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# *LTBP4*-Related Cutis Laxa

Synonyms: Autosomal Recessive Cutis Laxa Type 1C (ARCL1C), Urban-Rifkin-Davis Syndrome (URDS)

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## Summary

### Clinical characteristics

*LTBP4*-related cutis laxa is characterized by cutis laxa, early childhood-onset pulmonary emphysema, peripheral pulmonary artery stenosis, and other evidence of a generalized connective tissue disorder such as inguinal hernias and hollow visceral diverticula (e.g., intestine, bladder). Other manifestations can include pyloric stenosis, diaphragmatic hernia, rectal prolapse, gastrointestinal elongation/tortuosity, cardiovascular abnormality, pulmonary hypertension, hypotonia and frequent pulmonary infections. Bladder diverticula and hydronephrosis are common. Early demise has been associated with pulmonary emphysema.

### Diagnosis/testing

The diagnosis of *LTBP4*-related cutis laxa is established in a proband with cutis laxa and biallelic pathogenic variants in *LTBP4*.

### Management

*Treatment of manifestations:* Treatment is largely symptomatic and may include: treatment of pulmonary emphysema (inhaled corticosteroids, atropine, and selective β2-adrenergic bronchodilation, and supplemental oxygen as needed) medical or surgical treatment for gastrointestinal issues; education on complete bladder emptying when voiding; and treatment of clinically relevant pulmonary artery stenosis and pulmonary hypertension; physical therapy for muscle strength and stability. Routine immunizations against respiratory infections is important.

*Surveillance:* Yearly assessment of pulmonary function and oxygenation and repeat imaging of the GI tract, urinary tract, and cardiovascular system.

*Agents/circumstances to avoid:* Positive pressure ventilation (unless needed to treat life-threatening conditions); exposure to people with respiratory infections; tobacco smoking, which can result in rapid severe loss of lung

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function; isometric exercise and contact sports or activities that increase the risk for blunt abdominal trauma and/or joint injury or pain; sunbathing or tanning to preserve any residual skin elasticity.

## Genetic counseling

*LTBP4*-related cutis laxa is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *LTBP4* 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. Once the *LTBP4* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing, and preimplantation genetic testing for *LTBP4*-related cutis laxa are possible.

# Diagnosis

No formal clinical diagnostic criteria have been established for *LTBP4*-related cutis laxa.

## Suggestive Findings

*LTBP4*-related cutis laxa **should be suspected** in individuals with the following clinical and family history findings.

**Clinical findings**

- Loose redundant skin folds (cutis laxa)
- Pulmonary emphysema
- Gastrointestinal and/or urinary tract diverticula

**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 *LTBP4*-related cutis laxa **is established** in a proband with cutis laxa and biallelic pathogenic (or likely pathogenic) variants in *LTBP4* 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 *LTBP4* variants of uncertain significance (or of one known *LTBP4* pathogenic variant and one *LTBP4* variant of uncertain significance) does not establish or rule out the diagnosis.

Because the phenotype of *LTBP4*-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 *LTBP4*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **A cutis laxa multigene panel** that includes *LTBP4* 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 genes 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 *LTBP4*-Related Cutis Laxa

| Gene [1] | Method | Proportion of Pathogenic Variants [2] Detectable by Method |
|---|---|---|
| *LTBP4* | Sequence analysis [3] | 26/26 [4] |
| | Gene-targeted deletion/duplication analysis [5] | Unknown; none reported to date [4] |

*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.* Urban et al [2009], Callewaert et al [2013], Su et al [2015], Ritelli et al [2019], Gupta et al [2020], and Zhang 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.

# Clinical Characteristics

## Clinical Description

*LTBP4*-related cutis laxa is characterized by cutis laxa, early childhood-onset pulmonary emphysema, peripheral pulmonary artery stenosis, and other evidence of a generalized connective tissue disorder such as inguinal hernias and hollow visceral diverticula (e.g., intestine, bladder). *LTBP4*-related cutis laxa, a severe but variable disorder, has been reported to date in 25 individuals from 20 families [Urban et al 2009, Callewaert et al 2013, Su et al 2015, Ritelli et al 2019, Gupta et al 2020, Zhang et al 2020]. In most, cutis laxa was evident from birth. Pulmonary emphysema was present in nearly all.

