,2.46)	0.39534	0.84	(0.11	,6.46)	0.86524	1.27	(0.69	,2.35)	0.44575	0.55363	
16		rs3778607	1	2.40	(1.08	,5.34)	0.03193	1.04	(0.38	,2.84)	0.93837	1.90	(0.87	,4.15)	0.10657	0.91766	
17		rs3800262	0	0.96	(0.50	,1.87)	0.91562	1.26	(0.28	,5.63)	0.76055	1.00	(0.53	,1.87)	0.98958	0.92413	
18		rs6900384	14	1.12	(0.51	,2.46)	0.77553	-	-	-	1.09	(0.49	,2.38)	0.83839	0.91413		
19		rs6906608	0	0.65	(0.31	,1.37)	0.26199	-	-	-	0.62	(0.29	,1.30)	0.20581	0.17103		
20		rs768807	0	0.97	(0.52	,1.82)	0.92611	1.65	(0.60	,4.53)	0.32998	1.07	(0.60	,1.93)	0.81974	0.54757	
21		rs9378805	0	1.31	(0.64	,2.66)	0.45562	0.99	(0.42	,2.35)	0.98168	1.20	(0.61	,2.36)	0.59440	0.97294	
22		rs9405192	3	2.01	(1.08	,3.76)	0.02766	0.96	(0.27	,3.39)	0.95541	1.82	(0.99	,3.36)	0.05387	0.22912	
23		JAK1	rs107891166	1	0.98	(0.50	,1.94)	0.95869	2.19	(0.48	,9.92)	0.30822	1.07	(0.56	,2.03)	0.84270	0.63279
24		rs2256298	0	0.91	(0.48	,1.72)	0.78098	1.86	(0.72	,4.78)	0.19694	1.05	(0.59	,1.89)	0.86315	0.46388	
25		rs10211	1	0.68	(0.35	,1.34)	0.26762	2.38	(1.12	,5.06)	0.02392	1.00	(0.55	,1.79)	0.98831	0.15131	
26		rs54653535	39	0.78	(0.39	,1.55)	0.47849	1.73	(0.50	,6.01)	0.38626	0.88	(0.47	,1.65)	0.68759	0.99916	
27		SOCS1	rs149311	3	1.18	(0.61	,2.30)	0.61586	0.72	(0.09	,5.48)	0.74902	1.13	(0.59	,2.16)	0.70566	0.83909
28		rs149597	2	0.79	(0.41	,1.53)	0.48597	0.71	(0.31	,1.63)	0.41963	0.77	(0.41	,1.41)	0.39455	0.39078	
29		rs193778	1	1.72	(0.94	,3.14)	0.07598	1.36	(0.30	,6.05)	0.69309	1.69	(0.94	,3.04)	0.08188	0.12644	
30		rs243317	1	0.83	(0.45	,1.54)	0.54977	0.84	(0.28	,2.48)	0.74807	0.83	(0.46	,1.49)	0.53228	0.57590	
31		rs408665	28	0.56	(0.28	,1.10)	0.09307	1.06	(0.48	,2.31)	0.89036	0.68	(0.37	,1.26)	0.22126	0.82047	
32		rs9940551	1	0.66	(0.34	,1.27)	0.21275	1.01	(0.45	,2.25)	0.39895	0.74	(0.40	,1.37)	0.33978	0.78148	
33		SOCS5	rs13402099	3	0.91	(0.42	,2.00)	0.81857	-	-	-	0.86	(0.39	,1.88)	0.70791	0.60677	
34		SOCS6	rs17082355	0	0.94	(0.46	,1.93)	0.86794	-	-	-	0.87	(0.43	,1.79)	0.71524	0.57305	
35		rs17809666	1	0.95	(0.36	,2.46)	0.90777	7.39	(0.71	,76.47)	0.09345	1.11	(0.46	,2.68)	0.82499	0.56722	
36		rs4891398	29	0.89	(0.47	,1.70)	0.72855	1.25	(0.52	,2.99)	0.61416	0.97	(0.53	,1.77)	0.91020	0.77789	
37		STAT1	rs10173099	10	0.49	(0.26	,0.93)	0.03028	0.35	(0.10	,1.17)	0.08673	0.46	(0.25	,0.84)	0.01203	0.01414
38		rs10199181	2	0.52	(0.27	,0.98)	0.04392	0.63	(0.25	,1.57)	0.31859	0.54	(0.30	,0.98)	0.04127	0.10063	
39		rs1168	3	1.31	(0.63	,2.72)	0.47075	1.22	(0.51	,2.90)	0.65637	1.28	(0.64	,2.58)	0.48816	0.64560	
40		rs2468579	1	0.84	(0.44	,1.62)	0.60789	0.97	(0.42	,2.24)	0.94809	0.88	(0.48	,1.61)	0.67325	0.85151	
41		rs2693591	0	0.37	(0.15	,0.96)	0.04105	4.58	(1.20	,17.49)	0.02586	0.57	(0.26	,1.24)	0.15514	0.54666	
42		rs13029247	2	0.54	(0.29	,1.03)	0.06087	0.44	(0.13	,1.47)	0.18070	0.52	(0.29	,0.95)	0.03455	0.04162	
43		rs13029532	0	0.79	(0.33	,1.90)	0.59846	-	-	-	0.75	(0.31	,1.82)	0.53049	0.47781		
44		rs13035504	1	0.57	(0.28	,1.17)	0.12496	1.55	(0.35	,6.92)	0.56664	0.64	(0.32	,1.25)	0.18887	0.34419	
45		rs13395505	0	0.86	(0.46	,1.60)	0.62795	0.67	(0.26	,1.72)	0.40371	0.81	(0.45	,1.47)	0.48349	0.39148	
46		rs4006557	0	0.97	(0.46	,2.05)	0.94265	-	-	-	0.92	(0.44	,1.95)	0.83622	0.72508		
47		rs4671199	0	0.65	(0.33	,1.29)	0.21739	0.57	(0.13	,2.47)	0.45542	0.64	(0.34	,1.22)	0.17279	0.18658	
48		rs1547550	20	0.98	(0.53	,1.80)	0.93926	0.67	(0.19	,2.29)	0.51945	0.92	(0.51	,1.67)	0.79676	0.62364	
49		rs16824035	1	0.55	(0.27	,1.14)	0.10712	1.54	(0.34	,6.87)	0.57344	0.62	(0.32	,1.22)	0.16384	0.30802	
50		rs17749316	0	0.98	(0.41	,2.37)	0.98413	-	-	-	0.91	(0.38	,2.19)	0.82744	0.70457		
51		rs17817966	0	0.67	(0.36	,1.23)	0.19300	0.22	(0.07	,0.75)	0.01554	0.54	(0.30	,0.97)	0.03831	0.00896	
52		rs2067395	5	0.55	(0.24	,1.27)	0.12170	-	-	-	5.45	(1.44	,20.71)	0.01270	0.01270		
53		rs2068604	1	0.94	(0.50	,1.75)	0.84041	1.11	(0.25	,4.91)	0.88859	0.95	(0.52	,1.74)	0.87873	0.94129	
54		rs2280232	1	0.65	(0.34	,1.22)	0.17843	0.85	(0.25	,2.91)	0.80045	0.67	(0.37	,1.23)	0.19684	0.29322	
55		rs2280233	4	1.33	(0.62	,2.85)	0.45834	1.43	(0.61	,3.35)	0.41498	1.36	(0.66	,2.80)	0.39952	0.42070	
56		rs2280234	5	1.01	(0.55	,1.86)	0.98148	0.76	(0.25	,2.29)	0.62468	0.96	(0.53	,1.73)	0.89569	0.73215	
57		rs34997637	3	0.73	(0.38	,1.41)	0.34595	0.63	(0.15	,2.74)	0.53930	0.71	(0.38	,1.34)	0.29289	0.29855	
58		rs4327257	0	0.64	(0.30	,1.36)	0.24820	2.20	(0.48	,10.08)	0.31031	0.74	(0.37	,1.48)	0.39324	0.65504	
59		rs48535333	3	0.90	(0.49	,1.65)	0.73045	0.48	(0.14	,1.63)	0.23679	0.81	(0.45	,1.46)	0.48887	0.28984	
60		rs7562024	0	0.95	(0.51	,1.75)	0.85896	0.70	(0.26	,1.91)	0.48694	0.89	(0.49	,1.60)	0.69324	0.53576	
61		rs867637	2	1.05	(0.57	,1.92)	0.87794	0.65	(0.19	,2.24)	0.49228	0.98	(0.54	,1.76)	0.94334	0.69486	
62		rs1053005	1	0.74	(0.37	,1.47)	0.38689	3.20	(1.23	,8.31)	0.01669	0.99	(0.54	,1.82)	0.98024	0.32492	
63		rs1053023	1	0.74	(0.37	,1.47)	0.38689	3.20	(1.23	,8.31)	0.01669	0.99	(0.54	,1.82)	0.98024	0.32492	
64		rs12949918	1	1.57	(0.76	,3.25)	0.22467	2.10	(0.90	,4.91)	0.08537	1.71	(0.86	,3.41)	0.12836	0.08062	
65		rs17405722	0	1.18	(0.48	,2.86)	0.71788	4.17	(0.46	,38.19)	0.20635	1.31	(0.57	,3.02)	0.52083	0.37070	
66		rs2293152	2	0.69	(0.38	,1.26)	0.22845	0.08	(0.01	,0.59)	0.01314	0.51	(0.28	,0.93)	0.02667	0.00287	
67		rs4103200	0	1.32	(0.69	,2.51)	0.39678	2.36	(0.98	,5.66)	0.05455	1.49	(0.82	,2.73)	0.19162	0.07193	
68		rs5036959	0	1.56	(0.81	,3.02)	0.18733	1.63	(0.67	,3.98)	0.27909	1.58	(0.84	,2.96)	0.15621	0.19002	
69		rs8911119	0	1.25	(0.63	,2.49)	0.52920	2.58	(1.55								

		rs6790068	0	0.71	(0.37 ,1.37)	0.30998	1.29	(0.58 ,2.88)	0.52929	0.84	(0.46 ,1.53)	0.57425	0.81935
		rs6790258	0	1.49	(0.70 ,3.18)	0.30068	-	-	-	1.47	(0.69 ,3.12)	0.32178	0.35458
		rs9681004	3	0.75	(0.39 ,1.45)	0.39631	1.31	(0.58 ,2.94)	0.51344	0.88	(0.48 ,1.60)	0.66895	0.75598

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Supplementary Table 3 Odds Ratios (OR) and 95% Confidence Intervals of all SNPs with HL calculated with unconditional logistic regression adjusted for age (continuous), sex and study center													
HL (unconditional logistic regression)													
Gene_symbol	SNP_Name	no. of no calls	Heterozygous mutant			Homozygous Mutant			Dominant Model			p-trend	
			OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value		
BMF	rs10518679	0	0.90	(0.64, 1.26)	0.54116	0.79	(0.21, 2.99)	0.73227	0.89	(0.64, 1.25)	0.51041	0.49535	
	rs11630670	0	0.93	(0.67, 1.31)	0.68288	0.78	(0.51, 1.18)	0.24062	0.88	(0.64, 1.21)	0.44486	0.25514	
	rs11634257	1	1.08	(0.80, 1.47)	0.61528	1.05	(0.58, 1.91)	0.87138	1.08	(0.80, 1.44)	0.61955	0.67329	
	rs11858141	2	1.01	(0.73, 1.40)	0.94956	0.96	(0.62, 1.49)	0.84553	1.00	(0.73, 1.36)	0.98586	0.88038	
	rs12913170	2	0.84	(0.60, 1.18)	0.32480	0.71	(0.25, 2.03)	0.52116	0.83	(0.60, 1.16)	0.27560	0.25738	
	rs15406866	22	0.91	(0.65, 1.28)	0.58069	0.54	(0.34, 0.85)	0.00726	0.79	(0.57, 1.09)	0.15581	0.01036	
	rs16970325	2	1.14	(0.79, 1.63)	0.49222	6.78	(1.41, 32.53)	0.01678	1.21	(0.85, 1.73)	0.28572	0.14004	
	rs16970349	0	1.17	(0.75, 1.82)	0.49514	-	-	-	1.16	(0.75, 1.81)	0.50708	0.52161	
	rs3743129	2	0.86	(0.62, 1.20)	0.37845	0.80	(0.52, 1.23)	0.30931	0.85	(0.62, 1.15)	0.28768	0.27469	
	rs3923235	0	1.11	(0.82, 1.51)	0.50572	1.50	(0.85, 2.65)	0.16618	1.16	(0.87, 1.55)	0.32190	0.19022	
	rs537455	1	0.89	(0.65, 1.21)	0.46122	1.13	(0.63, 2.02)	0.68617	0.92	(0.69, 1.24)	0.59234	0.84289	
	rs546220	5	0.86	(0.62, 1.19)	0.36441	0.61	(0.39, 0.97)	0.03638	0.79	(0.58, 1.08)	0.14123	0.04196	
	rs588739	0	0.86	(0.62, 1.19)	0.36070	0.80	(0.52, 1.23)	0.31259	0.84	(0.62, 1.15)	0.28007	0.27481	
	rs648289	1	0.97	(0.69, 1.34)	0.83693	0.52	(0.33, 0.83)	0.05797	0.83	(0.61, 1.14)	0.24664	0.01315	
	rs652196	3	0.95	(0.70, 1.30)	0.75251	1.01	(0.52, 1.94)	0.97933	0.96	(0.71, 1.29)	0.78081	0.84365	
	rs675173	6	1.00	(0.73, 1.36)	0.99305	1.07	(0.63, 1.80)	0.81158	1.01	(0.75, 1.35)	0.94782	0.87088	
	rs7183977	2	1.29	(0.95, 1.77)	0.10790	1.43	(0.88, 2.31)	0.14764	1.32	(0.98, 1.77)	0.06903	0.06925	
	rs998713	6	1.39	(1.00, 1.93)	0.04896	1.59	(1.01, 2.50)	0.04499	1.43	(1.05, 1.96)	0.02477	0.02351	
CASP6	rs1541373	1	0.97	(0.71, 1.33)	0.66601	0.80	(0.50, 1.26)	0.33557	0.93	(0.69, 1.25)	0.62827	0.39933	
	rs1800627	3	1.30	(0.90, 1.87)	0.16335	1.40	(0.93, 2.12)	0.10497	1.33	(0.95, 1.88)	0.10000	0.10624	
	rs3181345	0	0.69	(0.47, 1.01)	0.05853	1.56	(0.37, 6.50)	0.54399	0.72	(0.49, 1.04)	0.08305	0.13877	
	rs3212153	1	1.04	(0.73, 1.47)	0.83229	0.96	(0.30, 3.04)	0.94786	1.03	(0.74, 1.45)	0.85107	0.88273	
	rs5030552	1	0.84	(0.56, 1.26)	0.39782	1.20	(0.30, 4.85)	0.79503	0.86	(0.58, 1.27)	0.44832	0.53239	
	rs68063	0	0.77	(0.43, 1.38)	0.37813	-	-	-	0.77	(0.43, 1.38)	0.37376	0.37059	
IFNG	rs12306852	0	0.99	(0.71, 1.39)	0.97019	1.42	(0.59, 3.44)	0.43366	1.03	(0.74, 1.42)	0.87613	0.70564	
	rs2069716	0	0.66	(0.41, 1.08)	0.09726	0.89	(0.18, 4.54)	0.89074	0.68	(0.42, 1.08)	0.10293	0.13195	
	rs2069718	8	1.08	(0.78, 1.50)	0.64233	1.80	(1.16, 2.79)	0.00878	1.22	(0.89, 1.66)	0.21008	0.02230	
	rs2069727	0	0.76	(0.55, 1.07)	0.11670	0.60	(0.39, 0.93)	0.02096	0.71	(0.52, 0.98)	0.03767	0.01840	
	rs6581795	1	1.47	(1.08, 2.01)	0.04136	1.91	(1.10, 3.29)	0.02080	1.53	(1.14, 2.06)	0.00499	0.00310	
IFNGR1	rs12529779	15	1.04	(0.77, 1.42)	0.78791	0.95	(0.40, 2.28)	0.91130	1.04	(0.77, 1.40)	0.81833	0.87611	
	rs1327474	1	1.12	(0.80, 1.55)	0.51714	1.07	(0.69, 1.64)	0.76480	1.10	(0.81, 1.51)	0.54084	0.68053	
	rs1327475	2	1.04	(0.75, 1.43)	0.82430	0.87	(0.31, 2.40)	0.76989	1.02	(0.75, 1.40)	0.87853	0.95892	
	rs1854154	6	1.10	(0.78, 1.56)	0.58045	1.00	(0.66, 1.53)	0.99314	1.07	(0.77, 1.49)	0.67942	0.94689	
	rs3799488	0	1.04	(0.74, 1.46)	0.82349	0.26	(0.03, 2.07)	0.20115	0.99	(0.71, 1.39)	0.96330	0.72393	
	rs4777676	8	0.75	(0.53, 1.05)	0.09717	1.44	(0.38, 5.44)	0.58957	0.77	(0.55, 1.06)	0.12523	0.18853	
	rs4896243	4	1.14	(0.81, 1.61)	0.45371	1.36	(0.89, 2.07)	0.15141	1.20	(0.87, 1.67)	0.27021	0.19430	
	rs608914	4	0.78	(0.57, 1.06)	0.11079	1.07	(0.64, 1.76)	0.80398	0.83	(0.62, 1.11)	0.20036	0.50809	
	rs759040	0	0.96	(0.71, 1.31)	0.80633	0.65	(0.35, 1.23)	0.18648	0.91	(0.68, 1.22)	0.52939	0.30050	
	rs9402877	3	0.99	(0.71, 1.38)	0.95990	1.07	(0.70, 1.63)	0.75478	1.01	(0.74, 1.38)	0.93584	0.79183	
IFNGR2	rs1015873	0	1.81	(0.98, 3.37)	0.05983	-	-	-	1.81	(0.98, 3.37)	0.05983	0.05983	
	rs2626735	0	1.24	(0.91, 1.68)	0.17558	1.24	(0.67, 2.28)	0.49778	1.24	(0.92, 1.66)	0.15726	0.19013	
	rs16909644	0	1.73	(0.95, 3.17)	0.07307	-	-	-	1.73	(0.95, 3.17)	0.07307	0.07307	
	rs2012075	45	0.89	(0.61, 1.29)	0.53749	1.41	(0.46, 4.27)	0.54794	0.92	(0.64, 1.32)	0.65567	0.81954	
	rs2284553	59	0.97	(0.70, 1.34)	0.83821	0.90	(0.58, 1.40)	0.65216	0.95	(0.70, 1.29)	0.74185	0.66002	
	rs2834211	0	0.87	(0.60, 1.26)	0.46766	0.50	(0.10, 2.47)	0.39651	0.85	(0.59, 1.22)	0.37775	0.31207	
	rs2834214	1	1.07	(0.77, 1.50)	0.69119	0.64	(0.42, 0.98)	0.03796	0.91	(0.67, 1.25)	0.56688	0.06282	
	rs8131980	2	1.35	(1.00, 1.84)	0.05288	0.89	(0.51, 1.55)	0.68774	1.26	(0.94, 1.69)	0.12245	0.44224	
	rs976971	0	0.84	(0.60, 1.17)	0.30156	0.74	(0.48, 1.13)	0.16640	0.81	(0.59, 1.11)	0.18744	0.14858	
	rs9781866	0	0.98	(0.69, 1.40)	0.93223	0.31	(0.07, 1.38)	0.12423	0.92	(0.65, 1.30)	0.62646	0.37055	
IL10	rs1554286	2	1.13	(0.82, 1.54)	0.45505	1.38	(0.67, 2.87)	0.38312	1.15	(0.85, 1.55)	0.35853	0.29461	
	rs17015767	0	1.00	(0.73, 1.38)	0.99344	0.53	(0.22, 1.25)	0.14544	0.94	(0.69, 1.28)	0.68209	0.38253	
	rs1800871	9	1.07	(0.79, 1.45)	0.66957	1.14	(0.62, 2.07)	0.67343	1.08	(0.80, 1.45)	0.61366	0.58682	
	rs1800872	10	1.07	(0.79, 1.45)	0.67813	1.01	(0.55, 1.85)	0.98677	1.06	(0.79, 1.42)	0.70674	0.78410	
	rs2222202	9	0.90	(0.65, 1.25)	0.51858	0.81	(0.53, 1.24)	0.33057	0.87	(0.64, 1.19)	0.38374	0.31735	
	rs3021094	2	0.87	(0.58, 1.30)	0.49415	-	-	-	0.82	(0.55, 1.22)	0.32988	0.21159	
	rs3024505	1	1.11	(0.79, 1.54)	0.55281	1.12	(0.40, 3.11)	0.83352	1.11	(0.80, 1.53)	0.53920	0.55135	
	rs3024509	0	0.75	(0.47, 1.20)	0.23387	-	-	-	0.74	(0.46, 1.18)	0.20141	0.17485	
	rs4399774	7	1.12	(0.81, 1.54)	0.49110	0.92	(0.59, 1.43)	0.69935	1.06	(0.79, 1.44)	0.69109	0.91800	
	rs4844553	1	0.80	(0.50, 1.27)	0.34357	1.23	(0.11, 1.31)	0.86692	0.81	(0.51, 1.28)	0.36408	0.40097	
	rs6767392	8	0.96	(0.70, 1.33)	0.82572	0.52	(0.23, 1.17)	0.11299	0.90	(0.66, 1.23)	0.50085	0.25051	
	rs6868931	2	1.17	(0.86, 1.59)	0.31346	0.79	(0.40, 1.57)	0.50033	1.12	(0.83, 1.50)	0.46396	0.79058	
	rs7548373	22	0.83	(0.52, 1.32)	0.43377	-	-	-	0.81	(0.51, 1.29)	0.36927	0.31053	
IL12A	rs1192751	6	1.04	(0.75, 1.43)	0.81079	1.11	(0.71, 1.74)	0.63875	1.06	(0.78, 1.43)	0.72229	0.64379	
	rs2243115	4	1.07	(0.75, 1.52)	0.70855	0.18	(0.02, 1.42)	0.10279	0.99	(0.70, 1.41)	0.97530	0.61158	
	rs2243131	3	0.80	(0.57, 1.13)	0.20130	1.51	(0.65, 3.50)	0.33645	0.85	(0.62, 1.18)	0.33887	0.61668	
	rs2243154	0	1.03	(0.70, 1.52)	0.88217	-	-	-	0.98	(0.67, 1.45)	0.93566	0.73758	
	rs4680534	0	0.77	(0.56, 1.06)	0.10651	0.90	(0.57, 1.43)	0.66152	0.80	(0.60, 1.07)	0.13699	0.30164	
	rs485497	1	1.00	(0.70, 1.43)	0.99250	1.06	(0.70, 1.59)	0.79326	1.02	(0.73, 1.43)	0.90094	0.79467	
	rs583911	2	0.91	(0.65, 1.27)	0.57460	0.98	(0.65, 1.50)	0.93974	0.93	(0.68, 1.27)	0.64990	0.86414	
	rs6441282	1	0.67	(0.48, 0.93)	0.01774	0.79	(0.53, 1.19)	0.26387	0.71	(0.52, 0.96)	0.02685	0.15540	
	rs6800657	6	0.90	(0.61, 1.32)	0.58529	0.66	(0.14, 3.00)	0.58742	0.88	(0.61, 1.28)	0.51685	0.46974	
	rs692890	0</											

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Supplementary Table 4. Odds Ratios and 95% Confidence Intervals for estimated Haplotypes for BNHL and subtypes (adjusted for age (continuous), sex)

	Gene	Block	Haplotype	Frequency	hapname	BNHL		
						OR	95% CI	p-value
BMF	BMF	Block 1	rs3923235-rs16970325					
			A_G	0.624	H1	1.00		
			g_G	0.268	H2	0.88	(0.76 ,1.02)	0.0845
			A_a	0.109	H3	1.14	(0.91 ,1.43)	0.2441
BMF	BMF	Block 2	HRare	0.000	HRare	-	-	-
			rs12913170-rs7183977-rs998713-rs546220					
			G_A_A_a	0.418	H1	1.00		
			G_g_g_C	0.331	H2	0.94	(0.82 ,1.08)	0.3881
			a_A_A_C	0.151	H3	1.03	(0.87 ,1.23)	0.7026
			G_A_g_C	0.060	H4	1.26	(0.97 ,1.63)	0.0858
BMF	BMF	Block 3	HRare	0.040	HRare	0.96	(0.70 ,1.32)	0.8139
			rs648289-rs10518679					
			g_A	0.450	H1	1.00		
			A_A	0.417	H2	1.02	(0.90 ,1.16)	0.7405
BMF	BMF	Block 4	A_g	0.132	H3	1.03	(0.86 ,1.23)	0.7571
			HRare	0.001	HRare	0.56	(0.05 ,6.29)	0.6392
			rs11634257-rs11858141-rs675173					
			A_g_G	0.429	H1	1.00		
BMF	BMF	Block 5	A_A_a	0.309	H2	0.92	(0.80 ,1.05)	0.2130
			t_A_G	0.252	H3	0.96	(0.83 ,1.12)	0.6162
			HRare	0.010	HRare	1.04	(0.59 ,1.82)	0.8955
			rs537455-rs11630670					
IFNGR1	IFNGR1	Block 1	A_G	0.534	H1	1.00		
			c_a	0.265	H2	0.98	(0.84 ,1.14)	0.7622
			A_a	0.201	H3	0.96	(0.81 ,1.13)	0.6249
			HRare	0.000	HRare	-	-	-
IFNG	IFNG	Block 1	rs7759040-rs3799488-rs1327475					
			A_A_G	0.564	H1	1.00		
			A_A_a	0.189	H2	0.89	(0.77 ,1.04)	0.1594
			t_A_G	0.126	H3	1.05	(0.88 ,1.26)	0.5774
			t_g_G	0.121	H4	0.92	(0.77 ,1.11)	0.4104
IFNG	IFNG	Block 2	HRare	0.001	HRare	0.55	(0.05 ,6.11)	0.6248
			rs2069727-rs2069718					
			g_G	0.482	H1	1.00		
			A_a	0.375	H2	0.97	(0.85 ,1.10)	0.5988
IFNG	IFNG	Block 2	A_G	0.142	H3	0.95	(0.79 ,1.13)	0.5558
			HRare	0.000	HRare	-	-	-
			rs2069716-rs6581795-rs12306852					
			A_A_C	0.509	H1	1.00		
IL10	IL10	Block 1	A_g_C	0.264	H2	1.01	(0.88 ,1.17)	0.8885
			A_A_g	0.155	H3	1.00	(0.83 ,1.21)	0.9923
			g_A_C	0.072	H4	1.01	(0.77 ,1.32)	0.9393
			HRare	0.001	HRare	-	-	-
IL12A	IL12A	Block 1	rs17015767-rs1800871-rs1800872-rs2222202-rs3021094-rs1554286-rs3024509-rs3024505-rs6673928-rs4844553-rs754837					
			G_G_C_G_A_G_A_G_C_G_C	0.309	H1	1.00		
			c_G_C_a_A_G_A_G_a_G_C	0.194	H2	1.00	(0.84 ,1.18)	0.9652
			G_G_C_a_A_G_A_a_C_G_C	0.149	H3	0.99	(0.83 ,1.20)	0.9564
			G_a_a_G_a_A_G_a_G_C_G_C	0.125	H4	0.94	(0.77 ,1.15)	0.5683
			G_G_C_a_A_G_g_G_C_a_a	0.070	H5	0.95	(0.75 ,1.22)	0.7043
			G_a_a_G_c_a_A_G_C_G_C	0.064	H6	1.05	(0.81 ,1.35)	0.7289
IL12A	IL12A	Block 1	HRare	0.090	HRare	0.97	(0.77 ,1.21)	0.7603
			rs9811792-rs7372767-rs4680534-rs6441282-rs6800657-rs747825					
			g_g_A_C_A_C	0.425	H1	1.00		
			A_A_g_a_A_a	0.179	H2	0.88	(0.75 ,1.04)	0.1476
			A_A_g_a_A_C	0.168	H3	1.07	(0.90 ,1.27)	0.4354
			A_A_A_a_g_C	0.102	H4	1.02	(0.83 ,1.25)	0.8686
IL12A	IL12A	Block 1	A_A_A_C_A_C	0.098	H5	0.93	(0.75 ,1.14)	0.4617
			HRare	0.028	HRare	1.03	(0.72 ,1.47)	0.8820
IL12A	IL12A	Block 2	rs2243115-rs583911-rs2243131-rs2243154-rs11927521					
			A_g_A_G_A	0.354	H1	1.00		
			A_A_A_G_g	0.274	H2	1.00	(0.86 ,1.16)	0.9721
			A_A_c_G_A	0.155	H3	0.98	(0.82 ,1.18)	0.8422
IL12A	IL12A	Block 2	c_A_A_G_g	0.112	H4	0.85	(0.70 ,1.04)	0.1207

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2								
3			A_g_A_a_A	0.104	H5	0.89	(0.72 ,1.10)	0.2909
4			HRare	0.001	HRare	1.41	(0.31 ,6.34)	0.6562
5	IL12B	Block 1	rs4921466-rs4921468-rs6870828-rs3181225-rs1368439-rs11574790-rs2853694					
6			A_G_A_G_A_G_c	0.291	H1	1.00		
7			A_G_A_G_A_G_A	0.230	H2	1.23	(1.04 ,1.45)	0.0136
8			A_G_g_G_c_G_c	0.178	H3	1.17	(0.98 ,1.40)	0.0803
9			A_a_g_a_A_G_A	0.168	H4	1.10	(0.91 ,1.31)	0.3189
10			g_a_g_G_A_a_A	0.115	H5	1.21	(0.99 ,1.49)	0.0660
11			HRare	0.018	HRare	0.87	(0.54 ,1.38)	0.5438
12	IL12B	Block 2	rs2569253-rs3181216					
13			A_T	0.540	H1	1.00		
14			g_a	0.286	H2	0.82	(0.72 ,0.94)	0.0056
15			g_T	0.172	H3	0.90	(0.77 ,1.06)	0.1964
16			HRare	0.001	HRare	1.17	(0.16 ,8.40)	0.8728
17	IL12B	Block 3	rs1433048-rs2546893					
18			A_a	0.464	H1	1.00		
19			A_G	0.352	H2	1.12	(0.97 ,1.29)	0.1212
20			g_G	0.183	H3	1.06	(0.89 ,1.27)	0.5225
21			HRare	0.001	HRare	-	-	-
22	IL12B	Block 4	rs2546890-rs10052709-rs7709212-rs6868898					
23			g_G_g_A	0.345	H1	1.00		
24			A_G_A_g	0.292	H2	0.83	(0.72 ,0.97)	0.0162
25			A_G_A_A	0.204	H3	0.93	(0.79 ,1.10)	0.3961
26			g_c_A_A	0.144	H4	0.96	(0.80 ,1.15)	0.6642
27			HRare	0.014	HRare	1.38	(0.82 ,2.32)	0.2210
28	IL7R	Block 1	rs11567694-rs11567697-rs11567701-rs6891095-rs3777090-rs11567762-rs10063294-rs10058453					
29			A_A_a_A_A_G_A_A	0.272	H1	1.00		
30			g_A_C_A_A_G_A_A	0.254	H2	0.95	(0.81 ,1.11)	0.5138
31			A_A_C_A_t_a_g_g	0.156	H3	1.21	(1.01 ,1.45)	0.0438
32			A_A_C_g_A_G_g_A	0.137	H4	1.08	(0.89 ,1.31)	0.4511
33			A_g_C_A_t_G_g_g	0.095	H5	0.92	(0.74 ,1.15)	0.4731
34			A_A_C_A_t_G_g_g	0.078	H6	1.09	(0.86 ,1.39)	0.4818
35			HRare	0.008	HRare	1.02	(0.53 ,1.96)	0.9480
36	IRF4	Block 1	rs9405192-rs1033180					
37			G_G	0.703	H1	1.00		
38			a_G	0.224	H2	1.04	(0.90 ,1.21)	0.5718
39			a_a	0.074	H3	0.95	(0.63 ,1.42)	0.7873
40			HRare	0.000	HRare	-	-	-
41	IRF4	Block 2	rs13208928-rs3778607					
42			T_G	0.500	H1	1.00		
43			T_a	0.429	H2	1.02	(0.90 ,1.15)	0.7914
44			a_a	0.070	H3	0.92	(0.73 ,1.16)	0.4756
45			HRare	0.001	HRare	1.05	(0.06 ,16.91)	0.9740
46	IRF4	Block 3	rs1050975-rs7768807					
47			A_A	0.667	H1	1.00		
48			A_g	0.246	H2	1.00	(0.87 ,1.15)	0.9897
49			g_A	0.086	H3	1.08	(0.87 ,1.34)	0.4947
50			HRare	0.001	HRare	4.46	(0.08 #####)	0.4622
51	IRF4	Block 4	rs12211228-rs1877175-rs6906608					
52			G_G_C	0.780	H1	1.00		
53			c_a_a	0.147	H2	0.91	(0.77 ,1.08)	0.2688
54			G_a_C	0.072	H3	0.81	(0.65 ,1.02)	0.0754
55			HRare	0.002	HRare	1.08	(0.27 ,4.33)	0.9168
56	IRF4	Block 5	rs11757491-rs9378805					
57			G_C	0.476	H1	1.00		
58			G_A	0.456	H2	1.06	(0.94 ,1.20)	0.3549
59			a_A	0.068	H3	0.85	(0.67 ,1.08)	0.1886
60			HRare	0.000	HRare	0.05	(0.00 #####)	0.5520
51	Jak1	Block 1	rs310211-rs2256298					
52			A_G	0.676	H1	1.00		
53			g_a	0.259	H2	0.99	(0.86 ,1.13)	0.8812
54			g_G	0.065	H3	0.95	(0.75 ,1.21)	0.6705
55	LIG4	Block 1	rs915047-rs9514825					
56			A_G	0.635	H1	1.00		
57			A_a	0.201	H2	1.08	(0.93 ,1.25)	0.2923
58			g_a	0.164	H3	1.07	(0.91 ,1.26)	0.3812

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1			HRare	0.000	HRare	-	-	-	
2									
3									
4									
5	LIG4	Block 2	rs868284-rs1151402-rs10131-rs3093772-rs3093748						
6			G_a_G_A_G	0.432	H1	1.00			
7			G_G_G_A_a	0.184	H2	0.94	(0.80 ,1.10)	0.4177	
8			G_G_G_A_G	0.142	H3	1.06	(0.88 ,1.26)	0.5495	
9			a_G_G_g_G	0.107	H4	0.96	(0.79 ,1.17)	0.6870	
10			G_G_a_A_G	0.092	H5	1.19	(0.97 ,1.47)	0.1016	
11			HRare	0.044	HRare	1.18	(0.88 ,1.58)	0.2663	
12	LIG4	Block 3	rs12428162-rs7322498-rs9520823						
13			C_A_A	0.353	H1	1.00			
14			C_A_c	0.283	H2	0.99	(0.85 ,1.17)	0.9284	
15	SOCS1	Block 1	rs193778-rs243317						
16			A_A	0.464	H1	1.00			
17			A_c	0.294	H2	0.97	(0.84 ,1.11)	0.6183	
18			g_A	0.241	H3	0.99	(0.86 ,1.15)	0.9118	
19	STAT1	Block 1	rs13035504-rs1168-rs12468579-rs1400657						
20			G_a_A_A	0.445	H1	1.00			
21			G_G_g_A	0.265	H2	1.12	(0.97 ,1.29)	0.1204	
22			c_G_g_A	0.171	H3	1.00	(0.84 ,1.18)	0.9711	
23			G_G_A_c	0.115	H4	1.03	(0.85 ,1.25)	0.7388	
24	STAT1	Block 2	rs16824035-rs13395505-rs17749316-rs2066804						
25			G_G_C_G	0.528	H1	1.00			
26			G_a_C_a	0.229	H2	1.05	(0.90 ,1.21)	0.5502	
27			a_a_C_G	0.172	H3	0.96	(0.82 ,1.13)	0.6520	
28			G_G_g_G	0.066	H4	0.96	(0.76 ,1.23)	0.7695	
29			HRare	0.005	HRare	0.58	(0.25 ,1.34)	0.2023	
30	STAT1	Block 3	rs432757-rs2280234-rs2280233						
31			A_G_g	0.455	H1	1.00			
32			A_a_A	0.377	H2	1.06	(0.94 ,1.21)	0.3361	
33	STAT1	Block 4	rs7562024-rs34997637						
34			c_G_A	0.139	H3	0.99	(0.83 ,1.19)	0.9425	
35			HRare	0.029	HRare	1.05	(0.74 ,1.49)	0.7897	
36	STAT1	Block 5	rs13029247-rs10173099-rs10199181						
37			A_G_T	0.616	H1	1.00			
38			g_a_a	0.315	H2	0.92	(0.81 ,1.05)	0.2217	
39			HRare	0.070	HRare	1.22	(0.96 ,1.54)	0.1004	
40	STAT1	Block 6	rs13029532-rs1467199-rs17817966						
41			A_C_A	0.563	H1	1.00			
42			A_g_g	0.234	H2	0.96	(0.83 ,1.10)	0.5347	
43			A_C_g	0.113	H3	0.98	(0.81 ,1.19)	0.8741	
44			c_C_g	0.089	H4	0.99	(0.81 ,1.23)	0.9586	
45	STAT3	Block 1	rs1053023-rs1053005						
46			A_A	0.801	H1	1.00			
47			g_g	0.199	H2	0.80	(0.69 ,0.93)	0.0029	
48	STAT3	Block 2	rs4103200-rs9891119-rs9912773-rs12949918-rs17405722						
49			G_A_C_A_G	0.588	H1	1.00			
50			c_c_g_g_G	0.267	H2	0.82	(0.72 ,0.94)	0.0052	
51			G_c_C_g_a	0.065	H3	0.95	(0.75 ,1.21)	0.6866	
52			G_A_C_g_G	0.053	H4	0.91	(0.69 ,1.19)	0.4712	
53	STAT4	Block 1	rs13020076-rs16833177-rs7558921						
54			A_A_C	0.600	H1	1.00			
55			A_g_C	0.205	H2	0.97	(0.83 ,1.14)	0.7166	
56			A_A_g	0.113	H3	0.89	(0.73 ,1.08)	0.2304	
57			g_A_C	0.081	H4	0.87	(0.68 ,1.12)	0.2893	
58			HRare	0.000	HRare	-	-	-	
59									
60									

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1	STAT4	Block 2	rs7574608-rs4853540					
2			A_C	0.766	H1	1.00		
3			A_a	0.170	H2	1.09	(0.93 ,1.28)	0.2746
4			t_a	0.062	H3	1.02	(0.80 ,1.31)	0.8658
5			HRare	0.002	HRare	1.69	(0.28 ,10.15)	0.5660
6	STAT4	Block 3	rs3024861-rs932169					
7			A_C	0.659	H1	1.00		
8			t_C	0.264	H2	1.07	(0.93 ,1.23)	0.3214
9			A_g	0.076	H3	1.07	(0.85 ,1.36)	0.5529
10			HRare	0.001	HRare	-	-	
11	STAT4	Block 4	rs10168266-rs2459611					
12			G_A	0.685	H1	1.00		
13			a_A	0.187	H2	1.05	(0.89 ,1.23)	0.5889
14			G_g	0.127	H3	1.05	(0.86 ,1.28)	0.6266
15			HRare	0.001	HRare	-	-	
16	STAT4	Block 5	rs7599504-rs4571082-rs17769459					
17			A_A_G	0.560	H1	1.00		
18			A_g_G	0.219	H2	1.07	(0.93 ,1.24)	0.3353
19			g_g_G	0.161	H3	1.06	(0.89 ,1.25)	0.5260
20			A_A_a	0.059	H4	1.18	(0.92 ,1.51)	0.1968
21			HRare	0.001	HRare	0.55	(0.05 ,6.18)	0.6318
22	STAT6	Block 1	rs3024979-rs703817-rs324015-rs3024974-rs3024971-rs324011					
23			A_a_G_G_A_a	0.358	H1	1.00		
24			A_G_a_G_A_G	0.232	H2	1.07	(0.91 ,1.25)	0.4205
25			t_a_G_G_A_G	0.114	H3	0.91	(0.75 ,1.12)	0.3832
26			A_G_G_G_c_G	0.114	H4	1.02	(0.84 ,1.26)	0.8196
27			A_G_G_a_A_G	0.087	H5	0.83	(0.66 ,1.03)	0.0949
28			A_G_G_G_A_G	0.067	H6	1.16	(0.90 ,1.49)	0.2603
29			HRare	0.028	HRare	0.98	(0.67 ,1.45)	0.9281
30	TP63	Block 1	rs6790068-rs9681004					
31			A_A	0.595	H1	1.00		
32			g_g	0.395	H2	0.97	(0.86 ,1.10)	0.6680
33			HRare	0.010	HRare	0.82	(0.43 ,1.54)	0.5313
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For Peer Review

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DLBCL

Supplementary Table 4. Odds Ratios and 95% Confidence Intervals for estimated Haplotypes for BNHL and subtypes (adjusted for age (continuous), se

