

THROMBOCYTOSIS

DEFINITIONS

Thrombocytosis: platelet counts $> 450 \times 10^9 / L$

Primary Thrombocytosis: thrombocytosis caused by an alteration in hematopoietic cells; the serum level of thrombopoietin (Tpo), the main cytokine responsible for the production of platelets, is low or normal. Primary thrombocytosis can be hereditary (rare) or acquired (more frequent, in myeloproliferative neoplasms (MPN) and in myelodysplastic syndromes (MDS)) In MDS, abnormalities of chromosome 5 or 3 are frequently found.

Secondary Thrombocytosis: thrombocytosis due to an external cause; the serum level of Tpo is frequently elevated. Secondary thrombocytosis is usually acquired: ailments resulting in elevated platelet counts include inflammation, iron deficiency, and asplenia. In rare cases, secondary thrombocytosis is hereditary (familial).

Thrombocythemia: myeloproliferative neoplasm characterized by thrombocytosis - see “**Essential Thrombocythemia (ET)**”.

Hereditary Thrombocytosis: primary or secondary thrombocytosis due a genetic alteration that can be transmitted to offspring - ie. with a familial, or hereditary, genetic cause.

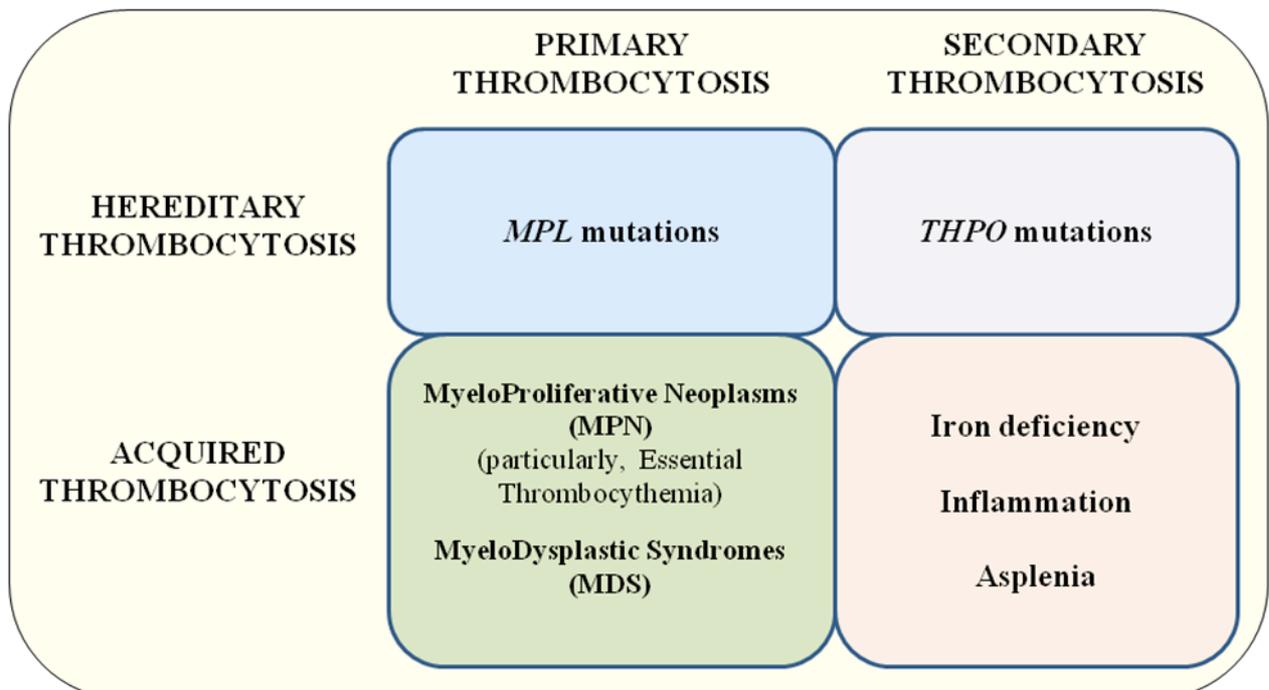


Figure 1. Classification (courtesy of Eric Lippert).

HEREDITARY THROMBOCYTOSIS

CURRENT KNOWLEDGE

Major progress has been made in recent years in understanding the biology of hereditary thrombocytosis. We now know that mutations in two genes, *THPO* and *MPL*, can cause hereditary thrombocytosis:

-*THPO*, the gene coding for thrombopoietin (secondary thrombocytosis, with high Tpo level)

-*MPL*, the gene coding for the receptor for thrombopoietin, expressed by hematopoietic progenitors (primary thrombocytosis, with low or normal Tpo level).

Interestingly, analysis of these mutations has also helped deciphering the physiological regulation of platelet homeostasis (Ghilardi et al. 1998). However, as not all patients carry mutations in the *THPO* or *MPL* genes, it is likely that hereditary thrombocytosis can be caused by alterations in other genes, not yet identified.

CONSIDER SCREENING FOR HEREDITARY THROMBOCYTOSIS THOSE PATIENTS WITH:

* Platelet counts $> 450 \times 10^9/L$

AND

* No essential thrombocythemia (no *JAK2V617F* mutation)

AND

* No identified cause of secondary thrombocytosis: inflammation, iron deficiency, asplenia.
No myelodysplastic syndrome and no acute myeloid leukemia (bone marrow biopsy or aspiration; karyotype)

* Young patients

* If positive family history

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- Ghilardi N, Wiestner A, Skoda RC. Thrombopoietin production is inhibited by a translational mechanism. *Blood* 1998; 92: 4023-30.

