U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Van Maldergem L, Dobyns W, Kornak U. *ATP6V0A2*-Related Cutis Laxa. 2009 Mar 19 [Updated 2023 Mar 16]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

ATP6V0A2-Related Cutis Laxa

Synonyms: ATP6V0A2-CDG, Autosomal Recessive Cutis Laxa Type 2A (ARCL2A)

Lionel Van Maldergem, MD, PhD,[1] William Dobyns, MD,[2] and Uwe Kornak, MD, PhD[3]

Created: March 19, 2009; Revised: March 16, 2023.

Summary

Clinical characteristics

ATP6V0A2-related cutis laxa is characterized by generalized cutis laxa, findings associated with generalized connective tissue disorder, developmental delays, and a variety of neurologic findings including abnormality on brain MRI. At birth, hypotonia, overfolded skin, and distinctive facial features are present and enlarged fontanelles are often observed. During childhood, the characteristic facial features and thick or coarse hair may become quite pronounced. The skin findings decrease with age, although easy bruising and Ehlers-Danlos-like scars have been described in some. In most (not all) affected individuals, cortical and cerebellar malformations are observed on brain MRI. Nearly all affected individuals have developmental delays, seizures, and neurologic regression.

Diagnosis/testing

The diagnosis of *ATP6V0A2*-related cutis laxa is established by the presence of suggestive findings and biallelic pathogenic variants in *ATP6V0A2* identified by molecular genetic testing.

Management

Treatment of manifestations: Standard treatment for congenital hip dislocation, inguinal hernias, high myopia, and seizure disorders. Early intervention and management of developmental delays and intellectual disability and psychological help as needed for self-image issues.

Surveillance: Annual ophthalmologic examination, EEG, and monitoring of anticonvulsive drug levels.

Genetic counseling

ATP6V0A2-related cutis laxa is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *ATP6V0A2* pathogenic variant, each sib of an affected individual has at conception a 25%

Author Affiliations: 1 Centre de génétique humaine, Université de Franche-Comté, Besançon, France; Email: vmald@skypro.be. 2 Seattle Children's Research Institute, Seattle, Washington; Email: wbd@uw.edu. 3 Institut für Humangenetik, Universitätsmedizin Göttingen, Göttingen, Germany; Email: uwe.kornak@med.uni-goettingen.de.

Copyright © 1993-2024, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.

chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *ATP6V0A2* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing for *ATP6V0A2*-related cutis laxa are possible.

GeneReview Scope

ATP6V0A2-Related Cutis Laxa: Included Phenotypes
• Debré-type cutis laxa • Wrinkly skin syndrome

Diagnosis

Suggestive Findings

ATP6V0A2-related cutis laxa, also known as autosomal recessive cutis laxa type 2A (ARCL2A), **should be considered** in individuals with the following findings.

Clinical Findings

Characteristic signs of cutis laxa

- Furrowing of the skin of the whole body; particularly obvious in neck, axillae, and groin
- Skin that when extended does not display marked hyperelasticity (as is observed in the Ehlers-Danlos syndromes) but rather maintains its consistency
- Droopy skin on the cheeks of the face and marked nasolabial folds, giving rise to distinctive facial features that also include prominent nasal root and downslanted palpebral fissures

Other evidence of a generalized connective tissue disorder

- Enlarged fontanelles (i.e., delayed closure of the fontanelles) manifest in newborns (anterior fontanelle >6x6 cm in the newborn; >3x3 cm at age 1 year)
- Congenital dislocation of the hips
- Inguinal hernias
- High myopia
- Bruch's membrane rupture, cataracts, corneal clouding (infrequent)

Laboratory Findings

Serum sialotransferrin isoelectric focusing (IEF) reveals the following findings in *ATP6V0A2*-related cutis laxa:

- Reduction of the main protein band, which corresponds to transferrin containing four sialic acid residues
- Increased amounts of disialo- and trisialo-transferrin that indicate altered N-glycosylation over the normal ranges of:
  - Disialotransferrin: 2.5%-9.8%
  - Trisialotransferrin: 3.4%-13.7%

