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Functional characterisation of naturally occurring genetic variants in the human TLR1-2-6 gene family

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Key Words:	TLRs, innate immunity, non-synonymous mutations, NF-kB activity

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RESPONSES TO REFEREE'S COMMENTS

Referee: 1

The present manuscript by Meriem Ben-Ali et al analyzes the functional impact of human TLR1-2-6 variants with altered amino-acid sequences.

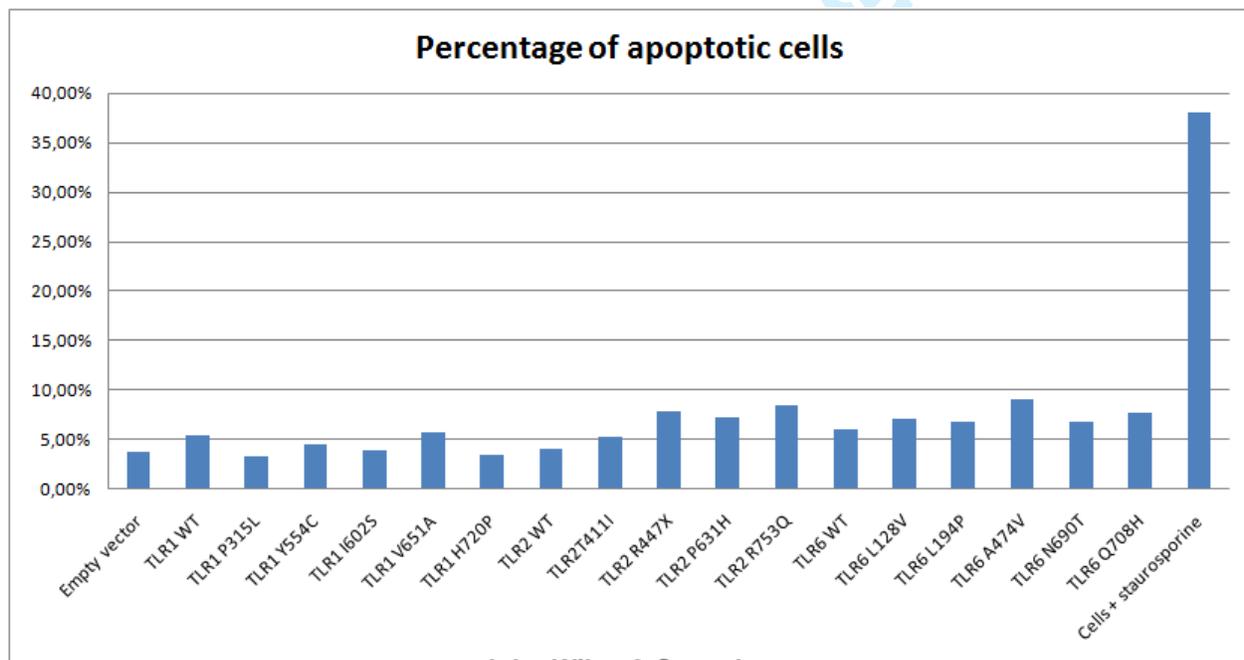
The study comprises the identification of new mutations by DNA sequencing and the subsequent functional characterisation of 41 variants with amino-acid alterations in the TLR1-2-6 family. Meriem Ben-Ali et al find 17 new sequence variations by investigating a total of 158 individuals (316 chromosomes from Sub-Saharan Africa, Europe and East-Asia). 14 variants (5 TLR1, 4 TLR2, and 5 TLR6 variants) displayed an impairment of NF- κ B activation in genetic complementation assays with HEK293T cells. Most of these variants are present at very low population frequencies and are population-specific.

The manuscript presents a comprehensive study dealing with the proper identification of sequence variations in genes of the innate immune system. Major points of criticism focus on the functional characterisation of these receptors.

The manuscript should only be published in Human Mutation after addressing the following points:

1-The authors can not exclude that their functionally relevant TLR-variants cause apoptosis by over-expression, explaining their results of hyporesponsiveness. Here, stimuli like TNF α (TLR-independent) should be included at least for the functionally relevant variants demonstrated.

In order to exclude the possibility that the functionally relevant TLR variants caused apoptosis upon 24 hr over-expression, we measured the percentage of apoptotic cells present in each transfected population using 7-amino actinomycin D (7-AAD) flow cytometry staining (see Figure below). In cells transfected with the empty vector, the percentage of apoptotic cells was about 4% (negative control). Upon treatment with an inducer of apoptosis, staurosporin, ~40% of the cells were apoptotic (positive control). In cells transfected with each of the 17 TLR constructs (14 functionally relevant TLR variants and the 3 ancestral forms), the percentage of apoptotic cells ranged between 3 and 8 %, and no correlation could be made with the level of NF κ B responsiveness of the variants. On this basis, we do not think that the overexpression of our functionally relevant TLR constructs causes apoptosis.



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3 **2- Other pathogen associated molecular patterns for TLR2 like peptidoglycan or zymosan were**
4 **not investigated.**

5 The reviewer is right in that it would be interesting to test other ligands of TLR2, as well as other
6 ligands of TLR1 and TLR6. However, our goal in this study was to perform a functional
7 comparison of a large number of naturally occurring variants in a single assay and not to dissect
8 the effects of each single mutation upon challenge with different ligands. Given the large number
9 of variants to be tested, we chose for each receptor the most commonly used ligand in order to
10 make our results comparable with previous studies.
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12

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14 **3-Most of the TLR2-data were published before (e.g. Lorenz et al 2000; Merx et al. 2007); is**
15 **there a need to do it again? If so, comparable and different results to previously reported**
16 **manuscripts must be discussed .**

17 Indeed, a large part of the TLR2 variants that we have studied had been previously identified.
18 Currently in the databases, for the human *TLR2* gene there are 13 non-synonymous variants and
19 one stop mutation. Our *TLR2* resequencing effort of a panel of 158 healthy individuals
20 originating from sub-Saharan Africa, Europe and East Asia, led us to identify 4 of these already
21 known variants, the stop mutation as well as two previously unknown non-synonymous variants.
22 The aim of our study was to characterize blindly all mutations identified in our population
23 genetics screen. Indeed, some discrepancies in the literature can be found concerning the
24 functional impact of two TLR2 variants (T411I and P631H).
25

26 As suggested by the reviewer, in the revised manuscript, we discuss how our study may help to
27 clarify previous discrepancies concerning TLR2 variants (see page 17)
28
29

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31 **4-The authors take cells that already express TLR6 in genetic complementation assays to**
32 **analyse TLR6. They do not mention that other cells than HEK293 (e.g. CHO or NIH3T3) were**
33 **investigated to solve this problem. The way to handle this problem in HEK293T is hardly**
34 **described.**

35 We agree with the reviewer that we did not describe in sufficient detail how we handled the
36 problem of expression of endogenous TLR6 in the recipient cells. In fact, we did extensive
37 preliminary work to set up transfection conditions and minimize the potential noise from
38 endogenous TLR6. Specifically, the amounts of transfected TLR6 and TLR2 constructs were
39 optimized so as to reduce reporter activation with TLR2 alone (potentially pairing with
40 endogenous TLR6) and to achieve maximal activation upon overexpression of exogenous TLR6.
41 We also tested the impact of the previously described dominant negative (DN) TLR6 P680H
42 variant. In this context, the level of NF- κ B activation induced by this DN form was reduced of
43 70% with respect to the ancestral TLR6 and, importantly, it was also considerably lower than that
44 observed with TLR2 alone. This suggests that, in our experimental setting, the transfected TLR6
45 construct is in large excess and overrides the contribution of the endogenous TLR6.
46

47 We now clarify this point in the revised version of the manuscript and provide details of our
48 procedure (see page 13)
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52 **5- Is there a reason for the double band in figure 2c for the TLR1 I602S variant?; lower panel**
53 **of all western blots: What was the loading control for these analyses?**

54 As to the double band of the TLR1 I602S variant, the *in silico* analysis of the protein sequence
55 predicts that the substitution of the isoleucine at position 602 with a serine residue creates a
56 potential serine/threonine kinase phosphorylation motif. Thus, the slower migrating band of
57 TLR1 I602S could correspond to the phosphorylated protein. This possibility is now presented in
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3 the manuscript (see page 12)

4 The reviewer is correct in that we omitted to mention that the loading control was β -actin. We
5 apologize for this and have amended the figures accordingly.
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8 ***6-The investigated populations are hardly described (how many individuals were investigated***
9 ***in the sub-Saharan population for instance?)***

10 This comment was expressed by the other reviewers as well. We now describe the populations
11 used in more detail in the revised Material and Methods section.
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14 ***7-The functional characterisation is reduced to Nf-kB reporter assays and FACS-analysis; the***
15 ***authors should include cytokine secretion of primary cells of mutation carriers and wild-type***
16 ***carriers as well .***

17 Indeed, it would be extremely interesting to study the *ex vivo* effects of the functionally relevant
18 variants by measuring cytokine secretion from primary donor cells. The difficulty is that most of
19 these variants are singletons, i.e. present in a single heterozygote individual. It would be virtually
20 impossible to recruit a sufficient number of healthy donors to test the *ex vivo* functional effects of
21 these rare mutations. One exception is the TLR1 I602S variant, which is present at high
22 frequency among Europeans (~50%). For this variant, it has already been demonstrated that
23 monocytes obtained from individuals who are homozygous for TLR1 602S secrete significantly
24 lower levels of TNF- α in response to Pam₃CSK₄, when compared to monocytes from individuals
25 who carry at least one TLR1 602I allele (Johnson et al. J Immunol 2007, cited in the discussion).
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29 ***8- The Polyphen algorithm is neither mentioned in the abstract nor the introduction but it is***
30 ***interpreted. Is it necessary to mention Polyphen when having functional data? What are the***
31 ***consequences, what is the major result, the take home message of the comparison of functional***
32 ***TLR-data on the one hand and software prediction on the other? Why was Polyphen included?***
33 ***Is this manuscript an evaluation of Polyphen prediction? If not, my suggestion is to omit it.***

34 The major aim of this study was to functionally characterize the variants identified. Because of
35 the wide use of the Polyphen algorithm by the scientific community, we believe it is important to
36 compare predicted and experimental functional data. However, as suggested by other reviewers,
37 we have now used the recently released version of Polyphen (PolyPhen-2), which is considered a
38 much better prediction algorithm (Adzhubei et al. 2010. Nature Methods). As suggested by this
39 reviewer, we are now more clearly comparing and discussing the results obtained by Polyphen
40 and our experimental data. Please, see page 18-19 in the Discussion section as well as the new
41 Table 1 where we have added an extra column reporting the actual NF- κ B activation data
42 compared to the Polyphen predictions.
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47 ***9. Table 1: the Polyphen data should be excluded and the results of the functional***
48 ***characterisation should be included here. How many alleles/chromosomes were***
49 ***investigated/population? Following this, figure 1 will not contain additional data and could be***
50 ***skipped.***

51 With respect to Polyphen, see previous point. As requested, the results of the functional
52 characterisation have been now included in Table 1. With respect to sequence variation for the
53 *TLR1-2-6* gene family, it was determined for a total of 158 individuals (316 chromosomes)
54 representative of the populations of major geographical regions (63 from Sub-Saharan Africa,
55 47 from Europe and 48 from East-Asia). This has now been clarified in the Materials and Methods
56 section.
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Referee: 2***Comments to the Author***

This is a very convincing study exploring the impact of naturally occurring mutation in the TLR1-2-6 gene family. I have a couple of minor comments that the authors may want to consider in the revised version of the manuscript:

1. It is a bit unfair to the reader to refer to Barreiro et 2009 for details on the populations that have been used here. I would appreciate a table summarizing the most important features.

This criticism has been expressed by all reviewers. We now describe the populations used in much more detail in the Material and Methods section.

2. the authors used the polyphen algorithm to predict the functional impact of non synonymous mutations. recently a new version of this algorithm has been released (Polyphen - 2) with, from my point of view, clearly improved prediction properties. Do they author used this last algorithm? if not I think this could be an interesting try.

The reviewer is correct in pointing out the release of the new version of the Polyphen algorithm, considered a better predictor than the previous version. We have used Polyphen v2 and discuss these new data accordingly in the revised version of the manuscript.

3. How was chosen the 20% threshold to define 'functionally relevant' variant?

The threshold was indeed arbitrarily chosen. We preferred to focus on the variants that exhibited strongest effects on NF- κ B activation, leaving behind those causing weak effects.

4. they mention 17 newly reported variant. Which database did they check to define a variant as new? In particular, did they used the 1000genomes project database? If not his could be also interesting.

We used dbSNP database to determine whether SNPs were new or not. As advised by the reviewer, we have now verified if these potentially new SNPs were present in 1000 genomes. Taking this into account, 14 SNPs remain novel in our paper.

5. there is no mention at all of the number of mutations per individual, i.e. did they observe individuals with two copy of NS mutations (either at the same position or not)?; on the same note is it correct to assume that these individuals did not present with any particular phenotype? if not this should be mention somewhere in the discussion.

Indeed, we found that some individuals were homozygous for a given NS mutation or had more than one NS mutation. We now provide the genotype information for each individual and each mutation as three [Supplementary Tables](#) (see Supp. Tables S1-S3)

As to the phenotype of the individuals, they are all considered as healthy donors. Obviously, we cannot exclude that individuals harboring more than one 'functionally relevant' mutation may be at higher risk for disease if exposed to particular pathogens. The healthy donor state of the individuals is now explicitly stated and clarified in the materials and methods.

Referee: 3***Comments to the Author***

Numerous studies have reported on the association between human Toll-like receptor polymorphisms and the incidence of disease. This paper by Meriem Ben-Ali and colleagues has systematically analyzed the function of naturally occurring nonsynonymous TLR variants in HEK cells using an NF- κ B reporter system. The authors have also considered whether certain receptor variants exhibit altered cell surface expression. Finally, the ability of an algorithm (PolyPhen) to predict the impact of nonsynonymous variants on function was compared with the actual experimental results. Overall, the paper is straight forward, well written, statistically sound. Moreover, the paper provides a resource for labs studying TLR polymorphisms while attempting to interpret the results of genetic association studies. One caveat to the work is that all of the data are derived from *in vitro* systems which may not accurately reflect the effect of polymorphisms *in vivo*. Additionally, the authors only examined one, albeit central signaling output namely, NF- κ B. These concerns merely reflect limitations of the experimental systems used and not the quality of work performed in this study. Addressable concerns are minor and as follows:

1) Table 1 should include a final column showing the actual results of the functional assays. This would allow the reader to directly compare the Polyphen results with that of the actual results for each individual polymorphism.

We thank the reviewer for this suggestion that will be helpful to the readers. We have now added an extra column in Table 1, showing the actual results (% of NF- κ B defect) for each of the 41 variants studied.

2) There is a vast literature on disease association with polymorphisms in TLRs 1, 2 and 6. The authors should take advantage (and perhaps reference) the excellent reviews that have been written on the subject such as: Garantziotis S, Hollingsworth JW, Zaas AK, Schwartz DA. The effect of toll-like receptors and toll-like receptor genetics in human disease. *Annu Rev Med.* 2008;59:343-59; Misch EA, Hawn TR. Toll-like receptor polymorphisms and susceptibility to human disease. *Clin Sci (Lond).* 2008 Mar;114(5):347-60; Tapping RI, Omueti KO, Johnson CM. Genetic polymorphisms within the human Toll-like receptor 2 subfamily. *Biochem Soc Trans.* 2007 Dec;35(Pt 6):1445-8.

We now discuss and cite these association studies in the revised version of the manuscript.

3) A systematic study of TLR diversity in humans was published last year and is certainly worthy of mention in the context of the work here: Georgel P, Macquin C, Bahram, S. The heterogeneous allelic repertoire of human toll-like receptor (TLR) genes. *PLoS One* 2009 Nov 17;4 (11): e7803.

We now discuss and cite this study in the revised version of the manuscript.

4) The most critical paper that the authors overlooked was one in which an association analysis of more than 1,500 individuals revealed consistent associations between genetic variants in both TLR1 I602S with susceptibility to leprosy. The paper provides an excellent discussion of the expansion of the polymorphism in European populations: Won, SH, Gochhait S, Malhotra D, et al. Leprosy and the adaptation of toll-like receptor 1. *PLoS Pathog.* 2010 Jul 1;6:e1000979.

We now discuss and cite this study in the revised version of the manuscript.

