



HAL
open science

The G allele of the rs10974944 SNP, part of 46/1 haplotype, is strongly associated with V617F-positive myeloproliferative neoplasms

Adrian P. Trifa, Andrei Cucuianu, Ljubomir Petrov, Laura Urian, Mariela S. Militaru, Delia Dima, Ioan V. Pop, Radu A. Popp

► To cite this version:

Adrian P. Trifa, Andrei Cucuianu, Ljubomir Petrov, Laura Urian, Mariela S. Militaru, et al.. The G allele of the rs10974944 SNP, part of 46/1 haplotype, is strongly associated with V617F-positive myeloproliferative neoplasms. *Annals of Hematology*, 2010, 89 (10), pp.979-983. 10.1007/s00277-010-0960-y . hal-00529917

HAL Id: hal-00529917

<https://hal.science/hal-00529917>

Submitted on 27 Oct 2010

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Editorial Manager(tm) for Annals of Hematology
Manuscript Draft

Manuscript Number: AOHE-D-10-00110

Title: The G allele of the JAK2 rs10974944 SNP, part of JAK2 46/1 haplotype, is strongly associated with JAK2 V617F - positive myeloproliferative neoplasms

Article Type: Original Article

Keywords: myeloproliferative neoplasms; JAK2 V617F; JAK2 46/1 haplotype; JAK2 rs10974944 SNP

Corresponding Author: Dr. Adrian Trifa,

Corresponding Author's Institution: "Iuliu Hatieganu" University of Medicine and Pharmacy

First Author: Adrian Trifa

Order of Authors: Adrian Trifa; Andrei Cucuianu; Ljubomir Petrov; Laura Urian; Mariela Militaru; Delia Dima; Ioan Pop; Radu Popp

Abstract: Polycythemia vera, essential thrombocythemia and primary myelofibrosis are myeloproliferative neoplasms, characterized in a majority of cases by a unique somatic point mutation, JAK2 V617F. Recently, it was shown that JAK2 V617F occurs more frequently on a specific JAK2 haplotype, named JAK2 46/1. We genotyped 149 myeloproliferative neoplasms patients (69 had polycythemia vera, 65 had essential thrombocythemia and 15 had primary myelofibrosis) with a known JAK2 V617F mutational status and 150 controls for the JAK2 rs10974944 (C/G) SNP (single nucleotide polymorphism), in which the G allele tags the 46/1 haplotype. We found that the rs10974944 GG/CG genotypes were significantly enriched in patients compared to controls ($p < 0.0001$). After stratifying for the JAK2 V617F mutational status and for the mutant allele burden, we demonstrated that GG/CG genotypes were significantly more frequent in V617F positive compared to V617F negative patients ($p = 0.001$), but not in V617F negative patients compared to controls ($p = 0.29$). Similarly, the GG/CG genotypes were significantly enriched in V617F positive patients with a mutant allele burden $>50\%$ compared to those with a mutant allele burden $<50\%$ ($p = 0.0006$). Our results indicate that the G allele, part of the JAK2 46/1 haplotype, contributes significantly to the occurrence of JAK2 V617F - positive myeloproliferative neoplasms. Moreover, the JAK2 46/1 haplotype seems to be associated with mutant allele burden $>50\%$ in JAK2 V617F - positive myeloproliferative neoplasms patients.

1
2
3
4 **The G allele of the *JAK2* rs10974944 SNP, part of *JAK2* 46/1 haplotype, is strongly**
5
6 **associated with *JAK2* V617F - positive myeloproliferative neoplasms**
7
8
9

10
11 Adrian P. Trifa¹, Andrei Cucuianu², Ljubomir Petrov², Laura Urian², Mariela S. Militaru¹

12
13
14 Delia Dima², Ioan V. Pop¹, Radu A. Popp¹
15
16
17

18
19 ¹ Department of Medical Genetics, “Iuliu Hatieganu” University of Medicine and
20
21 Pharmacy, Cluj-Napoca, Romania;
22

