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

Authors: Bekri S, D'Hooghe M, Vermeersch P

Date: March 2014

Note: The following information is provided by the authors listed above and has not been reviewed by *GeneReviews* staff.

Additional Information on Genetics of XLSA/A

It is worth noting that the identified variations are missense mutations with intermediate severity. Not all missense mutations are deleterious; some changes can have no effect. Because of the ambiguity of missense mutations, accurate tools that predict the effect of a given point mutation on protein function are mandatory. The use of prediction software is needed to conclude that a mutation is deleterious. However, there is no classification of these algorithms; thus, it is appropriate to use more than one algorithm [Hicks et al 2011]. The three algorithms used (SIFT, MutationTaster, Polyphen-2) enabled us to conclude that these variants alter the protein function. Another hint going along with the pathogenic effect of these mutations is their low frequency or absence in the general population. We checked for the presence of those variants in the Exome Variant Server (EVS), none of these mutations were found among at least 10.000 analyzed chromosomes (Table 4).

Table 4. Point Mutations Identified in *ABCB7*

AA Position	cDNA NM_004299.3	Protein	Prediction Algorithms			Variant Frequency	Reference
			SIFT	MutationTaster	Polyphen-2	EVS	
209	c.627A>T	p.Glu209Asp	Deleterious	Disease causing	Probably damaging	0/10.000	D'Hooghe et al [2012]
401	c.1203T>G	p.Ile401Met	Deleterious	Disease causing	Probably damaging	0/10.000	Allikmets et al [1999]
412	c.1234G>C	p.Val412Leu	Deleterious	Disease causing	Probably damaging	0/10.000	Maguire et al [2001]
434	c.1300G>A	p.Glu434Lys	Deleterious	Disease causing	Probably damaging	0/10.000	Bekri et al [2000]

SIFT: sift.jcvi.org/www/SIFT_aligned_seqs_submit.html

MutationTaster: doro.charite.de/MutationTaster/index.html

Polyphen-2: genetics.bwh.harvard.edu/pph2/

Exome Variant Server (EVS): evs.gs.washington.edu/EVS/

Functional studies of the c.1300G>A mutation, using yeast phenotypic complementation assays permit detection of partial loss of function alleles. Beside, no severe mutations (nonsense, splice-site mutation, gross deletion or insertion…) have been identified. Thus, mild mutations with partial loss of function severely affect the normal well-being of a human cell. Indeed, severe mutation leading to a significant loss of protein function must be lethal as illustrated by knock out mouse model [Pondarre et al 2006].

References

Allikmets R, Raskind WH, Hutchinson A, Schueck ND, Dean M, Koeller DM. Mutation of a putative mitochondrial iron transporter gene (ABC7) in X-linked sideroblastic anemia and ataxia (XLSA/A). Hum Mol Genet. 1999;8:743-9.

Bekri S, Kispal G, Lange H, Fitzsimons E, Tolmie J, Lill R, Bishop DF. Human ABC7 transporter: gene structure and mutation causing X-linked sideroblastic anemia with ataxia with disruption of cytosolic iron-sulfur protein maturation. Blood. 2000;96:3256-64.

D'Hooghe M, Selleslag D, Mortier G, Van Coster R, Vermeersch P, Billiet J, Bekri S. X-linked sideroblastic anemia and ataxia: a new family with identification of a fourth ABCB7 gene mutation. Eur J Paediatr Neurol. 2012;16:730-5.

Hicks S, Wheeler DA, Plon SE, Kimmel M. Prediction of missense mutation functionality depends on both the algorithm and sequence alignment employed. Hum Mutat. 2011;32:661-8.

Maguire A, Hellier K, Hammans S, May A. X-linked cerebellar ataxia and sideroblastic anaemia associated with a missense mutation in the ABC7 gene predicting V411L. Br J Haematol. 2001;115:910-7.

Pondarre C, Antiochos BB, Campagna DR, Clarke SL, Greer EL, Deck KM, McDonald A, Han AP, Medlock A, Kutok JL, Anderson SA, Eisenstein RS, Fleming MD. The mitochondrial ATP-binding cassette transporter Abcb7 is essential in mice and participates in cytosolic iron-sulphur cluster biogenesis. Hum Mol Genet. 2006;15:953-64.