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2
3 *5) When discussing evolution and selection of polymorphisms within the family the authors*
4 *should read and consider referencing the following paper: Enard D, Depaulis, F, Roest and*
5 *Crollius H. Human and non- human primate genomes share hotspots of positive selection.*
6 *PLoS Genet. 2010 Feb 5;6(2):e1000840.*
7

8 We thank the reviewer for this suggestion. We now discuss and cite this study in the revised
9 version of the manuscript.
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For Peer Review

EDITORIAL BOARD'S COMMENTS

All three referees gave a good evaluation of this work. There are, however, a rather large number of points that will require careful consideration and correction, in particular questions raised by referee1 on the use of HEK293 cells, the possibility of inducing apoptosis by receptor overexpression, etc. Please carefully answer these concerns. Please make edits to the manuscript using "track changes" if possible, or by highlighting added text.

First of all, we thank the Editorial Board as well as the three Referees for the useful suggestions, which we believe have improved the clarity and the quality of the manuscript. As you can see in the individual responses to the Referees (uploaded separately in the cover letter since there is a figure), we have now addressed all comments and concerns (paying special attention to the questions of the use of HEK293 cells, the possibility of inducing apoptosis by receptor overexpression, etc., see responses to referee 1). In addition, although Referee 1 suggested to leave out the PolyPhen predictions, Referees 2 and 3 appeared more interested in these information and thus we have kept this part. As requested by one Referee, we have re-analysed the data using the PolyPhen-2 version and, as suggested by Reviewer 1, we are more explicitly discussing and comparing the results of this predictive method with the actual experimental data.

Please, find here enclosed the revised version of the manuscript with the corresponding changes, which are now highlighted in red.

We hope that we have now satisfied both the reviewers' and the editorial board's comments and that the manuscript is suitable for publication in *Human Mutation*.

MANAGING EDITOR COMMENTS:

Please respond to these points under "Response to Managing Editor", otherwise the final decision could be delayed.

1) Please include the OMIM accession number for the genes discussed, at first mention in the Introduction.

--Human gene symbols must be in all caps-italics. Protein symbols should be all caps-Roman.

--Please ensure that you use HUGO HGNC-approved gene symbols. Common gene symbol aliases may also be used at first mention. OMIM entries do not always feature the approved symbol prominently. Verify gene symbols at

<http://www.genenames.org/>

Done

2) The mutation nomenclature must follow the format indicated in the Author Instructions (see the website <http://www.hgvs.org/mutnomen/> and also the nomenclature checklist at <http://www.hgvs.org/mutnomen/checklist.html>). Things to watch for:

a-Mention the GenBank reference sequence and version number for the genes studied (i.e., include the decimal point following the accession number in the sequence record) in the Materials and Methods and as a footnote to the relevant table.

Done

b-Clearly indicate in the Methods text and tables that the DNA mutation numbering system you use is based on cDNA sequence. Explanatory text is required in legends and text, for example:

“Nucleotide numbering reflects cDNA numbering with +1 corresponding to the A of the ATG translation initiation codon in the reference sequence, according to journal guidelines (www.hgvs.org/mutnomen). The initiation codon is codon 1.”

Done

c-Authors are advised to check sequence variant descriptions using the Mutalyzer program (<http://www.LOVD.nl/mutalyzer/>) - using batch mode, all variants for a gene can be analyzed at once.

Done

d-Please verify that the mutations reported (especially novel ones) have been or will be submitted to an existing locus-specific database for the genes involved. Visit the HGVS-LSDB list to search for databases: <http://www.hgvs.org/dblist/glsdb.html>

Novel SNPs have been now submitted to the dbSNP database, and we are waiting for the corresponding #rs numbers.

3) On resubmission:

a-Please double check the author names and affiliations carefully. These are often a source

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3 of typographical errors.

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5 Done

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8 **b-Title Page, Abstract (180-200 words max), Key Words, Main Text, References, and**
9 **Figure Legends should be combined into one file for the manuscript and submitted as a**
10 ***.doc file.**

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12 Done

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14
15 **c-Figures for main article must be submitted as separate files with high resolution (at least**
16 **200 dpi) as *.tif or *.eps format only.**

17 **--For color figures in print: submit two files for each color figure: one in CMYK color space**
18 **and one in RGB color space (with the true color you wish to have published). If you cannot**
19 **provide CMYK color e-files for the print version, please let me know. (see below regarding**
20 **color costs)**

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24 Only Figure 1 should be in color in print, and is submitted in two separate files (CMYK and
25 RGB). The other figures are online-only figures.

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28 **d-Tables must be submitted individually as separate *.doc files (with their titles and legends**
29 **included). Please use the MS Word table format if possible. Excel (*.xls) files should not be**
30 **submitted.**

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33 Table 1 is provided as a separate *.doc file, with its title and legend.

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35 **e-Any Supporting Tables or Figures should be named and cited from the text as follows:**
36 **'Supp. Table S1' and 'Supp. Figure S1' (see below).**

37 **--If possible, do not use custom paper sizes - Letter or A4 are preferred.**
38

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40 Done

41
42 **f-Supporting Figures and Tables should be prepared in a single MS Word *.doc file labeled**
43 **'Supp_Mat', with Figures preceding Tables. Each table/figure should be accompanied with**
44 **its legend.**

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47 The three supporting Tables S1-S3 have been merged into a single *.doc file

48
49 **4) Please check to see that the references follow the journal's standard format and are cited**
50 **properly. See our online Author Instructions**

51 [http://onlinelibrary.wiley.com/journal/10.1002/%28ISSN%291098-](http://onlinelibrary.wiley.com/journal/10.1002/%28ISSN%291098-1004/homepage/ForAuthors.html)
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58 **5) Figure 1 requires color in the print version in order to be fully understood, because the**
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3 colors “blue” and “orange” are required in order to see which mutations are being referred
4 to. As noted in our Author Instructions, there are no page charges for publication in
5 Human Mutation but there are costs associated with publication of color images in print:
6 \$500 USD per printed color page. Alternatively, there is an option of publishing the color
7 images in black-and-white in the print article and in color online, at no cost to you - but no
8 information must be lost in a conversion to b/w from color for the print version. For
9 example, if the “blue” text in the figure was also put in italic and the “orange” text was also
10 placed in bold type, and that information was added to the legend (“black, blue/italic, and
11 orange/bold”), then the figure could be interpreted in b/w. Please confirm your preference
12 in reply. (Non-essential color images can be published in color online only at no cost. The
13 other color figures appear to not require color in print, but color online will be attractive.)
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17 Figure 1 should be in color in print, and is submitted in two separate files (CMYK and RGB).
18 The other figures are online-only figures.
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21 **6) Human Mutation can accommodate researchers funded by agencies requiring open
22 access publication. More information on Wiley-Blackwell's policy is available at:**

23 **<http://olabout.wiley.com/WileyCDA/Section/id-406241.html>**

24 **7) IMPORTANT INFORMATION REGARDING PREPRINTS**

25 **a-Human Mutation is now publishing online preprints of accepted manuscripts prior to
26 typesetting and page proof corrections. It is therefore crucial that you revise your
27 manuscript carefully so that errors (typographical and grammatical) are corrected
28 BEFORE the final accepted manuscript is posted online. The accepted preprint version will
29 remain online until the corrected proofs are received and the typeset manuscript is
30 finalized. At that time, the preprint version will be replaced with the final, typeset version
31 online, in Early View.**

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33 **b-It is essential that you submit a copyright transfer agreement (CTA) upon submission of
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36 signed by all contributing authors if practical. All authors must be made aware of the CTA
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40 and must be filled out completely, including the article title and manuscript number. Please
41 fax it to this number: (201) 748-6091.
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45 The CTA has now been faxed.
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3 **Functional characterisation of naturally occurring genetic variants in the**
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6 **human TLR1-2-6 gene family**
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13 Meriem Ben-Ali^{1,2}, Beatrice Corre^{3,4}, Jérémy Manry^{1,2}, Luis B. Barreiro⁵, Hélène Quach^{1,2},
14 Michele Boniotto^{1,2}, Sandra Pellegrini^{3,4}, Lluís Quintana-Murci^{1,2,*}
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ABSTRACT

Toll-like receptors are considered an essential component of the innate immune system, initiating inflammatory responses following infection of the host. Humans have 10 functional TLRs, differing in their subcellular distributions and the microbial agonists they sense. The phylogenetically-conserved TLR1-2-6 family is unique in that TLR1 and TLR6 form heterodimers with TLR2 to mediate signalling in response to agonists. Epidemiological genetic studies have identified several TLR variants that appear to influence susceptibility to infectious diseases, but the functional consequences of which remain largely unknown. Here, we assessed the functional impact of the TLR1-2-6 variants with altered amino-acid sequences segregating naturally in the human population. We used an NF- κ B reporter assay in TLR-transfected human embryonic kidney 293T cells stimulated with the corresponding TLR agonists. We found that among the 41 naturally occurring variants with amino-acid alterations identified in the TLR1-2-6 family, 14 of them (5 TLR1, 4 TLR2, and 5 TLR6 variants) displayed marked impairment of NF- κ B activation. Most of these variants are present at very low population frequencies and are population-specific. These observations suggest that rare, non-synonymous TLR mutations are likely to have deleterious effects on immune responses and may therefore contribute to complex susceptibility to infection at the population level.

Key words: TLRs, innate immunity, non-synonymous mutations, NF- κ B activity

INTRODUCTION

The innate immune system constitutes the first line of host defence against infection and plays a crucial role in the immediate recognition of invading pathogens, subsequently triggering proinflammatory responses [Janeway and Medzhitov, 2002; Lemaitre and Hoffmann, 2007; Medzhitov and Janeway, 2000; Medzhitov and Janeway, 1997]. This early response involves the recognition of evolutionarily conserved structures on pathogens —pathogen-associated molecular patterns (PAMPs) — through a limited number of germline-encoded pattern recognition receptors (PRRs) [Akira et al., 2006; Beutler et al., 2003; Janeway and Medzhitov, 2002; Kimbrell and Beutler, 2001; Medzhitov and Janeway, 1997]. The Toll-like receptors (TLRs) are the PRRs most extensively studied from clinical, epidemiological and evolutionary angles [Akira and Takeda, 2004; Casanova et al., 2011; Kawai and Akira, 2007; Medzhitov, 2001]. TLRs are type-I transmembrane proteins belonging to the interleukin-1 receptor family. They possess an N-terminal leucine-rich repeat (LRR) ligand-binding domain, a transmembrane domain and a C-terminal TIR domain for intracellular signalling. TLR signalling is initiated by agonist-induced dimerisation, which triggers intracellular signals ultimately culminating in the production of proinflammatory cytokines and interferons (IFNs), which orchestrate adaptive immune responses [Akira and Takeda, 2004; Kawai and Akira, 2007; Medzhitov, 2001; West et al., 2006]. Humans have ten different TLRs, which differ in terms of the PAMPs they sense, subcellular distribution and the nature of their responses [Akira and Takeda, 2004; Akira et al., 2006; Beutler, 2004; Kawai and Akira, 2006; Kawai and Akira, 2007; Leulier and Lemaitre, 2008; Medzhitov, 2001; West et al., 2006]. TLR3 (MIM#603029), TLR7 (MIM#300365), TLR8 (MIM#300366) and TLR9 (MIM#605474) are typically located in intracellular compartments, such as the endosomes, whereas TLR1 (MIM#601194), TLR2 (MIM#603028), TLR4 (MIM#603030), TLR5 (MIM#603031) and TLR6 (MIM#605403) are generally expressed on the cell surface.

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3 Intracellular TLRs sense nucleic acid agonists and are involved principally in the recognition
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5 of viruses, whereas cell surface-expressed TLRs detect various other products, mostly of
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7 bacterial, parasite and fungal origin.
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10 Evolutionary analyses of vertebrate TLRs have revealed various phylogenetically
11 conserved TLR families, each of which recognises a general class of PAMPs [Beutler and
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13 Rehli, 2002; Leulier and Lemaitre, 2008; Roach et al., 2005]. The TLR family specific for
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15 lipopeptide PAMPs includes *TLR1*, *TLR2* and *TLR6*. Human *TLR10* (MIM#606270) also
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17 belongs to this family, but its agonists and specific functions remain unknown. This family,
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19 which is known under various names but, for convenience, will be referred to here as the
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21 “*TLR1-2-6* gene family”, is unique in that TLR1 and TLR6 must co-operate with TLR2,
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23 forming TLR2/TLR1 or TLR2/TLR6 heterodimers, to mediate signalling in response to
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25 microbial agonists [Ozinsky et al., 2000]. The TLR2/1 heterodimer recognizes various
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27 lipoproteins, including those from mycobacteria and meningococci [Takeuchi et al., 2002],
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29 whereas the TLR2/6 heterodimer senses peptidoglycan and mycoplasma lipoproteins
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31 [Takeuchi et al., 2001].
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38 Due to the central role of TLRs in the innate immune system, genetic variation in this
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40 gene family may affect protein function and consequently alter susceptibility to infections.
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42 Several epidemiological genetics studies have investigated the contribution of variation in the
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44 genes encoding TLR1, 2 and 6, and TLRs in general, to susceptibility to infectious diseases
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46 (for comprehensive reviews, see [Casanova et al., 2011; Garantziotis et al., 2008]). For
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48 example, the TLR1 p.Ile602Ser variant, which affects the trafficking of the receptor to the cell
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50 surface, has been associated with protection against leprosy and leprosy reversal reaction
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52 [Johnson et al., 2007; Misch et al., 2008; Wong et al., 2010]. Genetic variation in *TLR2* has
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54 been reported to alter the susceptibility to various inflammatory and infectious diseases.
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56 Specifically, the well known TLR2 p.Arg753Gln variant appears to be associated with
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3 increased susceptibility to tuberculosis and acute rheumatic fever in children [Berdeli et al.,
4 2005; Ogus et al., 2004]. Similarly, the TLR6 p.Ser249Pro variant has been associated with a
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6 decreased risk of asthma in African-Americans [Tantisira et al., 2004]. More generally, non-
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8 synonymous polymorphisms in the *TLR6-TLR1-TLR10* gene cluster have been found to be
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10 significantly associated with tuberculosis disease in certain ethnic groups [Ma et al., 2007].
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12 However, the clear involvement of *TLR* variants in the complex genetic control of infectious
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14 pathogenesis has yet to be replicated in most cases and the functional consequences of *TLR*
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16 mutations remain mostly unknown [Casanova et al., 2011].
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22 In this study, we investigated the functional impact of naturally occurring non-
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24 synonymous variations in the *TLR1-2-6* gene family. We used an NF- κ B gene reporter assay
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26 system for the functional testing of 40 non-synonymous variants and one stop mutation, all
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28 corresponding to amino acid-altering mutations identified in a previous comprehensive
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30 sequence-based population study [Barreiro et al., 2009]. Fourteen of these variants presented
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32 substantial functional impairment. Furthermore, most of these functionally relevant mutations
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34 were observed at low population frequencies (<5%), suggesting that low-frequency non-
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36 synonymous mutations probably have deleterious effects on host immunity to infection.
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MATERIALS AND METHODS

Population samples

Sequence variation for the *TLR1-2-6* gene family was determined for a total of 158 individuals (316 chromosomes) representative of the populations of major geographical regions (Sub-Saharan Africa, Europe and East-Asia) (see [Barreiro et al., 2009]). The description of the specific population samples can be found in ALFRED (<http://alfred.med.yale.edu>) using the unique IDs given in parentheses. Sub-Saharan Africans were represented by Yorubans from Nigeria (31 individuals from UID “SA000036J”) and Chaggas from Tanzania (32 individuals from UID “SA000487T”); Europeans were represented by Danes (23 individuals from UID “SA000046K”) and Chuvash from Russia (24 individuals from UID “SA000491O”), and East-Asians were represented by Han Chinese (24 individuals from UID “SA000009J”) and Japanese (24 individuals from UID “SA000010B”). All individuals were healthy donors from whom informed consent was obtained. This study was approved by the Institut Pasteur Institutional Review Board (no. RBM 2008.06).

Mutation detection

All of the exon regions of *TLR1* (accession no. NM_003263.3), *TLR2* (accession no. NM_003264.3) and *TLR6* (accession no. NM_006068.3) were sequenced (for details see [Barreiro et al., 2009]). Sequences were obtained with the Big Dye terminator kit and an Applied Biosystems 3730 automated sequencer. Sequence files and chromatograms were inspected with GENALYS software [Takahashi et al., 2003]. For quality control, and to prevent allele-specific amplification, we designed new primers and repeated sequence reactions whenever new mutations were identified in primer-binding regions. All singletons or ambiguous polymorphisms were systematically reamplified and resequenced. The gDNA nucleotides and the amino acids of the protein were numbered based on GenBank sequence

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3 information. The mutation nomenclature follows the journal's guidelines
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5 (www.hgvs.org/mutnomen) according to the reference sequence with +1 as the A of the ATG
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7 initiation codon.
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10 11 12 **Prediction of the functional impact of non-synonymous mutations**

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15 The functional impact of all amino acid-altering mutations (i.e. benign, possibly damaging or
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17 probably damaging) was predicted with the PolyPhen-2 algorithm [Adzhubei et al., 2010].