23
24 ² Department of Hematology, “Ion Chiricuta” Cancer Institute, Cluj-Napoca, Romania
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44

45
46
47 Correspondence: Adrian P. Trifa, Department of Medical Genetics, “Iuliu Hatieganu”
48

49 University of Medicine and Pharmacy, 6 Pasteur St, 400349, Cluj-Napoca, Romania.
50

51
52 Phone: +40-750-774406. Fax: +40-264-598606. E-mail:adi_trifa@yahoo.co.uk
53
54
55
56
57
58
59
60
61
62
63

1
2
3
4 **Abstract**
5

6 Polycythemia vera, essential thrombocythemia and primary myelofibrosis are
7 myeloproliferative neoplasms, characterized in a majority of cases by a unique somatic
8 point mutation, *JAK2* V617F. Recently, it was shown that *JAK2* V617F occurs more
9 frequently on a specific *JAK2* haplotype, named *JAK2* 46/1. We genotyped 149
10 myeloproliferative neoplasms patients (69 had polycythemia vera, 65 had essential
11 thrombocythemia and 15 had primary myelofibrosis) with a known *JAK2* V617F
12 mutational status and 150 controls for the *JAK2* rs10974944 (C/G) SNP (single
13 nucleotide polymorphism), in which the G allele tags the 46/1 haplotype. We found that
14 the rs10974944 GG/CG genotypes were significantly enriched in patients compared to
15 controls ($p < 0.0001$). After stratifying for the *JAK2* V617F mutational status and for the
16 mutant allele burden, we demonstrated that GG/CG genotypes were significantly more
17 frequent in V617F positive compared to V617F negative patients ($p = 0.001$), but not in
18 V617F negative patients compared to controls ($p = 0.29$). Similarly, the GG/CG
19 genotypes were significantly enriched in V617F positive patients with a mutant allele
20 burden $>50\%$ compared to those with a mutant allele burden $<50\%$ ($p = 0.0006$). Our
21 results indicate that the G allele, part of the *JAK2* 46/1 haplotype, contributes
22 significantly to the occurrence of *JAK2* V617F - positive myeloproliferative neoplasms.
23 Moreover, *JAK2* 46/1 seems to be associated with mutant allele burden $>50\%$ in *JAK2*
24 V617F - positive myeloproliferative neoplasms patients.
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Keywords: myeloproliferative neoplasms, *JAK2* V617F, *JAK2* 46/1 haplotype, *JAK2*
rs10974944 SNP

Introduction

Myeloproliferative neoplasms (MPN) represent a heterogeneous group of hematological malignancies, characterized by clonal hematopoiesis and increased number of mostly mature peripheral blood elements of myeloid origin [1]. The most common BCR-ABL negative MPN are polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). Even though William Dameshek pointed out some common features of these 3 entities, including them in the same group of “myeloproliferative disorders” more than 50 years ago, [2] their molecular common point remained obscure until 2005, when several independent research groups reported that the majority of PV patients and about half of ET and PMF cases harbor a unique somatic mutation in the gene coding for Janus-kinase 2 (JAK2), a pivotal component of the JAK-STAT signalling pathway, essential for the differentiation and survival of the myeloid lineage [3 – 6]. This point mutation, leading to a substitution Val-to-Phe in position 617 of the JAK2 molecule, is highly specific to MPN, being designated a major diagnosis criterion for PV, ET and PMF according to the latest World Health Organization classification of MPN [7]. Although the discovery of the *JAK2* V617F mutation represents a major breakthrough in understanding the molecular pathogenesis of PV, TE and PMF, concerns have been raised regarding the mechanisms leading to the acquisition of this mutation. While some studies have shown that pre-*JAK2* events, such as chromosome 20q deletion, characterize at least part of the MPN patients [8], other focused on the presence of host-modifying genetic factors [9] or concomitant mutations in other genes, such as *TET2*, *ASXL1* or *MPL*, that could modulate the MPN phenotype