Note: (1) These findings are also observed in type 2 congenital disorder of glycosylation (CDG type 2) [Morava et al 2005, Wopereis et al 2005, Morava et al 2008, Guillard et al 2009]. (2) In the authors' experience, all probands had a CDG type 2 sialotransferrin IEF pattern; however, it has been observed that infants may have a normal transferrin isofocusing profile in the first months of life, but develop the typical transferrin abnormality

later on. In these infants, the apolipoprotein C-III isofocusing was already abnormal in the first months of life [Morava et al 2005, Wopereis et al 2005].

Serum apolipoprotein C III IEF reveals the following changes of altered O-glycosylation:

- Reduction of the main protein band, which corresponds to apolipoprotein CIII containing two sialic acid residues
- Increased amounts of monosialotransferrin. Normal ranges depend on age; in adults:
  - Monosialotransferrin: 43%-69%
  - Disialotransferrin: 23%-50%

Note: Abnormal O-glycosylation is supportive of the diagnosis, but a normal or inconclusive result does not eliminate the possibility of *ATP6V0A2*-related cutis laxa. In the authors' experience, comparing the findings in the parents with those of the index case is most helpful in identifying the reduction of the main band.

Skin biopsy with orcein staining reveals the following:

- Light microscopy is normal.
- Electron microscopy (EM) shows rarefaction and fragmentation of the elastin network in which elastic fibers are small and misshapen. Within these fibers both elastin and elastofibrils can be distinguished based on their different densities [Beyens et al 2019b].

  Note: EM studies require a high level of expertise and are only available in specialized centers.

  The EM findings strongly support but are not specific for the diagnosis of *ATP6V0A2*-related cutis laxa.

Imaging Findings

Central nervous system (CNS) abnormalities. In most (not all) affected individuals, cortical and cerebellar malformations are observed on brain MRI.

- **Cortical malformation.** Abnormally thick (5-10 mm) cortex has subtle vertical streaks that appear smooth in some areas and irregular in others, resembling either lissencephaly or polymicrogyria.

  This cortical malformation differs from lissencephaly and polymicrogyria by a consistent and predominant bilateral, symmetric, and frontal distribution that is more severe in the posterior portion of the frontal lobe and the anterior portion of the parietal lobes (including the perisylvian cortex) and less severe in the anterior portion of the frontal lobe and often the superior portion of the temporal lobe. No well-defined microgyri are seen, which also distinguishes the disorder from true polymicrogyria.
- **Cerebellar malformation** ranges from mild cerebellar vermis hypoplasia to classic Dandy-Walker malformation, including severe hypoplasia and upward rotation of the vermis, cystic enlargement of the fourth ventricle, and enlarged posterior fossa.

Family History

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *ATP6V0A2*-related cutis laxa **is established** by the presence of suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *ATP6V0A2* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both

can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *ATP6V0A2* variants of uncertain significance (or of one known *ATP6V0A2* pathogenic variant and one *ATP6V0A2* variant of uncertain significance) does not establish or rule out the diagnosis.

Because the phenotype of *ATP6V0A2*-related cutis laxa may be indistinguishable from many other inherited disorders with cutis laxa, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *ATP6V0A2*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **A cutis laxa or connective tissue disorder or congenital disorder of glycosylation multigene panel** that includes *ATP6V0A2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

- **Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *ATP6V0A2*-Related Cutis Laxa

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
ATP6V0A2	Sequence analysis [3]	>95% [4]
	Gene-targeted deletion/duplication analysis [5]	Rare [4, 6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or 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.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Hucthagowder et al [2009] identified deletion of exon 16 in four unrelated individuals of Middle Eastern origin in their cohort of 17 affected individuals from 16 families. Jones et al [2013] described a deletion of exon 9. A deletion of the whole gene was identified by Gardeitchik et al [2014].