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19 This method, which considers protein structure and/or sequence conservation information for
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21 each gene, has been shown to be the best predictor of the fitness effects of amino-acid
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23 substitutions. The domains of the various TLR proteins were identified with TollML: a
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25 database of Toll-like receptor structural motifs [Gong et al., 2010].
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32 **Plasmid constructs and site-directed mutagenesis**

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34 The NF- κ B luciferase reporter construct, NF- κ B-luc, containing the luciferase gene under the
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36 control of six κ B sites from the thymidine kinase promoter was kindly provided by Oreste
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38 Acuto. The *Renilla* luciferase construct was purchased from Promega (Promega, Madison,
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40 WI). All TLR constructs were purchased from Invivogen (InvivoGen, San Diego, CA).

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42 Allelic variants of *TLR1*, *TLR2* and *TLR6* were generated with the QuikChange site-directed
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44 mutagenesis system, according to the manufacturer's instructions (Stratagene, La Jolla, CA).

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46 All constructs were systematically verified by sequencing the complete TLR gene with an
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48 Applied Biosystems 3730 automated sequencer (Applied Biosystems, Foster City, CA).
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55 **Cell culture, transfection and dual luciferase reporter assay**

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57 HEK 293T cells were cultured in DMEM supplemented with 10% FCS, 100 IU penicillin and
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59 100 μ g/ml streptomycin (Invitrogen, Carlsbad, CA), at 37°C, in a humidified incubator, under
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3 an atmosphere containing 5% CO₂. Cells were used to seed 24-well plates (5 x 10⁴ cells/well).
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6 The next day, cells (30 to 50% confluence) were transiently transfected with the pNF-κB-luc,
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8 along with constructs encoding the various TLRs, in the presence of FuGene 6 reagent (Roche
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10 Diagnostics), according to the manufacturer's recommendations. All plasmids used for
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12 transfection were purified with the Endofree plasmid kit (Qiagen, Chatworth, CA). Briefly,
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14 cells were cotransfected with 100 ng of NF-κB reporter construct, TLR constructs and 5 ng of
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16 pRL-TK-*Renilla* luciferase construct (Promega, Madison, WI) as a control for transfection
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18 efficiency. For each transfection, total DNA was adjusted to 300 or 400 ng with empty
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20 pcDNA3.1 vector. For TLR2/1 and TLR2/6 studies, cells were cotransfected with 2.5 or 5 ng
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22 of TLR2 and 100 ng of TLR 1 or 200 ng of TLR6. For TLR2 experiments, 300 ng of TLR2
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24 variants was used for transfection. After 24 h, TLR2/1- and TLR2/6-transfected cells were
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26 stimulated for 4 h with 5 ng/ml Pam₃CSK₄ and for 3 h with 10 ng/ml Pam₂CSK₄, respectively,
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28 and TLR2-transfected cells were stimulated for 16 h with 10 ng/ml Pam₃CSK₄ (EMC
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30 microcollections). Supernatants were discarded and cells were lysed in 100 μl of passive lysis
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32 buffer (Promega, Madison, WI) and used for dual luciferase assays (firefly and *Renilla*
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34 luciferase activities) carried out according to the manufacturer's instructions. Luciferase
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36 activity was normalised by dividing by *Renilla* luciferase activity, to correct for transfection
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38 efficiency, and the results are expressed as the mean relative stimulation (± SD) in three
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40 independent experiments, each performed in triplicate.
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51 **Flow cytometry analysis**

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53 HEK293T cells were transfected in six-well plates with HA-tagged TLR1, TLR2 or TLR6
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55 expression vector or empty vector alone (2 μg each). Transfections were performed with the
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57 FuGENE 6 transfection reagent (Roche), at a 3:1 ratio of FuGENE 6 to DNA. The medium
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59 was replaced 24 h after transfection, and cells were removed from the plate into chilled PBS
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3 (pH 7.4) 48 h after transfection and incubated with the corresponding Abs. Cell-surface
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5 expression of TLR1 and TLR2 was measured with the mAbs GD2.F4 and T2.5, respectively
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8 (eBioscience). Appropriate isotype-matched Abs were used as controls.
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10 11 12 **Protein analysis**

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14 For immunoblots, cells transfected with TLR variants were lysed in 100 μ l of passive lysis
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16 buffer (Promega, Madison, WI) and centrifuged. Equal volumes of cell lysate were subjected
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18 to 10% SDS-PAGE under reducing conditions, and the resulting bands were transferred to a
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20 membrane and probed with an anti-HA tag antibody (Invivogen, San Diego, CA), followed by
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22 horseradish peroxidase-conjugated rabbit anti mouse IgG (Jackson ImmunoResearch, West
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24 Grove, PA). The signal was detected by incubation with Pierce ECL western blotting reagent
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29 (Thermo Scientific, Rockford, IL).
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RESULTS

Our re-sequencing effort of the three members of the *TLR1-2-6* gene family in a panel of 158 healthy individuals originating from sub-Saharan Africa, Europe and East Asia allowed us to identify 40 non synonymous variants and one stop mutation that naturally segregate in the human population (Table 1, Supp. Tables S1-S3) [Barreiro et al., 2009]. The location of each variant within the protein (e.g. extracellular, transmembrane, TIR domains) is shown in Figure 1. When comparing these variants to those that are described in public databases, we found that 14 of them are newly identified mutations. We first used the PolyPhen-2 algorithm [Adzhubei et al., 2010] to predict the functional impact of all amino-acid altering variants described in this study. Interestingly, the vast majority of the variants predicted to be possibly or probably damaging (~ 80%) were observed at low frequencies (<5%) and most of them were population specific.

In order to obtain unbiased results, we systematically characterized the 41 amino acid altering variants regardless of their population frequencies and their effect on protein structure and function as predicted by the PolyPhen algorithm [Adzhubei et al., 2010]. Each variant was generated by site-directed mutagenesis from the reference *TLR1*, *TLR2* or *TLR6* template corresponding to the ancestral form in the human population, defined on the basis of the chimpanzee sequence. We then assessed the ability of these constructs to activate NF- κ B signalling, the major TLR-induced pathway, in transiently transfected human embryonic kidney (HEK) 293T cells stimulated with the most commonly used TLR-specific agonists. The variants found to be functionally relevant (i.e. TLR variants with levels of NF- κ B activation more than 20% lower than the ancestral form) were further studied by measuring their cell surface expression by flow cytometry.

Functional characterisation of TLR1 variants

Since TLR1 signals as a heterodimer with TLR2, the various TLR1 constructs were transfected into HEK293T cells together with the wild-type (ancestral) TLR2, and cells were stimulated with the PAM₃CSK₄ agonist. One of the 17 identified TLR1 non-synonymous variants (p.Ser248Asn) displayed a small loss of activity (<20%), whereas five others (p.Pro315Leu, p.Tyr554Cys, p.Ile602Ser, p.Val651Ala and p.His720Pro) displayed severe impairment of activity with respect to the ancestral form (Fig. 2A). The p.Pro315Leu and p.Ile602Ser variants displayed the greatest loss of activity (~70% and 60%, respectively), with levels of NF-κB activation similar to those obtained with TLR2 alone. The other three variants (p.His720Pro and the newly reported p.Tyr554Cys, p.Val651Ala variants) displayed losses of NF-κB activation of ~30%, 50% and 40%, respectively. In addition, two TLR1 variants (p.Ile75Thr and p.Ile460Val) were associated with levels of NF-κB activation ~25% and 12% higher, respectively, than for the ancestral form. The remaining 10 variants induced NF-κB activation to a similar extent to the ancestral form.

We further characterised the five functionally relevant TLR1 variants (p.Pro315Leu, p.Tyr554Cys, p.Ile602Ser, p.Val651Ala and p.His720Pro), by measuring their expression at the surface of transfected cells by flow cytometry with a widely used commercial anti-TLR1 mAb (GD2.F4) (Fig. 2B). No signal was detected on cells transfected with an empty vector, demonstrating an absence of endogenous TLR1 expression in HEK293T cells (data not shown). The p.Pro315Leu variant was not detected at the cell surface because, as reported in a previous study [Omueti et al., 2007], it is not recognized by the anti-TLR1 mAb.

Additionally, our flow cytometry analysis did not detect neither the p.Ile602Ser variant, whose intracellular trafficking is impaired [Johnson et al., 2007], nor the newly reported p.Tyr554Cys variant. By contrast, the p.Val651Ala and p.His720Pro variants were well expressed on the surface of transfected cells. Western blots of total cell lysates were

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3 performed to evaluate the overall expression levels of these variants. All variants were
4 expressed to similar levels (Fig. 2C). The TLR1 p.Ile602Ser variant gave rise to a double
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6 band. The altered migration may be due to the presence of a novel site of phosphorylation.
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10 11 12 **Functional characterisation of TLR2 variants**

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14 We then assessed the functional consequences of changes in the amino-acid sequence of
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16 TLR2 (6 non-synonymous variants and one stop mutation), by measuring the response of
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18 transfected cells to the agonist PAM₃CSK₄. As expected, cells transfected with the R447Stop
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20 construct, which contains a premature stop codon in the extracellular portion of the receptor
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22 resulting in a truncated protein, failed to respond to stimulation (Fig. 3A). Among the six non-
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24 synonymous changes, p.Thr411Ile and p.Arg753Gln reduced TLR2-mediated NF-κB
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26 activation by about 50 and 75%, respectively, whereas p.Pro631His reduced this activation by
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28 ~30%. The remaining three variants (i.e., p.Arg571His and the newly identified p.Asn89Asp
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30 and p.Ser636Arg) were functionally similar to the ancestral form (Fig. 3A).
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37 Flow cytometry analysis revealed that, with the exception of the p.Arg447X stop
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39 variant whose expression was abrogated, all TLR2 variants were expressed at the surface of
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41 transfected cells (Fig. 3B). Western blot analysis showed that the four functionally relevant
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43 HA-tagged TLR2 variants were expressed at similar levels (Fig. 3C).
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48 49 **Functional characterisation of TLR6 variants**

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51 Since TLR6 needs to heterodimerize with TLR2 for signalling, the different TLR6 variants
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53 (i.e. 17 non-synonymous variants) were co-transfected with TLR2 and cells were tested for
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55 their response to the synthetic lipopeptide PAM₂CSK₄ agonist. Background levels of reporter
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57 activation were observed in cells transfected with TLR2 alone (Fig. 4A), probably due to the
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59 expression of “endogenous” TLR6 in the recipient cells. The amounts of the TLR6 and TLR2
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3 constructs used for transfection were optimised so as to reduce reporter activation with TLR2
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5 alone (potentially pairing with endogenous TLR6) and to achieve maximal activation upon
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7 overexpression of exogenous TLR6 (Fig. 4A). As a control, we tested the impact on NF- κ B
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9 activation of the previously described dominant negative (DN) TLR6 p.Pro680His variant
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11 [Okusawa et al., 2004]. We observed that the level of NF- κ B activation induced by this TLR6
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13 DN form was reduced of ~70% with respect to the ancestral TLR6 and, importantly, it was
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15 also considerably lower than that observed with TLR2 alone (Fig. 4A). This suggests that, in
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17 our experimental setting, the transfected TLR6 construct is in large excess and overrides the
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19 contribution of the endogenous TLR6. Under these conditions, cells transfected with
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21 p.Ala210Thr, p.Ala210Gly or p.Arg247Lys showed a slight attenuation (<20% decrease) in
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23 their ability to respond to the PAM₂CSK₄ agonist, with respect to cells transfected with the
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25 ancestral TLR6. Cells transfected with p.Leu128Val, p.Leu194Pro, p.Ala474Val,
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27 p.Asn690Thr or p.Gln708His constructs displayed a stronger decrease in NF- κ B activation
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29 (Fig. 4A). p.Leu128Val showed the most severe impairment, with a loss of function of about
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31 40% with respect to the ancestral form. Indeed, the activity displayed by p.Leu128Val was
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33 similar to the background activity observed with TLR2 alone. All the remaining variants
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35 displayed levels of NF- κ B activation similar to those of the ancestral form.
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43 Western blots of HA-tagged TLR6 and its variants showed that all functionally
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45 relevant variants were expressed to similar extents (Fig. 4B). The cell surface levels of the
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47 TLR6 variants could not be adequately assessed by FACS, given the presence of endogenous
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49 TLR6 (data not shown).
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55 **PolyPhen predictions and functional characterisation**

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57 The use of computational methods to predict the functional impact of protein sequence
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59 variants is a useful tool in medical and evolutionary genetics. The PolyPhen algorithm
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3 predicts the impact of nonsynonymous variants (benign, possibly damaging, or probably
4 damaging) on the structure and function of the protein, using alignments of orthologous gene
5 sequences from multiple species and, when available, physical considerations, such as the
6 three-dimensional structures of proteins [Adzhubei et al., 2010]. We compared the PolyPhen
7 predictions for each of the 40 non-synonymous mutations tested in this study (Table 1) with
8 their actual, observed effect on the parameter considered here: NF- κ B activation. **The vast**
9 **majority of mutations predicted to be benign did not substantially affect NF- κ B activation. In**
10 **contrast, most variants predicted to be possibly or probably damaging showed indeed a**
11 **substantial decrease in NF- κ B activation (Fig. 5A). Specifically, among the eleven non-**
12 **synonymous SNPs that were predicted to be probably or possibly damaging by PolyPhen, our**
13 **functional analysis revealed that 8 of them (~73%) had a substantial effect on NF- κ B**
14 **activation (i.e., more than a 20% decrease in NF- κ B activation with respect to the ancestral**
15 **form). Conversely, only five of the 29 SNPs predicted to be “benign” (~17%) reduced**
16 **substantially NF- κ B activation. Interestingly, mutations located the TIR domain tended to**
17 **have a more severe impact on signalling than those affecting the extracellular domain (Fig.**
18 **5B). All TIR domain variants were maintained at low frequency (<5%) in each of the three**
19 **populations studied, suggesting that variation affecting the amino-acid sequence of this**
20 **domain is under strong evolutionary constraints.**
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DISCUSSION

Assessment of the extent to which amino acid sequence-altering variation segregating in the general population affects protein function constitutes a step towards a clearer understanding of the way in which host genetic variants contribute to complex disease susceptibility and/or progression in humans. We used the *TLR1-2-6* gene family as a model to investigate the functional consequences of 41 naturally occurring variants with altered amino-acid sequences previously identified in an unbiased population genetics resequencing scheme **in a multi-ethnic panel of healthy individuals** [Barreiro et al., 2009].

