



ELN-Related Cutis Laxa

Synonym: Autosomal Dominant Cutis Laxa Type 1 (ADCL1)

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Summary

Clinical characteristics

ELN-related cutis laxa is characterized by generalized cutis laxa (ranging from generalized skin redundancy causing excessive skin folds to skin hyperextensibility without obvious skin folds) and distinctive facial features that may become more prominent with age. Other common findings are joint hyperlaxity in infancy and increasing risk of inguinal hernia at all ages. Progressive findings that may be present as early as childhood include ptosis, aortic root dilatation, and emphysema.

Diagnosis/testing

The diagnosis of *ELN*-related cutis laxa is established in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *ELN* identified by molecular genetic testing.

Management

Treatment of manifestations: There is no cure for *ELN*-related cutis laxa. Experience in treating individuals with *ELN*-related cutis laxa is very limited. Supportive care to improve quality of life, maximize function, and reduce complications is recommended and ideally involves multidisciplinary care by specialists in general surgery, cardiothoracic surgery, cardiology, pulmonology, urology, physical therapy, ophthalmology, and medical genetics.

Surveillance: Monitor for known problems (e.g., inguinal hernias, joint hypermobility and pain) and new issues that may require interventions (e.g., ptosis, aortic root dilatation, emphysema, bladder diverticula).

Agents/circumstances to avoid: Positive pressure ventilation unless needed for life-threatening conditions; contact with people with respiratory infections; tobacco smoking; isometric exercise (which causes an increase in blood pressure); contact sports or activities that increase the risk for blunt abdominal trauma and/or joint injury or pain; sunbathing or tanning in order to preserve residual skin elasticity.

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Pregnancy management: Perinatal complications for mothers with *ELN*-related cutis laxa or affected neonates have not been reported to date. Nonetheless, recommended evaluations for women with *ELN*-related cutis laxa before conception and during pregnancy are pulmonary function testing and cardiovascular assessment (including aortic root diameter). Continued cardiac surveillance for six months post partum is also recommended. Additionally, women taking a beta-blocker should continue it during pregnancy; however, some other classes of medications, such as angiotensin receptor-blocking agents, are teratogenic and should be discontinued or changed to beta-blocking agents, given the increased risk for teratogenicity typically related to second- and third-trimester exposure.

Genetic counseling

ELN-related cutis laxa is inherited in an autosomal dominant manner. About one third of individuals diagnosed with *ELN*-related cutis laxa have an affected parent; about two thirds of affected individuals have the disorder as the result of a *de novo ELN* pathogenic variant. Each child of an individual with *ELN*-related cutis laxa has a 50% chance of inheriting the pathogenic variant. Once the *ELN* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *ELN*-related cutis laxa have been published.

Suggestive Findings

ELN-related cutis laxa **should be suspected** in individuals with the following clinical findings and family history.

Clinical findings include generalized cutis laxa (ranging from generalized skin redundancy causing excessive skin folds to skin hyperextensibility without obvious skin folds) (Figure 1) with or without the following:

- **Present at birth**
 - Inguinal hernia, with increased risk at all ages
 - Joint hyperlaxity
- **Progressive** (may be present as early as childhood)
 - Aortic root dilatation
 - Emphysema
 - Ptosis (eyelid drooping that can be caused by skin laxity)
 - Facial characteristics that may become more prominent with age: large ears, convex nasal ridge, long philtrum, aged appearance (Figure 1)

Note: The skin is hyperextensible if it can be stretched more than a standardized cutoff in three of the following areas: 1.5 cm for the distal part of the forearms and the dorsum of the hands; 3 cm for neck, elbows, and knees.

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *ELN*-related cutis laxa **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *ELN* 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



Figure 1. Findings in individuals with *ELN*-related cutis laxa

A, B, C. Girl age six years with generalized cutis laxa and typical facial features (convex nasal ridge, sagging cheeks, large ears, long philtrum, and increased folds of the perioral skin). Posture shows hyperlordosis.

D. Man age 39 years with hyperextensible skin without obvious skin folds

E. Boy age 18 months with generalized skin redundancy causing excessive skin folds

Figure 1A reprinted with permission from Beyens et al [2021a]; Figure 1D reprinted from Hadj-Rabia et al [2013]

is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *ELN* variant of uncertain significance does not establish or rule out a diagnosis.

