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X-Linked Sideroblastic Anemia and Ataxia – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

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Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical characteristics

X-linked sideroblastic anemia and ataxia (XLSA/A) is characterized by moderate anemia and early-onset spinocerebellar syndrome in males, manifest primarily as delayed walking, ataxia evident in early childhood, dysmetria, and dysdiadochokinesis. When present the intention tremor is mild and the dysarthria is mild to moderately severe. The ataxia has been described to be either non-progressive or slowly progressive. Upper motor neuron (UMN) signs in the legs, manifest by brisk deep tendon reflexes, unsustained ankle clonus, and equivocal or extensor plantar responses, are present in some males. Need for crutches or a wheelchair has been reported. Strabismus is seen in some males. Nystagmus and hypometric saccades may occur. Mild learning disability and depression are seen. The moderate hypochromic and microcytic anemia does not cause symptoms. Carrier (heterozygous) females have a normal neurologic examination and may show mild hematologic abnormalities.

Diagnosis/testing

The diagnosis of XLSA/A is suspected in males with characteristic neurologic findings and the presence of moderate hypochromic and microcytic anemia, elevated whole blood total erythrocyte protoporphyrin (TEP) and zinc erythrocyte protoporphyrin (ZnEP), and ring sideroblasts on bone marrow examination. Pappenheimer bodies are seen in peripheral blood smear. The diagnosis is confirmed in a male by identification of a hemizygous pathogenic variant in *ABCB7*.

Females have a normal neurologic examination and may have a dimorphic blood smear with both hypochromic microcytic red blood cells and normal red blood cells; they may have ring sideroblasts on bone marrow examination.

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Management

Treatment of manifestations: Males with XLSA/A benefit from early physical therapy to facilitate acquisition of gross motor skills. Adaptive devices such as ankle fixation orthoses and walkers may be needed. Weighted eating utensils may help promote independent skills in childhood. Speech therapy may improve intelligibility problems from dysarthria. Difficulty with handwriting may be managed with computers for word processing.

Genetic counseling

XLSA/A is inherited in an X-linked manner. Heterozygous females have a 50% chance of transmitting the pathogenic variant in each pregnancy. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be carriers and will usually not be affected. Males with XLSA/A will pass the pathogenic variant to all of their daughters and none of their sons. Carrier testing of at-risk female relatives and prenatal testing for a pregnancy at increased risk are possible if the *ABCB7* pathogenic variant in the family is known.

Diagnosis

Males with X-linked sideroblastic anemia and ataxia (XLSA/A) exhibit the following signs:

- Ataxia and incoordination. Note: Pagon et al [1985] described non-progressive ataxia; Hellier et al [2001] described ataxia that was possibly slowly progressive.
- Upper motor neuron (UMN) signs (i.e., brisk deep tendon reflexes, unsustained ankle clonus, and equivocal or extensor plantar responses) in the legs (present in some males)
- Mild asymptomatic hypochromic, microcytic anemia
  - Hematocrit ranges from 26% to 35%.
  - Mean corpuscular volume (MCV fl) is low (Table 1).
  - Peripheral blood smears show in affected males: (1) microcytic and hypochromic red cells with marked poikilocytosis, reticulocytosis, and heavy stippling; (2) Pappenheimer bodies (iron inclusions in more mature erythrocytes). These siderocytes are present in the peripheral blood of affected males and in some heterozygous females.
  - Bone marrow examination shows increased iron stores with ring sideroblasts (Figure 1). Note: Serum iron parameters are normal.
  - High levels of whole blood total erythrocyte protoporphyrin (TEP) and zinc erythrocyte protoporphyrin (ZnEP) further support the diagnosis [Pagon et al 1985, Bekri et al 2000, Hellier et al 2001, Maguire et al 2001, D'Hooghe et al 2012].

    Note: (1) Whole blood TEP may be used as a screening tool [Piomelli et al 1975, Hart & Piomelli 1981]. (2) If no *ABCB7* pathogenic variant is identified (see **The diagnosis of XLSA/A** below), the presence of characteristic bone marrow changes and high levels of TEP identified in at least one affected family member with a family history consistent with X-linked inheritance strongly suggests the diagnosis of XLSA/A.

