Host genetic variation contributes to phenotypic diversity in myeloproliferative disorders

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Running title: Genetic variation in myeloproliferative disorders

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Abstract

*JAK2*V617F is an acquired mutation associated with polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). We tested the hypothesis that the paradox of a single disease allele associated with three distinctive clinical phenotypes could be explained in part by host modifying influences. We screened for genetic variation within four candidate genes involved in JAK-STAT signaling, including receptors for erythropoietin (*EPOR*), thrombopoietin (*MPL*), and granulocyte colony stimulating factor (*GCSFR*), and *JAK2*. We genotyped 32 linkage disequilibrium tag single nucleotide polymorphism (SNP) loci in 179 Caucasian patients – 84 had PV, 58 PMF, and 37 ET. Genotype-phenotype analysis showed three *JAK2* SNPs (rs7046736, rs10815148, rs12342421) to be significantly, but reciprocally associated with PV (p=0.000004, 0.000002, and 0.000006; odds ratio = 0.16, 2.72, and 2.46, respectively) and ET (p = 0.0007, 0.00019, and 0.00125; odds ratio = 3.05, 0.29, and 0.30, respectively), but not PMF. Three additional *JAK2* SNPs (rs10758669, rs3808850, rs10974947) and a single *EPOR* SNP (rs318699) were also significantly associated with PV, but not ET or PMF. Finally, intragene haplotypes in *JAK2* were significantly associated with PV only. Thus, host genetic variation may contribute to phenotypic diversity among myeloproliferative disorders, including in the presence of a shared disease allele.
Introduction

The recent discovery of JAK2V617F and related mutations in bcr-abl-negative myeloproliferative disorders (MPDs) has spawned great interest in their precise role in the pathogenesis of these disorders.\textsuperscript{1} JAK2V617F is found in $\geq 90\%$ of polycythemia vera (PV) patients, and approximately $50\%$ of either primary myelofibrosis (PMF) or essential thrombocythemia (ET) patients.\textsuperscript{2} It was unexpected that a single disease allele would be associated with these three distinct, though overlapping, clinical phenotypes. There are at least two possible explanations for this apparent paradox: other disease alleles that influence phenotype, and/or host modifying influences. Several lines of evidence support a role for other disease alleles. These include (i) the demonstration of heritable predisposition alleles for development of JAK2V617F-positive PV;\textsuperscript{3,4} (ii) the demonstration of clonal hematopoiesis by X chromosome inactivation pattern (XCIP) analysis in informative females with JAK2V617F-negative ET;\textsuperscript{5} (iii) the observation that JAK2V617F-positive PV patients may progress to acute myeloid leukemia that is JAK2V617F-negative;\textsuperscript{6} and (iv) the demonstration that only a proportion of clonal PV cells are JAK2V617F-positive.\textsuperscript{7,8} On the other hand, host modifiers may contribute to phenotypic pleiotropy of MPDs, in the presence or absence of JAK2V617F. The observation that there is strain specific variation in leukocytosis and myelofibrosis in murine models of JAK2V617F mediated myeloproliferative disease provides indirect evidence in this regard.\textsuperscript{9}

In order to examine the contribution of genetic factors other than JAK2V617F in the distinction between PV, PMF, and ET, we used a candidate gene approach. The
choice of candidate genes reflects the key role of JAK-STAT signaling, which is
constitutively activated through acquisition of somatic mutations (eg. JAK2V617F), in
MPD pathogenesis. JAK2 plays a central role in mediating signaling downstream of key
cytokine receptors that are required for normal hematopoietic development including
receptors for erythropoietin (EPOR), thrombopoietin (MPL), and granulocyte colony
stimulating factor (GCSFR). Therefore, we hypothesized that single nucleotide
polymorphisms (SNPs) in EPOR, MPL, GCSFR, or JAK2 might influence MPD
phenotype, possibly through altered interaction of the involved cytokine receptor with
wild-type and/or mutant JAK2 (eg. erythrocytosis favoring a PV phenotype may ensue
from the interaction between a ‘gain-of-function’ SNP in EPOR and JAK2V617F). Data
supporting this hypothesis includes: (i) Janus kinases (JAKs) intimately associate with
cytokine receptors and regulate the cell surface expression of at least some of these
receptors (eg. JAK2 regulates EPOR and MPL expression); and (ii) JAK2V617F is
most efficient in transforming hematopoietic cells that express Type I cytokine receptors
that lack a common chain, including EPOR, MPL, and GCSFR. This analysis of host
genetic variation in these four candidate genes and its association with MPDs using SNP
association and haplotype analyses supports a role for host modifiers in the phenotypic
pleiotropy of MPDs.