Because the phenotype of *ELN*-related cutis laxa may be difficult to distinguish 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 *ELN*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **A cutis laxa multigene panel** that includes *ELN* 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 *ELN*-Related Cutis Laxa

| Gene ¹ | Method | Proportion of Probands with a Pathogenic Variant ² Detectable by Method |
|-------------------|--|--|
| <i>ELN</i> | Sequence analysis ³ | ~100% ^{4, 5} |
| | Gene-targeted deletion/duplication analysis ⁶ | 1 family reported ⁷ |

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. Percentage should include deep intronic sequencing, as c.2272+20C>G has been reported, resulting in partial retention of the intron [Vodo et al 2015].

6. 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.

7. In one family with a complex intragenic *ELN* duplication/triplication with a predicted extended open reading frame, affected individuals had severe emphysema with concomitant risk factors of tobacco use and an M/Z α 1-anti-trypsin genotype [Urban et al 2005]. In retrospect, the presentation in this family is likely not different from that of other individuals with *ELN*-related cutis laxa [Author, unpublished data].

Clinical Characteristics

Clinical Description

ELN-related cutis laxa is characterized by generalized cutis laxa (ranging from generalized skin redundancy causing excessive skin folds to skin hyperextensibility without obvious skin folds) and distinctive facial features that may become more prominent with age. Other common findings are joint hyperlaxity in infancy and increasing risk of inguinal hernia at all ages. Progressive findings that may be present as early as childhood include ptosis, aortic root dilatation, and emphysema.

To date, more than 46 individuals from 23 families have been identified with a pathogenic variant in *ELN* [Tassabehji et al 1998, Zhang et al 1999, Rodriguez-Revenga et al 2004, Urban et al 2005, Szabo et al 2006, Callewaert et al 2011, Hadj-Rabia et al 2013, Vodo et al 2015, Duz et al 2017, Okuneva et al 2019, Xiao et al 2019]. The following description (Table 2) of the phenotypic features associated with *ELN*-related cutis laxa is based on these reports. The phenotype is present at birth and affects males and females equally.

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

| Feature | Frequency | | |
|------------------------------|---------------|--------|------------|
| | In nearly all | Common | Infrequent |
| Cutis laxa | X | | |
| Craniofacial characteristics | X | | |
| Aged appearance | X | | |
| Hoarse voice | X | | |
| Joint hypermobility | | X | |
| Aortic root dilatation | | X | |
| COPD & emphysema | | X | |
| Inguinal hernia | | X | |
| Arterial tortuosity | | | X |
| Bicuspid aortic valve | | | X |

COPD = chronic obstructive pulmonary disease

Findings in Nearly All Individuals

Skin features in *ELN*-related cutis laxa include generalized loose and redundant skin, most prominent in the lower face, axillar, and inguinal regions, usually present at birth [Callewaert et al 2011]. Milder skin manifestations have been reported in adults as skin hyperlaxity [Szabo et al 2006, Hadj-Rabia et al 2013].

Nevertheless, all affected individuals have an aged appearance (see Figure 1), often with sagging eyelids, a convex nasal ridge, a long philtrum, prominent nasolabial folds, and skin redundancy in the chin and neck area. The external ears tend to be large.

Voice. The voice usually sounds hoarse and lower than expected.

Common Findings

Joint hypermobility. Affected individuals may show remarkable joint hypermobility of the small and large joints.

Aortic root dilatation. It has been estimated that up to 55% of affected individuals may develop aortic root aneurysm, with the risk increasing with age [Beyens et al 2021a, Beyens et al 2021b]. Aortic root dilatation has been observed in the first decade [Callewaert et al 2011]. Large diameters of the aortic root (up to 85 mm) and ascending aorta have been described [Szabo et al 2006, Callewaert et al 2011, Hadj-Rabia et al 2013].

Aortic aneurysms are amenable to surgery and there is no evidence of vascular fragility during surgery [Szabo et al 2006, Hadj-Rabia et al 2013].

Aortic dissection has been reported in multiple families as early as in the third decade [Szabo et al 2006]. The risk for aortic dissection has not been established.

Chronic obstructive pulmonary disease (COPD) and emphysema. Up to 35% of all affected individuals develop obstructive lung disease and emphysema, predisposing to airway infections [Beyens et al 2021a, Beyens et al 2021b].