We found that five of the 17 non-synonymous TLR1 variants displayed strong impairment of NF- κ B activation (Fig. 2A). Two of these strongly impaired variants (p.Pro315Leu and p.Ile602Ser) were previously shown to impair TLR1/2 function [Barreiro et al., 2009; Hawn et al., 2007; Johnson et al., 2007; Omueti et al., 2007]. The p.Pro315Leu amino-acid change, in the outer loop of LRR11, drastically reduced NF- κ B activation in response to PAM₃CSK₄, consistent with previous observations showing that p.Pro315Leu affects cellular responses to various microbe-derived agonists [Omueti et al., 2007]. The p.Ile602Ser variant, which was also associated with a major loss of NF- κ B activation, is known to affect receptor trafficking to the plasma membrane, impairing responses in both primary monocytes and heterologous expression systems [Barreiro et al., 2009; Hawn et al., 2007; Johnson et al., 2007]. **With respect to the three remaining functionally relevant TLR1 variants, (p.Tyr554Cys, p.Val651Ala and p.His720Pro), p.Tyr554Cys exhibits a substantial activity loss and is not detected on the surface of transfected cells** (Fig. 2B). The tyrosine 554 is located within the C-terminal LRR domain and its substitution with cysteine residue, may affect the conformation of the ectodomain. Finally, p.Val651Ala and p.His720Pro were well expressed on the surface of transfected cells, suggesting correct folding and trafficking to the plasma membrane (Fig. 2B). However, the location of these two

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3 amino-acid substitutions in the TIR-domain suggests a possible impact on interaction with
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5 intracellular partners, such as the adaptor MyD88.
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8 The case of the TLR1 p.Ile602Ser variant, which strongly impacts protein function,
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10 merits further discussion. This mutation characterises a haplotype, encompassing the *TLR10-*
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12 *TLR1-TLR6* gene cluster, which is present at high frequency in Europeans (up to 30%), while
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14 it is rare in Africans and Asians. Interestingly, this haplotype has been shown to be under
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16 strong positive selection in the European population [Barreiro et al., 2009; Pickrell et al.,
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18 2009]. Given both the signature of positive selection detected and the functional consequences
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20 of the TLR1 p.Ile602Ser variant, it is highly plausible that the attenuation of TLR1-mediated
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22 signaling, leading to a weaker inflammatory response, has conferred a selective advantage in
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24 Europeans. The association between the hyporesponsiveness p.Ile602Ser variant and
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26 protection against leprosy pathogenesis suggests that mycobacteria, or other pathogens that
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28 are recognized by TLR1, may be the agents underlying the patterns of selection and, as a
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30 consequence, may have contributed to the present global distribution of the p.Ile602Ser
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32 variant [Johnson et al., 2007; Misch et al., 2008; Wong et al., 2010]. Regardless of the
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34 genuine agent of selection, the TLR1 p.Ile602Ser variant falls in a genomic region that has
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36 been recently found to be a hotspot of positive selection in human and non-human primates
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38 [Enard et al., 2010]. The concomitant detection of positive selection targeting the *TLR10-*
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40 *TLR1-TLR6* gene cluster in human, chimpanzee and orangutan [Barreiro et al., 2009; Enard et
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42 al., 2010; Pickrell et al., 2009] strongly support the notion that this genomic region has played
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44 a major adaptive role in host resistance to a broad spectrum of bacteria in multiple species.
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52 With respect to TLR2 naturally-occurring amino-acid changes, three of them
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54 (p.Thr411Ile, p.Pro631His and p.Arg753Gln) displayed impaired activity and one
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56 (p.Arg447X) was non-responsive (Fig. 3A). This latter is truncated but still able to interact
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58 with TLR1, TLR6 and/or TLR2 via the extracellular domain, thereby forming non-functional
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3 heterodimers or homodimers, respectively [Merx et al., 2007]. p.Arg753Gln, which greatly
4 reduced NF- κ B activation, consistent with previous reports [Kormann et al., 2009; Merx et
5 al., 2007], is located in the TIR-domain, suggesting possible effects on its interaction with
6 MyD88. The prevalence of the p.Arg753Gln variant has been examined in several disease
7 contexts and this variant has been associated with an increase in susceptibility to tuberculosis,
8 acute rheumatic fever in children, and CMV disease after liver transplantation [Berdeli et al.,
9 2005; Kijpittayarit et al., 2007; Ogus et al., 2004]. With respect to the p.Thr411Ile variant, in
10 contrast with a recent study that observed no decrease in NF- κ B activity in response to
11 PAM₃CSK₄ [Kormann et al., 2009], our data showed that this variant drastically reduced NF-
12 κ B activation in agreement with early observations [Merx et al., 2007]. The location of the
13 p.Thr411Ile variant in the extracellular domain suggests an impact on the ligand-binding
14 properties of TLR2. Discrepancies between studies are also patent for the p.Pro631His
15 variant. While two previous studies reported that the NF- κ B pathway is not altered by
16 p.Pro631His [Kormann et al., 2009; Merx et al., 2007], we observed that this variant does
17 affect NF- κ B activation. In support of our observation, p.Pro631His has been shown to have a
18 dominant negative effect on wild-type TLR2 signalling in HEK 293T cells stimulated with
19 ligands such as *M. avium* extracts, PAM₃CSK₄ or FSL-1, which bind TLR2/1 or TLR2/6
20 heterodimers [Etokebe et al., 2010]. In addition, this variant has been shown to impair
21 internalisation from the cell surface to early endosomal compartments [Etokebe et al., 2010].

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49 For TLR6, five of the 17 non-synonymous variants segregating in the general population
50 (p.Leu128Val, p.Leu194Pro, p.Ala474Val, p.Asn690Thr and p.Gln708His) displayed
51 significant impairment in terms of their ability to induce NF- κ B activation (Fig. 4A). The
52 p.Leu128Val variant, which was the most strongly impaired, is located in the conserved
53 “LxxLxLxxN” motif of LRR4 responsible for the characteristic horseshoe-like shape of the
54 protein [Kang et al., 2009]. The other four variants — p.Leu194Pro and p.Ala474Val in the
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3 extracellular domain and p.Asn690Thr and p.Gln708His in the TIR domain — displayed
4
5 more modest impairments of NF- κ B activation (Fig. 4A). However, the actual decrease in
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7 NF- κ B activation displayed by these five functionally relevant variants may be more
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9 pronounced than described here, due to the small amounts of endogenous TLR6 in recipient
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11 cells.
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15 It is interesting to note that, despite similar protein length (Fig. 1), TLR2 displays a
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17 lower number of amino-acid changes (seven non-synonymous mutations) than TLR1 and
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19 TLR6 (17 non-synonymous mutations each), in accordance with a previous study [Georgel et
20
21 al., 2009]. Three of the seven non-synonymous TLR2 variants strongly decreased NF- κ B
22
23 activation and were present at very low population frequencies. This suggests stronger
24
25 selective constraints on amino-acid altering variation in TLR2 than in TLR1 and TLR6, a
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27 hypothesis formally supported by evolutionary genetics data across vertebrate species and in
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29 humans, showing that purifying selection has been stronger for TLR2 than for TLR1 and
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31 TLR6 [Barreiro et al., 2009; Roach et al., 2005]. In the context of the *TLR1-2-6* family,
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33 evolutionary and functional data converge to suggest that TLR2 fulfils an essential function in
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35 early innate immune responses. TLR2, by heterodimerising with TLR1 or TLR6, presents a
36
37 broader agonist repertoire, recognising a diverse set of pathogens [Takeuchi et al., 2001;
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39 Takeuchi et al., 2002]. In addition to its role as a prototypic cell surface-expressed TLR,
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41 TLR2 has also been shown to induce type-I IFN production when expressed in the endosomal
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43 compartment [Barbalat et al., 2009; Bauernfeind and Hornung, 2009]. Variants of the TLR2
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45 gene may therefore affect not only proinflammatory responses, but also IFN production,
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47 further constraining the evolution of this gene.
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56 Finally, the comparison between the PolyPhen predictive results and the actual,
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58 functional consequences of TLR variants showed that the vast majority of mutations predicted
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60 as “benign” do not substantially affect protein function (~80%), at least in terms of NF- κ B

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3 activation (Fig. 5A). Similarly, most mutations predicted as possibly or probably damaging
4 considerably impact protein function (~73%). Although in most cases there is a good
5 concordance between the PolyPhen predictions and the experimental observations, two
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7
8 exceptions are worth mentioning in this respect: TLR1 p.Pro315Leu and p.Ile602Ser. These
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10
11 two variants, which have been both convincingly shown to drastically reduce NF- κ B
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14 activation by us (Fig. 2A) and others [Barreiro et al., 2009; Hawn et al., 2007; Johnson et al.,
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16
17 2007; Omueti et al., 2007], are indeed predicted to be benign by PolyPhen (Table 1, Fig. 5A),
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20 highlighting some of the limitations of predictive methods. An interesting observation is that
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23 most of the variants either predicted to be damaging by PolyPhen or experimentally shown to
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26 impair NF- κ B activation are rare and population-specific, suggesting that considerable
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29 evolutionary pressure may maintain these variants at low population frequencies because of
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32 their probable deleterious effects. Most functionally relevant variants are singletons, but
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35 heterozygous individuals may have a higher risk of infection due to dominant negative or
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38 gene dosage effects, raising questions about the epidemiological relevance of rare TLR
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41 mutations. Indeed, associations between low-frequency TLR variants and infectious disease
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44 susceptibility have been reported for TLR4 and meningococcal susceptibility [Smirnova et al.,
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46
47 2003] and for TLR6-TLR1-TLR10 and tuberculosis [Ma et al., 2007].

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50 In summary, rare, functionally impaired TLR variants may be major risk factors in the
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53 host affecting the outcome and/or severity of infection. They should therefore be considered
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56 in the context of large-scale association studies of genetic susceptibility to disease. Indeed,
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59 rare variants are not generally tested in traditional genome-wide association studies, which are
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62 principally based on the genotyping of common polymorphisms (i.e., frequencies > 5%)
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65 present on commercial arrays. In this context, upcoming association studies based on whole-
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68 exome resequencing should compensate for this limitation and shed light on the ways in

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3 which rare, population-specific variants contribute to susceptibility to, or the pathogenesis of
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5 infectious diseases.
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For Peer Review

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Legends to Figures

Figure 1: Naturally occurring non-synonymous variants in the TLR1-2-6 family. Non-synonymous mutations in black, blue and orange correspond to those predicted to be benign, possibly damaging, and probably damaging, respectively. Mutations shown in red are nonsense mutations.

Figure 2. Functional analyses of TLR1 variants. (A) Dual luciferase assay of HEK293T cells transiently transfected with wild-type TLR1 and various naturally occurring variants. The amounts of plasmid DNA used for transfection were optimised so as to minimise baseline reporter activation with TLR2 alone (see Materials and Methods). The data shown are the means \pm standard deviations (SD) from three independent experiments each performed in triplicate, expressed as the percent relative firefly luciferase activity (RLU) (normalised with respect to *Renilla* luciferase activity). * $p < 0.05$ ** $p < 0.001$ (as determined by Student's *t* test) for comparisons of the various TLR1 allelic variants with the wild type (ancestral form). (B) Cell-surface expression of TLR1 variants, assessed by flow cytometry analysis. Cells were transfected with 2 μ g of TLR1 expression vector (solid line) or the empty vector (dashed line), as indicated. After 48 h, cells were detached and incubated with the anti-TLR1 mAbs GD2.F4. (C) Western-blot analyses of functionally relevant TLR1 variants. Cells were transfected with 100 ng of HA-tagged ancestral TLR1, HA-tagged TLR1 variant or the empty vector.

Figure 3. Functional analyses of TLR2 variants. (A) Dual luciferase assay of HEK293T cells transiently transfected with wild-type TLR2 and various naturally occurring variants. The data shown are the means \pm SD for three independent experiments, each performed in triplicate, expressed as the RLU (normalised with respect to *Renilla* luciferase activity). *

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2
3 $p < 0.05$ ** $p < 0.001$ (as determined by Student's *t* test) for comparisons of the various TLR2
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5 allelic variants with the wild type (ancestral form). (B) Cell-surface expression of TLR1
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7 variants, analysed by flow cytometry. Cells were transfected with 2 μ g of TLR2 vector (solid
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9 line), or the empty vector (dashed line) as indicated. After 48 h, cells were detached and
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11 incubated with the anti-TLR2 mAbs T2.5. (C) Western-blot analyses of functionally relevant
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13 TLR2 variants. Cells were transfected with 100 ng of HA-tagged ancestral TLR2, HA-tagged
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15 TLR2 variant or the empty vector.
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22 **Figure 4. Functional analyses of TLR6 variants.** (A) Dual luciferase assay of HEK293T
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24 cells transiently transfected with wild-type TLR6 and various naturally occurring variants.
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26 The data shown are the means \pm SD for three independent experiments, each performed in
27
28 triplicate, expressed as the RLU (normalised with respect to *Renilla* luciferase activity). *
29
30 $p < 0.05$ ** $p < 0.001$ (as determined by Student's *t* test) for comparison of the various TLR6
31
32 allelic variants with the wild type (ancestral form). For TLR2/6 P680H, "DN" indicates
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34 "dominant negative" mutation. (B) Western-blot analyses of functionally relevant TLR6
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36 variants. Cells were transfected with 100 ng of HA-tagged ancestral TLR6, HA-tagged TLR6
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38 variant or the empty vector.
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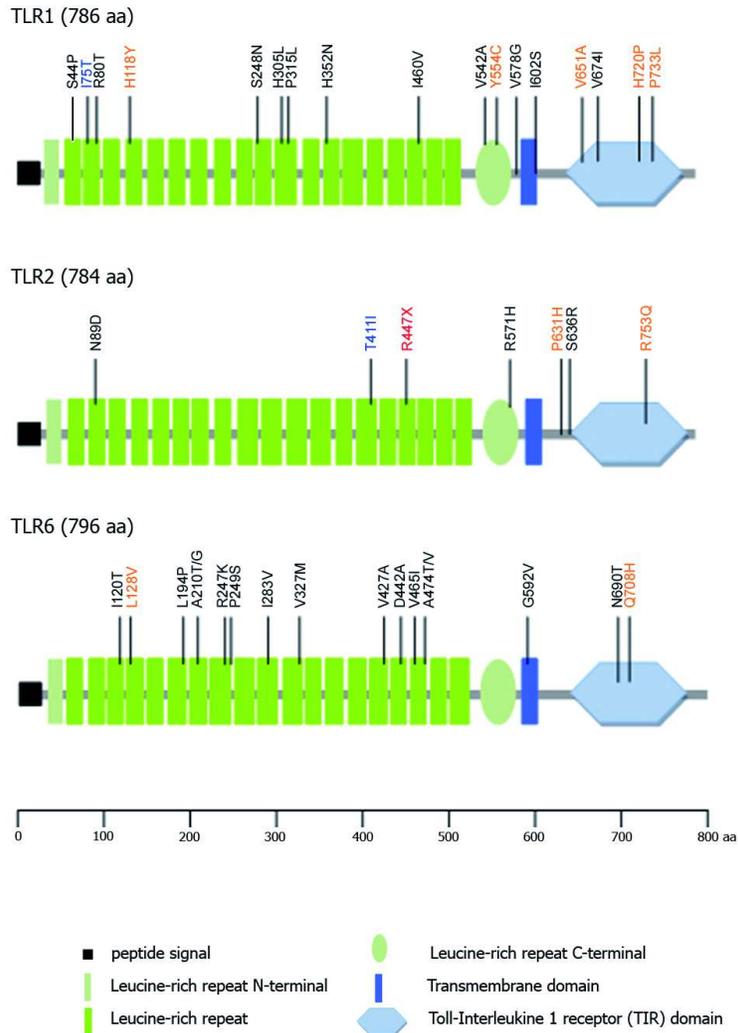
46 **Figure 5. Functional impact of TLR1-2-6 variants.** NF- κ B activation impairment is
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48 presented with respect to (A) PolyPhen predictions and (B) protein domains. Variants
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50 predicted to be "damaging" have a more severe effect on NF- κ B activation than variants
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52 predicted to be "benign". Mutations affecting the TIR domain generally seem to have a
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54 greater impact on TLR signalling than those affecting the extracellular domain.
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Table 1. Description of the studied *TLR1-2-6* gene family amino-acid altering variants