Materials and Methods

The current study was approved by the Mayo Clinic institutional review board.
All patients provided verbal and written informed consent, and research was carried out
according to the principles of the Declaration of Helsinki. We identified Caucasian
patients with PV, ET, or PMF from our database of MPD patients, for analysis. Patient
clinical data was carefully reviewed by AP and AT, and diseases were classified according to World Health Organization criteria. DNA from peripheral blood granulocytes was isolated and genotyping for JAK2V617F was performed using a previously described assay (sensitivity ≤1%).

Granulocyte DNA was used for SNP genotyping. We selected 32 LD tagSNPs using the Carlson method with a minimum allele frequency of at least 5% and an $r^2$ value of 0.80 in the four candidate genes using the HapMap CEU database ($JAK2=13$, $EPOR=4$, $MPL=5$, $GCSFR=10$) (Supplemental Table 1).

Genotyping was performed using the GenomeLab SNPstream Genotyping System (Beckman Coulter, Fullerton, CA), with details provided in Supplemental Methods. Primers were designed using the web-based design site http://www.autoprimer.com provided by Beckman Coulter (primer sequences are available on request). Controls included two genomic DNAs, each with 8 replicates per 384 well plate and 6 no DNA template wells. Call rates for each SNP ranged between 90 and 99.9%.

Assessment of linkage disequilibrium between the 32 tagSNPs and JAK2V617F using the measures of D' and $r^2$ was completed using the software package Haploview. The contribution of genetic variation in candidate genes in discriminating between PV, ET, and PMF was assessed with a logistic regression adjusting for covariates of age at diagnosis, gender and JAK2V617F status. The SNPs were coded as 0, 1, or 2 based on the number of rare alleles (i.e. additive model), and JAK2V617F status was modeled as presence (either homozygous or heterozygous) or absence of the mutation. A total of six models were fit, one for presence or absence of each MPD, including and excluding JAK2V617F status from the model. Since the study individuals were all of a similar
‘population’ (i.e. Caucasian), controlling for population stratification was not completed. Nominal p-values for the single SNP analysis were reported, with many of the significant findings still maintaining significance after applying the over-conservative Bonferroni correction for multiple testing.

For haplotype analysis, both intragene haplotypes as well as haplotypes based on a sliding window of 3 SNPs within each gene were considered, due to the large number of possible intragene haplotypes for JAK2 and GCSFR genes. Since haplotypes are not observed directly, we accounted for unknown phase of haplotypes composed of tagSNPs by use of the score statistics developed by Schaid et al.,19 and implemented in Splus library Haplo.Stats. Simulated p-values are reported for haplotype analysis, adjusting for multiple testing within the haplotype analysis. Since parameter estimates and effect sizes are not estimated with the score test, logistic regression models were fit to produce estimates of the haplotype effect sizes, for haplotypes with observed counts greater than 5. Since haplotypes are not observed directly, we first estimated for each person, all possible haplotypes and the posterior probability associated with each haplotype using the EM algorithm outlined by Excoffier and Slatkin,20 which is implemented in the Splus library Haplostat.19 This produces a design matrix containing the expected proportion of haplotypes for each person. Using this design matrix with posterior probabilities, logistic regression models were fit treating the expected haplotypes as covariates in the model, resulting in an additive haplotype genetic model. Maximum likelihood estimates for the haplotype effect sizes were subsequently produced. This approach for haplotype analysis, where the analysis is based on the expected proportion of haplotypes, is described in detail by Zaykin et al.21 Two models were fit; one in which covariates of age of
diagnosis and gender were adjusted for in the haplotype analysis and one in which covariates of age of diagnosis, gender and JAK2V617F status were adjusted for the in the haplotype analysis.