THPO MUTATIONS

Patients with *THPO* mutations present with an elevated level of thrombopoietin in blood.

Linkage disequilibrium studies have allowed the discovery of mutations in the gene encoding thrombopoietin (*THPO*) in several families. Thrombopoietin is the main cytokine involved in the production of platelets but it also plays a critical role on the maintenance and fate of early myeloid progenitors.

The *THPO* mutations found in families with thrombocytosis were located in the 5'UTR of the mRNA or at exon/intron boundaries, resulting in defective alternative splicing (Wiestner et al. 1998; Ghilardi et al. 1999a; Ghilardi et al. 1999b). In all instances, *in vitro* studies have proved these mutations to increase the effectiveness of thrombopoietin translation (Figure 2).

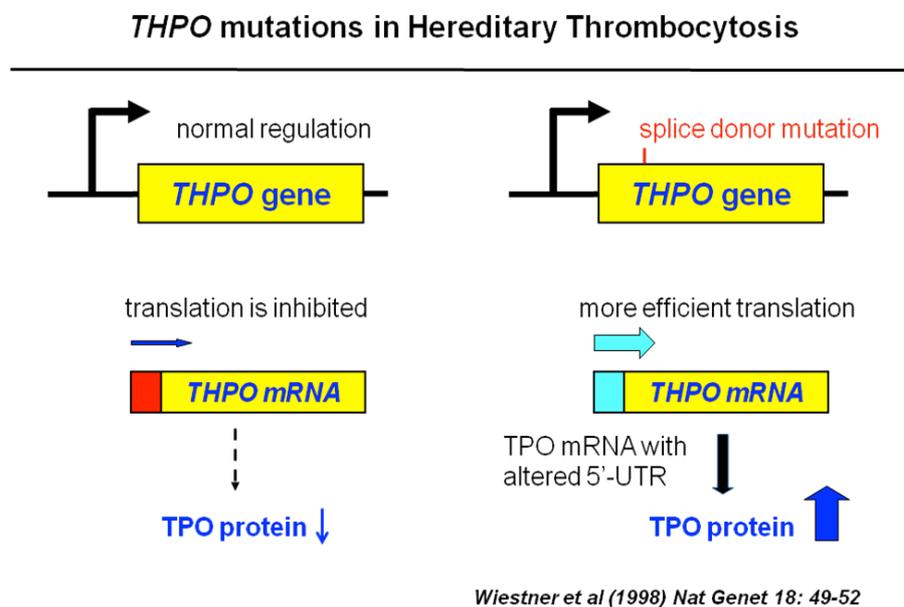


Figure 2. *THPO* mutations in Hereditary Thrombocytosis (courtesy of Radek Skoda).

Upstream of the start codon for *THPO*, alternative ATG code for small uORF, the translation of which impairs thrombopoietin translation. All mutations found in the *THPO* gene so far result in alteration of these uORF, thus lifting the repression on thrombopoietin translation, leading to increased expression of thrombopoietin, high level of thrombopoietin in peripheral blood, and increased production of platelets.

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MPL MUTATIONS

Patients with *MPL* mutations present with a low level of thrombopoietin in blood.

Anomalies in the receptor for thrombopoietin (Mpl) have also been shown to result in thrombocytosis with familial presentation (Figure 3).

In such cases, the alterations can either be single nucleotide polymorphisms (SNP) restricted to specific ethnic groups (Moliterno et al. 2004; El Harith et al. 2009) or *bona fide* mutations, such as the S505N mutation (Ding et al. 2004).

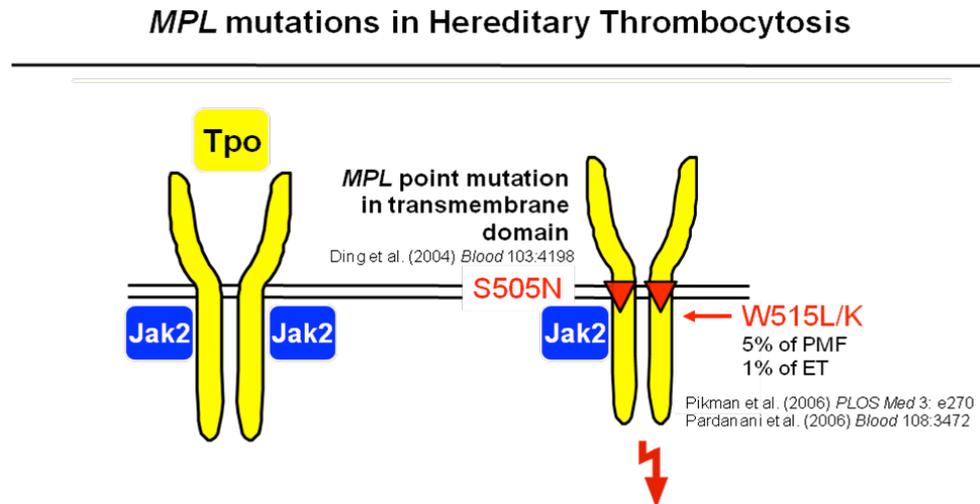


Figure 3. MPL mutations in Hereditary Thrombocytosis (courtesy of Radek Skoda)

Of note, MPL W515 mutations are mostly found in acquired myeloproliferative neoplasms (MPNs), where they are present in about 5% of primary myelofibrosis and 1% of essential thrombocythemia (Pikman et al. 2006; Pardanani et al. 2006). The S505N and W515L mutations were recently reported associated and present in the same cells in one MPN patient (Boyd et al. 2010).

All *MPL* mutations published so far result in constitutive activation of the Mpl receptor.

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