	Gene	Block	Haplotype	Frequency	hapname	DLBCL		
						OR	95% CI	p-value
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	BMF	Block 1	rs3923235-rs16970325 A_G g_G A_a HRare	0.624 0.268 0.109 0.000	H1 H2 H3 HRare	1.00 0.69 0.87 -	(0.56 ,0.85) (0.63 ,1.21) (0.63 ,1.21)	0.0006 0.4221 0.4221
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	BMF	Block 2	rs12913170-rs7183977-rs998713-rs546220 G_A_A_a G_g_C a_A_A_C G_A_g_C HRare	0.418 0.331 0.151 0.060 0.040	H1 H2 H3 H4 HRare	1.00 0.83 1.09 1.11 1.08	(0.68 ,1.00) (0.86 ,1.39) (0.77 ,1.60) (0.71 ,1.64)	0.0551 0.4789 0.5779 0.7146
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	BMF	Block 3	rs648289-rs10518679 g_A A_A A_g HRare	0.450 0.417 0.132 0.001	H1 H2 H3 HRare	1.00 0.94 1.03 1.24	(0.79 ,1.13) (0.81 ,1.33) (0.10 ,14.85)	0.5118 0.7916 0.8659
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	BMF	Block 4	rs11634257-rs11858141-rs675173 A_g_G A_A_a t_A_G HRare	0.429 0.309 0.252 0.010	H1 H2 H3 HRare	1.00 0.88 1.10 0.98	(0.72 ,1.08) (0.89 ,1.34) (0.43 ,2.24)	0.2184 0.3775 0.9544
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	BMF	Block 5	rs537455-rs11630670 A_G c_a A_a HRare	0.534 0.265 0.201 0.000	H1 H2 H3 HRare	1.00 0.91 0.95	(0.73 ,1.14) (0.75 ,1.19)	0.4092 0.6467
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	IFNGR1	Block 1	rs7759040-rs3799488-rs1327475 A_A_G A_A_a t_A_G t_g_G HRare	0.564 0.189 0.126 0.121 0.001	H1 H2 H3 H4 HRare	1.00 0.94 1.07 1.30	(0.76 ,1.17) (0.84 ,1.38) (0.90 ,1.88)	0.5900 0.5701 0.1626
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	IFNG	Block 1	rs2069727-rs2069718 g_G A_a A_G HRare	0.482 0.375 0.142 0.000	H1 H2 H3 HRare	1.00 0.99 1.03	(0.82 ,1.18) (0.81 ,1.32)	0.8825 0.8168
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	IFNG	Block 2	rs2069716-rs6581795-rs12306852 A_A_C A_g_C A_A_g g_A_C HRare	0.509 0.264 0.155 0.072 0.001	H1 H2 H3 H4 HRare	1.00 1.10 1.07 1.05	(0.90 ,1.35) (0.82 ,1.39) (0.74 ,1.51)	0.3298 0.6399 0.7729
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	IL10	Block 1	rs17015767-rs1800871-rs1800872-rs2222202-rs3021094-rs1554286-rs3024509-rs3024505-rs6673928-rs4844553-rs754837 G_G_C_G_A_G_A_G_C_G_C c_G_C_a_A_G_A_G_a_G_C G_G_C_a_A_G_A_a_C_G_C G_a_a_G_a_A_G_C_G_C G_G_C_a_A_G_g_G_C_a_a G_a_a_G_c_a_A_G_C_G_C HRare	0.309 0.194 0.149 0.125 0.070 0.064 0.090	H1 H2 H3 H4 H5 H6 HRare	1.00 1.06 1.06 0.95 0.85 0.93 1.12	(0.83 ,1.34) (0.82 ,1.36) (0.72 ,1.25) (0.64 ,1.35) (0.59 ,1.23) (0.64 ,1.35) (0.83 ,1.52)	0.6391 0.6470 0.6975 0.3950 0.7123 0.4513
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	IL12A	Block 1	rs9811792-rs7372767-rs4680534-rs6441282-rs6800657-rs747825 g_g_A_C_A_C A_A_g_a_A_a A_A_g_A_A_C A_A_A_g_C A_A_A_C_A_C HRare	0.425 0.179 0.168 0.102 0.098 0.028	H1 H2 H3 H4 H5 HRare	1.00 0.81 0.96 0.99 1.01 1.06	(0.64 ,1.03) (0.76 ,1.22) (0.74 ,1.23) (0.75 ,1.31) (0.76 ,1.34) (0.66 ,1.71)	0.0874 0.7627 0.9620 0.9415 0.9415 0.8017
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	IL12A	Block 2	rs2243115-rs583911-rs2243131-rs2243154-rs11927521 A_g_A_G_A A_A_A_G_g A_A_c_G_A c_A_A_G_g	0.354 0.274 0.155 0.112	H1 H2 H3 H4	1.00 1.01 0.96 0.91	(0.82 ,1.24) (0.74 ,1.23) (0.74 ,1.23) (0.69 ,1.19)	0.9452 0.7385 0.4829

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2								
3			A_g_A_a_A	0.104	H5	0.89	(0.67 ,1.20)	0.4476
4			HRare	0.001	HRare	1.13	(0.11 ,11.27)	0.9180
5	IL12B	Block 1	rs4921466-rs4921468-rs6870828-rs3181225-rs1368439-rs11574790-rs2853694					
6			A_G_A_G_A_G_c	0.291	H1	1.00		
7			A_G_A_G_A_G_A	0.230	H2	1.13	(0.90 ,1.41)	0.3081
8			A_G_g_G_c_G_c	0.178	H3	1.07	(0.84 ,1.36)	0.6019
9			A_a_g_a_A_G_A	0.168	H4	0.88	(0.68 ,1.14)	0.3421
10			g_a_g_G_A_a_A	0.115	H5	1.28	(0.97 ,1.69)	0.0817
11			HRare	0.018	HRare	1.00	(0.52 ,1.94)	1.0000
12	IL12B	Block 2	rs2569253-rs3181216					
13			A_T	0.540	H1	1.00		
14			g_a	0.286	H2	0.88	(0.72 ,1.07)	0.2074
15			g_T	0.172	H3	0.73	(0.57 ,0.94)	0.0131
16			HRare	0.001	HRare	-	-	-
17	IL12B	Block 3	rs1433048-rs2546893					
18			A_a	0.464	H1	1.00		
19			A_G	0.352	H2	1.14	(0.94 ,1.38)	0.1957
20			g_G	0.183	H3	1.13	(0.89 ,1.44)	0.3090
21			HRare	0.001	HRare	-	-	-
22	IL12B	Block 4	rs2546890-rs10052709-rs7709212-rs6868898					
23			g_G_g_A	0.345	H1	1.00		
24			A_G_A_g	0.292	H2	0.87	(0.70 ,1.07)	0.1910
25			A_G_A_A	0.204	H3	0.99	(0.79 ,1.25)	0.9589
26			g_c_A_A	0.144	H4	1.06	(0.82 ,1.37)	0.6573
27			HRare	0.014	HRare	1.73	(0.88 ,3.40)	0.1135
28	IL7R	Block 1	rs11567694-rs11567697-rs11567701-rs6891095-rs3777090-rs11567762-rs10063294-rs10058453					
29			A_A_a_A_A_G_A_A	0.272	H1	1.00		
30			g_A_C_A_A_G_A_A	0.254	H2	1.04	(0.83 ,1.30)	0.7388
31			A_A_C_A_t_a_g_g	0.156	H3	1.17	(0.90 ,1.52)	0.2339
32			A_A_C_g_A_G_g_A	0.137	H4	1.20	(0.92 ,1.58)	0.1828
33			A_g_C_A_t_G_g_g	0.095	H5	1.13	(0.84 ,1.54)	0.4172
34			A_A_C_A_t_G_g_g	0.078	H6	1.27	(0.91 ,1.77)	0.1555
35			HRare	0.008	HRare	0.94	(0.36 ,2.43)	0.9022
36	IRF4	Block 1	rs9405192-rs1033180					
37			G_G	0.703	H1	1.00		
38			a_G	0.224	H2	0.97	(0.80 ,1.18)	0.7740
39			a_a	0.074	H3	1.01	(0.72 ,1.40)	0.9753
40			HRare	0.000	HRare	-	-	-
41	IRF4	Block 2	rs13208928-rs3778607					
42			T_G	0.500	H1	1.00		
43			T_a	0.429	H2	0.94	(0.79 ,1.11)	0.4451
44			a_a	0.070	H3	1.00	(0.72 ,1.38)	0.9828
45			HRare	0.001	HRare	-	-	-
46	IRF4	Block 3	rs1050975-rs7768807					
47			A_A	0.667	H1	1.00		
48			A_g	0.246	H2	0.96	(0.78 ,1.17)	0.6719
49			g_A	0.086	H3	1.10	(0.79 ,1.54)	0.5737
50			HRare	0.001	HRare	-	-	-
51	Jak1	Block 1	rs310211-rs2256298					
52			A_G	0.676	H1	1.00		
53			g_a	0.259	H2	1.14	(0.94 ,1.38)	0.1873
54			g_G	0.065	H3	1.01	(0.72 ,1.41)	0.9541
55			HRare	0.000	HRare	-	-	-
56	LIG4	Block 1	rs915047-rs9514825					
57			A_G	0.635	H1	1.00		
58			A_a	0.201	H2	0.97	(0.79 ,1.20)	0.7839
59			g_a	0.164	H3	1.07	(0.86 ,1.34)	0.5465
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DLBCL

1			HRare	0.000	HRare	-	-	-	-
2									
3									
4									
5	LIG4	Block 2	rs868284-rs1151402-rs10131-rs3093772-rs3093748						
6			G_a_G_A_G	0.432	H1	1.00			
7			G_G_G_A_a	0.184	H2	1.03	(0.83 ,1.28)	0.8044	
8			G_G_G_A_G	0.142	H3	1.08	(0.84 ,1.39)	0.5573	
9			a_G_G_g_G	0.107	H4	0.98	(0.75 ,1.29)	0.8958	
10			G_G_a_A_G	0.092	H5	1.03	(0.76 ,1.39)	0.8543	
11			HRare	0.044	HRare	1.13	(0.75 ,1.71)	0.5478	
12	LIG4	Block 3	rs12428162-rs7322498-rs9520823						
13			C_A_A	0.353	H1	1.00			
14			C_A_c	0.283	H2	0.89	(0.71 ,1.12)	0.3294	
15			g_g_A	0.267	H3	1.02	(0.81 ,1.28)	0.8759	
16			C_g_A	0.097	H4	0.90	(0.67 ,1.21)	0.4829	
17			HRare	0.000	HRare	-			
18	SOCS1	Block 1	rs193778-rs243317						
19			A_A	0.464	H1	1.00			
20			A_c	0.294	H2	0.93	(0.75 ,1.15)	0.5233	
21			g_A	0.241	H3	0.85	(0.66 ,1.09)	0.1890	
22			HRare	0.001	HRare	-			
23	STAT1	Block 1	rs13035504-rs1168-rs12468579-rs1400657						
24			G_a_A_A	0.445	H1	1.00			
25			G_G_g_A	0.265	H2	1.12	(0.92 ,1.38)	0.2569	
26			c_G_g_A	0.171	H3	1.03	(0.82 ,1.31)	0.7840	
27			G_G_A_c	0.115	H4	1.25	(0.96 ,1.62)	0.0950	
28			HRare	0.004	HRare	0.70	(0.14 ,3.36)	0.6518	
29	STAT1	Block 2	rs16824035-rs13395505-rs17749316-rs2066804						
30			G_G_C_G	0.528	H1	1.00			
31			G_a_C_a	0.229	H2	0.99	(0.81 ,1.22)	0.9563	
32			a_a_C_G	0.172	H3	0.94	(0.75 ,1.19)	0.6054	
33			G_G_g_G	0.066	H4	0.95	(0.68 ,1.32)	0.7450	
34			HRare	0.005	HRare	0.84	(0.29 ,2.48)	0.7570	
35	STAT1	Block 3	rs432757-rs2280234-rs2280233						
36			A_G_g	0.455	H1	1.00			
37			A_a_A	0.377	H2	1.10	(0.92 ,1.32)	0.2894	
38			c_G_A	0.139	H3	0.99	(0.76 ,1.28)	0.9362	
39			HRare	0.029	HRare	1.33	(0.84 ,2.09)	0.2209	
40	STAT1	Block 4	rs7562024-rs34997637						
41			G_G	0.606	H1	1.00			
42			a_a	0.230	H2	0.97	(0.80 ,1.19)	0.7860	
43			a_G	0.164	H3	1.23	(0.99 ,1.53)	0.0621	
44			HRare	0.000	HRare	-			
45	STAT1	Block 5	rs13029247-rs10173099-rs10199181						
46			A_G_T	0.616	H1	1.00			
47			g_a_a	0.315	H2	0.89	(0.74 ,1.07)	0.2147	
48			HRare	0.070	HRare	1.31	(0.95 ,1.80)	0.0959	
49	STAT1	Block 6	rs13029532-rs1467199-rs17817966						
50			A_C_A	0.563	H1	1.00			
51			A_g_g	0.234	H2	0.98	(0.80 ,1.19)	0.8242	
52			A_C_g	0.113	H3	1.06	(0.81 ,1.38)	0.6892	
53			c_C_g	0.089	H4	1.10	(0.83 ,1.46)	0.5193	
54	STAT3	Block 1	rs1053023-rs1053005						
55			A_A	0.801	H1	1.00			
56			g_g	0.199	H2	0.79	(0.64 ,0.98)	0.0282	
57			HRare	0.000	HRare	-			
58	STAT3	Block 2	rs4103200-rs9891119-rs9912773-rs12949918-rs17405722						
59			G_A_C_A_G	0.588	H1	1.00			
60			c_c_g_g_G	0.267	H2	0.81	(0.67 ,0.98)	0.0317	
			G_c_C_g_a	0.065	H3	0.89	(0.64 ,1.25)	0.5054	
			G_A_C_g_G	0.053	H4	0.94	(0.65 ,1.35)	0.7206	
			HRare	0.027	HRare	0.65	(0.37 ,1.16)	0.1482	
	STAT4	Block 1	rs13020076-rs16833177-rs7558921						
			A_A_C	0.600	H1	1.00			
			A_g_C	0.205	H2	0.96	(0.77 ,1.19)	0.6860	
			A_A_g	0.113	H3	0.93	(0.72 ,1.21)	0.6142	
			g_A_C	0.081	H4	0.80	(0.55 ,1.17)	0.2506	
			HRare	0.000	HRare	-			

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4	STAT4	Block 2	rs7574608-rs4853540						
5			A_C	0.766	H1	1.00			
6			A_a	0.170	H2	1.15	(0.92 ,1.42)	0.2130	
7			t_a	0.062	H3	1.12	(0.80 ,1.57)	0.5126	
8			HRare	0.002	HRare	1.03	(0.09 ,11.75)	0.9797	
9	STAT4	Block 3	rs3024861-rs932169						
10			A_C	0.659	H1	1.00			
11			t_C	0.264	H2	1.14	(0.94 ,1.38)	0.1864	
12	STAT4	Block 4	rs10168266-rs2459611						
13			G_A	0.685	H1	1.00			
14			a_A	0.187	H2	1.01	(0.81 ,1.27)	0.9097	
15			G_g	0.127	H3	1.00	(0.75 ,1.32)	0.9899	
16	STAT4	Block 5	rs7599504-rs4571082-rs17769459						
17			A_A_G	0.560	H1	1.00			
18			A_g_G	0.219	H2	1.14	(0.93 ,1.40)	0.2045	
19			g_g_G	0.161	H3	0.97	(0.76 ,1.22)	0.7716	
20			A_A_a	0.059	H4	1.07	(0.75 ,1.52)	0.7201	
21	STAT6	Block 1	rs3024979-rs703817-rs324015-rs3024974-rs3024971-rs324011						
22			A_a_G_G_A_a	0.358	H1	1.00			
23			A_G_a_G_A_G	0.232	H2	1.09	(0.87 ,1.36)	0.4487	
24			t_a_G_G_A_G	0.114	H3	0.83	(0.62 ,1.11)	0.2063	
25			A_G_G_G_c_G	0.114	H4	0.97	(0.73 ,1.29)	0.8367	
26			A_G_G_a_A_G	0.087	H5	0.74	(0.53 ,1.03)	0.0717	
27	TP63	Block 1	rs6790068-rs9681004						
28			A_A	0.595	H1	1.00			
29			g_g	0.395	H2	0.96	(0.80 ,1.13)	0.6004	
30			HRare	0.010	HRare	1.01	(0.44 ,2.32)	0.9744	
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For Peer Review

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Supplementary Table 4. Odds Ratios and 95% Confidence Intervals for estimated Haplotypes for BNHL and subtypes (adjusted for age (continuous), sex)

	Gene	Block	Haplotype	Frequency	hapname	FL		
						OR	95% CI	p-value
1	BMF	Block 1	rs3923235-rs16970325					
			A_G	0.624	H1	1.00		
			g_G	0.268	H2	1.13	(0.87 ,1.47)	0.3508
			A_a	0.109	H3	1.53	(1.02 ,2.29)	0.0385
2	BMF	Block 2	HRare	0.000	HRare	-	-	-
			rs12913170-rs7183977-rs998713-rs546220					
			G_A_A_a	0.418	H1	1.00		
			G_g_g_C	0.331	H2	1.17	(0.91 ,1.50)	0.2260
			a_A_A_C	0.151	H3	1.03	(0.74 ,1.43)	0.8526
3	BMF	Block 3	G_A_g_C	0.060	H4	1.26	(0.77 ,2.07)	0.3619
			HRare	0.040	HRare	0.81	(0.43 ,1.54)	0.5205
			rs648289-rs10518679					
			g_A	0.450	H1	1.00		
4	BMF	Block 4	A_A	0.417	H2	1.24	(0.96 ,1.59)	0.1028
			A_g	0.132	H3	1.44	(1.02 ,2.03)	0.0385
			HRare	0.001	HRare	-	-	-
			rs11634257-rs11858141-rs675173					
5	BMF	Block 5	A_g_G	0.429	H1	1.00		
			A_A_a	0.309	H2	0.82	(0.63 ,1.07)	0.1376
			t_A_G	0.252	H3	0.82	(0.62 ,1.08)	0.1543
			HRare	0.010	HRare	1.73	(0.74 ,4.06)	0.2039
6	BMF	Block 5	rs537455-rs11630670					
			A_G	0.534	H1	1.00		
			c_a	0.265	H2	1.05	(0.80 ,1.39)	0.7182
			A_a	0.201	H3	1.00	(0.74 ,1.35)	0.9934
			HRare	0.000	HRare	-	-	-
7	IFNGR1	Block 1	rs7759040-rs3799488-rs1327475					
			A_A_G	0.564	H1	1.00		
			A_A_a	0.189	H2	1.16	(0.87 ,1.53)	0.3099
			t_A_G	0.126	H3	1.14	(0.70 ,1.86)	0.5860
			t_g_G	0.121	H4	0.96	(0.68 ,1.36)	0.8184
8	IFNG	Block 1	HRare	0.001	HRare	-	-	-
			rs2069727-rs2069718					
			g_G	0.482	H1	1.00		
			A_a	0.375	H2	0.91	(0.72 ,1.15)	0.4423
			A_G	0.142	H3	0.78	(0.56 ,1.10)	0.1631
9	IFNG	Block 2	HRare	0.000	HRare	-	-	-
			rs2069716-rs6581795-rs12306852					
			A_A_C	0.509	H1	1.00		
			A_g_C	0.264	H2	0.98	(0.74 ,1.30)	0.9035
			A_A_g	0.155	H3	0.86	(0.58 ,1.27)	0.4552
10	IL10	Block 1	HRare	0.001	HRare	-	-	-
			rs17015767-rs1800871-rs1800872-rs2222202-rs3021094-rs1554286-rs3024509-rs3024505-rs6673928-rs4844553-rs754837					
			G_G_C_G_A_G_A_G_C_G_C	0.309	H1	1.00		
			c_G_C_a_A_G_A_G_a_G_C	0.194	H2	0.98	(0.71 ,1.34)	0.8829
			G_G_C_a_A_G_A_a_C_G_C	0.149	H3	0.87	(0.62 ,1.23)	0.4374
11	IL10	Block 1	G_a_a_G_a_A_G_C_G_C	0.125	H4	1.17	(0.82 ,1.65)	0.3894
			G_G_C_a_A_G_g_G_C_a_a	0.070	H5	1.03	(0.65 ,1.62)	0.9010
			G_a_a_G_c_a_A_G_C_G_C	0.064	H6	1.17	(0.74 ,1.87)	0.4971
			HRare	0.090	HRare	0.84	(0.54 ,1.30)	0.4268
			-	-	-	-	-	-
12	IL12A	Block 1	rs9811792-rs7372767-rs4680534-rs6441282-rs6800657-rs747825					
			g_g_A_C_A_C	0.425	H1	1.00		
			A_A_g_a_A_a	0.179	H2	0.97	(0.72 ,1.32)	0.8501
			A_A_g_a_A_C	0.168	H3	1.06	(0.78 ,1.44)	0.7196
			A_A_A_a_g_C	0.102	H4	0.94	(0.65 ,1.38)	0.7598
13	IL12A	Block 1	A_A_A_C_A_C	0.098	H5	0.68	(0.44 ,1.04)	0.0736
			HRare	0.028	HRare	0.90	(0.46 ,1.77)	0.7533
			-	-	-	-	-	-
			rs2243115-rs583911-rs2243131-rs2243154-rs11927521					
			A_g_A_G_A	0.354	H1	1.00		
14	IL12A	Block 2	A_A_A_G_g	0.274	H2	1.08	(0.82 ,1.42)	0.5858
			A_A_c_G_A	0.155	H3	1.02	(0.73 ,1.42)	0.9259
			c_A_A_G_g	0.112	H4	0.72	(0.48 ,1.09)	0.1173
			-	-	-	-	-	-

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3			A_g_A_a_A	0.104	H5	1.10	(0.76 ,1.60)	0.6190
4			HRare	0.001	HRare			
5	IL12B	Block 1	rs4921466-rs4921468-rs6870828-rs3181225-rs1368439-rs11574790-rs2853694					
6			A_G_A_G_A_G_c	0.291	H1	1.00		
7			A_G_A_G_A_G_A	0.230	H2	1.38	(1.01 ,1.89)	0.0439
8			A_G_g_G_c_G_c	0.178	H3	1.38	(0.98 ,1.92)	0.0622
9			A_a_g_a_A_G_A	0.168	H4	1.39	(1.00 ,1.94)	0.0505
10			g_a_g_G_A_a_A	0.115	H5	1.44	(0.98 ,2.11)	0.0607
11			HRare	0.018	HRare	1.20	(0.49 ,2.93)	0.6863
12	IL12B	Block 2	rs2569253-rs3181216					
13			A_T	0.540	H1	1.00		
14			g_a	0.286	H2	0.71	(0.55 ,0.93)	0.0129
15			g_T	0.172	H3	1.00	(0.76 ,1.32)	0.9959
16			HRare	0.001	HRare			
17	IL12B	Block 3	rs1433048-rs2546893					
18			A_a	0.464	H1	1.00		
19			A_G	0.352	H2	1.36	(1.06 ,1.75)	0.0166
20			g_G	0.183	H3	1.04	(0.74 ,1.46)	0.8128
21			HRare	0.001	HRare			
22	IL12B	Block 4	rs2546890-rs10052709-rs7709212-rs6868898					
23			g_G_g_A	0.345	H1	1.00		
24			A_G_A_g	0.292	H2	0.63	(0.48 ,0.84)	0.0014
25			A_G_A_A	0.204	H3	0.78	(0.58 ,1.06)	0.1138
26			g_c_A_A	0.144	H4	0.90	(0.64 ,1.26)	0.5437
27			HRare	0.014	HRare	1.18	(0.47 ,2.97)	0.7240
28	IL7R	Block 1	rs11567694-rs11567697-rs11567701-rs6891095-rs3777090-rs11567762-rs10063294-rs10058453					
29			A_A_a_A_A_G_A_A	0.272	H1	1.00		
30			g_A_C_A_A_G_A_A	0.254	H2	0.91	(0.68 ,1.21)	0.5089
31			A_A_C_A_t_a_g_g	0.156	H3	1.37	(1.00 ,1.87)	0.0533
32			A_A_C_g_A_G_g_A	0.137	H4	1.05	(0.73 ,1.49)	0.8072
33			A_g_C_A_t_G_g_g	0.095	H5	0.71	(0.46 ,1.10)	0.1241
34			A_A_C_A_t_G_g_g	0.078	H6	0.90	(0.56 ,1.44)	0.6525
35			HRare	0.008	HRare	1.00	(0.28 ,3.52)	0.9963
36	IRF4	Block 1	rs9405192-rs1033180					
37			G_G	0.703	H1	1.00		
38			a_G	0.224	H2	0.89	(0.68 ,1.17)	0.4163
39			a_a	0.074	H3	1.13	(0.75 ,1.70)	0.5622
40			HRare	0.000	HRare			
41	IRF4	Block 2	rs13208928-rs3778607					
42			T_G	0.500	H1	1.00		
43			T_a	0.429	H2	0.94	(0.75 ,1.19)	0.6154
44			a_a	0.070	H3	1.00	(0.57 ,1.76)	0.9901
45			HRare	0.001	HRare			
46	IRF4	Block 3	rs1050975-rs7768807					
47			A_A	0.667	H1	1.00		
48			A_g	0.246	H2	1.12	(0.86 ,1.45)	0.4109
49			g_A	0.086	H3	1.32	(0.87 ,2.01)	0.1896
50			HRare	0.001	HRare			
51	IRF4	Block 4	rs12211228-rs1877175-rs6906608					
52			G_G_C	0.780	H1	1.00		
53			c_a_a	0.147	H2	0.88	(0.64 ,1.20)	0.4099
54			G_a_C	0.072	H3	0.77	(0.50 ,1.20)	0.2470
55			HRare	0.002	HRare			
56	IRF4	Block 5	rs11757491-rs9378805					
57			G_C	0.476	H1	1.00		
58			G_A	0.456	H2	1.11	(0.89 ,1.39)	0.3625
59			a_A	0.068	H3	0.88	(0.56 ,1.38)	0.5739
60			HRare	0.000	HRare			
51	Jak1	Block 1	rs310211-rs2256298					
52			A_G	0.676	H1	1.00		
53			g_a	0.259	H2	0.88	(0.68 ,1.14)	0.3475
54			g_G	0.065	H3	0.98	(0.64 ,1.52)	0.9436
55			HRare	0.000	HRare			
56	LIG4	Block 1	rs915047-rs9514825					
57			A_G	0.635	H1	1.00		
58			A_a	0.201	H2	1.10	(0.83 ,1.44)	0.5140
59			g_a	0.164	H3	1.18	(0.87 ,1.58)	0.2820
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1			HRare	0.000	HRare	-	-	-	-
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5	LIG4	Block 2	rs868284-rs1151402-rs10131-rs3093772-rs3093748						
6			G_a_G_A_G	0.432	H1	1.00			
7			G_G_G_A_a	0.184	H2	0.77	(0.56 ,1.06)	0.1116	
8			G_G_G_A_G	0.142	H3	0.98	(0.70 ,1.37)	0.8983	
9			a_G_G_g_G	0.107	H4	1.00	(0.70 ,1.42)	0.9927	
10			G_G_a_A_G	0.092	H5	0.95	(0.63 ,1.43)	0.8045	
11			HRare	0.044	HRare	1.45	(0.88 ,2.39)	0.1442	
12	LIG4	Block 3	rs12428162-rs7322498-rs9520823						
13			C_A_A	0.353	H1	1.00			
14			C_A_c	0.283	H2	1.06	(0.79 ,1.42)	0.7059	
15	SOCS1	Block 1	rs193778-rs243317						
16			A_A	0.464	H1	1.00			
17			A_c	0.294	H2	1.08	(0.82 ,1.44)	0.5726	
18			g_A	0.241	H3	1.24	(0.90 ,1.69)	0.1839	
19	STAT1	Block 1	rs13035504-rs1168-rs12468579-rs1400657						
20			G_a_A_A	0.445	H1	1.00			
21			G_G_g_A	0.265	H2	0.85	(0.65 ,1.12)	0.2585	
22			c_G_g_A	0.171	H3	0.92	(0.68 ,1.25)	0.5913	
23			G_G_A_c	0.115	H4	0.87	(0.61 ,1.25)	0.4500	
24			HRare	0.004	HRare	2.43	(0.61 ,9.66)	0.2072	
25	STAT1	Block 2	rs16824035-rs13395505-rs17749316-rs2066804						
26			G_G_C_G	0.528	H1	1.00			
27			G_a_C_a	0.229	H2	0.80	(0.60 ,1.06)	0.1201	
28			a_a_C_G	0.172	H3	0.94	(0.70 ,1.27)	0.6832	
29			G_G_g_G	0.066	H4	0.88	(0.56 ,1.40)	0.6032	
30			HRare	0.005	HRare	0.83	(0.20 ,3.47)	0.7958	
31	STAT1	Block 3	rs432757-rs2280234-rs2280233						
32			A_G_g	0.455	H1	1.00			
33			A_a_A	0.377	H2	0.90	(0.71 ,1.14)	0.3958	
34			c_G_A	0.139	H3	0.95	(0.68 ,1.32)	0.7597	
35			HRare	0.029	HRare	0.69	(0.33 ,1.44)	0.3267	
36	STAT1	Block 4	rs7562024-rs34997637						
37			G_G	0.606	H1	1.00			
38			a_a	0.230	H2	0.87	(0.67 ,1.13)	0.3065	
39			a_G	0.164	H3	1.03	(0.76 ,1.39)	0.8661	
40	STAT1	Block 5	rs13029247-rs10173099-rs10199181						
41			A_G_T	0.616	H1	1.00			
42			g_a_a	0.315	H2	0.81	(0.64 ,1.03)	0.0900	
43			HRare	0.070	HRare	1.31	(0.87 ,1.99)	0.1992	
44	STAT1	Block 6	rs13029532-rs1467199-rs17817966						
45			A_C_A	0.563	H1	1.00			
46			A_g_g	0.234	H2	0.77	(0.59 ,1.01)	0.0592	
47			A_C_g	0.113	H3	0.86	(0.60 ,1.23)	0.4089	
48			c_C_g	0.089	H4	0.97	(0.66 ,1.41)	0.8611	
49	STAT3	Block 1	rs1053023-rs1053005						
50			A_A	0.801	H1	1.00			
51			g_g	0.199	H2	0.78	(0.59 ,1.03)	0.0820	
52			HRare	0.000	HRare	-	-	-	-
53	STAT3	Block 2	rs4103200-rs9891119-rs9912773-rs12949918-rs17405722						
54			G_A_C_A_G	0.588	H1	1.00			
55			c_c_g_g_G	0.267	H2	0.79	(0.61 ,1.02)	0.0695	
56			G_c_C_g_a	0.065	H3	1.04	(0.68 ,1.59)	0.8560	
57			G_A_C_g_G	0.053	H4	0.72	(0.42 ,1.23)	0.2319	
58	STAT4	Block 1	rs13020076-rs16833177-rs7558921						
59			A_A_C	0.600	H1	1.00			
60			A_g_C	0.205	H2	0.74	(0.54 ,1.00)	0.0529	
			A_A_g	0.113	H3	0.80	(0.54 ,1.18)	0.2664	
			g_A_C	0.081	H4	0.78	(0.51 ,1.19)	0.2533	
			HRare	0.000	HRare	-	-	-	-

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4	STAT4	Block 2	rs7574608-rs4853540						
5			A_C	0.766	H1	1.00			
6			A_a	0.170	H2	1.15	(0.87 ,1.52)	0.3280	
7			t_a	0.062	H3	0.83	(0.51 ,1.34)	0.4417	
8			HRare	0.002	HRare	2.19	(0.19 ,25.32)	0.5305	
9	STAT4	Block 3	rs3024861-rs932169						
10			A_C	0.659	H1	1.00			
11			t_C	0.264	H2	0.94	(0.72 ,1.21)	0.6245	
12			A_g	0.076	H3	0.96	(0.59 ,1.57)	0.8819	
13			HRare	0.001	HRare	-	-	-	
14	STAT4	Block 4	rs10168266-rs2459611						
15			G_A	0.685	H1	1.00			
16			a_A	0.187	H2	0.99	(0.73 ,1.34)	0.9662	
17			G_g	0.127	H3	1.14	(0.81 ,1.62)	0.4453	
18			HRare	0.001	HRare	-	-	-	
19	STAT4	Block 5	rs7599504-rs4571082-rs17769459						
20			A_A_G	0.560	H1	1.00			
21			A_g_G	0.219	H2	1.02	(0.77 ,1.35)	0.8802	
22			g_g_G	0.161	H3	1.20	(0.89 ,1.61)	0.2286	
23			A_A_a	0.059	H4	1.09	(0.68 ,1.74)	0.7295	
24			HRare	0.001	HRare	-	-	-	
25	STAT6	Block 1	rs3024979-rs703817-rs324015-rs3024974-rs3024971-rs324011						
26			A_a_G_G_A_a	0.358	H1	1.00			
27			A_G_a_G_A_G	0.232	H2	1.14	(0.85 ,1.51)	0.3841	
28			t_a_G_G_A_G	0.114	H3	0.94	(0.64 ,1.37)	0.7442	
29			A_G_G_G_c_G	0.114	H4	1.04	(0.71 ,1.51)	0.8568	
30			A_G_G_a_A_G	0.087	H5	0.88	(0.58 ,1.33)	0.5381	
31			A_G_G_G_A_G	0.067	H6	1.14	(0.72 ,1.83)	0.5734	
32			HRare	0.028	HRare	1.02	(0.51 ,2.03)	0.9589	
33	TP63	Block 1	rs6790068-rs9681004						
34			A_A	0.595	H1	1.00			
35			g_g	0.395	H2	0.82	(0.65 ,1.03)	0.0810	
36			HRare	0.010	HRare	0.54	(0.12 ,2.35)	0.4112	
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For Peer Review

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TNHL

Supplementary Table 4. Odds Ratios and 95% Confidence Intervals for estimated Haplotypes for TNHL (adjusted for age (continuous), sex and study co

	Gene	Block	Haplotype	Frequency	hapname	T-NHL		
						OR	95% CI	p-value
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	BMF	Block 1	rs3923235-rs16970325 A_G g_G A_a HRare	0.624 0.268 0.109 0.000	H1	1.00		
					H2	1.30	(0.89 ,1.89)	0.1705
					H3	1.82	(1.06 ,3.13)	0.0290
					HRare	-	-	-
BMF	Block 2	rs12913170-rs7183977-rs998713-rs546220 G_A_A_a G_g_g_C a_A_A_C G_A_g_C HRare	0.418 0.331 0.151 0.060 0.040	H1	1.00			
				H2	1.17	(0.82 ,1.66)	0.3911	
				H3	0.55	(0.31 ,0.98)	0.0437	
				H4	1.82	(1.02 ,3.25)	0.0435	
				HRare	1.23	(0.60 ,2.52)	0.5796	
BMF	Block 3	rs648289-rs10518679 g_A A_A A_g HRare	0.450 0.417 0.132 0.001	H1	1.00			
				H2	1.21	(0.86 ,1.71)	0.2628	
				H3	0.85	(0.48 ,1.50)	0.5761	
				HRare	-	-	-	
BMF	Block 4	rs11634257-rs11858141-rs675173 A_g_G A_A_a t_A_G HRare	0.429 0.309 0.252 0.010	H1	1.00			
				H2	1.00	(0.68 ,1.48)	0.9831	
				H3	1.40	(0.97 ,2.02)	0.0760	
				HRare	1.04	(0.23 ,4.71)	0.9565	
BMF	Block 5	rs537455-rs11630670 A_G c_a A_a HRare	0.534 0.265 0.201 0.000	H1	1.00			
				H2	1.03	(0.70 ,1.51)	0.8852	
				H3	0.73	(0.47 ,1.14)	0.1619	
				HRare	-	-	-	
IFNGR1	Block 1	rs7759040-rs3799488-rs1327475 A_A_G A_A_a t_A_G t_g_G HRare	0.564 0.189 0.126 0.121 0.001	H1	1.00			
				H2	1.16	(0.78 ,1.72)	0.4643	
				H3	1.26	(0.64 ,2.46)	0.5031	
				H4	1.00	(0.61 ,1.64)	0.9986	
				HRare	-	-	-	
IFNG	Block 1	rs2069727-rs2069718 g_G A_a A_G HRare	0.482 0.375 0.142 0.000	H1	1.00			
				H2	0.92	(0.65 ,1.29)	0.6221	
				H3	0.99	(0.62 ,1.56)	0.9500	
				HRare	-	-	-	
IFNG	Block 2	rs2069716-rs6581795-rs12306852 A_A_C A_g_C A_A_g g_A_C HRare	0.509 0.264 0.155 0.072 0.001	H1	1.00			
				H2	0.94	(0.65 ,1.37)	0.7614	
				H3	0.83	(0.51 ,1.35)	0.4591	
				H4	0.81	(0.40 ,1.64)	0.5634	
				HRare	-	-	-	
IL10	Block 1	rs17015767-rs1800871-rs1800872-rs2222202-rs3021094-rs1554286-rs3024509-rs3024505-rs6673928-rs4844553-rs754837 G_G_C_G_A_G_A_G_C_G_C c_G_C_a_A_G_A_G_a_G_C G_G_C_a_A_G_A_a_C_G_C G_a_a_G_a_A_G_C_G_C G_G_C_a_A_G_g_G_C_a_a G_a_a_G_c_a_A_G_C_G_C HRare	0.309 0.194 0.149 0.125 0.070 0.064 0.090	H1	1.00			
				H2	0.77	(0.49 ,1.22)	0.2732	
				H3	0.90	(0.56 ,1.43)	0.6461	
				H4	1.05	(0.64 ,1.72)	0.8511	
				H5	0.96	(0.52 ,1.76)	0.8853	
				H6	0.75	(0.36 ,1.52)	0.4215	
				HRare	0.70	(0.37 ,1.31)	0.2628	
IL12A	Block 1	rs9811792-rs7372767-rs4680534-rs6441282-rs6800657-rs747825 g_g_A_C_A_C A_A_g_a_A_a A_A_g_a_A_C A_A_A_a_g_C A_A_A_C_A_C HRare	0.425 0.179 0.168 0.102 0.098 0.028	H1	1.00			
				H2	0.92	(0.60 ,1.41)	0.6927	
				H3	1.06	(0.69 ,1.64)	0.7935	
				H4	0.57	(0.29 ,1.09)	0.0897	
				H5	0.86	(0.48 ,1.53)	0.6074	
				HRare	1.72	(0.82 ,3.60)	0.1532	
IL12A	Block 2	rs2243115-rs583911-rs2243131-rs2243154-rs11927521 A_g_A_G_A A_A_A_G_g A_A_c_G_A c_A_A_G_g	0.354 0.274 0.155 0.112	H1	1.00			
				H2	0.95	(0.65 ,1.40)	0.8087	
				H3	0.80	(0.49 ,1.32)	0.3805	
				H4	0.86	(0.51 ,1.44)	0.5650	

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3			A_g_A_a_A	0.104	H5	0.90	(0.52 ,1.54)	0.6936
4			HRare	0.001	HRare			
5	IL12B	Block 1	rs4921466-rs4921468-rs6870828-rs3181225-rs1368439-rs11574790-rs2853694					
6			A_G_A_G_A_G_c	0.291	H1	1.00		
7			A_G_A_G_A_G_A	0.230	H2	0.86	(0.56 ,1.31)	0.4716
8			A_G_g_G_c_G_c	0.178	H3	0.95	(0.62 ,1.48)	0.8338
9			A_a_g_a_A_G_A	0.168	H4	0.63	(0.38 ,1.05)	0.0737
10	IL12B	Block 2	rs2569253-rs3181216					
11			A_T	0.540	H1	1.00		
12			g_a	0.286	H2	1.15	(0.82 ,1.61)	0.4170
13			g_T	0.172	H3	0.65	(0.40 ,1.07)	0.0893
14	IL12B	Block 3	rs1433048-rs2546893					
15			A_a	0.464	H1	1.00		
16			A_G	0.352	H2	1.26	(0.90 ,1.78)	0.1832
17			g_G	0.183	H3	1.19	(0.79 ,1.81)	0.4041
18	IL12B	Block 4	rs2546890-rs10052709-rs7709212-rs6868898					
19			g_G_g_A	0.345	H1	1.00		
20			A_G_A_g	0.292	H2	1.34	(0.91 ,1.99)	0.1420
21			A_G_A_A	0.204	H3	1.06	(0.67 ,1.66)	0.8150
22			g_c_A_A	0.144	H4	1.14	(0.70 ,1.87)	0.5909
23			HRare	0.014	HRare	2.43	(0.80 ,7.37)	0.1168
24	IL7R	Block 1	rs11567694-rs11567697-rs11567701-rs6891095-rs3777090-rs11567762-rs10063294-rs10058453					
25			A_A_a_A_A_G_A_A	0.272	H1	1.00		
26			g_A_C_A_A_G_A_A	0.254	H2	0.96	(0.63 ,1.46)	0.8475
27			A_A_C_A_t_a_g_g	0.156	H3	1.31	(0.82 ,2.08)	0.2549
28			A_A_C_g_A_G_g_A	0.137	H4	0.95	(0.56 ,1.60)	0.8425
29			A_g_C_A_t_G_g_g	0.095	H5	1.15	(0.67 ,1.96)	0.6130
30			A_A_C_A_t_G_g_g	0.078	H6	1.02	(0.53 ,1.97)	0.9480
31			HRare	0.008	HRare	0.75	(0.10 ,5.90)	0.7863
32	IRF4	Block 1	rs9405192-rs1033180					
33			G_G	0.703	H1	1.00		
34			a_G	0.224	H2	1.08	(0.75 ,1.55)	0.6680
35			a_a	0.074	H3	1.08	(0.59 ,1.99)	0.7976
36	IRF4	Block 2	rs13208928-rs3778607					
37			T_G	0.500	H1	1.00		
38			T_a	0.429	H2	0.99	(0.72 ,1.37)	0.9577
39			a_a	0.070	H3	0.95	(0.42 ,2.16)	0.9062
40			HRare	0.001	HRare			
41	IRF4	Block 3	rs1050975-rs7768807					
42			A_A	0.667	H1	1.00		
43			A_g	0.246	H2	0.97	(0.66 ,1.43)	0.8968
44			g_A	0.086	H3	1.27	(0.71 ,2.27)	0.4171
45			HRare	0.001	HRare			
46	IRF4	Block 4	rs12211228-rs1877175-rs6906608					
47			G_G_C	0.780	H1	1.00		
48			c_a_a	0.147	H2	0.90	(0.58 ,1.40)	0.6392
49			G_a_C	0.072	H3	0.77	(0.41 ,1.46)	0.4256
50			HRare	0.002	HRare			
51	IRF4	Block 5	rs11757491-rs9378805					
52			G_C	0.476	H1	1.00		
53			G_A	0.456	H2	1.02	(0.74 ,1.41)	0.8996
54			a_A	0.068	H3	1.01	(0.47 ,2.16)	0.9737
55	Jak1	Block 1	rs310211-rs2256298					
56			A_G	0.676	H1	1.00		
57			g_a	0.259	H2	1.24	(0.88 ,1.75)	0.2243
58			g_G	0.065	H3	0.89	(0.45 ,1.75)	0.7405
59	LIG4	Block 1	rs915047-rs9514825					
60			A_G	0.635	H1	1.00		
			A_a	0.201	H2	0.96	(0.65 ,1.43)	0.8547
			g_a	0.164	H3	1.04	(0.67 ,1.60)	0.8739

