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Hemochromatosis, erythrocytosis and the *JAK2* p.V617F mutation

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LETTER TO THE EDITOR

Hereditary hemochromatosis (HH) is an inherited iron overload disorder, particularly prevalent in Irish and Scandinavian populations (1), characterised by abnormal iron metabolism, leading to excess iron deposition in the parenchymal cells of the liver, heart, and endocrine organs. HH is commonly associated with mutations in the *HFE* gene and in other genes such as *HJV*, that regulate the biology of hepcidin, a key regulator of iron homeostasis, and *TRF2* that is responsible for uptake of transferrin bound iron (2, 3). A rare but recurrent hematological manifestation of HH is a raised hematocrit due to an excess of red cells (erythrocytosis) possibly an important clue to an underlying hepatoma (4). Therapy is based on the removal of excess iron by phlebotomy or erythrocytapharesis, with ferritin levels used to monitor treatment effectiveness (5). The most common cause of acquired primary erythrocytosis is the myeloproliferative neoplasm polycythemia vera (PV). Approximately 95% of PV patients harbour the *JAK2* p.V617F mutation. In hematopoietic stem cells, this mutation leads to constitutively activated, intracellular JAK-STAT signalling resulting in increased production of red and white blood cells and platelets. For many years the mainstay of PV therapy has been

phlebotomy and cytoreductive agents to prevent thrombotic events and transformation to acute leukemia, however recently developed targeted therapies have shown considerable efficacy (6).

A sporadically observed trigger for requesting *JAK2* p.V617F analysis is for investigation of an erythrocytosis or raised hematocrit in patients with known HH. In order to address the clinical value and laboratory impact of such requests, a retrospective audit was performed on all *JAK2* p.V617F requests received at a molecular diagnostics centre for hematological malignancies. From January 2006 to December 2016 inclusive, 14617 diagnostic requests for *JAK2* p.V617F mutation analysis were received. Of these, 48 requests (0.3%) were received from known HH patients with accompanying clinical details of a raised hemoglobin and/or hematocrit or erythrocytosis. Using an allele-specific PCR screening assay capable of detecting 2% mutant alleles, the *JAK2* p.V617F mutation was not detected in any of these 48 patients.

The role of *HFE* genotypes as risk factors for development of a myeloproliferative disorder remains somewhat confounding (7, 8). However, considering the above data and, while the number of requests for *JAK2* p.V617F mutation in patients with HH does not considerably impact on overall laboratory workload, routine screening for the PV-associated *JAK2* p.V617F mutation in patients with HH with raised red cell counts appears inappropriate.

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