Clinical Characteristics

Clinical Description

ATP6V0A2-related cutis laxa is characterized by generalized cutis laxa, findings associated with generalized connective tissue disorder, developmental delays, and a variety of neurologic findings including abnormality on brain MRI.

This disorder spans a phenotypic spectrum that includes the historical diagnoses of Debré-type cutis laxa at the severe end and wrinkly skin syndrome at the mild end; these two phenotypes were thought to be distinct clinical entities until their molecular genetic nature was determined. Children diagnosed in the past with Debré-type cutis laxa had more severe developmental and neurologic abnormalities and a less severe cutaneous phenotype than children diagnosed with wrinkly skin syndrome, in whom the skin showed tighter wrinkles and the changes in facial features were milder [Al-Gazali et al 2001].

To date, about 80 individuals have been identified with a pathogenic variant in *ATP6V0A2* [Morlino et al 2021; Authors, unpublished observations]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *ATP6V0A2*-Related Cutis Laxa: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Cutis laxa	100%	Combination of fine wrinkles & sagging skin; can vanish during childhood.
Prominent nasal root	100%	
Downslanted palpebral fissures	100%	Recognizable facial dysmorphism
Enlarged fontanels w/delayed closure	100%	
Congenital dislocation of hips	60%	
Inguinal hernia	60%	
High myopia	20%	
Other ophthalmic issues	20%	
Developmental delay / Intellectual disability	100%	Always speech delay; some can attend normal school
Seizure disorder	100%	Onset variable; may occur as late as adolescence
Neurologic decline	Possibly up to 40%	Unclear; few w/follow-up data
Abnormal brain imaging	90%	Brain malformation experts can make diagnosis from MRI.

Presentation and progression. At birth, hypotonia, overfolded skin, and distinctive facial features are present and enlarged fontanelles are often observed. During childhood, the characteristic facial features and thick or coarse hair may become quite pronounced. In *ATP6V0A2*-related cutis laxa the skin findings decrease with age, although easy bruising and Ehlers-Danlos-like scars have been described in some [Greally et al 2014]. Adults with this disorder can show progressive neurologic issues.

Skin findings. Findings of cutis laxa include:

- Facial features
  - Droopy skin on cheeks
  - Prominent nasal bridge
  - Premature aged appearance

- Downslanting palpebral fissures
- In most, borderline microcephaly with head circumference 2-3 standard deviations below the mean

- Findings of a generalized connective tissue disorder including:
  - Enlarged fontanels
  - Congenital dislocation of the hips
  - Inguinal hernia
  - Heart valve dysplasia and/or widening of aortic root
  - Scoliosis
  - Joint laxity

Ophthalmologic concerns. High myopia (>-5 diopters) has been observed in the majority of affected individuals.

- One Portuguese individual had an unclassified corneal dysplasia requiring engraftment.
- A Belgian individual had unilateral rupture of Bruch's membrane.
- Strabismus has been observed in nearly half of individuals.

Developmental delay. Nearly all affected children described to date have had delayed developmental milestones (especially speech delay) and intellectual disability. Despite delays in developmental milestones and language, affected children are said to be cheerful and outgoing.

Neurologic findings

- **Cognitive.** Many children have a degenerative course including cognitive decline that begins about the end of the first decade.
- **Seizures.** Generalized or partial complex seizures begin between ages eight and 12 years.
- **Neurologic regression** (with or without seizures) can include spasticity and cerebellar signs and symptoms (ataxia, slurred speech). Some adolescents become wheelchair bound. A unique individual with mild brain dysgenesis and compound heterozygosity for *ATP6V0A2* pathogenic variants had a normal IQ with no history of seizures, and was doing well in mainstream school at age 15 years [Van Maldergem et al 2008].

Abnormal brain imaging. Cortical and/or cerebellar abnormality is identified in most individuals on brain MRI. See Suggestive Findings, Imaging Findings.

Other. Bleeding disorder linked to coagulation factor deficiencies may occur [Beyens et al 2019b].

Genotype-Phenotype Correlations

No genotype-phenotype correlations are known.