1
2
3
4 [10 – 13]. More recently, several independent groups reported that a particular *JAK2*
5
6 haplotype, designated “46/1” or “GGCC”, is strongly associated with the development of
7
8 *JAK2* V617F - positive MPN [14 – 16], or with MPN development, regardless of the
9
10 V617F mutational status [17, 18].
11
12
13

14 In the present study, we attempted to analyze whether the G allele of the *JAK2*
15
16 rs10974944 SNP, which is in complete linkage disequilibrium with the 46/1 haplotype
17
18 [14, 15] is associated with the predisposition to MPN and especially with the
19
20 development of *JAK2* V617F - positive MPN. Moreover, we aimed to test the hypothesis
21
22 of a possible relationship between *JAK2* rs10974944 SNP and mutant allele burden in
23
24 *JAK2* V617F - positive MPN patients.
25
26
27
28
29
30

31 **Materials and methods**

32
33
34
35

36 *Patients and controls*

37

38 One hundred and forty-nine consecutive MPN patients (69 PV, 65 ET and 15
39
40 PMF), diagnosed between 1985 and 2009, were included in the study, after carefully
41
42 revising their diagnosis according to the latest World Health Organization classification
43
44 of MPN. The control group comprised 150 unrelated local volunteers, which were
45
46 referred for routine blood workup at the Department of Hematology, “Ion Chiricuta”
47
48 Cancer Institute, Cluj-Napoca, Romania and satisfied the following conditions: age above
49
50 60 years and absence of hematological malignancy. Written consent regarding genetic
51
52 testing was obtained from all patients and controls. All experiments were performed
53
54 according to the World Medical Association Declaration of Helsinki. This study was
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 reviewed and approved by the Ethics Committee of the “Iuliu Hatieganu” University of
5
6 Medicine and Pharmacy, Cluj-Napoca, Romania.
7
8
9

10
11 *Molecular analysis for JAK2 V617F mutation and JAK2 rs10974944 SNP*
12

13
14 Genomic DNA was obtained from peripheral leukocytes, using a commercially
15
16 available kit (Wizard Genomic DNA Purification Kit, Promega, WI, USA). The *JAK2*
17
18 *V617F* mutational status was assessed semiquantitatively in all patients by a tetra-primer
19
20 PCR assay, as previously described [1].
21
22

23
24 In order to obtain a rapid screening method for the putative *JAK2 V617F* –
25
26 predisposing haplotype, we developed a PCR-RFLP (Polymerase Chain Reaction –
27
28 Restriction Fragments Length Polymorphism) assay for analyzing the *JAK2 rs10974944*
29
30 SNP, which belongs to this haplotype. We described in detail the method elsewhere [19].
31
32 The PCR-RFLP assay was validated by DNA sequencing.
33
34

35
36 As it has been previously described, the *JAK2 V617F* mutation tends to occur
37
38 more frequently in *cis* with the G allele of the *rs10974944* [16]; thus, a CG heterozygous
39
40 peripheral blood sample would be erroneously labelled as GG homozygous if it contained
41
42 almost exclusively the *JAK2 V617F* mutation. In order to avoid this potential
43
44 misinterpretation, genomic DNA was obtained from buccal cells from 22 MPN patients
45
46 (20 PV patients and 2 ET patients), which harboured *JAK2 V617F* in a proportion close
47
48 to 100% and seemed homozygous for the G allele of the *rs10974944* SNP, when their
49
50 peripheral blood DNA was analyzed. These patients were genotyped once again for the
51
52 *JAK2 rs10974944* SNP using their buccal cell DNA, which provided their correct
53
54 constitutional genotype, which was proven to be CG in 14 of them (13 PV patients and 1
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 PV patient); these patients were subsequently included in the CG group for the statistical
5
6
7 analysis.