Table 1. Mean Corpuscular Volume (MCV fl) in XLSA/A

Group	Mean Corpuscular Volume (MCV fl)
Normal male	89.1 ± 5.01

Table 1. continued from previous page.

Group	Mean Corpuscular Volume (MCV fl)
Normal female	87.6 ± 5.5
Affected male	58 to 68
Carrier female	83 to 90

Pagon et al [1985] (4 affected males and 3 obligate carrier females)

Heterozygous females have a normal neurologic examination and may show mild hematologic abnormalities, including Pappenheimer bodies in peripheral blood smear [Hellier et al 2001] and ringed sideroblasts in bone marrow aspirate [Pagon et al 1985]. Some heterozygous females also have increased levels of whole blood TEP and ZnEP [Pagon et al 1985].

The diagnosis of XLSA/A is confirmed in a male by presence of a hemizygous pathogenic variant in *ABCB7*.

- **One genetic testing strategy** is molecular genetic testing of *ABCB7,* the only gene in which pathogenic variants are known to cause XLSA/A. Sequence analysis should be performed first; if no pathogenic variant is identified, deletion/duplication analysis may be considered.
- **An alternative genetic testing strategy** is use of a multigene panel that includes *ABCB7* and other genes of interest (see Differential Diagnosis). Note: The genes included and the methods used in multigene panels vary by laboratory and over time.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 2. Molecular Genetic Testing Used in X-Linked Sideroblastic Anemia and Ataxia

Gene [1]	Method	Proportion of Male Probands with a Pathogenic Variant Detectable by Method
ABCB7	Sequence analysis [2, 3]	4/4 families tested [4]
	Deletion/duplication analysis [5]	Unknown, none reported [6]

1. See Table A. Genes and Databases for chromosome locus and protein. See Molecular Genetics for information on allelic variants.
2. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
3. Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation may require additional testing by deletion/duplication analysis.
4. Allikmets et al [1999], Bekri et al [2000], Hellier et al [2001], Maguire et al [2001], D'Hooghe et al [2012]
5. Testing that identifies exon or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
6. No deletions/duplications of *ABCB7* have been reported to cause XLSA/A.

Clinical Characteristics

Clinical Description

To date, four unrelated families with X-linked sideroblastic anemia and ataxia (XLSA/A) have been reported [Allikmets et al 1999, Bekri et al 2000, Hellier et al 2001, Maguire et al 2001, D'Hooghe et al 2012].

Pagon et al [1985] reported two families with a non-progressive spinocerebellar syndrome and sideroblastic anemia, both segregating in an X-linked recessive mode of inheritance. Four males in two generations and a fifth

