

To the editor:

Hereditary thrombocytosis not as innocent as thought? Development into acute leukemia and myelofibrosis

Essential thrombocythemia (ET) is frequently characterized by clonal hematopoiesis and an acquired JAK2-V617F mutation. Mutations in the thrombopoietin gene (*THPO*) and in the thrombopoietin receptor gene (*MPL*) can cause hereditary thrombocytosis (HT).¹ HT, like ET, can present with complications such as thrombosis or bleeding, but progression to malignant disease has not been described for HT.

Here we report acute myeloid leukemia (AML) in one family member and myelofibrosis in another affected member of the same family previously described as having HT caused by a G>C transversion in the splice donor of intron 3 of the *THPO* gene.^{2,3} After the initial diagnosis of HT in 1991, the proband (patient II/8 in Figure 1) was treated with acetyl salicylic acid 100 mg/d, but he never received cytoreductive treatment. The patient was referred in 2008 because of fever, fatigue, and anemia. His medical history consisted of diabetes, hypertension, and a transient ischemic attack in 1989. Physical examination revealed splenomegaly. Laboratory results were as follows: hemoglobin 6.1 mmol/L (8.8-10.9 mmol/L), leukocytes $4.8 \times 10^9/L$ ($3.5-11.0 \times 10^9/L$) with 4% blasts and dysplastic signs) and thrombocytopenia $91 \times 10^9/L$ ($150-400 \times 10^9/L$). Lactate dehydrogenase was 1509 U/L (0-200 U/L). Bone marrow cytology showed 40% myeloid blasts (CD34⁺/CD117⁺/MPO⁺/CD13⁺/CD33⁺/HLA DR⁺) and allowed the diagnosis of AML with maturation not otherwise classified (according to the WHO classification). Cytogenetic analysis showed a complex pattern: 47, XY, add(2)(p273), del(5)(q173q375), i(8)(q10), +i(8)(q10), -18, -20, i(21)(q10), +2-5mar (cp5). By fluorescence in situ hybridization (FISH) no MLL abnormalities were detected.

No JAK2V617F, NPM1-, or CEBPA mutation, *AML1-ETO* or *CBFB-MYH11* fusion gene, or FLT3 internal tandem duplication (ITD) were present. The AML did not show high levels of EVI mRNA expression. The leukemia of our patient was refractory to standard remission induction with cytarabine, mitoxantrone, and etoposide. Four months after the AML diagnosis, the patient died as a result of progressive disease.

An update of the family history revealed that the patient's sister, also affected by HT (patient II/2, Figure 1), had died 4 years earlier due to myelofibrosis with severe pancytopenia. Her bone marrow showed myelofibrosis with dysplastic megakaryopoiesis, granulopoiesis and erythropoiesis, and 10% blasts; the peripheral blood showed leukoerythroblastosis, macrothrombocytes, and teardrop cells (not shown). She died 3 months after the diagnosis of myelofibrosis with severe pancytopenia and highly elevated LDH. A second bone marrow examination in this terminal phase was not performed. Patient II/2 was also treated with low-dose aspirin, but did not receive cytoreductive treatment. Two other affected members of the same family should be mentioned: one, patient IV/3 displayed a leukemoid reaction at birth (leukocytes $60 \times 10^9/L$) that persisted for 1 year, but normal at follow-up.⁴ The other, patient II/3, had dry tap during follow-up; however, re-examination of the bone marrow showed only a mild increase in reticulin fibers.⁵

Malignant progression of HT due to overproduction of Tpo has not been reported previously. Our results suggest that the *THPO* mutation, which results in elevated Tpo serum levels, may increase the risk of progression to myelofibrosis and leukemia. To clarify this potential association, a careful follow-up of patients with HT is warranted.

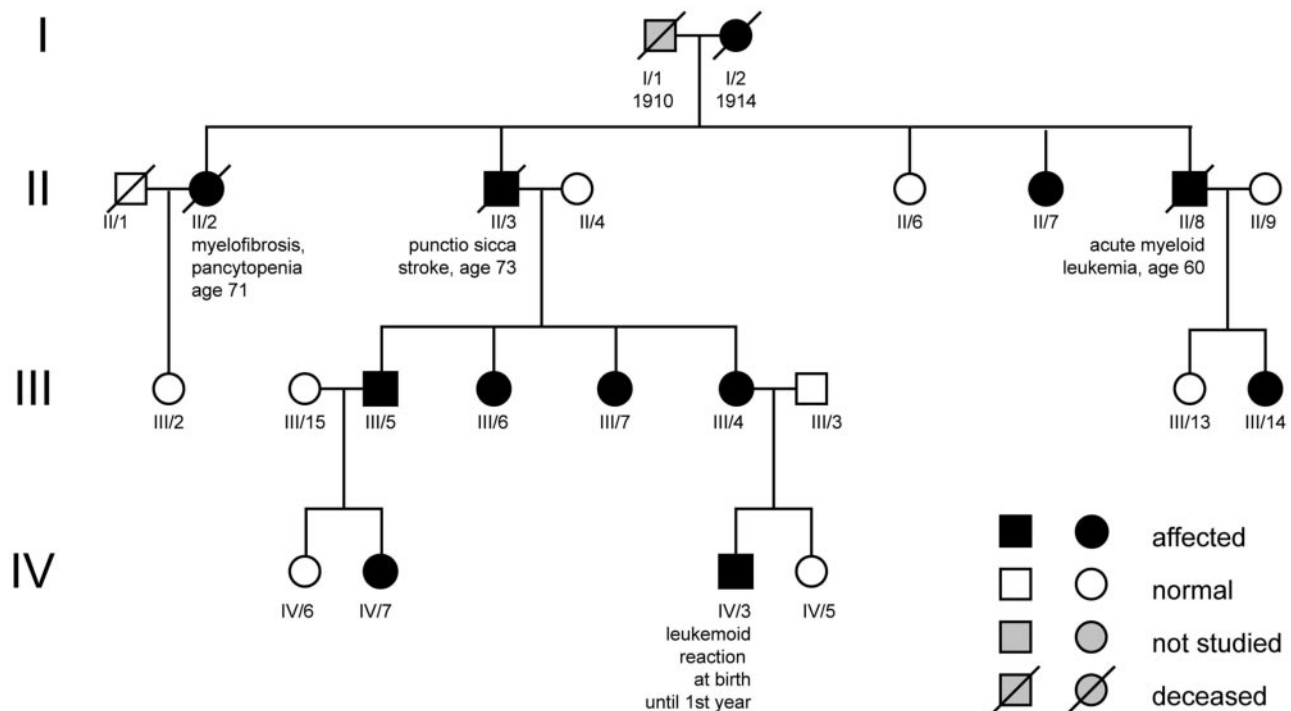


Figure 1. Pedigree of family with hereditary thrombocytosis. Roman numerals reflect generation; Arabic numbers reflect individuals per generation.

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