Severe emphysema requiring lung transplantation has been observed in the context of concomitant excessive use of tobacco [Urban et al 2005, Hadj-Rabia et al 2013].

Inguinal hernias may occur and are prone to recurrence after surgery. Wound healing is normal.

Infrequent Findings

Arterial tortuosity. Increased tortuosity of the arteries (mainly of the supra-aortic vasculature) has been incidentally noted but not systematically assessed [Zhang et al 1999].

Bicuspid aortic valve. Three individuals had a bicuspid aortic valve associated with aneurysm formation of the ascending aorta [Callewaert et al 2011].

Other Observations

A splice site variant was reported in exon 25 of *ELN* (c.1708C>T) in an individual with cutis laxa, congenital emphysema, and epilepsy [Graul-Neumann et al 2008]. The facial characteristics do not fit with typical *ELN*-related cutis laxa. The variant was also present in the unaffected father. The variant results in exclusion of exon 25, containing lysine residues important for elastin crosslinking. Alternatively, if exon 25 is not spliced out, the variant creates a stop codon at position 541. The authors hypothesized that differences in expression of the mutated gene accounted for the interfamilial clinical variability. Of note, the c.1708C>T variant has been reported multiple times in individuals with supravalvular aortic stenosis (SVAS) (see Genetically Related Disorders). It is unclear if the variant explains all or part of the phenotype observed in the proband.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified in individuals with *ELN*-related cutis laxa.

Penetrance

ELN-related cutis laxa has 100% penetrance on detailed clinical observation [Hadj-Rabia et al 2013].

Prevalence

ELN-related cutis laxa is extremely rare; fewer than 50 individuals with a molecularly confirmed diagnosis have been reported to date.

While affected individuals have been mostly of European descent, individuals of other ethnicities have been reported, and there is no evidence to suspect ethnic preponderance.

Genetically Related (Allelic) Disorders

Supravalvular aortic stenosis (SVAS, OMIM 185500) is an autosomal dominant condition characterized by the variable presence of arterial stenoses. Stenoses are typically localized above the aortic valve, but may occur elsewhere on large and middle-sized arteries of both systemic and pulmonary circulation. Stenoses can be progressive. There is increased vascular wall stiffness, and affected individuals are prone to arterial hypertension. Associated connective tissue manifestations that may occur include a hoarse voice, inguinal/umbilical hernia, bowel/bladder diverticula, rectal prolapse, joint limitation or laxity, and soft, hyperextensible (rather than lax) skin. Neuromotor development and intellectual capacities are normal [Merla et al 2012].

Pathogenic variants in *ELN* causing SVAS result in haploinsufficiency, and typically induce premature truncation of the *ELN* transcript through introduction of a stop codon or an out-of-frame splicing defect. Most variants are in the first 19 exons, but variants at the C terminus have been reported [Mefford et al 2008, Merla et al 2012].

This differs from the variants causing *ELN*-related cutis laxa, which result in a transcript coding a 3' extended protein that is deposited in the extracellular matrix and acts via a dominant-negative effect [Callewaert et al 2011].

An *ELN* intronic deletion, c.2132-14_2161del (NM_000501.3), has been reported in an individual without features of *ELN*-related cutis laxa but with features of SVAS [Velandia-Piedrahita et al 2020]. The variant was also present in the unaffected father. Two other children of the father died prematurely, probably in the context of SVAS. Complementary DNA analysis indicated three transcripts. Transcript 1 skips the coding region of exon 33 and uses a cryptic splice site in the 3' UTR predicting a protein with a C terminus containing 49 additional residues and lacking the conserved KxxxRKRK motif. Transcript 2 shows the presence of 92 bp of intronic sequence adjacent to exon 32, indicating intron 32 retention. The predicted protein has 17 additional amino acids at the C terminus and disrupts the KxxxRKRK motif. The third transcript predicts consequences at the protein level similar to transcript 2, but shows physiologic splicing of exon 31. Nevertheless, abundance of the different RNA molecules has not been investigated and no protein expression analysis was performed; thus, a haploinsufficiency mechanism for the c.2132-14_2161del variant cannot be ruled out. Familial segregation was incomplete, as the variant was not assessed in the paternal grandparents of the proband.