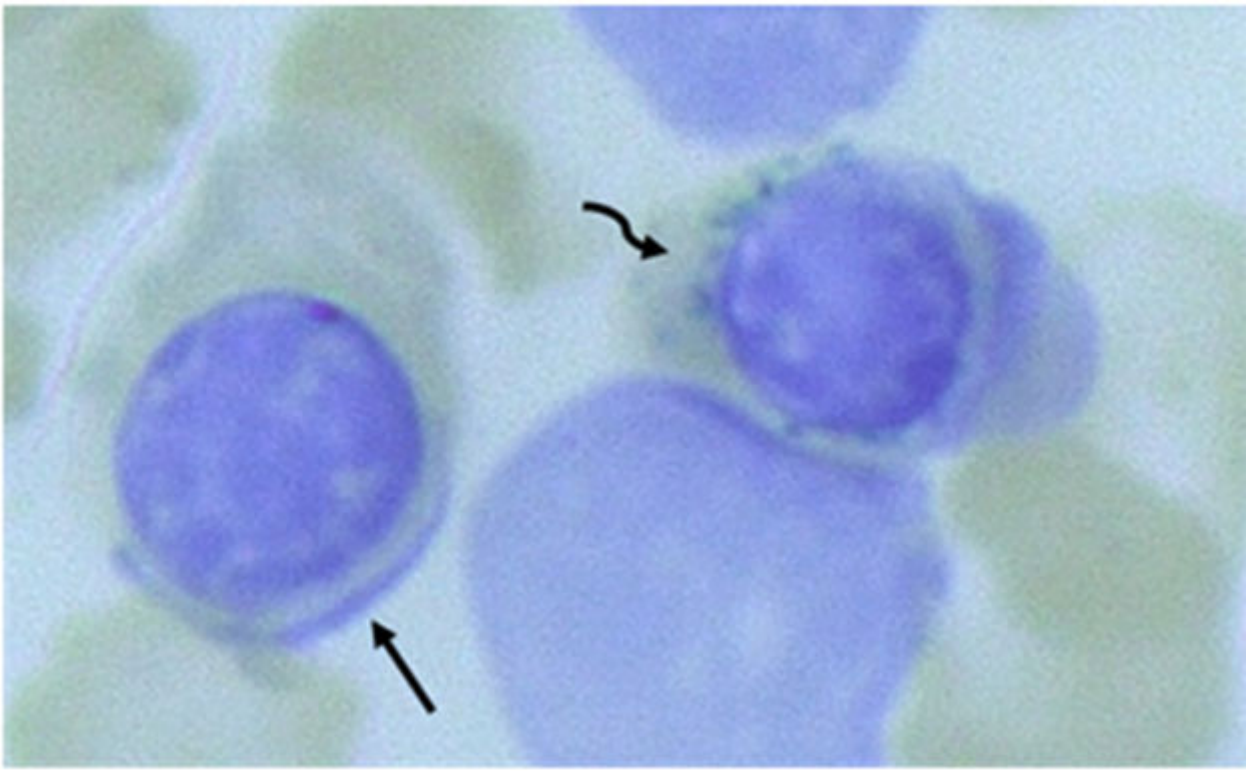

Figure 1. Ringed sideroblast

Prussian blue staining of the bone marrow aspirate (x1000) showing a normal erythroid precursor (straight arrow) and a ringed sideroblast containing many iron granules around the nucleus (curved arrow).

From D'Hooghe et al [2012] with permission

male from an unrelated family were affected. Bekri et al [2000] reported two affected brothers with XLSA/A. Maguire et al [2001] reported another family with two affected brothers and two affected maternal uncles. D'Hooghe et al [2012] reported a boy with XLSA/A.

Ataxia/neurologic findings. Males have an early-onset spinocerebellar syndrome manifesting primarily as delayed walking, ataxia evident from early childhood, dysmetria, and dysdiadochokinesis. When present, intention tremor is mild and dysarthria is mild to moderately severe.

In some, but not all, affected members of one family, the ataxia appeared to improve with time, such that truncal titubation decreased and walking became progressively easier [Pagon et al 1985]. However, in older patients slow deterioration of walking can be seen in the fifth or sixth decade [Pagon et al 1985, Bekri et al 2000, Hellier et al 2001].

Need for crutches and/or a wheel chair have been reported.

Upper motor neuron (UMN) signs in the legs, manifest by brisk deep tendon reflexes, unsustained ankle clonus, and equivocal or extensor plantar responses are present in some males.

Strabismus is seen in some males. Extraocular movements are normal; however, nystagmus and hypometric saccades may occur.

Intellectual abilities are generally within the normal range. Mild learning disability and depression have been seen [Pagon & Bird, personal communication] and one person was reported to have "schizophrenia" [Hellier et al 2001].

Pes cavus, scoliosis, and muscle wasting are not present.

Impairment of visual acuity either from optic atrophy or retinal dystrophy is not seen.

In most cases brain MRI shows cerebellar atrophy/hypoplasia [Raskind et al 1991].

Anemia. The anemia is mild and does not cause symptoms.

Iron storage. Despite the finding of increased iron stores and ring sideroblasts on bone marrow examination, systemic iron overload has not been described. Serum iron studies including serum concentration of iron, total iron binding capacity (TIBC), per cent TIBC saturation, and serum concentration of ferritin were normal in the families reported by Pagon et al [1985] and Hellier et al [2001].

