Title: X-Linked Sideroblastic Anemia and Ataxia *GeneReview* – Additional information on pathogenesis

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Additional Information on Pathogenesis

Aconitase is a cytosolic Fe-S protein that is converted in iron regulatory protein 1 (IRP1) when the cytosolic Fe-S cluster level is low. IRP1 regulates posttranscriptionally several proteins involved in iron metabolism such as erythroid 5-aminolevulinate synthase (ALAS2, this enzyme catalyzes the first step of heme biosynthesis), divalent metal transporter (DMT1), L and H-ferritin (FTL and FTH), and transferrin receptor (TFRC1). IRP1 binds to iron-responsive elements (RNA stem-loop elements) found in the target transcripts and either (1) activates translation by repressing mRNA degradation when the iron-responsive element (IRE) is located at the 3'UTR region (*TFRC1*) or (2) represses translation when the IRE is located at the 5'UTR (*ALAS2, FTL, FTH*).

IRP2, a functional ortholog of IRP1, binds to the same transcripts. Despite their sequence homology (70%), the mechanism by which IRP1 and IRP2 are inactivated is different. Indeed, IRP2 degradation in iron-repleted cells is mediated by the hemerythrin-like domain of F-box and leucine-rich repeat protein 5 (FBXL5). FBXL5 senses iron availability and promotes IRP2 ubiquitination and degradation by the proteasome [Ruiz et al 2013]. Both IRP1 and IRP2 have a key role in the control of iron metabolism as illustrated by the embryonic lethality of the deletion of both IRPs. IRP2 knock-out mice develop anemia and neurodegeneration [Smith et al 2006].

The pathophysiological mechanism underlying anemia in XLSA/A was first attributed to ALAS2 decrease upon IRP1 repression of *ALAS2* mRNA translation. Thus, ABCB7 deficiency may decrease Fe-S cluster level in the cytosol; resulting in less IRP1 conversion to aconitase and repression of ALAS2 translation leading to a decrease of heme synthesis [Bekri et al 2000, Rouault & Tong 2009, Ye & Rouault 2010a]. However, in contrast to the other congenital sideroblastic anemias, the total erythrocyte protoporphyrin (TEP) concentration and the zinc erythrocyte protoporphyrin (ZnEP) concentration are raised in XLSA/A. Most of the accumulated porphyrin is ZnEP [Bekri et al 2000, Maguire et al 2001, Ye & Rouault 2010b]. The elevation of protoporphyrins (TEP and ZnEP) suggests that the first steps of heme synthesis are not impaired. Indeed, the putative decrease of ALAS2 upon the IRP1-mediated repression of its translation seems inconsistent with the finding of increased protoporphyrins in patients [Camaschella 2008]. Thus, the blockade seems to concern iron incorporation into protoporphyrin.

Ferrochelatase, another Fe-S protein important in heme biosynthesis, is unstable without its [2Fe-2S] cluster. The last step in the heme synthesis pathway is the insertion of a ferrous iron into protoporphyrin IX by ferrochelatase to result in heme formation (Figure 2) [Ye & Rouault 2010a]. It was first thought that ferrochelatase activity is

decreased since Taketani et al reported that ABCB7 binds ferrochelatase and enhances its activity [Taketani et al 2003]; however, ferrochelatase activity is normal in the mouse model [Pondarre et al 2007]. Moreover, since ferrochelatase is required for the formation of ZnEP, the increase of ZnEP indicates that ferrochelatase is functional [Pondarre al 2007, Ye & Rouault 2010a]. Alternatively, one can hypothesize that mitochondrial iron is not in the appropriate form to be incorporated and that the accumulated iron is likely to be in the ferric form that is not incorporated during heme synthesis. Thus, this ineffective erythropoiesis may be caused by mitochondrial iron toxicity [Cavadini et al 2007]. Cellular models indicate that ABCB7 deficiency causes a strong deregulation of mitochondrial iron homeostasis, and that excess iron is not easily available to ferrochelatase for heme production, which may explain the increased formation of ZnEP [Camaschella 2008, Ye & Rouault 2010b].