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		HRare	0.000	HRare	-	-	-
5	LIG4	Block 2	rs868284-rs1151402-rs10131-rs3093772-rs3093748				
6			G_a_G_A_G	0.432	H1	1.00	
7			G_G_G_A_a	0.184	H2	1.18 (0.78 ,1.78)	0.4344
8			G_G_G_A_G	0.142	H3	1.08 (0.67 ,1.73)	0.7481
9			a_G_G_g_G	0.107	H4	0.93 (0.55 ,1.57)	0.7938
10			G_G_a_A_G	0.092	H5	1.17 (0.68 ,2.01)	0.5691
11			HRare	0.044	HRare	0.85 (0.35 ,2.05)	0.7219
12	LIG4	Block 3	rs12428162-rs7322498-rs9520823				
13			C_A_A	0.353	H1	1.00	
14			C_A_c	0.283	H2	0.94 (0.65 ,1.38)	0.7652
15	SOCS1	Block 1	rs193778-rs243317				
16			A_A	0.464	H1	1.00	
17			A_c	0.294	H2	0.99 (0.68 ,1.44)	0.9617
18			g_A	0.241	H3	1.37 (0.94 ,1.99)	0.0991
19	STAT1	Block 1	rs13035504-rs1168-rs12468579-rs1400657				
20			G_a_A_A	0.445	H1	1.00	
21			G_G_g_A	0.265	H2	0.79 (0.54 ,1.16)	0.2286
22			c_G_g_A	0.171	H3	0.91 (0.59 ,1.42)	0.6891
23			G_G_A_c	0.115	H4	0.92 (0.56 ,1.51)	0.7458
24	STAT1	Block 2	rs16824035-rs13395505-rs17749316-rs2066804				
25			G_G_C_G	0.528	H1	1.00	
26			G_a_C_a	0.229	H2	0.79 (0.53 ,1.18)	0.2484
27			a_a_C_G	0.172	H3	0.99 (0.64 ,1.51)	0.9501
28			G_G_g_G	0.066	H4	1.24 (0.69 ,2.22)	0.4656
29			HRare	0.005	HRare	0.84 (0.11 ,6.17)	0.8602
30	STAT1	Block 3	rs432757-rs2280234-rs2280233				
31			A_G_g	0.455	H1	1.00	
32			A_a_A	0.377	H2	0.86 (0.61 ,1.20)	0.3799
33	STAT1	Block 4	rs7562024-rs34997637				
34			G_G	0.606	H1	1.00	
35			a_a	0.230	H2	0.62 (0.41 ,0.95)	0.0283
36			a_G	0.164	H3	1.27 (0.87 ,1.85)	0.2233
37	STAT1	Block 5	rs13029247-rs10173099-rs10199181				
38			A_G_T	0.616	H1	1.00	
39			g_a_a	0.315	H2	0.72 (0.50 ,1.03)	0.0706
40	STAT1	Block 6	rs13029532-rs1467199-rs17817966				
41			HRare	0.070	HRare	1.56 (0.94 ,2.59)	0.0865
42			A_C_A	0.563	H1	1.00	
43			A_g_g	0.234	H2	0.62 (0.41 ,0.93)	0.0210
44			A_C_g	0.113	H3	0.84 (0.51 ,1.40)	0.5088
45	STAT3	Block 1	rs1053023-rs1053005				
46			c_C_g	0.089	H4	0.73 (0.42 ,1.29)	0.2803
47			HRare	0.000	HRare	-	-
48	STAT3	Block 2	rs4103200-rs9891119-rs9912773-rs12949918-rs17405722				
49			G_A_C_A_G	0.588	H1	1.00	
50			c_c_g_G	0.267	H2	0.78 (0.54 ,1.13)	0.1907
51			G_c_C_g_a	0.065	H3	0.89 (0.47 ,1.68)	0.7129
52			G_A_C_g_G	0.053	H4	1.01 (0.52 ,1.96)	0.9756
53	STAT4	Block 1	rs13020076-rs16833177-rs7558921				
54			HRare	0.027	HRare	1.00 (0.42 ,2.38)	0.9927
55			A_A_C	0.600	H1	1.00	
56			A_g_C	0.205	H2	0.62 (0.39 ,0.98)	0.0407
57			A_A_g	0.113	H3	0.66 (0.39 ,1.12)	0.1250
58			g_A_C	0.081	H4	0.80 (0.43 ,1.50)	0.4823
59			HRare	0.000	HRare	-	-
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4	STAT4	Block 2	rs7574608-rs4853540						
5			A_C	0.766	H1	1.00			
6			A_a	0.170	H2	1.68	(1.18 ,2.40)	0.0043	
7			t_a	0.062	H3	1.05	(0.55 ,2.01)	0.8809	
8			HRare	0.002	HRare	6.43	(0.53 ,78.67)	0.1451	
9	STAT4	Block 3	rs3024861-rs932169						
10			A_C	0.659	H1	1.00			
11			t_C	0.264	H2	0.88	(0.60 ,1.29)	0.5120	
12			A_g	0.076	H3	1.26	(0.69 ,2.32)	0.4497	
13			HRare	0.001	HRare	-	-	-	
14	STAT4	Block 4	rs10168266-rs2459611						
15			G_A	0.685	H1	1.00			
16			a_A	0.187	H2	0.86	(0.55 ,1.32)	0.4842	
17			G_g	0.127	H3	1.33	(0.87 ,2.04)	0.1845	
18			HRare	0.001	HRare	-	-	-	
19	STAT4	Block 5	rs7599504-rs4571082-rs17769459						
20			A_A_G	0.560	H1	1.00			
21			A_g_G	0.219	H2	1.29	(0.89 ,1.87)	0.1846	
22			g_g_G	0.161	H3	1.21	(0.79 ,1.83)	0.3791	
23			A_A_a	0.059	H4	1.04	(0.51 ,2.09)	0.9235	
24			HRare	0.001	HRare	-	-	-	
25	STAT6	Block 1	rs3024979-rs703817-rs324015-rs3024974-rs3024971-rs324011						
26			A_a_G_G_A_a	0.358	H1	1.00			
27			A_G_a_G_A_G	0.232	H2	0.81	(0.50 ,1.29)	0.3718	
28			t_a_G_G_A_G	0.114	H3	1.34	(0.81 ,2.22)	0.2471	
29			A_G_G_G_c_G	0.114	H4	1.69	(1.03 ,2.77)	0.0381	
30			A_G_G_a_A_G	0.087	H5	1.15	(0.65 ,2.03)	0.6366	
31			A_G_G_G_A_G	0.067	H6	1.13	(0.57 ,2.26)	0.7255	
32			HRare	0.028	HRare	3.03	(1.41 ,6.47)	0.0043	
33	TP63	Block 1	rs6790068-rs9681004						
34			A_A	0.595	H1	1.00			
35			g_g	0.395	H2	1.01	(0.74 ,1.39)	0.9383	
36			HRare	0.010	HRare	3.37	(1.21 ,9.39)	0.0199	
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For Peer Review

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CLL

Supplementary Table 4. Odds Ratios and 95% Confidence Intervals for estimated Haplotypes for BNHL and subtypes (adjusted for age (continuous), sex)

	Gene	Block	Haplotype	Frequency	hapname	CLL		
						OR	95% CI	p-value
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	BMF	Block 1	rs3923235-rs16970325 A_G g_G A_a HRare	0.624 0.268 0.109 0.000	H1	1.00		
					H2	0.94	(0.76 ,1.18)	0.6071
					H3	1.32	(0.95 ,1.84)	0.0966
					HRare	-	-	-
BMF	Block 2	rs12913170-rs7183977-rs998713-rs546220 G_A_A_a G_g_C a_A_A_C G_A_g_C HRare	0.418 0.331 0.151 0.060 0.040	H1	1.00			
				H2	1.01	(0.81 ,1.24)	0.9553	
				H3	1.04	(0.80 ,1.36)	0.7566	
				H4	1.41	(0.97 ,2.05)	0.0751	
				HRare	0.95	(0.59 ,1.52)	0.8218	
				-	-	-	-	
BMF	Block 3	rs648289-rs10518679 g_A A_A A_g HRare	0.450 0.417 0.132 0.001	H1	1.00			
				H2	1.05	(0.87 ,1.28)	0.5987	
				H3	1.00	(0.76 ,1.33)	0.9766	
				HRare	-	-	-	
BMF	Block 4	rs11634257-rs11858141-rs675173 A_g_G A_A_a t_A_G HRare	0.429 0.309 0.252 0.010	H1	1.00			
				H2	1.01	(0.81 ,1.24)	0.9585	
				H3	0.93	(0.74 ,1.17)	0.5273	
				HRare	0.99	(0.40 ,2.43)	0.9759	
BMF	Block 5	rs537455-rs11630670 A_G c_a A_a HRare	0.534 0.265 0.201 0.000	H1	1.00			
				H2	1.11	(0.90 ,1.37)	0.3475	
				H3	1.01	(0.80 ,1.28)	0.9105	
				HRare	-	-	-	
IFNGR1	Block 1	rs7759040-rs3799488-rs1327475 A_A_G A_A_a t_A_G t_g_G HRare	0.564 0.189 0.126 0.121 0.001	H1	1.00			
				H2	0.76	(0.59 ,0.98)	0.0315	
				H3	0.90	(0.68 ,1.20)	0.4803	
				H4	0.82	(0.61 ,1.09)	0.1711	
				HRare	2.32	(0.21 ,26.03)	0.4962	
IFNG	Block 1	rs2069727-rs2069718 g_G A_a A_G HRare	0.482 0.375 0.142 0.000	H1	1.00			
				H2	1.03	(0.85 ,1.24)	0.7857	
				H3	1.00	(0.76 ,1.31)	0.9923	
				HRare	-	-	-	
IFNG	Block 2	rs2069716-rs6581795-rs12306852 A_A_C A_g_C A_A_g g_A_C HRare	0.509 0.264 0.155 0.072 0.001	H1	1.00			
				H2	0.90	(0.73 ,1.12)	0.3639	
				H3	1.00	(0.76 ,1.31)	0.9928	
				H4	0.73	(0.48 ,1.13)	0.1586	
				HRare	-	-	-	
IL10	Block 1	rs17015767-rs1800871-rs1800872-rs2222202-rs3021094-rs1554286-rs3024509-rs3024505-rs6673928-rs4844553-rs754837 G_G_C_G_A_G_A_G_C_G_C c_G_C_a_A_G_A_G_a_G_C G_G_C_a_A_G_A_a_C_G_C G_a_a_G_a_A_G_C_G_C G_G_C_a_A_G_g_G_C_a_a G_a_a_G_c_a_A_G_C_G_C HRare	0.309 0.194 0.149 0.125 0.070 0.064 0.090	H1	1.00			
				H2	0.96	(0.74 ,1.24)	0.7671	
				H3	0.97	(0.74 ,1.28)	0.8435	
				H4	0.92	(0.68 ,1.26)	0.6101	
				H5	0.99	(0.69 ,1.42)	0.9510	
				H6	1.19	(0.82 ,1.73)	0.3507	
				HRare	0.90	(0.64 ,1.27)	0.5503	
IL12A	Block 1	rs9811792-rs7372767-rs4680534-rs6441282-rs6800657-rs747825 g_g_A_C_A_C A_A_g_a_A_a A_A_g_A_A_C A_A_A_g_C A_A_A_C_A_C HRare	0.425 0.179 0.168 0.102 0.098 0.028	H1	1.00			
				H2	0.92	(0.71 ,1.17)	0.4842	
				H3	1.08	(0.83 ,1.39)	0.5671	
				H4	0.86	(0.62 ,1.20)	0.3795	
				H5	0.91	(0.66 ,1.25)	0.5476	
				HRare	0.99	(0.57 ,1.73)	0.9721	
IL12A	Block 2	rs2243115-rs583911-rs2243131-rs2243154-rs11927521 A_g_A_G_A A_A_A_G_g A_A_c_G_A c_A_A_G_g	0.354 0.274 0.155 0.112	H1	1.00			
				H2	1.00	(0.80 ,1.25)	0.9844	
				H3	0.92	(0.70 ,1.21)	0.5347	
				H4	0.88	(0.65 ,1.20)	0.4287	
				-	-	-	-	

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3			A_g_A_a_A	0.104	H5	0.93	(0.68 ,1.28)	0.6484
4			HRare	0.001	HRare	2.22	(0.36 ,13.92)	0.3930
5	IL12B	Block 1	rs4921466-rs4921468-rs6870828-rs3181225-rs1368439-rs11574790-rs2853694					
6			A_G_A_G_A_G_c	0.291	H1	1.00		
7			A_G_A_G_A_G_A	0.230	H2	1.43	(1.11 ,1.83)	0.0053
8			A_G_g_G_c_G_c	0.178	H3	1.17	(0.89 ,1.53)	0.2543
9			A_a_g_a_A_G_A	0.168	H4	1.14	(0.87 ,1.51)	0.3436
10			g_a_g_G_A_a_A	0.115	H5	1.07	(0.78 ,1.48)	0.6590
11			HRare	0.018	HRare	0.92	(0.47 ,1.79)	0.7965
12	IL12B	Block 2	rs2569253-rs3181216					
13			A_T	0.540	H1	1.00		
14			g_a	0.286	H2	0.79	(0.64 ,0.98)	0.0335
15			g_T	0.172	H3	0.90	(0.70 ,1.15)	0.3821
16			HRare	0.001	HRare	3.87	(0.50 ,29.93)	0.1954
17	IL12B	Block 3	rs1433048-rs2546893					
18			A_a	0.464	H1	1.00		
19			A_G	0.352	H2	1.01	(0.83 ,1.24)	0.8863
20			g_G	0.183	H3	0.96	(0.75 ,1.22)	0.7308
21			HRare	0.001	HRare	-	-	-
22	IL12B	Block 4	rs2546890-rs10052709-rs7709212-rs6868898					
23			g_G_g_A	0.345	H1	1.00		
24			A_G_A_g	0.292	H2	0.80	(0.63 ,1.00)	0.0527
25			A_G_A_A	0.204	H3	0.81	(0.63 ,1.04)	0.0955
26			g_c_A_A	0.144	H4	0.81	(0.61 ,1.08)	0.1500
27			HRare	0.014	HRare	1.28	(0.61 ,2.68)	0.5070
28	IL7R	Block 1	rs11567694-rs11567697-rs11567701-rs6891095-rs3777090-rs11567762-rs10063294-rs10058453					
29			A_A_a_A_A_G_A_A	0.272	H1	1.00		
30			g_A_C_A_A_G_A_A	0.254	H2	0.81	(0.63 ,1.02)	0.0781
31			A_A_C_A_t_a_g_g	0.156	H3	1.04	(0.79 ,1.37)	0.7644
32			A_A_C_g_A_G_g_A	0.137	H4	1.01	(0.75 ,1.34)	0.9701
33			A_g_C_A_t_G_g_g	0.095	H5	0.87	(0.62 ,1.21)	0.4113
34			A_A_C_A_t_G_g_g	0.078	H6	1.17	(0.83 ,1.67)	0.3703
35			HRare	0.008	HRare	1.06	(0.38 ,2.96)	0.9072
36	IRF4	Block 1	rs9405192-rs1033180					
37			G_G	0.703	H1	1.00		
38			a_G	0.224	H2	1.08	(0.87 ,1.33)	0.4833
39			a_a	0.074	H3	0.94	(0.65 ,1.35)	0.7389
40			HRare	0.000	HRare	-	-	-
41	IRF4	Block 2	rs13208928-rs3778607					
42			T_G	0.500	H1	1.00		
43			T_a	0.429	H2	1.01	(0.83 ,1.21)	0.9495
44			a_a	0.070	H3	0.95	(0.61 ,1.48)	0.8142
45			HRare	0.001	HRare	-	-	-
46	IRF4	Block 3	rs1050975-rs7768807					
47			A_A	0.667	H1	1.00		
48			A_g	0.246	H2	1.00	(0.81 ,1.24)	0.9948
49			g_A	0.086	H3	0.87	(0.61 ,1.23)	0.4241
50			HRare	0.001	HRare	-	-	-
51	Jak1	Block 1	rs310211-rs2256298					
52			A_G	0.676	H1	1.00		
53			g_a	0.259	H2	0.93	(0.75 ,1.14)	0.4707
54			g_G	0.065	H3	0.89	(0.61 ,1.31)	0.5604
55			HRare	0.000	HRare	-	-	-
56	LIG4	Block 1	rs915047-rs9514825					
57			A_G	0.635	H1	1.00		
58			A_a	0.201	H2	1.18	(0.94 ,1.46)	0.1469
59			g_a	0.164	H3	1.09	(0.85 ,1.40)	0.5160
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1			HRare	0.000	HRare	-	-	-	
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5	LIG4	Block 2	rs868284-rs1151402-rs10131-rs3093772-rs3093748						
6			G_a_G_A_G	0.432	H1	1.00			
7			G_G_G_A_a	0.184	H2	1.05	(0.82 ,1.34)	0.7157	
8			G_G_G_A_G	0.142	H3	1.21	(0.92 ,1.58)	0.1677	
9			a_G_G_g_G	0.107	H4	1.01	(0.75 ,1.36)	0.9637	
10			G_G_a_A_G	0.092	H5	1.56	(1.15 ,2.12)	0.0041	
11			HRare	0.044	HRare	1.23	(0.78 ,1.95)	0.3704	
12	LIG4	Block 3	rs12428162-rs7322498-rs9520823						
13			C_A_A	0.353	H1	1.00			
14			C_A_c	0.283	H2	1.00	(0.78 ,1.28)	0.9994	
15	SOCS1	Block 1	rs193778-rs243317						
16			A_A	0.464	H1	1.00			
17			A_c	0.294	H2	1.16	(0.92 ,1.46)	0.2022	
18			g_A	0.241	H3	1.19	(0.92 ,1.53)	0.1835	
19	STAT1	Block 1	rs13035504-rs1168-rs12468579-rs1400657						
20			G_a_A_A	0.445	H1	1.00			
21			G_G_g_A	0.265	H2	1.33	(1.07 ,1.65)	0.0097	
22			c_G_g_A	0.171	H3	1.18	(0.92 ,1.51)	0.1956	
23			G_G_A_c	0.115	H4	0.97	(0.71 ,1.32)	0.8454	
24	STAT1	Block 2	rs16824035-rs13395505-rs17749316-rs2066804						
25			G_G_C_G	0.528	H1	1.00			
26			G_a_C_a	0.229	H2	1.29	(1.04 ,1.60)	0.0211	
27			a_a_C_G	0.172	H3	1.15	(0.90 ,1.47)	0.2574	
28			G_G_g_G	0.066	H4	1.07	(0.74 ,1.54)	0.7207	
29			HRare	0.005	HRare	0.48	(0.11 ,2.02)	0.3153	
30	STAT1	Block 3	rs432757-rs2280234-rs2280233						
31			A_G_g	0.455	H1	1.00			
32			A_a_A	0.377	H2	1.17	(0.96 ,1.42)	0.1208	
33	STAT1	Block 4	rs7562024-rs34997637						
34			c_G_A	0.139	H3	1.19	(0.91 ,1.55)	0.2069	
35			HRare	0.029	HRare	1.24	(0.74 ,2.08)	0.4127	
36	STAT1	Block 5	rs13029247-rs10173099-rs10199181						
37			A_G_T	0.616	H1	1.00			
38			g_a_a	0.315	H2	1.11	(0.92 ,1.34)	0.2827	
39			HRare	0.070	HRare	1.21	(0.86 ,1.72)	0.2778	
40	STAT1	Block 6	rs13029532-rs1467199-rs17817966						
41			A_C_A	0.563	H1	1.00			
42			A_g_g	0.234	H2	1.07	(0.86 ,1.31)	0.5524	
43			A_C_g	0.113	H3	1.21	(0.91 ,1.59)	0.1851	
44			c_C_g	0.089	H4	0.89	(0.64 ,1.24)	0.4800	
45	STAT3	Block 1	rs1053023-rs1053005						
46			A_A	0.801	H1	1.00			
47			g_g	0.199	H2	0.81	(0.65 ,1.01)	0.0659	
48	STAT3	Block 2	rs4103200-rs9891119-rs9912773-rs12949918-rs17405722						
49			G_A_C_A_G	0.588	H1	1.00			
50			c_c_g_g_G	0.267	H2	0.85	(0.69 ,1.05)	0.1352	
51			G_c_C_g_a	0.065	H3	0.99	(0.69 ,1.41)	0.9536	
52			G_A_C_g_G	0.053	H4	1.06	(0.71 ,1.60)	0.7607	
53	STAT4	Block 1	rs13020076-rs16833177-rs7558921						
54			A_A_C	0.600	H1	1.00			
55			A_g_C	0.205	H2	1.10	(0.87 ,1.38)	0.4174	
56			A_A_g	0.113	H3	0.79	(0.58 ,1.09)	0.1491	
57			g_A_C	0.081	H4	1.16	(0.81 ,1.67)	0.4112	
58			HRare	0.000	HRare	-	-	-	
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4	STAT4	Block 2	rs7574608-rs4853540			
5			A_C	0.766	H1	1.00
6			A_a	0.170	H2	1.19 (0.95 ,1.50)
7			t_a	0.062	H3	1.02 (0.70 ,1.49)
8			HRare	0.002	HRare	3.64 (0.30 ,44.27)
9	STAT4	Block 3	rs3024861-rs932169			
10			A_C	0.659	H1	1.00
11			t_C	0.264	H2	1.11 (0.91 ,1.36)
12			A_g	0.076	H3	1.18 (0.84 ,1.65)
13			HRare	0.001	HRare	-
14	STAT4	Block 4	rs10168266-rs2459611			
15			G_A	0.685	H1	1.00
16			a_A	0.187	H2	1.15 (0.91 ,1.47)
17			G_g	0.127	H3	1.20 (0.90 ,1.60)
18			HRare	0.001	HRare	-
19	STAT4	Block 5	rs7599504-rs4571082-rs17769459			
20			A_A_G	0.560	H1	1.00
21			A_g_G	0.219	H2	1.02 (0.81 ,1.28)
22			g_g_G	0.161	H3	1.10 (0.82 ,1.47)
23			A_A_a	0.059	H4	1.36 (0.96 ,1.94)
24			HRare	0.001	HRare	-
25	STAT6	Block 1	rs3024979-rs703817-rs324015-rs3024974-rs3024971-rs324011			
26			A_a_G_G_A_a	0.358	H1	1.00
27			A_G_a_G_A_G	0.232	H2	0.98 (0.77 ,1.26)
28			t_a_G_G_A_G	0.114	H3	0.91 (0.67 ,1.23)
29			A_G_G_G_c_G	0.114	H4	1.10 (0.81 ,1.49)
30			A_G_G_a_A_G	0.087	H5	0.89 (0.64 ,1.25)
31			A_G_G_G_A_G	0.067	H6	0.96 (0.65 ,1.43)
32			HRare	0.028	HRare	1.14 (0.64 ,2.04)
33	TP63	Block 1	rs6790068-rs9681004			
34			A_A	0.595	H1	1.00
35			g_g	0.395	H2	1.08 (0.90 ,1.29)
36			HRare	0.010	HRare	0.17 (0.02 ,1.28)
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For Peer Review

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MZL

Supplementary Table 4. Odds Ratios and 95% Confidence Intervals for estimated Haplotypes for BNHL and subtypes (adjusted for age (continuous), sex)

	Gene	Block	Haplotype	Frequency	hapname	MZL		
						OR	95% CI	p-value
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	BMF	Block 1	rs3923235-rs16970325 A_G g_G A_a HRare	0.624 0.268 0.109 0.000	H1	1.00		
					H2	1.03	(0.74 ,1.45)	0.8472
					H3	1.43	(0.87 ,2.36)	0.1560
					HRare	-	-	-
BMF	Block 2	rs12913170-rs7183977-rs998713-rs546220 G_A_A_a G_g_g_C a_A_A_C G_A_g_C HRare	0.418 0.331 0.151 0.060 0.040	H1	1.00			
				H2	0.95	(0.68 ,1.32)	0.7547	
				H3	0.85	(0.55 ,1.32)	0.4629	
				H4	1.84	(1.08 ,3.13)	0.0255	
				HRare	0.97	(0.48 ,1.97)	0.9383	
BMF	Block 3	rs648289-rs10518679 g_A A_A A_g HRare	0.450 0.417 0.132 0.001	H1	1.00			
				H2	1.06	(0.79 ,1.42)	0.7100	
				H3	0.85	(0.53 ,1.36)	0.4908	
				HRare	-	-	-	
BMF	Block 4	rs11634257-rs11858141-rs675173 A_g_G A_A_a t_A_G HRare	0.429 0.309 0.252 0.010	H1	1.00			
				H2	0.88	(0.63 ,1.25)	0.4833	
				H3	0.91	(0.64 ,1.30)	0.5982	
				HRare	0.37	(0.05 ,2.81)	0.3388	
BMF	Block 5	rs537455-rs11630670 A_G c_a A_a HRare	0.534 0.265 0.201 0.000	H1	1.00			
				H2	0.86	(0.59 ,1.25)	0.4273	
				H3	0.77	(0.52 ,1.15)	0.1969	
				HRare	-	-	-	
IFNGR1	Block 1	rs7759040-rs3799488-rs1327475 A_A_G A_A_a t_A_G t_g_G HRare	0.564 0.189 0.126 0.121 0.001	H1	1.00			
				H2	0.66	(0.43 ,1.00)	0.0523	
				H3	1.27	(0.85 ,1.88)	0.2393	
				H4	1.05	(0.68 ,1.61)	0.8299	
				HRare	-	-	-	
IFNG	Block 1	rs2069727-rs2069718 g_G A_a A_G HRare	0.482 0.375 0.142 0.000	H1	1.00			
				H2	0.94	(0.70 ,1.28)	0.7069	
				H3	0.98	(0.64 ,1.51)	0.9432	
				HRare	-	-	-	
IFNG	Block 2	rs2069716-rs6581795-rs12306852 A_A_C A_g_C A_A_g g_A_C HRare	0.509 0.264 0.155 0.072 0.001	H1	1.00			
				H2	0.97	(0.67 ,1.40)	0.8719	
				H3	0.97	(0.60 ,1.56)	0.8883	
				H4	0.73	(0.39 ,1.34)	0.3065	
				HRare	-	-	-	
IL10	Block 1	rs17015767-rs1800871-rs1800872-rs2222202-rs3021094-rs1554286-rs3024509-rs3024505-rs6673928-rs4844553-rs754837 G_G_C_G_A_G_A_G_C_G_C c_G_C_a_A_G_A_G_a_G_C G_G_C_a_A_G_A_a_C_G_C G_a_a_G_a_A_G_C_G_C G_G_C_a_A_G_g_G_C_a_a G_a_a_G_c_a_A_G_C_G_C HRare	0.309 0.194 0.149 0.125 0.070 0.064 0.090	H1	1.00			
				H2	0.96	(0.63 ,1.46)	0.8503	
				H3	1.30	(0.87 ,1.95)	0.1982	
				H4	0.83	(0.50 ,1.37)	0.4601	
				H5	1.12	(0.66 ,1.92)	0.6668	
				H6	0.92	(0.48 ,1.77)	0.8132	
				HRare	1.16	(0.69 ,1.95)	0.5654	
IL12A	Block 1	rs9811792-rs7372767-rs4680534-rs6441282-rs6800657-rs747825 g_g_A_C_A_C A_A_g_a_A_a A_A_g_A_A_C A_A_A_g_C A_A_A_C_A_C HRare	0.425 0.179 0.168 0.102 0.098 0.028	H1	1.00			
				H2	0.90	(0.60 ,1.36)	0.6200	
				H3	1.24	(0.83 ,1.85)	0.2897	
				H4	1.28	(0.80 ,2.05)	0.3006	
				H5	1.25	(0.77 ,2.02)	0.3607	
				HRare	1.09	(0.46 ,2.56)	0.8517	
IL12A	Block 2	rs2243115-rs583911-rs2243131-rs2243154-rs11927521 A_g_A_G_A A_A_A_G_g A_A_c_G_A c_A_A_G_g	0.354 0.274 0.155 0.112	H1	1.00			
				H2	0.74	(0.51 ,1.06)	0.1011	
				H3	1.03	(0.69 ,1.55)	0.8877	
				H4	0.76	(0.47 ,1.25)	0.2832	
				HRare	-	-	-	

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1								
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3			A_g_A_a_A	0.104	H5	0.58	(0.33 ,1.01)	0.0537
4			HRare	0.001	HRare			
5	IL12B	Block 1	rs4921466-rs4921468-rs6870828-rs3181225-rs1368439-rs11574790-rs2853694					
6			A_G_A_G_A_G_c	0.291	H1	1.00		
7			A_G_A_G_A_G_A	0.230	H2	1.07	(0.71 ,1.60)	0.7473
8			A_G_g_G_c_G_c	0.178	H3	1.34	(0.90 ,2.01)	0.1535
9			A_a_g_a_A_G_A	0.168	H4	1.19	(0.77 ,1.82)	0.4350
10			g_a_g_G_A_a_A	0.115	H5	1.03	(0.63 ,1.69)	0.9063
11			HRare	0.018	HRare	0.37	(0.09 ,1.56)	0.1751
12	IL12B	Block 2	rs2569253-rs3181216					
13			A_T	0.540	H1	1.00		
14			g_a	0.286	H2	0.93	(0.66 ,1.31)	0.6875
15			g_T	0.172	H3	1.00	(0.68 ,1.47)	0.9963
16			HRare	0.001	HRare			
17	IL12B	Block 3	rs1433048-rs2546893					
18			A_a	0.464	H1	1.00		
19			A_G	0.352	H2	1.06	(0.78 ,1.45)	0.7018
20			g_G	0.183	H3	1.30	(0.91 ,1.88)	0.1530
21			HRare	0.001	HRare			
22	IL12B	Block 4	rs2546890-rs10052709-rs7709212-rs6868898					
23			g_G_g_A	0.345	H1	1.00		
24			A_G_A_g	0.292	H2	1.08	(0.74 ,1.56)	0.6953
25			A_G_A_A	0.204	H3	1.31	(0.90 ,1.92)	0.1637
26			g_c_A_A	0.144	H4	1.07	(0.68 ,1.67)	0.7716
27			HRare	0.014	HRare	1.12	(0.32 ,3.87)	0.8586
28	IL7R	Block 1	rs11567694-rs11567697-rs11567701-rs6891095-rs3777090-rs11567762-rs10063294-rs10058453					
29			A_A_a_A_A_G_A_A	0.272	H1	1.00		
30			g_A_C_A_A_G_A_A	0.254	H2	1.06	(0.73 ,1.55)	0.7565
31			A_A_C_A_t_a_g_g	0.156	H3	1.53	(1.02 ,2.31)	0.0408
32			A_A_C_g_A_G_g_A	0.137	H4	0.79	(0.48 ,1.29)	0.3402
33			A_g_C_A_t_G_g_g	0.095	H5	0.81	(0.47 ,1.39)	0.4450
34			A_A_C_A_t_G_g_g	0.078	H6	0.68	(0.34 ,1.37)	0.2841
35			HRare	0.008	HRare	1.93	(0.57 ,6.54)	0.2933
36	IRF4	Block 1	rs9405192-rs1033180					
37			G_G	0.703	H1	1.00		
38			a_G	0.224	H2	1.22	(0.88 ,1.68)	0.2332
39			a_a	0.074	H3	1.93	(1.22 ,3.06)	0.0049
40			HRare	0.000	HRare			
41	IRF4	Block 2	rs13208928-rs3778607					
42			T_G	0.500	H1	1.00		
43			T_a	0.429	H2	1.42	(1.07 ,1.88)	0.0166
44			a_a	0.070	H3	0.68	(0.34 ,1.35)	0.2691
45			HRare	0.001	HRare			
46	IRF4	Block 3	rs1050975-rs7768807					
47			A_A	0.667	H1	1.00		
48			A_g	0.246	H2	0.84	(0.58 ,1.22)	0.3639
49			g_A	0.086	H3	1.23	(0.73 ,2.08)	0.4402
50			HRare	0.001	HRare			
51	IRF4	Block 4	rs12211228-rs1877175-rs6906608					
52			G_G_C	0.780	H1	1.00		
53			c_a_a	0.147	H2	1.35	(0.94 ,1.95)	0.1076
54			G_a_C	0.072	H3	0.66	(0.36 ,1.21)	0.1812
55			HRare	0.002	HRare			
56	IRF4	Block 5	rs11757491-rs9378805					
57			G_C	0.476	H1	1.00		
58			G_A	0.456	H2	1.41	(1.06 ,1.89)	0.0195
59			a_A	0.068	H3	0.75	(0.39 ,1.44)	0.3943
60			HRare	0.000	HRare			
Jak1	Block 1	rs310211-rs2256298						
			A_G	0.676	H1	1.00		
			g_a	0.259	H2	0.76	(0.54 ,1.07)	0.1158
			g_G	0.065	H3	0.55	(0.26 ,1.14)	0.1076
			HRare	0.000	HRare			
LIG4	Block 1	rs915047-rs9514825						
			A_G	0.635	H1	1.00		
			A_a	0.201	H2	1.25	(0.88 ,1.77)	0.2108
			g_a	0.164	H3	1.28	(0.88 ,1.87)	0.1966

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		HRare	0.000	HRare			
5	LIG4	Block 2	rs868284-rs1151402-rs10131-rs3093772-rs3093748				
6			G_a_G_A_G	0.432	H1	1.00	
7			G_G_G_A_a	0.184	H2	0.98	(0.66 ,1.45)
8			G_G_G_A_G	0.142	H3	1.13	(0.74 ,1.73)
9			a_G_G_g_G	0.107	H4	0.96	(0.59 ,1.55)
10			G_G_a_A_G	0.092	H5	1.32	(0.80 ,2.16)
11			HRare	0.044	HRare	1.46	(0.77 ,2.77)
12	LIG4	Block 3	rs12428162-rs7322498-rs9520823				
13			C_A_A	0.353	H1	1.00	
14			C_A_c	0.283	H2	1.09	(0.73 ,1.62)
15	SOCS1	Block 1	rs193778-rs243317				
16			A_A	0.464	H1	1.00	
17			A_c	0.294	H2	0.85	(0.61 ,1.20)
18			g_A	0.241	H3	1.04	(0.74 ,1.47)
19	STAT1	Block 1	rs13035504-rs1168-rs12468579-rs1400657				
20			G_a_A_A	0.445	H1	1.00	
21			G_G_g_A	0.265	H2	1.21	(0.87 ,1.68)
22			c_G_g_A	0.171	H3	0.75	(0.48 ,1.16)
23			G_G_A_c	0.115	H4	1.00	(0.64 ,1.59)
24	STAT1	Block 2	rs16824035-rs13395505-rs17749316-rs2066804				
25			G_G_C_G	0.528	H1	1.00	
26			G_a_C_a	0.229	H2	1.17	(0.83 ,1.65)
27			a_a_C_G	0.172	H3	0.77	(0.50 ,1.18)
28			G_G_g_G	0.066	H4	0.90	(0.49 ,1.66)
29	STAT1	Block 3	rs432757-rs2280234-rs2280233				
30			A_G_g	0.455	H1	1.00	
31			A_a_A	0.377	H2	1.12	(0.84 ,1.52)
32			c_G_A	0.139	H3	0.71	(0.44 ,1.15)
33	STAT1	Block 4	rs7562024-rs34997637				
34			G_G	0.606	H1	1.00	
35			a_a	0.230	H2	1.18	(0.86 ,1.64)
36			a_G	0.164	H3	1.21	(0.83 ,1.76)
37	STAT1	Block 5	rs13029247-rs10173099-rs10199181				
38			A_G_T	0.616	H1	1.00	
39			g_a_a	0.315	H2	0.92	(0.68 ,1.25)
40			HRare	0.070	HRare	1.05	(0.60 ,1.84)
41	STAT1	Block 6	rs13029532-rs1467199-rs17817966				
42			A_C_A	0.563	H1	1.00	
43			A_g_g	0.234	H2	1.07	(0.76 ,1.51)
44			A_C_g	0.113	H3	0.73	(0.43 ,1.23)
45	STAT3	Block 1	rs1053023-rs1053005				
46			A_A	0.801	H1	1.00	
47			g_g	0.199	H2	0.64	(0.44 ,0.93)
48			HRare	0.000	HRare	-	-
49	STAT3	Block 2	rs4103200-rs9891119-rs9912773-rs12949918-rs17405722				
50			G_A_C_A_G	0.588	H1	1.00	
51			c_c_g_g_G	0.267	H2	0.64	(0.45 ,0.90)
52			G_c_C_g_a	0.065	H3	0.74	(0.40 ,1.34)
53	STAT4	Block 1	G_A_C_g_G	0.053	H4	0.87	(0.45 ,1.71)
54			HRare	0.027	HRare	1.14	(0.57 ,2.31)
55			rs13020076-rs16833177-rs7558921				
56			A_A_C	0.600	H1	1.00	
57			A_g_C	0.205	H2	0.99	(0.68 ,1.44)
58			A_A_g	0.113	H3	1.03	(0.66 ,1.60)
59			g_A_C	0.081	H4	0.32	(0.13 ,0.80)
60			HRare	0.000	HRare	-	-

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4	STAT4	Block 2	rs7574608-rs4853540					
5			A_C	0.766	H1	1.00		
6			A_a	0.170	H2	0.62	(0.40 ,0.96)	0.0339
7			t_a	0.062	H3	2.37	(0.95 ,5.95)	0.0652
8			HRare	0.002	HRare	-	-	
9	STAT4	Block 3	rs3024861-rs932169					
10			A_C	0.659	H1	1.00		
11			t_C	0.264	H2	1.09	(0.79 ,1.51)	0.5888
12			A_g	0.076	H3	0.91	(0.46 ,1.80)	0.7806
13			HRare	0.001	HRare	-	-	
14	STAT4	Block 4	rs10168266-rs2459611					
15			G_A	0.685	H1	1.00		
16			a_A	0.187	H2	1.10	(0.76 ,1.59)	0.6182
17			G_g	0.127	H3	0.86	(0.52 ,1.40)	0.5359
18			HRare	0.001	HRare	-	-	
19	STAT4	Block 5	rs7599504-rs4571082-rs17769459					
20			A_A_G	0.560	H1	1.00		
21			A_g_G	0.219	H2	1.13	(0.80 ,1.59)	0.4988
22			g_g_G	0.161	H3	1.19	(0.81 ,1.74)	0.3714
23			A_A_a	0.059	H4	1.12	(0.61 ,2.03)	0.7207
24			HRare	0.001	HRare	-	-	
25	STAT6	Block 1	rs3024979-rs703817-rs324015-rs3024974-rs3024971-rs324011					
26			A_a_G_G_A_a	0.358	H1	1.00		
27			A_G_a_G_A_G	0.232	H2	1.35	(0.94 ,1.95)	0.1028
28			t_a_G_G_A_G	0.114	H3	0.97	(0.60 ,1.57)	0.9134
29			A_G_G_G_c_G	0.114	H4	0.94	(0.56 ,1.55)	0.7999
30			A_G_G_a_A_G	0.087	H5	0.74	(0.42 ,1.31)	0.3075
31			A_G_G_G_A_G	0.067	H6	0.85	(0.44 ,1.65)	0.6313
32			HRare	0.028	HRare	0.77	(0.26 ,2.24)	0.6322
33	TP63	Block 1	rs6790068-rs9681004					
34			A_A	0.595	H1	1.00		
35			g_g	0.395	H2	0.92	(0.69 ,1.23)	0.5915
36			HRare	0.010	HRare	2.44	(0.89 ,6.70)	0.0840
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For Peer Review

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Supplementary Table 4. Odds Ratios and 95% Confidence Intervals for estimated Haplotypes for BNHL and subtypes (adjusted for age (continuous), sex)