Williams syndrome (WS) is an autosomal dominant disorder characterized by cardiovascular disease (including SVAS), distinctive facies, connective tissue abnormalities, intellectual disability, a specific cognitive profile, unique personality characteristics, and growth and endocrine abnormalities. WS is caused by a recurrent 7q11.23 contiguous gene deletion of the Williams-Beuren syndrome critical region (WBSCR) that encompasses *ELN*. Hence, deletion of *ELN* contributes to the phenotype of Williams-Beuren syndrome.

7q11.23 duplication syndrome (Williams syndrome region duplication syndrome) is caused by duplication of the 1.5-Mb region most commonly deleted in Williams syndrome. Vascular disease in the 7q11.23 duplication syndrome may include aortic root dilatation.

Differential Diagnosis

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

| Gene | Disorder | MOI | Clinical Findings | | | | | Comment |
|-----------------|--|-----|-------------------|-----------|-----------|-----------|---------------------|--|
| | | | Cutis laxa | Emphysema | Aneurysms | ID/D D | Bladder diverticula | |
| <i>ALDH18A1</i> | De Barsy syndrome A (ARCL3A) (OMIM 219150) | AR | + | - | - | ++ | - | Translucent skin (See also Neurometabolic Cutis Laxa.) |
| | ADCL3 (OMIM 616603) | AD | + | - | - | + | - | |
| <i>ATP6V1A</i> | ARCL2D (OMIM 617403) | AR | ++ | - | + | + | - | Facial appearance similar to ARCL2A; myopathy, lipodystrophy, marfanoid habitus, potentially lethal respiratory problems in infancy; no seizures; often no ID. |
| <i>ATP6V1E1</i> | ARCL2C (OMIM 617402) | AR | ++ | - | + | + | - | Like ARCL2A, ARCL2D & ARCL2C are CDGs. (See also Neurometabolic Cutis Laxa.) |

Table 3. continued from previous page.

| Gene | Disorder | MOI | Clinical Findings | | | | | Comment |
|----------------------------|--|----------|-------------------|-----------|-----------|--------|---------------------|---|
| | | | Cutis laxa | Emphysema | Aneurysms | ID/D D | Bladder diverticula | |
| <i>ATP7A</i> ¹ | Occipital horn syndrome (OHS) / Menkes disease (See ATP7A Copper Transport Disorders .) | XL | + | - | + | + | +++ | Bony exostoses, intracranial & retinal tortuosity (See also Neurometabolic Cutis Laxa.) |
| <i>ATP6V0A2</i> | ATP6V0A2-related cutis laxa (ARCL2A) | AR | ++ | + | - | + | - | See also Neurometabolic Cutis Laxa. |
| <i>EFEMP1</i> ² | <i>EFEMP1</i> -related cutis laxa | AR | + | - | - | - | - | Multiple hernias, marfanoid habitus |
| <i>EFEMP2</i> | EFEMP2-related cutis laxa (ARCL1B) | AR | ++ | ++ | +++ | - | - | Bone fragility, arachnodactyly, widespread arterial tortuosity |
| <i>FBLN5</i> | FBLN5-related cutis laxa (ARCL1A & ADCL2) | AR AD | +++ | +++ | - | - | ++ | SVAS |
| <i>GORAB</i> | Geroderma osteodysplastica (GO) (OMIM 231070) | AR | ++ | - | - | - | - | See also Neurometabolic Cutis Laxa. |
| <i>LOX</i> ³ | <i>LOX</i> -related cutis laxa | AR | ++ | + | ++ | - | - | |
| <i>LTBP1</i> ⁴ | <i>LTBP1</i> -related cutis laxa (ARCL2E) | AR | + | - | - | - | - | Craniosynostosis, short stature, congenital cardiac defects |
| <i>LTBP4</i> | LTBP4-related cutis laxa (ARCL1C) | AR | +++ | +++ | - | - | ++ | Pulmonary artery stenosis |
| <i>NBAS</i> | Short stature, optic nerve atrophy, & Pelger-Huet anomaly (SOPH syndrome) (OMIM 614800) | AR | + | - | - | ++ | - | Hepatopathy, optic atrophy, hypogammaglobulinemia, liver failure during episodes of fever, Pelger-Huet anomaly (See also Neurometabolic Cutis Laxa.) |
| <i>PTDSS1</i> | 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 facies w/ prominent eyes distinguish LMS in early stages from other forms of cutis laxa. ⁵ (See also Neurometabolic Cutis Laxa.) |
| <i>PYCR1</i> | De Barsy syndrome B (ARCL3B) (OMIM 614438) | AR | + | - | - | +++ | - | Translucent skin; chorea-athetosis (See also Neurometabolic Cutis Laxa.) |
| | ARCL2B (OMIM 612940) | AR | + | - | - | +++ | - | Translucent skin (See also Neurometabolic Cutis Laxa.) |