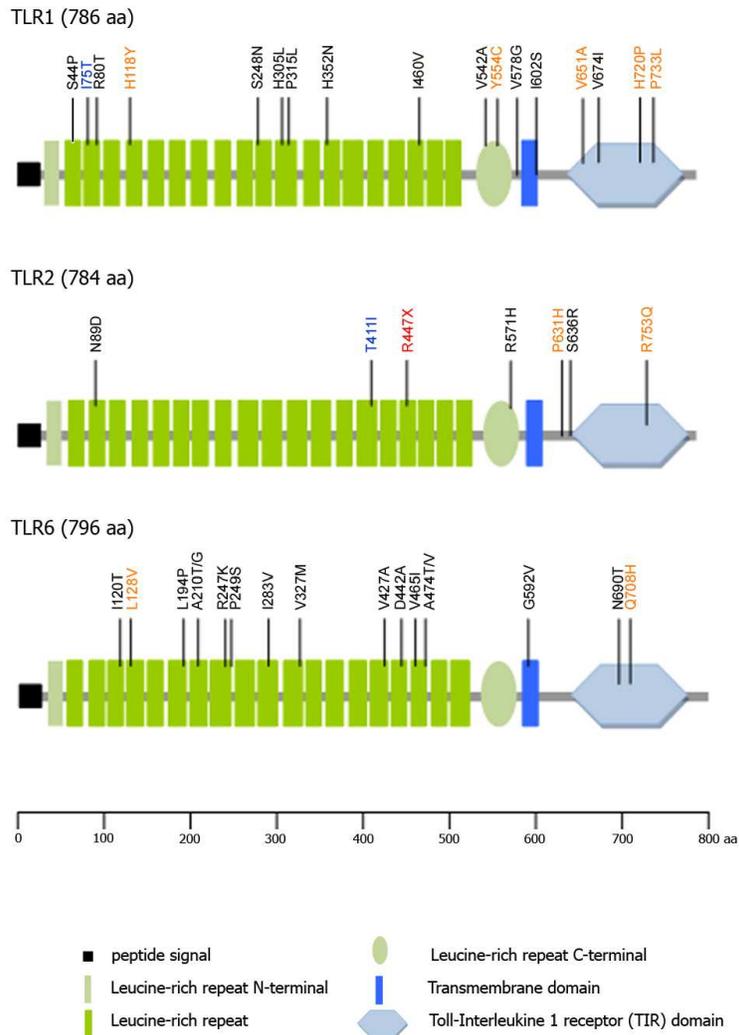
Gene	rs# dbSNP	cSNP ^a	Frequency (%) ^b			AA change ^c	PolyPhen-2	NF-κB (%) ^d
			AFR	EUR	ASN			
TLR1	rs76600635	c.130T>C	0	3.19	4.17	p.Ser44Pro	benign	102.54
TLR1	New	c.224T>C	0.79	0	0	p.Ile75Thr	possibly damaging	125.38
TLR1	rs5743611	c.239G>C	0	7.45	0	p.Arg80Thr	benign	94.62
TLR1	rs5743612	c.352C>T	13.5	0	0	p.His118Tyr	probably damaging	101.50
TLR1	rs4833095	c.743G>A	10.3	37.2	58.3	p.Ser248Asn	benign	91.12
TLR1	rs3923647	c.914A>T	3.97	2.13	0	p.His305Leu	benign	101.36
TLR1	rs5743613	c.944C>T	0.79	0	0	p.Pro315Leu	benign	32.79
TLR1	rs76796448	c.1054C>A	5.56	0	0	p.His352Asn	benign	103.24
TLR1	New	c.1378A>G	0	0	1.04	p.Ile460Val	benign	112.79
TLR1	New	c.1625T>C	0.79	0	0	p.Val542Ala	benign	96.25
TLR1	New	c.1661A>G	0	0	1.04	p.Tyr554Cys	probably damaging	54.22
TLR1	rs5743617	c.1760T>G	5.56	0	0	p.Val587Gly	benign	101.67
TLR1	rs5743618	c.1805T>G	0	51.1	2.08	p.Ile602Ser	benign	45.08
TLR1	New	c.1952T>C	1.59	0	0	p.Val651Ala	probably damaging	63.68
TLR1	New	c.2020G>A	0.79	0	0	p.Val674Ala	benign	111.19
TLR1	rs113706342	c.2159A>C	0	2.13	0	p.His720Pro	probably damaging	69.84
TLR1	rs5743621	c.2198C>T	1.59	0	0	p.Pro733Leu	probably damaging	101.91
TLR2	New	c.265A>G	0	1.06	0	p.Asn89Asp	benign	101.34
TLR2	rs5743699	c.1232C>T	0	1.06	0	p.Thr411Ile	possibly damaging	44.46
TLR2	rs62323857	c.1339C>T	0	1.06	0	p.Arg447X	STOP	9.10
TLR2	rs61735277	c.1712G>A	0.79	0	0	p.Arg571His	benign	99.17
TLR2	rs5743704	c.1892C>A	0	5.32	0	p.Pro631His	probably damaging	72.75
TLR2	New	c.1906A>C	0.79	0	0	p.Ser636Arg	benign	110.84
TLR2	rs5743708	c.2258G>A	0	2.13	0	p.Arg753Gln	probably damaging	26.00
TLR6	rs5743808	c.359T>C	10.3	0	1.04	p.Ile120Thr	benign	91.12
TLR6	New	c.382C>G	0	0	2.08	p.Leu128Val	probably damaging	58.49
TLR6	rs5743809	c.581T>C	7.14	0	0	p.Leu194Pro	benign	74.64
TLR6	New	c.628G>A	0	0	1.04	p.Ala210Thr	benign	87.64
TLR6	New	c.629C>G	0	0	1.04	p.Ala210Gly	benign	88.77
TLR6	rs35220466	c.740G>A	3.97	0	0	p.Arg247Lys	benign	84.42
TLR6	rs5743810	c.745C>T	2.38	28.7	0	p.Pro249Ser	benign	92.66
TLR6	New	c.847A>G	0.79	0	0	p.Ile283Val	benign	95.27
TLR6	rs3796508	c.979G>A	1.59	0	1.04	p.Val327Met	benign	104.29
TLR6	rs5743815	c.1280T>C	0	1.06	0	p.Val427Ala	benign	91.00
TLR6	New	c.1325A>C	0.79	0	0	p.Asp442Ala	benign	97.63
TLR6	rs5743816	c.1393G>A	7.14	0	1.04	p.Val465Ile	benign	92.04
TLR6	rs5743817	c.1420G>A	8.73	0	0	p.Ala474Thr	benign	88.58
TLR6	rs35762983	c.1421C>T	0.79	0	0	p.Ala474Val	benign	77.30
TLR6	rs5743617	c.1775T>G	0	0	9.38	p.Val592Gly	benign	92.86
TLR6	1000 Genomes	c.2069A>C	3.17	0	0	p.Asn690Thr	benign	72.28
TLR6	New	c.2124G>C	1.59	0	0	p.Gln708His	probably damaging	72.86

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3 ^aThe first nucleotide corresponds to the ancestral state and the second to the derived allele, as
4 defined on the basis of the chimpanzee sequence; ^bPopulation allele frequency of the derived
5 allele in sub-Saharan African (AFR), European (EUR) and Asian (ASN) populations; ^cThe
6 first amino-acid corresponds to the ancestral state; ^dLevels of NF- κ B activation for each TLR
7 variant with respect to the ancestral form (normalized at 100%). In bold, functionally relevant
8 variants (i.e. TLR variants with levels of NF- κ B activation more than 20% lower than the
9 ancestral form)
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For Peer Review

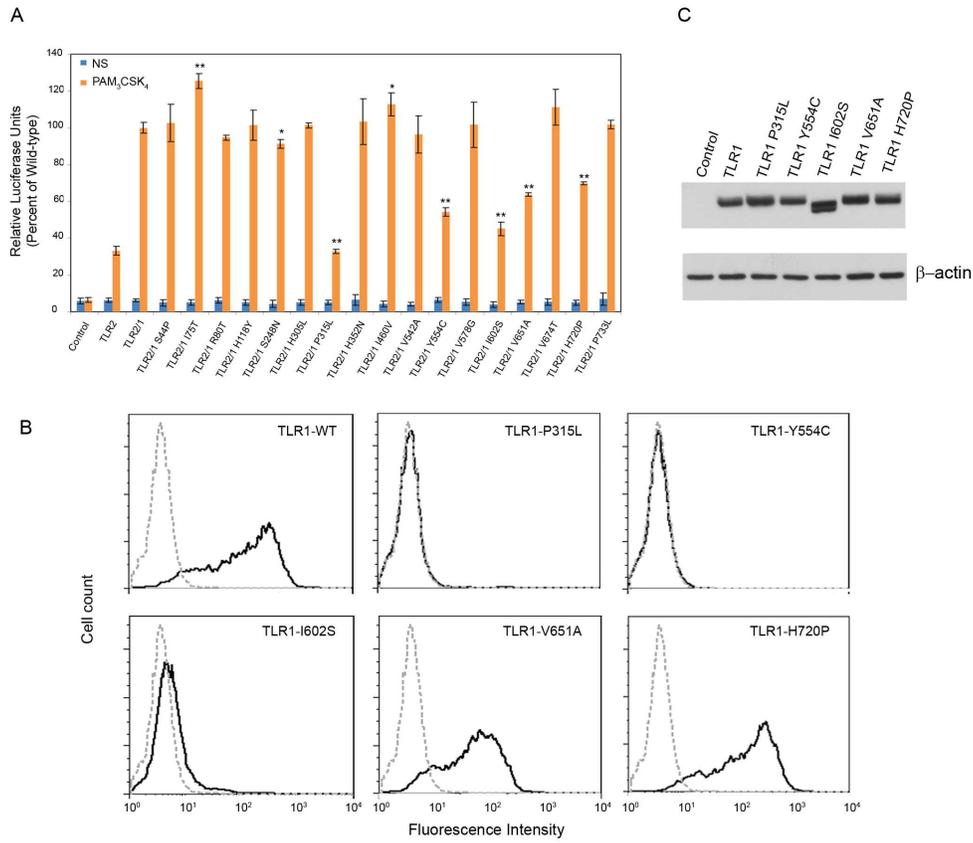


Naturally occurring non-synonymous variants in the TLR1-2-6 family
86x129mm (300 x 300 DPI)



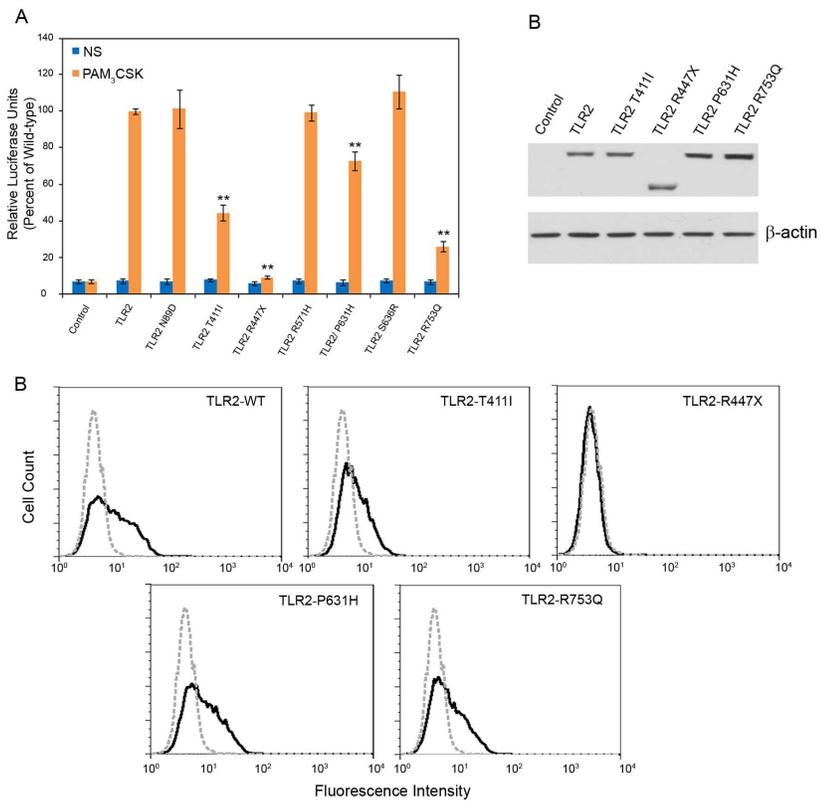
Naturally occurring non-synonymous variants in the TLR1-2-6 family
86x129mm (300 x 300 DPI)

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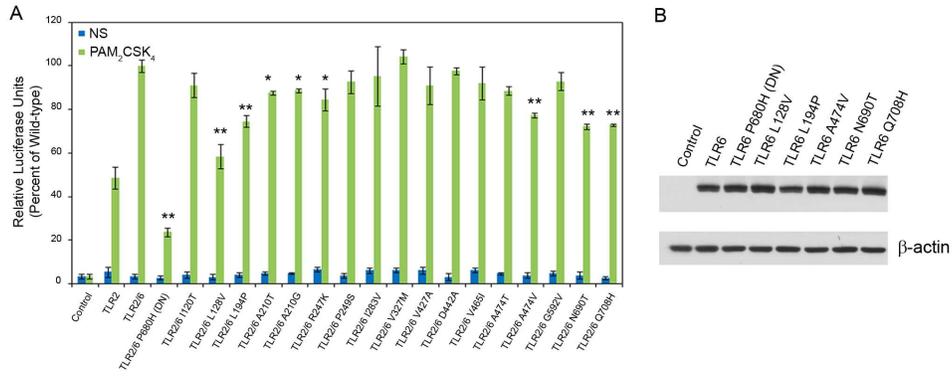


Functional analyses of TLR1 variants
180x160mm (300 x 300 DPI)

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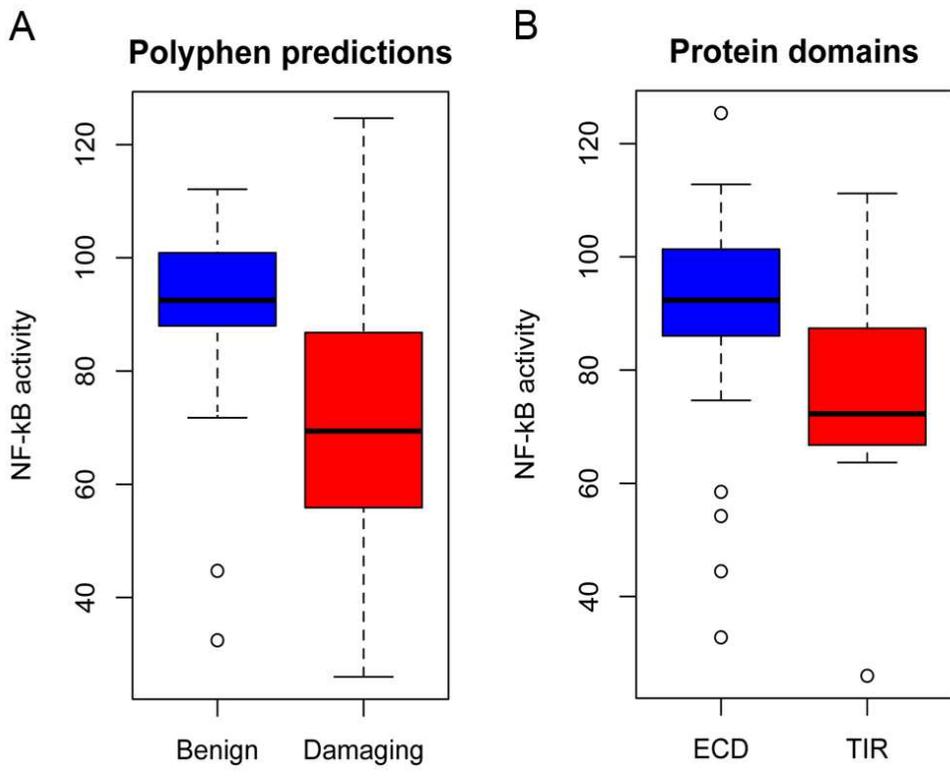
Functional analyses of TLR2 variants
180x160mm (300 x 300 DPI)



Functional analyses of TLR6 variants
180x83mm (300 x 300 DPI)

Peer Review

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Functional impact of TLR1-2-6 variants
86x67mm (300 x 300 DPI)

review

Supporting Information

“Functional characterisation of naturally occurring genetic variants in the human TLR1-2-6 gene family”

Supp. Table S1. Genotype information per individual of the TLR1 non-synonymous variants

			SNP	SNP	SNP	SNP	SNP	SNP	SNP	SNP	SNP	SNP							
Continent	Population	ID	c.130T >C	c.224T >C	c.239G >C	c.352 C>T	c.743G >A	c.914 A>T	c.944 C>T	c.1054 C>A	c.1378 A>G	c.1625 T>C	c.1661 A>G	c.1760 T>G	c.1805 T>G	c.1952 T>C	c.2020 G>A	c.2159 A>C	c.2198 C>T
AFRICA	Chagga	CHA_JK 4125	T	T	G	C	G	A	C	A	A	T	A	T	T	T	G	A	C
AFRICA	Chagga	CHA_JK 4125	T	T	G	T	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRICA	Chagga	CHA_JK 4126	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRICA	Chagga	CHA_JK 4126	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRICA	Chagga	CHA_JK 4127	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	T
AFRICA	Chagga	CHA_JK 4127	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRICA	Chagga	CHA_JK 4128	T	T	G	C	A	A	C	C	A	T	A	G	T	T	G	A	C
AFRICA	Chagga	CHA_JK 4128	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRICA	Chagga	CHA_JK 4129	T	T	G	C	G	A	C	A	A	T	A	T	T	T	G	A	C
AFRICA	Chagga	CHA_JK 4129	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRICA	Chagga	CHA_JK 4130	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRICA	Chagga	CHA_JK 4130	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRICA	Chagga	CHA_JK 4131	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRICA	Chagga	CHA_JK 4131	T	T	G	C	G	T	C	C	A	T	A	T	T	T	G	A	C
AFRICA	Chagga	CHA_JK 4132	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
AFRICA	Chagga	CHA_JK 4132	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRICA	Chagga	CHA_JK 4133	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRICA	Chagga	CHA_JK	T	T	G	T	G	A	C	C	A	T	A	T	T	T	G	A	C