Like the other sideroblastic anemias ABCB7 deficiency led to mitochondrial iron overload, but in this case, there is no systemic iron overload. This systemic overload is likely to be due to IRP2 inhibition. It was proposed that in XLSA/A the heme decrease do not reach the threshold to exert the IRP2 inhibition [Camaschella 2008]. Ineffective erythropoiesis causes growth differentiation factor 15 (GDF15) surexpression; this hepcidin suppressor factor lead to hepcidin level reduction and thus subsequently to iron overload [Tanno et al 2010]. GDF15 level is increased [Ramirez et al 2009] and hepcidin level is low in refractory anemia with ringed sideroblasts [Santini et al 2011, Gu et al 2013, Zipperer et al 2013]. Of note, GDF15 and hepcidin levels were not evaluated in XLSA/A.

References

Camaschella C. Recent advances in the understanding of inherited sideroblastic anaemia. Br J Haematol. 2008;143:27-38.

Cavadini P, Biasiotto G, Poli M, Levi S, Verardi R, Zanella I, Derosas M, Ingrassia R, Corrado M, Arosio P. RNA silencing of the mitochondrial ABCB7 transporter in HeLa cells causes an iron-deficient phenotype with mitochondrial iron overload. Blood. 2007;109:3552-9.

Gu S, Song X, Zhao Y, Guo J, Fei C, Xu F, Wu L, Zhang X, Zhao J, Chang C, Li X. The evaluation of iron overload through hepcidin level and its related factors in myelodysplastic syndromes. Hematology. 2013;18:286-94.

Pondarré C, Campagna DR, Antiochos B, Sikorski L, Mulhern H, Fleming MD. Abcb7, the gene responsible for X-linked sideroblastic anemia with ataxia, is essential for hematopoiesis. Blood. 2007;109:3567-9.

Ramirez JM, Schaad O, Durual S, Cossali D, Docquier M, Beris P, Descombes P, Matthes T. Growth differentiation factor 15 production is necessary for normal erythroid differentiation and is increased in refractory anaemia with ring-sideroblasts. Br J Haematol. 2009;144:251-62.

Rouault TA, Tong WH. Tangled up in red: intertwining of the heme and iron-sulfur cluster biogenesis pathways. Cell Metab. 2009;10:80-1.

Ruiz JC, Walker SD, Anderson SA, Eisenstein RS, Bruick RK. F-box and leucine-rich repeat protein 5 (FBXL5) is required for maintenance of cellular and systemic iron homeostasis. J Biol Chem. 2013;288:552-60.

Santini V, Girelli D, Sanna A, Martinelli N, Duca L, Campostrini N, Cortelezzi A, Corbella M, Bosi A, Reda G, Olivieri O, Cappellini MD. Hepcidin levels and their determinants in different types of myelodysplastic syndromes. PLoS One. 2011;6:e23109.

Smith SR, Ghosh MC, Ollivierre-Wilson H, Hang Tong W, Rouault TA. Complete loss of iron regulatory proteins 1 and 2 prevents viability of murine zygotes beyond the blastocyst stage of embryonic development. Blood Cells Mol Dis. 2006;36:283-7.

Taketani S, Kakimoto K, Ueta H, Masaki R, Furukawa T. Involvement of ABC7 in the biosynthesis of heme in erythroid cells: interaction of ABC7 with ferrochelatase. Blood. 2003;101:3274-80.

Tanno T, Noel P, Miller JL. Growth differentiation factor 15 in erythroid health and disease. Curr Opin Hematol. 2010;17:184-90.

Zipperer E, Post JG, Herkert M, Kündgen A, Fox F, Haas R, Gattermann N, Germing U. Serum hepcidin measured with an improved ELISA correlates with parameters of iron metabolism in patients with myelodysplastic syndrome. Ann Hematol. 2013;92:1617-23.

Ye H, Rouault TA. Erythropoiesis and iron sulfur cluster biogenesis. Adv Hematol. 2010a;2010.

Ye H, Rouault TA. Human iron-sulfur cluster assembly, cellular iron homeostasis, and disease. Biochemistry. 2010b;49:4945-56.