Prevalence

The prevalence of all types of cutis laxa is 1:4,000,000 according to Rhône-Alpes Eurocat registry [E Robert, personal observation]. It is the second- to third-most common form of autosomal recessive cutis laxa.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ATP6V0A2*.

Differential Diagnosis

Other disorders characterized by cutis laxa are summarized in Table 3.

Table 3. Disorders to Consider in the Differential Diagnosis of *ATP6V0A2*-Related Cutis Laxa

Gene	Disorder	MOI	Clinical Findings					Comment
			Cutis laxa	Emphysema	Aneurysms	ID/DD	Bladder diverticulae	
ALDH18A1	De Barsy syndrome A (ARCL3A) (OMIM 219150)	AR	+	–	–	++	–	ID (variable), translucent skin
	ADCL3 (OMIM 616603)	AD	+	–	–	+	–	ID (variable), translucent skin
ATP6V1A	ARCL2D (OMIM 617403)	AR	++	–	–	+	–	Facial appearance similar to ARCL2A; myopathy; respiratory problems in infancy can be lethal; no seizures; often no ID. Like ARCL2A, ARCL2D & ARCL2C are CDGs.
ATP6V1E1	ARCL2C (OMIM 617402)	AR	++	–	–	+	–	
EFEMP2	*EFEMP2*-related cutis laxa	AR	++	++	+++	–	–	
ELN	*ELN*-related cutis laxa (ADCL1)	AD	+	+	+	–	–	
EMILIN1	*EMILIN1*-related cutis laxa [1]	AR	+	–	+++	–	–	Bone fragility, congenital anomalies of kidney & urinary tract
FBLN5	*FBLN5*-related cutis laxa (ARCL1A & ADCL2)	AR AD	+++	+++	–	–	++	
GORAB	Gerodermia osteodysplastica (GO) (OMIM 231070)	AR	++	–	–	–	–	
LTBP4	*LTBP4*-related cutis laxa (URDS, ARCL1C)	AR	+	++	+	+	++	Characterized by severe assoc malformations incl major CHD & severe pulmonary hypertension; diaphragmatic hernia & multiple bladder diverticulae w/vesicoureteral reflux → life-threatening complications & short life span.
NBAS	Short stature, optic nerve atrophy, & Pelger-Huet anomaly (SOPH syndrome) (OMIM 614800)	AR	+	–	–	++	–	Hepatopathy; optic atrophy; hypogammaglobulinemia
PTDSS1	Lenz-Majewski syndrome hyperostotic dwarfism (LMS) (OMIM 151050)	AD	+	–	–	+++	Unknown	Early cutis laxa followed by progressive thinning of skin w/ prominent veins; severe brachydactyly & unique facial appearance w/prominent eyes distinguish LMS in early stages from other forms of cutis laxa. [2]

Table 3. continued from previous page.

Gene	Disorder	MOI	Clinical Findings					Comment
			Cutis laxa	Emphysema	Aneurysms	ID/DD	Bladder diverticulae	
PYCR1	De Barsy syndrome B (ARCL3B) (OMIM 614438)	AR	+	–	–	+++	–	ID (variable); translucent skin; movement disorder
	ARCL2B 612940	AR	+	–	–	+++	–	ID (variable); translucent skin
RIN2	RIN2-related cutis laxa (MACS syndrome) (OMIM 613075)	AR	+	–	–	±	Unknown	Very characteristic facial gestalt [3]; cutis laxa is mild & mostly manifests as redundant facial skin.
SLC2A10	Arterial tortuosity syndrome	AR	+	–	++	–	Unknown	Individuals may display droopy facial appearance similar to that observed in other forms of cutis laxa [4] & have a high palate w/ dental crowding.