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A	a	4133																	
AFRIC A	Chagg a	CHA_JK 4134	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4134	T	T	G	T	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4135	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4135	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4136	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4136	T	T	G	T	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4137	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4137	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4138	T	T	G	C	G	A	C	A	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4138	T	C	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4139	T	T	G	C	G	A	C	A	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4139	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4140	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4140	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4141	T	T	G	C	G	A	C	C	A	T	A	G	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4141	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4142	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4142	T	T	G	C	G	T	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4143	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4143	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4144	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4144	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC	Chagg	CHA_JK	T	T	G	C	G	A	C	C	A	T	A	G	T	T	G	A	C

A	a	4145																	
AFRIC A	Chagg a	CHA_JK 4145	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4146	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4146	T	T	G	C	G	T	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4147	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4147	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4148	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4148	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4149	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4149	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4150	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4150	T	T	G	T	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4151	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4151	T	T	G	T	G	A	C	C	A	T	A	T	T	C	G	A	C
AFRIC A	Chagg a	CHA_JK 4152	T	T	G	C	G	A	T	A	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4152	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4153	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4153	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4154	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4154	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4155	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4155	T	T	G	T	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Chagg a	CHA_JK 4156	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC	Chagg	CHA_JK	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C

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AFRIC A	Yoruba	YRB_JK3 878	T	T	G	C	G	A	C	A	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 878	T	T	G	T	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 879	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 879	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 880	T	T	G	C	G	A	C	C	A	T	A	G	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 880	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 881	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 881	T	T	G	C	G	A	C	C	A	C	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 882	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 882	T	T	G	T	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 883	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 883	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 884	T	T	G	C	G	A	C	C	A	T	A	G	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 884	T	T	G	T	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 885	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 885	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 886	T	T	G	C	G	A	C	C	A	T	A	G	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 886	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 887	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 887	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 888	T	T	G	C	G	A	C	C	A	T	A	G	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 888	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C

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AFRIC A	Yoruba	YRB_JK3 889	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 891	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 891	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 892	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 892	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 893	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 893	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 894	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 894	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 845	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 845	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 846	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 846	T	T	G	T	G	A	C	C	A	T	A	T	T	T	A	A	C
AFRIC A	Yoruba	YRB_JK3 847	T	T	G	C	G	A	C	A	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 847	T	T	G	T	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 848	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 848	T	T	G	C	G	A	C	C	A	T	A	T	T	C	G	A	C
AFRIC A	Yoruba	YRB_JK3 849	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 849	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 850	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 850	T	T	G	T	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 851	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC	Yoruba	YRB_JK3	T	T	G	T	G	A	C	C	A	T	A	T	T	T	G	A	C

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AFRIC A	Yoruba	YRB_JK3 852	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 852	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 853	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 853	T	T	G	C	G	T	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 854	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 854	T	T	G	T	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 855	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 855	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 856	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	T
AFRIC A	Yoruba	YRB_JK3 856	T	T	G	T	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 860	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 860	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 858	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 858	T	T	G	T	G	T	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 859	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
AFRIC A	Yoruba	YRB_JK3 859	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH2 5	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH2 5	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH0 2	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH0 2	C	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH0 3	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH0 3	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH0 3	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C

Asia		4																	
East-Asia	China	CH_CHO4	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CHO5	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CHO5	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CHO6	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CHO6	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CHO7	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CHO7	C	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CHO8	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CHO8	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CHO9	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CHO9	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH10	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH10	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH11	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH11	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH12	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH12	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH13	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH13	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH14	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH14	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH15	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH15	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C

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Asia		5																	
East-Asia	China	CH_CH1_6	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH1_6	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH1_7	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH1_7	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH1_8	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH1_8	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH1_9	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
East-Asia	China	CH_CH1_9	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH2_0	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH2_0	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH2_1	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH2_1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH2_2	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH2_2	C	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH2_3	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH2_3	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	China	CH_CH2_4	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
East-Asia	China	CH_CH2_4	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_J36	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_J36	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_J37	T	T	G	C	A	A	C	C	G	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_J37	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_J38	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C

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2	East-Asia	Japane	JPN_J38	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
3	East-Asia	Japane	JPN_J39	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
4	East-Asia	Japane	JPN_J39	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
5	East-Asia	Japane	JPN_J40	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
6	East-Asia	Japane	JPN_J40	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
7	East-Asia	Japane	JPN_J41	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
8	East-Asia	Japane	JPN_J41	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
9	East-Asia	Japane	JPN_J42	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
10	East-Asia	Japane	JPN_J42	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
11	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
12	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
13	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
14	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
15	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
16	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
17	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
18	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
19	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
20	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
21	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
22	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
23	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
24	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
25	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
26	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
27	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
28	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
29	East-Asia	Japane	JPN_J30	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
30	East-Asia	Japane	JPN_J30	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
31	East-Asia	Japane	JPN_JK1	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
32	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
33	East-Asia	Japane	JPN_JK1	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
34	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
35	East-Asia	Japane	JPN_JK1	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
36	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
37	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
38	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
39	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
40	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
41	East-Asia	Japane	JPN_JK1	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
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Asia	se	790																	
East-Asia	Japane se	JPN_JK1 793	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_JK1 793	C	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_JK1 850	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_JK1 850	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_JK1 851	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_JK1 851	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_JK1 852	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_JK1 852	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_JK1 853	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_JK1 853	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_JK1 856	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_JK1 856	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_JK1 857	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_JK1 857	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_JK1 860	T	T	G	C	G	A	C	C	A	T	G	T	T	T	G	A	C
East-Asia	Japane se	JPN_JK1 860	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_JK1 863	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_JK1 863	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_TM KH	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
East-Asia	Japane se	JPN_TM KH	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Chuvas h	CHU_JK 4051	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Chuvas h	CHU_JK 4051	T	T	C	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Chuvas	CHU_JK	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C

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Europe	Chuvash	CHU_JK 4052	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Chuvash	CHU_JK 4053	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Chuvash	CHU_JK 4053	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Chuvash	CHU_JK 4054	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Chuvash	CHU_JK 4054	T	T	C	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Chuvash	CHU_JK 4055	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Chuvash	CHU_JK 4055	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Chuvash	CHU_JK 4056	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Chuvash	CHU_JK 4056	C	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Chuvash	CHU_JK 4057	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Chuvash	CHU_JK 4057	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Chuvash	CHU_JK 4058	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Chuvash	CHU_JK 4058	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Chuvash	CHU_JK 4059	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Chuvash	CHU_JK 4059	C	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Chuvash	CHU_JK 4060	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Chuvash	CHU_JK 4060	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Chuvash	CHU_JK 4061	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Chuvash	CHU_JK 4061	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Chuvash	CHU_JK 4062	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Chuvash	CHU_JK 4062	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Chuvash	CHU_JK 4063	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Chuvash	CHU_JK	T	T	G	C	G	T	C	C	A	T	A	T	T	T	G	A	C

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e	h	4063																	
Europ e	Chuvas h	CHU_JK 4064	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
Europ e	Chuvas h	CHU_JK 4064	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europ e	Chuvas h	CHU_JK 4065	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europ e	Chuvas h	CHU_JK 4065	T	T	C	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europ e	Chuvas h	CHU_JK 4066	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europ e	Chuvas h	CHU_JK 4066	T	T	C	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europ e	Chuvas h	CHU_JK 4067	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europ e	Chuvas h	CHU_JK 4067	C	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europ e	Chuvas h	CHU_JK 4068	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europ e	Chuvas h	CHU_JK 4068	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
Europ e	Chuvas h	CHU_JK 4069	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
Europ e	Chuvas h	CHU_JK 4069	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europ e	Chuvas h	CHU_JK 4070	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europ e	Chuvas h	CHU_JK 4070	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
Europ e	Chuvas h	CHU_JK 4071	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europ e	Chuvas h	CHU_JK 4071	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europ e	Chuvas h	CHU_JK 4072	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europ e	Chuvas h	CHU_JK 4072	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europ e	Chuvas h	CHU_JK 4073	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
Europ e	Chuvas h	CHU_JK 4073	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europ e	Chuvas h	CHU_JK 4074	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europ e	Chuvas h	CHU_JK 4074	T	T	G	C	G	T	C	C	A	T	A	T	T	T	G	A	C
Europ	Danes	DAN_BK	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C

e		113																	
Europe	Danes	DAN_BK_113	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Danes	DAN_BK_116	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_BK_116	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_BK_117	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_BK_117	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_BK_119	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_BK_119	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	C	C
Europe	Danes	DAN_BK_120	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_BK_120	T	T	C	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_BK_124	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_BK_124	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_BK_127	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_BK_127	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_BK_141	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Danes	DAN_BK_141	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	C	C
Europe	Danes	DAN_BK_144	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_BK_144	T	T	C	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_BK_146	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_BK_146	T	T	G	C	A	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Danes	DAN_BK_153	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Danes	DAN_BK_153	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Danes	DAN_BK_157	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_BK	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C

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e		157																	
Europe	Danes	DAN_BK 160	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_BK 160	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Danes	DAN_BK 171	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_BK 171	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_BK 172	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_BK 172	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Danes	DAN_BK 180	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_BK 180	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Danes	DAN_JK 3330	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_JK 3330	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Danes	DAN_JK 3331	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_JK 3331	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Danes	DAN_JK 3332	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_JK 3332	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_JK 3333	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_JK 3333	T	T	C	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_JK 3334	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_JK 3334	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_JK 3335	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_JK 3335	T	T	G	C	G	A	C	C	A	T	A	T	T	T	G	A	C
Europe	Danes	DAN_JK 3336	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C
Europe	Danes	DAN_JK 3336	T	T	G	C	A	A	C	C	A	T	A	T	G	T	G	A	C

Supp. Table S2. Genotype information per individual of the TLR2 non-synonymous variants

			SNP	SNP	SNP	SNP	SNP	SNP	SNP
Continent	Population	ID	c.265A>G	c.1232C>T	c.1339C>T	c.1712G>A	c.1892C>A	c.1906A>C	c.2258G>A
AFRICA	Chagga	CHA_JK4125	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4125	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4126	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4126	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4127	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4127	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4128	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4128	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4129	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4129	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4130	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4130	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4131	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4131	A	C	C	G	C	C	G
AFRICA	Chagga	CHA_JK4132	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4132	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4133	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4133	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4134	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4134	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4135	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4135	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4136	A	C	C	A	C	A	G
AFRICA	Chagga	CHA_JK4136	A	C	C	G	C	A	G

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AFRICA	Chagga	CHA_JK4137	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4137	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4138	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4138	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4139	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4139	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4140	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4140	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4141	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4141	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4142	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4142	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4143	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4143	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4144	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4144	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4145	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4145	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4146	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4146	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4147	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4147	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4148	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4148	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4149	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4149	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4150	A	C	C	G	C	A	G
AFRICA	Chagga	CHA_JK4150	A	C	C	G	C	A	G

1	AFRICA	Chagga	CHA_JK4151	A	C	C	G	C	A	G
2	AFRICA	Chagga	CHA_JK4151	A	C	C	G	C	A	G
3	AFRICA	Chagga	CHA_JK4152	A	C	C	G	C	A	G
4	AFRICA	Chagga	CHA_JK4152	A	C	C	G	C	A	G
5	AFRICA	Chagga	CHA_JK4153	A	C	C	G	C	A	G
6	AFRICA	Chagga	CHA_JK4153	A	C	C	G	C	A	G
7	AFRICA	Chagga	CHA_JK4154	A	C	C	G	C	A	G
8	AFRICA	Chagga	CHA_JK4154	A	C	C	G	C	A	G
9	AFRICA	Chagga	CHA_JK4155	A	C	C	G	C	A	G
10	AFRICA	Chagga	CHA_JK4155	A	C	C	G	C	A	G
11	AFRICA	Chagga	CHA_JK4156	A	C	C	G	C	A	G
12	AFRICA	Chagga	CHA_JK4156	A	C	C	G	C	A	G
13	AFRICA	Yoruba	YRB_JK3878	A	C	C	G	C	A	G
14	AFRICA	Yoruba	YRB_JK3878	A	C	C	G	C	A	G
15	AFRICA	Yoruba	YRB_JK3879	A	C	C	G	C	A	G
16	AFRICA	Yoruba	YRB_JK3879	A	C	C	G	C	A	G
17	AFRICA	Yoruba	YRB_JK3880	A	C	C	G	C	A	G
18	AFRICA	Yoruba	YRB_JK3880	A	C	C	G	C	A	G
19	AFRICA	Yoruba	YRB_JK3881	A	C	C	G	C	A	G
20	AFRICA	Yoruba	YRB_JK3881	A	C	C	G	C	A	G
21	AFRICA	Yoruba	YRB_JK3882	A	C	C	G	C	A	G
22	AFRICA	Yoruba	YRB_JK3882	A	C	C	G	C	A	G
23	AFRICA	Yoruba	YRB_JK3883	A	C	C	G	C	A	G
24	AFRICA	Yoruba	YRB_JK3883	A	C	C	G	C	A	G
25	AFRICA	Yoruba	YRB_JK3884	A	C	C	G	C	A	G
26	AFRICA	Yoruba	YRB_JK3884	A	C	C	G	C	A	G
27	AFRICA	Yoruba	YRB_JK3885	A	C	C	G	C	A	G
28	AFRICA	Yoruba	YRB_JK3885	A	C	C	G	C	A	G
29	AFRICA	Yoruba	YRB_JK3885	A	C	C	G	C	A	G
30	AFRICA	Yoruba	YRB_JK3885	A	C	C	G	C	A	G
31	AFRICA	Yoruba	YRB_JK3885	A	C	C	G	C	A	G
32	AFRICA	Yoruba	YRB_JK3885	A	C	C	G	C	A	G
33	AFRICA	Yoruba	YRB_JK3885	A	C	C	G	C	A	G
34	AFRICA	Yoruba	YRB_JK3885	A	C	C	G	C	A	G
35	AFRICA	Yoruba	YRB_JK3885	A	C	C	G	C	A	G
36	AFRICA	Yoruba	YRB_JK3885	A	C	C	G	C	A	G
37	AFRICA	Yoruba	YRB_JK3885	A	C	C	G	C	A	G
38	AFRICA	Yoruba	YRB_JK3885	A	C	C	G	C	A	G
39	AFRICA	Yoruba	YRB_JK3885	A	C	C	G	C	A	G
40	AFRICA	Yoruba	YRB_JK3885	A	C	C	G	C	A	G
41	AFRICA	Yoruba	YRB_JK3885	A	C	C	G	C	A	G
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AFRICA	Yoruba	YRB_JK3886	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3886	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3887	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3887	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3888	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3888	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3889	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3889	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3891	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3891	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3892	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3892	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3893	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3893	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3894	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3894	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3845	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3845	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3846	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3846	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3847	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3847	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3848	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3848	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3849	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3849	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3850	A	C	C	G	C	A	G
AFRICA	Yoruba	YRB_JK3850	A	C	C	G	C	A	G

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	AFRICA	Yoruba	YRB_JK3851	A	C	C	G	C	A	G
	AFRICA	Yoruba	YRB_JK3851	A	C	C	G	C	A	G
	AFRICA	Yoruba	YRB_JK3852	A	C	C	G	C	A	G
	AFRICA	Yoruba	YRB_JK3852	A	C	C	G	C	A	G
	AFRICA	Yoruba	YRB_JK3853	A	C	C	G	C	A	G
	AFRICA	Yoruba	YRB_JK3853	A	C	C	G	C	A	G
	AFRICA	Yoruba	YRB_JK3854	A	C	C	G	C	A	G
	AFRICA	Yoruba	YRB_JK3854	A	C	C	G	C	A	G
	AFRICA	Yoruba	YRB_JK3855	A	C	C	G	C	A	G
	AFRICA	Yoruba	YRB_JK3855	A	C	C	G	C	A	G
	AFRICA	Yoruba	YRB_JK3856	A	C	C	G	C	A	G
	AFRICA	Yoruba	YRB_JK3856	A	C	C	G	C	A	G
	AFRICA	Yoruba	YRB_JK3860	A	C	C	G	C	A	G
	AFRICA	Yoruba	YRB_JK3860	A	C	C	G	C	A	G
	AFRICA	Yoruba	YRB_JK3858	A	C	C	G	C	A	G
	AFRICA	Yoruba	YRB_JK3858	A	C	C	G	C	A	G
	AFRICA	Yoruba	YRB_JK3859	A	C	C	G	C	A	G
	AFRICA	Yoruba	YRB_JK3859	A	C	C	G	C	A	G
	East-Asia	China	CH_CH25	A	C	C	G	C	A	G
	East-Asia	China	CH_CH25	A	C	C	G	C	A	G
	East-Asia	China	CH_CH02	A	C	C	G	C	A	G
	East-Asia	China	CH_CH02	A	C	C	G	C	A	G
	East-Asia	China	CH_CH03	A	C	C	G	C	A	G
	East-Asia	China	CH_CH03	A	C	C	G	C	A	G
	East-Asia	China	CH_CH04	A	C	C	G	C	A	G
	East-Asia	China	CH_CH04	A	C	C	G	C	A	G
	East-Asia	China	CH_CH05	A	C	C	G	C	A	G
	East-Asia	China	CH_CH05	A	C	C	G	C	A	G

