The name counts: the case of 'congenital amegakaryocytic thrombocytopenia'

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In this issue of *Haematologica*, Capaci *et al.* describe a young Palestinian patient with inherited thrombocytopenia and severely reduced bone marrow megakaryocytes due to a homozygous mutation (c.-323C>T) in the promoter region of the gene for thrombopoietin (*THPO*).[1] This report adds further information on the etiology and treatment of this recently identified form of amegakaryocytic thrombocytopenia and provides new insights into the mechanisms of *THPO* transcription.

Recent advances in the understanding of the etiology of inherited thrombocytopenias have revealed that mutations in several genes may be responsible for the reduction or absence of bone marrow megakaryocytes.[2] The resulting diseases share the shortage of megakaryocytes but, due to their different etiologies, differ for the other associated clinical features, have different clinical courses and prognoses, and require specific therapeutic approaches (Table 1). Thus, each gene causes a specific disease and it would be desirable for this to be highlighted by the name given to the illness. Unfortunately, this is not always so, and disorders with different clinical features and causative genes have the same name. This has led to misunderstandings and uncertainties both in clinical practice and in scientific reports. The aim of this editorial is

Table 1. Essential features of the five inherited thrombocytopenias presenting with congenital amegakaryocytic thrombocytopenia. New names have been recently proposed for four of these disorders.

Causative gene	*MPL*	*THPO*	*HOXA11*	*MECOM*	*RBM8A*
Current name of the disorder(s)	Congenital amegakaryocytic thrombocytopenia (CAMT)		Congenital amegakaryocytic thrombocytopenia with radio ulnar synostosis (CTRUS)		Thrombocytopenia absent radius syndrome (TAR)
New proposed name	CAMT-*MPL*	CAMT-*THPO*	CTRUS-*HOXA11*	*MECOM*-associated syndrome (*MECOM*-AS)	TAR
Inheritance	AR	AR	AD	AD	AR
Reduced/absent megakaryocytes at birth	All patients	All patients	All patients	All patients	All patients
Progression to bone marrow failure	All patients	All patients	Most patients	All patients*	No, platelet count rises over time
Radio-ulnar synostosis	No	No	All patients	Most patients	No
Bilateral radial aplasia	No	No	No	No	Yes
Other defects	No°	No	Some patients	Some patients	Many patients
Serum thrombopoietin	High	Low	High	High	High
Treatment	HSCT	THPO-RA (no HSCT!)	HSCT	HSCT	Supportive

*Spontaneous improvement of pancytopenia reported in one patient. °Central nervous system defects have been reported, but they were probably secondary to brain hemorrhages during intrauterine life. AR: autosomal recessive; AD: autosomal dominant; HSCT: hematopoietic stem cell transplantation; THPO-RA: thrombopoietin-receptor agonists