Heterozygotes. Carrier females have a normal neurologic examination.

Genotype-Phenotype Correlations

No genotype-phenotype correlations are known.

Prevalence

Four families and one male who was a simplex case (i.e., a single occurrence in a family) have been reported to date [Pagon et al 1985, Bekri et al 2000, Hellier et al 2001, D'Hooghe et al 2012]. The prevalence of the disorder is probably underestimated because of failure to recognize the mild anemia in males with the characteristic ataxia.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ABCB7*.

In investigations of individuals with refractory anemia with ring sideroblasts (RARS), an acquired myelodysplastic syndrome (MDS) characterized by excess iron accumulation in the mitochondria of erythroblasts, Boultwood et al [2008] identified a strong relationship between an increasing percentage of bone marrow ring sideroblasts and decreasing *ABCB7* expression levels, suggesting that *ABCB7* is a candidate gene for RARS. Pathogenic variants in *SF3B1*, a component of the RNA splicing machinery, were associated with a majority of RARS [Yoshida et al 2011]. Nikpour et al [2013] showed that *ABCB7* expression is downregulated when *SF3B1* is mutated. Moreover, ABCB7 downregulation reduces erythroid differentiation, growth, and colony formation of K562 cells [Nikpour et al 2013].

Differential Diagnosis

Sideroblastic anemia. The sideroblastic anemias are a heterogeneous group of acquired and heritable anemias characterized by ringed sideroblasts (erythroid precursors - present in the bone marrow - that have pathologic iron overload in the mitochondria); the perinuclear location of mitochondria leads to the characteristic ringed appearance [Camaschella 2008, Bergmann et al 2010]. Iron inclusions, called Pappenheimer bodies, may also be observed in more mature erythrocytes [Sears & Udden 2004, Camaschella 2008] (Figure 1).

The most common congenital sideroblastic anemia is X-linked sideroblastic anemia (XLSA) caused by mutation of *ALAS2*. XLSA is characterized by hepatic and systemic iron overload but not ataxia (as expression of *ALAS2* is confined to erythroid tissues) [Napier et al 2005].

Other causes of congenital sideroblastic anemia include mutation of genes that encode proteins affecting mitochondrial metabolism [Bergmann et al 2010, Fujiwara & Harigae 2013] and/or affect iron-sulfur (Fe-S) cluster protein biosynthesis, assembly, or function. Fe-S proteins, which are essential for fundamental metabolic

processes such as respiration and gene expression, are synthesized in the mitochondria and are either associated with mitochondrial apoprotein to form mitochondrial Fe/S proteins or exported to the cytosol (via the ABCB7 transporter) to assist in the formation of cytosolic and nuclear Fe-S proteins [Sheftel et al 2010]. These genes include the following:

- *SLC25A38* (encoding an erythroid specific mitochondrial transporter) [Guernsey et al 2009]
- *SLC19A2* (encoding a high-affinity thiamine transporter)
- *PUS1* (RNA-modifying enzyme pseudouridine synthase 1) [Bykhovskaya et al 2004]
- *ABCB7* (encoding mitochondrial ATP-binding cassette transporter), the cause of XLSA/A
- *GLRX5* (encoding monothiol glutaredoxin 5) [Camaschella et al 2007], associated with a Fe-S cluster biosynthetic defect (the assembly of mitochondrial Fe/S proteins). The deregulation of mitochondrial iron metabolism results in sideroblastic anemia.
- *YARS2* (mitochondrial tyrosyl-tRNA synthase) [Riley et al 2010]
- Mitochondrial DNA deletions, duplications and rearrangements (Pearson marrow-pancreas syndrome) [Fleming 2002]

Another ataxia linked to Fe-S cluster protein is Friedreich ataxia (FRDA), caused by mutation of *FXN*, which encodes the mitochondrial protein frataxin whose main role is to supply iron in a bioavailable form for mitochondrial Fe-S cluster synthesis (Figure 2) [Ye & Rouault 2010b]. In persons with FRDA excess iron accumulation is observed in mitochondria of cardiac myocytes and neurons [Rouault & Tong 2008, Ye & Rouault 2010b]; however, persons with FRDA do not demonstrate significant anemia, suggesting either that frataxin is not essential for heme synthesis and erythropoiesis or that frataxin deficiency does not compromise erythropoietic tissues [Stemmler et al 2010, Ye & Rouault 2010a].