11 *Statistical analysis*

14 The distribution of qualitative variables between different groups was compared
15
16 by the Fisher's exact test. Odds-ratio (OR) and 95% confidence interval (CI) were also
17
18 calculated for each comparison performed. The *p* values were two-tailed and the results
19
20 were considered statistically significant if the *p* value was less than 0.05. The statistical
21
22 analysis was performed using the GraphPad InStat software, version 3 (GraphPad, San
23
24 Diego, CA, USA).

31 **Results**

36 *The JAK2 V617F mutation and mutant allele burden distribution in MPN patients*

38 Overall, 107 MPN patients (71.8%) were *JAK2* V617F-positive. When analyzing
39
40 each MPN entity in part, it was found that 61 PV patients (88.4%), 37 ET patients (57%)
41
42 and 9 PMF patients (60%) were *JAK2* V617F-positive. Of the *JAK2* V617F positive
43
44 patients, 69 (64.5%) had an allele burden >50%, of which 49 (80.3%) were PV, 12
45
46 (32.4%) were ET and 8 (88.9%) were PMF patients.

53 *The JAK2 rs10974944 SNP distribution in patients and controls*

56 Table 1 shows in detail the distribution of *JAK2* rs10974944 SNP genotypes and
57
58 alleles in patients, stratified by *JAK2* V617F mutational status and mutant allele burden,
59
60
61
62

1
2
3
4 and controls. The GG/CG genotypes were significantly enriched in the MPN group
5
6 compared to controls ($p < 0.0001$; OR = 3.4; 95% CI = 2.1 – 5.5). Similarly, the G allele
7
8 was found at a significantly higher frequency in patients than in controls ($p < 0.0001$; OR
9
10 = 2.3; 95% CI = 1.7 -3.3). Moreover, we noticed a significant excess of GG/CG
11
12 genotypes in PV compared to ET patients ($p = 0.0001$; OR = 5.4; 95% CI = 2.2 – 13.2),
13
14 which was also true for the G allele frequency ($p = 0.0004$; OR = 2.5; 95% CI = 1.5 – 4),
15
16 which could be due to the higher incidence of the *JAK2* V617F mutation in PV compared
17
18 to ET.
19
20
21
22
23
24
25

26 *The JAK2 rs10974944 SNP distribution in MPN patients stratified by the JAK2*
27
28 *V617F mutational status and by the mutant allele burden*
29
30

31 Eighty seven out of one hundred and seven (81.3%) MPN patients, positive for
32
33 *JAK2* V617F mutation, carried at least one copy of the G allele, compared to 23 out 42
34
35 (54.8%) patients, negative for *JAK2* V617F mutation ($p = 0.001$; OR = 3.6; 95% CI = 1.7
36
37 – 7.8). Also, the G allele had a significantly increased frequency in V617F - positive
38
39 patients compared to V617F - negative patients ($p = 0.006$; OR = 2.1; 95% CI = 1.2 –
40
41 3.5). Similarly, the CG/GG genotypes, as well as the G allele, were significantly more
42
43 frequent in *JAK2* V617F - positive MPN patients than in controls ($p < 0.0001$; OR = 5.2;
44
45 95% CI = 2.9 – 9.4 for GG/CG genotypes and $p < 0.0001$; OR = 2.8; 95% CI = 2 – 4.1
46
47 for the G allele). Meanwhile, when comparing the rs10974944 GG/CG genotypes
48
49 distribution and G allele frequency between *JAK2* V617F negative MPN patients and
50
51 controls, no significant differences were observed ($p = 0.29$; OR = 1.5; 95% CI = 0.7 –
52
53 2.9 for GG/CG genotypes and $p = 0.27$; OR = 1.4; 95% CI = 0.8 – 2.3 for the G allele).
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 Sixty three out of sixty nine (91.3%) V617F positive MPN patients with a mutant
5
6 allele burden >50% harboured either the GG or CG genotype compared to 24 out 38
7
8 (63.2%) MPN patients with a mutant allele burden <50% ($p = 0.0006$; OR = 6.1; 95% CI
9
10 = 2.1 – 17.8). Also, the G allele had a significantly increased frequency in patients with a
11
12 mutant allele burden >50% than in those with <50% ($p = 0.001$; OR = 2.7; 95% CI = 1.5
13
14 – 4.7). Similarly, the GG/CG genotypes, as well as the G allele, were significantly
15
16 enriched in MPN patients with a mutant allele burden >50% compared to controls ($p <$
17
18 0.0001; OR = 12.7; 95% CI = 5.2 – 31.1 for GG/CG genotypes and $p < 0.0001$; OR = 4;
19
20 95% CI = 2.6 - 6.1 for the G allele). However, neither the GG/CG genotypes, nor the G
21
22 allele were significantly enriched in patients with a mutant allele burden <50% compared
23
24 to controls ($p = 0.06$; OR = 2.1; 95% CI = 1 – 4.3 for GG/CG genotypes and $p = 0.15$;
25
26 OR = 1.5; 95% CI = 0.9 – 2.6 for the G allele). Table 2 analyses the relationship between
27
28 the *JAK2* V617F mutation and the rs10974944 SNP, while table 3 presents the
29
30 relationship between *JAK2* mutant allele burden and the rs10974944 SNP.
31
32
33
34
35
36
37
38
39
40

