

## Genetic Forms of Iron Deficiency Anaemia

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Iron deficiency anaemia is the most frequent form of anaemia and is generally acquired. “Low-cost” diet; increased iron needs during childhood, pregnancy, or lactation; bleeding from the gastrointestinal or urogenital tract; and gastric pathology constitute the main settings leading to “classical” iron deficiency anaemia. The clinical observation of unexplained forms of iron deficiency anaemia, together with growing evidence that we are dealing with inherited disorders and advances in knowledge concerning iron metabolism, have led to the description of a new group of diseases in hematology known as genetic forms of iron deficiency anaemia.

Mutations in the gene encoding DMT1, the genetic forms of sideroblastic anaemias (ie, mutations in glutaredoxin 5, aminolevulinic acid synthetase 2, and ABCB7 genes), atransferrinaemia, the deficiency of ceruloplasmin, and the recently described mutations in the matriptase-2 [TMPRSS6] gene comprise this new entity of iron deficiency anaemia.

The main characteristics of families described with iron deficiency anaemia secondary to a mutation in the gene encoding DMT1 are the early appearance of severe microcytic, hypochromic anaemia (usually at birth) and high serum iron and transferrin saturation with low or normal ferritin levels. Because heme iron absorption is not disturbed, in nonvegetarian humans, DMT1 mutations primarily affect iron utilization and not absorption.

The recently described mutation in the glutaredoxin 5 (GLRX5) gene leads to microcytic, hypochromic anaemia with iron overload and the presence of ringed sideroblasts in the bone marrow upon Perl’s staining. This is due to defective heme synthesis secondary to iron regulatory proteins (IRPs) deregulation linked to the decreased production of iron-sulphur by the mutated GLRX5. This mechanism operates at least partially in the other forms of microcytic, congenital, or acquired sideroblastic anaemias as well.

The main characteristics of atransferrinaemia and aceruloplasminaemia are the presence of moderate microcytic-hypochromic anaemia (late onset in the case of aceruloplasminaemia), with low serum iron, liver iron overload, and high ferritin. In ceruloplasmin deficiency, brain damage is found. Because transferrin is missing, there is reduced delivery of iron to bone marrow erythroblasts leading to decreased haemoglobin synthesis. In aceruloplasminaemia, there is a deficiency in ceruloplasmin, a ferroxidase. As a result, ferroportin can not release iron to plasma transferrin, leading to iron deficiency anaemia with concomitant deposition of iron to different organs (liver, pancreas, basal ganglia, etc).

The description by Beutler and colleagues of a transmembrane serine protease product of the TMPRSS6 gene that interferes with hepcidin production led to the discovery of a severe form of iron deficiency anaemia due to mutations in both paternal and maternal TMPRSS6 genes that is refractory to iron treatment (**Iron-Refractory, Iron-Deficiency Anaemia**, or IRIDA syndrome). At least nine families have been described with this syndrome. Affected members suffer from a congenital severe hypochromic, microcytic anaemia with low serum iron and

low transferrin saturation. The most pathognomonic finding is high hepcidin levels in serum and urine of these patients, despite severe iron deficiency. There is no response to oral iron and slight response to intravenous iron administration.

Although these genetic forms of iron deficiency anaemia are rare, haematologists should be aware of their existence when investigating microcytosis of unknown origin, in cases of peculiar forms of iron deficiency anaemia refractory to classical oral or intravenous iron administration, or forms combining iron deficiency anaemia with iron overload of different parenchyma organs. These forms of genetic iron deficiency anaemia are excellent models to further increase our knowledge concerning iron metabolism and erythropoiesis.

### **Suggested Readings**

Andrews NC. Forging a field: the golden age of iron biology. *Blood*. 2008;112:219-230.

Beaumont C, Delaunay J, Hetet G, et al. Two new human *DMT1* gene mutations in a patient with microcytic anaemia, low ferritinemia, and liver iron overload. *Blood*. 2006;107:4168-4170.

Beutler E, Gelbart T, Lee P, et al. Molecular characterization of a case of atransferrinemia. *Blood*. 2000;96:4071-4074.

Camaschella C, Campanella A, De Falco L, et al. The human counterpart of zebrafish *shiraz* shows sideroblastic-like microcytic anaemia and iron overload. *Blood*. 2007;110:1353-1358.

Di Raimondo D, Pinto A, Tuttolomondo A, et al. Aceruloplasminemia: a case report. *Intern Emerg Med*. 2008 Apr 12 [Epub ahead of print] PMID 18408989.

Du X, She E, Gelbart T, et al. The serine protease *TMPRSS6* is required to sense iron deficiency. *Science*. 2008;320:1088-1092.

Finberg KE, Heeney MM, Campagna DR, et al. Mutations in *TMPRSS6* cause iron-refractory iron deficiency anaemia (IRIDA). *Nat Genet*. 2008;40:569-571.

Folgueras AR, Martin de Lara F, Pendas AM, et al. The membrane-bound serine protease matrilysin-2 (*Tmprss6*) is an essential regulator of iron homeostasis. *Blood*. 2008 Jun 3. [Epub ahead of print] PMID: 18523150.

Guillem F, Lawson S, Kannengiesser C, et al. Two nonsense mutations in the *TMPRSS6* gene in a patient with microcytic anaemia and iron deficiency. *Blood*. 2008 Jul 2. [Epub ahead of print] PMID: 18596229.

Harris LZ, Takahashi Y, Miyajima H, et al. Aceruloplasminemia: molecular characterization of this disorder of iron metabolism. *Proc Natl Acad Sci U S A*. 1995;92:2539-2543.

Iolascon A, d'Apolito M, Servedio V, et al. Microcytic anaemia and hepatic iron in a child with compound heterozygous mutations in DMT1. *Blood*. 2006;107:349-354.

Melis MA, Cau M, Congiu R, et al. A mutation in the *TMPRSS6* gene, encoding a transmembrane serine protease that suppresses hepcidin production, in familial iron deficiency anaemia refractory to oral iron. *Haematologica*. 2008 July 4. [Epub ahead of print] PMID: 18603562.

Mims MP, Guan Y, Pospisilova D, et al. Identification of a human mutation in a patient with microcytic anaemia and iron overload. *Blood*. 2005;105:1337-1342.

Miyajima H. Aceruloplasminemia, an iron metabolic disorder. *Neuropathology*. 2003;23:345-350.

Pospisilova D, Mims MP, Nemeth E, et al. DMT1 mutation: response of anaemia to darbepoetin administration and implications for iron homeostasis. *Blood*. 2006;108:404-405.

Priwitzerova M, Pospisilova D, Prchal JT, et al. Severe hypochromic microcytic anaemia caused by a congenital defect of the iron transport pathway in erythroid cells. *Blood*. 2004;103:3991-3992.

Ramsay AJ, Reid JC, Velasco G, et al. The type II transmembrane serine protease Matriptase-2 – identification, structural features, enzymology, expression pattern and potential roles. *Front Biosci*. 2008;13:569-579.