Table 3. continued from previous page.

| Gene | Disorder | MOI | Clinical Findings | | | | | Comment |
|----------------|---|-----|-------------------|-----------|-----------|-------|---------------------|---|
| | | | Cutis laxa | Emphysema | Aneurysms | ID/DD | Bladder diverticula | |
| <i>RIN2</i> | <i>RIN2</i> -related cutis laxa (MACS syndrome) (OMIM 613075) | AR | + | - | - | ± | Unknown | Very characteristic facial gestalt; ⁶ alopecia; mild cutis laxa, mostly manifest as redundant, hyperextensible facial skin (See also Neurometabolic Cutis Laxa.) |
| <i>SLC2A10</i> | Arterial tortuosity syndrome | AR | + | - | + | - | - | May display droopy facial appearance similar to other forms of cutis laxa ⁷ & have a high palate w/dental crowding; widespread arterial tortuosity |

ADCL = autosomal dominant cutis laxa; ARCL = autosomal recessive cutis laxa; CDG = congenital disorder of glycosylation; DD = developmental delay; ID = intellectual disability; MACS = macrocephaly, alopecia, cutis laxa, & scoliosis; MOI = mode of inheritance; SVAS = supravalvular aortic stenosis

1. Beyens et al [2019]
2. Verlee et al [2021]
3. McKenzie et al [2021]
4. Pottie et al [2021]
5. Sousa et al [2014], Piard et al [2018]
6. Basel-Vanagaite et al [2009]
7. Callewaert et al [2008], Beyens et al [2019]

Neurometabolic Cutis Laxa

The term "neurometabolic cutis laxa" has been suggested for a group of diseases related to inborn errors of metabolism. These disorders combine cutis laxa and skeletal defects with neurometabolic findings and result from pathogenic variants causing aberrant intracellular processing of extracellular matrix proteins as well as other proteins necessary for neurometabolic homeostasis.

Known genetic defects involved in neurometabolic cutis laxa include:

- Aberrant glycosylation due to reduced acidification of the secretory vesicles (caused by defects in subunits of the v-ATPase transporter, including *ATP6V0A2*, *ATP6V1E1*, *ATP6V1A*, and *ATP6AP1* [OMIM 300972]);
- Defects in transporters for cofactors necessary for enzymes in the glycosylation pathway (*ATP7A*, encoding a copper transporter);
- Defects in proteins involved in retrograde Golgi-to-ER transport (*COG7* [see [Congenital Disorders of N-Linked Glycosylation and Multiple Pathway Overview](#)], *GORAB*, *NBAS*, *RIN2*);
- Defects in enzymes involved in mitochondrial processes that include proline synthesis (*PYCR1*, encoding pyrroline-5-carboxylate reductase 1, and *ALDH18A1*, encoding delta-1-pyrroline-5-carboxylate synthase);
- Defects in enzymes involved in the synthesis of reducing equivalents to protect the cell from reactive oxygen species (*TALDO1* [OMIM 606003]);
- Defects in phosphatidylserine synthesis (*PTDSS1*) and mitochondrial fatty acid beta-oxidation (*ECHS1*).

Note: For simplicity and clarity, not all of the growing list of genes involved in neurometabolic cutis laxa have been included in Table 3.

Management

No clinical practice guidelines for *ELN*-related cutis laxa have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *ELN*-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 *ELN*-Related Cutis Laxa