	Gene	Block	Haplotype	Frequency	hapname	MCL		
						OR	95% CI	p-value
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	BMF	Block 1	rs3923235-rs16970325 A_G g_G A_a HRare	0.624 0.268 0.109 0.000	H1	1.00		
					H2	0.89	(0.54 ,1.46)	0.6439
					H3	0.66	(0.25 ,1.75)	0.4054
					HRare	-	-	-
BMF	Block 2	rs12913170-rs7183977-rs998713-rs546220 G_A_A_a G_g_C a_A_A_C G_A_g_C HRare	0.418 0.331 0.151 0.060 0.040	H1	1.00			
				H2	0.78	(0.48 ,1.28)	0.3247	
				H3	0.95	(0.53 ,1.71)	0.8596	
				H4	0.58	(0.17 ,1.97)	0.3857	
				HRare	0.84	(0.26 ,2.74)	0.7701	
				-	-	-	-	
BMF	Block 3	rs648289-rs10518679 g_A A_A A_g HRare	0.450 0.417 0.132 0.001	H1	1.00			
				H2	0.70	(0.44 ,1.11)	0.1266	
				H3	0.76	(0.35 ,1.65)	0.4802	
				HRare	-	-	-	
BMF	Block 4	rs11634257-rs11858141-rs675173 A_g_G A_A_a t_A_G HRare	0.429 0.309 0.252 0.010	H1	1.00			
				H2	0.97	(0.60 ,1.58)	0.9100	
				H3	0.81	(0.47 ,1.38)	0.4359	
				HRare	1.05	(0.13 ,8.42)	0.9645	
BMF	Block 5	rs537455-rs11630670 A_G c_a A_a HRare	0.534 0.265 0.201 0.000	H1	1.00			
				H2	1.06	(0.64 ,1.73)	0.8276	
				H3	0.71	(0.39 ,1.30)	0.2688	
				HRare	-	-	-	
IFNGR1	Block 1	rs7759040-rs3799488-rs1327475 A_A_G A_A_a t_A_G t_g_G HRare	0.564 0.189 0.126 0.121 0.001	H1	1.00			
				H2	0.83	(0.47 ,1.45)	0.5129	
				H3	0.70	(0.20 ,2.42)	0.5708	
				H4	1.00	(0.52 ,1.95)	0.9922	
				HRare	-	-	-	
IFNG	Block 1	rs2069727-rs2069718 g_G A_a A_G HRare	0.482 0.375 0.142 0.000	H1	1.00			
				H2	0.77	(0.48 ,1.25)	0.2932	
				H3	0.69	(0.34 ,1.41)	0.3111	
				HRare	-	-	-	
IFNG	Block 2	rs2069716-rs6581795-rs12306852 A_A_C A_g_C A_A_g g_A_C HRare	0.509 0.264 0.155 0.072 0.001	H1	1.00			
				H2	1.15	(0.69 ,1.94)	0.5920	
				H3	0.90	(0.40 ,2.05)	0.8052	
				H4	1.54	(0.73 ,3.26)	0.2577	
				HRare	-	-	-	
IL10	Block 1	rs17015767-rs1800871-rs1800872-rs2222202-rs3021094-rs1554286-rs3024509-rs3024505-rs6673928-rs4844553-rs754837 G_G_C_G_A_G_A_G_C_G_C c_G_C_a_A_G_A_G_a_G_C G_G_C_a_A_G_A_a_C_G_C G_a_a_G_a_A_G_C_G_C G_G_C_a_A_G_g_G_C_a_a G_a_a_G_c_a_A_G_C_G_C HRare	0.309 0.194 0.149 0.125 0.070 0.064 0.090	H1	1.00			
				H2	0.81	(0.46 ,1.41)	0.4538	
				H3	0.63	(0.33 ,1.22)	0.1731	
				H4	0.60	(0.28 ,1.30)	0.1956	
				H5	0.87	(0.37 ,2.04)	0.7521	
				H6	0.56	(0.19 ,1.65)	0.2917	
				HRare	0.52	(0.22 ,1.27)	0.1526	
IL12A	Block 1	rs9811792-rs7372767-rs4680534-rs6441282-rs6800657-rs747825 g_g_A_C_A_C A_A_g_a_A_a A_A_g_a_A_C A_A_A_a_g_C A_A_A_C_A_C HRare	0.425 0.179 0.168 0.102 0.098 0.028	H1	1.00			
				H2	0.96	(0.52 ,1.79)	0.9010	
				H3	1.63	(0.93 ,2.85)	0.0891	
				H4	1.42	(0.75 ,2.71)	0.2844	
				H5	1.14	(0.54 ,2.41)	0.7376	
				HRare	1.18	(0.28 ,5.09)	0.8207	
IL12A	Block 2	rs2243115-rs583911-rs2243131-rs2243154-rs11927521 A_g_A_G_A A_A_A_G_g A_A_c_G_A c_A_A_G_g	0.354 0.274 0.155 0.112	H1	1.00			
				H2	1.15	(0.68 ,1.93)	0.6083	
				H3	1.18	(0.65 ,2.11)	0.5884	
				H4	0.87	(0.41 ,1.83)	0.7100	
				-	-	-	-	

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2								
3			A_g_A_a_A	0.104	H5	0.54	(0.21 ,1.42)	0.2101
4			HRare	0.001	HRare			
5	IL12B	Block 1	rs4921466-rs4921468-rs6870828-rs3181225-rs1368439-rs11574790-rs2853694					
6			A_G_A_G_A_G_c	0.291	H1	1.00		
7			A_G_A_G_A_G_A	0.230	H2	0.92	(0.50 ,1.69)	0.7913
8			A_G_g_G_c_G_c	0.178	H3	1.03	(0.56 ,1.89)	0.9236
9			A_a_g_a_A_G_A	0.168	H4	1.20	(0.65 ,2.19)	0.5634
10			g_a_g_G_A_a_A	0.115	H5	0.97	(0.46 ,2.06)	0.9453
11			HRare	0.018	HRare			
12	IL12B	Block 2	rs2569253-rs3181216					
13			A_T	0.540	H1	1.00		
14			g_a	0.286	H2	1.07	(0.67 ,1.72)	0.7804
15			g_T	0.172	H3	1.20	(0.69 ,2.08)	0.5214
16			HRare	0.001	HRare			
17	IL12B	Block 3	rs1433048-rs2546893					
18			A_a	0.464	H1	1.00		
19			A_G	0.352	H2	0.82	(0.49 ,1.37)	0.4489
20			g_G	0.183	H3	1.04	(0.57 ,1.89)	0.8948
21			HRare	0.001	HRare			
22	IL12B	Block 4	rs2546890-rs10052709-rs7709212-rs6868898					
23			g_G_g_A	0.345	H1	1.00		
24			A_G_A_g	0.292	H2	1.15	(0.68 ,1.95)	0.5893
25			A_G_A_A	0.204	H3	1.12	(0.61 ,2.05)	0.7169
26			g_c_A_A	0.144	H4	0.96	(0.47 ,1.96)	0.9005
27			HRare	0.014	HRare	1.12	(0.14 ,8.96)	0.9130
28	IL7R	Block 1	rs11567694-rs11567697-rs11567701-rs6891095-rs3777090-rs11567762-rs10063294-rs10058453					
29			A_A_a_A_A_G_A_A	0.272	H1	1.00		
30			g_A_C_A_A_G_A_A	0.254	H2	1.24	(0.71 ,2.18)	0.4478
31			A_A_C_A_t_a_g_g	0.156	H3	1.33	(0.70 ,2.51)	0.3807
32			A_A_C_g_A_G_g_A	0.137	H4	1.54	(0.78 ,3.02)	0.2123
33			A_g_C_A_t_G_g_g	0.095	H5	1.02	(0.46 ,2.28)	0.9521
34			A_A_C_A_t_G_g_g	0.078	H6	0.82	(0.31 ,2.20)	0.6975
35			HRare	0.008	HRare			
36	IRF4	Block 1	rs9405192-rs1033180					
37			G_G	0.703	H1	1.00		
38			a_G	0.224	H2	1.29	(0.79 ,2.08)	0.3062
39			a_a	0.074	H3	1.37	(0.65 ,2.91)	0.4044
40			HRare	0.000	HRare			
41	IRF4	Block 2	rs13208928-rs3778607					
42			T_G	0.500	H1	1.00		
43			T_a	0.429	H2	0.93	(0.61 ,1.43)	0.7352
44			a_a	0.070	H3	1.29	(0.60 ,2.75)	0.5143
45			HRare	0.001	HRare			
46	IRF4	Block 3	rs1050975-rs7768807					
47			A_A	0.667	H1	1.00		
48			A_g	0.246	H2	1.30	(0.81 ,2.10)	0.2724
49			g_A	0.086	H3	1.48	(0.68 ,3.20)	0.3206
50			HRare	0.001	HRare			
51	IRF4	Block 4	rs12211228-rs1877175-rs6906608					
52			G_G_C	0.780	H1	1.00		
53			c_a_a	0.147	H2	0.62	(0.30 ,1.28)	0.1949
54			G_a_C	0.072	H3	1.22	(0.60 ,2.51)	0.5820
55			HRare	0.002	HRare			0.9893
56	IRF4	Block 5	rs11757491-rs9378805					
57			G_C	0.476	H1	1.00		
58			G_A	0.456	H2	0.94	(0.61 ,1.45)	0.7795
59			a_A	0.068	H3	1.31	(0.62 ,2.76)	0.4791
60			HRare	0.000	HRare			
Jak1	Block 1	rs310211-rs2256298						
			A_G	0.676	H1	1.00		
			g_a	0.259	H2	1.27	(0.80 ,2.01)	0.3202
			g_G	0.065	H3	1.76	(0.87 ,3.59)	0.1175
			HRare	0.000	HRare			
LIG4	Block 1	rs915047-rs9514825						
			A_G	0.635	H1	1.00		
			A_a	0.201	H2	1.20	(0.73 ,1.95)	0.4750
			g_a	0.164	H3	0.09	(0.01 ,0.65)	0.0169

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1			HRare	0.000	HRare	-	-	-	-
2									
3									
4									
5	LIG4	Block 2	rs868284-rs1151402-rs10131-rs3093772-rs3093748						
6			G_a_G_A_G	0.432	H1	1.00			
7			G_G_G_A_a	0.184	H2	0.44	(0.22	,0.87)	0.0181
8			G_G_G_A_G	0.142	H3	0.35	(0.15	,0.83)	0.0168
9			a_G_G_g_G	0.107	H4	0.60	(0.29	,1.27)	0.1841
10			G_G_a_A_G	0.092	H5	1.40	(0.77	,2.54)	0.2696
11			HRare	0.044	HRare	0.39	(0.09	,1.67)	0.2039
12	LIG4	Block 3	rs12428162-rs7322498-rs9520823						
13			C_A_A	0.353	H1	1.00			
14			C_A_c	0.283	H2	1.40	(0.82	,2.40)	0.2144
15			g_g_A	0.267	H3	0.66	(0.32	,1.38)	0.2739
16			C_g_A	0.097	H4	1.84	(0.98	,3.44)	0.0559
17			HRare	0.000	HRare	-	-	-	-
18	SOCS1	Block 1	rs193778-rs243317						
19			A_A	0.464	H1	1.00			
20			A_c	0.294	H2	0.92	(0.55	,1.53)	0.7413
21			g_A	0.241	H3	1.31	(0.76	,2.24)	0.3298
22			HRare	0.001	HRare	-	-	-	-
23	STAT1	Block 1	rs13035504-rs1168-rs12468579-rs1400657						
24			G_a_A_A	0.445	H1	1.00			
25			G_G_g_A	0.265	H2	1.08	(0.64	,1.80)	0.7791
26			c_G_g_A	0.171	H3	0.74	(0.40	,1.38)	0.3380
27			G_G_A_c	0.115	H4	0.84	(0.40	,1.77)	0.6510
28			HRare	0.004	HRare	-	-	-	-
29	STAT1	Block 2	rs16824035-rs13395505-rs17749316-rs2066804						
30			G_G_C_G	0.528	H1	1.00			
31			G_a_C_a	0.229	H2	0.91	(0.53	,1.56)	0.7252
32			a_a_C_G	0.172	H3	0.69	(0.37	,1.29)	0.2501
33			G_G_g_G	0.066	H4	0.75	(0.32	,1.77)	0.5094
34			HRare	0.005	HRare	-	-	-	-
35	STAT1	Block 3	rs432757-rs2280234-rs2280233						
36			A_G_g	0.455	H1	1.00			
37			A_a_A	0.377	H2	0.88	(0.55	,1.41)	0.5976
38			c_G_A	0.139	H3	0.83	(0.44	,1.57)	0.5613
39			HRare	0.029	HRare	0.30	(0.04	,2.22)	0.2387
40	STAT1	Block 4	rs7562024-rs34997637						
41			G_G	0.606	H1	1.00			
42			a_a	0.230	H2	0.76	(0.44	,1.31)	0.3253
43			a_G	0.164	H3	1.06	(0.59	,1.90)	0.8570
44			HRare	0.000	HRare	-	-	-	-
45	STAT1	Block 5	rs13029247-rs10173099-rs10199181						
46			A_G_T	0.616	H1	1.00			
47			g_a_a	0.315	H2	0.60	(0.37	,1.00)	0.0478
48			HRare	0.070	HRare	1.11	(0.50	,2.47)	0.7899
49	STAT1	Block 6	rs13029532-rs1467199-rs17817966						
50			A_C_A	0.563	H1	1.00			
51			A_g_g	0.234	H2	0.60	(0.35	,1.04)	0.0676
52			A_C_g	0.113	H3	0.40	(0.17	,0.95)	0.0388
53			c_C_g	0.089	H4	0.62	(0.26	,1.46)	0.2728
54	STAT3	Block 1	rs1053023-rs1053005						
55			A_A	0.801	H1	1.00			
56			g_g	0.199	H2	1.27	(0.79	,2.06)	0.3235
57			HRare	0.000	HRare	-	-	-	-
58	STAT3	Block 2	rs4103200-rs9891119-rs9912773-rs12949918-rs17405722						
59			G_A_C_A_G	0.588	H1	1.00			
60			c_c_g_g_G	0.267	H2	1.57	(0.99	,2.47)	0.0530
			G_c_C_g_a	0.065	H3	1.62	(0.75	,3.50)	0.2230
			G_A_C_g_G	0.053	H4	0.68	(0.20	,2.26)	0.5259
			HRare	0.027	HRare	1.07	(0.25	,4.51)	0.9282
54	STAT4	Block 1	rs13020076-rs16833177-rs7558921						
55			A_A_C	0.600	H1	1.00			
56			A_g_C	0.205	H2	0.65	(0.35	,1.20)	0.1687
57			A_A_g	0.113	H3	0.73	(0.35	,1.51)	0.3947
58			g_A_C	0.081	H4	0.55	(0.21	,1.43)	0.2163
59			HRare	0.000	HRare	-	-	-	-

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3									
4	STAT4	Block 2	rs7574608-rs4853540						
5		A_C		0.766	H1	1.00			
6		A_a		0.170	H2	0.91	(0.51 ,1.62)	0.7404	
7		t_a		0.062	H3	1.81	(0.47 ,6.94)	0.3839	
8		HRare		0.002	HRare	-	-		
9	STAT4	Block 3	rs3024861-rs932169						
10		A_C		0.659	H1	1.00			
11		t_C		0.264	H2	0.68	(0.39 ,1.19)	0.1742	
12		A_g		0.076	H3	1.00	(0.45 ,2.23)	0.9914	
13		HRare		0.001	HRare	-	-		
14	STAT4	Block 4	rs10168266-rs2459611						
15		G_A		0.685	H1	1.00			
16		a_A		0.187	H2	0.71	(0.39 ,1.29)	0.2610	
17		G_g		0.127	H3	0.71	(0.33 ,1.52)	0.3778	
18		HRare		0.001	HRare	-	-		
19	STAT4	Block 5	rs7599504-rs4571082-rs17769459						
20		A_A_G		0.560	H1	1.00			
21		A_g_G		0.219	H2	1.04	(0.62 ,1.75)	0.8882	
22		g_g_G		0.161	H3	0.91	(0.42 ,1.97)	0.8021	
23		A_A_a		0.059	H4	1.12	(0.51 ,2.47)	0.7849	
24		HRare		0.001	HRare	-	-		
25	STAT6	Block 1	rs3024979-rs703817-rs324015-rs3024974-rs3024971-rs324011						
26		A_a_G_G_A_a		0.358	H1	1.00			
27		A_G_a_G_A_G		0.232	H2	0.62	(0.33 ,1.17)	0.1399	
28		t_a_G_G_A_G		0.114	H3	1.17	(0.60 ,2.30)	0.6421	
29		A_G_G_G_c_G		0.114	H4	0.90	(0.42 ,1.94)	0.7938	
30		A_G_G_a_A_G		0.087	H5	0.96	(0.45 ,2.08)	0.9271	
31		A_G_G_G_A_G		0.067	H6	1.84	(0.84 ,4.02)	0.1253	
32		HRare		0.028	HRare	1.85	(0.67 ,5.16)	0.2375	
33	TP63	Block 1	rs6790068-rs9681004						
34		A_A		0.595	H1	1.00			
35		g_g		0.395	H2	1.06	(0.69 ,1.63)	0.7873	
36		HRare		0.010	HRare	1.03	(0.13 ,8.18)	0.9789	
37									
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For Peer Review

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Supplementary Table 4. Odds Ratios and 95% Confidence Intervals for estimated Haplotypes for HL (adjusted for age (continuous), sex and study center)

Gene	Block	Haplotype	Frequency	Hapname	HL		
					OR	95% CI	p-value
BMF	Block 1	rs3923235-rs16970325					
		A_G	0.628	H1	1.00		
		g_G	0.271	H2	1.33	(1.03 ,1.72)	0.0282
		A_a	0.101	H3	1.67	(1.12 ,2.48)	0.0119
BMF	Block 2	HRare	0.000	HRare	-	-	
		rs12913170-rs7183977-rs998713-rs546220					
		G_A_A_a	0.418	H1	1.00		
		G_g_g_C	0.335	H2	1.31	(1.03 ,1.67)	0.0296
		a_A_A_C	0.151	H3	0.99	(0.72 ,1.37)	0.9593
		G_A_g_C	0.056	H4	1.25	(0.79 ,1.97)	0.3354
		HRare	0.040	HRare	1.28	(0.77 ,2.12)	0.3367
BMF	Block 3	rs648289-rs10518679					
		g_A	0.450	H1	1.00		
		A_A	0.413	H2	1.40	(1.11 ,1.75)	0.0040
		A_g	0.136	H3	1.07	(0.76 ,1.49)	0.7089
BMF	Block 4	HRare	0.001	HRare	-	-	
		rs11634257-rs11858141-rs675173					
		A_g_G	0.424	H1	1.00		
		A_A_a	0.313	H2	1.03	(0.80 ,1.32)	0.8255
BMF	Block 5	t_A_G	0.254	H3	1.05	(0.81 ,1.36)	0.7258
		HRare	0.010	HRare	0.65	(0.21 ,2.07)	0.4692
		rs537455-rs11630670					
BMF	Block 5	A_G	0.538	H1	1.00		
		c_a	0.265	H2	0.99	(0.76 ,1.29)	0.9497
		A_a	0.197	H3	0.78	(0.58 ,1.05)	0.1030
		HRare	0.000	HRare	-	-	
IFNGR1	Block 1	rs7759040-rs3799488-rs1327475					
		A_A_G	0.563	H1	1.00		
		A_A_a	0.182	H2	0.96	(0.72 ,1.29)	0.7904
		t_A_G	0.129	H3	0.92	(0.66 ,1.28)	0.6286
		t_g_G	0.125	H4	0.83	(0.60 ,1.15)	0.2624
IFNG	Block 1	HRare	0.001	HRare	-	-	
		rs2069727-rs2069718					
		g_G	0.467	H1	1.00		
		A_a	0.388	H2	1.34	(1.07 ,1.68)	0.0119
IFNG	Block 2	A_G	0.144	H3	1.13	(0.79 ,1.59)	0.5045
		HRare	0.000	HRare	-	-	
		rs2069716-rs6581795-rs12306852					
		A_A_C	0.496	H1	1.00		
IFNG	Block 2	A_g_C	0.278	H2	1.48	(1.12 ,1.94)	0.0054
		A_A_g	0.157	H3	1.21	(0.86 ,1.71)	0.2756
		g_A_C	0.069	H4	0.85	(0.52 ,1.38)	0.5112
		HRare	0.000	HRare	-	-	
IL10	Block 1	rs17015767-rs1800871-rs1800872-rs2222202-rs3021094-rs1554286-rs3024509-rs3024505-rs6673928-rs4844553-rs7548373					
		G_G_C_G_A_G_A_G_C_G_C	0.309	H1	1.00		
		c_G_C_a_A_G_A_G_a_G_C	0.194	H2	0.86	(0.63 ,1.16)	0.3175
		G_G_C_a_A_G_A_a_C_G_C	0.152	H3	1.02	(0.74 ,1.41)	0.9004
		G_a_a_G_A_a_A_G_C_G_C	0.128	H4	1.14	(0.82 ,1.60)	0.4332
		G_G_C_a_A_G_g_G_C_a_a	0.066	H5	0.71	(0.44 ,1.15)	0.1663
		G_a_a_G_c_a_A_G_C_G_C	0.065	H6	0.89	(0.56 ,1.40)	0.6156
		HRare	0.085	HRare	0.71	(0.46 ,1.08)	0.1091
IL12A	Block 1	rs9811792-rs7372767-rs4680534-rs6441282-rs6800657-rs747825					
		g_g_A_C_A_C	0.413	H1	1.00		
		A_A_g_a_A_a	0.189	H2	0.91	(0.68 ,1.21)	0.5162
		A_A_g_a_A_C	0.161	H3	0.89	(0.65 ,1.22)	0.4695
		A_A_A_a_g_C	0.107	H4	0.87	(0.61 ,1.25)	0.4516
		A_A_A_C_A_C	0.105	H5	1.15	(0.81 ,1.64)	0.4285
IL12A	Block 2	HRare	0.026	HRare	1.20	(0.67 ,2.15)	0.5445
		rs2243115-rs583911-rs2243131-rs2243154-rs11927521					
		A_g_A_G_A	0.355	H1	1.00		
		A_A_A_G_g	0.270	H2	1.09	(0.84 ,1.42)	0.5111
IL12A	Block 2	A_A_c_G_A	0.161	H3	0.94	(0.69 ,1.28)	0.6810
		c_A_A_G_g	0.122	H4	0.91	(0.64 ,1.29)	0.5950
		A_g_A_a_A	0.092	H5	0.94	(0.64 ,1.39)	0.7592
		HRare	0.001	HRare	3.54	(0.34 ,36.59)	0.2889
IL12B	Block 1	rs4921466-rs4921468-rs6870828-rs3181225-rs1368439-rs11574790-rs2853694					
		A_G_A_G_A_G_c	0.313	H1	1.00		
		A_G_A_G_A_G_A	0.213	H2	0.81	(0.61 ,1.09)	0.1624

1										
2										
3			A_a_g_a_A_G_A	0.179	H3	1.08	(0.80 ,1.46)	0.6107		
4			g_a_g_G_A_a_A	0.169	H4	0.81	(0.59 ,1.11)	0.1953		
5			HRare	0.108	H5	0.83	(0.57 ,1.21)	0.3370		
6		IL12B	Block 2	rs2569253-rs3181216	0.017	HRare	0.67	(0.27 ,1.71)	0.4063	
7			A_T							
8			g_a	0.514	H1	1.00				
9			g_T	0.309	H2	1.12	(0.88 ,1.41)	0.3665		
10			HRare	0.175	H3	0.80	(0.59 ,1.08)	0.1424		
11		IL12B	Block 3	rs1433048-rs2546893	0.001	HRare	-	-		
12			A_a							
13			A_G	0.481	H1	1.00				
14			g_G	0.333	H2	0.90	(0.71 ,1.13)	0.3636		
15			HRare	0.185	H3	1.05	(0.79 ,1.39)	0.7400		
16		IL12B	Block 4	rs2546890-rs10052709-rs7709212-rs6868898	0.001	HRare	-	-		
17			g_G_g_A							
18			A_G_A_g	0.328	H1	1.00				
19		IL7R	Block 1	rs11567694-rs11567697-rs11567701-rs6891095-rs3777090-rs11567762-rs10063294-rs10058453	0.276	H1	1.00			
20			A_A_a_A_A_G_A_A	0.250	H2	0.98	(0.73 ,1.30)	0.8687		
21			A_A_C_A_A_G_A_A	0.152	H3	1.18	(0.86 ,1.62)	0.3087		
22			A_A_C_A_t_a_g_g	0.132	H4	0.85	(0.60 ,1.22)	0.3829		
23			A_A_C_g_A_G_g_A	0.104	H5	1.06	(0.73 ,1.53)	0.7665		
24			A_g_C_A_t_G_g_g	0.077	H6	0.94	(0.62 ,1.42)	0.7560		
25		IRF4	Block 1	rs9405192-rs1033180	0.009	HRare	0.44	(0.12 ,1.59)	0.2085	
26			G_G							
27			a_G	0.707	H1	1.00				
28			a_a	0.221	H2	1.06	(0.83 ,1.37)	0.6244		
29		IRF4	Block 2	rs13208928-rs3778607	0.072	H3	1.11	(0.73 ,1.69)	0.6176	
30			HRare	0.000	HRare	-	-			
31			T_G							
32		IRF4	Block 3	rs13208928-rs3778607	0.502	H1	1.00			
33			T_a	0.426	H2	1.09	(0.88 ,1.35)	0.4395		
34			a_a	0.070	H3	0.85	(0.56 ,1.30)	0.4579		
35		IRF4	Block 4	rs1050975-rs7768807	0.001	HRare	2.17	(0.13 ,36.12)	0.5899	
36			HRare							
37		IRF4	Block 4	rs12211228-rs1877175-rs6906608	0.659	H1	1.00			
38			A_A	0.256	H2	1.25	(0.98 ,1.60)	0.0757		
39			A_g	0.085	H3	1.13	(0.72 ,1.77)	0.5898		
40		IRF4	Block 5	rs1050975-rs7768807	0.000	HRare	-	-		
41			g_A							
42			HRare							
43		Jak1	Block 1	rs12211228-rs1877175-rs6906608	0.777	H1	1.00			
44			G_G_C	0.148	H2	0.92	(0.68 ,1.24)	0.5990		
45			c_a_a	0.073	H3	0.91	(0.61 ,1.35)	0.6332		
46			G_a_C	0.001	HRare	-	-			
47		LIG4	Block 1	rs11757491-rs9378805	0.777	H1	1.00			
48			G_c	0.474	H2	1.29	(1.03 ,1.60)	0.0242		
49			G_A	0.455	H3	1.01	(0.65 ,1.55)	0.9818		
50			a_A	0.070	HRare	-	-			
51			HRare	0.001	HRare	-	-			
52		LIG4	Block 1	rs915047-rs9514825	0.673	H1	1.00			
53			A_G	0.261	H2	0.91	(0.71 ,1.16)	0.4424		
54			g_a	0.066	H3	0.69	(0.44 ,1.09)	0.1106		
55		LIG4	Block 2	rs915047-rs9514825	0.000	HRare	-	-		
56			A_a							
57			g_G							
58			HRare							
59		LIG4	Block 3	rs868284-rs1151402-rs10131-rs3093772-rs3093748	0.648	H1	1.00			
60			G_a_G_A_G	0.196	H2	1.08	(0.81 ,1.43)	0.5832		
			G_G_G_A_a	0.137	H3	1.08	(0.78 ,1.48)	0.6509		
			G_G_G_A_G	0.106	H4	1.12	(0.79 ,1.59)	0.5135		
			a_G_G_g_G	0.088	H5	1.05	(0.72 ,1.55)	0.7974		
			G_G_a_A_G	0.042	HRare	0.81	(0.44 ,1.48)	0.4933		
			HRare							
			C_A_A	0.345	H1	1.00				

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3		C_A_c	0.288	H2	1.02	(0.75 ,1.38)	0.9231		
4		g_g_A	0.275	H3	1.23	(0.91 ,1.66)	0.1738		
5		C_g_A	0.091	H4	1.10	(0.75 ,1.62)	0.6090		
6		HRare	0.000	HRare	-	-	-		
7	SOCS1	Block 1	rs193778-rs243317						
8		A_A	0.466	H1	1.00				
9		A_c	0.294	H2	0.84	(0.64 ,1.09)	0.1922		
10		g_A	0.240	H3	0.96	(0.71 ,1.30)	0.7866		
11		HRare	0.001	HRare	-	-	-		
12	STAT1	Block 1	rs13035504-rs1168-rs12468579-rs1400657						
13		G_a_A_A	0.460	H1	1.00				
14		G_G_g_A	0.264	H2	0.91	(0.70 ,1.18)	0.4742		
15		c_G_g_A	0.158	H3	1.01	(0.74 ,1.37)	0.9525		
16		G_G_A_c	0.113	H4	0.89	(0.63 ,1.26)	0.4980		
17		HRare	0.004	HRare	1.95	(0.46 ,8.26)	0.3669		
18	STAT1	Block 2	rs16824035-rs13395505-rs17749316-rs2066804						
19		G_G_C_G	0.532	H1	1.00				
20		G_a_C_a	0.229	H2	0.91	(0.70 ,1.18)	0.4819		
21		a_a_C_G	0.159	H3	1.02	(0.76 ,1.37)	0.9037		
22		G_G_g_G	0.072	H4	1.17	(0.78 ,1.75)	0.4496		
23		HRare	0.007	HRare	0.51	(0.11 ,2.48)	0.4082		
24	STAT1	Block 3	rs432757-rs2280234-rs2280233						
25		A_G_g	0.468	H1	1.00				
26		A_a_A	0.373	H2	0.93	(0.74 ,1.17)	0.5489		
27		c_G_A	0.129	H3	0.97	(0.70 ,1.35)	0.8508		
28		HRare	0.030	HRare	0.93	(0.51 ,1.70)	0.8125		
29	STAT1	Block 4	rs7562024-rs34997637						
30		G_G	0.608	H1	1.00				
31		a_a	0.233	H2	0.89	(0.69 ,1.15)	0.3684		
32		a_G	0.159	H3	1.03	(0.78 ,1.37)	0.8278		
33		HRare	0.000	HRare	-	-	-		
34	STAT1	Block 5	rs13029247-rs10173099-rs10199181						
35		A_G_T	0.619	H1	1.00				
36		g_a_a	0.317	H2	0.92	(0.73 ,1.16)	0.4978		
37		HRare	0.064	HRare	1.06	(0.69 ,1.63)	0.8073		
38	STAT1	Block 6	rs13029532-rs1467199-rs17817966						
39		A_C_A	0.567	H1	1.00				
40		A_g_g	0.231	H2	0.87	(0.66 ,1.13)	0.2914		
41		A_C_g	0.109	H3	1.01	(0.71 ,1.43)	0.9546		
42		c_C_g	0.093	H4	0.91	(0.56 ,1.46)	0.6861		
43		HRare	0.000	HRare	-	-	-		
44	STAT3	Block 1	rs1053023-rs1053005						
45		A_A	0.787	H1	1.00				
46		g_g	0.213	H2	0.83	(0.64 ,1.08)	0.1628		
47		HRare	0.000	HRare	-	-	-		
48	STAT3	Block 2	rs4103200-rs9891119-rs9912773-rs12949918-rs17405722						
49		G_A_C_A_G	0.571	H1	1.00				
50		c_c_g_g_G	0.275	H2	0.72	(0.56 ,0.92)	0.0093		
51		G_c_C_g_a	0.069	H3	0.94	(0.62 ,1.43)	0.7835		
52		G_A_C_g_G	0.058	H4	1.01	(0.65 ,1.57)	0.9531		
53		HRare	0.027	HRare	0.70	(0.36 ,1.38)	0.3057		
54	STAT4	Block 1	rs13020076-rs16833177-rs7558921						
55		A_A_C	0.601	H1	1.00				
56		A_g_C	0.197	H2	0.87	(0.64 ,1.17)	0.3506		
57		A_A_g	0.123	H3	0.86	(0.60 ,1.23)	0.4046		
58		g_A_C	0.078	H4	0.93	(0.62 ,1.39)	0.7271		
59		HRare	0.000	HRare	-	-	-		
60	STAT4	Block 2	rs7574608-rs4853540						
61		A_C	0.774	H1	1.00				
62		A_a	0.156	H2	1.18	(0.89 ,1.55)	0.2448		
63		t_a	0.067	H3	1.11	(0.74 ,1.67)	0.6254		
64		HRare	0.003	HRare	0.28	(0.03 ,2.44)	0.2497		
65	STAT4	Block 3	rs3024861-rs932169						
66		A_C	0.647	H1	1.00				
67		t_C	0.270	H2	0.97	(0.77 ,1.24)	0.8203		
68		A_g	0.082	H3	1.06	(0.72 ,1.57)	0.7557		
69		HRare	0.001	HRare	-	-	-		
70	STAT4	Block 4	rs10168266-rs2459611						
71		G_A	0.688	H1	1.00				
72		a_A	0.191	H2	0.90	(0.67 ,1.21)	0.4917		
73		G_g	0.121	H3	1.12	(0.79 ,1.59)	0.5148		
74		HRare	0.000	HRare	-	-	-		

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4	STAT4	Block 5	rs7599504-rs4571082-rs17769459					
5		A_A_G		0.559	H1	1.00		
6		A_g_G		0.214	H2	0.96	(0.73 ,1.27)	0.7887
7		g_g_G		0.166	H3	1.07	(0.78 ,1.47)	0.6898
8		A_A_a		0.060	H4	1.19	(0.77 ,1.84)	0.4414
9		HRare		0.001	HRare	-	-	-
10	STAT6	Block 1	rs3024979-rs703817-rs324015-rs3024974-rs3024971-rs324011					
11		A_a_G_G_A_a		0.362	H1	1.00		
12		A_G_a_G_A_G		0.235	H2	1.43	(1.08 ,1.88)	0.0110
13		t_a_G_G_A_G		0.111	H3	1.10	(0.77 ,1.56)	0.6076
14		A_G_G_G_c_G		0.108	H4	1.12	(0.76 ,1.64)	0.5635
15		A_G_G_a_A_G		0.098	H5	1.06	(0.72 ,1.55)	0.7817
16		A_G_G_G_A_G		0.059	H6	1.49	(0.95 ,2.33)	0.0817
17		HRare		0.026	HRare	0.71	(0.33 ,1.56)	0.3978
18	TP63	Block 1	rs6790068-rs9681004					
19		A_A		0.588	H1	1.00		
20		g_g		0.403	H2	1.37	(1.11 ,1.69)	0.0033
21		HRare		0.009	HRare	0.79	(0.22 ,2.89)	0.7262
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For Peer Review

Gene	rs Number	no. of no calls	BNHL (below 50)												Dominant Model	p-value	p-trend			
			Heterozygous Mutant				Homozygous Mutant													
			OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value						
BMF	rs10518679	0	0.85 (0.56)	1.27*	0.4216	0.87 (0.19)	4.02*	0.8807	0.85 (0.57)	1.26*	0.4167	0.85 (0.57)	1.26*	0.4167	0.4254					
	rs11630670	0	1.03 (0.67)	1.57*	0.9076	0.80 (0.49)	1.33*	0.3953	0.95 (0.63)	1.42*	0.7971	0.4132								
	rs11634257	1	1.07 (0.74)	1.56*	0.7185	1.19 (0.58)	2.41*	0.6382	1.09 (0.76)	1.56*	0.6379	0.5903								
	rs11858141	2	0.84 (0.56)	1.24*	0.3795	0.94 (0.56)	1.59*	0.8262	0.86 (0.59)	1.26*	0.4423	0.6778								
	rs12913170	2	1.29 (0.87)	1.92*	0.2020	0.73 (0.37)	3.16*	0.6739	1.26 (0.85)	1.95*	0.2500	0.3549								
	rs1540686	22	0.78 (0.52)	1.19*	0.2472	0.93 (0.57)	1.49*	0.7542	0.83 (0.57)	1.22*	0.3448	0.6829								
	rs16970349	2	0.97 (0.62)	1.49*	0.8732	-	-	-	1.07 (0.70)	1.64*	0.7685	0.4239								
	rs1743129	2	0.62 (0.41)	0.93*	0.0212	1.11 (0.67)	1.84*	0.6962	0.73 (0.50)	1.07*	0.1122	0.9273								
	rs3923235	0	0.85 (0.58)	1.23*	0.3856	1.10 (0.53)	2.29*	0.8026	0.88 (0.61)	1.26*	0.4877	0.6394								
	rs373455	1	0.76 (0.52)	1.10	0.1507	1.38 (0.71)	2.70*	0.3397	0.84 (0.59)	1.20*	0.3427	0.8710								
	rs546220	5	1.07 (0.72)	1.59*	0.7425	0.92 (0.56)	1.52*	0.7450	1.02 (0.70)	1.48*	0.9102	0.8308								
	rs588739	0	0.63 (0.42)	0.95*	0.0258	0.92 (0.55)	1.55*	0.7654	0.70 (0.48)	1.02*	0.0662	0.4260								
	rs648289	1	0.87 (0.58)	1.31*	0.5147	0.93 (0.58)	1.50*	0.7667	0.89 (0.62)	1.30*	0.5522	0.7081								
	rs652196	3	1.28 (0.88)	1.86*	0.1914	1.13 (0.50)	2.56*	0.7660	1.26 (0.88)	1.81*	0.2025	0.2785								
	rs675173	6	0.90 (0.62)	1.31*	0.5948	1.23 (0.66)	2.29*	0.5064	0.96 (0.67)	1.36*	0.8037	0.8329								
	rs7183977	2	0.88 (0.60)	1.28*	0.4972	0.86 (0.48)	1.55*	0.6258	0.87 (0.61)	1.25*	0.4566	0.4918								
	rs998713	6	0.91 (0.62)	1.34*	0.6193	1.12 (0.66)	1.88*	0.6775	0.96 (0.67)	1.38*	0.8169	0.8521								
CASP6	rs1541373	1	1.02 (0.69)	1.51*	0.9211	0.95 (0.56)	1.67*	0.8678	1.01 (0.69)	1.46*	0.9760	0.9212								
	rs1800627	3	0.87 (0.57)	1.33*	0.5266	0.67 (0.40)	2.05*	0.1130	0.80 (0.54)	1.19*	0.2700	0.1182								
	rs3181345	0	1.31 (0.84)	2.05*	0.2274	-	-	-	1.47 (0.96)	2.27*	0.0796	0.0233								
	rs3212153	1	0.98 (0.64)	1.50*	0.9120	0.52 (0.13)	2.05*	0.3471	0.93 (0.61)	1.41*	0.7324	0.5618								
	rs3030552	1	1.81 (1.12)	2.92*	0.0157	6.84 (0.79)	59.545	0.0813	1.94 (1.22)	3.11*	0.0054	0.0029								
	rs676063	0	0.85 (0.39)	1.84*	0.6765	-	-	-	0.92 (0.43)	1.96*	0.8312	0.9974								
IFNG1	rs12306852	0	0.86 (0.57)	1.29*	0.4552	1.26 (0.47)	3.40*	0.6431	0.89 (0.60)	1.32*	0.5768	0.7757								
	rs2069716	0	1.54 (0.92)	2.57*	0.0104	0.42 (0.04)	4.11*	0.4536	1.44 (0.87)	2.37*	0.1543	0.2607								
	rs2069718	8	1.08 (0.73)	1.59*	0.6977	1.50 (0.85)	2.65*	0.1607	1.16 (0.80)	1.67*	0.4309	0.2101								
	rs2069727	0	1.10 (0.72)	1.67*	0.6733	0.82 (0.50)	1.37*	0.4554	1.00 (0.67)	1.50*	0.9865	0.4913								
	rs6581795	1	1.28 (0.87)	1.87*	0.2110	1.08 (0.52)	2.26*	0.8331	1.25 (0.86)	1.79*	0.2393	0.3592								
IFNGR1	rs12529779	15	0.99 (0.67)	1.46*	0.9510	1.84 (0.80)	4.28*	0.1534	1.08 (0.74)	1.56*	0.6975	0.3866								
	rs327474	1	0.96 (0.65)	1.43*	0.8473	0.77 (0.46)	1.29*	0.3187	0.90 (0.62)	1.31*	0.5969	0.3566								
	rs327475	2	1.18 (0.79)	1.76*	0.4244	1.47 (0.59)	3.69*	0.4191	1.21 (0.83)	1.77*	0.3286	0.2832								
	rs8515415	6	1.04 (0.69)	1.57*	0.8401	0.81 (0.48)	1.35*	0.4165	0.97 (0.66)	1.42*	0.8782	0.4890								
	rs3799488	0	1.05 (0.69)	1.61*	0.8232	0.24 (0.03)	2.08*	0.1948	0.99 (0.65)	1.50*	0.9558	0.6972								
	rs477768	8	0.82 (0.54)	1.24*	0.3433	1.83 (0.42)	7.92*	0.4178	0.86 (0.57)	1.29*	0.4648	0.6631								
	rs46966243	4	0.94 (0.62)	1.43*	0.7786	1.07 (0.64)	1.76*	0.8046	0.98 (0.66)	1.45*	0.9119	0.8445								
	rs608914	4	1.10 (0.76)	1.60*	0.6000	0.97 (0.47)	2.01*	0.9296	1.09 (0.76)	1.55*	0.6535	0.7850								
	rs759040	0	0.97 (0.66)	1.41*	0.8534	1.07 (0.54)	2.11*	0.8520	0.98 (0.69)	1.40*	0.9193	0.9841								
IFNGR2	rs402877	3	0.89 (0.59)	1.32*	0.5534	0.96 (0.58)	1.60*	0.8784	0.91 (0.63)	1.32*	0.6103	0.7859								
	rs1515873	0	0.92 (0.59)	1.59*	0.0641	-	-	-	1.23 (0.93)	1.59*	0.0641	0.0641								
	rs6390664	0	1.48 (0.92)	2.05*	0.3672	0.87 (0.44)	1.73*	0.6982	1.12 (0.87)	1.60*	0.5335	0.8468								
	rs2014575	45	2.27 (1.02)	5.07*	0.0543	-	-	-	2.04 (1.02)	5.07*	0.0454	0.0454								
	rs284553	59	1.95 (0.88)	1.69*	0.0531	0.8401	1.48*	0.4165	0.97 (0.66)	1.42*	0.8782	0.4890								
	rs2834211	0	0.63 (0.40)	1.00*	0.0524	1.24 (0.24)	6.29*	0.7983	0.66 (0.42)	1.03*	0.0862	0.1143								
	rs2834214	1	1.08 (0.71)	1.63*	0.7260	0.87 (0.53)	1.41*	0.5946	1.09 (0.68)	1.46*	0.0931	0.6714								
	rs83131980	2	1.06 (0.72)	1.55*	0.7694	0.98 (0.53)	1.82*	0.9482	1.04 (0.73)	1.49*	0.8247	0.9164								
	rs9769711	0	0.76 (0.51)	1.31*	0.1772	0.97 (0.56)	1.67*	0.9037	0.80 (0.55)	1.17*	0.2580	0.6014								
	rs978166	0	1.24 (0.81)	1.88*	0.3186	0.40 (0.11)	1.51*	0.1775	1.13 (0.75)	1.69*	0.5631	0.9616								
IL10	rs15542486	2	0.95 (0.65)	1.40*	0.8018	2.98 (1.11)	7.99*	0.0305	1.08 (0.74)	1.56*	0.6931	0.2560								
	rs7017567	0	1.05 (0.72)	1.55*	0.7854	1.02 (0.40)	2.57*	0.9731	1.05 (0.72)	1.53*	0.7940	0.8260								
	rs1800871	9	0.92 (0.63)	1.34*	0.6719	1.26 (0.60)	2.66*	0.5433	0.96 (0.67)	1.38*	0.8453	0.9036								
	rs1800872	10	0.93 (0.64)	1.36*	0.7178	1.18 (0.57)	2.47*	0.6559	0.97 (0.59)	1.22*	0.8523	0.9517								
	rs2222202	9	1.06 (0.70)	1.59*	0.9798	0.93 (0.56)	1.55*	0.7834	1.02 (0.69)	1.50*	0.9305	0.8330								
	rs3021094	2	1.23 (0.76)	1.99*	0.3999	0.46 (0.09)	2.40*	0.3545	1.14 (0.72)	1.81*	0.5824	0.8281								
	rs324505	1	0.98 (0.65)	1.48*	0.9078	0.72 (0.23)	2.26*	0.5691	0.95 (0.64)	1.41*	0.7895	0.6845								
	rs3245050	0	0.88 (0.52)	1.47*	0.6174	1.92 (0.31)	11.85*	0.4825	0.92 (0.56)	1.52*	0.7590	0.9250								
	rs4390174	7	0.92 (0.63)	1.34*	0.6521	0.67 (0.37)	1.22*	0.1912	0.86 (0.60)	1.24*	0.4133	0.2307								
	rs8444553	1	0.90 (0.53)	1.52*	0.6941	1.92 (0.31)	11.87*	0.4811	0.95 (0.57)	1.58*	0.8410	0.9960								
	rs673928	8	1.14 (0.78)	1.67*	0.5010	0.67 (0.27)	1.68*	0.3906	1.08 (0.75)	1.56*	0.6862	0.9895								
	rs6868931	2	0.84 (0.58)	1.23*	0.3782	0.90 (0.42)	1.95*	0.7925	0.85 (0.59)	1.22*	0.3828	0.4526								
	rs7548373	22	0.96 (0.56)	1.62*	0.8714	1.29 (0.25)	6.60*	0.7584	0.98 (0.59)	1.63*	0.9430	0.9812								
IL12A	rs1927521	6	0.71 (0.49)	1.05*	0.0843	1.21 (0.67)	2.17*	0.5336	0.79 (0.55)	1.14*	0.2125	0.7669								
	rs2243115	4	0.80 (0.50)	1.27*	0.3370	1.75 (0.38)	8.02*	0.4732	0.84 (0.54)	1.32*	0.4578	0.6417								
	rs2243131	3	1.12 (0.76)	1.65*	0.5820	1.45 (0.43)	9.50*	0.5501	1.14 (0.78)	1.66*	0.5132	0.4573								
	rs2243154	0	0.73 (0.46)	1.16*	0.1789	1.72 (0.47)	6.24*	0.4125	0.79 (0.51)	1.23*	0.3018	0.5309								
	rs4680534	0	1.03 (0.70)	1.50*</																