Of note, in murine cultured fibroblasts with decreased levels of frataxin, some Fe-S cluster proteins are deficient, iron accumulates in mitochondria, and oxidant sensitivity is observed as in the human disease [Calmels et al 2009]. The causal links among these effects are not well defined [Stemmler et al 2010].

Ataxia. The diagnostic approach to the numerous heritable ataxias can be quite challenging. Some hereditary ataxias typically present before age three years, including ataxia-telangiectasia, infantile-onset spinocerebellar ataxia, X-linked sideroblastic anemia with ataxia (XLSA/A), congenital disorders of glycosylation, and cerebellar malformations (e.g., Dandy-Walker malformation) [Bernard & Shevell 2008].

X-linked spinocerebellar ataxia has been reported, but is rare (see Hereditary Ataxia Overview). None has been associated with anemia. Mutation of *ABCB7* should be considered in any unexplained X-linked spinocerebellar ataxia, even in the absence of clear hematologic changes.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with sideroblastic anemia and ataxia (XLSA/A), the following evaluations are recommended:

- Neurologic examination
- Brain CT or MRI
- Psychological testing if indicated
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

There is no effective treatment for XLSA/A.

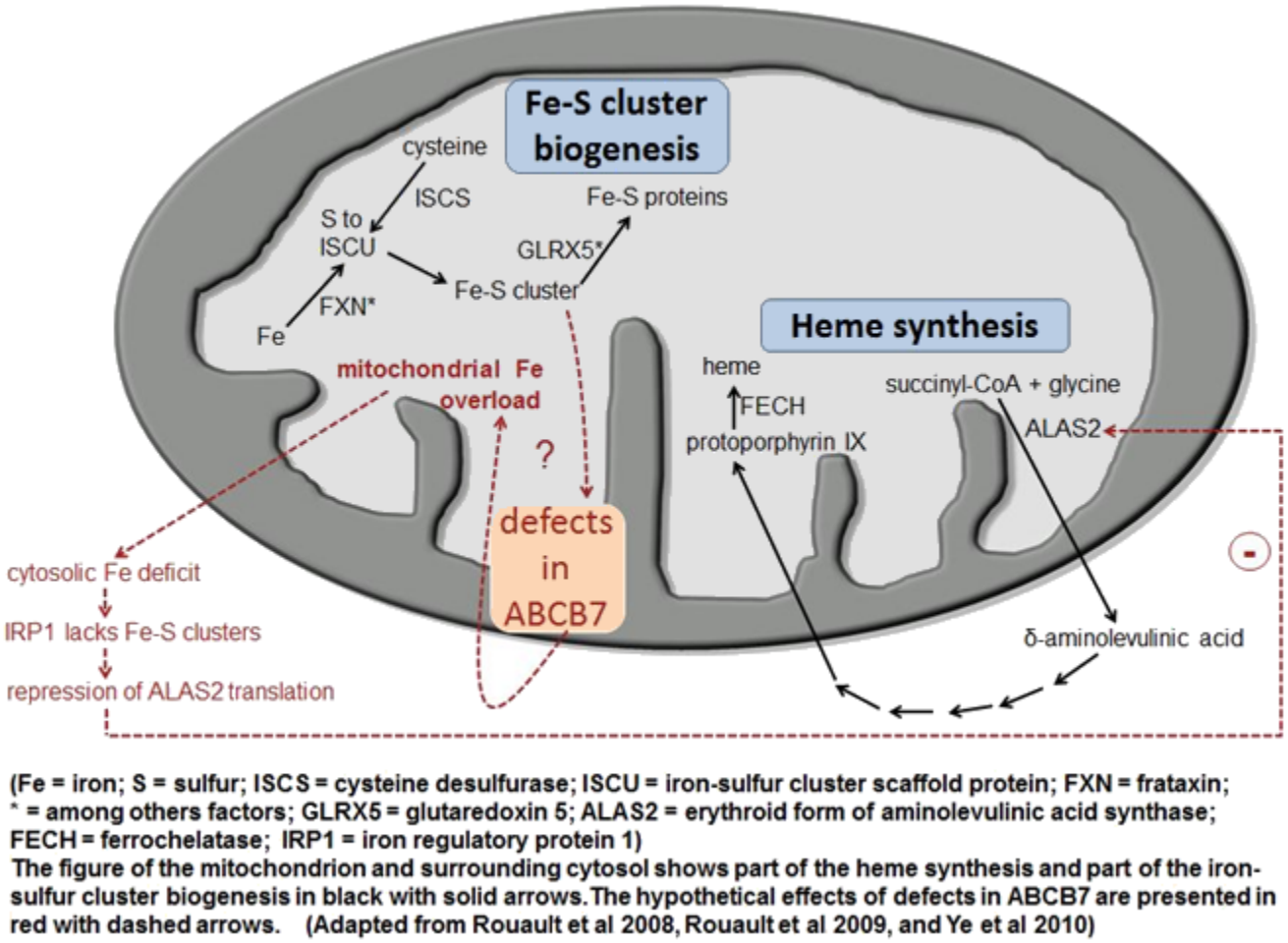

Figure 2. Fe-S cluster biogenesis, heme synthesis and hypothetic effects of defects in ABCB7
Adapted from D'Hooghe et al [2012] with permission

Males with ataxia benefit from early physical therapy to facilitate acquisition of gross motor skills. Adaptive devices such as ankle fixation orthoses and walkers may be needed.

Weighted eating utensils may help promote independent skills in childhood.

Speech therapy may improve intelligibility problems resulting from dysarthria.

Difficulty with handwriting may be managed with computers for word processing.

The anemia is usually mild and asymptomatic and does not require treatment; hepatic and systemic iron overload does not occur.

Surveillance

It is debated whether monitoring for possible iron overload is warranted in older individuals through routine screening of serum iron concentration, total iron binding capacity (TIBC), and serum ferritin concentration; iron overload is theoretically possible but has not been reported.