| System/Concern | Evaluation | Comment |
|---------------------------------------|---|---|
| Cardiovascular | Echocardiography | To evaluate: <ul style="list-style-type: none"> • Aortic valve morphology • Diameter of aortic root & ascending aorta |
| | MR angiography | <ul style="list-style-type: none"> • To evaluate arterial tortuosity • To enable visualization of ascending aorta when echocardiography is inadequate • Baseline testing at age 15 yrs |
| Pulmonary | Chest radiography | Baseline eval before puberty |
| | High-resolution computed tomography | To evaluate severity of emphysema in symptomatic persons |
| | Peak flow measurement | Baseline testing usually at age 5 yrs |
| | Pulmonary function tests | Baseline testing at age 7 yrs |
| Urogenital system | Ultrasound exam | To evaluate for bladder diverticula |
| Ophthalmologic | Routine eye exam by ophthalmologist | W/attn to whether ptosis is obscuring pupil & causing person to adopt head tilt to clear pupillary axis |
| Joint laxity/pain | Physical therapy | <ul style="list-style-type: none"> • To identify joint hyperlaxity & joint instability/subluxations • To evaluate general posture |
| Self-esteem | Psychological screening | Assess for need for intervention for significant self-esteem issues requiring proactive psychological support. |
| Genetic counseling | By genetics professionals ¹ | To inform affected persons & their families re nature, MOI, & implications of <i>ELN</i> -related cutis laxa to facilitate medical & personal decision making |
| Family support & resources | Assess need for: <ul style="list-style-type: none"> • Community or online resources such as Parent to Parent; • Social work involvement for parental support. | |

MOI = mode of inheritance

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *ELN*-related cutis laxa.

Supportive treatment. Experience in treating individuals with *ELN*-related cutis laxa is very limited. Treatment is largely symptomatic and serves to improve quality of life, maximize function, and reduce complications. It ideally involves multidisciplinary care by specialists in relevant fields (Table 5).

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

| Manifestation/ Concern | Treatment | Considerations/Other |
|-------------------------------|--|---|
| Inguinal hernia | Repair w/mesh. | ↑ risk for recurrence |
| Aortic root dilatation | Aortic root repair (Bentall or David procedure depending on aortic valve function) | <ul style="list-style-type: none"> • Best thresholds for aortic repair are not established. In general, criteria for Marfan syndrome can be used. • Effectiveness of beta-blocking agents or angiotensin receptor antagonists in slowing aortic root dilatation has not been evaluated, but (as w/other connective tissue disorders) these are likely beneficial. • For beta-blocking agents, caution is appropriate in persons w/ (reversible) obstructive airway disease, & cardio-selective beta-blocking agents may be preferred. |
| Emphysema | Beta mimetics, anticholinergic agents | Avoid use of anticholinergic agents in persons w/bladder diverticula. |
| Bladder diverticula | <ul style="list-style-type: none"> • Education on complete bladder emptying when voiding • Antibiotic prophylaxis in case of incomplete voiding & recurrent urinary tract infections • PT to strengthen pelvic floor to help prevent prolapse of pelvic organs • Catheterization if significant urinary residual after voiding | |
| Joint hypermobility | PT | Encourage non-weight-bearing exercise such as cycling & swimming. |
| Joint pain | <ul style="list-style-type: none"> • PT • Pain medications in case of acute aggravation of pain | <ul style="list-style-type: none"> • Lifestyle recommendations • Non-weight-bearing exercise such as cycling & swimming |
| Ptosis | Eyelid surgery | Surgery is recommended when eyelid obscures pupil &/or sagging results in recurrent conjunctival infection/irritation. |
| Skin | Cosmetic surgery, lipofilling | <ul style="list-style-type: none"> • Skin laxity often recurs. • Cosmetic interventions are currently not encouraged. |
| Self-esteem | Psychological support | Such as giving children age-appropriate language to describe their condition to help w/curious peers |

PT = physical therapy

Surveillance

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

| System/Concern | Evaluation | Frequency |
|-----------------------|--------------------------------|---|
| Cardiovascular | Echocardiography | Annually (or depending on measurements/progression) |
| | Magnetic resonance angiography | Post puberty, frequency based on observations or every 5 yrs ¹ |

Table 6. continued from previous page.

| System/Concern | Evaluation | Frequency |
|----------------------------|---|--|
| Pulmonary | Lung function tests | <ul style="list-style-type: none"> • Baseline testing at age 7 yrs • Repeat if there is shortness of breath or decline in peak flow measurement. |
| | Peak flow measurement | <ul style="list-style-type: none"> • Baseline testing at age 5 yrs • Repeat every 6 mos. |
| Inguinal hernia | Clinical eval (Valsalva maneuver) | Annually |
| Joint pain | Clinical eval | |
| Ptosis | | |
| Bladder diverticula | <ul style="list-style-type: none"> • Ultrasound of urinary tract • Voiding cystography | Whenever there is incomplete voiding or urinary tract infections |
| Family/Community | Assess family need for social work support (e.g., other local resources) & follow-up genetic counseling if new questions arise (e.g., family planning). | At each visit |

1. Although the risk for arterial aneurysms beyond the ascending aorta is likely low, given the small number of individuals reported with *ELN*-related cutis laxa and the known risks for arterial aneurysm in other connective tissue disorders, it is recommended that the potential risks and benefits of screening with MR angiography be discussed with the patient.