41 Discussion

42
43
44
45 The recent studies have shown an association between *JAK2* V617F - positive
46
47 MPN and the *JAK2* 46/1 haplotype [14 – 18], our data confirming these results.
48
49
50 However, we could not confirm the previous reports that the *JAK2* 46/1 haplotype also
51
52 increases susceptibility to *JAK2* V617F negative ET [17] and PMF [18]. The analysis
53
54 based on *JAK2* V617F stratification revealed that only the *JAK2* V617F - positive MPN
55
56 cases were significantly associated with the rs10974944 SNP, either in heterozygous or
57
58
59
60
61
62
63
64
65

1
2
3
4 homozygous state. As these discrepancies could be related to the differences regarding
5
6 the size of the analyzed patients cohorts, larger studies would probably clarify the
7
8 contribution of the *JAK2* 46/1 haplotype to the V617F negative MPN. The association
9
10 between the 46/1 haplotype and both the *JAK2* V617F - positive and negative MPN cases
11
12 would support the hypothesis that this haplotype acts as a functional variant influencing
13
14 the clonal expansion and disease manifestation [17].
15
16
17

18
19 The “GGCC” haplotype seems to confer susceptibility not only to the *JAK2*
20
21 V617F mutation, but to *JAK2* exon 12 mutations as well. Recently, it was observed that
22
23 the rs10974944, which tags the “GGCC” haplotype, is significantly enriched in PV
24
25 patients positive for *JAK2* exon 12 point mutations or deletions, which characterize a
26
27 minority of PV patients negative for the V617F mutation [20]. Based on these
28
29 observations, it is presumable that a specific *JAK2* haplotype induces a hypermutable
30
31 milieu within the *JAK2* gene. This hypothesis is supported by the findings that the *JAK2*
32
33 V617F mutation occurred preferentially in *cis* with the C allele of *JAK2* rs12343867 SNP
34
35 (part of the 46/1 haplotype) [14, 15] and the G allele of the *JAK2* rs10974944 SNP [16].
36
37
38
39

40
41 We also attempted to assess whether the *JAK2* 46/1 haplotype influences the
42
43 expansion of the *JAK2* V617F mutant clone and indeed we found that the G allele, either
44
45 in heterozygous or homozygous state was significantly enriched in patients with >50%
46
47 V617F mutant allele compared to patients with <50% mutant allele; these data are in
48
49 agreement with two recent reports, which have shown that the *JAK2* 46/1 haplotype was
50
51 significantly enriched in ET patients with mutant allele burden higher than 10%
52
53 compared to those who had less than 10% [17] and PMF patients with mutant allele
54
55 burden higher than 20% compared to those who had less than 20% [18]. These findings
56
57
58
59
60
61
62
63
64
65