The Cochran-Armitage trend test was used to assess differences in genotype frequencies between MPD patients and the HapMap founder CEU population, with nominal p-values reported.

Results

We studied a total of 179 Caucasian patients seen in our MPD practice for whom complete clinical information as well as archived granulocyte DNA was available. Of these, 84 had PV, 58 PMF, and 37 ET. Demographic data, JAK2V617F-status, and other relevant clinical data for study patients are presented in Table 1. PV and PMF patients were older than ET patients at time of diagnosis (median age 56 and 58 years versus 47 years, respectively), and PMF patients were tested for JAK2V617F approximately a year later in the disease course as compared to PV and ET (median 21 months versus 12 and 11 months after diagnosis, respectively). Prevalence of JAK2V617F in each MPD was in accordance with published data.22

We selected 32 linkage disequilibrium (LD) tagSNPs using specific criteria (see Methods) in the four candidate genes: JAK2=13, EPOR=4, MPL=5, and GCSFR=10 (Supplemental Table 1). One SNP within GCSFR showed evidence of deviation from Hardy Weinberg Equilibrium (rs4026505, p-value = 0.00000019). The association of individual SNPs with a particular MPD was studied after adjusting for age at diagnosis and gender. Here, we compared amongst the study patients with PV, PMF, or ET. In this analysis, three SNP loci within JAK2 (rs7046736, rs10815148, rs12342421) were found
to be significantly, but reciprocally associated with PV (p = 0.000004, 0.000002, and 0.000006, respectively; odds ratio = 0.16, 2.72, and 2.46, respectively) and ET (p = 0.0007, 0.00019, and 0.00125, respectively; odds ratio = 3.05, 0.29, and 0.30, respectively) (Table 2). In other words, presence of the minor allele increased the odds of one phenotype (say ET), while decreasing the odds of the other phenotype (PV). For instance, for SNP rs7046736, presence of the ‘C’ allele increased the odds of ET (odds ratio = 3.05), but decreased the odds of PV (odds ratio = 0.16) (Table 2). These 3 SNPs, which were not associated with PMF, exhibited high LD, with ‘r^2’ measures of LD between 0.78 and 0.87 (Figure 1). Furthermore, three additional JAK2 SNPs (rs10758669, rs3808850, and rs10974947) were significantly associated with PV (p = 0.0025, 0.0086, and 0.0047, respectively; odds ratio = 2.71, 0.36, and 0.34, respectively) (Table 2), but not ET or PMF (data not shown). Finally, presence of the ‘A’ allele at a single SNP locus in EPOR (rs318699, p=0.0012) significantly increased the odds of PV only (odds ratio 1.87) (Table 2).

When there are multiple causative variants, haplotypes offer increased power over individual SNPs to detect genotype-phenotype associations. When assessing haplotypes that span the gene (i.e. intragene haplotypes), we found a significant or marginally significant association between haplotypes within JAK2 (p<0.0001) and PV, but not ET and PMF (Table 3). When we looked instead at haplotypes based on a sliding window of 3 SNPs, we similarly observed haplotypes within JAK2 to be associated with PV alone (data not shown). Likewise, many of the SNPs found to be individually associated with PV (Table 2) were significant in the sliding window haplotype analysis (e.g. rs7046736,
rs10815148, rs12342421) (data not shown). In contrast, no haplotypes within any of the candidate genes examined were found to be associated with ET or PMF.