Agents/Circumstances to Avoid

Avoid the following:

- Positive pressure ventilation unless needed to treat life-threatening conditions. No data exist on the potential risk of continuous positive airway pressure (CPAP) for the treatment of sleep apnea. Close follow up is warranted when CPAP is started.
- Contracting respiratory infections
- Tobacco smoking, which can result in rapid, severe loss of lung function in persons with *ELN*-related cutis laxa
- Isometric exercise (which causes an increase in blood pressure)
- Contact sports. The increased risk for joint injury or pain related to contact sports should be discussed. In case of arterial aneurysms reaching diameters necessitating surgery, blunt trauma should be prevented as much as possible (similar to [Marfan syndrome](#) guidelines).
- Sunbathing or tanning, to preserve residual skin elasticity. Vitamin D supplementation should be considered in this context, and monitored annually.

Evaluation of Relatives at Risk

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

Pregnancy Management

At least 21 pregnancies have been reported in affected females. No perinatal complications for the affected mother or the neonate were reported [Zhang et al 1999, Rodriguez-Revenga et al 2004, Urban et al 2005, Szabo et al 2006, Hadj-Rabia et al 2013, Vodo et al 2015, Okuneva et al 2019, Xiao et al 2019, Velandia-Piedrahita et al 2020].

Per guidelines used for women with [Marfan syndrome](#) who are planning a pregnancy, women with *ELN*-related cutis laxa require preconception cardiovascular evaluation, including assessment of the aortic root diameter, as well as increased surveillance throughout the pregnancy and six months post partum.

Additionally, pulmonary evaluation and follow up are warranted before and during pregnancy. Pregnancy may aggravate respiratory symptoms as a result of reduced lung volume, resulting in increased respiratory effort in the third trimester.

Uterine prolapse may occur [Urban et al 2005].

Affected women who anticipate pregnancy or become pregnant and are taking a beta-blocker should continue it during pregnancy; however, some other classes of medications, such as angiotensin receptor-blocking agents, are teratogenic and should be discontinued or changed to beta-blocking agents, given the increased risk for teratogenicity (i.e., increased risk for fetal loss, oligohydramnios, and abnormal fetal development) typically related to second- and third-trimester exposure. Women who are planning a pregnancy or who become pregnant while taking an angiotensin receptor blocker can be transitioned to a beta-blocker.

See [MotherToBaby](#) for further information on medication use during pregnancy.

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

ELN-related cutis laxa is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- About one third of individuals diagnosed with ELN-related cutis laxa have an affected parent.
- About two thirds of individuals diagnosed with ELN-related cutis laxa have the disorder as the result of a *de novo* ELN pathogenic variant.
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
 - The proband has a *de novo* pathogenic variant.
 - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Thus far, germline mosaicism has not been reported in ELN-related cutis laxa. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with ELN-related cutis laxa may appear to be negative because of a milder personal appreciation of a phenotypic presentation in the affected parent. Therefore,

an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- A sib who inherits a pathogenic variant is expected to have manifestations of the disorder; however, intrafamilial clinical variability is observed in *ELN*-related cutis laxa.
- If the *ELN* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *ELN* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for *ELN*-related cutis laxa because of the possibility of a mild presentation in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *ELN*-related cutis laxa has a 50% chance of inheriting the *ELN* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *ELN* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

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 or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ELN* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing 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

- **Genodermatoses Network - Fondation René Touraine**

The network on rare genetic skin diseases for professionals and patients.

