JAK2 mutations to the fore in hereditary thrombocythemia

Stephen E Langabeer*

Cancer Molecular Diagnostics; St. James's Hospital; Dublin, Ireland

Acquired mutations of the gene that encodes the intracellular signalling molecule *JAK2* are the most frequently observed disease-driving events of the common myeloproliferative neoplasms. A number of germline *JAK2* mutations have recently been described in several kindred with the rare disease of hereditary thrombocythemia, also known as familial thrombocythemia or familial thrombocytosis. These inherited mutations are all located within the pseudo-kinase and kinase domains of *JAK2* and have been shown to directly contribute to the thrombocytic phenotype. Molecular characterisation of the resulting, aberrant signalling signatures may provide insights into genotype-phenotype relationships of both hereditary thrombocythemia and the common myeloproliferative neoplasms.

The interaction of the cytokine thrombopoietin with its receptor MPL and subsequent signal transduction via the intracellular JAK and STAT signaling proteins is a major pathway in the control of megakaryopoiesis and platelet production. Activating mutations, be they somatic or germline, in any of the genes that encode the proteins involved in this pathway are likely to cause a deregulation of platelet production and therefore thrombocytosis. When considering the classical, Philadelphia chromosome-negative myeloproliferative neoplasms (MPN), the acquired *JAK2* exon 14 V617F mutation is observed in 98% of patients with polycythemia vera (PV) and in half of patients with essential thrombocythemia (ET) and primary myelofibrosis (PMF). The V617F occurs in the pseudo-kinase domain of the protein resulting in the loss of the inhibitory effect it normally exerts on the adjacent kinase domain. Furthermore, several

JAK2 exon 12 mutations are detected in the remainder of PV patients with activating mutations of MPL evident in approximately 3–10% of ET and PMF patients. Detection of these mutations is integral to the MPN molecular diagnostic algorithm with discovery also driving the development of successful therapies that target these abnormal proteins.^{1,2}

Hereditary thrombocythemia (HT), also known as familial thrombocytosis or familial thrombocythemia, is a rare congenital disease that arises from a single genetic defect that only affects the platelet lineage, exhibits a Mendelian inheritance pattern and displays polyclonal hematopoiesis. HT requires clinical diagnostic distinction from the sporadic clonal disorder of ET and also from multi-lineage involved familial MPN that also exhibits clonal hematopoiesis. Unsurprisingly, germline substitution or intron/exon splice site mutations in the genes that encode both thrombopoietin and its receptor (THPO and MPL) have been documented in several HT kindreds.³ More recently, several mutations within *JAK2* that disrupt intracellular signaling have been described in 5 HT kindred: 4 mutations occur in single families with 2 mutations present in cis in a further kindred.^{4–7} These mutations are germline as they occur in patient constitutional material, appear to locate exclusively in the pseudo-kinase or kinase domain-encoding exons (Fig. 1) and, in either primary material or transfected cell lines, exhibit varying degrees of either downstream STAT phosphorylation and/or growth factor-independent expansion indicating a pivotal role in potentiating the HT phenotypes. Intriguingly, in those mutants extensively studied, their location and specific activation signatures may provide some biological insight into HT/MPN

Keywords: germline, hereditary thrombocythemia, *JAK2*, mutations, therapy

*Correspondence to: Stephen E Langabeer; Email: slangabeer@stjames.ie

Submitted: 08/13/2014

Accepted: 08/20/2014

<http://dx.doi.org/10.4161/21623988.2014.957618>

Figure 1. Location of JAK2 mutations associated with myeloproliferative neoplasms and 5 hereditary thrombocythaemia kindred. FERM: 4.1 protein ezrin radixin moesin; SH2: Src homology-2.

pathogenesis and clinically, JAK2 inhibitor responses: the kinase domain R867Q and R938Q mutants appear to be less sensitive to known JAK2 inhibitors than V617F and wild type JAK2 whereas the pseudo-kinase domain R564Q displays a greater sensitivity to inhibition than the commonly acquired V617F.^{6,7} Alternatively, the V617I appears to be sufficient to induce a HT phenotype in a qualitatively distinct manner to that of V617F.⁸