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East-Asia	China	CH_CH06	A	C	C	G	C	A	G
East-Asia	China	CH_CH06	A	C	C	G	C	A	G
East-Asia	China	CH_CH07	A	C	C	G	C	A	G
East-Asia	China	CH_CH07	A	C	C	G	C	A	G
East-Asia	China	CH_CH08	A	C	C	G	C	A	G
East-Asia	China	CH_CH08	A	C	C	G	C	A	G
East-Asia	China	CH_CH09	A	C	C	G	C	A	G
East-Asia	China	CH_CH09	A	C	C	G	C	A	G
East-Asia	China	CH_CH10	A	C	C	G	C	A	G
East-Asia	China	CH_CH10	A	C	C	G	C	A	G
East-Asia	China	CH_CH11	A	C	C	G	C	A	G
East-Asia	China	CH_CH11	A	C	C	G	C	A	G
East-Asia	China	CH_CH12	A	C	C	G	C	A	G
East-Asia	China	CH_CH12	A	C	C	G	C	A	G
East-Asia	China	CH_CH13	A	C	C	G	C	A	G
East-Asia	China	CH_CH13	A	C	C	G	C	A	G
East-Asia	China	CH_CH14	A	C	C	G	C	A	G
East-Asia	China	CH_CH14	A	C	C	G	C	A	G
East-Asia	China	CH_CH15	A	C	C	G	C	A	G
East-Asia	China	CH_CH15	A	C	C	G	C	A	G
East-Asia	China	CH_CH16	A	C	C	G	C	A	G
East-Asia	China	CH_CH16	A	C	C	G	C	A	G
East-Asia	China	CH_CH17	A	C	C	G	C	A	G
East-Asia	China	CH_CH17	A	C	C	G	C	A	G
East-Asia	China	CH_CH18	A	C	C	G	C	A	G
East-Asia	China	CH_CH18	A	C	C	G	C	A	G
East-Asia	China	CH_CH19	A	C	C	G	C	A	G
East-Asia	China	CH_CH19	A	C	C	G	C	A	G

1	East-Asia	China	CH_CH20	A	C	C	G	C	A	G
2	East-Asia	China	CH_CH20	A	C	C	G	C	A	G
3	East-Asia	China	CH_CH21	A	C	C	G	C	A	G
4	East-Asia	China	CH_CH21	A	C	C	G	C	A	G
5	East-Asia	China	CH_CH22	A	C	C	G	C	A	G
6	East-Asia	China	CH_CH22	A	C	C	G	C	A	G
7	East-Asia	China	CH_CH23	A	C	C	G	C	A	G
8	East-Asia	China	CH_CH23	A	C	C	G	C	A	G
9	East-Asia	China	CH_CH24	A	C	C	G	C	A	G
10	East-Asia	China	CH_CH24	A	C	C	G	C	A	G
11	East-Asia	Japanese	JPN_J36	A	C	C	G	C	A	G
12	East-Asia	Japanese	JPN_J36	A	C	C	G	C	A	G
13	East-Asia	Japanese	JPN_J37	A	C	C	G	C	A	G
14	East-Asia	Japanese	JPN_J37	A	C	C	G	C	A	G
15	East-Asia	Japanese	JPN_J38	A	C	C	G	C	A	G
16	East-Asia	Japanese	JPN_J38	A	C	C	G	C	A	G
17	East-Asia	Japanese	JPN_J39	A	C	C	G	C	A	G
18	East-Asia	Japanese	JPN_J39	A	C	C	G	C	A	G
19	East-Asia	Japanese	JPN_J40	A	C	C	G	C	A	G
20	East-Asia	Japanese	JPN_J40	A	C	C	G	C	A	G
21	East-Asia	Japanese	JPN_J41	A	C	C	G	C	A	G
22	East-Asia	Japanese	JPN_J41	A	C	C	G	C	A	G
23	East-Asia	Japanese	JPN_J42	A	C	C	G	C	A	G
24	East-Asia	Japanese	JPN_J42	A	C	C	G	C	A	G
25	East-Asia	Japanese	JPN_JK1424	A	C	C	G	C	A	G
26	East-Asia	Japanese	JPN_JK1424	A	C	C	G	C	A	G
27	East-Asia	Japanese	JPN_JK1425	A	C	C	G	C	A	G
28	East-Asia	Japanese	JPN_JK1425	A	C	C	G	C	A	G
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East-Asia	Japanese	JPN_JK1426	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1426	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_J30	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_J30	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1785	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1785	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1788	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1788	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1790	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1790	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1793	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1793	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1850	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1850	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1851	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1851	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1852	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1852	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1853	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1853	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1856	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1856	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1857	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1857	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1860	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1860	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1863	A	C	C	G	C	A	G
East-Asia	Japanese	JPN_JK1863	A	C	C	G	C	A	G

1	East-Asia	Japanese	JPN_TMKH	A	C	C	G	C	A	G
2	East-Asia	Japanese	JPN_TMKH	A	C	C	G	C	A	G
3	Europe	Chuvash	CHU_JK4051	A	C	C	G	C	A	G
4	Europe	Chuvash	CHU_JK4051	A	C	C	G	A	A	G
5	Europe	Chuvash	CHU_JK4052	A	C	C	G	C	A	G
6	Europe	Chuvash	CHU_JK4052	A	C	C	G	C	A	G
7	Europe	Chuvash	CHU_JK4053	A	C	C	G	C	A	G
8	Europe	Chuvash	CHU_JK4053	A	C	C	G	C	A	G
9	Europe	Chuvash	CHU_JK4054	A	C	C	G	C	A	G
10	Europe	Chuvash	CHU_JK4054	A	C	C	G	C	A	G
11	Europe	Chuvash	CHU_JK4055	A	C	C	G	C	A	G
12	Europe	Chuvash	CHU_JK4055	A	C	C	G	C	A	G
13	Europe	Chuvash	CHU_JK4056	A	C	C	G	C	A	G
14	Europe	Chuvash	CHU_JK4056	A	C	C	G	C	A	G
15	Europe	Chuvash	CHU_JK4057	A	C	C	G	C	A	G
16	Europe	Chuvash	CHU_JK4057	A	C	C	G	C	A	G
17	Europe	Chuvash	CHU_JK4058	A	C	C	G	C	A	G
18	Europe	Chuvash	CHU_JK4058	A	C	C	G	C	A	G
19	Europe	Chuvash	CHU_JK4059	A	C	C	G	C	A	G
20	Europe	Chuvash	CHU_JK4059	A	C	C	G	C	A	A
21	Europe	Chuvash	CHU_JK4060	A	C	C	G	C	A	G
22	Europe	Chuvash	CHU_JK4060	A	C	C	G	C	A	G
23	Europe	Chuvash	CHU_JK4061	A	C	C	G	C	A	G
24	Europe	Chuvash	CHU_JK4061	A	C	C	G	C	A	G
25	Europe	Chuvash	CHU_JK4062	A	C	C	G	C	A	G
26	Europe	Chuvash	CHU_JK4062	A	C	C	G	C	A	G
27	Europe	Chuvash	CHU_JK4063	A	C	C	G	C	A	G
28	Europe	Chuvash	CHU_JK4063	A	C	C	G	C	A	G
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3	Europe	Chuvash	CHU_JK4064	A	C	C	G	C	A	G
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5	Europe	Chuvash	CHU_JK4065	A	C	C	G	C	A	G
6	Europe	Chuvash	CHU_JK4065	A	C	C	G	C	A	G
7	Europe	Chuvash	CHU_JK4065	A	C	C	G	C	A	G
8	Europe	Chuvash	CHU_JK4066	A	C	C	G	C	A	G
9	Europe	Chuvash	CHU_JK4066	A	C	C	G	C	A	G
10	Europe	Chuvash	CHU_JK4066	A	C	C	G	C	A	G
11	Europe	Chuvash	CHU_JK4067	A	C	C	G	C	A	G
12	Europe	Chuvash	CHU_JK4067	A	C	C	G	C	A	G
13	Europe	Chuvash	CHU_JK4067	A	C	C	G	C	A	G
14	Europe	Chuvash	CHU_JK4068	A	C	C	G	C	A	G
15	Europe	Chuvash	CHU_JK4068	A	C	C	G	C	A	G
16	Europe	Chuvash	CHU_JK4068	A	C	C	G	C	A	G
17	Europe	Chuvash	CHU_JK4069	A	C	C	G	C	A	G
18	Europe	Chuvash	CHU_JK4069	A	C	C	G	C	A	G
19	Europe	Chuvash	CHU_JK4069	A	C	C	G	C	A	G
20	Europe	Chuvash	CHU_JK4070	A	C	C	G	C	A	G
21	Europe	Chuvash	CHU_JK4070	A	C	C	G	C	A	G
22	Europe	Chuvash	CHU_JK4071	A	C	C	G	C	A	G
23	Europe	Chuvash	CHU_JK4071	A	C	C	G	C	A	G
24	Europe	Chuvash	CHU_JK4071	A	C	C	G	C	A	G
25	Europe	Chuvash	CHU_JK4072	A	C	C	G	C	A	G
26	Europe	Chuvash	CHU_JK4072	A	C	C	G	C	A	G
27	Europe	Chuvash	CHU_JK4072	A	C	C	G	C	A	G
28	Europe	Chuvash	CHU_JK4073	A	C	C	G	C	A	G
29	Europe	Chuvash	CHU_JK4073	A	C	C	G	C	A	G
30	Europe	Chuvash	CHU_JK4073	A	C	C	G	C	A	G
31	Europe	Chuvash	CHU_JK4074	A	C	C	G	C	A	G
32	Europe	Chuvash	CHU_JK4074	A	C	C	G	C	A	G
33	Europe	Chuvash	CHU_JK4074	A	C	C	G	C	A	G
34	Europe	Danes	DAN_BK113	A	C	C	G	C	A	G
35	Europe	Danes	DAN_BK113	A	C	C	G	C	A	G
36	Europe	Danes	DAN_BK116	A	C	C	G	C	A	G
37	Europe	Danes	DAN_BK116	A	C	C	G	C	A	G
38	Europe	Danes	DAN_BK116	A	C	C	G	C	A	G
39	Europe	Danes	DAN_BK117	A	C	C	G	C	A	G
40	Europe	Danes	DAN_BK117	A	C	C	G	C	A	G
41	Europe	Danes	DAN_BK117	A	C	C	G	C	A	G
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1	Europe	Danes	DAN_BK119	A	C	C	G	C	A	G
2	Europe	Danes	DAN_BK119	A	C	C	G	C	A	A
3	Europe	Danes	DAN_BK120	A	C	C	G	C	A	G
4	Europe	Danes	DAN_BK120	A	C	C	G	C	A	G
5	Europe	Danes	DAN_BK124	A	C	C	G	C	A	G
6	Europe	Danes	DAN_BK124	A	C	C	G	C	A	G
7	Europe	Danes	DAN_BK127	A	C	C	G	C	A	G
8	Europe	Danes	DAN_BK127	A	C	C	G	C	A	G
9	Europe	Danes	DAN_BK141	A	C	C	G	C	A	G
10	Europe	Danes	DAN_BK141	A	C	C	G	C	A	G
11	Europe	Danes	DAN_BK144	G	C	T	G	C	A	G
12	Europe	Danes	DAN_BK144	A	C	C	G	C	A	G
13	Europe	Danes	DAN_BK146	A	T	C	G	C	A	G
14	Europe	Danes	DAN_BK146	A	C	C	G	C	A	G
15	Europe	Danes	DAN_BK153	A	C	C	G	C	A	G
16	Europe	Danes	DAN_BK153	A	C	C	G	C	A	G
17	Europe	Danes	DAN_BK157	A	C	C	G	C	A	G
18	Europe	Danes	DAN_BK157	A	C	C	G	C	A	G
19	Europe	Danes	DAN_BK160	A	C	C	G	C	A	G
20	Europe	Danes	DAN_BK160	A	C	C	G	C	A	G
21	Europe	Danes	DAN_BK171	A	C	C	G	C	A	G
22	Europe	Danes	DAN_BK171	A	C	C	G	C	A	G
23	Europe	Danes	DAN_BK172	A	C	C	G	C	A	G
24	Europe	Danes	DAN_BK172	A	C	C	G	C	A	G
25	Europe	Danes	DAN_BK180	A	C	C	G	C	A	G
26	Europe	Danes	DAN_BK180	A	C	C	G	A	A	G
27	Europe	Danes	DAN_JK3330	A	C	C	G	C	A	G
28	Europe	Danes	DAN_JK3330	A	C	C	G	C	A	G
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Europe	Danes	DAN_JK3331	A	C	C	G	C	A	G
Europe	Danes	DAN_JK3331	A	C	C	G	C	A	G
Europe	Danes	DAN_JK3332	A	C	C	G	C	A	G
Europe	Danes	DAN_JK3332	A	C	C	G	A	A	G
Europe	Danes	DAN_JK3333	A	C	C	G	C	A	G
Europe	Danes	DAN_JK3333	A	C	C	G	C	A	G
Europe	Danes	DAN_JK3334	A	C	C	G	C	A	G
Europe	Danes	DAN_JK3334	A	C	C	G	C	A	G
Europe	Danes	DAN_JK3335	A	C	C	G	C	A	G
Europe	Danes	DAN_JK3335	A	C	C	G	C	A	G
Europe	Danes	DAN_JK3336	A	C	C	G	C	A	G
Europe	Danes	DAN_JK3336	A	C	C	G	A	A	G

Supp. Table S3. Genotype information per individual of the TLR6 non-synonymous variants

			SNP	SNP	SNP	SNP	SNP	SNP	SNP	SNP									
Continent	Population	ID	c.359T >C	c.382C >G	c.581T >C	c.628G >A	c.629C >G	c.740G >A	c.745C >T	c.847A >G	c.979G >A	c.1280 T>C	c.1325 A>C	c.1393 G>A	c.1420 G>A	c.1421 C>T	c.1775T >G	c.2069 A>C	c.2124 G>C
AFRICA	Chagga	CHA_JK 4125	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRICA	Chagga	CHA_JK 4125	C	C	T	G	C	G	C	A	G	T	A	A	G	C	G	A	G
AFRICA	Chagga	CHA_JK 4126	T	C	T	G	C	A	C	A	G	T	A	G	G	C	G	A	G
AFRICA	Chagga	CHA_JK 4126	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRICA	Chagga	CHA_JK 4127	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRICA	Chagga	CHA_JK 4127	T	C	T	G	C	A	C	A	G	T	A	G	G	C	G	A	G
AFRICA	Chagga	CHA_JK 4128	T	C	T	G	C	G	C	A	G	T	A	G	A	C	G	A	G
AFRICA	Chagga	CHA_JK 4128	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
AFRICA	Chagga	CHA_JK 4129	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	C
AFRICA	Chagga	CHA_JK 4129	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRICA	Chagga	CHA_JK 4130	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRICA	Chagga	CHA_JK 4130	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	C	G
AFRICA	Chagga	CHA_JK 4131	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRICA	Chagga	CHA_JK 4131	T	C	C	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRICA	Chagga	CHA_JK 4132	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRICA	Chagga	CHA_JK 4132	T	C	T	G	C	G	T	G	G	T	A	G	G	C	G	A	G
AFRICA	Chagga	CHA_JK 4133	C	C	T	G	C	G	C	A	G	T	A	A	G	C	G	A	G
AFRICA	Chagga	CHA_JK 4133	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRICA	Chagga	CHA_JK 4134	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRICA	Chagga	CHA_JK 4134	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G

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AFRIC A	Chagg a	CHA_JK 4135	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4135	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4136	C	C	T	G	C	G	C	A	G	T	A	A	G	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4136	T	C	C	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4137	T	C	C	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4137	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4138	C	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4138	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4139	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	C
AFRIC A	Chagg a	CHA_JK 4139	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4140	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4140	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4141	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4141	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4142	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4142	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4143	T	C	T	G	C	G	C	A	G	T	A	G	A	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4143	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4144	T	C	C	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4144	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4145	T	C	T	G	C	A	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4145	T	C	T	G	C	G	C	A	G	T	A	G	A	C	G	A	G
AFRIC A	Chagg a	CHA_JK 4146	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G

