The V617F mutation of *JAK2* is very uncommon in patients with thrombosis

Given that many cases of thrombosis do not have a clear cause, a myeloproliferative disease could be involved. We investigated the V617F mutation of the *JAK2* gene in 295 patients with thrombosis. Only one case was positive. Therefore, the study of this mutation is not necessary in all patients with idiopathic thrombosis.

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Chronic myeloproliferative diseases (MPD) are clonal hematologic malignant disorders characterized by the proliferation of one or more of the myeloid lineages.[1] Activation of tyrosine kinase pathways is implicated in the pathogenesis of MPD.[2]

Polycythemia vera (PV) and essential thrombocytemia (ET) are characterized by overactive hematopoiesis. Thrombosis is the main clinical complication in the early stages of PV and ET.[3] Recently, a single mutation in the cytoplasmic tyrosine kinase JAK2 has been detected in most patients with PV and in half of those with ET. A single point mutation (Val617Phe) dysregulates the kinase activity of JAK2[4] leading to abnormal hematopoiesis.[5]

Moreover, MPD hve been implicated in cases of unusually located thrombosis, such as thrombosis of the portal district.[6-8] Therefore, the study of the *JAK2* mutation could be used to identity the presence of an underlying MPD as the cause of thrombosis.

In this work, the presence of the *JAK2* mutation was studied in a cohort of 295 cases with thrombosis in common locations. This cohort includes the 239 patients of a previous study[9] and 56 additional subjects recruited following the same inclusion criteria (i.e., consecutive patients with a first, objectively diagnosed, thrombotic event when younger than 70 years of age, excluding those with malignancies, a history of liver failure or nephrotic syndrome).

These first thromboembolic events were spontaneous in 134 patients (45%) and 103 patients (35%) were older than 50 years at presentation. In 41 out of these 103 older patients the thrombotic event was spontaneous.

The samples were analyzed using the methodology described by Baxter *et al.*[4] DNA samples from 25 patients who met the WHO criteria for having PV[1] were also assessed as positive controls. As negative controls, 65 patients with other hematologic non-MPD disorders were evaluated. All the procedures were reviewed and approved by the Institutional Review Board of our hospital.

The *JAK2* mutation was found in 24 of the 25 cases with PV (96%), but was not present in any of the 65 subjects with other hematologic disorders. As for the patients with thrombosis, one out of the 295 patients was positive. This case was a 69-year old male who had had three episodes of spontaneous venous thrombosis in common locations (three proximal deep venous thromboses in the popliteal, femoropopliteal and femoroiliac veins, at the age of 56, 57 and 69 years, respectively) and two episodes of superficial thrombophlebitis. His thrombophilia study was negative. This patient has been followed-up in our department since 1997 and his hemoglobin has ranged from 160-168 g/L. His platelet and leukocyte counts have always been normal. Subsequent studies demonstrated an increased red cell mass (38 mg/kg, normal < 36 mg/kg), low serum erythropoietin level (2 U/L), and spontaneous peripheral blood erythroid colony formation.

Thromboses are common in patients with PV or ET. On the other hand, many patients suffer from thrombosis without an underlying cause. In a few patients, a MPD has been demonstrated to be present, especially in those in whom the thrombosis has occurred in an unusual location, such as in Budd-Chiari syndrome.

In these cases the diagnosis of the MPD is often very difficult and requires sophisticated methods. Before the discovery of the *JAK2* mutation, X-chromosome inactivation patterns and *in vitro* erythroid colony formation were used for the diagnosis of the underlying MPD.[3,6-8,10] However, these methods are cumbersome with the result that their use is restricted to some laboratories.

Investigations to determine the presence of the single point mutation (V617F) of *JAK2* are now readily available.[4,5] Given that we found this mutation in only one of 295 patients with thromboses in common locations, an undetected MPD is a very improbable cause of thromboses in general. Therefore, investigation for the V617F mutation of the *JAK2* gene is not mandatory in all patients with idiopathic thrombophilia.

This genetic study should be reserved for special cases, such as patients with thrombosis in uncommon sites[6-8] or patients with cell counts suggesting the presence of a MPD.

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