3		rs6900384	14	0.67	(0.40	-1.13)	0.1341	0.63	(0.06	-7.09)	0.7048	0.67	(0.40	-1.12)	0.1259	0.1314
4		rs6906608	0	0.63	(0.41	-0.96)	0.0304	0.59	(0.19	-1.88)	0.3749	0.62	(0.41	-0.94)	0.0236	0.0293
5		rs7592905	0	1.00	(0.65	-1.53)	0.9563	1.23	(0.74	-2.03)	0.4203	1.07	(0.71	-1.59)	0.7501	0.4553
6		rs9405192	3	1.09	(0.75	-1.59)	0.6377	1.18	(0.68	-2.29)	0.6070	1.10	(0.77	-1.58)	0.5846	0.5489
7	JAK1	rs0789166	1	0.70	(0.46	-1.08)	0.0915	0.80	(0.29	-2.16)	0.6531	0.71	(0.48	-1.06)	0.0906	0.1276
8		rs2262308	0	1.16	(0.80	-1.69)	0.4248	1.35	(0.82	-2.92)	0.4505	1.19	(0.83	-1.70)	0.3618	0.3176
9		rs3102111	1	1.11	(0.76	-1.62)	0.5863	1.33	(0.72	-2.46)	0.3662	1.15	(0.80	-1.64)	0.4542	0.3544
10		rs7546535	39	1.12	(0.74	-1.68)	0.5925	1.21	(0.58	-2.55)	0.6142	1.14	(0.78	-1.66)	0.5128	0.4660
11	SOCS1	rs149311	3	1.52	(1.02	-2.26)	0.0386	1.41	(0.54	-3.71)	0.4807	1.51	(1.03	-2.21)	0.0351	0.0523
12		rs149597	2	1.34	(0.86	-2.10)	0.1914	1.67	(1.01	-2.76)	0.0437	1.45	(0.96	-2.20)	0.0789	0.0441
13		rs193778	1	0.82	(0.56	-1.20)	0.3005	0.99	(0.43	-2.29)	0.9775	0.84	(0.58	-1.21)	0.3397	0.4556
14		rs243317	1	0.97	(0.66	-1.41)	0.8547	1.19	(0.65	-2.18)	0.5698	1.01	(0.71	-1.44)	0.9695	0.7433
15		rs409665	28	0.83	(0.55	-1.25)	0.3694	1.18	(0.70	-1.99)	0.5237	0.91	(0.62	-1.35)	0.6518	0.6967
16	SOCS5	rs13402099	3	0.88	(0.57	-1.38)	0.5826	0.43	(0.08	-2.28)	0.3207	0.85	(0.55	-1.30)	0.4461	0.3437
17		rs13412085	0	1.08	(0.71	-1.66)	0.7122	0.28	(0.06	-1.33)	0.1088	0.98	(0.65	-1.49)	0.9373	0.5881
18	SOCS6	rs17082355	0	1.26	(0.80	-1.99)	0.3148	0.34	(0.07	-1.70)	0.1900	1.14	(0.74	-1.77)	0.5517	0.9160
19		rs17809666	1	1.29	(0.77	-2.16)	0.3320	-	-	-	-	1.25	(0.75	-2.09)	0.3906	0.4674
20		rs4891398	29	0.84	(0.56	-1.25)	0.3778	0.96	(0.57	-1.63)	0.8898	0.87	(0.60	-1.26)	0.4595	0.7181
21	STAT1	rs10173099	10	0.70	(0.48	-1.02)	0.0625	0.69	(0.38	-1.25)	0.2229	0.70	(0.48	-1.00)	0.0485	0.0772
22		rs10199181	2	0.86	(0.58	-1.26)	0.4380	0.77	(0.44	-1.35)	0.3629	0.84	(0.58	-1.21)	0.3464	0.3134
23	rs168	rs168	3	1.23	(0.82	-1.85)	0.3142	1.23	(0.74	-2.05)	0.4274	1.23	(0.84	-1.81)	0.2881	0.3725
24		rs2468579	1	0.95	(0.64	-1.43)	0.8146	0.76	(0.45	-1.28)	0.3054	0.90	(0.61	-1.31)	0.5740	0.3380
25		rs2693591	0	0.92	(0.61	-1.38)	0.6891	1.50	(0.44	-5.08)	0.5183	0.96	(0.64	-1.42)	0.8194	0.9958
26		rs3029247	2	0.69	(0.47	-1.01)	0.0564	0.63	(0.34	-1.17)	0.1453	0.68	(0.47	-0.97)	0.0350	0.0445
27		rs3029532	0	0.92	(0.58	-1.48)	0.7953	0.32	(0.03	-2.90)	0.3099	0.88	(0.55	-1.39)	0.5809	0.4480
28		rs3035504	1	0.94	(0.63	-1.39)	0.7459	1.37	(0.48	-3.89)	0.5548	0.97	(0.67	-1.42)	0.8796	0.9454
29		rs3395505	0	0.85	(0.58	-1.26)	0.4271	0.75	(0.44	-1.28)	0.2966	0.83	(0.57	-1.20)	0.3130	0.2654
30		rs400657	0	1.00	(0.64	-1.56)	0.9907	1.02	(0.27	-3.91)	0.9758	1.00	(0.65	-1.54)	0.9973	0.9952
31		rs467199	0	0.97	(0.66	-1.41)	0.8653	0.34	(0.12	-0.96)	0.0408	0.87	(0.60	-1.25)	0.4587	0.1698
32		rs547550	20	0.85	(0.58	-1.23)	0.3830	0.68	(0.45	-1.50)	0.5250	0.84	(0.59	-1.20)	0.3438	0.3755
33		rs6824035	1	0.88	(0.59	-1.30)	0.5212	1.34	(0.47	-3.79)	0.5872	0.91	(0.63	-1.34)	0.6455	0.8387
34		rs7749316	0	1.21	(0.71	-2.05)	0.4859	0.99	(0.06	-16.45)	0.9934	1.20	(0.71	-2.02)	0.4942	0.5165
35		rs7817966	0	0.81	(0.54	-1.21)	0.3015	0.58	(0.35	-0.99)	0.0462	0.74	(0.51	-1.09)	0.1240	0.0478
36		rs2066795	0	1.26	(0.35	-4.46)	0.7224	-	-	-	-	1.26	(0.35	-4.46)	0.7224	0.7224
37		rs2066804	1	0.84	(0.58	-1.23)	0.3739	0.63	(0.24	-1.66)	0.3532	0.82	(0.57	-1.18)	0.2893	0.2350
38		rs2280232	1	0.88	(0.60	-1.27)	0.4865	1.09	(0.55	-2.13)	0.8123	0.91	(0.64	-1.29)	0.5917	0.8050
39		rs2280233	4	1.32	(0.87	-2.01)	0.1924	1.29	(0.77	-2.15)	0.3285	1.31	(0.88	-1.95)	0.1797	0.2888
40		rs2280234	5	1.01	(0.69	-1.47)	0.9625	0.64	(0.35	-1.18)	0.1521	0.93	(0.64	-1.33)	0.6802	0.2876
41		rs34997637	3	0.86	(0.59	-1.25)	0.4246	0.50	(0.19	-1.36)	0.1763	0.82	(0.57	-1.18)	0.2753	0.1711
42		rs4327257	0	0.97	(0.65	-1.45)	0.8840	1.21	(0.38	-3.85)	0.7526	0.99	(0.67	-1.46)	0.9533	0.9530
43		rs4853533	3	0.79	(0.54	-1.15)	0.2098	0.70	(0.39	-1.26)	0.2352	0.77	(0.54	-1.10)	0.1485	0.1452
44		rs562024	0	1.25	(0.85	-1.84)	0.2508	0.66	(0.37	-1.19)	0.1679	1.10	(0.76	-1.58)	0.6230	0.5212
45		rs867637	2	0.86	(0.59	-1.25)	0.4383	0.70	(0.38	-1.30)	0.2627	0.83	(0.58	-1.19)	0.3279	0.2300
46		rs1053005	1	0.79	(0.54	-1.21)	0.2314	0.49	(0.18	-1.31)	0.1541	0.75	(0.51	-1.09)	0.1307	0.0841
47		rs1234919	1	1.13	(0.77	-1.67)	0.2314	0.49	(0.18	-1.31)	0.1541	0.75	(0.51	-1.09)	0.1307	0.0841
48		rs17405722	0	0.89	(0.52	-1.53)	0.6814	0.60	(0.35	-1.04)	0.0694	0.87	(0.67	-1.40)	0.8649	0.347
49		rs2293152	2	1.18	(0.79	-1.75)	0.4230	1.03	(0.60	-1.76)	0.9189	1.14	(0.78	-1.65)	0.5038	0.7504
50		rs4103200	0	1.02	(0.70	-1.49)	0.9259	0.64	(0.32	-1.30)	0.2171	0.94	(0.66	-1.35)	0.7497	0.4242
51		rs5039595	0	1.07	(0.73	-1.57)	0.7214	0.64	(0.35	-1.77)	0.1451	0.98	(0.67	-1.37)	0.8164	0.3391
52		rs8911119	0	1.01	(0.69	-1.49)	0.9400	0.61	(0.34	-1.12)	0.1108	0.91	(0.64	-1.31)	0.6183	0.2378
53		rs912773	0	1.06	(0.73	-1.54)	0.7739	0.64	(0.29	-1.39)	0.2612	0.99	(0.69	-1.41)	0.9353	0.5850
54	STAT3	rs10168266	0	0.86	(0.58	-1.28)	0.4628	1.46	(0.47	-4.50)	0.5119	0.90	(0.62	-1.32)	0.5896	0.7381
55		rs10189918	1	1.05	(0.71	-1.55)	0.8125	0.67	(0.31	-1.42)	0.2970	0.97	(0.67	-1.41)	0.8850	0.5724
56		rs10931481	0	0.84	(0.58	-1.22)	0.3678	0.76	(0.40	-1.44)	0.3991	0.83	(0.58	-1.18)	0.2934	0.2789
57		rs16856878	4	1.15	(0.78	-1.72)	0.4793	1.18	(0.70	-1.99)	0.5430	1.16	(0.80	-1.69)	0.4395	0.4839
58		rs13020076	56	0.70	(0.43	-1.31)	0.1446	1.20	(0.23	-6.19)	0.8311	0.72	(0.45	-1.16)	0.1761	0.2467
59		rs13994008	0	1.08	(0.69	-1.68)	0.7346	0.81	(0.13	-5.01)	0.8237	1.07	(0.69	-1.65)	0.7741	0.8119
60		rs1517352	2	0.74	(0.50	-1.09)	0.1297	0.68	(0.40	-1.17)	0.1628	0.72	(0.50	-1.05)	0.0897	0.1094
61		rs16833177	0	0.99	(0.67	-1.46)	0.9481	0.33	(0.09	-1.23)	0.0983	0.91	(0.62	-1.33)	0.6315	0.3408
62		rs16833239	1	0.63	(0.38	-1.05)	0.0763	1.11	(0.07	-18.10)	0.9417	0.64	(0.38	-1.06)	0.0826	0.0998
63		rs16833437	1	1.23	(0.84	-1.80)	0.2888	1.35	(0.76	-2.39)	0.3015	1.25	(0.87	-1.80)	0.2179	0.2132
64		rs7769459	0	1.51	(0.83	-2.74)	0.1751	-	-	-	1.38	(0.77	-2.48)	0.2786	0.4608	
65		rs2459611	0	0.83	(0.55	-1.27)	0.3956	0.81	(0.22	-2.94)	0.7450	0.83	(0.55	-1.25)	0.3750	0.3869
66		rs3024861	1	1.03	(0.71	-1.49)	0.8909	0.91	(0.43	-1.94)	0.8029	1.01	(0.71	-1.44)	0.9578	0.9445
67		rs3024877	0	0.72	(0.49	-1.04)	0.0828	0.82	(0.43	-1.56)	0.5371	0.73	(0.51	-1.05)	0.0898	0.0715
68		rs3024908	0	0.86	(0.55	-1.34)	0.4952	0.31	(0.07	-1.52)	0.1502	0.79	(0.52	-1.22)	0.2927	0.1754
69		rs3024912	1	0.95	(0.65	-1.39)	0.8084	0.32	(0.10	-0.98)	0.0458	0.87	(0.60	-1.25)	0.4441	0.1754
70		rs3024921	0	1.39	(0.78	-2.50)	0.2679	-	-	-	1.33	(0.75	-2.38)	0.3269	0.4216	
71		rs3024936	0	0.63	(0.28	-1.41)	0.2642	-	-	-	0.63	(0.28	-1.41)	0.2642	0.2642	
72		rs4571082	0	0.98												

Supplementary Table 5. age-stratified Odds Ratios (OR) and 95% Confidence Intervals for NHL (adjusted for age (continuous), sex and study centre)													
Gene	rs Number	no. of no calls	BNHL (equal and above 50)										
			Heterozygous Mutant			Homozygous Mutant			Dominant Model				
			OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	p-trend	
BMF	rs10518679	0	1.09	(0.87 , 1.36)	0.4653	1.01	(0.51 , 2.00)	0.9789	1.08	(0.87 , 1.35)	0.4939	0.5386	
	rs11630670	0	1.03	(0.83 , 1.29)	0.7627	0.97	(0.74 , 1.28)	0.8440	1.02	(0.82 , 1.25)	0.8753	0.8881	
	rs11634257	1	1.06	(0.87 , 1.28)	0.5819	0.79	(0.51 , 1.21)	0.2789	1.02	(0.84 , 1.23)	0.8351	0.7784	
	rs11858141	2	0.99	(0.80 , 1.23)	0.9234	1.24	(0.94 , 1.63)	0.1281	1.05	(0.86 , 1.29)	0.6275	0.1851	
	rs12913170	2	1.05	(0.85 , 1.30)	0.6343	0.98	(0.53 , 1.81)	0.9519	1.05	(0.85 , 1.29)	0.6640	0.7255	
	rs1540686	22	0.91	(0.73 , 1.15)	0.4339	0.98	(0.75 , 1.28)	0.8793	0.93	(0.75 , 1.16)	0.5252	0.8423	
	rs16970325	2	1.15	(0.91 , 1.47)	0.2456	2.93	(1.13 , 7.61)	0.0272	1.22	(0.96 , 1.54)	0.1032	0.0406	
	rs16970349	0	1.10	(0.80 , 1.51)	0.5474	0.77	(0.13 , 4.62)	0.7729	1.09	(0.80 , 1.49)	0.5849	0.6368	
	rs3743129	2	1.08	(0.87 , 1.34)	0.4705	1.10	(0.84 , 1.43)	0.4839	1.09	(0.89 , 1.33)	0.4154	0.4492	
	rs3923235	0	0.91	(0.75 , 1.11)	0.3734	0.64	(0.43 , 0.94)	0.0221	0.87	(0.72 , 1.05)	0.1413	0.0392	
	rs374355	1	0.88	(0.72 , 1.07)	0.2096	1.12	(0.76 , 1.66)	0.5560	0.91	(0.76 , 1.10)	0.3412	0.6733	
	rs546220	5	0.90	(0.73 , 1.11)	0.3283	1.08	(0.82 , 1.42)	0.5934	0.94	(0.77 , 1.15)	0.5678	0.8258	
	rs588739	0	1.11	(0.89 , 1.38)	0.3718	1.21	(0.92 , 1.59)	0.1797	1.13	(0.92 , 1.40)	0.2428	0.1748	
	rs648289	1	0.88	(0.71 , 1.10)	0.2564	0.98	(0.75 , 1.29)	0.8063	0.91	(0.74 , 1.12)	0.3700	0.7851	
	rs652196	3	1.09	(0.90 , 1.34)	0.3790	1.23	(0.82 , 1.85)	0.0238	1.11	(0.92 , 1.35)	0.2764	0.2257	
	rs675173	6	0.80	(0.65 , 0.97)	0.0244	0.94	(0.67 , 1.33)	0.7270	0.82	(0.68 , 0.99)	0.0388	0.1390	
	rs7183977	2	0.93	(0.76 , 1.14)	0.4880	0.82	(0.59 , 1.12)	0.2093	0.91	(0.75 , 1.10)	0.3186	0.2074	
	rs998713	6	0.87	(0.71 , 1.07)	0.1980	0.98	(0.73 , 1.31)	0.8974	0.90	(0.74 , 1.09)	0.2767	0.5863	
CASP6	rs1541373	1	0.93	(0.76 , 1.15)	0.5083	1.07	(0.80 , 1.44)	0.6358	0.96	(0.79 , 1.17)	0.7006	0.8864	
	rs1800627	3	1.02	(0.81 , 1.28)	0.8794	1.01	(0.77 , 1.32)	0.9299	1.02	(0.82 , 1.26)	0.8851	0.9269	
	rs3181345	0	1.13	(0.88 , 1.44)	0.3326	0.38	(0.14 , 0.84)	0.0593	1.06	(0.84 , 1.35)	0.6107	0.9770	
	rs3212153	1	1.04	(0.83 , 1.30)	0.7200	0.74	(0.35 , 1.55)	0.4270	1.02	(0.82 , 1.27)	0.8722	0.9369	
	rs5030552	1	1.27	(0.99 , 1.62)	0.0608	0.51	(0.16 , 1.67)	0.2670	1.22	(0.96 , 1.56)	0.1039	0.2005	
	rs68063	0	0.75	(0.51 , 1.12)	0.1569	-	-	-	0.74	(0.50 , 1.10)	0.1352	0.1182	
IFNG	rs12306852	0	1.00	(0.81 , 1.24)	0.9767	1.05	(0.55 , 1.99)	0.8811	1.01	(0.82 , 1.24)	0.9497	0.9211	
	rs2069716	0	0.95	(0.72 , 1.26)	0.7142	0.56	(0.14 , 2.24)	0.4096	0.93	(0.71 , 1.23)	0.6114	0.5206	
	rs2069718	8	0.89	(0.72 , 1.09)	0.2433	0.87	(0.65 , 1.17)	0.0359	0.88	(0.73 , 1.07)	0.2038	0.2426	
	rs2069727	0	1.24	(0.99 , 1.56)	0.0583	1.15	(0.88 , 1.50)	0.0309	1.21	(0.98 , 1.50)	0.0752	0.2705	
	rs6581795	1	0.93	(0.76 , 1.13)	0.4523	1.02	(0.70 , 1.48)	0.0143	0.94	(0.78 , 1.14)	0.5273	0.7055	
IFNGR1	rs1259779	15	0.88	(0.72 , 1.08)	0.2260	0.81	(0.53 , 1.25)	0.3395	0.87	(0.72 , 1.06)	0.1701	0.1569	
	rs327474	1	1.06	(0.85 , 1.31)	0.6226	1.26	(0.96 , 1.66)	0.0889	1.11	(0.91 , 1.36)	0.3061	0.1058	
	rs327475	2	0.76	(0.62 , 0.94)	0.0112	0.88	(0.54 , 1.43)	0.5994	0.78	(0.63 , 0.95)	0.0129	0.0306	
	rs851454	6	0.91	(0.73 , 1.14)	0.4181	0.82	(0.63 , 1.08)	0.1611	0.89	(0.72 , 1.09)	0.2544	0.1605	
	rs799488	0	0.89	(0.71 , 1.13)	0.3455	1.27	(0.57 , 2.87)	0.5853	0.91	(0.73 , 1.15)	0.4362	0.5840	
	rs477768	8	0.90	(0.72 , 1.12)	0.3398	0.96	(0.50 , 1.87)	0.0119	0.90	(0.73 , 1.12)	0.3504	0.4011	
	rs48966243	4	1.04	(0.83 , 1.30)	0.7235	1.48	(1.14 , 1.92)	0.0036	1.17	(0.95 , 1.43)	0.1449	0.0056	
	rs608914	4	1.08	(0.88 , 1.31)	0.4606	1.17	(0.84 , 1.61)	0.0341	1.09	(0.91 , 1.32)	0.3496	0.2951	
	rs759040	0	0.95	(0.78 , 1.16)	0.6078	1.23	(0.82 , 1.83)	0.0175	0.98	(0.81 , 1.19)	0.8740	0.7573	
IFNGR2	rs402877	3	0.98	(0.79 , 1.21)	0.8479	0.90	(0.68 , 1.18)	0.4308	0.96	(0.78 , 1.17)	0.6561	0.4607	
	rs1915583	0	0.76	(0.48 , 1.22)	0.2604	-	-	-	0.76	(0.48 , 1.22)	0.2604	0.2694	
	rs1426735	0	1.03	(0.85 , 1.28)	0.7370	1.42	(0.96 , 2.09)	0.0755	1.06	(0.90 , 1.31)	0.4014	0.8164	
	rs16930684	0	0.80	(0.58 , 1.19)	0.0251	-	-	-	0.80	(0.58 , 1.37)	0.3554	0.5654	
	rs20140675	45	1.19	(0.94 , 1.51)	0.1473	1.52	(0.77 , -3.01)	0.2284	1.22	(0.97 , 1.53)	0.0229	0.0713	
	rs284535	59	1.01	(0.82 , 1.25)	0.9184	1.05	(0.82 , 1.44)	0.0559	1.03	(0.85 , 1.25)	0.7592	0.5869	
	rs2834211	0	0.89	(0.69 , 1.14)	0.3465	1.03	(0.49 , 2.16)	0.9340	0.90	(0.70 , 1.14)	0.3865	0.4694	
	rs2834214	1	1.00	(0.80 , 1.29)	0.9720	1.00	(0.76 , 1.30)	0.0760	1.00	(0.82 , 1.22)	0.9690	0.9723	
	rs8131980	2	0.81	(0.66 , 0.99)	0.0391	0.98	(0.69 , 1.33)	0.7954	0.84	(0.69 , 1.01)	0.0638	0.2033	
	rs9769761	0	0.94	(0.76 , 1.16)	0.5438	1.05	(0.80 , 1.38)	0.1780	0.97	(0.79 , 1.18)	0.7460	0.8503	
	rs978166	0	0.89	(0.71 , 1.13)	0.3355	0.57	(0.21 , 1.56)	0.2742	0.88	(0.70 , 1.10)	0.2538	0.1933	
IL10	rs1554246	2	0.94	(0.76 , 1.15)	0.5368	0.98	(0.58 , 1.59)	0.8714	0.94	(0.77 , 1.15)	0.5373	0.5791	
	rs17015767	0	0.93	(0.76 , 1.14)	0.4932	1.28	(0.79 , 2.07)	0.3203	0.96	(0.79 , 1.17)	0.7159	0.9334	
	rs1800871	9	0.97	(0.79 , 1.18)	0.7315	0.86	(0.57 , 1.29)	0.6969	0.95	(0.79 , 1.15)	0.6040	0.4944	
	rs1800872	10	0.96	(0.79 , 1.17)	0.6839	0.91	(0.61 , 1.38)	0.6702	0.95	(0.79 , 1.15)	0.6237	0.5902	
	rs2222202	9	1.11	(0.89 , 1.38)	0.3549	1.06	(0.81 , 1.40)	0.6703	1.09	(0.89 , 1.34)	0.3874	0.5826	
	rs3021094	2	0.88	(0.68 , 1.15)	0.3519	4.39	(0.93 , 20.79)	0.0621	0.93	(0.72 , 1.20)	0.5760	0.8965	
	rs324505	1	1.10	(0.89 , 1.36)	0.3684	0.81	(0.44 , 1.51)	0.5076	1.07	(0.87 , 1.32)	0.5146	0.7283	
	rs3245059	0	1.04	(0.79 , 1.38)	0.7627	0.19	(0.02 , 1.60)	0.1271	1.00	(0.76 , 1.33)	0.9277	0.7878	
	rs4390174	7	1.01	(0.82 , 1.24)	0.9472	1.12	(0.84 , 1.50)	0.4436	1.03	(0.85 , 1.25)	0.7486	0.5223	
	rs4444553	1	1.07	(0.81 , 1.41)	0.6448	0.33	(0.07 , 1.59)	0.1656	1.03	(0.78 , 1.35)	0.8431	0.9188	
	rs6739298	8	1.04	(0.85 , 1.27)	0.7240	1.04	(0.66 , 1.63)	0.8719	1.04	(0.85 , 1.26)	0.7134	0.7308	
	rs6868931	2	0.91	(0.75 , 1.11)	0.3673	0.89	(0.58 , 1.35)	0.5732	0.91	(0.75 , 1.10)	0.3258	0.3357	
	rs7548373	22	1.03	(0.78 , 1.37)	0.8137	0.19	(0.02 , 1.61)	0.1284	1.00	(0.75 , 1.32)	0.9743	0.7384	
IL12A	rs1927521	6	1.03	(0.83 , 1.26)	0.8117	0.93	(0.70 , 1.22)	0.5906	1.00	(0.82 , 1.21)	0.9881	0.7065	
	rs2243115	4	0.90	(0.71 , 1.15)	0.3988	0.62	(0.29 , 1.31)	0.2096	0.88	(0.70 , 1.10)	0.2619	0.1798	
	rs2243131	3	0.97	(0.78 , 1.21)	0.8163	0.95	(0.51 , 1.77)	0.8691	0.97	(0.79 , 1.20)	0.7949	0.7852	
	rs2243154	0	0.95	(0.74 , 1.21)	0.6834	0.69	(0.22 , 1.21)	0.5119	0.94	(0.74 , 1.20)	0.6103	0.5398	
	rs4680534	0	1.04	(0.85 , 1.27)	0.6914	0.97	(0.71 , 1.31)	0.8302	1.03	(0.85 , 1.24)	0.7947	0.9938	
	rs4854947	1	0.98	(0.78 , 1.23)	0.8585	0.92	(0.70 , 1.21)	0.5578	0.96	(0.78 , 1.19)	0.7214	0.5652	
	rs4863129	1	1.10	(0.79 , 1.29)	0.6051	0.64	(0.56 , 1.09)	0.0561	0.81	(0.66 , 1.01)	0.0618	0.0777	
	rs4921466	0	1.22	(0.97 , 1.54)	0.0694	0.32	(0.09 , 1.14)	0.0792	1.17	(0.93 , 1.47)	0.3744	0.3764	
	rs4921468	0	1.05	(0.86 , 1.28)	0.6145								

	rs6900384	14	0.90	(0.69, .117)	0.4405	2.26	(0.56, .911)	0.2507	0.93	(0.72, .120)	0.5734	0.7552	
	rs6906608	0	0.91	(0.73, .119)	0.3641	1.68	(0.87, .325)	0.1248	0.95	(0.77, .118)	0.6523	0.9423	
	rs7597895	0	0.99	(0.72, .128)	0.1686	1.01	(0.68, .150)	0.9501	1.00	(0.92, .120)	0.5314	0.9933	
	rs9405192	3	1.00	(0.82, .148)	0.1686	0.87	(0.65, .150)	0.9588	0.98	(0.92, .120)	0.8173	0.9489	
	JAK1	1	0.99	(0.95, .141)	0.1503	0.90	(0.63, .128)	0.5658	1.11	(0.92, .134)	0.2837	0.6830	
	rs2265298	0	0.98	(0.70, .104)	0.1191	1.10	(0.75, .161)	0.6158	0.89	(0.74, .107)	0.2201	0.5271	
	rs3102114	1	0.95	(0.70, .104)	0.1143	0.99	(0.72, .139)	0.9723	0.88	(0.73, .106)	0.1729	0.4096	
	rs7546535	39	0.94	(0.76, .116)	0.5646	1.22	(0.76, .197)	0.4094	0.97	(0.80, .119)	0.7670	0.9407	
	SOCS1	3	1.30	(1.05, .160)	0.0175	1.27	(0.78, .206)	0.3241	1.29	(1.05, .159)	0.0136	0.0218	
	rs149597	2	1.06	(0.85, .139)	0.5847	1.04	(0.80, .136)	0.3497	1.06	(0.86, .130)	0.6001	0.7286	
	rs193778	1	0.98	(0.72, .107)	0.2019	1.50	(0.99, .225)	0.0531	0.95	(0.78, .114)	0.5599	0.6984	
	rs243317	1	0.93	(0.77, .114)	0.5018	0.92	(0.65, .130)	0.6340	0.93	(0.77, .112)	0.4612	0.4778	
	rs409665	28	0.94	(0.76, .117)	0.5841	0.96	(0.72, .128)	0.7812	0.95	(0.77, .116)	0.5959	0.7042	
	rs9405051	1	0.97	(0.78, .119)	0.7530	1.05	(0.82, .146)	0.5428	1.00	(0.82, .121)	0.9640	0.6764	
	SOCS5	3	0.94	(0.73, .119)	0.5924	1.32	(0.66, .264)	0.4360	0.97	(0.76, .122)	0.7716	0.9905	
	rs13412085	0	0.91	(0.73, .115)	0.4425	1.21	(0.64, .227)	0.5598	0.94	(0.75, .117)	0.5743	0.7697	
	rs17082355	0	1.16	(0.93, .146)	0.1947	0.98	(0.48, .193)	0.9120	1.15	(0.92, .143)	0.2272	0.3095	
	rs17809666	1	0.77	(0.57, .104)	0.0844	1.32	(0.40, .437)	0.6520	0.79	(0.59, .106)	0.1142	0.1762	
	rs4891398	29	1.02	(0.83, .126)	0.8352	1.11	(0.84, .147)	0.4619	1.04	(0.86, .127)	0.6648	0.4990	
	STAT1	rs10173099	10	1.01	(0.83, .124)	0.9071	0.91	(0.67, .124)	0.5554	0.99	(0.82, .120)	0.9171	0.6923
	rs10199181	2	0.99	(0.81, .122)	0.9573	0.98	(0.74, .130)	0.8836	0.99	(0.82, .120)	0.9238	0.8905	
	rs168	3	0.89	(0.72, .111)	0.2968	0.80	(0.61, .105)	0.1043	0.86	(0.70, .106)	0.1581	0.0993	
	rs2468579	1	1.22	(0.98, .151)	0.0710	1.21	(0.93, .159)	0.1575	1.22	(0.99, .149)	0.0564	0.1084	
	rs2693591	0	0.96	(0.77, .120)	0.7302	1.85	(0.94, .364)	0.0738	1.01	(0.82, .126)	0.9045	0.5174	
	rs3029247	2	0.99	(0.82, .121)	0.9541	0.88	(0.63, .122)	0.4374	0.97	(0.80, .117)	0.7612	0.5523	
	rs3029532	0	1.11	(0.86, .143)	0.4270	0.75	(0.26, .211)	0.9835	1.09	(0.85, .140)	0.5105	0.6328	
	rs3035504	1	0.89	(0.72, .110)	0.2782	1.11	(0.63, .195)	0.07105	0.91	(0.74, .112)	0.3587	0.5221	
	rs3395505	0	1.21	(0.98, .149)	0.0764	1.05	(0.80, .139)	0.7219	1.16	(0.96, .142)	0.1290	0.4293	
	rs400657	0	1.03	(0.82, .130)	0.8092	0.79	(0.35, .179)	0.5711	1.01	(0.81, .127)	0.9144	0.9592	
	rs467199	0	1.02	(0.84, .125)	0.8096	0.96	(0.65, .142)	0.8459	1.01	(0.84, .123)	0.8794	0.9824	
	rs547550	20	1.04	(0.85, .127)	0.7274	1.20	(0.88, .163)	0.2537	1.07	(0.88, .129)	0.4975	0.3074	
	rs6824035	1	0.89	(0.72, .109)	0.2592	1.20	(0.69, .209)	0.5085	0.91	(0.74, .112)	0.3797	0.6133	
	rs7749316	0	0.94	(0.70, .125)	0.6616	0.72	(0.20, .258)	0.6186	0.93	(0.70, .123)	0.6009	0.5533	
	rs7817866	0	1.11	(0.90, .138)	0.3384	1.06	(0.81, .139)	0.6521	1.10	(0.90, .134)	0.3712	0.5628	
	rs2066795	0	1.70	(0.86, .336)	0.1296	-	-	-	1.70	(0.86, .336)	0.1296	0.1296	
	rs2066804	1	1.11	(0.91, .136)	0.2930	1.26	(0.83, .191)	0.2731	1.13	(0.94, .137)	0.2034	0.1629	
	rs2280232	1	1.00	(0.82, .122)	0.9886	1.16	(0.80, .168)	0.4420	1.02	(0.85, .124)	0.8039	0.6022	
	rs2280233	4	0.90	(0.72, .111)	0.3236	0.80	(0.62, .105)	0.1096	0.87	(0.71, .106)	0.1718	0.1068	
	rs2280234	5	1.09	(0.89, .134)	0.4060	1.28	(0.96, .170)	0.0877	1.14	(0.94, .138)	0.1987	0.0936	
	rs34997637	3	1.07	(0.88, .131)	0.4943	0.92	(0.62, .136)	0.6779	1.05	(0.87, .127)	0.6357	0.8754	
	rs4327257	0	0.87	(0.70, .108)	0.2126	1.21	(0.61, .240)	0.5832	0.89	(0.72, .111)	0.2928	0.4486	
	rs4853533	3	1.10	(0.90, .135)	0.3388	1.24	(0.93, .165)	0.1471	1.13	(0.94, .138)	0.1963	0.1307	
	rs562024	0	1.16	(0.94, .143)	0.1601	1.13	(0.86, .149)	0.3645	1.15	(0.95, .140)	0.1499	0.2425	
	rs867637	2	1.05	(0.86, .129)	0.6139	1.23	(0.91, .165)	0.1823	1.09	(0.90, .132)	0.3741	0.2133	
	STAT3	1	0.70	(0.54, .085)	0.0007	0.94	(0.62, .151)	0.8915	0.73	(0.60, .089)	0.0019	0.0159	
	rs101353	0	0.71	(0.56, .088)	0.0006	0.99	(0.64, .154)	0.8738	0.78	(0.65, .089)	0.0019	0.0180	
	rs1294918	1	0.81	(0.68, .100)	0.0003	0.92	(0.56, .098)	0.8326	0.79	(0.66, .089)	0.0020	0.0184	
	rs17405722	0	1.10	(0.82, .148)	0.5070	0.98	(0.36, .202)	0.9563	1.10	(0.82, .149)	0.5571	0.5768	
	rs2293152	2	1.18	(0.96, .145)	0.1216	0.97	(0.73, .227)	0.7999	1.12	(0.92, .136)	0.2680	0.8180	
	rs4102920	0	0.74	(0.61, .090)	0.0028	0.73	(0.52, .103)	0.0710	0.74	(0.61, .089)	0.0015	0.0037	
	rs4503895	0	0.78	(0.64, .098)	0.0183	0.70	(0.52, .098)	0.0206	0.76	(0.63, .093)	0.0056	0.0063	
	rs9891119	0	0.79	(0.65, .097)	0.0233	0.74	(0.55, .100)	0.0508	0.78	(0.64, .095)	0.0112	0.0150	
	rs912773	0	0.74	(0.61, .090)	0.0029	0.77	(0.54, .110)	0.1500	0.74	(0.62, .090)	0.0022	0.0065	
	STAT4	0	1.08	(0.88, .133)	0.4400	0.98	(0.60, .158)	0.9274	1.07	(0.88, .130)	0.4933	0.6103	
	rs10186266	1	1.20	(0.98, .147)	0.0765	0.92	(0.59, .144)	0.7201	1.16	(0.96, .141)	0.1290	0.3044	
	rs10918918	1	1.23	(1.01, .150)	0.0434	1.18	(0.86, .163)	0.3102	1.22	(1.01, .147)	0.0397	0.0798	
	rs16858578	4	0.95	(0.77, .117)	0.6265	0.96	(0.73, .129)	0.7520	0.95	(0.78, .116)	0.6215	0.6979	
	rs3020076	56	0.94	(0.71, .124)	0.6677	1.29	(0.43, .385)	0.6540	0.96	(0.73, .125)	0.7488	0.8486	
	rs3398409	0	1.09	(0.87, .137)	0.4563	1.12	(0.51, .243)	0.7807	1.09	(0.87, .136)	0.4369	0.4431	
	rs1517352	2	1.37	(1.11, .169)	0.0034	1.27	(0.96, .168)	0.0911	1.34	(1.10, .164)	0.0036	0.0260	
	rs16833177	0	1.11	(0.90, .136)	0.3287	0.96	(0.63, .146)	0.8382	1.08	(0.89, .132)	0.4141	0.5988	
	rs16833239	1	1.14	(0.87, .149)	0.3478	4.49	(0.50, .407)	0.1809	1.16	(0.89, .152)	0.2640	0.1954	
	rs16833437	1	0.97	(0.80, .119)	0.8054	1.03	(0.77, .137)	0.6830	0.99	(0.82, .119)	0.8924	0.9613	
	rs7769459	0	1.16	(0.86, .155)	0.3279	0.85	(0.19, .381)	0.8302	1.15	(0.86, .153)	0.3559	0.4043	
	rs2459611	0	1.14	(0.90, .143)	0.2764	0.82	(0.36, .186)	0.6330	1.11	(0.89, .139)	0.3435	0.4664	
	rs3024861	1	1.17	(0.96, .143)	0.1191	1.09	(0.76, .158)	0.6315	1.16	(0.96, .140)	0.1272	0.2063	
	rs3024877	0	1.21	(0.99, .147)	0.0569	1.00	(0.71, .140)	0.9904	1.17	(0.97, .141)	0.0988	0.3091	
	rs3024908	0	1.04	(0.82, .131)	0.7660	0.58	(0.26, .132)	0.1954	1.00	(0.79, .125)	0.9771	0.7036	
	rs3024912	1	1.03	(0.84, .126)	0.7871	0.93	(0.63, .137)	0.6951	1.01	(0.84, .122)	0.9080	0.9292	
	rs3024921	0	0.99	(0.72, .137)	0.9730	3.32	(0.34, .328)	0.2992	1.02	(0.74, .140)	0.9018	0.7712	
	rs3024936	0	0.64	(0.41, .100)	0.0497	-	-	-	0.66	(0.42, .103)	0.0650	0.0888	
	rs4517082	0	1.04	(0.85, .127)	0.7315	1.21	(0.91, .162)	0.1945	1.07	(0.89, .130)	0.4645	0.2436	
	rs4853540	6	1.22	(1.00, .150)	0.0518	1.30	(0.86, .197)	0.2113	1.23	(1.02, .150)	0.0330	0.0367	
	rs4853546	1	0.97	(0.79, .119)	0.7853	0.82	(0.61, .110)	0.1872	0.94	(0.77, .113)	0.5000	0.2524	
	rs48544345	0	1.10	(0.89, .135)	0.3636	1.59	(0.96, .265)	0.0743	1.15	(0.94, .140)	0.1811	0.0867	
	rs6752770	0	1.25	(1.03, .152)	0.0267	0.99	(0.69, .141)	0.9450	1.20	(1.00, .145)	0.0550	0.2201	
	rs7558921	1	1.05	(0.82, .133)	0.7153	0.58	(0.26, .132)	0.1973	1.00	(0.80, .126)	0.9717	0.7468	
	rs7574608	1	1.08	(0.81, .144)	0.6139	3.37	(0.35, .328)	0.2933	1.10	(0.82, .147)	0.5185	0.4325	
	rs7595904	1	1.12	(0.90, .138)	0.3030	0.8							