ADCL = autosomal dominant cutis laxa; ARCL = autosomal recessive cutis laxa; CDG = congenital disorder of glycosylation; CHD = congenital heart disease; DD = developmental delay; ID = intellectual disability; MACS = *m*acrocephaly, *a*lopecia, *c*utis laxa, & *s*coliosis; MOI = mode of inheritance

1. Adamo et al [2022]
2. Sousa et al [2014], Piard et al [2018]
3. Basel-Vanagaite et al [2009]
4. Callewaert et al [2008], Beyens et al [2019a]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *ATP6V0A2*-related cutis laxa, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *ATP6V0A2*-Related Cutis Laxa

System/Concern	Evaluation	Comment
Congenital hip dislocation	• For newborns: clinical exam w/hip ultrasound as needed • For older child at diagnosis: pelvic x-ray (1x only) to identify hip dysplasia in the event that hip dislocation was not treated properly	
Inguinal hernia(s)	Clinical eval	
Cardiac valvular dysplasia	Echocardiogram	
High myopia & other ophthalmic abnormality	Ophthalmologic exam, incl refraction (for myopia), slit-lamp exam, fundus exam	Slit-lamp exam allows diagnosis of corneal dysplasia (seen in 1 person).
DD/ID / Neurologic abnormality	• Baseline neurodevelopmental eval • Brain MRI • EEG if seizures are suspected	
Coagulation factor deficiencies	Full screening, incl von Willebrand factor [Beyens et al 2019b]	

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *ATP6V0A2*-related cutis laxa to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with *ATP6V0A2*-Related Cutis Laxa

Manifestation/Concern	Treatment	Considerations/Other
Congenital hip dislocation	Standard treatment as recommended by orthopedist	
Inguinal hernia(s)	Surgical repair	
High myopia	Standard treatment(s) as recommended by ophthalmologist	
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Seizure disorder	Standardized treatment w/ASM by experienced neurologist	See footnote 1.
Self-image difficulties related to cutis laxa	Psychological help as needed	

ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Social/Behavioral Concerns

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Surveillance

Table 6. Recommended Surveillance for Individuals with *ATP6V0A2*-Related Cutis Laxa

System/Concern	Evaluation	Frequency
High myopia & other ophthalmic issues	Ophthalmologic exam, incl refraction for evidence of progressive myopia & fundus exam to inspect Bruch's membrane	Annually
Seizures	EEG; monitoring of anticonvulsive drug levels	

Evaluation of Relatives at Risk

It is appropriate to test older and younger sibs for presence of the *ATP6V0A2* pathogenic variants found in the proband in order to identify as early as possible those who would benefit from institution of treatment and preventive measures.

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

Therapies Under Investigation

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

ATP6V0A2-related cutis laxa is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *ATP6V0A2* pathogenic variant based on family history).
- Molecular genetic testing of the parents is recommended to confirm that both parents are heterozygous for an *ATP6V0A2* pathogenic variant and to allow reliable recurrence risk assessment. (In rare families, only one parent of a proband with an autosomal recessive disorder is heterozygous and the proband is affected as the result of either: (1) one pathogenic variant inherited from the heterozygous parent and a second pathogenic variant that occurred *de novo* in the proband; or (2) uniparental isodisomy and consequent homozygosity for the pathogenic variant transmitted by a heterozygous parent [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *ATP6V0A2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Because cognitive development and possible regression depends on the onset, type, and severity of seizures, considerable intrafamilial variability is observed.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- The offspring of an individual with *ATP6V0A2*-related cutis laxa are obligate heterozygotes (carriers) for a pathogenic variant in *ATP6V0A2*.
- To date, individuals with *ATP6V0A2*-related cutis laxa who have brain malformation are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ATP6V0A2* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *ATP6V0A2* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk 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.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ATP6V0A2* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for *ATP6V0A2*-related cutis laxa are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. 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.