France

[Our Network](#)

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. ELN-Related Cutis Laxa: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---------------------|-------------------------|-------------------------|------------------------------|---------------------|---------------------|
| ELN | 7q11.23 | Elastin | ELN database | ELN | ELN |

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 ELN-Related Cutis Laxa ([View All in OMIM](#))

| | |
|------------------------|---|
| 123700 | CUTIS LAXA, AUTOSOMAL DOMINANT 1; ADCLI |
| 130160 | ELASTIN; ELN |

Molecular Pathogenesis

ELN pathogenic variants causing *ELN*-related cutis laxa result in a shift in the reading frame in the last four exons of the *ELN* transcript, causing an elongated sequence at the C terminus of the protein tropoelastin. The altered tropoelastin is stable and secreted [Szabo et al 2006, Callewaert et al 2011]. When in the secretory pathway, the abnormal protein interacts with wild type tropoelastin increasing self-aggregation (coacervation) and clump formation that impedes proper crosslinking in elastic fibers by lysyl oxidases [Callewaert et al 2011]. As a result, electron microscopy of skin biopsies shows abnormal elastic fibers that appear as amorphous clumps without parallel directionality to the microfibrils [Callewaert et al 2011].

Mechanism of disease causation. *ELN* pathogenic variants that cause *ELN*-related cutis laxa result in an abnormal protein with an extended C terminal. The pathogenic variant may result in a frameshift with a readthrough in the 3' untranslated region or result in inclusion of noncoding sequences in the mature mRNA. Mutated tropoelastin has been shown to aggregate with wild type elastin. Hence, the likely mechanism is a dominant-negative effect [Callewaert et al 2011].

Although other mechanisms of *ELN* variants have been described, confirmation is necessary to establish a causal relationship with typical *ELN*-related cutis laxa [Graul-Neumann et al 2008, Velandia-Piedrahita et al 2020].

***ELN*-specific laboratory technical considerations.** Most identified pathogenic variants in *ELN*-related cutis laxa cause an *ELN* frameshift affecting exons 30-34 and result in an extended open reading frame.

A more complex gene duplication/triplication was reported in one family by Urban et al [2005]. The predicted open reading frame similarly extended beyond the typical stop codon.

Molecular testing should include analysis for deep intronic variants. One reported intronic splice variant (c.2272+20), causing inclusion of a 19-base pair intronic sequence in the mature *ELN* mRNA resulting in a

frameshift, was reported in a boy age five years with a phenotype indistinguishable from other individuals with *ELN*-related cutis laxa [Vodo et al 2015].

Table 7. Notable *ELN* Pathogenic Variants

| Reference Sequences | DNA Nucleotide Change (Alias ¹) | Predicted Protein Change | Comment [Reference] |
|----------------------------------|---|--------------------------|--|
| NM_001278939.2 NP_001265868.1 | c.1708C>T ² (1621C>T) | p.Arg570Ter | Typically assoc w/SVAS & reported in 1 family w/ <i>ELN</i> -related cutis laxa [Graul-Neumann et al 2008] |
| | c.2272+20C>G (2086+20) | p.Val697ArgfsTer57 | Deep intronic variant [Vodo et al 2015] |

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.

1. Variant designation that does not conform to current naming conventions

2. This nucleotide change affects the nucleotide immediately upstream of the donor splice site of intron 25 and is predicted to affect splicing.

Chapter Notes

Author Notes

Bert Callewaert is an Associate Professor at Ghent University and a pediatrician/clinical geneticist at the Center for Medical Genetics of the Ghent University Hospital. His research focuses on connective tissue disorders (including arterial tortuosity syndrome, cutis laxa syndromes, and familial thoracic aortic aneurysms). Both zebra fish and mouse models are used to gain insight into the pathogenesis of these disorders.

Dr Callewaert is actively involved in clinical research regarding individuals with *ELN*-related cutis laxa. He would be happy to communicate with persons who have any questions regarding diagnosis of *ELN*-related cutis laxa or other considerations.

Contact Dr Callewaert to inquire about the interpretation of *ELN* variants of uncertain significance.

Dr Callewaert is also interested in hearing from clinicians treating families affected by cutis laxa in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

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Zsolt Urban is an Associate Professor of Human Genetics at the Graduate School of Public Health of the University of Pittsburgh. His research is focused on cutis laxa and related disorders. His research team pursues clinical, cell culture, and animal model studies to characterize the natural history of cutis laxa and identify the genetic causes and underlying molecular mechanisms responsible for this group of disorders.

For more information, go to the [Cutis Laxa Research Study](#) website or email urbanz@pitt.edu.

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