1
2
3
4 suggest that the *JAK2* 46/1 could play a role not only in the acquisition of *JAK2* V617F
5
6 mutation, but also in the survival and expansion of the V617F mutant clone, probably by
7
8 conferring a selective advantage. These findings could also suggest an influence that the
9
10 *JAK2* 46/1 haplotype might have in the mitotic recombination of chromosome 9p, a
11
12 common mechanism by which the *JAK2* V617F mutation becomes homozygous [3].
13
14

15
16 In conclusion, we demonstrated that the G allele of the *JAK2* rs10974944 SNP is
17
18 a significant risk factor for *JAK2* V617F - positive MPN. Our results would support the
19
20 hypothesis of a hypermutagenesis milieu within the *JAK2* gene, given that we did not
21
22 observe the association of the G allele with *JAK2* V617F - negative MPN; however, a
23
24 possible functional consequence of the *JAK2* 46/1 haplotype influencing the JAK-STAT
25
26 signalling pathway cannot be ruled out. Even though the mechanisms behind *JAK2*
27
28 V617F acquisition are not yet well understood, these recent findings could provide novel
29
30 insights in understanding the molecular pathophysiology of MPN. Future studies will
31
32 probably identify other germline variants involved in the pathogenesis of MPN.
33
34
35
36
37
38
39

40 **Authorship and conflict of interest disclosure**

41
42 APT designed research, performed genetic analysis, analyzed data and wrote the
43
44 manuscript. AC designed research, collected the samples and patients data, analyzed data
45
46 and wrote the manuscript. LP, LU and DD collected the samples and patients data. MSM
47
48 and IVP performed genetic analysis. RAP designed research and analyzed data.
49
50
51
52

53
54 The authors reported no potential conflict of interest.
55
56
57
58
59
60
61
62

1
2
3
4 **Acknowledgement**
5
6
7
8

9 The authors would like to thank to Dr. Adriana Stan, Genetic Lab, Bucharest, Romania,
10
11 for her help with the sequencing experiments.
12
13
14

15
16 **References**
17
18
19
20

- 21 1. Jones AV, Kreil S, Zoi K, Waghorn K, Curtis C, Zhang L, et al (2005)
22
23 Widespread occurrence of the JAK2 V617F mutation in chronic
24
25 myeloproliferative disorders. Blood 106:2162-2168
26
27
28 2. Dameshek W (1951) Some speculations on the myeloproliferative syndromes.
29
30 Blood 6:372–375
31
32
33 3. Kralovics R, Passamonti F, Buser AS, Teo SS, Tiedt R, Passweg JR, et al (2005)
34
35 A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J
36
37 Med 352:1779-1790
38
39
40 4. James C, Ugo V, Le Couedic JP, Staerk J, Delhommeau F, Lacout C, et al (2005)
41
42 A unique clonal JAK2 mutation leading to constitutive signaling causes
43
44 polycythaemia vera. Nature 434:1144-1148
45
46
47 5. Baxter EJ, Scott LM, Campbell PJ, East C, Fourouclas N, Swanton S, et al (2005)
48
49 Acquired mutations of the tyrosine kinase JAK2 in human myeloproliferative
50
51 disorders. Lancet 365:1054-1061
52
53
54 6. Levine RL, Wadleigh M, Cools J, Ebert BL, Wernig G, Huntly BJ, et al (2005)
55
56 Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential
57
58
59
60
61
62
63
64
65

1
2
3
4 thrombocythemia, and myeloid metaplasia with myelofibrosis. *Cancer Cell* 7:387-
5
6 397