- **DermNet NZ**
  New Zealand
  Cutis Laxa
- **MedlinePlus**

Cutis laxa

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. ATP6V0A2-Related Cutis Laxa: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ATP6V0A2	12q24.31	V-type proton ATPase 116 kDa subunit a 2	ATP6V0A2 database	ATP6V0A2	ATP6V0A2

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 ATP6V0A2-Related Cutis Laxa (View All in OMIM)

219200	CUTIS LAXA, AUTOSOMAL RECESSIVE, TYPE IIA; ARCL2A
278250	WRINKLY SKIN SYNDROME; WSS
611716	ATPase, H+ TRANSPORTING, LYSOSOMAL, V0 SUBUNIT A2; ATP6V0A2

Molecular Pathogenesis

ATP6V0A2 encodes the alpha-2 subunit of the v-ATPase complex, which mainly resides in the trans Golgi compartment and adjacent endosomal vesicles. The subunit anchors the complex in the membrane and is part of the channel for proton transport. Loss of this subunit likely perturbs pH regulation and ion homeostasis in Golgi cisternae and vesicles and, possibly through loss of interaction with additional proteins involved in vesicular function, impairs vesicular transport. This leads to impaired posttranslational modification through malpositioning and malfunction of glycosylation enzymes, but also affects secretion, endocytosis, and lysosomal function. The phenotype of *ATP6V0A2*-related cutis laxa is partially of developmental origin, but the neurologic decline seen in many individuals also hints at a progressive neuronal disease mechanism.

Mechanism of disease causation. *ATP6V0A2*-related cutis laxa is thought to occur via a loss-of-function mechanism.

Chapter Notes

Acknowledgments

We thank the families for their continuing participation.

Revision History

- 16 March 2023 (aa) Revision: *EMILIN1* added to Differential Diagnosis
- 28 January 2021 (ha) Comprehensive update posted live
- 12 February 2015 (me) Comprehensive update posted live
- 10 May 2011 (cd) Revision: deletion/duplication analysis available clinically; *ALDH18A1*-related cutis laxa added to differential diagnosis
- 23 September 2010 (me) Comprehensive update posted live
- 19 March 2009 (me) Review posted live
- 10 September 2008 (lvm) Original submission

References

Literature Cited

Adamo CS, Beyens A, Schiavinato A, Keene DR, Tufa SF, Mörgelin M, Brinckmann J, Sasaki T, Niehoff A, Dreiner M, Pottie L, Muiño-Mosquera L, Gulec EY, Gezdirici A, Braghetta P, Bonaldo P, Wagener R, Paulsson M, Bornaun H, De Rycke R, De Bruyne M, Baeke F, Devine WP, Gangaram B, Tam A, Balasubramanian M, Ellard S, Moore S, Symoens S, Shen J, Cole S, Schwarze U, Holmes KW, Hayflick SJ, Wiszniewski W, Nampoothiri S, Davis EC, Sakai LY, Sengle G, Callewaert B. EMILIN1 deficiency causes arterial tortuosity with osteopenia and connects impaired elastogenesis with defective collagen fibrillogenesis. Am J Hum Genet. 2022;109:2230–52. PubMed PMID: 36351433.

Al-Gazali LI, Sztriha L, Skaff F, Haas D. Gerodermia osteodysplastica and wrinkly skin syndrome: are they the same? Am J Med Genet. 2001;101:213–20. PubMed PMID: 11424136.

Basel-Vanagaite L, Sarig O, Hershkovitz D, Fuchs-Telem D, Rapaport D, Gat A, Isman G, Shirazi I, Shohat M, Enk CD, Birk E, Kohlhase J, Matysiak-Scholze U, Maya I, Knopf C, Peffekoven A, Hennies HC, Bergman R, Horowitz M, Ishida-Yamamoto A, Sprecher E. RIN2 deficiency results in macrocephaly, alopecia, cutis laxa, and scoliosis: MACS syndrome. Am J Hum Genet. 2009;85:254–63. PubMed PMID: 19631308.