**Table 2.** *LTBP4*-Related Cutis Laxa: Frequency of Select Features

| Feature | Frequency | | |
|---|---|---|---|
| | In nearly all | Common | Infrequent |
| Cutis laxa | ● | | |
| Pulmonary emphysema | ● | | |
| Pulmonary infections | | ● | |
| Pyloric stenosis | | | ● |
| Diaphragmatic issues | | ● | |

*Table 2. continued from previous page.*

| Feature | Frequency | | |
|---|---|---|---|
| | In nearly all | Common | Infrequent |
| Rectal prolapse | | | ● |
| Gastrointestinal diverticula | ● | | |
| Gastrointestinal elongation/tortuosity | | | ● |
| Bladder diverticula | | ● | |
| Hydronephrosis | | ● | |
| Cardiovascular abnormality | | ● | |
| Pulmonary hypertension | | ● | |
| Hypotonia/motor delay | | ● | |
| Inguinal &/or umbilical hernias | | ● | |

**Prenatal findings.** Polyhydramnios has been described in two instances in association with esophageal tortuosity or diverticulosis in the newborn [Callewaert et al 2013]. Major complications, such as preterm premature rupture of membranes, have not been reported during pregnancy with affected fetuses.

**Skin.** Cutis laxa is evident from birth and is often generalized. Although the face may be relatively spared, it usually shows prominent, sagging cheeks and ears with a prematurely aged appearance. In one affected individual cutis laxa was limited to the trunk; another affected individual had hyperextensible skin rather than overfolded skin.

The skin may show thinning and visible veins, as well as small wrinkles on the dorsum of hands and feet.

Hair may be sparse and slowly growing, especially temporally.

**Pulmonary.** Pulmonary emphysema is variable, but most commonly becomes clinically manifest during the first months of life as respiratory distress or hypoxia and may be evident on routine x-rays or lung CT. It is often progressive and severe. One individual without pulmonary emphysema did show lung atelectasis and suffered from a pneumonia with significant respiratory distress at the age of 18 months [Ritelli et al 2019].

Precipitating/aggravating factors may include bronchiolitis, pneumonia, and positive pressure ventilation. Tracheomalacia, pulmonary hypertension, and congenital diaphragmatic hernia may worsen the respiratory problems.

In three individuals who survived beyond age five years, pulmonary emphysema was clinically less severe. In one of these individuals CT of the lungs showed emphysema, and lung function tests were consistent with severe obstructive lung disease ($FEV_1$/FVC 51% of predicted value) at age 23 years.

**Gastrointestinal (GI).** All segments of the GI tract can be affected.

- Newborns are at risk for pyloric stenosis (3/25 individuals).
- Diaphragmatic involvement includes sliding hernias, congenital hernias, hiatal hernia, and diaphragmatic eventration (12/25 individuals). Often gastroesophageal reflux is associated with diaphragmatic insufficiency (sliding hernia). These hernias are rarely encountered in other types of cutis laxa.
- Rectal prolapse may occur.
- Diverticula, elongation, and dilatation of the gastrointestinal tract increase the risk for intestinal wall fragility, rupture, and necrosis.

**Genitourinary.** Bladder diverticula are frequent and may worsen over time. Incomplete voiding may result from bladder diverticula and/or urethral weakness, prolapse, or diverticula.

Hydronephrosis, which is also frequent, may result from inherent weakness of the collecting system and/or vesicoureteral reflux.

Both incomplete voiding and dilatation of the collecting system may predispose to urinary tract infections.