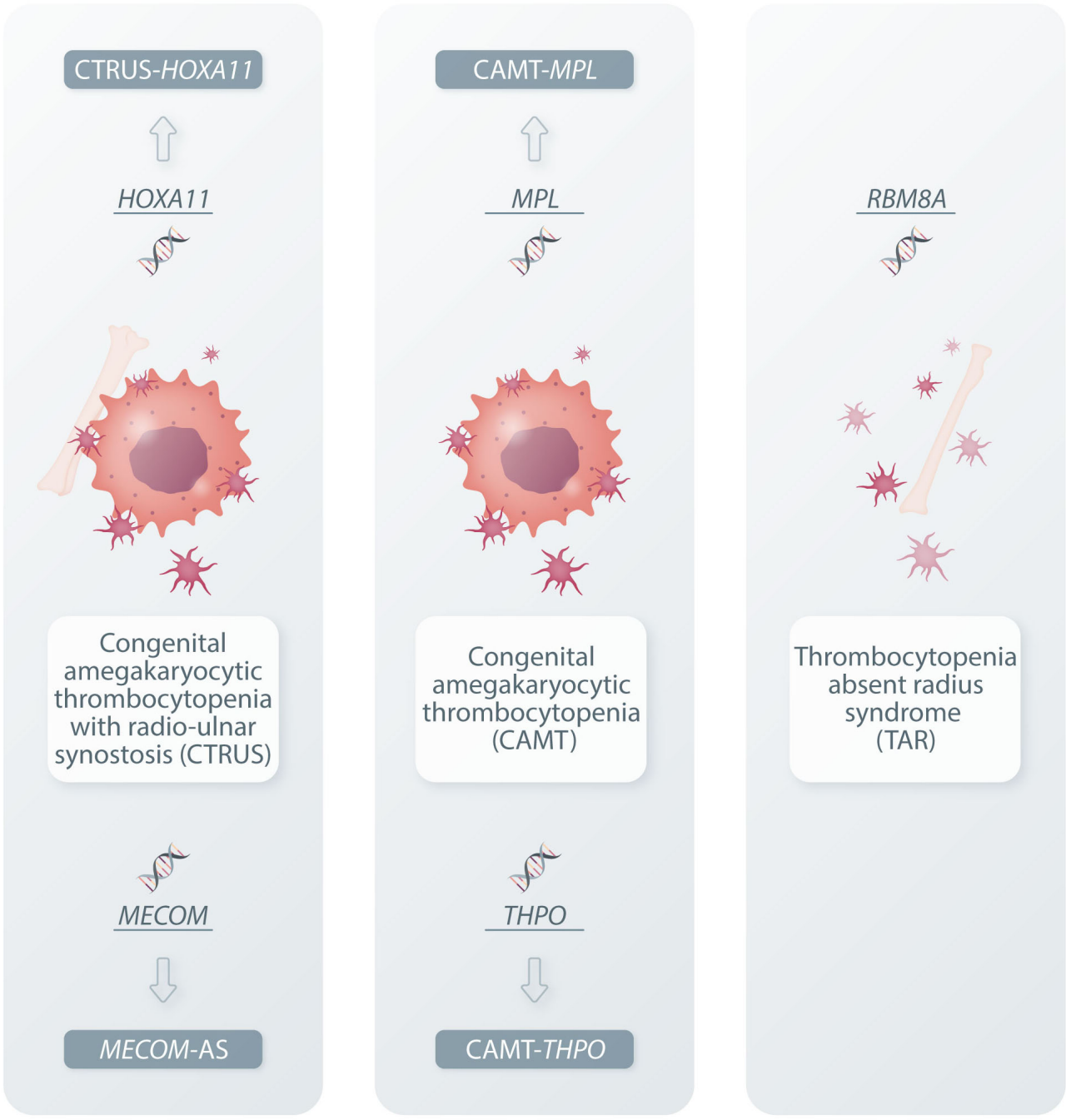

Figure 1. The spectrum of inherited thrombocytopenias with defective bone marrow megakaryocytes. Mutations of five different genes cause congenital amegakaryocytic thrombocytopenia in the context of clinical phenotypes peculiar to each etiopathogenetic mechanism. The only three names in use today for these diseases are therefore unable to properly describe the five diseases, and new names have been proposed that include the defective gene to emphasize that etiological differences result in clinically relevant differences.

to illustrate this matter briefly and comment on the recent proposals for more effective names to be assigned to the inherited thrombocytopenias with reduced bone marrow megakaryocytes.

The first patient with a congenital essential thrombocytopenia was described in 1929 by Greenwald and Sherman.[3] Seventy years later a series of papers[4,5] concluded that many, but not all patients with this clinical picture had biallelic mutations in the gene *MPL*, which encodes the THPO receptor. This form of inherited thrombocytopenia received the name of congenital amegakaryocytic thrombocytopenia (CAMT). Large case series revealed that the prognosis of affected patients is very poor, because all patients are destined to die either from hemorrhage or from the severe bone marrow aplasia that always arises in the first years of life.[2] The only hope of reaching adulthood is offered by hematopoietic stem cell transplantation.