Beyens A, Albuisson J, Boel A, Al-Essa M, Al-Manea W, Bonnet D, Bostan O, Boute O, Busa T, Canham N, Cil E, Coucke PJ, Cousin MA, Dasouki M, De Backer J, De Paepe A, De Schepper S, De Silva D, Devriendt K, De Wandele I, Deyle DR, Dietz H, Dupuis-Girod S, Fontenot E, Fischer-Zirnsak B, Gezdirici A, Ghoumid J, Giuliano F, Baena N, Haider MZ, Hardin JS, Jeunemaitre X, Klee EW, Kornak U, Landecho MF, Legrand A, Loeys B, Lyonnet S, Michael H, Moceri P, Mohammed S, Muiño-Mosquera L, Nampoothiri S, Pichler K, Prescott K, Rajeb A, Ramos-Arroyo M, Rossi M, Salih M, Seidahmed MZ, Schaefer E, Steichen-Gersdorf E, Temel S, Uysal F, Vanhomwegen M, Van Laer L, Van Maldergem L, Warner D, Willaert A, Collins Ii TR, Taylor A, Davis EC, Zarate Y, Callewaert B. Correction: Arterial tortuosity syndrome: 40 new families and literature review. Genet Med. 2019a;21:1894–5.

Beyens A, Moreno-Artero E, Bodemer C, Cox E, Gezdirici A, Yilmaz-Gulec E, Kahloul N, Khau-Van-Kien P, Ogur G, Vasse M, Sahli A, Symoens S, Hadj-Rabia S, Callewaert B. ATP6V0A2-related cutis laxa in 10 new patients: focus on clinical variability and expansion of the phenotype. Exp Dermatol. 2019b;28:1142–5. PubMed PMID: 29952037.

Callewaert BL, Willaert A, Kerstjens-Frederikse WS, De Backer J, Devriendt K, Albrecht B, Ramos-Arroyo MA, Doco-Fenzy M, Hennekam RC, Pyeritz RE, Krogmann ON, Gillessen-kaesbach G, Wakeling EL, Nik-zainal S, Francannet C, Mauran P, Booth C, Barrow M, Dekens R, Loeys BL, Coucke PJ, De Paepe AM. Arterial tortuosity syndrome: clinical and molecular findings in 12 newly identified families. Hum Mutat. 2008;29:150–8. PubMed PMID: 17935213.

Gardeitchik T, Mohamed M, Fischer B, Lammens M, Lefeber D, Lace B, Parker M, Ki-Joong Kim K-J, Lim BC, Haberle M, Garavelli L, Jagadeesh S, Kariminejad A, Guerra D, Leao M, Keski-Filppula R, Brunner H, Nijtmans L, van den Heuvel B, Wevers R, Kornak U, Morava E. Clinical and biochemical features guiding the diagnostics in neurometabolic cutis laxa. Eur J Hum Genet. 2014;22:888–95. PubMed PMID: 23963297.

Greally MT, Kalis NN, Agab W, Ardati K, Giurgea S, Kornak U, Van Maldergem L. Autosomal recessive cutis laxa type 2A (ARCL2A) mimicking Ehlers-Danlos syndrome by its dermatological manifestations: report of three patients. Am J Med Genet A. 2014;164A:1245–53. PubMed PMID: 24478233.

Guillard M, Dimopoulou A, Fischer B, Morava E, Lefeber DJ, Kornak U, Wevers RA. Vacuolar H+-ATPase meets glycosylation in patients with cutis laxa. Biochim Biophys Acta. 2009;1792:903–14. PubMed PMID: 19171192.

Hucthagowder V, Morava E, Kornak U, Lefeber DJ, Fischer B, Dimopoulou A, Aldinger A, Choi J, Davis EC, Abuelo DN, Adamowicz M, Al-Aama J, Basel-Vanagaite L, Fernandez B, Greally MT, Gillessen-Kaesbach G, Kayserili H, Lemyre E, Tekin M, Türkmen S, Tuysuz B, Yüksel-Konuk B, Mundlos S, Van Maldergem L, Wevers RA, Urban Z. Loss-of-function mutations in ATP6V0A2 impair vesicular trafficking, tropoelastin secretion and cell survival. Hum Mol Genet. 2009;18:2149–65. PubMed PMID: 19321599.