**Cardiovascular.** Problems may include the following:

- Congenital stenosis of the peripheral pulmonary arteries
- Septal defects
- Atrial aneurysm (in 1 individual)
- Valvular dysfunction (including dysplasia of any valve that may result in stenosis or regurgitation)
- Arterial tortuosity and aortic root widening at the upper limit of normal (reported in 2 individuals) [Su et al 2015, Ritelli et al 2019]

Pulmonary hypertension is a common complication that further impairs oxygenation. It is likely that emphysema and peripheral arterial stenoses contribute to the pulmonary hypertension.

No long-term follow-up data are available on the aortic root or the arterial tree.

**Neurologic.** Hypotonia may be evident from birth and can be followed by motor development delay. Some individuals may have normal muscle strength or lack hypotonia [Zhang et al 2020].

Cognitive functioning is expected to be within the normal range; however, experience is limited because most affected individuals have died early or were critically ill. Of four children who survived longer than five years, one had slightly delayed expressive language development. Two affected individuals who survived to adulthood had normal cognitive function.

**Infections.** Pulmonary infections and especially bronchiolitis may be more frequent and have a severe course due to the severe emphysema and anatomic abnormalities of the respiratory tract.

One child had a late-onset infection with group B streptococcus; one died from brain abscesses.

No immunologic tests have been performed in these children.

**Other**

- Inguinal and umbilical hernias can be present.
- Postnatal growth delay may occur, but may be secondary to failure to thrive due to chronic, critical illness and respiratory problems rather than inherent to the condition.
- One proband was reported to have a coagulopathy with subhyaloid hemorrhage [Zhang et al 2020].

**Skin histology.** Light microscopy shows fragmented and weakly stained dermal elastic fibers with less defined edges compared to controls. In addition, the fine candelabra-like fibers in the upper dermis are missing.

Electron microscopy shows elastic fiber anomalies specific for this type of cutis laxa: very small amounts of elastin within the microfibrillar network and large globular elastin deposits that are separate from the microfibrillar bundles.

**Prognosis.** The overall prognosis is poor, with an average survival of 2.4 years (range 1 month to 13 years). Longer survival is possible and has included four females, ages 7-23 years at the time of reporting. Early demise has been associated with pulmonary emphysema; brain abscess and gastric perforation were each reported once as a cause of death.

## Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

## Prevalence

The prevalence is unknown, but the disorder is expected to be very rare (<1:1,000,000) with only 20 families reported to date.

There are no data on specific populations in which the prevalence may be greater or less than expected for the general population.

# Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants of *LTBP4*.

# Differential Diagnosis

The primary clinical differential diagnoses to consider are autosomal recessive cutis laxa type 1A (ARCL1A), autosomal recessive cutis laxa type 1B (ARCL1B), and autosomal dominant cutis laxa type 1 (ADCL1):

- **ARCL1A** (*FBLN5*-related cutis laxa) is characterized by cutis laxa, early childhood-onset pulmonary emphysema, peripheral pulmonary artery stenosis, and other evidence of a generalized connective tissue disorder such as inguinal hernias and hollow visceral diverticula (e.g., intestine, bladder). Occasionally, supravalvular aortic stenosis is observed. Considerable overlap exists between *FBLN5*- and *LTBP4*-related cutis laxa and the two entities are difficult to distinguish from each other purely on a clinical basis. In *FBLN5*-related cutis laxa, the skin features may be more pronounced. In *LTBP*-related cutis laxa, supravalvular aortic stenosis has not yet been observed, while bladder and gastrointestinal diverticula as well as rectal prolapse are more frequent.
- **ARCL1B** (*EFEMP2*-related cutis laxa) is characterized by cutis laxa and systemic involvement, most commonly arterial tortuosity, aneurysms, and stenosis; retrognathia; joint laxity; and arachnodactyly. The severe arterial tortuosity seen in *EFEMP2*-related cutis laxa is absent in *LTBP4*-related cutis laxa.
- **ADCL1** (*ELN*-related cutis laxa) presents with generalized cutis laxa of variable severity. Aortic root dilatation and emphysema may occur as early as childhood and are progressive. However, emphysema is usually milder than in *LTBP4*-related cutis laxa [Szabo et al 2006, Callewaert et al 2011, Hadj-Rabia et al 2013].

