Hereditary thrombocytosis caused by *MPL*^{Ser505Asn} is associated with a high thrombotic risk, splenomegaly and progression to bone marrow fibrosis

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Supplementary Appendix

The proband of Family A was a young male diagnosed as having essential thrombocythemia at the age of 18 years old (C_2). His elder sister was followed for essential thrombocythemia at a different hospital (C_5); his father (C_1) had thrombocytosis and died suddenly at the age of 76 from an unknown cause. The patient started low dose aspirin soon after the diagnosis and so far has not had thrombotic complications.

Family B included a 62-year old man (I_2) affected by essential thrombocythemia from the age of 18 and his offspring. The father is receiving antiplatelet and antiproliferative therapy, while all his children are in good health without therapy. The grandfather (I_1) was known to be affected by thrombocytosis, but a detailed medical history was not available. A cousin (I_8) and his two daughters (I_7 and I_6) had high platelet counts as well, without complications.

Probands of Family C were two sisters diagnosed as having essential thrombocythemia at the age of 14 (T_8) and 8 (T_9) years old. Another sister died of Budd Chiari syndrome at the age of 17 (T_{10}). Bone marrow histology at diagnosis highlighted megakaryocytic hyperplasia with clusters, in the absence of fibrosis. Thrombocytosis was present also in the father (T_1), (who was found to carry the mutation), in an uncle (T_3) and in the offspring of the uncle (T_5, T_6 and T_7). One of the two sister receives low dose aspirin and carried a pregnancy without complications (T_8). The neonate had thrombocytosis at the time of birth and wsa shown to be positive for the mutation at the age of 1 year old (T_{11}).

The proband of Family D was a 54-year old woman observed for the first time at the age of 41 because of thrombocytosis and recurrent deep vein thrombosis of the leg (S_2); at this time her spleen volume was normal. She refused bone marrow biopsy and antiplatelet therapy. Two years later she was admitted again to hospital because of a transient ischemic attack. Bone marrow biopsy showed megakaryocytic hyperplasia with low grade reticulin fibrosis (Figure 1, C-D, *main text*); splenomegaly was present. Therapy with low dose aspirin and hydroxycarbamide was started. Meanwhile, her mother, who had a long history of persistent thrombocytosis, underwent a splenectomy because of traumatic rupture of her spleen (S_1). The spleen weighed 3.8 kilograms. A bone marrow biopsy performed at the time of surgery revealed widespread fibrosis. Both mother and daughter proved to be positive for the *MPL*^{Ser505Asn} mutation. The mother died of cerebral vein thrombosis at the age of 76. The daughter's children were also investigated: the *MPL*^{Ser505Asn} mutation was found in the one with thrombocytosis (S_3), while the two with normal platelet counts had the wild-type gene (S_4 and S_5).

The proband of Family E was a 54-year old woman referred to our department because of splenomegaly and thrombocytosis (F_3). Her bone marrow showed megakaryocytic hyperplasia. Her mother had been affected by essential thrombocythemia since the age of 76 (F_1) and had died of cerebral vein thrombosis when she was 80. Her aunt (F_2) was also affected by essential thrombocythemia, but died of an unknown cause at the age of 42. The *MPL*^{Ser505Asn} mutation was detected in the proband and, at post-mortem, in her mother, using DNA extracted from a previous gastric biopsy. In addition, the proband's daughter (F_5), was diagnosed as having essential thrombocythemia, at a different pediatric hematology department, when she was 12 years old.

The probands of Family F were two sisters, diagnosed as having essential thrombocythemia at the ages of 16 (M_9) and 20 (M_{10}). At diagnosis, neither patient had splenomegaly or bone marrow fibrosis. Figure 1 A-B shows the bone marrow biopsy taken from M_9, exhibiting slight hypercellularity, with an increased number of neutrophils, atypical megakaryocytes and no reticulin fibrosis. At the time of investigation for the *MPL* mutation (7 years later), the sisters had marked splenomegaly and the bone marrow contained focal (M_{10}) and diffuse (M_9) reticulin fibrosis. The mutation was detected in both probands, while it was absent in the mother (M_{5a}), who had a normal platelet count. Both patients received therapy with low dose aspirin and one (M_9) has begun treatment with interferon because of discomfort due to splenomegaly. The father (M_5), the grandfather (M_2) and the great-grandfather (M_1) of the probands died of myocardial infarction when they were 52, 67 and 50 years, respectively; all of them had reported thrombocytosis. In addition, two sisters of the grandfather, both with thrombocytosis, died of myelofibrosis secondary

to essential thrombocythemia (M_3) and from eclampsia (M_4) at the ages of 57 and 23, respectively. The daughter of this latter patient (M_8), experienced a fetal loss during an untreated pregnancy.

The probands of Family G were a 31-year old man (B_{13}) and his father (B_8). The former was admitted to a coronary care unit because of a myocardial infarction. He was a smoker. A bone marrow biopsy, carried out because of the patient's thrombocytosis and splenomegaly, documented the presence of reticulin fibrosis. The father (B_8), aged 72 years, was being followed for essential thrombocythemia at the same institution and was on therapy with low dose aspirin and hydroxycarbamide. His latest bone marrow biopsy revealed a high grade of reticulin fibrosis (Figure 1 E -F). Both patients were positive for the *MPL*^{Ser505Asn} mutation. Another son (B_{14}) was followed for essential thrombocythemia in a different hospital: he also was found to carry the mutation. The grandfather (B_2) was known to have thrombocytosis: he died of liver cirrhosis at the age of 78, while his brother (B_1) died of myocardial infarction at the age of 60. The patient had six offspring: three of them had thrombocytosis and died of myocardial infarction (B_6), complications related to essential thrombocythemia (B_7) and gastric cancer (B_3) at the ages of 81, 50 and 76, respectively. The daughter of this last patient had thrombocytosis as well (B_{11}), and suffered from a myocardial infarction at the age of 40. Finally, the sister of the proband (B_{10}) suffered from a stroke at the age of 72 years old.