To examine the effect of JAK2V617F, we examined the association between each SNP and MPD phenotype after adjusting for presence or absence of JAK2V617F, in addition to age at diagnosis and gender (Table 4). We found the three previously identified JAK2 SNPs (rs7046736, rs10815148, and rs12342421) to remain significantly associated with PV and ET, even after adjusting for JAK2V617F status (Table 4), with JAK2V617F in low LD (r^2 < 0.13) with tag SNPs in the four genes (Figure 1). Likewise, when JAK2V617F status was included as a covariate for haplotype analysis, several haplotypes within JAK2 maintained global significance of association with PV (Table 3).

We compared genotype frequencies for the study population to those found in the HapMap Caucasian population (founder CEU population; http://www.hapmap.org/) (Supplemental Table 2). When considering the entire group of MPD patients compared to the HapMap Caucasian founder population, we found highly significant differences in genotype frequency at 6 SNP loci in the JAK2 gene (rs10758669, rs3808850, rs7849191, rs7046736, rs10815148, and rs12342421), but not in EPOR, MPL, or GCSFR (p ≤ 0.0005). While the HapMap population may not be the ideal control for this comparative analysis, it does underscore the point that genetic variability in JAK2, and not EPOR, MPL, or GCSFR genes is the distinguishing characteristic between the 2 populations.

Finally, we tested for the clinical correlates of PV-associated alleles in PMF and ET patients. Complete clinical and pathologic information at diagnosis was available for 32 (of 58) PMF patients – we grouped patients based on frequency of the PV-associated allele (0, 1, or 2) at the relevant SNP loci. The PV-associated allele was present
homozygously at one or more of the following SNPs - rs7046736, rs10815148, and rs12342421 (Group 1; n=4), or SNPs rs7046736, rs10815148, rs12342421, and rs10758669 (Group 2; n=8). Both groups showed significant association with leukocytosis (p=0.009 and 0.03, respectively). Furthermore, Group 1 showed a significant association with JAK2V617F (p=0.02) and Group 2 with lower platelet count (p=0.05). Both groups also showed a trend towards higher hemoglobin level although the association did not achieve statistical significance. Other clinical variables (eg. splenomegaly) did not show a significant association in this analysis. Similarly, we had complete data at diagnosis for 17 (of 37) ET patients – again, both groups showed a significant association with JAK2V617F (p<0.05).

Discussion

Our findings reflect the distinctive genetic underpinnings of phenotypically related MPDs, including in the presence of a shared disease allele. The data suggest that i) several SNPs and haplotypes within *JAK2* show strong association with PV and/or ET, but not PMF, and the particular distribution of alleles at the involved loci contributes to phenotypic discrimination between the two MPDs; and (ii) in contrast, genetic variation in *EPOR, MPL*, and *GCSFR* genes does not contribute to MPD phenotypic diversity (with one exception; *EPOR* SNP rs318699 in PV).

Since we analyzed LD tagSNPs, the currently identified *JAK2* and *EPOR* alleles represent markers for genomic regions of interest and not necessarily ‘disease-predisposing’ or ‘causative’ alleles for MPDs. Thus, it would be premature to speculate on the potential mechanism(s) underlying the association of a particular SNP allele with
PV and/or ET based on current data. In this regard, higher resolution SNP analysis within *JAK2* and its flanking regions on chromosome 9p in a larger cohort of patients and relevant controls will be required to identify specific alleles relevant for MPD pathogenesis.

Our analysis indicates that the currently identified *JAK2* SNP alleles contribute to PV or ET expression regardless of *JAK2*V617F status (through accounting for *JAK2*V617F in our statistical model). This point has limited relevance for PV given that virtually all patients (up to 95%) with PV harbor *JAK2*V617F. In contrast, the contribution of these alleles to the phenotypic distinction between *JAK2*V617F-harboring ET and PV will need to be confirmed in a large enough sample size that allows for such a stratified analysis.

