Myeloproliferative Neoplasms and Somatic Mosaicism in the 23andMe Participant Community


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Introduction

Myeloproliferative neoplasms (MPNs) are disorders that result in unregulated overproduction of one or more myeloid blood cell types by the bone marrow. Polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) comprise the three classic MPNs. A somatic JAK2 mutation, V617F, is present in 95% of PV and 50-60% of ET and PMF patients. Past work has identified a germline haplotype of JAK2 associated with risk of developing a V617F-positive MPN1-3. This does not fully explain familial aggregation of MPNs.

Methods

We have recruited a web-based participatory cohort of patients with MPNs to better understand the genetic basis of these conditions. We have enrolled and collected saliva samples from more than 800 participants. Subjects have been genotyped using a derivative of the Illumina Human OmniExpress with additional custom content, including probes for JAK2 V617F. We selected 447 unrelated individuals with self-reported diagnoses of classic MPNs, including ET (n=150), PV (n=148), PMF (n=60), and 88 with related multiple diagnoses (‘MD’), i.e. PV+PMF. We used 65,051 additional unrelated 23andMe research participants as population controls. We imputed genotypes against the August 2010 release of 1000 Genomes haplotypes, using BEAGLE and mimac. We performed a GWAS of classic MPNs, adjusting for age, gender, and ancestry.

Results

In addition to replicating the known germline association at the JAK2 locus, we see a strong association in the TERT gene, telomerase reverse transcriptase (Fig. 1, Table 1, Fig. 2). Other variants in TERT have been associated with a variety of solid tumors and with red blood cell count. While not genome-wide significant, our third ranking association is strong (P=0.9) with rs1800056, a non-synonymous variant, F858L, in ATM, or ataxia telangiectasia mutated. This variant has previously been associated with chronic lymphocytic leukemia and breast cancer.

Consistent with a previous report2, JAK2 rs1327494 is more strongly associated with PV than with ET or MF. In contrast, we see consistent effects across diagnoses for TERT rs2853677 and ATM rs1800056 (Fig. 3).

Somewhat unexpectedly, we found that using probes for the V617F mutation on our genotyping arrays, we were able to detect the mutation in MPN study participants, with good agreement with self-reported mutation status (Fig. 4).

We found that we could also detect the V617F mutation in a subset of controls. The prevalence and extent of mutation burden increases with participant age (Fig. 6).

We tested whether each MPN risk variant was associated with V617F mutation status, among MPN cases, and among controls (Fig. 7). In cases, JAK2 rs1327494 is strongly associated with V617F status, while TERT rs2853677 is not. The three variants are all associated with somatic V617F status among the controls.

Discussion

Our study represents a significant addition to our understanding of the genetic predispositions for classic myeloproliferative neoplasms. The identification of risk alleles in TERT and ATM helps to link the genetics of MPNs with the genetics of other blood neoplasms and solid tumors. The work also demonstrates the power of web-based recruitment for studying uncommon diseases.

The rate of V617F positivity we see in our controls is higher than the prevalence of MPNs. It seems likely that this group includes individuals with undiagnosed or indolent disease, as well as some who will never develop an active hematological neoplasm. We are currently validating the V617F assay and are developing a strategy for returning these test results to our participants.

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References