The name CAMT is also used for the recently discovered inherited thrombocytopenia caused by biallelic *THPO* mutations.[6-8] Similarly to patients with CAMT due to *MPL* mutations, subjects with mutated *THPO* also present with CAMT which evolves towards bone marrow aplasia. However, they do not benefit from hematopoietic stem cell transplantation because the scarcity of megakaryocytes does not result from a defect of progenitor cells, but is instead caused by the inability of liver cells to produce THPO (as evidenced by the fact that serum THPO levels are low in this condition whereas they are elevated in all other forms of CAMT). Indeed, the outcome of hematopoietic stem cell transplantation was poor due to failure of engraftment in all patients with *THPO* mutations who underwent this treatment. Instead, and not surprisingly, the THPO-receptor agonists romiplostim or eltrombopag have proven very effective in quickly increasing platelet count and also making pancytopenia disappear in cases in which it had already been established. Another difference that may be relevant for the diagnostic process and genetic counseling is the mode of transmission, in that some subjects with monoallelic *THPO* mutations have mild thrombocytopenia, while those with monoallelic *MPL* mutations always have a normal phenotype. Based on these considerations, Germeshausen and Ballmaier proposed that names of the affected genes are added as suf-

fixes to CAMT to emphasize that CAMT from *MPL* or *THPO* mutations differs in some relevant respects.[2] The authors of the article that prompted this editorial have adhered to this recommendation and use the terms CAMT-*MPL* and CAMT-*THPO* in their paper.

Besides *MPL* and *THPO*, abnormalities in the genes *HOXA11*[9] and *MECOM*[10] can also cause congenital thrombocytopenia due to megakaryocyte shortage and a propensity to bone marrow aplasia, in these cases variably associated with radio-ulnar synostosis and/or other malformations. If patients develop signs of bone marrow failure, there is an indication for hematopoietic stem cell transplantation. Regardless of the affected gene, the name radio-ulnar synostosis with amegakaryocytic thrombocytopenia (RUSAT) or congenital amegakaryocytic thrombocytopenia with radio-ulnar synostosis (CTRUS) has been used for both conditions. The main difference between the disorders caused by *HOXA11* and *MECOM* is that the very few patients with *HOXA11* mutations reported so far all have proximal radio-ulnar synostosis, but only some of them have the hematologic phenotype. In contrast, all subjects with *MECOM* mutations have the hematologic phenotype but some of them do not present radio-ulnar synostosis and are therefore at risk of being misdiagnosed with CAMT-*THPO* or CAMT-*MPL*. Moreover, the spectrum of possible malformations caused by *MECOM* is broader than that caused by *HOXA11*. Based on these differences, the names CTRUS-*HOXA11* and *MECOM*-associated syndrome (*MECOM*-AS) have been proposed by Germeshausen *et al.*[11] Thrombocytopenia-absent radius syndrome (TAR) is a further genetic disorder characterized by congenital thrombocytopenia with reduced bone marrow megakaryocytes, in this case always associated with bilateral radial aplasia and sometimes with other congenital defects. It is caused by compound heterozygosity for a null mutation involving the *RBM8A* gene and one or two low-frequency noncoding single-nucleotide polymorphisms in *RBM8A* on the other allele[12] (Figure 1). In contrast to the disorders with amegakaryocytic thrombocytopenia mentioned above, TAR never progresses to bone marrow failure, but instead tends to improve spontaneously because the platelet count usually begins to rise after the first year of life and sometimes even normalizes. Hematopoietic stem cell transplantation is not therefore indicated and the therapy is supportive in anticipation of the spontaneous improvement of the thrombocytopenia. Of note, one patient with TAR needing surgery had her platelet count normalized by the THPO-receptor agonist romiplostim.[13] Recognizing that a CAMT is due to TAR does therefore have important practical consequences, but fortunately the diagnosis is easy because the association of congenital thrombocytopenia with bilateral radial aplasia is pathognomonic of this condition. The name TAR is therefore appropriate because it well describes this disease with very peculiar characteristics.

The case of CAMT exemplifies well how the advancement of knowledge about hereditary diseases has increased the number of known causative genes and has revealed that what we once considered a single disease actually consists of multiple disorders with clinically relevant differences. Although trying to change the name of long-known diseases risks creating more harm than good, I believe that Germeshausen and Ballmaier's proposal for including the causative gene in the name of some CAMT is to be accepted because it tidies up a complex matter that in the past has been subject to misunderstandings. The observation that the names of the many new forms of inherited thrombocytopenia discovered in recent years make mention of the defective gene testifies that this idea is shared by those who deal with these diseases. The time in which the name of an inherited thrombocytopenia was that of whoever discovered it or was derived from one of the features of the first described patients is ending. It is possible that other diseases identified long ago will have their names changed in the future.

Disclosures

No conflicts of interest to disclose.

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