Identification of the rare HT is also clinically important as an increased risk of thrombotic/hemorrhagic events, splenomegaly, bone marrow fibrosis, and also transformation to acute myeloid leukemia has been noted in previously documented HT kindred.^{9,10} Therefore, these recent reports of germline JAK2 mutations in HT compel the incorporation of JAK2 gene analysis, including at least those exons that encode the pseudo-kinase and kinase domains, into the molecular

diagnostic algorithm for suspected HT.¹¹ It is likely that further HT kindreds harbouring other JAK2 mutations will be discovered, with increasing characterization likely to improve our understanding of the genotype-phenotype relationship in both HT and MPN; the immediate goal being able to select appropriately targeted, JAK2 pathway inhibitor therapies currently available or in development for MPN patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Quintás-Cardama A, Verstovsek S. Molecular pathways: JAK-STAT pathway: mutations, inhibitors, and resistance. *Clin Cancer Res* 2013; 19:1933-40; PMID:23406773; <http://dx.doi.org/10.1158/1078-0432.CCR-12-0284>
2. Gong JZ, Cook JR, Greiner TC, Hedvat C, Hill CE, Lim MS, Longtine JA, Sabath D, Wang YL. Laboratory practice guidelines for detecting and reporting JAK2 and MPL mutations in myeloproliferative neoplasms: a report of the Association for Molecular pathology. *J Mol Diagn* 2013; 15:733-44; PMID:23978506; <http://dx.doi.org/10.1016/j.jmoldx.2013.07.002>
3. Teofili L, Larocca LM. Advances in the understanding the pathogenesis of familial thrombocythaemia. *Br J Haematol* 2011; 152:701-12; PMID:21303356; <http://dx.doi.org/10.1111/j.1365-2141.2010.08500.x>
4. Mead AJ, Rugless MJ, Jacobsen SE, Schuh A. Germline JAK2 mutation in a family with hereditary thrombocytosis. *N Engl J Med* 2012; 366:967-9; PMID:22397670; <http://dx.doi.org/10.1056/NEJMc1200349>
5. Rumi E, Harutyunyan AS, Casetti I, Pietra D, Nivarthi H, Moriggl R, Cleary C, Baginski K, Astori C, Bellini M, et al. A novel germline JAK2 mutation in familial myeloproliferative neoplasms. *Am J Hematol* 2014; 89:117-8; PMID:24142793; <http://dx.doi.org/10.1002/ajh.23614>
6. Etheridge SL, Cosgrove ME, Sangkhav V, Corbo LM, Roh ME, Seeliger MA, Chan EL, Hitchcock IS. A novel activating, germline JAK2 mutation, JAK2 R564Q, causes familial essential thrombocytosis. *Blood* 2014; 123:1059-68; PMID:24381227; <http://dx.doi.org/10.1182/blood-2012-12-473777>
7. Marty C, Saint-Martin C, Pecquet C, Grosjean S, Saliba J, Mouton C, Leroy E, Harutyunyan AS, Abgrall JF, Favier R, et al. Germ-line JAK2 mutations in the kinase domain are responsible for hereditary thrombocytosis and are resistant to JAK2 and HSP90 inhibitors. *Blood* 2014; 123:1372-83; PMID:24398328; <http://dx.doi.org/10.1182/blood-2013-05-504555>
8. Mead AJ, Chowdhury O, Pecquet C, Dusa A, Woll P, Atkinson D, Burns A, Score J, Rugless M, Clifford R, et al. Impact of isolated germline JAK2 V617I on human hematopoiesis. *Blood* 2013; 121:4156-65; PMID:23535062; <http://dx.doi.org/10.1182/blood-2012-05-430926>
9. Teofili L, Giona F, Torti L, Cenci T, Ricerca BM, Rumi C, Nunes V, Foà R, Leone G, Martini M, et al. Hereditary thrombocytosis caused by MPL Ser505-Asn is associated with a high thrombotic risk, splenomegaly and progression to bone marrow fibrosis. *Haematologica* 2010;95:65-70; PMID:19713221; <http://dx.doi.org/10.3324/haematol.2009.007542>
10. Posthuma HL, Skoda RC, Jacob FA, van der Maas AP, Valk PJ, Posthuma EF. Hereditary thrombocytosis not as innocent as thought? Development into acute leukemia and myelofibrosis. *Blood* 2010; 116:3375-6; PMID:21030572; <http://dx.doi.org/10.1182/blood-2010-06-290718>
11. Hussein K, Percy M, McMullin MF, Schwarz J, Schnittger S, Porret N, Martinez-Aviles LM, Paricio BB, Giraudier S, Skoda R, et al. Clinical utility gene card for: hereditary thrombocythemia. *Eur J Hum Genet* 2014; 22:e1-e5; PMID:23736217; <http://dx.doi.org/10.1038/ejhg.2013.117>