Supplementary Table 5. age-stratified Odds Ratios (OR) and 95% Confidence Intervals for HL (adjusted for age (continuous), sex and study centre)																
	Gene	rs Nummer	no. of no calls	HL (below 40)												
				OR	95% CI	p-value		OR	95% CI	p-value		OR	95% CI	p-value	p-trend	
BMF	rs10518679	0	1.03 (0.67 ,1.59)	0.9009	0.35 (0.35 ,0.323)	0.3522		0.99 (0.65 ,1.52)	0.9635			0.7969				
	rs11630670	0	0.75 (0.48 ,1.17)	0.2062	0.61 (0.35 ,1.08)	0.0887		0.71 (0.47 ,1.08)	0.1062			0.0776				
	rs11634257	1	1.04 (0.69 ,1.57)	0.8451	1.14 (0.54 ,2.43)	0.7300		1.06 (0.72 ,1.56)	0.7823			0.7278				
	rs11858141	2	0.86 (0.55 ,1.33)	0.4871	1.03 (0.58 ,1.85)	0.9146		0.90 (0.59 ,1.36)	0.6093			0.9306				
	rs12913170	2	0.91 (0.58 ,1.41)	0.6733	0.79 (0.22 ,2.85)	0.7245		0.90 (0.59 ,1.37)	0.6284			0.6017				
	rs1540666	22	0.78 (0.49 ,1.23)	0.2796	0.52 (0.29 ,0.93)	0.0286		0.70 (0.45 ,1.08)	0.1077			0.0302				
	rs16970325	2	1.01 (0.62 ,1.62)	0.9829	-	-		1.09 (0.69 ,1.74)	0.7068			0.4370				
	rs16970349	0	1.43 (0.82 ,2.51)	0.2077	-	-		1.43 (0.82 ,2.51)	0.2077			0.2077				
	rs1743129	2	0.90 (0.58 ,1.39)	0.6241	0.98 (0.56 ,1.72)	0.9358		0.92 (0.60 ,1.39)	0.6842			0.8638				
	rs1923235	0	1.09 (0.73 ,1.64)	0.6767	1.49 (0.66 ,3.36)	0.3368		1.14 (0.77 ,1.68)	0.5101			0.3757				
	rs537455	1	0.80 (0.53 ,1.21)	0.2901	1.06 (0.48 ,2.36)	0.8827		0.84 (0.56 ,1.24)	0.3699			0.5640				
	rs546220	5	0.73 (0.47 ,1.12)	0.1435	0.60 (0.33 ,1.08)	0.0889		0.69 (0.46 ,1.04)	0.0760			0.0640				
	rs588739	0	0.90 (0.58 ,1.39)	0.6245	0.71 (0.39 ,1.28)	0.2537		0.84 (0.56 ,1.28)	0.4294			0.2682				
	rs588289	1	0.84 (0.54 ,1.30)	0.4260	0.46 (0.25 ,0.84)	0.0123		0.72 (0.48 ,1.10)	0.1335			0.0179				
	rs562196	3	1.09 (0.72 ,1.65)	0.6782	1.10 (0.49 ,2.45)	0.8179		1.09 (0.74 ,1.62)	0.6601			0.6797				
	rs675173	6	0.90 (0.60 ,1.35)	0.6017	1.20 (0.59 ,2.41)	0.6197		0.94 (0.64 ,1.39)	0.7642			0.9529				
	rs183977	2	1.20 (0.80 ,1.81)	0.3700	1.17 (0.59 ,2.33)	0.6454		1.20 (0.81 ,1.77)	0.3584			0.4236				
	rs998713	6	1.38 (0.90 ,2.12)	0.1425	1.49 (0.81 ,2.72)	0.1996		1.40 (0.93 ,2.11)	0.1053			0.1242				
	CASP6	rs1541373	1	1.08 (0.72 ,1.65)	0.6890	0.59 (0.32 ,1.10)	0.0956		0.95 (0.64 ,1.40)	0.7797			0.2302			
	rs1800627	3	1.58 (0.98 ,2.58)	0.0581	1.56 (0.90 ,2.68)	0.1099		1.58 (1.01 ,2.49)	0.0473			0.1132				
	rs1811345	0	0.70 (0.43 ,1.15)	0.1583	-	-		0.77 (0.47 ,1.24)	0.2815			0.5286				
	rs3212153	1	1.03 (0.65 ,1.65)	0.8939	0.87 (0.15 ,5.02)	0.8803		1.02 (0.65 ,1.61)	0.9228			0.9599				
	rs5030552	1	0.92 (0.55 ,1.54)	0.7439	2.69 (0.42 ,17.26)	0.2981		0.98 (0.59 ,1.62)	0.3933			0.8444				
	rs769063	0	0.93 (0.46 ,1.92)	0.8539	-	-		0.93 (0.46 ,1.92)	0.8539			0.8539				
	IFNG	rs12306852	0	1.31 (0.85 ,2.02)	0.2250	2.32 (0.66 ,8.11)	0.1876		1.37 (0.90 ,2.09)	0.1421			0.0967			
	rs2069716	0	0.60 (0.32 ,1.13)	0.1168	1.74 (0.24 ,12.80)	0.5889		0.65 (0.36 ,1.20)	0.1683			0.2709				
	rs2069718	8	1.02 (0.67 ,1.66)	0.9127	1.16 (0.62 ,2.19)	0.4651		1.05 (0.70 ,1.57)	0.8170			0.6892				
	rs2069727	0	0.82 (0.52 ,1.30)	0.3881	0.67 (0.38 ,1.18)	0.1649		0.78 (0.50 ,1.19)	0.2484			0.1626				
	rs5891795	1	1.18 (0.79 ,1.76)	0.4243	1.34 (0.58 ,3.08)	0.4897		1.20 (0.81 ,1.77)	0.3671			0.3423				
	IFNGR1	rs12527779	15	1.37 (0.91 ,2.06)	0.1299	1.13 (0.30 ,4.28)	0.8543		1.35 (0.91 ,2.02)	0.1366			0.1752			
	rs1327474	1	0.89 (0.58 ,1.37)	0.5944	0.89 (0.50 ,1.60)	0.7044		0.89 (0.59 ,1.34)	0.5769			0.6395				
	rs1327475	2	1.24 (0.81 ,1.90)	0.3249	0.59 (0.11 ,3.11)	0.5331		1.18 (0.79 ,1.82)	0.4057			0.5327				
	rs1854154	6	1.07 (0.67 ,1.71)	0.7200	1.11 (0.64 ,1.94)	0.7100		1.08 (0.70 ,1.69)	0.7214			0.7065				
	rs799468	0	0.99 (0.63 ,1.55)	0.9568	0.36 (0.04 ,3.40)	0.3758		0.95 (0.61 ,1.48)	0.8265			0.6814				
	rs477766	8	0.65 (0.42 ,1.02)	0.0626	1.10 (0.09 ,13.33)	0.9426		0.66 (0.42 ,1.03)	0.0674			0.0682				
	rs4896243	4	1.02 (0.65 ,1.60)	0.9274	1.18 (0.68 ,2.05)	0.5618		1.07 (0.70 ,1.63)	0.7704			0.5869				
	rs608914	4	0.71 (0.47 ,1.08)	0.1130	1.23 (0.63 ,2.40)	0.5397		0.80 (0.54 ,1.18)	0.2563			0.7083				
	rs759040	0	1.04 (0.69 ,1.57)	0.8438	0.69 (0.32 ,1.47)	0.3367		0.97 (0.66 ,1.43)	0.8877			0.5799				
	rs4042877	3	1.10 (0.70 ,1.70)	0.6848	1.19 (0.68 ,2.09)	0.3535		1.12 (0.74 ,1.70)	0.5879			0.5275				
	IFNGR2	rs1015873	0	2.60 (0.99 ,6.80)	0.0518	-	-		2.60 (0.99 ,6.80)	0.0518			0.0518			
	rs2626735	0	1.24 (0.88 ,1.87)	0.3050	1.23 (0.54 ,2.84)	0.6215		1.24 (0.84 ,1.84)	0.2853			0.3234				
	rs16990664	0	2.28 (0.94 ,5.55)	0.0695	-	-		2.28 (0.94 ,5.55)	0.0695			0.0695				
	rs2012075	45	0.76 (0.46 ,1.27)	0.3015	2.10 (0.45 ,9.87)	0.3471		0.83 (0.51 ,1.36)	0.4602			0.7048				
	rs2284553	59	0.88 (0.56 ,1.36)	0.5543	0.89 (0.51 ,1.56)	0.6844		0.88 (0.58 ,1.33)	0.5417			0.6222				
	rs2834211	0	0.96 (0.59 ,1.55)	0.8564	0.58 (0.11 ,3.18)	0.5340		0.93 (0.58 ,1.48)	0.7461			0.6476				
	rs2834214	1	0.89 (0.57 ,1.41)	0.6316	0.55 (0.32 ,0.93)	0.0265		0.75 (0.49 ,1.14)	0.1816			0.0305				
	rs8131980	2	1.69 (1.12 ,2.56)	0.0130	1.10 (0.54 ,2.22)	0.7897		1.56 (1.05 ,2.30)	0.0268			0.1304				
	rs9796791	0	0.80 (0.51 ,1.24)	0.3158	0.78 (0.45 ,1.34)	0.3612		0.79 (0.52 ,1.20)	0.2661			0.3206				
	rs9797166	0	0.60 (0.36 ,0.98)	0.0399	0.36 (0.07 ,1.77)	0.2086		0.57 (0.35 ,0.92)	0.0223			0.0192				
	IL10	rs1554286	2	1.22 (0.81 ,1.83)	0.3454	1.06 (0.39 ,2.88)	0.9075		1.20 (0.81 ,1.78)	0.3650			0.4445			
	rs17015767	0	1.12 (0.73 ,1.72)	0.6054	0.49 (0.17 ,1.45)	0.1978		1.02 (0.67 ,1.55)	0.9152			0.6809				
	rs1800871	9	1.18 (0.79 ,1.77)	0.4155	0.94 (0.42 ,2.09)	0.8726		1.15 (0.78 ,1.69)	0.4943			0.6842				
	rs1800872	10	1.18 (0.79 ,1.77)	0.4165	0.89 (0.40 ,1.97)	0.7667		1.14 (0.77 ,1.68)	0.5226			0.7575				
	rs2222202	9	0.69 (0.45 ,1.08)	0.1046	0.95 (0.54 ,1.67)	0.8620		0.76 (0.50 ,1.15)	0.1906			0.5915				
	rs3021094	2	0.76 (0.46 ,1.27)	0.3006	-	-		0.72 (0.43 ,1.20)	0.2078			0.1457				
	rs3024505	1	1.03 (0.66 ,1.60)	0.8973	2.44 (0.39 ,15.41)	0.3434		1.07 (0.69 ,1.64)	0.7698			0.6251				
	rs3024509	0	0.88 (0.48 ,1.62)	0.6782	-	-		0.85 (0.46 ,1.57)	0.6076			0.5376				
	rs4390174	7	1.03 (0.67 ,1.59)	0.8891	0.89 (0.50 ,1.56)	0.6758		0.99 (0.66 ,1.48)	0.9504			0.7480				
	rs4844553	1	0.92 (0.50 ,1.67)	0.7752	-	-		0.89 (0.49 ,1.62)	0.7007			0.6243				
	rs6673928	8	1.07 (0.70 ,1.64)	0.7677	0.53 (0.19 ,1.46)	0.2179		0.98 (0.65 ,1.48)	0.9262			0.5737				
	rs6686931	2	1.28 (0.85 ,1.91)	0.2385	0.60 (0.24 ,1.50)	0.2744		1.17 (0.79 ,1.72)	0.4433			0.9214				
	rs7548373	22	0.82 (0.44 ,1.52)	0.5234	-	-		0.79 (0.43 ,1.47)	0.4617			0.4050				
	IL12A	rs1927512	6	1.08 (0.71 ,1.66)	0.7112	1.21 (0.66 ,2.23)	0.5334		1.11 (0.74 ,1.67)	0.6123			0.5289			
	rs2243115	4	1.08 (0.68 ,1.75)	0.7132	0.21 (0.02 ,1.78)	0.1513		1.00 (0.63 ,1.59)	0.9988			0.6679				
	rs2243131	3	0.88 (0.57 ,1.37)	0.5762	2.54 (0.76 ,8.53)	0.1302		0.97 (0.64 ,1.48)	0.8913			0.7111				
	rs2243154	0	1.05 (0.63 ,1.76)	0.8538	-	-		1.03 (0.61 ,1.71)	0.9214			0.9957				
	rs6806534	0	0.82 (0.51 ,1.24)	0.3491	0.91 (0.49 ,1.69)	0.7665		0.84 (0.57 ,1.24)	0.3787			0.5202				
	rs485497	1	1.10 (0.68 ,1.77)	0.7025	1.29 (0.75 ,2.24)	0.3597		1.16 (0.74 ,1.82)	0.5198			0.3594				
	rs583911	2	0.88 (0.57 ,1.38)	0.5876	0.78 (0.44 ,1.38)	0.3918		0.85 (0.56 ,1.30)	0.4628			0.3844				
	rs6441282	1	0.74 (0.48 ,1.16)	0.1												

1		rs11757491	0	0.88 (0.50 ,1.56)	0.6701	2.87	(0.24 ,33.88)	0.4017	0.93 (0.54 ,1.62)	0.8089	0.9740
2		rs12211228	1	0.81 (0.52 ,1.25)	0.3450	0.76	(0.17 ,3.36)	0.7216	0.81 (0.53 ,1.24)	0.3264	0.3337
3		rs13208928	0	0.76 (0.43 ,1.34)	0.3447	4.38	(0.43 ,44.16)	0.2108	0.84 (0.49 ,1.46)	0.5396	0.8241
4		rs1514346	0	1.12 (0.68 ,1.82)	0.6349	0.68	(0.12 ,3.90)	0.6686	1.09 (0.68 ,1.75)	0.7181	0.8347
5		rs1877175	0	0.86 (0.57 ,1.29)	0.4648	0.90	(0.37 ,2.22)	0.8198	0.86 (0.58 ,1.28)	0.4654	0.5192
6		rs2001508	0	1.06 (0.68 ,1.63)	0.8018	0.71	(0.12 ,4.15)	0.7064	1.04 (0.68 ,1.59)	0.8617	0.9454
7		rs3778607	1	0.93 (0.58 ,1.50)	0.7730	0.84	(0.47 ,1.48)	0.5394	0.90 (0.58 ,1.42)	0.6585	0.5412
8		rs380262	0	1.30 (0.85 ,2.00)	0.2246	1.77	(0.64 ,4.90)	0.2735	1.35 (0.89 ,2.03)	0.1561	0.1264
9		rs6900384	14	0.84 (0.50 ,1.41)	0.5210	1.36	(0.18 ,10.20)	0.7645	0.87 (0.52 ,1.43)	0.5727	0.6537
10		rs6906608	0	0.81 (0.52 ,1.25)	0.3450	0.76	(0.17 ,3.36)	0.7216	0.81 (0.53 ,1.24)	0.3264	0.3337
11		rs7688007	0	1.41 (0.94 ,2.12)	0.1002	1.51	(0.69 ,3.28)	0.2992	1.42 (0.96 ,2.10)	0.0783	0.0918
12		rs9378805	0	1.06 (0.67 ,1.67)	0.7966	0.60	(0.33 ,1.09)	0.9399	0.92 (0.59 ,1.42)	0.7039	0.1371
13		rs4045192	3	1.41 (0.94 ,2.13)	0.0988	0.97	(0.44 ,2.12)	0.9375	1.34 (0.90 ,1.99)	0.1478	0.3534
14	JAK1	rs10789166	1	0.81 (0.52 ,1.26)	0.3488	0.36	(0.07 ,1.77)	0.2101	0.77 (0.50 ,1.18)	0.2299	0.1550
15		rs256298	0	0.64 (0.43 ,0.97)	0.0344	0.74	(0.27 ,1.97)	0.5418	0.65 (0.44 ,0.97)	0.0344	0.0573
16		rs310211	1	0.65 (0.43 ,0.98)	0.0381	0.62	(0.29 ,1.32)	0.2153	0.64 (0.44 ,0.95)	0.0284	0.0411
17		rs546535	39	1.20 (0.79 ,1.83)	0.3940	0.96	(0.34 ,2.73)	0.9365	1.17 (0.78 ,1.76)	0.4414	0.5552
18	SOCS1	rs149311	3	1.60 (1.03 ,2.49)	0.0383	0.70	(0.25 ,1.90)	0.4796	1.43 (0.94 ,2.17)	0.0994	0.3323
19		rs149597	2	0.94 (0.60 ,1.49)	0.8007	0.99	(0.59 ,1.66)	0.9710	0.96 (0.63 ,1.46)	0.8505	0.9598
20		rs193778	1	1.10 (0.73 ,1.64)	0.6556	0.76	(0.28 ,2.07)	0.5853	1.06 (0.72 ,1.56)	0.7746	0.9837
21		rs243317	1	0.94 (0.62 ,1.41)	0.7519	0.73	(0.37 ,1.41)	0.3473	0.89 (0.60 ,1.31)	0.5471	0.3912
22		rs408665	28	1.39 (0.88 ,2.19)	0.1599	1.28	(0.72 ,2.29)	0.4002	1.36 (0.88 ,2.10)	0.1673	0.3165
23		rs940551	1	1.53 (0.97 ,2.41)	0.0657	1.43	(0.81 ,2.54)	0.2170	1.50 (0.98 ,2.31)	0.0637	0.1522
24	SOCS5	rs13402099	3	1.01 (0.62 ,1.65)	0.9713	0.97	(0.17 ,5.59)	0.9749	1.01 (0.62 ,1.62)	0.9781	0.9866
25		rs13412085	0	0.96 (0.60 ,1.53)	0.8523	1.21	(0.27 ,5.32)	0.8053	0.97 (0.62 ,1.53)	0.9061	0.9710
26	SOCS6	rs17082355	0	1.08 (0.67 ,1.76)	0.7424	0.78	(0.19 ,3.19)	0.7302	1.05 (0.66 ,1.68)	0.8265	0.9381
27		rs17809666	1	0.85 (0.46 ,1.58)	0.6117	1.86	(0.11 ,32.53)	0.6699	0.88 (0.48 ,1.61)	0.6733	0.7530
28		rs4891398	29	1.02 (0.66 ,1.56)	0.9443	1.37	(0.75 ,2.50)	0.3069	1.09 (0.73 ,1.63)	0.6804	0.3965
29	STAT1	rs10173099	10	0.74 (0.49 ,1.12)	0.1542	0.68	(0.34 ,1.36)	0.2777	0.73 (0.49 ,1.08)	0.1165	0.1313
30		rs10199181	2	0.98 (0.65 ,1.49)	0.9379	0.60	(0.31 ,1.17)	0.1354	0.89 (0.60 ,1.33)	0.5844	0.2359
31		rs1168	3	1.67 (1.04 ,2.70)	0.0355	1.43	(0.81 ,2.53)	0.2193	1.60 (1.01 ,2.52)	0.0448	0.1968
32		rs12468579	1	0.87 (0.57 ,1.34)	0.5343	0.76	(0.43 ,1.36)	0.3578	0.84 (0.56 ,1.26)	0.4097	0.3402
33		rs12693591	0	1.15 (0.73 ,1.80)	0.5544	0.65	(0.12 ,3.63)	0.6241	1.11 (0.71 ,1.73)	0.6390	0.7681
34		rs13029247	2	0.78 (0.52 ,1.77)	0.2355	0.69	(0.33 ,1.46)	0.3241	0.77 (0.52 ,1.19)	0.1833	0.1815
35		rs13029532	0	0.98 (0.56 ,1.72)	0.9484	1.01	(0.16 ,6.36)	0.9922	0.98 (0.57 ,1.69)	0.9526	0.9800
36		rs13035504	1	1.13 (0.72 ,1.77)	0.5975	1.24	(0.31 ,4.95)	0.7585	1.14 (0.73 ,1.76)	0.5652	0.5555
37		rs13396505	0	0.78 (0.51 ,1.18)	0.2332	0.81	(0.45 ,1.45)	0.4691	0.78 (0.53 ,1.16)	0.2211	0.3121
38		rs1400507	0	0.84 (0.51 ,1.40)	0.5051	0.95	(0.16 ,5.51)	0.9556	0.85 (0.52 ,1.39)	0.5131	0.5476
39		rs1467169	0	0.82 (0.54 ,1.25)	0.3586	0.50	(0.19 ,1.33)	0.1631	0.77 (0.52 ,1.15)	0.2077	0.1284
40		rs1547550	20	1.06 (0.68 ,1.53)	0.9427	0.60	(0.30 ,1.22)	0.1614	0.93 (0.63 ,1.37)	0.7056	0.3262
41		rs16824035	1	1.12 (0.62 ,1.27)	0.6136	1.24	(0.31 ,4.95)	0.7600	1.13 (0.73 ,1.74)	0.5869	0.5691
42		rs17749316	0	1.20 (0.71 ,2.05)	0.4962	-	-	-	1.15 (0.68 ,1.95)	0.6107	0.7700
43		rs17817966	0	0.95 (0.62 ,1.47)	0.8312	0.60	(0.33 ,1.09)	0.9390	0.85 (0.57 ,1.28)	0.4393	0.1409
44		rs206795	0	0.63 (0.31 ,3.49)	0.5954	-	-	-	0.63 (0.11 ,3.49)	0.5954	0.5954
45		rs2066804	1	0.85 (0.57 ,1.28)	0.4430	0.42	(0.16 ,1.12)	0.0831	0.78 (0.53 ,1.16)	0.2231	0.1030
46		rs2280232	1	1.09 (0.73 ,1.62)	0.6759	0.67	(0.25 ,1.84)	0.4388	1.04 (0.70 ,1.53)	0.8442	0.8896
47		rs2280233	4	1.82 (1.11 ,2.97)	0.0169	1.53	(0.86 ,2.72)	0.1447	1.72 (1.08 ,2.75)	0.0224	0.1436
48		rs2280234	5	0.93 (0.61 ,1.41)	0.7366	0.50	(0.25 ,1.01)	0.0520	0.83 (0.56 ,1.24)	0.3661	0.1040
49		rs34997637	3	0.83 (0.55 ,1.26)	0.3933	0.38	(0.13 ,1.08)	0.0690	0.76 (0.51 ,1.14)	0.1895	0.0827
50		rs4327257	0	1.00 (0.63 ,1.60)	0.9884	3.77	(0.64 ,22.21)	0.1420	1.08 (0.68 ,1.70)	0.7497	0.5004
51		rs4853533	3	0.83 (0.55 ,1.25)	0.3700	0.48	(0.24 ,0.94)	0.0318	0.74 (0.50 ,1.10)	0.1425	0.0412
52		rs5672024	0	1.03 (0.68 ,1.57)	0.8833	0.61	(0.33 ,1.15)	0.1251	0.92 (0.62 ,1.36)	0.6680	0.2425
53		rs867637	2	0.88 (0.59 ,1.32)	0.5410	0.46	(0.22 ,0.93)	0.0303	0.78 (0.53 ,1.15)	0.2160	0.0557
54	STAT3	rs1053005	1	0.77 (0.51 ,1.16)	0.2085	0.52	(0.18 ,1.52)	0.2328	0.74 (0.49 ,1.10)	0.1369	0.1042
55		rs1053023	1	0.77 (0.51 ,1.16)	0.2085	0.52	(0.18 ,1.52)	0.2328	0.74 (0.49 ,1.10)	0.1369	0.1042
56		rs12949198	1	0.82 (0.54 ,1.27)	0.3823	0.69	(0.39 ,1.20)	0.1843	0.78 (0.52 ,1.17)	0.2314	0.1715
57		rs17405722	0	1.10 (0.62 ,1.97)	0.7383	-	-	-	1.04 (0.59 ,1.85)	0.8855	0.9507
58		rs2293152	2	0.74 (0.48 ,1.14)	0.1704	0.79	(0.45 ,1.37)	0.3999	0.75 (0.50 ,1.13)	0.1667	0.2802
59		rs4103200	0	0.83 (0.55 ,1.25)	0.3783	0.53	(0.25 ,1.13)	0.1010	0.77 (0.52 ,1.14)	0.1908	0.0978
60		rs5053695	0	0.93 (0.61 ,1.41)	0.7386	0.61	(0.33 ,1.13)	0.1149	0.84 (0.57 ,1.24)	0.3862	0.1647
61		rs8991119	0	0.80 (0.53 ,1.21)	0.2955	0.65	(0.34 ,1.21)	0.1741	0.76 (0.52 ,1.13)	0.1811	0.1356
62		rs9912773	0	0.87 (0.58 ,1.31)	0.5124	0.37	(0.14 ,0.97)	0.0431	0.79 (0.53 ,1.17)	0.2372	0.0805
63	STAT4	rs10168266	0	0.97 (0.64 ,1.48)	0.8892	0.87	(0.26 ,2.94)	0.0248	0.96 (0.64 ,1.45)	0.8534	0.8212
64		rs10189819	1	0.84 (0.55 ,1.28)	0.4235	0.34	(0.12 ,0.95)	0.0404	0.75 (0.50 ,1.13)	0.1682	0.0585
65		rs10931481	0	1.22 (0.81 ,1.84)	0.3337	0.88	(0.41 ,1.86)	0.7297	1.16 (0.79 ,1.72)	0.4506	0.7520
66		rs1685878	4	0.66 (0.43 ,1.01)	0.0575	0.54	(0.30 ,0.96)	0.0373	0.62 (0.42 ,0.94)	0.0232	0.0209
67		rs13020076	56	0.98 (0.58 ,1.67)	0.9472	-	-	-	1.01 (0.60 ,1.71)	0.9752	0.8872
68		rs13389408	0	0.96 (0.58 ,1.57)	0.8623	0.93	(0.14 ,5.97)	0.9373	0.96 (0.59 ,1.55)	0.8540	0.8521
69		rs1517352	2	1.02 (0.67 ,1.57)	0.9103	0.98	(0.55 ,1.76)	0.9571	1.01 (0.68 ,1.52)	0.9441	0.9906
70		rs16833177	0	0.91 (0.59 ,1.39)	0.6537	0.57	(0.17 ,1.93)	0.3679	0.87 (0.57 ,1.32)	0.5150	0.3993
71		rs16833239	1	0.92 (0.52 ,1.61)	0.7614	-	-	-	0.89 (0.51 ,1.55)	0.6730	0.5823
72		rs16833437	1	0.79 (0.52 ,1.19)	0.2560	0.60	(0.33 ,1.11)	0.1055	0.74 (0.50 ,1.09)	0.1287	0.0832
73		rs17769459	0	1.50 (0.81 ,2.77)	0.1961	-	-	-	1.45 (0.79 ,2.66)	0.2325	0.2883
74		rs4595111	0	0.88 (0.55 ,1.43)	0.6145	1.77	(0.42 ,7.47)	0.4378	0.93 (0.59 ,1.48)	0.7702	0.9734
75		rs3024861	1	1.13 (0.75 ,1.70)	0.5495	0.74	(0.32 ,1.70)	0.4761	1.07 (0.72 ,1.57)	0.7448	0.9392
76		rs3024877	0	1.05 (0.70 ,1.58)	0.8130	1.31	(0.64 ,2.67)	0.4591	1.09 (0.74 ,1.61)	0.6734	0.5221
77		rs3024908	0	0.73 (0.44 ,1.23)	0.2429	0.58	(0.15 ,2.35)	0.4495	0.72 (0.44 ,1.18)	0.1876	0.1790
78		rs3024912	1	0.84 (0.56 ,1.28)	0.4205	0.39	(0.12 ,1.22)	0.1060	0.78 (0.52 ,1.17)	0.2317	0.1193
79		rs3024921	0	1.57 (0.84 ,2.93)	0.1606	-	-	-	1.45 (0.78 ,2.69)	0.2359	0.3717
80		rs3024936	0	0.43 (0.18 ,1.03)	0.0586	-					

Supplementary Table 5. age-stratified Odds Ratios (OR) and 95% Confidence Intervals for HL (adjusted for age (continuous), sex and study centre)												
Gene	rs Nummer	no. of no calls										
HL (equal and above 40)												
			Heterozygous Mutant			Homozygous Mutant		Dominant Model				
			OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	p-trend
BMF	rs10518679	0	0.71	(0.39, 1.29)	0.2595	1.42	(0.31, 6.48)	0.6501	0.76	(0.43, 1.33)	0.3315	0.4666
	rs1630670	0	1.34	(0.76, 2.35)	0.3148	1.16	(0.59, 2.30)	0.6621	1.28	(0.75, 2.20)	0.3665	0.6275
	rs1634257	1	1.10	(0.68, 1.76)	0.7056	0.89	(0.30, 2.61)	0.8277	1.07	(0.68, 1.69)	0.7766	0.9013
	rs1858141	2	1.23	(0.73, 2.08)	0.4273	0.86	(0.41, 1.80)	0.6813	1.14	(0.69, 1.88)	0.6136	0.8994
	rs12913170	2	0.70	(0.38, 1.23)	0.2145	0.52	(0.07, 3.97)	0.5242	0.68	(0.39, 1.19)	0.1795	0.1741
	rs1540666	22	1.06	(0.62, 1.81)	0.8267	0.52	(0.25, 1.10)	0.0885	0.88	(0.53, 1.48)	0.6327	0.1233
	rs16970325	2	1.33	(0.76, 2.32)	0.3205	3.79	(0.40, 35.94)	0.2455	1.37	(0.80, 2.38)	0.2547	0.1975
	rs16970349	0	0.74	(0.31, 1.76)	0.4973	-	-	-	0.73	(0.31, 1.73)	0.4750	0.4585
	rs3743129	2	0.79	(0.48, 1.29)	0.3442	0.56	(0.27, 1.13)	0.1059	0.72	(0.45, 1.15)	0.1677	0.0964
	rs3923235	0	1.19	(0.74, 1.93)	0.4732	1.60	(0.71, 3.63)	0.2573	1.25	(0.79, 1.98)	0.3393	0.2420
	rs537455	1	1.06	(0.66, 1.72)	0.8022	1.35	(0.57, 3.19)	0.4963	1.10	(0.70, 1.74)	0.6791	0.5517
	rs46220	5	1.11	(0.67, 1.85)	0.6862	0.59	(0.27, 1.31)	0.1938	0.97	(0.59, 1.60)	0.9154	0.3270
	rs588739	0	0.80	(0.48, 1.34)	0.3951	0.94	(0.49, 1.79)	0.8419	0.84	(0.52, 1.35)	0.4660	0.7221
	rs482289	1	1.12	(0.67, 1.89)	0.6571	0.59	(0.28, 1.23)	0.1595	0.96	(0.58, 1.57)	0.8573	0.2419
	rs562196	3	0.75	(0.46, 1.25)	0.2739	0.76	(0.23, 2.57)	0.6639	0.76	(0.47, 1.23)	0.2572	0.2892
	rs675173	6	1.15	(0.71, 1.86)	0.5606	0.98	(0.41, 2.30)	0.9564	1.12	(0.71, 1.79)	0.6220	0.7841
	rs7183977	2	1.54	(0.92, 2.58)	0.0977	1.97	(0.98, 3.94)	0.0565	1.63	(1.00, 2.66)	0.0505	0.0360
	rs998713	6	1.48	(0.87, 2.52)	0.1512	1.81	(0.90, 3.63)	0.0945	1.55	(0.93, 2.59)	0.0937	0.0733
CASP6	rs1541373	1	0.85	(0.51, 1.40)	0.5220	1.20	(0.62, 2.32)	0.5837	0.93	(0.58, 1.48)	0.7583	0.8097
	rs1800627	3	1.02	(0.58, 1.81)	0.9416	1.28	(0.67, 2.42)	0.4547	1.10	(0.65, 1.89)	0.7192	0.4498
	rs3181345	0	0.62	(0.32, 1.20)	0.1575	-	-	-	0.58	(0.30, 1.13)	0.1094	0.0869
	rs3212153	1	1.05	(0.62, 1.80)	0.8559	1.12	(0.25, 5.14)	0.8812	1.06	(0.63, 1.78)	0.8350	0.8230
	rs5030552	1	0.71	(0.35, 1.41)	0.3232	-	-	-	0.66	(0.33, 1.32)	0.2386	0.1910
	rs768063	0	0.51	(0.15, 1.68)	0.2677	-	-	-	0.50	(0.15, 1.66)	0.2608	0.2584
IFNG	rs12306852	0	0.63	(0.35, 1.13)	0.1217	0.77	(0.17, 3.43)	0.7318	0.64	(0.37, 1.13)	0.1219	0.1591
	rs2069716	0	0.73	(0.34, 1.57)	0.4218	-	-	-	0.68	(0.32, 1.46)	0.3231	0.2636
	rs2069718	8	1.16	(0.67, 2.02)	0.5890	2.90	(1.57, 5.37)	0.0007	1.55	(0.94, 2.56)	0.0869	0.0019
	rs2069727	0	0.66	(0.40, -1.10)	0.1142	0.51	(0.26, 1.00)	0.0490	0.61	(0.38, 0.99)	0.0448	0.0370
	rs6581795	1	2.10	(1.27, -3.49)	0.0041	3.00	(1.44, 6.25)	0.0035	2.25	(1.39, 3.66)	0.0010	0.0005
IFNGR1	rs12529779	15	0.68	(0.41, 1.13)	0.1370	0.71	(0.21, 2.38)	0.5752	0.68	(0.42, 1.11)	0.1258	0.1563
	rs1327474	1	1.58	(0.90, 2.76)	0.1110	1.51	(0.76, 3.01)	0.2379	1.56	(0.91, 2.67)	0.1046	0.1915
	rs1327475	2	0.93	(0.46, 1.31)	0.3438	1.11	(0.32, 3.79)	0.8734	0.81	(0.49, 1.33)	0.3882	0.5190
	rs1854154	6	1.11	(0.65, 1.88)	0.7003	0.78	(0.39, 1.56)	0.4865	1.01	(0.61, 1.67)	0.9739	0.5683
	rs7594948	0	1.11	(0.65, 1.90)	0.6983	-	-	-	1.05	(0.61, 1.78)	0.8710	0.2121
	rs477766	8	0.86	(0.50, -1.50)	0.6041	1.79	(0.39, 8.28)	0.4546	0.91	(0.54, 1.55)	0.7321	0.9108
	rs4896243	4	1.39	(0.78, 2.48)	0.2590	1.77	(0.91, 3.44)	0.0944	1.50	(0.87, 2.59)	0.1486	0.0923
	rs608914	4	0.87	(0.54, 1.41)	0.5814	0.87	(0.37, 2.01)	0.7380	0.87	(0.55, 1.38)	0.5570	0.5886
	rs7590940	0	0.87	(0.54, 1.41)	0.5687	0.57	(0.17, 1.92)	0.3676	0.83	(0.52, 1.32)	0.4314	0.3349
	rs4042877	3	0.84	(0.50, 1.40)	0.5006	0.88	(0.46, 1.70)	0.7112	0.85	(0.53, 1.37)	0.5086	0.6274
IFNGR2	rs1015873	0	1.42	(0.58, 3.48)	0.4457	-	-	-	1.42	(0.58, 3.48)	0.4457	0.4457
	rs2626735	0	1.27	(0.79, 2.04)	0.3318	1.35	(0.54, 3.38)	0.5236	1.28	(0.81, 2.02)	0.2938	0.3057
	rs1690664	0	1.38	(0.56, 3.37)	0.4817	-	-	-	1.38	(0.56, 3.37)	0.4817	0.4817
	rs2012075	45	1.08	(0.63, -1.87)	0.7774	0.82	(0.10, 6.52)	0.8516	1.07	(0.62, 1.82)	0.8171	0.8752
	rs2284553	59	1.15	(0.69, 1.93)	0.5899	0.90	(0.42, 1.94)	0.7909	1.09	(0.67, 1.80)	0.7238	0.9771
	rs2834211	0	0.81	(0.44, 1.48)	0.4849	-	-	-	0.77	(0.42, 1.42)	0.4064	0.3449
	rs2834214	1	1.35	(0.80, 2.29)	0.2603	0.79	(0.38, 1.64)	0.53	1.18	(0.71, 1.96)	0.5146	0.7482
	rs1313980	2	1.01	(0.63, 1.62)	0.9658	0.62	(0.24, 1.62)	0.33	0.94	(0.59, 1.48)	0.7859	0.5072
	rs9796791	0	0.95	(0.57, 1.58)	0.8501	0.64	(0.30, 1.38)	0.26	0.88	(0.54, 1.43)	0.5959	0.3113
	rs9798166	0	1.75	(1.07, -2.87)	0.0262	-	-	-	1.61	(0.98, 2.63)	0.0581	0.1669
IL10	rs1554286	2	1.01	(0.61, 1.68)	0.9593	2.00	(0.73, 5.48)	0.18	1.11	(0.69, 1.79)	0.6748	0.4148
	rs17015767	0	0.83	(0.50, 1.38)	0.4675	0.51	(0.12, 2.18)	0.36	0.79	(0.48, 1.30)	0.3467	0.2745
	rs1800871	9	0.93	(0.57, 1.52)	0.7720	1.57	(0.66, 3.72)	0.31	1.01	(0.64, 1.61)	0.9563	0.6349
	rs1800872	10	0.93	(0.57, 1.52)	0.7602	1.32	(0.53, 3.29)	0.56	0.98	(0.61, 1.56)	0.9233	0.8603
	rs2222202	9	1.21	(0.73, -2.02)	0.4661	0.57	(0.27, 1.21)	0.14	1.01	(0.62, 1.65)	0.9701	0.2688
	rs3021094	2	1.04	(0.56, 1.95)	0.8919	-	-	-	1.00	(0.53, 1.86)	0.9909	0.8652
	rs3024505	1	1.23	(0.74, 2.06)	0.4219	0.80	(0.18, 3.45)	0.76	1.18	(0.72, 1.94)	0.5096	0.6636
	rs3024509	0	0.57	(0.25, 1.27)	0.1700	-	-	-	0.56	(0.25, 1.26)	0.1634	0.1598
	rs4390174	7	1.25	(0.76, 2.06)	0.3799	0.94	(0.44, 1.99)	0.86	1.18	(0.73, 1.90)	0.5059	0.8489
	rs4844553	1	0.61	(0.27, 1.36)	0.2248	2.53	(0.25, 25.15)	0.43	0.67	(0.31, 1.43)	0.3005	0.4221
	rs6773928	8	0.82	(0.49, 1.36)	0.4365	0.40	(0.09, 1.71)	0.22	0.76	(0.46, 1.24)	0.2700	0.1767
	rs6866931	2	1.06	(0.65, 1.72)	0.8108	1.25	(0.47, 3.37)	0.65	1.08	(0.68, 1.72)	0.7315	0.6615
	rs7548373	22	0.81	(0.38, 1.68)	0.5767	-	-	-	0.80	(0.38, 1.65)	0.5372	0.5016
IL12A	rs1927521	6	0.99	(0.60, 1.63)	0.9703	1.00	(0.50, 1.98)	1.00	0.99	(0.62, 1.59)	0.9751	0.9874
	rs2243115	4	1.01	(0.58, 1.76)	0.9736	-	-	-	0.95	(0.54, 1.66)	0.8553	0.6577
	rs2243131	3	0.70	(0.40, 1.23)	0.2128	0.80	(0.18, 3.51)	0.76	0.71	(0.41, 1.22)	0.2108	0.2516
	rs2243154	0	1.05	(0.57, 1.94)	0.8674	-	-	-	0.99	(0.54, 1.82)	0.9670	0.7928
	rs6805344	0	0.69	(0.42, 1.14)	0.1464	0.88	(0.43, 1.78)	0.72	0.73	(0.46, 1.16)	0.1845	0.3730
	rs4854937	1	0.88	(0.51, 1.50)	0.6306	0.81	(0.42, 1.55)	0.52	0.85	(0.52, 1.42)	0.5437	0.5166
	rs583911	2	0.90	(0.53, 1.54)	0.7047	1.29	(0.69, 2.40)	0.43	1.01	(0.61, 1.66)	0.9688	0.4899
	rs6441282	1	0.56	(0.33, 0.94)	0.0284	0.68	(0.36, 1.27)	0.23	0.60	(0.37, 0.96)	0.0324	0.1365
	rs6860657	6	0.57	(0.28, 1.18)	0.1334	1.34	(0.29, 6.14)	0.71	0.64	(0.33, 1.25)	0.1802	0.3137
	rs692890	0	0.52	(0.31, 0.88)	0.0156	1.09	(0.54, 2.21)	0.81	0.63	(0.39, 1.00)	0.0522	0.3156
	rs7372767	2	1.07	(0.64, 1.80)	0.7921	1.27	(0.67, 2.42)	0.47	1.13	(0.69, 1.83)	0.6327	0.4895
	rs747825	1	0.83	(0.49, 1.38)	0.4668	0.85	(0.26, 2.86)	0.79	0.83	(0.56, 1.26)	0.4645	0.4903
	rs755004	2	1.04	(0.61, 1.80)	0.8768							