- 7
8
9 7. Tefferi A, Vardiman JW (2008) Classification and diagnosis of myeloproliferative
10 neoplasms: The 2008 World Health Organization criteria and point-of-care
11 diagnostic algorithms. *Leukemia* 22:14-22
12
13
14
15
16 8. Kralovics R, Teo SS, Li S, Theodorides A, Buser AS, Tichelli A, et al (2006)
17 Acquisition of the V617F mutation of JAK2 is a late genetic event in a subset of
18 patients with myeloproliferative disorders. *Blood* 108:1377–1380
19
20
21
22
23 9. Pardanani A, Fridley BL, Lasho TL, Gilliland DG, Tefferi A (2008) Host genetic
24 variation contributes to phenotypic diversity in myeloproliferative disorders.
25
26
27 *Blood* 111:2785–2789
28
29
30
31 10. Delhommeau F, Dupont S, Della Valle V, James C, Trannoy S, Masse A, et al
32 (2009) Mutation in TET2 in myeloid cancers. *N Engl J Med* 360:2289–2301
33
34
35
36 11. Tefferi A, Pardanani A, Lim KH, Abdel-Wahab O, Lasho TL, Patel J, et al (2009)
37 TET2 mutations and their clinical correlates in polycythemia vera, essential
38 thrombocythemia and myelofibrosis. *Leukemia* 23:905–911
39
40
41
42
43 12. Carubbia N, Murati A, Trouplin V, Brecqueville M, Adelaide J, Rey J, et al
44 (2009) Mutations of ASXL1 gene in myeloproliferative neoplasms. *Leukemia*
45 23:2183-2186
46
47
48
49
50 13. Lasho TL, Pardanani A, McClure RF, Mesa RA, Levine RL, Gilliland DG, et al
51 (2006) Concurrent MPL515 and JAK2V617F mutations in myelofibrosis:
52 chronology of clonal emergence and changes in mutant allele burden over time.
53
54
55
56
57 *Br J Haematol* 135:683–687
58
59
60
61
62
63
64
65

- 1
2
3
4 14. Jones AV, Chase A, Silver RT, Oscier D, Zoi K, Wang YL, et al (2009) JAK2
5
6 haplotype is a major risk factor for the development of myeloproliferative
7
8 neoplasms. Nat Genet 41(4):446-449
9
10
11 15. Olcaydu D, Harutyunyan A, Jäger R, Berg T, Gisslinger B, Pabinger I, et al
12
13 (2009) A common JAK2 haplotype confers susceptibility to myeloproliferative
14
15 neoplasms. Nat Genet 41(4):450-454
16
17
18 16. Kilpivaara O, Mukherjee S, Schram AM, Wadleigh M, Mullally A, Ebert BL, et
19
20 al (2009) A germline JAK2 SNP is associated with predisposition to the
21
22 development of JAK2V617F-positive myeloproliferative neoplasms. Nat Genet
23
24 41(4):455-459
25
26
27 17. Pardanani A, Lasho TL, Finke CM, Gangat N, Wolanskyj AP, Hanson CA, et al
28
29 (2010) The JAK2 46/1 confers susceptibility to essential thrombocythemia
30
31 regardless of JAK2V617F mutational status – clinical correlates in a study of 226
32
33 consecutive patients. Leukemia 24(1):110-114
34
35
36 18. Tefferi A, Lasho TL, Patnaik MM, Finke CM, Hussein K, Hogan WJ, et al (2010)
37
38 *JAK2* germline genetic variation affects disease susceptibility in primary
39
40 myelofibrosis regardless of V617F mutational status: nullizygosity for the *JAK2*
41
42 46/1 haplotype is associated with inferior survival. Leukemia 24(1):105-119
43
44
45 19. Trifa AP, Cucuianu A, Popp RA (2010) Development of a reliable PCR-RFLP
46
47 assay for investigation of the *JAK2* rs10974944 SNP, which might predispose to
48
49 the acquisition of somatic mutation *JAK2*^{V617F}. Acta Haematol 123(2):84-87
50
51
52 20. Olcaydu D, Skoda RC, Looser R, Li S, Cazzola M, Pietra D, et al (2009) The
53
54 ‘GGCC’ haplotype of *JAK2* confers susceptibility to *JAK2* exon 12 mutation-
55
56
57
58
59
60
61
62
63
64
65