Evaluation of Relatives at Risk

See Related Genetic Counseling Issues for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

One possible therapeutic approach to some of the disorders involving iron misdistribution is drug-mediated iron relocation. Deferiprone (DFP), an iron chelator used to treat iron overload, has iron-relocating abilities when used to treat disorders of regional iron accumulation. Because of their possible side effects, siderophores (small, high-affinity iron chelating compounds secreted by microorganisms) and other chelators must be administered with care; thus, the potential use of iron-redistributing agents in some iron-misdistribution diseases (such as XLSA/A) warrants rigorous investigation [Boddaert et al 2007, Camaschella 2008, Kakhlon et al 2010].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

X-linked sideroblastic anemia and ataxia (XLSA/A) is inherited in an X-linked manner.

Risk to Family Members

Parents of a proband

- The father of an affected male will not have the disease nor will he be a carrier of the pathogenic *ABCB7* allelic variant.
- In a family with more than one affected individual, the mother of an affected male is an obligate carrier.
- If pedigree analysis reveals that a male proband is the only affected family member, his mother may be a carrier or the pathogenic variant may be *de novo* in him (in which case the mother is not a carrier).
- If a woman has more than one affected son and the pathogenic variant cannot be detected in her DNA, she has germline mosaicism. To date germline mosaicism has not been reported in XLSA/A.

Sibs of a proband

- The risk to sibs depends on the carrier status of the mother.
- If the mother of the proband is a carrier, the chance of transmitting the pathogenic variant in each pregnancy is 50%. Male sibs who inherit the pathogenic *ABCB7* variant will be affected; female sibs who inherit the pathogenic variant will be carriers and will not be affected.
- If the pathogenic variant cannot be detected in the DNA of the mother of the only affected male in the family, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband. Males with XLSA/A will pass the pathogenic variant to all of their daughters and none of their sons.