Finally, it is possible that genetic variation at the currently identified SNPs also contributes to inter-individual variation in blood counts in healthy individuals, an effect that may be amplified through acquisition of somatic mutations such as *JAK2*V617F. A study of allele distribution at these SNPs and correlation with blood counts (eg. hemoglobin and platelet count) in a large cohort of healthy individuals may be informative in this regard.

**Acknowledgements**

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**Contributions**

AP, BF, DGG, and AT wrote the paper.
AP and AT participated in conception and design of the study.

AP, BF, TL, DGG, and AT performed research and/or participated in data analysis.

AP, TL, and AT participated in collecting clinical data.

**Competing Interests Statement**

The authors declare that they have no competing financial interests.
References
**Table 1. Demographic data, JAK2V617F-status, and other characteristics of MPD patients**

<table>
<thead>
<tr>
<th>Disease</th>
<th>No.</th>
<th>Age at diagnosis (y) Median (range)</th>
<th>No. male (%)</th>
<th>JAK2V617F+ No. (%)</th>
<th>JAK2V617F-HOM No. (%)</th>
<th>Diagnosis to JAK2V617F test Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV</td>
<td>84</td>
<td>56 (16-84)</td>
<td>40 (48)</td>
<td>79 (94)</td>
<td>22 (28)</td>
<td>12 (0-552)</td>
</tr>
<tr>
<td>PMF</td>
<td>58</td>
<td>58 (18-80)</td>
<td>40 (69)</td>
<td>28 (48)</td>
<td>7 (25)</td>
<td>21 (0-324)</td>
</tr>
<tr>
<td>ET</td>
<td>37</td>
<td>47 (17-81)</td>
<td>15 (41)</td>
<td>19 (51)</td>
<td>1 (5)</td>
<td>11 (0-240)</td>
</tr>
</tbody>
</table>

MPD indicates myeloproliferative disorders; PV, polycythemia vera; PMF, primary myelofibrosis; ET, essential thrombocythemia; No., number; y, years; %, percentage; and HOM, homozygous (by PCR sequencing of granulocyte DNA).
Table 2. Significant associations between individual SNPs and PV and/or ET using logistic regression with covariates of age at diagnosis and gender

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene, dbSNP</th>
<th>N(^a)</th>
<th>MAF(^b)</th>
<th>Minor Allele(^c)</th>
<th>p-value(^d)</th>
<th>Odds Ratio ((95% \text{ CI})^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV</td>
<td>JAK2:</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>RS10758669</td>
<td>95</td>
<td>84</td>
<td>0.42 0.58</td>
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<td>0.00245 2.707 (1.342-5.459)</td>
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<td></td>
<td>RS3808850</td>
<td>95</td>
<td>84</td>
<td>0.22 0.13</td>
<td>T (0.45)</td>
<td>0.00859 0.356 (0.176-0.722)</td>
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<td>93</td>
<td>77</td>
<td>0.61 0.36</td>
<td>C (0.73)</td>
<td>0.000004 0.156 (0.072-0.332)</td>
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<tr>
<td></td>
<td>RS10815148</td>
<td>93</td>
<td>82</td>
<td>0.37 0.63</td>
<td>A (0.27)</td>
<td>0.000002 2.720 (1.344-5.506)</td>
</tr>
<tr>
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<td>RS12342421</td>
<td>91</td>
<td>79</td>
<td>0.37 0.59</td>
<td>G (0.75)</td>
<td>0.00006 2.459 (1.231-4.911)</td>
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<td>RS10974947</td>
<td>95</td>
<td>83</td>
<td>0.26 0.13</td>
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<td>0.00468 0.339 (0.174-0.661)</td>
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<td>JAK2:</td>
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<td>37</td>
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<td>37</td>
<td>0.52 0.3</td>
<td>G (0.75)</td>
<td>0.00125 0.300 (0.136-0.665)</td>
</tr>
</tbody>
</table>

\(^a\) Number of people with and without the disorder successfully genotyped for the particular SNP locus
\(^b\) Minor Allele Frequencies of those with and without the disorder. Allele defined as ‘minor’ based on frequency of the particular allele in the overall study population. Allele frequencies for HapMap CEU population are indicated separately (see ‘c’)
\(^c\) Frequency of the allele in the HapMap Project CEU population
\(^d\) P-values computed under an additive genetic model.
\(^e\) Odds ratios and confidence intervals computed under a dominant genetic model.