1		rs11757491	0	0.43	(0.17 ,1.09)	0.0756	2.00	0.23	17.69	0.53	0.49	(0.21 ,1.17)	0.1089	0.1774	
2		rs12211228	1	0.92	(0.54 ,1.59)	0.7770	2.11	0.58	7.69	0.26	1.00	(0.60 ,1.68)	0.9990	0.7378	
3		rs13208928	0	0.44	(0.17 ,1.11)	0.0833	1.67	0.20	14.32	0.64	0.50	(0.21 ,1.18)	0.1149	0.1823	
4		rs1514346	0	0.61	(0.38 ,1.25)	0.1765	1.49	0.17	12.75	0.72	0.65	(0.32 ,1.29)	0.2149	0.2880	
5		rs1877175	0	0.85	(0.51 ,1.40)	0.5258	1.01	0.34	2.98	0.98	0.87	(0.54 ,1.40)	0.5659	0.6638	
6		rs2001508	0	0.68	(0.38 ,1.18)	0.1709	0.60	0.14	2.60	0.49	0.67	(0.39 ,1.14)	0.1395	0.1490	
7		rs3778607	1	1.22	(0.69 ,2.15)	0.4957	1.02	0.52	1.98	0.96	1.15	(0.67 ,1.97)	0.6163	0.9637	
8		rs380262	0	1.15	(0.70 ,1.91)	0.5814	2.02	0.67	6.14	0.21	1.23	(0.76 ,1.98)	0.4069	0.2717	
9		rs6900384	14	0.68	(0.32 ,1.46)	0.3256	2.56	0.26	25.56	0.42	0.74	(0.36 ,1.53)	0.4206	0.5573	
JAK1		rs6906608	0	0.92	(0.54 ,1.59)	0.7778	2.11	0.58	7.69	0.26	1.00	(0.60 ,1.68)	0.9979	0.7370	
		rs768807	0	1.05	(0.64 ,1.72)	0.8413	1.43	0.61	3.38	0.41	1.11	(0.70 ,1.76)	0.6692	0.5058	
		rs9378805	0	0.78	(0.47 ,1.31)	0.3534	0.61	0.32	1.19	0.15	0.73	(0.45 ,1.18)	0.1994	0.1395	
		rs405192	3	0.96	(0.59 ,1.56)	0.8813	1.05	0.47	2.34	0.91	0.98	(0.62 ,1.55)	0.9277	0.9979	
10		rs10789166	1	1.04	(0.61 ,1.75)	0.8940	-	-	-	-	0.93	(0.55 ,1.57)	0.7990	0.5033	
11		rs256298	0	1.23	(0.76 ,2.00)	0.3925	1.52	0.65	3.58	0.34	1.27	(0.80 ,2.02)	0.3009	0.2517	
12		rs310211	1	1.03	(0.63 ,1.67)	0.9100	1.04	0.48	2.25	0.92	1.03	(0.65 ,1.64)	0.8962	0.8948	
13		rs7546535	39	1.11	(0.68 ,1.83)	0.6670	0.76	0.22	2.58	0.66	1.07	(0.66 ,1.72)	0.7934	0.9769	
14		SOCS1	rs149311	3	1.20	(0.72 ,1.99)	0.4836	1.10	0.32	3.74	0.88	1.19	(0.73 ,1.93)	0.4915	0.5465
15		rs149597	2	1.15	(0.68 ,1.94)	0.5969	0.61	0.30	1.25	0.18	0.97	(0.59 ,1.61)	0.9144	0.2562	
16		rs193778	1	0.83	(0.51 ,1.36)	0.4669	1.24	0.47	3.33	0.66	0.88	(0.55 ,1.40)	0.5853	0.8065	
17		rs243317	1	0.81	(0.51 ,1.30)	0.3892	0.38	0.11	1.26	0.11	0.74	(0.47 ,1.17)	0.2021	0.1006	
18		rs408665	28	0.70	(0.42 ,1.16)	0.1631	0.81	0.41	1.58	0.53	0.72	(0.45 ,1.17)	0.1837	0.3624	
19		rs9490551	1	0.69	(0.42 ,1.14)	0.1504	0.87	0.45	1.69	0.68	0.73	(0.46 ,1.17)	0.1956	0.4341	
20		SOCS5	rs13402099	3	0.84	(0.46 ,1.55)	0.5836	-	-	-	-	0.75	(0.41 ,1.37)	0.3553	0.2191
21		rs13412085	0	0.88	(0.49 ,1.57)	0.6658	-	-	-	-	0.77	(0.43 ,1.37)	0.3735	0.2062	
22		SOCS6	rs17082355	0	0.97	(0.55 ,1.70)	0.9059	-	-	-	-	0.90	(0.51 ,1.59)	0.7158	0.5030
23		rs17809666	1	1.29	(0.65 ,2.56)	0.4603	3.78	0.29	49.10	0.31	1.36	(0.70 ,2.63)	0.3679	0.2906	
24		rs4891398	29	1.19	(0.71 ,1.99)	0.5150	1.45	0.75	2.81	0.27	1.25	(0.77 ,2.03)	0.3641	0.2685	
25		STAT1	rs10173099	10	1.27	(0.78 ,2.07)	0.3424	1.01	0.47	2.20	0.97	1.21	(0.76 ,1.94)	0.4219	0.6574
26		rs10199181	2	1.18	(0.71 ,1.95)	0.5205	1.09	0.53	2.21	0.82	1.16	(0.72 ,1.86)	0.5504	0.6849	
27		rs1168	3	0.92	(0.55 ,1.55)	0.7618	0.74	0.37	1.48	0.39	0.87	(0.53 ,1.42)	0.5813	0.4088	
28		rs12468579	1	1.29	(0.76 ,2.19)	0.3502	1.16	0.58	2.30	0.68	1.25	(0.75 ,2.08)	0.3843	0.5770	
29		rs12693591	0	0.94	(0.54 ,1.64)	0.8348	1.67	0.36	7.68	0.51	0.99	(0.58 ,1.68)	0.9614	0.8933	
30		rs13029247	2	1.18	(0.73 ,1.92)	0.4929	1.11	0.51	2.41	0.79	1.17	(0.74 ,1.86)	0.5041	0.5973	
31		rs13029253	0	1.68	(0.98 ,2.86)	0.0575	0.00	0.00	-	-	0.98	(0.90 ,2.62)	0.1139	0.2643	
32		rs13035504	1	1.01	(0.60 ,1.69)	0.9734	0.82	0.19	3.61	0.80	0.99	(0.60 ,1.63)	0.9712	0.9082	
33		rs13395605	0	1.23	(0.74 ,2.04)	0.4264	0.98	0.48	2.01	0.96	1.17	(0.72 ,1.89)	0.5371	0.8403	
34		rs1400057	0	1.05	(0.61 ,1.84)	0.8513	0.67	0.08	5.23	0.70	1.02	(0.60 ,1.76)	0.9334	0.9703	
35		rs1467169	0	1.16	(0.72 ,1.86)	0.5372	0.37	0.09	1.58	0.18	1.05	(0.65 ,1.64)	0.8890	0.6329	
36		rs1547550	20	1.66	(1.00 ,2.79)	0.0506	1.78	0.86	3.88	0.12	1.68	(1.03 ,2.75)	0.0359	0.0486	
37		rs16824035	1	0.94	(0.56 ,1.54)	0.8034	0.80	0.18	3.52	0.77	0.92	(0.56 ,1.53)	0.5565	0.7229	
38		rs17749316	0	1.39	(0.74 ,2.62)	0.3078	-	-	-	-	1.35	(0.72 ,2.53)	0.3562	0.4320	
39		rs17819766	0	1.05	(0.61 ,1.78)	0.8705	1.16	0.62	2.18	0.65	1.08	(0.66 ,1.77)	0.7588	0.6551	
40		rs2067695	0	1.69	(0.97 ,2.75)	0.5020	-	-	-	-	1.69	(0.97 ,2.75)	0.5020	0.5020	
41		rs2068604	1	1.28	(0.80 ,2.04)	0.3118	0.83	0.24	2.79	0.76	1.22	(0.77 ,1.93)	0.3945	0.5843	
42		rs2280232	1	0.86	(0.53 ,1.40)	0.5511	1.13	0.48	2.65	0.78	0.90	(0.57 ,1.43)	0.6617	0.8660	
43		rs2280233	4	0.89	(0.53 ,1.51)	0.6745	0.87	0.45	1.66	0.67	0.89	(0.54 ,1.45)	0.6307	0.6520	
44		rs2280234	5	1.65	(0.98 ,2.78)	0.0576	1.40	0.69	2.87	0.35	1.59	(0.97 ,2.62)	0.0675	0.1758	
45		rs4397637	3	1.14	(0.70 ,1.84)	0.6066	1.04	0.39	2.74	0.94	1.12	(0.71 ,1.78)	0.6301	0.7061	
46		rs432757	0	0.98	(0.57 ,1.68)	0.9312	0.51	0.07	3.87	0.51	0.93	(0.55 ,1.59)	0.7978	0.6712	
47		rs4853533	3	1.31	(0.79 ,2.16)	0.2972	1.15	0.56	2.34	0.70	1.27	(0.78 ,2.05)	0.3319	0.5070	
48		rs5672024	0	1.56	(0.93 ,2.61)	0.0592	1.08	0.53	2.17	0.84	1.41	(0.86 ,2.31)	0.1689	0.5351	
49		rs867637	2	1.24	(0.75 ,2.04)	0.3970	1.27	0.63	2.59	0.50	1.25	(0.78 ,2.00)	0.3585	0.3954	
50		STAT3	rs1053005	1	1.03	(0.64 ,1.68)	0.8903	0.53	0.12	2.29	0.40	0.97	(0.61 ,1.57)	0.9149	0.6870
51		rs1053023	1	1.03	(0.64 ,1.68)	0.8903	0.53	0.12	2.29	0.40	0.97	(0.61 ,1.57)	0.9149	0.6870	
52		rs1294918	1	0.79	(0.49 ,1.29)	0.3520	0.51	0.24	1.07	0.07	0.71	(0.45 ,1.13)	0.1508	0.0697	
53		rs17405722	0	1.21	(0.64 ,2.29)	0.5487	-	-	-	-	1.18	(0.63 ,2.22)	0.6119	0.6976	
54		rs293152	2	1.58	(0.93 ,2.70)	0.0592	1.75	0.91	3.36	0.09	1.63	(0.98 ,2.70)	0.0576	0.0670	
55		rs4103200	0	0.60	(0.37 ,0.98)	0.0433	0.40	0.14	1.14	0.09	0.57	(0.35 ,0.90)	0.0174	0.0149	
56		rs5053695	0	0.67	(0.41 ,1.08)	1.008	0.48	(0.21 ,1.09)	0.0807	0.62	(0.39 ,0.98)	0.0414	0.0333		
57		rs8911119	0	0.81	(0.50 ,1.29)	0.3723	0.33	(0.13 ,0.87)	0.0242	0.69	(0.44 ,1.10)	0.1161	0.0271		
58		rs9912773	0	0.64	(0.39 ,1.05)	0.0743	0.49	(0.17 ,1.41)	0.1867	0.61	(0.38 ,0.98)	0.0424	0.0427		
59		STAT4	rs10168266	0	0.92	(0.56 ,1.51)	0.7374	0.27	(0.04 ,2.05)	0.2080	0.84	(0.52 ,1.37)	0.4961	0.3026	
60		rs10189819	1	1.06	(0.64 ,1.73)	0.8320	1.34	(0.53 ,3.36)	0.5352	1.10	(0.69 ,1.75)	0.7019	0.5896		
61		rs10931481	0	0.98	(0.61 ,1.57)	0.9204	0.59	(0.24 ,1.45)	0.2502	0.89	(0.57 ,1.41)	0.6295	0.3641		
62		rs1685878	4	1.13	(0.67 ,1.89)	0.6543	1.01	(0.50 ,2.01)	0.9861	1.09	(0.67 ,1.79)	0.7222	0.8994		
63		rs1302076	56	0.91	(0.45 ,1.84)	0.8011	1.36	(0.16 ,1.14)	0.7767	0.94	(0.48 ,1.85)	0.8631	0.9342		
64		rs13389408	0	1.34	(0.80 ,2.26)	0.2696	-	-	-	-	1.26	(0.75 ,2.11)	0.3911	0.6065	
65		rs1517352	2	1.19	(0.71 ,1.99)	0.5185	1.15	(0.59 ,2.25)	0.6814	1.18	(0.72 ,1.92)	0.5155	0.6088		
66		rs16833177	0	1.25	(0.78 ,2.02)	0.3558	0.23	(0.03 ,1.73)	0.1537	1.10	(0.69 ,1.76)	0.6936	0.7657		
67		rs16833239	1	1.24	(0.69 ,2.22)	0.4683	-	-	-	-	1.21	(0.68 ,2.17)	0.5161	0.5864	
68		rs16833437	1	1.38	(0.83 ,2.30)	0.2095	1.42	(0.70 ,2.87)	0.3318	1.39	(0.86 ,2.26)	0.1806	0.2255		
69		rs17769459	0	1.10	(0.55 ,2.22)	0.7810	-	-	-	-	1.07	(0.53 ,2.14)	0.8573	0.9454	
70		rs2459611	0	1.76	(1.06 ,2.92)	0.2825	-	-	-	-	1.63	(0.99 ,2.70)	0.0560	0.1426	
71		rs3024861	1	1.07	(0.67 ,1.73)	0.7732	0.71								

1
2 **1 Title: Association of JAK-STAT pathway related genes with lymphoma risk: results of a**
3 **2 European case-control study (EpiLymph)**

3
4 **Running Title: Association of JAK-STAT pathway related genes with lymphoma risk**

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26

1 1 Summary

2 Previous studies have suggested an important role of the JAK-STAT signalling pathway
3 in tumour development. Therefore, we explored genetic variants in JAK-STAT pathway
4 associated genes with lymphoma risk. In samples of the EpiLymph case-control study we
5 genotyped 1536 single nucleotide polymorphisms (SNPs) using GoldenGate BeadArrayTM
6 Technology (Illumina, San Diego, CA). Here, we report the associations between selected
7 SNPs and haplotypes of the JAK-STAT pathway and risk of Hodgkin lymphoma (HL), B-cell
8 lymphoma (B-NHL) and most frequent B-NHL subtypes. Among 210 relevant JAK-STAT
9 pathway-related SNPs, polymorphisms in nine genes (*BMF*, *IFNG*, *IL12A*, *SOCS1*, *STAT1*,
10 *STAT3*, *STAT5A*, *STAT6*, *TP63*) were significantly associated with lymphoma risk. At a
11 study-wise significance level, we obtained a risk reduction of 28 % among carriers of the
12 heterozygous genotype of the *STAT3* variant (rs1053023) for B-NHL. For six other variants
13 within the *STAT3* gene we observed an inverse association with different lymphoma subtypes.
14 A reduced risk for HL was observed for the heterozygous genotype of the *STAT6* SNP
15 (rs324011). **This is an explorative investigation to examine associations between JAK-**
16 **STAT signalling related genes and lymphoma risk. The results implicate a relevant role**
17 **of certain pathway-related genes in the lymphomagenesis, but still need to be approved**
18 **by independent studies.**

19
20 **Keywords:** lymphoma, susceptibility, JAK-STAT, epidemiology, association study

22 22 Introduction

23 Lymphomas are a heterogeneous group of malignancies originating from lymphocytes,
24 with the main types of non-Hodgkin lymphoma and Hodgkin lymphoma (Jaffe E. S. 2001)
25 and multiple subtypes within these categories. Strong risk factors for these lymphoid
26 malignancies are genetic and acquired immunodeficiencies (Ekstrom Smedby, *et al* 2008),

1 infectious agents (Hjalgrim and Engels 2008) and several occupational exposures (Cocco, *et*
2 *al* 2010, Miligi, *et al* 2006). Apart from these, various studies (Mensah, *et al* 2007,
3 Villeneuve, *et al* 2009, Wang, *et al* 2007, Zhang, *et al* 2007) reported an increased risk of
4 NHL for those with a first degree relative diagnosed with a haematopoietic malignancy. This
5 data indicates the importance of genetic predisposition for lymphoma risk (Skibola, *et al*
6 2007), and the interplay with environmental factors as the possible etiological mechanism.

7 The signal-transducer and activator of transcription (STAT) family consists of 7 members
8 latently expressed in the cytoplasm and which are phosphorylated by Janus kinases (JAK)
9 cytosolic tyrosine kinases in response to different cytokine stimuli (Schindler, *et al* 2007).
10 They are involved in signalling cascades of various immune regulatory pathways (Egwuagu
11 2009). Among these factors, particularly stat3 is emerging as an important player in the
12 development of malignancies. It is constitutively activated in different cancer types (Coppo, *et*
13 *al* 2009, Ding, *et al* 2008, Frank 2003, Hazan-Halevy, *et al* 2010, Mackenzie, *et al* 2008,
14 Tomita, *et al* 2006), and known to promote tumourigenesis by enhancing expression of pro-
15 survival factors such as B-cell lymphoma 2 (bcl-2), bcl-xL and myeloid cell leukaemia
16 sequence 1 (mcl-1) (reviewed by (Hu and Ivashkiv 2009, Yu, *et al* 2009)). Also other factors
17 of this family, such as stat 1, 5 and 6 appear to play a role in the pathogenesis of human
18 cancers (Adamkova, *et al* 2007, Bruns and Kaplan 2006, Martini, *et al* 2008, Yu and Jove
19 2004) and present constitutive activation in breast cancer, head and neck cancer, leukaemia
20 and multiple myeloma (Bowman, *et al* 2000, Bromberg 2002, Yu and Jove 2004). Their
21 prominent role in signalling pathways of well-established risk factors for cancer and their
22 implication in various cancer types prompted us to investigate the association between genetic
23 variants of selected genes of the JAK-STAT pathway and lymphoma risk in samples of
24 participants to the European EpiLymph multi-centre case-control study.
25

1
2
3 **1 Material and Methods**
4
5 **2 Study design**

6 A detailed description of the EpiLymph study has been published elsewhere (de Sanjose,
7 *et al* 2006). Briefly, the EpiLymph study was carried out in six European countries (Spain,
8 France, Germany, Italy, Ireland, and Czech Republic) from 1998 to 2004. Incident cases of
9 lymphoid malignancies were recruited for the study and their diagnoses were categorized
10 according to the WHO classification (Jaffe E. S. 2001). Controls were selected from the same
11 hospitals as the cases in all centers, except in Germany and Italy where they were randomly
12 sampled from population registries. Controls were frequency-matched to cases by age, sex,
13 and study centre. The study included 2,348 cases and 2,462 controls. All participants were
14 asked to donate a blood sample for DNA extraction and underwent a personal interview
15 gathering sociodemographic information, familial and medical history, smoking and alcohol
16 habits, a complete occupational history and details on recreational and occupational exposure
17 to sunlight. The study was approved by the competent ethical committee in each study area,
18 and informed consent was obtained from each study subject. The present genotyping study
19 was restricted to EpiLymph study subjects for whom DNA was available: a total of 1,481
20 cases of lymphoma, including Hodgkin lymphoma (HL, $n=272$), T-cell lymphoma (T-NHL,
21 $n=95$), and B-cell lymphoma (B-NHL, $n=1,114$), in turn including the subtypes diffuse large
22 B-cell lymphoma (DLBCL, $n=408$), follicular lymphoma (FL, $n=200$), chronic lymphocytic
23 leukaemia (CLL, $n=340$), marginal zone B-cell lymphoma (MZL, $n=112$), and mantle cell
24 lymphoma (MCL, $n=54$). The corresponding EpiLymph controls ($n=1,491$) were frequency-
25 matched by age (< 30, 30-39, 40-49, 50-59, 60-69, 70-79, ≥ 80), sex, and study centre. The
26 German cases and controls were individually matched by gender and age (± 1 year of birth).

1
2 1 *SNP selection*

3 2 Genes and single nucleotide polymorphisms (SNPs) which have either previously been
4 3 associated with lymphomagenesis or have a high biological plausibility to be involved in the
5 4 development of lymphoid neoplasms, were selected from public databases. Tagging SNPs for
6 5 the selected genes and their ±10kb flanking region were selected via pairwise SNP selection
7 6 with an r^2 threshold of 0.9 using Haplovew (Barrett, *et al* 2005, Carlson, *et al* 2004, de
8 7 Bakker, *et al* 2005) and the genotyping information for the CEU population of the HapMap
9 8 database (Consortium 2003) (<http://hapmap.ncbi.nlm.nih.gov>, NCBI 36 assembly, dbSNP
10 9 b126, phase II).

11 10 Only SNPs with a minor allele frequency (MAF) $\geq 5\%$ and an Illumina GoldenGate
12 11 Design Score of at least 0.6 were included into the oligonucleotide pooled assay (OPA).

13 12

14 13 *Genotyping and sample preparation*

15 14 Genotyping was performed using the IlluminaTM GoldenGate assay technology (Illumina,
16 15 San Diego, CA). The 1,481 cases and 1,491 controls were newly plated in a 96-well format.
17 16 350 ng of DNA was required, with a concentration of at least 70 ng/ μ l. The available DNA
18 17 concentration was measured using PicoGreen[®] (Invitrogen, Darmstadt, Germany). Samples
19 18 with insufficient DNA ($n=822$) were whole-genome amplified according to the
20 19 manufacturer's protocol for the Illustra GenomePhi V2 DNA Amplification Kit (GE
21 20 Healthcare, Buckinghamshire, UK). In addition, DNA extraction from blood clots was
22 21 performed for 312 samples using the Gentra Puregene Blood Kit (Qiagen, Hilden, Germany).
23 22 For quality control, three random DNA samples were placed on each plate for replication.

24 23 The genotyping was carried out according to the manufacturer's protocol and as specified
25 24 by Fan et al. (Fan, *et al* 2006, Fan, *et al* 2003), in cooperation with the Genomics &
26 25 Proteomics Core Facility at the German Cancer Research Centre in Heidelberg.

1
2 After generation of genotype calls with the GenCall version (5.2.0), all SNPs were
3 visually examined for individual clustering. Loci with poor performance or monomorphic
4 characteristics were excluded.

5
6 Individual DNA samples with a call rate below 0.96 were removed from the dataset.

7 *Statistical analysis*

8 To test for deviation of genotype distribution from Hardy-Weinberg equilibrium (HWE)
9 among the controls we conducted a chi-square test. SNPs with deviation from HWE in
10 controls were excluded from further analysis. We used an adjusted *p*-value of 3×10^{-5}
11 (Bonferroni correction for 1,418 SNPs relevant after quality control). We also determined
12 whether the allelic frequency distribution differed between cases and controls.

13 Heterogeneity of risks according to sex, age (cut-off for B-NHL: 50years, HL: 40years)
14 and study centres was tested using a chi-square test.

15 *SNP analysis*

16 Of the 1,536 SNPs genotyped in 1,481 cases and 1,491 controls, 97 were excluded from
17 analyses due to clustering and low call frequency, 21 due to being monomorphic in our study
18 population, and 42 because they showed a deviation from HWE (*p*-value less than 3×10^{-5})
19 among the controls. Irrespectively, a total of 109 samples were excluded on the basis of a call
20 rate less than 0.96, leading to a failure rate of 3.6 %. The failure rates for cases and controls
21 were 4.5 % (*n*=65) and 3 % (*n*=44), respectively.

22 The associations between polymorphisms and risk of HL, T-NHL and B-NHL, as well as
23 the most frequent B-NHL subtypes, were estimated by calculating odds ratios (OR), and the
24 corresponding 95 % confidence intervals (CI) using unconditional logistic regression,
25 adjusting for age (continuous), sex and study centre, using SAS 9.2 (SAS Institute Inc. Cary,
26 NC). **After quality control of the genotyping data, samples were excluded from the**

1 statistical analysis. To avoid loss of power in conditional logistic regression analysis,
2 frequency matching for the whole study population using the matching variables (age,
3 sex and study centre) was performed as was done in previous publications of the
4 EpiLymph study (Besson, et al 2006, de Sanjose, et al 2006). Previous analysis presented
5 similar results from conditional and unconditional logistic regression analysis of
6 EpiLymph data (Boffetta, et al 2008). Therefore, subsequent statistical analyses were
7 performed using unconditional logistic regression adjusted for the matching variables
8 (de Sanjose, et al 2006).

9 The homozygote genotype of the most common allele was used as reference group. To
10 increase statistical power and detect the allelic effect, we performed tests under the dominant
11 model by combining the heterozygous and mutant genotype. We also calculated the risk
12 association for each genotype by using the co-dominant model for the logistic regression.

13 The test for trend was calculated including a continuous SNP variable in the log-additive
14 model (Breslow NE 2000). As positive association we defined an odds ratio larger than 1,
15 whereas an inverse association was specified by an OR below 1.

16 Additionally, we conducted analysis for risk of HL with conditional logistic regression
17 with complete case sets, 1:1 matched within each age-category (< 30, 30-39, 40-49, 50-59,
18 60-69, 70-79, ≥ 80) and by sex and study centre. As sensitivity analysis for B-NHL we
19 conducted stratified analysis by sex and age, with cut point set at 50 years as performed by
20 Lan et al. and Wang et al. (Lan, et al 2009, Wang, et al 2007). For HL cases the stratified
21 analysis by age was done with a cut point of less than 40 years versus equal or older than 40
22 years, due to the bimodal age distribution.

23 As a large number of tests were performed, we had to control the family-wise error
24 rate. The gold standard to adjust for multiple comparison is a permutation test, which is
25 computational extensive. Since, this is a candidate gene approach based on prior
26 knowledge of the relevance of the included genes, we selected the SNP Spectral

1
2 1 **Decomposition Approach (*simpleM* method) (Gao, et al 2008), which yields similar**
3 2 **results as a permutation based approach (Johnson, et al 2010). The *simpleM* method**
4 3 **starts with the calculation of the effective number of independent SNPs, M_{eff} , for each**
5 4 **gene, based on the underlying LD structure of the genotyping data.** Gene-specific M_{eff}

6 5 values ($^G M_{eff}$) were received, which were added up to a study-wise M_{eff} value, $^{SG} M_{eff} =$
7 6 $\sum(^G M_{eff})$ under the assumption that the genes are independent with respect to the endpoints.
8 7 By applying the Bonferroni correction to the number of independent tests, we obtained a
9 8 study-wise significance level of $0.05/^{SG} M_{eff} = 2.9 \times 10^{-4}$. **Based on the distinct aetiology of**
10 9 **the three main lymphoma subtypes (B-NHL, T-NHL, and HL) (Morton, et al 2008), we**
11 10 **considered the tested association between SNPs and the subtypes as independent from**
12 11 **each other and did not take them into account for the multiple comparison correction.**

13 12 Statistical interaction was assessed for the SNPs of the most prominent genes for which
14 13 biological interaction was plausible based on the current knowledge of the JAK-STAT
15 14 pathway (Yu, et al 2009), by adding an interaction term in the regression model. To formally
16 15 test statistical interaction, the log-likelihood ratio test was applied. Furthermore, if the
17 16 interaction *p*-value was below 0.05 as well as for the most promising SNPs of the single SNP
18 17 analysis, where biological interaction was likely, we calculated risk estimates for one genetic
19 18 variant stratified by the genotype of the second variant included in the previous regression
20 19 model.

21 *Haplotype analysis*

22 22 The genotyping data of the controls was transformed into Haplovew format (linkage
23 23 format) using the SNPtool (http://www.dkfz.de/de/molgen_epidemiology/tools/SNPtool.html)
24 24 to reconstruct haplotype blocks with Haplovew, using the implemented algorithm based on
25 25 confidence bounds by Gabriel et al. (Gabriel, et al 2002). The cut-off values for the haplotype

1 block generation are: MAF > 5 %, Hardy Weinberg *p*-value cut-off ≥ 0.01 and 75 % of non-
2 missing genotypes of this marker.

3 Maximum likelihood haplotype frequency estimates were generated based on the
4 expectation-maximization (EM) algorithm implemented in the *PROC HAPLOTYPE*
5 procedure of the SAS/Genetics package (SAS 9.2). Haplotypes with a frequency < 0.05 were
6 defined as rare haplotypes and combined. The haplotype with the highest frequency was used
7 as reference.

9 Results

10 Descriptive Statistics

11 Details regarding the main characteristics of the study population used for the statistical
12 analysis and the distribution of cases are presented in Table I. Briefly, 1,414 cases and 1,447
13 controls were included in the statistical analysis. The age distribution was similar among
14 cases and controls and the mean age is 55 years for both. To assess if the frequency matching
15 had worked properly, heterogeneity between cases and controls was checked by applying the
16 chi-square test, which revealed non-significant *p*-values for all three matching variables (age-
17 group: *p*=0.9; sex: *p*=0.9 and study centre: *p*=1.0). The largest lymphoma subtypes were
18 Hodgkin lymphoma (*n*=259), chronic lymphocytic leukaemia (*n*=321), and diffuse large B-
19 cell lymphoma (*n*=391).

21 Results of Single SNP analyses

22 Supplemental Table 1 (S1) summarizes the genes and the 210 SNPs belonging to the
23 JAK-STAT signalling pathway we studied. Eight SNPs (rs1053005, rs1053023, rs12949918,
24 rs4103200, rs6503695, rs9891119, rs9912773, rs2293158) in *STAT3* and *STAT5A* showed a
25 nominal significant association (*p*-trend < 0.01) with B-cell lymphomas combined. Five SNPs
26 (rs6581795, rs4103200, rs9912773, rs6790068, rs9681004) in interferon gamma gene

1
2
3 1 (*IFNG*), *STAT3*, *STAT6* and tumour protein 63 gene (*TP63*) showed a nominal sufficient
4
5 2 association with HL risk (*p*-trend < 0.05). Two of these SNPs showed a study-wise significant
6
7 3 association with lymphoma risk (*p*-value ≤ 0.0003). The heterozygous genotype of variant
8
9 4 rs1053023, located in *STAT3*, was associated with a 28 % risk reduction for B-NHL (OR_{AG} of
10
11 5 0.72, 95 % CI 0.60-0.86, *p*-value 0.0003). Moreover, for the *STAT6* variant, rs324011, a risk
12
13 6 reduction of 45 % was obtained for carriers of the heterozygous genotype (OR_{GA} of 0.55, 95
14
15 7 % CI 0.40-0.76, *p*-value 0.0003). The corresponding odds ratios and 95 % confidence
16
17 8 intervals of the most prominent SNPs are shown in Table II, as for the main B-cell lymphoma
18
19 9 subtypes in Table III.

20
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25
26
27 11 *Associations with B-NHL and subtypes*
28
29
30 12 Among the 10 tagSNPs of *STAT3*, 7 SNPs (rs1053005, rs1053023, rs12949918,
31
32 13 rs4103200, rs6503695, rs9891119, rs9912773) showed a nominal statistically significant (*p*-
33
34 14 value <0.01) inverse association with B-NHL overall, and stayed significant at the $\alpha=0.05$
35
36 15 level for DLBCL (see Table III and S2). *STAT3* rs4103200 was related to B-NHL risk with an
37
38 16 OR_{CG/CC} of 0.78 (95 % CI 0.66-0.92) and a *p*-value for trend of 0.003. Similar risk reductions
39
40 17 in association with this variant were also evident for DLBCL (OR_{GC/CC} of 0.76, 95 % CI 0.60-
41
42 18 0.96); FL (OR_{GC/CC} of 0.73, 95% CI 0.54-0.99); and HL (OR_{CC} of 0.49, 95 % CI 0.27-0.90, *p*-
43
44 19 value for trend 0.006).

45
46
47 20 Furthermore, a nominal significant association was observed for *STAT5A* – homozygous
48
49 21 mutant carriers of rs2293158 were at 32 % reduced risk of B-NHL (95 % CI 0.51-0.92, *p*-
50
51 22 trend 0.002). An inverse association could also be seen for the other B-NHL subtypes, but
52
53 23 with lower significance.

54
55
56
57 24 The mutant allele of the suppressor of cytokine signalling 1 gene (*SOC51*) variant
58
59 25 showed a nominal significant association with an increased risk for B-NHL (OR
60 26 rs149311_{GA/AA} 1.42, 95% CI 1.12-1.60) as well as for DLBCL (*p*-trend of 0.003).

1 Two variants in Bcl-2 modifying factor gene (*BMF*) (rs3923235, rs7183977) were
2 associated with risk for DLBCL (OR rs3923235_{GG} of 0.43, 95 % CI 0.24-0.77; OR
3 rs7183977_{GG} of 0.69, 95 % CI 0.46-1.02), but neither with total B-cell lymphomas nor other
4 subentities (Table III). The GG genotype of interferon gamma receptor 1 gene (*IFNGR1*)
5 variant (rs4896243) was positively associated with CLL risk (OR_{GG} 1.69, 95 % CI 1.19-2.40).

6

7 *Associations with T-NHL*

8 The analysis between the genetic variants and risk for T-NHL did not reveal any
9 association with a p-value less than 0.01. However, for the *STAT5A* variant (rs2293158) we
10 observed an inverse association with the risk of T-NHL for the GG genotype (OR_{GG} 0.18,
11 95 % CI 0.04-0.76) with a p-trend of 0.03 (see Table II). Among carriers of the interleukin
12 12A gene (*IL12A*) variant, for heterozygous mutants a nearly 2-fold increase in the T-NHL
13 risk was detected (OR rs755004_{GA} 1.93, 95 % CI 1.22-3.05).

14

15 *Associations with HL*

16 Within the HL analysis we obtained one SNP with study-wide significance, and
17 additionally 11 SNPs showed nominal significant association with HL risk. (Table II and
18 Supplementary Table 3). HL risk was most strikingly associated with variants in *STAT6*.
19 Here, rs324011 and rs703817 showed a 40-45 % risk reduction for HL (OR rs324011_{GA/AA} of
20 0.61, 95 % CI 0.45-0.82; OR rs703817_{GA/AA} of 0.62, 95 % CI 0.45-0.85). Statistical
21 significance for the association of HL risk with both *STAT6* variants at the $\alpha = 0.01$ level was
22 lost when only complete case sets were analyzed (Supplemental Table S3).

23 In addition, the conditional logistic regression analyses revealed an association of caspase
24 6 (*CASP6*) (rs1800627) with an increased risk (OR rs1800627_{AG/GG} of 1.75, 95 % CI 1.16-
25 2.64, p-value 0.007) and *STAT4* (rs4853546) with decreased risk for HL (OR rs4853546_{GA/AA}
26 0.59, 95 % CI 0.40-0.85, p-value 0.005), respectively.

1

2 *Associations within the stratified analysis*

3 The age-stratified analysis revealed significant associations for HL with the variants of
4 *IFNG* (rs2069718) and *STAT4* (rs7599504) as well as with *TP63* variants (rs6790068,
5 rs9681004) among the older age-group (S5). Within the younger B-NHL cases (age < 50 y)
6 the *CASP6* variant (rs5030552) was associated with an increased risk ($OR_{AG/GG}$ 1.94, 95 % CI
7 1.22-3.11, *p*-trend 0.003). The analysis by sex showed a decreased risk for women, who were
8 heterozygous for the *IL7R* variant rs12516866 (OR rs12516866_{CA} 0.61, 95 % CI 0.47-0.81, *p*-
9 trend 0.03) (data not shown). For the stratified analyses all herein presented *p*-values for
10 heterogeneity were below 0.05.

11

12 *Haplotype associations*

13 The estimated haplotype frequencies with the most frequent haplotype taken as the
14 reference are presented in Supplemental Table (S4). Mainly the haplotype-based associations
15 were consistent with those of single SNP based analyses. The *STAT3* haplotype (rs4103200-
16 rs9891119-rs9912773-rs12949918-rs17405722) with a frequency of 27 % and containing the
17 two most significant *STAT3* SNPs, rs4103200 and rs9912773, showed a reduced risk for B-
18 NHL (OR of 0.82, 95 % CI 0.72-0.94) and DLBCL (OR of 0.81, 95 % CI 0.67-0.98). HL risk
19 was significantly increased for carriers of haplotypes of *BMF* (Block 1-3), *IFNG* (Block1 and
20 2), *STAT6* and *TP63* (see Supplemental Table 4).

21

22 *Gene-gene interaction*

23 We formally investigated interaction between different genes of the JAK-STAT pathway
24 by comparing the genetic variants of *CASP6*, *STAT3*, *STAT1*, *IFNG* and *IL12A* between B-
25 NHL cases and controls stratified by genotype of *BMF*, *STAT1*, *IL10*, *IFNG*, *SOCS1* and
26 *STAT4*, respectively. Significant results are summarized in Table IV.

1 Interaction between the homozygous mutant carriers of *IL12A* (rs4680534) and the
2 homozygous mutants of *STAT4* (rs517352) resulted in a nearly 3-fold increased B-NHL risk
3 (OR of 2.80, 95 % CI 1.30-6.05). Interaction between the *CASP6* variant (rs5030552) and two
4 *BMF* variants (rs537455, rs16970325) showed a 57 % and 50 % increased risk, respectively.
5 The interaction analysis of *STAT3* and *STAT1* revealed a 40 % reduced risk for carriers of the
6 homozygous mutant of the *STAT3* variant (rs6503695) in carriers of the AA genotype of
7 *STAT1* (OR rs6503695 of 0.60, 95 % CI 0.41-0.88). Among those of the *IL10* wildtype,
8 carriers of the heterozygous mutant of the *STAT3* variant (rs1053023) showed decreased risk
9 for B-NHL at the study-wise significance level (Table IV). Additionally, the heterozygous
10 mutant of the *STAT3* SNP (rs4103200) was associated with a 29 % decreased risk for B-NHL
11 among carriers of the *IFNG* wildtype.

12 **Discussion**

13 Our study identified 9 SNPs in 3 genes (*SOCS1*, *STAT3*, *STAT5A*) implicated in the JAK-
14 STAT pathways significantly associated with risk of B-cell lymphoma, and 10 SNPs in 7
15 genes of this pathway (*BMF*, *CASP6*, *IFNG*, *STAT3*, *STAT4*, *STAT6*, *TP63*) associated with
16 HL risk.

17 Seven SNPs in *STAT3* presented a statistically significant inverse association with B-cell
18 lymphoma risk, and particularly with the DLBCL and FL subtypes. One of these, the
19 rs1053023, located in haplotype block 1, showed even study-wise significance. To our
20 knowledge this is the first time that genetic variants in *STAT3* have been associated with
21 lymphoma risk. Stat3 is a major mediator of il6 activation (Leonard and O'Shea 1998) and it
22 is induced by several exogenous factors, such as like lipopolysaccharid (LPS) (Samavati, *et al*
23 2009), cigarette smoke (Liu 2007), and infection with Hepatitis C virus (Yoshida, *et al* 2002).
24 In normal cells stat3 activation is usually transient, whereas it is often constitutively activated
25 in many cancers (reviewed in (Benekli, *et al* 2003, Bowman, *et al* 2000)). The transcription

1 factor promotes tumour development and survival of tumour cells by regulating pro-survival
2 factors, such as bcl-xL, bcl-2 and mcl-1 (reviewed (Hu and Ivashkiv 2009)). Aberrant stat3
3 activation has also been shown for HL (Kube, *et al* 2001), NK/T-cell lymphoma (Chiarle, *et*
4 *al* 2005, Zhang, *et al* 2002, Zheng, *et al* 2002), and activated DLBCL (Ding, *et al* 2008, Lam,
5 *et al* 2008). The interplay between STAT and nuclear factor kappa B (NF κ B) pathways
6 appears to be implicated in lymphomagenesis (Bollrath and Greten 2009, Lam, *et al* 2008,
7 Scheeren, *et al* 2008).

8 Mutations in *STAT3* are a hallmark of Hyper-IgE-syndrome (HIES), a complex primary
9 immunodeficiency (Minegishi and Karasuyama 2009) and several case reports also suggest an
10 increased risk for certain lymphoma types and HL among HIES patients (Belada, *et al* 2010,
11 Kashef, *et al* 2006, Minegishi 2009, Wallet, *et al* 2007). This adds to the eminent role of stat3
12 in immune response and the remarkable impact of its dysfunction in the aetiology of various
13 immune diseases.

