

# Familial essential thrombocythemia associated with *JAK2 V617F* mutation in siblings

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Three myeloproliferative neoplasms (MPN), polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), are associated with an abnormal somatic mutation of the *JAK2* gene. Essential thrombocythemia is considered when there is a persistent increase in the peripheral blood platelet count, associated with a proliferation of atypical megakaryocytes in the bone marrow. The manifestations of PV, ET, and PMF all typically occur within the sixth or seventh decade of life. A patient may present with an abnormal blood count but be asymptomatic at the time. Over the course and progression of the disease, increases in hematocrit or platelet counts along with symptoms such as headaches, blurred vision, and plethora may occur.<sup>1</sup> The *JAK2 V617F* mutation is responsible for the production of the *JAK2* protein, which is continuously activated, promoting the growth and division of cells such as erythrocytes, granulocytes, and platelets. It has been reported that there is a nearly 100% incidence of the *JAK2* mutation in patients with polycythemia vera, and a 50% incidence in patients with essential thrombocythemia and primary myelofibrosis.<sup>2</sup>

The discovery of the *JAK2* mutation in PV, ET, and PMF was an important advancement in helping distinguish these disorders from other MPNs, including chronic myelogenous leukemia, but its presence does not explain why some individuals develop ET and others, PV or PMF.<sup>3</sup> Although there have been familial cases proven of ET, the somatic *JAK2* mutation is acquired and not inherited. In this report, we describe the unusual circumstance of *JAK2 V617F* mutation in a brother and a sister who were both diagnosed with essential thrombocythemia.

## Case presentations and summaries

RS, a 69-year-old white man, was referred to our ser-

vice in 2006 for continued care of previously diagnosed essential thrombocythemia. At the time of his initial visit to our clinic, his complete blood count was normal, the platelet count being adequately controlled by anagrelide at a daily dose of 4.0 mg. He complained of palpitations and peripheral neuropathy. A bone marrow biopsy was performed, revealing moderate hypercellularity, atypical megakaryocytosis, and a negative *BCR-ABL* mutation but a positive *JAK2 V617F* mutation. The patient is now treated with hydroxyurea 1,000 mg daily in divided doses, which better controls his counts and does not have the side effects of anagrelide.

SW, a 73-year-old woman, and brother of RS (they share the same biological mother and father), was noted to have a mild thrombocytosis in 2008. In 2013, her platelet count rose to 865,000 cells/uL (normal, 150,000–450,000 cells/uL, age and sex adjusted) and she was referred to our clinic. A bone marrow biopsy was performed, revealing borderline hypercellularity with atypical megakaryocytosis and the presence of a *JAK2 V617F* mutation. As with her brother, the *BCR-ABL* mutation was not present. She has also responded to treatment with hydroxyurea, but at a reduced dosage of 500 mg daily.

A third sibling, AS, again of the same biological mother and father, had died of multiple veno-occlusive cerebral vascular events long before the diagnoses on his younger siblings had been made. The suggestion of any underlying hematologic pathology would be interesting, but speculative. Nothing is known about the parents' medical history. None of the three siblings had children.

## Discussion

Much research has been done to understand the pathogenesis of and find a cure for myeloproliferative disorders, but despite some progress, a cure

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remains elusive. However, there have been some advances that have contributed to partial cures for MPNs. One of the major breakthroughs in MPN research, about 50 years ago, was related to the “sporadic vs familial debate” around the Philadelphia chromosome.<sup>4</sup> It led to the discovery of the reciprocal translocation between chromosomes 9 and 22, known as the *BCR-ABL* mutation, which is found in many CML patients. This discovery allowed researchers to focus their attention on other tyrosine kinase domains, such as the *JAK2 V617F* mutation, which is presented in the three other MPNs; PV, ET, and PMF. Both the *JAK2 V617F* and *BCR-ABL* mutations are active in signaling transcription, more commonly growth of cells.<sup>4</sup>

Since the discovery of the *JAK2 V617F* mutation in early 2005, it has become a leading diagnostic criteria for myeloproliferative diseases. The presence of the *JAK2 V617F* mutation and the measurement of its allele burden can be assessed by examination of either peripheral blood or bone marrow samples.<sup>5</sup>

The *JAK2 V617F* mutation is a result of a single change in the DNA nucleotide base pair that causes a substitution of a valine amino acid for a phenylalanine amino acid at the 617 position on exon 14 within the *JAK2* kinase regulatory domain. This point mutation disrupts the regular control of the *JAK2* by removing its ability to turn off, leading to uncontrolled blood cell growth.<sup>6</sup> When the *JAK2 V617F* mutation cannot be demonstrated in a patient with the hallmarks of an MPN, the detection of other *JAK2* and *MPL* proto-oncogene, thrombopoietin receptor mutations may be used as a diagnostic procedure for other MPNs.<sup>7</sup>

Other mutations incorporated in *JAK2* domain can be detected in the coding portions of the DNA known as exons. One such mutation is the *JAK2* exon 12, which is involved in *JAK2 V617F*-negative PV patients. This mutation is not detected in patients with ET or PMF and is 2%-5% present in patients with PV. There are other somatic mutations in the thrombopoietin receptors that work in accordance with thrombopoietin: *MPL W515L* and *MPL W515K*, which are found at chromosome 1p34, are identified in about 5% of PMF and 1% of ET patients, but are not present in PV patients.<sup>8,9</sup>

Pikman and colleagues reported in 2009 that the *JAK2*

*V617F* mutation is not acquired randomly.<sup>9</sup> Their findings showed that, only in white populations, does the *JAK2 V617F* mutation arise preferentially on a specific constitutional *JAK2* 46/1 haplotype. According to the authors, the preconceived notion of a randomly acquired *JAK2 V617F* mutation does not account for familial MPNs. Familial MPNs are thought to be produced by sporadic and extremely penetrant substitutions in genes that still are not identified and the 46/1 haplotype does not explain for the phenotypic diversity correlated with the *JAK2 V617F* gene. The 46/1 haplotype, however, correlates more frequently with different MPN subtypes. There are two hypotheses that try to explain how an acquired mutation as prevailing as the *JAK2 V617F* mutation can be associated with certain inherited backgrounds. The first hypothesis asserts the *V617F* accumulates at a faster rate than other genes because of the fundamentally unstable genetics of the 46/1 haplotype. The second theory is that all the mutated genes, including the *V617F*, arise at equal rates, but 46/1 may grant a selective advantage to the *V617F*-positive clone or interacts in some way to increase the likelihood of abnormal blood counts. A study that examined both these hypotheses concluded that the 46/1 haplotype was present more frequently in patients with myeloproliferative disorders than in their control groups and even more so in cases that were proven to be *V617F*-positive.<sup>10</sup>

There are very few cases that have reported familial MPNs, especially as the pedigrees of the familial MPNs illustrate that inheritance patterns are notably heterogeneous, indicating that there may be a range of different germline mutations driving the susceptibility. With recent data, the *JAK2 V617F* mutation in tandem with *MPL W515L/K* and inactivating *TET2* mutations still continue to be the most frequently acquired mutations involved in both familial and sporadic MPN. As far as we know, there have been no cases to prove that *JAK2 V617F* and *MPL W515L/K* mutations are inherited through the germline, but there are other alleles that may pass through the germline that can be associated with hereditary thrombocytosis.<sup>11</sup> Further cytogenetic studies will clarify the pathogenesis of these disorders and possibly lead to effective targeted therapies.

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