PV indicates polycythemia vera; ET, essential thrombocythemia; SNP, single nucleotide polymorphism; N, sample size; MAF, minor allele frequency; JAK2, Janus kinase 2; EPOR, receptor for erythropoietin; and CI, confidence interval.
Table 3. Significant association between JAK2 intragene haplotypes and PV

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Disorder</th>
<th>Gene</th>
<th>Significant Individual Haplotypes</th>
<th>Global p-value&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
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<tr>
<td>Age diagnosis, Gender</td>
<td>PV</td>
<td>JAK2</td>
<td>Haplotype Frequency Odds Ratios&lt;sup&gt;b&lt;/sup&gt; p-value</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td>AAAACTCAAGGGT 0.015 2000.2 0.0028</td>
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<td>AAATCTTCTCGGT 0.148 0.528 0.0054</td>
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<td>AACACTCAAGGGT* 0.192 1.608 0.0262</td>
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<td>GAAACTTCTCAGG 0.014 --- 0.0384</td>
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<td>GACACTCAAGGGT 0.178 1.765 0.023</td>
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<td>GGAAACCCCTCAAG* 0.130 0.556 0.0192</td>
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<tr>
<td>Age of diagnosis, Gender, JAK2 mutation status</td>
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<td>GGAAACCCCTCAAG* 0.130 0.36 0.027</td>
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</table>

*JAK2 intragene haplotypes that are significantly associated with PV, even after adjusting for JAK2V617F status

<sup>a</sup>Simulation based p-values
<sup>b</sup>Odds ratios computed for haplotypes with observed counts greater than 5.

PV indicates polycythemia vera; and JAK2, Janus kinase2.
Table 4. Significant associations between individual SNPs and PV and/or ET using logistic regression with covariates of age at diagnosis, gender, and JAK2V617F status

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene, dbSNP</th>
<th>N&lt;sup&gt;a&lt;/sup&gt;</th>
<th>MAF&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Minor Allele&lt;sup&gt;c&lt;/sup&gt;</th>
<th>p-value&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Odds Ratio (95% CI)&lt;sup&gt;e&lt;/sup&gt;</th>
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<td>0.37</td>
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<td>0.21</td>
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<td>0.68</td>
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<td>37</td>
<td>0.55</td>
<td>0.3</td>
<td>A (0.27)</td>
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<td>RS12342421</td>
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<td>37</td>
<td>0.52</td>
<td>0.3</td>
<td>G (0.75)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Number of people with and without the disorder successfully genotyped for the particular SNP locus  
<sup>b</sup> Minor Allele Frequencies of those with and without the disorder. Allele defined as 'minor' based on frequency of the particular allele in the overall study population. Allele frequencies for HapMap CEU population are indicated separately (see 'c')  
<sup>c</sup> Frequency of the allele in the HapMap Project CEU population  
<sup>d</sup> P-values computed under an additive genetic model.  
<sup>e</sup> Odds ratios and confidence intervals computed under a dominant genetic model

PV indicates polycythemia vera; ET, essential thrombocytemia; SNP, single nucleotide polymorphism; N, number; MAF, minor allele frequency; JAK2, Janus kinase 2; EPOR, receptor for erythropoietin; and CI, confidence interval.
Figure 1: Linkage Disequilibrium (LD) plot based on the 179 PV, ET and PMF study participants. The numbers in the boxes are the $r^2$ measure, while the boxes are colored according to $|D'|$ measure.
Host genetic variation contributes to phenotypic diversity in myeloproliferative disorders

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