Other family members. The proband's maternal aunts may be at risk of being carriers and the aunt's offspring, depending on their gender, may be at risk of being carriers or of being affected.

Heterozygote (Carrier) Detection

Heterozygous females (carriers) are asymptomatic.

- They have a normal neurologic examination with no cerebellar dysfunction.
- They have a normal hematocrit, but may have a dimorphic blood smear with hypochromic microcytic red blood cells and normal red blood cells, sideroblasts on bone marrow examination. Some also have increased levels of whole blood total erythrocyte protoporphyrin (TEP) and zinc erythrocyte protoporphyrin (ZnEP) [Pagon et al 1985, D'Hooghe et al 2012].

Carrier testing of at-risk female relatives is possible if the pathogenic variant has been identified in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ABCB7* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  Ataxia UK
  Lincoln House, Kennington Park, 1-3 Brixton Road
  London SW9 6DE
  United Kingdom
  Phone: +44 (0) 207 582 1444

Email: smillman@ataxia.org.uk
www.euroataxia.org

- **Medline Plus**
  Bone Marrow Diseases
- **National Ataxia Foundation**
  2600 Fernbrook Lane
  Suite 119
  Minneapolis MN 55447
  Phone: 763-553-0020
  Email: naf@ataxia.org
  www.ataxia.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. X-Linked Sideroblastic Anemia and Ataxia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ABCB7	Xq13.3	ATP-binding cassette sub-family B member 7, mitochondrial	ABCB7 @ LOVD	ABCB7	ABCB7

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for X-Linked Sideroblastic Anemia and Ataxia (View All in OMIM)

300135	ATP-BINDING CASSETTE, SUBFAMILY B, MEMBER 7; ABCB7
301310	ANEMIA, SIDEROBLASTIC, AND SPINOCEREBELLAR ATAXIA; ASAT

Molecular Pathogenesis

ABCB7 encodes a mitochondrial adenosine triphosphate (ATP)-binding cassette (ABC) transporter protein involved in iron homeostasis. The family of ABC transporters consists of a large group of ATP-dependent transmembrane proteins that specifically transport a wide variety of substrates across cell and organelle membranes [Holland 2011, Moitra & Dean 2011]. The human genome contains 49 ABC genes. Compared to bacteria, human mitochondria surprisingly harbor a very small number (≤4) of ABC transporters [Burke & Ardehali 2007, Zutz et al 2009]. Mitochondrial ABC transporters belong to the subfamily B and assemble as homodimers of half-transporters [Zutz et al 2009]. ABCB7 is found in the inner mitochondrial membrane.

The substrate transported by the ABCB7 transporter is not fully characterized. Initially, ABCB7 was thought to be involved in transport of heme from the mitochondria to the cytosol [Shimada et al 1998]. Recent studies in different species suggest relationships between heme biosynthetic pathways, iron-sulfur (Fe–S) cluster biogenesis, and mitochondrial iron homeostasis. The most common Fe–S clusters in eukaryotes are the [2Fe–2S] and [4Fe–4S] clusters. Fe–S clusters are ancient biologic prosthetic groups essential for numerous biologic processes, including mitochondrial respiratory chain activity and various other enzymatic and regulatory functions. Mitochondrial iron overload is a prominent feature of the human Fe–S cluster assembly disorders

[Rouault & Tong 2008, Sheftel et al 2010]. It is possible that ABCB7 transports Fe-S clusters and/or an as-yet-unknown regulatory molecule from mitochondria to convey the signal that mitochondria have sufficient iron (Figure 2). Then, if either Fe-S cluster synthesis or heme synthesis is disrupted, the cytosolic/nuclear compartment would perceive mitochondrial iron deficiency and could respond by significantly increasing mitochondrial iron stores.

See Additional information on pathogenesis (pdf).