14 On the basis of the close functional relationship between stat3/stat1 and the cytokines il6
15 and il10, joint effects have been explored. For B-cell lymphoma we found evidence for
16 statistical interaction between *STAT3* and *IL10*, as well as between *STAT3* and *STAT1*.
17 Immunoregulatory il10 is upregulated by stat3 and is part of the stat3 feedforward loop (Yu,
18 *et al* 2007). The opponent factor of the JAK-STAT signalling socs1, a member of the family
19 of suppressors of cytokine signalling (Alexander 2002), was associated with increased risk for
20 B-NHL. This is in line with recent publications indicating socs1 as tumour suppressor
21 (Weniger, *et al* 2006), and data reporting inactivation of this gene due to mutation or
22 hypermethylation in B-cell lymphoma entities and multiple myeloma, respectively (Galm, *et*
23 *al* 2003, Mottok, *et al* 2009).

24 One of our most prominent results was the inverse association of *STAT5A* rs2293158
25 mutant genotype (GG) with risk of all main B-cell lymphoma subtypes (DLBCL, FL, CLL),
26 as well as for T-NHL and HL. Constitutively activated stat5 in B-cell lymphoma cell lines

1 induces the important cell cycle regulator cylinD1 (Melzner, *et al* 2005). A prominent target
2 gene of stat5 is *BCL6*, encoding bcl-6, which regulates the expression of stat3 (Ding, *et al*
3 2008) and is crucial for germinal centre development. Genetic variability of *BCL6* has
4 previously been associated with NHL risk (Jardin, *et al* 2007, Morton, *et al* 2009, Parekh, *et*
5 *al* 2007, Saito, *et al* 2009, Tibiletti, *et al* 2009, Zhang, *et al* 2005). Taken together, our results
6 add epidemiological evidence to the significant role of STAT genes in lymphomagenesis.

7 Bmf binds to bcl-2 and functions as an apoptotic activator. Recent mice data suggests a
8 relevance of this factor in c-myc-driven B-cell lymphomagenesis (Frenzel, *et al* 2010) and γ
9 irradiation-induced thymic lymphoma development (Labi, *et al* 2008). In our study, variants
10 in *BMF* (rs7183977, rs3923235) were specifically associated with DLBCL risk, but not with
11 the other lymphoma subtypes. Noteworthy is the evidence for gene-gene interactions between
12 variants in *BMF* and *CASP6*, which were seen for B-cell lymphoma. This supports the
13 connection between variability in genes of apoptotic pathways and the pathogenesis of
14 lymphomas (Lan, *et al* 2009, Morton, *et al* 2009).

15 Pathogenesis of the various lymphoma subentities differs in relation to some
16 environmental (Fisher and Fisher 2004, Landgren and Caporaso 2007, Smedby, *et al* 2006,
17 Thomas, *et al* 2002) and also underlying genetic risk factors (Caporaso, *et al* 2009, El-Zein, *et*
18 *al* 2009, Skibola, *et al* 2007, Wang, *et al* 2006). In this study of the JAK-STAT pathway
19 related genes, HL risk has been associated with variants in *STAT3* (rs4103200, rs9912773),
20 *STAT6* (rs324011, rs703817) and *TP63* (rs6790068, rs9681004).

21 A hallmark of classical HL is the deregulated cytokine expression, particularly of il6 and
22 il13, which might promote the oncogenic transformation (Skinnider, *et al* 2002, Skinnider and
23 Mak 2002). These cytokines are well-known activators of the JAK-STAT pathway. Previous
24 data on HL cell lines support an important role of stat3 in the genesis of HL (Baus and
25 Pfitzner 2006, Kube, *et al* 2001, Skinnider, *et al* 2002, Skinnider and Mak 2002), and
26 inhibition of this pathway via small molecules is discussed as a therapeutic option (Holtick, *et*

1
2 1 *al* 2005, Kim, *et al* 2008, Mackenzie, *et al* 2008). Adding to this point, are observations from
3 tissue microarrays, where stat3 was identified as heavily over expressed in Hodgkin and Reed
4 Sternberg (HRS) cells (Garcia, *et al* 2003).

5 4 Carriers of the rare putatively functional variant in *STAT6* (rs324011) were at reduced
6 risk for HL. This *STAT6* variant located in a NF κ B binding site in intron2 appears to have an
7 impact on stat6 isoform expression (Schedel, *et al* 2004, Schedel, *et al* 2009) and was
8 previously associated with elevated serum IgE levels (Kabesch, *et al* 2006, Weidinger, *et al*
9 2004). Stat6 activation is a common and distinct feature of HRS cells (Skinnider and Mak
10 2002) and has been associated with HRS cell survival antagonistic to stat1 activity (Baus and
11 Pfitzner 2006). Genomic imbalances detected in HRS cells revealed a frequent gain of *STAT6*
12 (Feys, *et al* 2007, Hartmann, *et al* 2008).

13 12 We observed an 80 % increased risk for HL among homozygous carriers of the mutant
14 allele of the *IFNG* SNP rs2069718. For this variant located in intron 3, an influence on ifng
15 expression was reported (Pravica, *et al* 2000) and an association with the risk of SLE (OR
16 2.42 for CC vs TT/TC) (Kim, *et al* 2009), a reported risk factor for NHL and HL (Bernatsky,
17 *et al* 2007, Gayed, *et al* 2009, Landgren, *et al* 2006, Mellemkjaer, *et al* 2008).

18 17 A major strength of our study is the sample size, which allowed analysis of genetic
19 variants for lymphoma overall, as well as for the major subtypes like DLBCL, FL and CLL.
20 However, the power to detect associations with rare subtypes such as T-NHL, MZL and MCL
21 was limited, and the same holds true for the analysis of strata by sex and age.

22 21 Power for the detection of GxG interactions was limited in this study. However our
23 analysis of biologically plausible interactions may put forward good candidates for replication
24 in the framework of pooled analyses.

25 24 Another limitation of the presented study setup is the incomplete coverage of genes
26 related to the JAK-STAT pathway. Though, we were not able to give information about the
risk profile of variants in genes of the entire pathway in the context of lymphomagenesis.

1 Since the EpiLymph study was conducted in different European countries we checked for
2 heterogeneity of our results across the different study centres. Among the SNPs with
3 significant association, four variants (rs6503685, rs9912773, rs34997637, rs4853546)
4 presented heterogeneity between study centres. Considering the high LD of the associated
5 *STAT3* variants, their independent role in lymphoma aetiology is questionable. Thus, a more
6 in-depth analysis of this gene is recommended to identify the functional variant(s) underlying
7 differential risk for lymphoma associated with this region.

8 **This exploration of the implication of JAK-STAT signalling related genes in**
9 **lymphoma aetiology involved a large number of performed tests and required an**
10 **adjustment for multiple comparison.** Since, prior knowledge about the biological
11 relevance of the genes was used for the selection of candidate genes, a less stringent
12 significance threshold can be used (Hirschhorn and Altshuler 2002), as compared to
13 GWAS. We applied the SNP Spectral Decomposition Approach (*simpleM* method) first
14 introduced by Gao et al. (Gao, et al 2008) and applied in several recent association
15 studies (He, et al 2010, Reynolds, et al 2010). This method takes the correlation between
16 the different SNPs into account and calculates the effective number of independent tests
17 for each gene.

18 Within the single SNP analysis two variants showed study-wise significance and support
19 their relevance for lymphomagenesis. Furthermore, the results from the single point analyses
20 were underlined by the haplotype analysis as well as by the GxG analysis. Nevertheless, to
21 our knowledge there is no convenient and comprehensible solution to account for multiple
22 comparisons due to subtype analyses. As a result, we only considered for the number of tests
23 due to the number of analyzed SNPs.

24 SNPs associated with DLBCL in this study were not listed among the top 30 ranked
25 SNPs associated with DLBCL in Skibola et al. (Skibola, et al 2009). But their analysis was
26 based on a moderate number of DLBCL cases (n=221) and had limited power to identify

1 variants of moderate risk. In general, there is an ongoing discussion that GWAS only identify
2 genetic variants with a strong impact on disease development and are not able to detect those
3 with smaller effects (Wu, *et al* 2010).

4 Nevertheless, recent experimental and clinical data (Baran-Marszak, *et al* 2010, Baus, *et*
5 *al* 2009, Cotto, *et al* 2010, Ding, *et al* 2008, Hazan-Halevy, *et al* 2010, Kupferman, *et al*
6 2009, Mackenzie, *et al* 2008, Martini, *et al* 2008, Stewart, *et al* 2009, Verma, *et al* 2010,
7 Zhang, *et al* 2010), linking JAK-STAT pathway genes with the pathogenesis of lymphomas
8 provide strong biological support for the observed associations.

9 To our knowledge, we reported for the first time inter-individual differences in
10 susceptibility to the major lymphoma subtypes in relation to variability in genes related to the
11 JAK-STAT pathway, specifically *STAT3* (all lymphoma), *STAT6* (HL) and *STAT5A* (B-cell
12 lymphoma). Our data adds to the growing evidence of a pivotal role of this pathway in cancer
13 pathogenesis and other inflammation-driven phenotypes. Replication of our findings in
14 independent studies and pooled analyses are warranted to assess subtype-specific risks and
15 gene-gene interactions, for which statistical power in our study was limited.

16

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1
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10 9 **10 Conflict of interest**

11 The authors declare no conflict of interest.

1 1 **Table I.** Selected characteristics of the final sample subset of the EpiLymph study

Characteristics	Case	Control
	patients N (%)*	subjects N (%)*
Age		
<30	147 (10)	129 (9)
30-39	147 (10)	153 (11)
40-49	175 (12)	183 (13)
50-59	269 (19)	274 (19)
60-69	390 (28)	397 (27)
≥70	286 (21)	311 (21)
Study Centre		
Spain	301 (21)	318 (22)
France	149 (11)	152 (10)
Germany	518 (37)	530 (37)
Italy	106 (7)	110 (8)
Ireland	105 (7)	102 (7)
Czech Republic	235 (17)	235 (16)
Sex		
Male	787 (56)	802 (55)
Female	627 (44)	645 (45)
Lymphoma subtype		
Hodgkin lymphoma (HL)	259 (18)	-
T-cell lymphoma (T-NHL)	90 (6)	
B-cell lymphoma (B-NHL)	1,114 (76)	-

Diffuse large B-cell lymphoma (DLBCL)	391 (28)	-
Follicular lymphoma (FL)	195 (14)	-
Chronic lymphocytic leukemia (CLL)	321 (23)	-
Mantle cell lymphoma (MCL)	48 (3)	-
Marginal zone B-cell lymphoma (MZL)	110 (8)	-
removed samples [†]	67	44
	1,481	1,491

* Percentage is based on the final population for statistical analysis

† 65 cases and 44 controls were removed due to low performance of the genotyping (call-rate below 0.96); additionally, 2 cases were excluded due to missing information on age

1
2 **Table II.** Odds ratios (OR) and 95% confidence intervals (CI) for associated SNPs of the JAK-STAT pathway with B-cell lymphoma,
3
4 T-cell lymphoma and Hodgkin lymphoma.
5

Genotype	Controls*	B-NHL			T-NHL			Controls*			HL		
		N (%)	N (%)	OR [†] (95%CI)	p-value	N (%)	N (%)	OR [†] (95%CI)	p-value	N (%)	N (%)	OR [†] (95%CI)	p-value
BMF rs1540686													
AA	316 (26)	300 (28)	Reference		27 (30)	Reference		297 (26)	76 (29)	Reference			
AG	608 (51)	513 (48)	0.88 (0.72-1.07)	0.2	45 (50)	0.92 (0.56-1.53)	0.8	582 (50)	140 (54)	0.91 (0.65-1.28)	0.6		
GG	268 (22)	246 (23)	0.96 (0.76-1.22)	0.8	18 (20)	0.84 (0.45-1.56)	0.6	273 (24)	39 (15)	0.54 (0.34-0.85)	0.007		
AG/GG			0.91 (0.75-1.09)	0.3		0.90 (0.56-1.44)	0.7			0.79 (0.57-1.09)	0.2		
			p-trend	0.7		p-trend	0.6			p-trend	0.01		
BMF rs648289													
AA	357 (30)	339 (32)	Reference		31 (34)	Reference		337 (29)	84 (32)	Reference			
AG	590 (49)	497 (47)	0.88 (0.73-1.07)	0.2	43 (48)	0.91 (0.56-1.48)	0.7	569 (49)	142 (55)	0.97 (0.69-1.34)	0.8		
GG	249 (21)	230 (22)	0.97 (0.77-1.23)	0.8	16 (18)	0.79 (0.42-1.48)	0.5	250 (22)	33 (13)	0.52 (0.33-0.83)	0.006		
AG/GG			0.91 (0.76-1.09)	0.3		0.87 (0.55-1.38)	0.6			0.83 (0.61-1.14)	0.3		
			p-trend	0.7		p-trend	0.5			p-trend	0.01		
IFNG rs2069718													
GG	456 (38)	420 (40)	Reference		76 (84)	Reference		436 (38)	87 (34)	Reference			

GA	573 (48)	494 (46)	0.93 (0.77-1.11)	0.4	14 (16)	1.24 (0.68-2.27)	0.5	558 (48)	124 (48)	1.08 (0.78-1.50)	0.6
AA	164 (14)	149 (14)	0.98 (0.76-1.27)	0.9	-	-	-	159 (14)	48 (19)	1.80 (1.16-2.79)	0.009
GA/AA			0.94 (0.79-1.11)	0.5		1.17 (0.64-2.14)	0.6			1.22 (0.89-1.66)	0.2
			p-trend	0.7		p-trend	0.8			p-trend	0.02

<i>IFNG</i> rs6581795											
AA	648 (54)	577 (54)	Reference	51 (57)	Reference		619 (54)	115 (44)	Reference		
AG	464 (39)	411 (39)	1.00 (0.83-1.19)	1.0	33 (37)	0.92 (0.58-1.46)	0.7	454 (39)	120 (46)	1.47 (1.08-2.01)	0.01
GG	84 (7)	78 (7)	1.04 (0.75-1.45)	0.8	6 (7)	0.95 (0.39-2.31)	0.9	83 (7)	24 (9)	1.91 (1.10-3.29)	0.02
AG/GG			1.00 (0.85-1.19)	1.0		0.93 (0.60-1.44)	0.7			1.53 (1.14-2.06)	0.005
			p-trend	0.9		p-trend	0.8			p-trend	0.003

<i>IL12A</i> rs755004											
GG	903 (76)	802 (75)	Reference	56 (62)	Reference		876 (76)	188 (73)	Reference		
GA	272 (23)	239 (22)	0.99 (0.81-1.21)	0.9	32 (36)	1.93 (1.22-3.05)	0.005	263 (23)	66 (25)	1.08 (0.77-1.52)	0.6
AA	21 (2)	25 (2)	1.35 (0.75-2.43)	0.3	1 (1)	0.76 (0.10-5.86)	0.8	17 (1)	5 (2)	1.42 (0.47-4.30)	0.5
GA/AA			1.01 (0.84-1.23)	0.9		1.84 (1.17-2.90)	0.008			1.10 (0.79-1.54)	0.6
			p-trend	0.7		p-trend	0.02			p-trend	0.5

Table II. cont.'d

Genotype	Controls*	B-NHL			T-NHL			Controls*	HL			
		N (%)	N (%)	OR [†] (95%CI)	p-	N (%)	OR [†] (95%CI)	p-	N (%)	N (%)	OR [†] (95%CI)	p-
				value								value
<i>SOCS1 rs149311</i>												
GG	857 (72)	697 (65)	Reference		68 (76)	Reference		823 (71)	171 (66)	Reference		
GA	295 (25)	321 (30)	1.34 (1.11-1.62)	0.002	18 (20)	0.77 (0.45-1.32)	0.3	284 (25)	79 (31)	1.37 (0.99-1.90)	0.06	
AA	43 (4)	45 (4)	1.30 (0.85-2.01)	0.2	4 (4)	1.12 (0.39-3.27)	0.8	48 (4)	9 (3)	0.81 (0.37-1.79)	0.6	
GA/AA			1.34 (1.12-1.60)	0.002		0.81 (0.49-1.35)	0.4			1.29 (0.94-1.76)	0.1	
			p-trend	0.003		p-trend	0.6			p-trend	0.3	
<i>STAT1 rs34997637</i>												
GG	709 (59)	634 (59)	Reference		64 (71)	Reference		682 (59)	158 (61)	Reference		
GA	410 (34)	374 (35)	1.02 (0.85-1.22)	0.8	24 (27)	0.63 (0.39-1.03)	0.07	397 (34)	91 (35)	0.93 (0.68-1.27)	0.7	
AA	76 (6)	57 (5)	0.84 (0.59-1.21)	0.4	2 (2)	0.28 (0.07-1.18)	0.08	76 (7)	10 (4)	0.64 (0.31-1.33)	0.2	
GA/AA			0.99 (0.84-1.17)	0.9		0.58 (0.36-0.93)	0.02			0.89 (0.66-1.20)	0.5	
			p-trend	0.6		p-trend	0.01			p-trend	0.3	
<i>STAT3 rs1053005</i>												
AA	737 (62)	732 (69)	Reference		55 (61)	Reference		708 (61)	169 (65)	Reference		
AG	401 (34)	287 (27)	0.72 (0.60-0.86)	0.0004	34 (38)	1.16 (0.74-1.82)	0.5	391 (34)	83 (32)	0.89 (0.65-1.21)	0.5	

GG	57 (5)	48 (5)	0.85 (0.57-1.27)	0.4	1 (1)	0.23 (0.03-1.71)	0.1	57 (5)	7 (3)	0.54 (0.23-1.26)	0.2
AG/GG			0.73 (0.62-0.87)	0.0005		1.04 (0.67-1.63)	0.9			0.84 (0.62-1.15)	0.3
			p-trend	0.003		p-trend	0.7			p-trend	0.2
STAT3 rs1053023											
AA	737 (62)	732 (69)	Reference		55 (61)	Reference		708 (61)	169 (65)	Reference	
AG	401 (34)	286 (27)	0.72 (0.60-0.86)	0.0003	34 (38)	1.16 (0.74-1.82)	0.5	391 (34)	83 (32)	0.89 (0.65-1.21)	0.5
GG	57 (5)	49 (5)	0.87 (0.58-1.29)	0.5	1 (1)	0.23 (0.03-1.71)	0.2	57 (5)	7 (3)	0.54 (0.23-1.26)	0.2
AG/GG			0.73 (0.62-0.87)	0.0005		1.04 (0.67-1.63)	0.9			0.84 (0.62-1.15)	0.3
			p-trend	0.003		p-trend	0.7			p-trend	0.2
STAT3 rs12949918											
AA	402 (34)	403 (38)	Reference		30 (33)	Reference		387 (33)	103 (40)	Reference	
AG	574 (48)	506 (47)	0.87 (0.73-1.05)	0.2	49 (54)	1.14 (0.71-1.84)	0.6	538(47)	115 (44)	0.81 (0.59-1.11)	0.2
GG	220 (18)	158 (15)	0.72 (0.56-0.92)	0.008	10 (11)	0.61 (0.29-1.27)	0.2	231 (20)	41 (16)	0.63 (0.41-0.97)	0.03
AG/GG			0.83 (0.70-0.99)	0.03		0.99 (0.63-1.57)	0.9			0.75 (0.56-1.02)	0.07
			p-trend	0.008		p-trend	0.3			p-trend	0.03

Table II. cont.'d

Genotype	Controls*	B-NHL			T-NHL			Controls*		HL		
		N (%)	N (%)	OR [†] (95%CI)	p-	N (%)	OR [†] (95%CI)	p-	N (%)	N (%)	OR [†] (95%CI)	p-
		value				value						value
STAT3 rs4103200												
GG	575 (48)	577 (54)	Reference		50 (56)	Reference		556 (48)	148 (57)	Reference		
GC	506 (42)	407(38)	0.79 (0.67-0.95)	0.01	33 (37)	0.76 (0.48-1.21)	0.2	483 (42)	96 (37)	0.74 (0.54-1.00)	0.05	
CC	115 (10)	83 (8)	0.72 (0.53-0.97)	0.03	7 (8)	0.73 (0.32-1.65)	0.5	117 (10)	15 (6)	0.49 (0.27-0.90)	0.02	
GC/CC		0.78 (0.66-0.92)	0.003		0.76 (0.49-1.17)	0.2			0.69 (0.51-0.92)	0.01		
		p-trend	0.003		p-trend	0.2			p-trend	0.006		
STAT3 rs6503695												
AA	504 (42)	505 (47)	Reference		39 (43)	Reference		483 (42)	126 (49)	Reference		
AG	523 (44)	444 (42)	0.84 (0.70-1.00)	0.06	44 (49)	1.08 (0.69-1.70)	0.7	501 (43)	106 (41)	0.80 (0.59-1.10)	0.2	
GG	169 (14)	118 (11)	0.69 (0.53-0.91)	0.007	7 (8)	0.53 (0.23-1.22)	0.1	172 (15)	27 (10)	0.57 (0.35-0.92)	0.02	
AG/GG		0.81 (0.68-0.95)	0.01		0.94 (0.61-1.46)	0.8			0.74 (0.55-1.00)	0.05		
		p-trend	0.004		p-trend	0.3			p-trend	0.02		
STAT3 rs9891119												
AA	461 (39)	464 (43)	Reference		40 (44)	Reference		447 (39)	119 (46)	Reference		
AC	566 (47)	480 (45)	0.84 (0.70-1.00)	0.05	41 (46)	0.85 (0.54-1.34)	0.5	533 (46)	115 (44)	0.81 (0.59-1.10)	0.2	

CC	169 (14)	123 (12)	0.72 (0.55-0.94)	0.02	9 (10)	0.64 (0.30-1.35)	0.2	176 (15)	25 (10)	0.54 (0.32-0.88)	0.01
AC/CC			0.81 (0.68-0.96)	0.02		0.80 (0.52-1.24)	0.3			0.74 (0.55-1.00)	0.05
			p-trend	0.008		p-trend	0.2			p-trend	0.01
STAT3 rs9912773											
CC	613 (51)	606 (57)	Reference		54 (60)	Reference		588 (51)	153 (59)	Reference	
CG	485 (41)	388 (36)	0.80 (0.67-0.95)	0.01	30 (33)	0.72 (0.45-1.15)	0.2	470 (41)	96 (37)	0.78 (0.57-1.06)	0.1
GG	98 (9)	73 (7)	0.75 (0.54-1.04)	0.08	6 (7)	0.74 (0.31-1.77)	0.5	98 (8)	10 (4)	0.43 (0.21-0.87)	0.02
CG/GG			0.79 (0.67-0.94)	0.006		0.72 (0.47-1.12)	0.2			0.72 (0.54-0.97)	0.03
			p-trend	0.008		p-trend	0.2			p-trend	0.009
STAT5A rs2293158											
AA	556 (46)	561 (53)	Reference		49 (54)	Reference		547 (47)	125 (48)	Reference	
AG	513 (43)	418 (39)	0.80 (0.67-0.95)	0.01	39 (43)	0.89 (0.57-1.38)	0.6	484 (42)	114 (44)	1.07 (0.78-1.45)	0.7
GG	127 (11)	88 (8)	0.68 (0.51-0.92)	0.01	2 (2)	0.18 (0.04-0.76)	0.02	125 (11)	20 (8)	0.62 (0.36-1.08)	0.09
AG/GG			0.78 (0.66-0.92)	0.003		0.75 (0.48-1.15)	0.2			0.97 (0.72-1.30)	0.8
			p-trend	0.002		p-trend	0.03			p-trend	0.3

Table II. cont.'d

Genotype	Controls*	B-NHL			T-NHL			Controls*			HL		
		N (%)	N (%)	OR [†] (95%CI)	p-value	N (%)	N (%)	OR [†] (95%CI)	p-value	N (%)	N (%)	OR [†] (95%CI)	p-value
STAT6 rs324011													
GG	471 (39)	435 (41)	Reference			38 (42)	Reference			437 (38)	119 (46)	Reference	
GA	557 (47)	470 (44)	0.91 (0.76-1.09)	0.3		39 (43)	0.83 (0.52-1.33)	0.4		552 (48)	97 (37)	0.55 (0.40-0.76)	0.0003
AA	166 (14)	159 (15)	1.04 (0.80-1.34)	0.8		13 (14)	0.91 (0.47-1.76)	0.8		166 (14)	43 (17)	0.80 (0.52-1.23)	0.03
GA/AA			0.94 (0.79-1.11)	0.5			0.85 (0.55-1.32)	0.5				0.61 (0.45-0.82)	0.001
			p-trend	0.9			p-trend	0.6				p-trend	0.04
STAT6 rs703817													
GG	310 (26)	289 (27)	Reference			23 (26)	Reference			292 (25)	87 (34)	Reference	
GA	599 (50)	525 (49)	0.94 (0.77-1.14)	0.5		47 (52)	1.00 (0.60-1.69)	1.0		578 (50)	113 (44)	0.60 (0.42-0.84)	0.003
AA	287 (24)	247 (23)	0.92 (0.73-1.17)	0.5		20 (22)	0.90 (0.48-1.67)	0.7		286 (25)	59 (23)	0.65 (0.44-0.98)	0.04
GA/AA			0.93 (0.77-1.12)	0.5			0.97 (0.59-1.59)	0.9				0.62 (0.45-0.85)	0.003
			p-trend	0.5			p-trend	0.7				p-trend	0.03
TP63 rs6790068													
AA	424 (35)	398 (37)	Reference			32 (36)	Reference			426 (37)	77 (30)	Reference	
AG	588 (49)	498 (47)	0.90 (0.75-1.08)	0.3		43 (48)	0.96 (0.59-1.54)	0.9		556 (48)	123 (47)	1.19 (0.85-1.67)	0.3
GG	184 (15)	171 (16)	0.99 (0.77-1.27)	0.9		15 (17)	1.06 (0.56-2.02)	0.9		174 (15)	59 (23)	1.94 (1.28-2.94)	0.002

1	AG/GG	0.92 (0.78-1.09)	0.4	0.98 (0.62-1.54)	0.9	1.37 (1.00-1.87)	0.05
2		p-trend	0.7	p-trend	0.9	p-trend	0.003
3	TP63 rs9681004						
4	AA	417 (35)	393 (37)	Reference	33 (37)	Reference	415 (36)
5	AG	588 (49)	497 (47)	0.90 (0.75-1.08)	0.2	40 (44)	0.85 (0.52-1.37)
6	GG	189 (16)	177 (17)	0.99 (0.77-1.27)	1.0	17 (19)	1.12 (0.61-2.08)
7	AG/GG		0.92 (0.77-1.09)	0.3		0.91 (0.58-1.43)	0.7
8		p-trend	0.7		p-trend	0.9	p-trend
9							0.004

* 1196 controls were taken into account for the risk analysis with the B-cell and T-cell lymphoma cases and 1153 controls were taken into account for the risk analysis with the Hodgkin lymphoma cases

† Odds ratios were adjusted for the matching variables: age (continuous), sex and study center (categorical); the common homozygote was used as reference group for each SNP
Significant *p*-values (< 0.01) are printed in bold

Table III. Odds ratios (OR) and 95 % confidence intervals (CI) for associated SNPs of the JAK-STAT pathway with B-cell lymphoma subtypes:

DLBCL, FL and CLL

Genotype	Controls*	DLBCL			FL			CLL			
		N (%)	N (%)	OR [†] (95%CI)	p-value	N (%)	OR [†] (95%CI)	p-value	N (%)	OR [†] (95%CI)	p-value
BMF rs7183977											
AA	519 (43)	199 (51)	Reference			79 (41)	Reference		138 (43)	Reference	
AG	535 (45)	155 (39)	0.75 (0.58-0.95)	0.02		87 (45)	1.07 (0.76-1.48)	0.7	155 (48)	1.09 (0.84-1.42)	0.5
GG	142 (12)	38 (10)	0.69 (0.46-1.02)	0.06		29 (15)	1.31 (0.82-2.10)	0.3	27 (8)	0.76 (0.48-1.21)	0.3
AG/GG			0.73 (0.58-0.93)	0.009			1.12 (0.82-1.53)	0.5		1.02 (0.79-1.32)	0.9
			p-trend	0.01			p-trend	0.3		p-trend	0.6
BMF rs3923235											
AA	622 (52)	230 (59)	Reference			102 (52)	Reference		171 (53)	Reference	
AG	482 (40)	148 (38)	0.82 (0.65-1.05)	0.1		76 (39)	0.97 (0.70-1.34)	0.9	133 (41)	1.00 (0.77-1.30)	1.00
GG	92 (8)	15 (4)	0.43 (0.24-0.77)	0.004		17 (9)	1.15 (0.65-2.02)	0.6	17 (5)	0.67 (0.39-1.16)	0.2
AG/GG			0.76 (0.60-0.96)	0.02			1.00 (0.74-1.36)	1.0		0.95 (0.74-1.22)	0.7
			p-trend	0.003			p-trend	0.8		p-trend	0.4
IFNGR1 rs4896243											
AA	370 (31)	113 (29)	Reference			65 (33)	Reference		81 (25)	Reference	
AG	588 (49)	172 (44)	0.93 (0.71-1.23)	0.6		92 (47)	0.90 (0.63-1.27)	0.5	149(46)	1.15 (0.85-1.56)	0.4

1	GG	238 (20)	107 (27)	1.47 (1.06-2.00)	0.02	38 (19)	0.90 (0.58-1.40)	0.7	89 (28)	1.69 (1.19-2.40)	0.003
2	AG/GG			1.09 (0.84-1.40)	0.5		0.90 (0.65-1.25)	0.5		1.30 (0.98-1.73)	0.07
3				p-trend	0.03		p-trend	0.6		p-trend	0.003
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SOCs1 rs149311

1	GG	857 (72)	244 (62)	Reference		132 (68)	Reference		219 (68)	Reference	
2	GA	295 (35)	131 (34)	1.54 (1.19-1.98)	0.0009	54 (28)	1.17 (0.83-1.66)	0.4	89 (28)	1.23 (0.92-1.63)	0.2
3	AA	43 (4)	16 (4)	1.36 (0.74-2.47)	0.3	9 (5)	1.50 (0.71-3.19)	0.3	12 (4)	1.05 (0.54-2.05)	0.9
4	GA/AA			1.51 (1.19-1.93)	0.0009		1.21 (0.87-1.68)	0.3		1.20 (0.92-1.58)	0.2
5				p-trend	0.003		p-trend	0.2		p-trend	0.3
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STAT3 rs1053005

1	AA	737 (62)	271 (69)	Reference		133 (68)	Reference		218 (68)	Reference	
2	AG	401 (34)	107 (27)	0.73 (0.57-0.95)	0.02	54 (28)	0.71 (0.51-1.01)	0.06	89 (28)	0.75 (0.57-0.99)	0.04
3	GG	57 (5)	15 (4)	0.77 (0.43-1.40)	0.4	8 (4)	0.79 (0.36-1.70)	0.5	14 (5)	0.81 (0.44-1.49)	0.5
4	AG/GG			0.74 (0.58-0.94)	0.02		0.72 (0.52-1.00)	0.05		0.76 (0.58-0.99)	0.04
5				p-trend	0.03		p-trend	0.08		p-trend	0.06
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Table III. cont'd.

Genotype	Controls*	DLBCL			FL			CLL			
		N (%)	N (%)	OR [†] (95%CI)	p-value	N (%)	OR [†] (95%CI)	p-value	N (%)	OR [†] (95%CI)	p-value
STAT3 rs1053023											
AA	737 (62)	271 (69)	Reference			133 (68)	Reference		218 (68)	Reference	
AG	401 (34)	107 (27)	0.73 (0.57-0.95)	0.02		54 (28)	0.71 (0.51-1.01)	0.06	89 (28)	0.75 (0.57-0.99)	0.04
GG	57 (5)	15 (4)	0.77 (0.43-1.40)	0.4		8 (4)	0.79 (0.36-1.70)	0.5	14 (4)	0.81 (0.44-1.49)	0.5
AG/GG			0.74 (0.58-0.94)	0.02			0.72 (0.52-1.00)	0.05		0.76 (0.58-0.99)	0.04
			p-trend	0.03			p-trend	0.08		p-trend	0.06
STAT3 rs12949918											
AA	402 (34)	150 (38)	Reference			77 (39)	Reference		115 (36)	Reference	
AG	574 (48)	189 (48)	0.87 (0.68-1.13)	0.3		89 (46)	0.80 (0.57-1.12)	0.2	158 (49)	0.96 (0.73-1.27)	0.8
GG	220 (18)	54 (14)	0.67 (0.47-0.95)	0.03		29 (15)	0.65 (0.41-1.04)	0.07	48 (15)	0.79 (0.54-1.16)	0.2
AG/GG			0.82 (0.64-1.04)	0.1			0.76 (0.55-1.04)	0.09		0.91 (0.70-1.19)	0.5
			p-trend	0.03			p-trend	0.06		p-trend	0.3
STAT3 rs4103200											
GG	575 (48)	216 (55)	Reference			107 (55)	Reference		172 (56)	Reference	
GC	506(42)	149 (38)	0.78 (0.61-1.00)	0.05		74 (38)	0.75 (0.54-1.04)	0.08	124 (39)	0.84 (0.64-1.09)	0.2
CC	115 (10)	28 (7)	0.68 (0.43-1.06)	0.09		14 (7)	0.62 (0.34-1.14)	0.1	25 (8)	0.74 (0.46-1.19)	0.2

GC/CC	0.76 (0.60-0.96)	0.02	0.73 (0.54-0.99)	0.04	0.82 (0.64-1.06)	0.1
	p-trend	0.02	p-trend	0.04	p-trend	0.1

STAT3 rs6503695

AA	504 (42)	184 (47)	Reference	95 (49)	Reference	153 (48)	Reference
AG	523(44)	169 (43)	0.86 (0.67-1.10)	0.2	81 (42)	0.78 (0.56-1.07)	0.1
GG	169 (14)	40 (10)	0.66 (0.45-0.98)	0.04	19 (10)	0.56 (0.33-0.95)	0.03
AG/GG			0.81 (0.64-1.02)	0.08		0.72 (0.53-0.98)	0.04
			p-trend	0.03		p-trend	0.02
							p-trend
							0.2

STAT3 rs9891119

AA	461 (39)	179 (46)	Reference	87 (45)	Reference	131 (41)	Reference
AC	566 (47)	171 (42)	0.79 (0.62-1.01)	0.07	85 (44)	0.79 (0.57-1.09)	0.2
CC	169 (14)	43 (11)	0.68 (0.47-1.00)	0.05	23 (12)	0.70 (0.43-1.16)	0.2
AC/CC			0.77 (0.61-0.97)	0.03		0.77 (0.56-1.05)	0.1
			p-trend	0.02		p-trend	0.09
							p-trend
							0.2

* 1196 controls were taken into account for the risk analysis with the B-cell lymphoma cases

† Odds Ratios were adjusted for the matching variables: age (continuous), sex and study center (categorical); the common homozygote was used as reference group for each SNP

Significant *p*-values (< 0.01) are printed in bold

1
2 **Table IV.** Statistical interaction between genotypes of the *BMF*, *IFNG*, *IL10*, *STAT1*, *STAT4* and *SOCS1* variants and *CASP6*, *STAT3*, *IL12*, *INFG*
3 SNPs among B-cell lymphoma cases
4
5
6
7

	No. of Controls	No. of Cases	OR* (95% CI)	p-value	No. of Controls	No. of Cases	OR* (95% CI)	p-value	No. of Controls	No. of Cases	OR* (95% CI)	p-value
<hr/>												
<i>BMF</i> (rs16970325)												
GG												
<i>CASP6</i> (rs5030552)												
AA	819 (85)	658 (79)	Reference		177 (80)	167 (80)	Reference		5 (83)	18 (90)	Reference	
AG	140 (14)	169 (20)	1.50 (1.17-1.92)	0.001	43 (19)	41 (19)	1.00 (0.62-1.63)		1 (17)	2 (10)	-	-
GG	8 (1)	7 (1)	1.10 (0.40-3.06)	0.9	2 (1)	2 (1)	1.14 (0.15-8.41)		-	-	-	-
<i>BMF</i> (rs537455)												
AA												
<i>CASP6</i> (rs5030552)												
AA	532 (85)	458 (78)	Reference		415 (84)	322 (82)	Reference		55 (75)	62 (77)	Reference	
AG	91 (15)	123 (21)	1.57 (1.16-2.11)	0.003	76 (15)	71 (18)	1.18 (0.82-1.68)		17 (23)	18 (22)	-	-
GG	4 (1)	6 (1)	1.74 (0.48-6.22)	0.4	5 (1)	2 (1)	0.50 (0.10-2.64)		1 (1)	1 (1)	-	-
<i>IFNG</i> (rs6581795)												
AA												
AG												
GG												

1
2 STAT3 (rs4103200)
3

4 GG	308 (48)	323 (56)	Reference		228 (49)	216 (53)	Reference		39 (46)	38 (49)	Reference
6 GC	272 (42)	200 (35)	0.70 (0.55-0.89)	0.003	193 (42)	169 (41)	0.92 (0.70-1.22)	0.6	41 (49)	35 (45)	0.82 (0.42-1.56)
8 CC	68 (10)	52 (9)	0.72 (0.49-1.07)	0.1	43 (9)	26 (6)	0.65 (0.38-1.10)	0.1	4 (5)	5 (6)	1.69 (0.36-7.94)

10
11 IL10 (rs6673928)
12

13 CC CA AA

14 STAT3 (rs6503695)
15

17 AA	290 (39)	303 (47)	Reference		186 (47)	177 (47)	Reference		27 (47)	24 (50)	Reference
19 AG	351 (48)	271 (42)	0.74 (0.59-0.92)	0.008	147 (37)	151 (42)	1.07 (0.79-1.46)	0.7	24 (42)	20 (42)	0.94 (0.40-2.23)
21 GG	98 (13)	71 (11)	0.69 (0.49-0.98)	0.04	64 (16)	42 (11)	0.69 (0.44-1.07)	0.1	6 (11)	4 (8)	0.58 (0.13-2.62)

24 IL10 (rs6673928)
25

26 CC CA AA

27 STAT3 (rs4103200)
28

30 GG	335 (45)	346 (54)	Reference		208 (52)	294 (55)	Reference		31 (54)	26 (54)	Reference
32 GC	235 (45)	245 (38)	0.70 (0.56-0.88)	0.002	146 (37)	140 (38)	0.99 (0.73-1.34)	0.9	23 (40)	19 (40)	-
34 CC	69 (9)	54 (8)	0.76 (0.51-1.11)	0.2	43 (11)	26 (7)	0.63 (0.37-1.07)	0.08	3 (5)	3 (6)	-

Table IV. cont'd.

	No. of Controls	No. of Cases	OR* (95 % CI)	p-value	No. of Controls	No. of Cases	OR* (95 % CI)	p-value	No. of Controls	No. of Cases	OR* (95 % CI)	p-value	
	IL10 (rs6673928)				STAT3 (rs1053023)				STAT1 (rs13029247)				
	CC				CA				AA				
<i>IL10</i> (rs6673928)	AA	443 (60)	449 (70)	Reference	CA	249 (63)	247 (67)	Reference	AA	44 (77)	34 (71)	Reference	
STAT3 (rs1053023)	AG	257 (35)	166 (26)	0.64 (0.50-0.80)	0.0002	129 (32)	107 (29)	0.85 (0.62-1.28)	0.3	13 (23)	11 (23)	-	
	GG	38 (5)	30 (5)	0.78 (0.47-1.28)	0.3	19 (5)	16 (4)	0.87 (0.43-1.73)	0.7	-	3 (6)	-	
<i>STAT1</i> (rs13029247)	AA	AA				AG				GG			
STAT3 (rs6503695)	AA	223 (41)	242 (47)	Reference	AG	235 (45)	212 (47)	Reference	GG	46 (35)	50 (50)	Reference	
	AG	232 (43)	212 (41)	0.84 (0.65-1.09)	0.2	223 (43)	187 (42)	0.91 (0.70-1.20)	0.5	67 (51)	43 (42)	0.68 (0.38-1.23)	
	GG	90 (17)	60 (12)	0.60 (0.41-0.88)	0.008	60 (12)	50 (11)	0.91 (0.60-1.39)	0.7	19 (14)	8 (8)	0.39 (0.15-1.00)	
<i>STAT4</i> (rs1517352)	CC	CC				CA				AA			
<i>IL12A</i> (rs4680534)	CC	CC				CA				AA			

AA	173 (40)	159 (46)	Reference		249 (44)	225(42)	Reference		85 (42)	66 (37)	Reference
AG	197 (46)	148 (43)	0.84 (0.62-1.14)	0.3	242 (43)	261 (49)	1.19 (0.93-1.54)	0.2	103 (51)	88 (49)	1.11 (0.72-1.72) 0.6
GG	61 (14)	41 (12)	0.74 (0.47-1.16)	0.2	72 (13)	52 (10)	0.79 (0.53-1.18)	0.3	13 (6)	24 (13)	2.80 (1.30-6.05) 0.009

SOCS1 (rs243317)

	AA		AC		CC						
<i>IFNG (rs2069727)</i>											
AA	176 (30)	125 (23)	Reference	137 (27)	117 (27)	Reference	21 (20)	25 (26)	Reference		
AG	286 (49)	291 (55)	1.44 (1.09-1.91)	0.01	236 (47)	216 (50)	1.08 (0.79-1.47)	0.6	59 (56)	51 (54)	0.72 (0.36-1.46) 0.4
GG	124 (21)	120 (22)	1.36 (0.97-1.92)	0.07	131 (26)	106 (23)	0.89 (0.62-1.27)	0.5	26 (25)	19 (20)	0.62 (0.27-1.45) 0.3

*Odds Ratios were adjusted for the matching variables: age (continuous), sex and study center (categorical);

p-values (<0.05) are printed in bold

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