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Sideroblastic anemias

The sideroblastic anemias are a heterogeneous group of inherited and acquired disorders characterized by anemia of varying severity and the presence of ringed sideroblasts in the bone marrow.[1] These latter are immature red cells with iron-loaded mitochondria visualized by Prussian blue staining as a perinuclear ring of blue granules. The most common of the inherited forms is X-linked sideroblastic anemia (XLSA, OMIM 301300), which is caused by mutations in the erythroid-specific ALA synthase gene (*ALAS2*). The most common acquired sideroblastic anemia is a myelodysplastic syndrome (MDS) defined as refractory anemia with ringed sideroblasts (RARS).[2] The nature of the iron deposited in iron-loaded mitochondria of ring sideroblasts has been clarified in the last few years. Mitochondrial ferritin is encoded by an intronless gene on chromosome 5q23.1.3 Most of the iron deposited in perinuclear mitochondria of ring sideroblasts is present in the form of mitochondrial ferritin.[4]

In patients with XLSA, defective ALAS2 enzyme activity leads to insufficient protoporphyrin IX synthesis, mitochondrial iron accumulation, and apoptosis of red cell precursors.[5] Overexpression of mitochondrial ferritin likely results from defective iron utilization and partly protects mitochondria from iron-induced damage. However, the expanded erythropoiesis suppresses hepcidin production leading to excessive iron absorption and reticuloendothelial iron release. Almost, but not all XLSA patients are hemizygous males. Most heterozygous females have only minor red cell abnormalities (in particular, an increased red-cell distribution width, or RDW) but no clinical signs, since immature red cells expressing the normal *ALAS2* are sufficient to sustain a normal level of red cell production. Affected males may present in the first two decades of life with symptoms of anemia, or later with either anemia or manifestations of parenchymal iron overload. Symptoms of hemochromatosis can be the first manifestation of disease in middle-aged men, but occasional patients may present late in life with symptoms of anemia.[6,7] Phenotypic expression of XLSA varies considerably in males and is partly related to the type of *ALAS2* mutation, but phenotypic manifestations can also be absent in a few individuals.[8] Modifying genes such as those for genetic hemochromatosis may significantly exacerbate XLSA in

hemizygous males, and coinheritance of the *HFE* C282Y mutation worsens parenchymal iron overload.[9] Distinctive features of XLSA are microcytic anemia with hypochromic red cells, increased RDW, and laboratory evidence of parenchymal iron overload. Bone marrow aspiration and Perls staining are required to demonstrate ring sideroblasts, while the genetic nature of the disease is established through mutation detection. Mutation detection can be achieved by studying either genomic DNA or cDNA derived from the RNA of reticulocytes. Any subject who is suspected as having XLSA or belongs to a family with XLSA should have, at least once, DNA or reticulocyte RNA tested for *ALAS2* mutations, irrespective of sex and age. DNA-based diagnosis facilitates testing of other family members. Most patients with XLSA are to some extent responsive to pyridoxine; iron overload may suppress this responsiveness, and its reversal by phlebotomy generally results in higher hemoglobin levels during pyridoxine supplementation.

X-linked sideroblastic anemia associated with cerebellar ataxia (XLSA/A; OMIM 301310) is characterized by neurological manifestations early in infancy with impaired gross motor and cognitive development.[10] Cerebellar ataxia is accompanied by selective cerebellar hypoplasia on computed tomography and does not worsen with age. The severity of anemia varies considerably among the few families reported. XLSA/A is caused by missense mutations in the human *ABC7* gene, which encodes a *half-type* ATP binding cassette (ABC) transporter. This X-linked sideroblastic anemia differs clinically from the classic XLSA (OMIM 301300), which does not have neurological manifestations, is associated with iron overload, and is generally at least partially responsive to pyridoxine. In contrast to the anemia, cerebellar ataxia is always clinically relevant, so that *ABC7* mutations should be considered in any unexplained X-linked ataxias, even in the absence of hematological abnormalities.

The *GLRX5* gene encodes glutaredoxin 5 (GRLX5), which is essential for the synthesis of Fe/S clusters. The first case of GLRX5 deficiency has been recently reported in a middle-aged anemic male with iron overload and a low number of ringed sideroblasts.[11] The patient had a homozygous (c.294A>G) mutation that interferes with intron 1 splicing and drastically reduces *GLRX5* RNA. This case is the human counterpart of the zebrafish mutant shiraz,[12] which has severe anemia and is embryonically lethal because of *GRLX5* deletion, insufficient biogenesis of mitochondrial iron-sulfur (Fe/S) clusters, and deregulated iron-regulatory protein 1 (IRP1) activity.

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