Jones MA, Rhodenizer D, da Silva C, Huff IJ, Keong L, Bean LJ, Coffee B, Collins C, Tanner AK, He M, Hegde MR. Molecular diagnostic testing for congenital disorders of glycosylation (CDG): detection rate for single gene testing and next generation sequencing panel testing. Mol Genet Metab. 2013;110:78–85. PubMed PMID: 23806237.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Morava E, Lefeber DJ, Urban Z, de Meirleir L, Meinecke P, Gillessen Kaesbach G, Sykut-Cegielska J, Adamowicz M, Salafsky I, Ranells J, Lemyre E, van Reeuwijk J, Brunner HG, Wevers RA. Defining the phenotype in an autosomal recessive cutis laxa syndrome with a combined congenital defect of glycosylation. Eur J Hum Genet. 2008;16:28–35. PubMed PMID: 17971833.

Morava E, Wopereis S, Coucke P, Gillessen-Kaesbach G, Voit T, Smeitink J, Wevers R, Grünewald S. Defective protein glycosylation in patients with cutis laxa syndrome. Eur J Hum Genet. 2005;13:414–21. PubMed PMID: 15657616.

Morlino S, Nardella G, Castellana S, Micale L, Copetti M, Fusco C, Castori M. Review of clinical and molecular variability in autosomal recessive cutis laxa 2A. Am J Med Genet. 2021;185:955–65. PubMed PMID: 33369135.

Piard J, Lespinasse J, Vlckova M, Mensah MA, Iurian S, Simandlova M, Malikova M, Bartsch O, Rossi M, Lenoir M, Nugues F, Mundlos S, Kornak U, Stanier P, Sousa SB, Van Maldergem L. Cutis laxa and excessive bone growth due to de novo mutations in PTDSS1. Am J Med Genet. 2018;176:668–75. PubMed PMID: 29341480.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Sousa SB, Jenkins D, Chanudet E, Tasseva G, Ishida M, Anderson G, Stanier P, Ryten M, Sa J, Saraiva JM, Barnicoat A, Scott R, Calder A, Wattanasirichaigoon D, Chrzanowska K, Simandlová M, Van Maldergem L, Beales PL, Vance JE, Moore GE. Gain-of-function mutations in the Phosphatidylserine Synthase 1 (PTDSS1) gene cause Lenz-Majewski syndrome. Nat Genet. 2014;46:70–6. PubMed PMID: 24241535.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. PubMed PMID: 32596782.

Van Maldergem L, Yuksel-Apak M, Kayserili H, Seemanova E, Giurgea S, Basel-Vanagaite L, Leao-Teles E, Vigneron J, Foulon M, Greally M, Jaeken J, Mundlos S, Dobyns WB. Cobblestone-like brain dysgenesis and altered glycosylation in congenital cutis laxa, Debré-type. Neurology. 2008;71:1602–8. PubMed PMID: 18716235.

Wopereis S, Morava E, Grünewald S, Mills PB, Winchester BG, Clayton P, Coucke P, Huijben KM, Wevers RA. A combined defect in the biosynthesis of N- and O-glycans in patients with cutis laxa and neurological

involvement: the biochemical characteristics. Biochim Biophys Acta. 2005;1741:156–64. PubMed PMID: 15955459.

License

GeneReviews® chapters are owned by the University of Washington. Permission is hereby granted to reproduce, distribute, and translate copies of content materials for noncommercial research purposes only, provided that (i) credit for source (http://www.genereviews.org/) and copyright (© 1993-2024 University of Washington) are included with each copy; (ii) a link to the original material is provided whenever the material is published elsewhere on the Web; and (iii) reproducers, distributors, and/or translators comply with the GeneReviews® Copyright Notice and Usage Disclaimer. No further modifications are allowed. For clarity, excerpts of GeneReviews chapters for use in lab reports and clinic notes are a permitted use.

For more information, see the GeneReviews® Copyright Notice and Usage Disclaimer.

For questions regarding permissions or whether a specified use is allowed, contact: admasst@uw.edu.