positive polycythemia vera. Leukemia 23:1924-1926

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Table 1. JAK2 rs10974944 SNP genotype and allele frequency in MPN patients and controls

rs10974944 genotype/ allele	MPN overall (N = 149)				Controls (N = 150)
	V617F positive (N = 107)		V617F negative (N = 42)	Total	
	allele burden >50% (N = 69)	allele burden <50% (N = 38)			
Genotype frequency; n (%)					
CC	6 (8.7)	14 (36.8)	19 (45.2)	39 (26.2)	82 (54.7)
CG	46 (66.7)	22 (57.9)	19 (45.2)	87 (58.4)	59 (39.3)
GG	17 (24.6)	2 (5.3)	4 (9.6)	23 (15.4)	9 (6)
Allele frequency; n (%)					
C allele	58 (42)	50 (66)	57 (67.8)	165 (55.4)	223 (74.3)
G allele	80 (58)	26 (34)	27 (32.2)	133 (44.6)	77 (25.7)

Table 2. Correlation between *JAK2* rs10974944 SNP genotypes/ alleles stratified by *JAK2* V617F mutational status

rs 10974944 genotype/ allele	MPN overall vs controls		<i>JAK2</i> V617F positive vs <i>JAK2</i> V617F negative MPN		<i>JAK2</i> V617F positive MPN vs control group		<i>JAK2</i> V617F negative MPN vs control group	
	OR [95% CI]	<i>p</i> value	OR [95% CI]	<i>p</i> value	OR [95% CI]	<i>p</i> value	OR [95% CI]	<i>p</i> value
GG vs CG/CC	2.9 [1.3-6.4]	0.008	2.1 [0.7-6.4]	0.3	3.4 [1.5-7.8]	0.004	1.7 [0.5-5.7]	0.48
GG vs CC	5.4 [2.3-2.7]	<0.0001	4.5 [1.3-15.7]	0.01	8.7 [3.4-22]	<0.0001	1.9 [0.5-6.9]	0.29
CG vs CC	3.2 [1.9-5.1]	<0.0001	3.4 [1.5-7.6]	0.003	4.7 [2.6-8.6]	<0.0001	1.4 [0.7-2.9]	0.46
GG/CG vs CC	3.4 [2.1-5.5]	<0.0001	3.6 [1.7-7.8]	0.001	5.2 [2.9-9.4]	<0.0001	1.5 [0.7-2.9]	0.29
G allele vs C allele	2.3 [1.7-3.3]	<0.0001	2.1 [1.2-3.5]	0.006	2.8 [2-4.1]	<0.0001	1.4 [0.8-2.3]	0.27

Table 3. Correlation between *JAK2* rs10974944 SNP genotypes/ alleles stratified by *JAK2* V617F allele burden

rs 10974944 genotype/ allele	V617F allele burden higher than 50% vs allele burden lower than 50%		V617F allele burden higher than 50% vs control group		V617F allele burden lower than 50% vs control group	
	OR [95% CI]	<i>p</i> value	OR [95% CI]	<i>p</i> value	OR [95% CI]	<i>p</i> value
GG vs CG/CC	5.9 [1.3-27]	0.01	5.1 [2.1-12.2]	0.0002	0.9 [0.2-4.2]	1
GG vs CC	19.8 [3.4-114]	0.0002	25.8 [8.1-82.2]	<0.0001	1.3 [0.3-46.7]	0.66
CG vs CC	4.9 [1.7-14.4]	0.004	10.7 [4.3-26.6]	<0.0001	2.2 [1-4.6]	0.04
GG/CG vs CC	6.1 [2.1-17.8]	0.0006	12.7 [5.2-31.1]	<0.0001	2.1 [1-4.3]	0.06
G allele vs C allele	2.7 [1.5-4.7]	0.001	4 [2.6-6.1]	<0.0001	1.5 [0.9-2.6]	0.15

***Conflict of interest**

[Click here to download Conflict of interest: signed disclosure form Adrian Trifa.tif](#)