Gene structure. *ABCB7* comprises 16 exons [Shimada et al 1998, Bekri et al 2000]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. See Table 2 and Table 3. Only four unrelated families with XLSA/A have been reported, each with a distinct missense variant. It is worth noting that the identified pathogenic variants are missense variants with intermediate severity.

- Pagon et al [1985] reported four males in two generations and a fifth male from an unrelated family who were affected. In the four members of the first kindred, Allikmets et al [1999] found a hemizygous pathogenic missense variant in exon 9 (c.1203T>G; p.Ile401Met) resulting in a substitution in the fifth putative transmembrane region of the ABCB7 protein. This pathogenic variant was identified in the heterozygous state in female obligate carriers.
- Bekri et al [2000] reported two affected brothers with XLSA/A and found a hemizygous pathogenic missense variant in exon 10 (c.1300G>A; p.Glu434Lys) causing a substitution adjacent to the sixth putative transmembrane region of the ABCB7 protein; this variant was present in one allele in their mother.
- Maguire et al [2001] reported a family with two affected brothers and two affected maternal uncles. In the two brothers and in one uncle who was still alive, Maguire et al [2001] found a hemizygous pathogenic missense variant in exon 10 (c.1234G>C; p.Val412Leu) leading to a substitution in the last of six putative transmembrane regions of the ABCB7 protein. The mother was heterozygote for this variant.
- D'Hooghe et al [2012] reported a male child with a novel hemizygous pathogenic missense variant in exon 6 (c.627A>T; p.Glu209Asp) causing a substitution adjacent to the second transmembrane domain at the mitochondrial side; his mother was heterozygous for the same variant.

Table 3. *ABCB7* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.627A>T	p.Glu209Asp	NM_004299.3 NP_004290.2
c.1203T>G	p.Ile401Met	
c.1234G>C	p.Val412Leu	
c.1300G>A	p.Glu434Lys	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

See Additional information on genetics of XLSA/A (pdf).

Normal gene product. The ATP-binding cassette, subfamily B, member 7 protein (ABCB7) belongs to the adenosine triphosphate-binding cassette transporter superfamily; its yeast ortholog, Atm1p, plays a central role in the maturation of cytosolic iron-sulfur (Fe-S) cluster-containing proteins [Bekri et al 2000]. *ABCB7* contributes to the production of heme during the differentiation of erythroid cells [Taketani et al 2003]. It is also thought to transport a component required for the maturation of cytosolic Fe-S clusters from the mitochondrion

to the cytosol [Napier et al 2005]. Thus, the mitochondrion appears to be important in both heme synthesis and in the biogenesis of Fe-S clusters.

ABCB7 is highly expressed in bone marrow as well as in the cerebellum, which may explain why males with ABCB7 deficiency have ataxia [Allikmets et al 1999, Ye & Rouault 2010a, Ye & Rouault 2010b]. The ataxia observed in XLSA/A may be related to the damage mediated by the iron loading in the mitochondrion and/or disruption to mitochondrial iron homeostasis in neural cells [Napier et al 2005].

Abnormal gene product. Complementation studies in yeast suggest that the human mutated ATP-binding cassette, subfamily B, member 7 proteins (ABCB7) are caused by mild, partial loss-of-function alleles [Allikmets et al 1999, Bekri et al 2000] that result in diminished cytosolic Fe-S cluster protein.

Pondarré et al [2006] created a conditional knockout allele of the murine ortholog *Abcb7* and formally demonstrated that XLSA/A is caused by partial-loss-of-function variants that directly or indirectly inhibit heme biosynthesis [Pondarré et al 2007]. Indeed, mutation leading to a significant loss of protein function must be lethal as illustrated by a knockout mouse model [Pondarré et al 2006].

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Revision History

- 20 August 2020 (ma) Chapter retired: extremely rare disorder
- 3 April 2014 (me) Comprehensive update posted live
- 7 April 2009 (me) Comprehensive update posted live
- 1 May 2008 (cd) Revision: sequencing of exons 5-16 and the intron/exon junctions available clinically
- 24 March 2008 (cd) Revision: clinical testing not available
- 1 March 2006 (me) Review posted live
- 12 November 1998 (bp) Original submission

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