1	AFRIC	Chagg	CHA_JK	T	C	T	G	C	G	C	A	G	T	A	G	G	T	G	A	G
2	A	a	4146																	
3	AFRIC	Chagg	CHA_JK	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
4	A	a	4147																	
5	AFRIC	Chagg	CHA_JK	T	C	C	G	C	G	C	A	G	T	A	G	G	C	G	A	G
6	A	a	4147																	
7	AFRIC	Chagg	CHA_JK	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
8	A	a	4148																	
9	AFRIC	Chagg	CHA_JK	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
10	A	a	4148																	
11	AFRIC	Chagg	CHA_JK	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	C	G
12	A	a	4149																	
13	AFRIC	Chagg	CHA_JK	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
14	A	a	4149																	
15	AFRIC	Chagg	CHA_JK	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
16	A	a	4150																	
17	AFRIC	Chagg	CHA_JK	T	C	C	G	C	G	C	A	G	T	A	G	G	C	G	A	G
18	A	a	4150																	
19	AFRIC	Chagg	CHA_JK	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
20	A	a	4151																	
21	AFRIC	Chagg	CHA_JK	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
22	A	a	4151																	
23	AFRIC	Chagg	CHA_JK	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
24	A	a	4152																	
25	AFRIC	Chagg	CHA_JK	C	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
26	A	a	4152																	
27	AFRIC	Chagg	CHA_JK	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
28	A	a	4153																	
29	AFRIC	Chagg	CHA_JK	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
30	A	a	4154																	
31	AFRIC	Chagg	CHA_JK	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
32	A	a	4154																	
33	AFRIC	Chagg	CHA_JK	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
34	A	a	4155																	
35	AFRIC	Chagg	CHA_JK	T	C	C	G	C	G	C	A	G	T	A	G	G	C	G	A	G
36	A	a	4155																	
37	AFRIC	Chagg	CHA_JK	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
38	A	a	4156																	
39	AFRIC	Chagg	CHA_JK	T	C	C	G	C	G	C	A	G	T	A	G	G	C	G	A	G
40	A	a	4156																	
41	AFRIC	Yoruba	YRB_JK3	C	C	T	G	C	G	C	A	A	T	A	G	G	C	G	A	G
42	A		878																	
43	AFRIC	Yoruba	YRB_JK3	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
44	A		878																	
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AFRIC A	Yoruba	YRB_JK3 879	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 879	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 880	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 880	T	C	T	G	C	G	C	A	G	T	C	G	A	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 881	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 881	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 882	C	C	T	G	C	G	C	A	G	T	A	A	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 882	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 883	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 883	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	C	G
AFRIC A	Yoruba	YRB_JK3 884	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 884	T	C	T	G	C	G	C	A	G	T	A	G	A	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 885	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 885	T	C	T	G	C	G	C	A	G	T	A	G	A	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 886	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 886	T	C	T	G	C	A	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 887	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	C	G
AFRIC A	Yoruba	YRB_JK3 887	T	C	T	G	C	G	C	A	G	T	A	G	A	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 888	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 888	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 889	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 889	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 891	T	C	T	G	C	G	C	A	G	T	A	G	A	C	G	A	G

1	AFRIC A	Yoruba	YRB_JK3 891	T	C	C	G	C	G	C	A	G	T	A	G	G	C	G	A	G
2	AFRIC A	Yoruba	YRB_JK3 892	T	C	T	G	C	G	C	A	G	T	A	G	A	C	G	A	G
3	AFRIC A	Yoruba	YRB_JK3 892	T	C	T	G	C	G	C	A	G	T	A	G	A	C	G	A	G
4	AFRIC A	Yoruba	YRB_JK3 893	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
5	AFRIC A	Yoruba	YRB_JK3 893	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
6	AFRIC A	Yoruba	YRB_JK3 894	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
7	AFRIC A	Yoruba	YRB_JK3 894	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
8	AFRIC A	Yoruba	YRB_JK3 845	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
9	AFRIC A	Yoruba	YRB_JK3 845	T	C	T	G	C	G	C	A	G	T	A	A	G	C	G	A	G
10	AFRIC A	Yoruba	YRB_JK3 846	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
11	AFRIC A	Yoruba	YRB_JK3 846	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
12	AFRIC A	Yoruba	YRB_JK3 847	C	C	T	G	C	G	C	A	G	T	A	A	G	C	G	A	G
13	AFRIC A	Yoruba	YRB_JK3 847	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
14	AFRIC A	Yoruba	YRB_JK3 848	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
15	AFRIC A	Yoruba	YRB_JK3 848	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
16	AFRIC A	Yoruba	YRB_JK3 849	T	C	T	G	C	A	C	A	G	T	A	G	G	C	G	A	G
17	AFRIC A	Yoruba	YRB_JK3 849	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
18	AFRIC A	Yoruba	YRB_JK3 850	C	C	T	G	C	G	C	A	A	T	A	G	G	C	G	A	G
19	AFRIC A	Yoruba	YRB_JK3 850	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
20	AFRIC A	Yoruba	YRB_JK3 851	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
21	AFRIC A	Yoruba	YRB_JK3 851	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
22	AFRIC A	Yoruba	YRB_JK3 852	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
23	AFRIC A	Yoruba	YRB_JK3 852	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G

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AFRIC A	Yoruba	YRB_JK3 853	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 853	T	C	T	G	C	G	C	A	G	T	A	G	A	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 854	C	C	T	G	C	G	C	A	G	T	A	A	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 854	T	C	T	G	C	G	C	A	G	T	A	A	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 855	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 855	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 856	C	C	T	G	C	G	C	A	G	T	A	A	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 856	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 860	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 860	C	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 858	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 858	C	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 859	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
AFRIC A	Yoruba	YRB_JK3 859	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
East-Asia	China	CH_CH2 5	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
East-Asia	China	CH_CH2 5	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
East-Asia	China	CH_CH0 2	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
East-Asia	China	CH_CH0 2	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
East-Asia	China	CH_CH0 3	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
East-Asia	China	CH_CH0 3	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
East-Asia	China	CH_CH0 4	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
East-Asia	China	CH_CH0 4	T	C	T	G	C	G	C	A	G	T	A	G	G	C	T	A	G
East-Asia	China	CH_CH0 5	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G

1	East-Asia	China	CH_CH0_5	T	C	T	A	C	G	C	A	G	T	A	G	G	C	G	A	G
2	East-Asia	China	CH_CH0_6	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
3	East-Asia	China	CH_CH0_6	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
4	East-Asia	China	CH_CH0_7	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
5	East-Asia	China	CH_CH0_7	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
6	East-Asia	China	CH_CH0_8	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
7	East-Asia	China	CH_CH0_8	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
8	East-Asia	China	CH_CH0_9	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
9	East-Asia	China	CH_CH0_9	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
10	East-Asia	China	CH_CH1_0	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
11	East-Asia	China	CH_CH1_0	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
12	East-Asia	China	CH_CH1_1	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
13	East-Asia	China	CH_CH1_1	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
14	East-Asia	China	CH_CH1_2	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
15	East-Asia	China	CH_CH1_2	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
16	East-Asia	China	CH_CH1_3	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
17	East-Asia	China	CH_CH1_3	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
18	East-Asia	China	CH_CH1_4	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
19	East-Asia	China	CH_CH1_4	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
20	East-Asia	China	CH_CH1_5	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
21	East-Asia	China	CH_CH1_5	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
22	East-Asia	China	CH_CH1_6	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
23	East-Asia	China	CH_CH1_6	T	C	T	G	C	G	C	A	G	T	A	G	G	C	T	A	G

1	East-Asia	China	CH_CH1_7	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
2	East-Asia	China	CH_CH1_7	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
3	East-Asia	China	CH_CH1_8	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
4	East-Asia	China	CH_CH1_8	T	C	T	G	G	G	C	A	G	T	A	G	G	C	G	A	G
5	East-Asia	China	CH_CH1_9	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
6	East-Asia	China	CH_CH1_9	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
7	East-Asia	China	CH_CH2_0	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
8	East-Asia	China	CH_CH2_0	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
9	East-Asia	China	CH_CH2_1	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
10	East-Asia	China	CH_CH2_1	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
11	East-Asia	China	CH_CH2_2	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
12	East-Asia	China	CH_CH2_2	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
13	East-Asia	China	CH_CH2_3	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
14	East-Asia	China	CH_CH2_3	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
15	East-Asia	China	CH_CH2_4	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
16	East-Asia	China	CH_CH2_4	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
17	East-Asia	Japane se	JPN_J36	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
18	East-Asia	Japane se	JPN_J36	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
19	East-Asia	Japane se	JPN_J37	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
20	East-Asia	Japane se	JPN_J37	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
21	East-Asia	Japane se	JPN_J38	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
22	East-Asia	Japane se	JPN_J38	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
23	East-Asia	Japane se	JPN_J39	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
24	East-Asia	Japane se	JPN_J39	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
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Ben-Ali *et al.*

1	East-Asia	Japanese	JPN_J39	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
2	East-Asia	Japanese	JPN_J40	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
3	East-Asia	Japanese	JPN_J40	T	C	T	G	C	G	C	A	G	T	A	G	G	C	T	A	G
4	East-Asia	Japanese	JPN_J41	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
5	East-Asia	Japanese	JPN_J41	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
6	East-Asia	Japanese	JPN_J42	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
7	East-Asia	Japanese	JPN_J42	T	C	T	G	C	G	C	A	G	T	A	G	G	C	T	A	G
8	East-Asia	Japanese	JPN_JK1 424	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
9	East-Asia	Japanese	JPN_JK1 424	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
10	East-Asia	Japanese	JPN_JK1 425	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
11	East-Asia	Japanese	JPN_JK1 425	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
12	East-Asia	Japanese	JPN_JK1 426	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
13	East-Asia	Japanese	JPN_JK1 426	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
14	East-Asia	Japanese	JPN_J30	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
15	East-Asia	Japanese	JPN_J30	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
16	East-Asia	Japanese	JPN_JK1 785	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
17	East-Asia	Japanese	JPN_JK1 785	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
18	East-Asia	Japanese	JPN_JK1 788	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
19	East-Asia	Japanese	JPN_JK1 788	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
20	East-Asia	Japanese	JPN_JK1 790	T	G	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
21	East-Asia	Japanese	JPN_JK1 790	T	G	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
22	East-Asia	Japanese	JPN_JK1 793	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
23	East-Asia	Japanese	JPN_JK1 793	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
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East-Asia	Japanese	JPN_JK1 850	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
East-Asia	Japanese	JPN_JK1 850	T	C	T	G	C	G	C	A	G	T	A	G	G	C	T	A	G
East-Asia	Japanese	JPN_JK1 851	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
East-Asia	Japanese	JPN_JK1 851	T	C	T	G	C	G	C	A	G	T	A	G	G	C	T	A	G
East-Asia	Japanese	JPN_JK1 852	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
East-Asia	Japanese	JPN_JK1 852	T	C	T	G	C	G	C	A	G	T	A	G	G	C	T	A	G
East-Asia	Japanese	JPN_JK1 853	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
East-Asia	Japanese	JPN_JK1 853	T	C	T	G	C	G	C	A	G	T	A	G	G	C	T	A	G
East-Asia	Japanese	JPN_JK1 856	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
East-Asia	Japanese	JPN_JK1 856	T	C	T	G	C	G	C	A	G	T	A	G	G	C	T	A	G
East-Asia	Japanese	JPN_JK1 857	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
East-Asia	Japanese	JPN_JK1 857	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
East-Asia	Japanese	JPN_JK1 860	C	C	T	G	C	G	C	A	A	T	A	G	G	C	G	A	G
East-Asia	Japanese	JPN_JK1 860	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
East-Asia	Japanese	JPN_JK1 863	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
East-Asia	Japanese	JPN_JK1 863	T	C	T	G	C	G	C	A	G	T	A	A	G	C	G	A	G
East-Asia	Japanese	JPN_TM KH	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
East-Asia	Japanese	JPN_TM KH	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4051	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4051	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4052	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4052	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4053	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G

1	Europe	Chuvash	CHU_JK_4053	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
2	Europe	Chuvash	CHU_JK_4054	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
3	Europe	Chuvash	CHU_JK_4054	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
4	Europe	Chuvash	CHU_JK_4055	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
5	Europe	Chuvash	CHU_JK_4055	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
6	Europe	Chuvash	CHU_JK_4056	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
7	Europe	Chuvash	CHU_JK_4056	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
8	Europe	Chuvash	CHU_JK_4057	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
9	Europe	Chuvash	CHU_JK_4057	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
10	Europe	Chuvash	CHU_JK_4058	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
11	Europe	Chuvash	CHU_JK_4058	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
12	Europe	Chuvash	CHU_JK_4059	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
13	Europe	Chuvash	CHU_JK_4059	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
14	Europe	Chuvash	CHU_JK_4060	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
15	Europe	Chuvash	CHU_JK_4060	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
16	Europe	Chuvash	CHU_JK_4061	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
17	Europe	Chuvash	CHU_JK_4061	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
18	Europe	Chuvash	CHU_JK_4062	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
19	Europe	Chuvash	CHU_JK_4062	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
20	Europe	Chuvash	CHU_JK_4063	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
21	Europe	Chuvash	CHU_JK_4063	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
22	Europe	Chuvash	CHU_JK_4064	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
23	Europe	Chuvash	CHU_JK_4064	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
24	Europe	Chuvash	CHU_JK_4064	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
25	Europe	Chuvash	CHU_JK_4064	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
26	Europe	Chuvash	CHU_JK_4064	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
27	Europe	Chuvash	CHU_JK_4064	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
28	Europe	Chuvash	CHU_JK_4064	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
29	Europe	Chuvash	CHU_JK_4064	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
30	Europe	Chuvash	CHU_JK_4064	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
31	Europe	Chuvash	CHU_JK_4064	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
32	Europe	Chuvash	CHU_JK_4064	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
33	Europe	Chuvash	CHU_JK_4064	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
34	Europe	Chuvash	CHU_JK_4064	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
35	Europe	Chuvash	CHU_JK_4064	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
36	Europe	Chuvash	CHU_JK_4064	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
37	Europe	Chuvash	CHU_JK_4064	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
38	Europe	Chuvash	CHU_JK_4064	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
39	Europe	Chuvash	CHU_JK_4064	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
40	Europe	Chuvash	CHU_JK_4064	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
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Europe	Chuvash	CHU_JK 4065	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4065	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4066	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4066	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4067	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4067	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4068	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4068	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4069	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4069	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4070	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4070	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4071	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4071	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4072	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4072	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4073	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4073	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4074	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Chuvash	CHU_JK 4074	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_BK 113	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_BK 113	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_BK 116	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G

1	Europe	Danes	DAN_BK 116	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
2	Europe	Danes	DAN_BK 117	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
3	Europe	Danes	DAN_BK 117	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
4	Europe	Danes	DAN_BK 119	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
5	Europe	Danes	DAN_BK 119	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
6	Europe	Danes	DAN_BK 120	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
7	Europe	Danes	DAN_BK 120	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
8	Europe	Danes	DAN_BK 124	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
9	Europe	Danes	DAN_BK 124	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
10	Europe	Danes	DAN_BK 127	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
11	Europe	Danes	DAN_BK 127	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
12	Europe	Danes	DAN_BK 141	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
13	Europe	Danes	DAN_BK 141	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
14	Europe	Danes	DAN_BK 144	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
15	Europe	Danes	DAN_BK 144	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
16	Europe	Danes	DAN_BK 146	T	C	T	G	C	G	C	A	G	C	A	G	G	C	G	A	G
17	Europe	Danes	DAN_BK 146	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
18	Europe	Danes	DAN_BK 153	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
19	Europe	Danes	DAN_BK 153	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
20	Europe	Danes	DAN_BK 157	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
21	Europe	Danes	DAN_BK 157	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
22	Europe	Danes	DAN_BK 160	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
23	Europe	Danes	DAN_BK 160	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
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Europe	Danes	DAN_BK 171	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_BK 171	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_BK 172	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_BK 172	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_BK 180	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_BK 180	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_JK 3330	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_JK 3330	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_JK 3331	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_JK 3331	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_JK 3332	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_JK 3332	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_JK 3333	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_JK 3333	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_JK 3334	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_JK 3334	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_JK 3335	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_JK 3335	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_JK 3336	T	C	T	G	C	G	C	A	G	T	A	G	G	C	G	A	G
Europe	Danes	DAN_JK 3336	T	C	T	G	C	G	T	A	G	T	A	G	G	C	G	A	G