ARCL1A, ARCL1B, ADCL1 and other disorders to consider in the differential diagnosis of *LTBP4*-related cutis laxa are summarized in Table 3.

**Table 3.** Disorders to Consider in the Differential Diagnosis of *LTBP4*-Related Cutis Laxa

| Gene | Disorder | MOI | Clinical Findings | | | | | Comment |
|---|---|---|---|---|---|---|---|---|
| | | | Cutis laxa | Emphysema | Aneurysms | ID/DD | Bladder diverticula | |
| *ALDH18A1* | De Barsy syndrome A (ARCL3A) (OMIM 219150) | AR | + | – | – | ++ | – | Translucent skin |
| | ADCL3 (OMIM 616603) | AD | + | – | – | + | – | |

*Table 3. continued from previous page.*

| Gene | Disorder | MOI | Clinical Findings | | | | | Comment |
|---|---|---|---|---|---|---|---|---|
| | | | Cutis laxa | Emphysema | Aneurysms | ID/DD | Bladder diverticula | |
| *ATP6V1A* | ARCL2D (OMIM 617403) | AR | ++ | – | + | + | – | Facial appearance similar to ARCL2A; myopathy; lipodystrophy, marfanoid habitus, potentially lethal respiratory problems in infancy; no seizures; often no ID. Like ARCL2A, ARCL2D & ARCL2C are CDGs. |
| *ATP6V1E1* | ARCL2C (OMIM 617402) | AR | ++ | – | + | + | – | |
| *ATP7A* [1] | Occipital horn syndrome (OHS) / Menkes (See *ATP7A* Copper Transport Disorders.) | XL | + | – | + | + | +++ | Bony exostoses, intracranial & retinal tortuosity |
| *ATP6V0A2* | *ATP6V0A2*-related cutis laxa (ARCL2A) | AR | ++ | + | – | + | – | |
| *EFEMP1* [2] | *EFEMP1*-related cutis laxa | AR | + | – | – | – | – | Multiple hernias, marfanoid habitus |
| *EFEMP2* | *EFEMP2*-related cutis laxa (ARCL1B) | AR | ++ | ++ | +++ | – | – | Bone fragility, arachnodactyly |
| *EMILIN1* [3] | *EMILIN1*-related cutis laxa | AR | + | – | +++ | – | – | Bone fragility, congenital anomalies of kidney & urinary tract |
| *ELN* | *ELN*-related cutis laxa (ADCL1) | AD | + | + | + | – | – | |
| *FBLN5* | *FBLN5*-related cutis laxa (ARCL1A & ADCL2) | AR AD | +++ | +++ | – | – | ++ | Supravalvular aortic stenosis |
| *GORAB* | Gerodermia osteodysplastica (GO) (OMIM 231070) | AR | ++ | – | – | – | – | |
| *LOX* [4] | *LOX*-related cutis laxa | AR | ++ | + | ++ | – | – | |
| *LTBP1* [5] | *LTBP1*-related cutis laxa | AR | + | – | – | – | – | Craniosynostosis, short stature, congenital cardiac defects |
| *NBAS* | Short stature, optic nerve atrophy, & Pelger-Huet anomaly (SOPH syndrome) (OMIM 614800) | AR | + | – | – | ++ | – | Hepatopathy; optic atrophy; hypogamma-globulinemia, liver failure during episodes of fever, Pelger-Huet anomaly |

*Table 3. continued from previous page.*

| Gene | Disorder | MOI | Clinical Findings | | | | | Comment |
|---|---|---|---|---|---|---|---|---|
| | | | Cutis laxa | Emphysema | Aneurysms | ID/DD | Bladder diverticula | |
| *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. [6] |
| *PYCR1* | De Barsy syndrome B (ARCL3B) (OMIM 614438) | AR | + | – | – | +++ | – | Translucent skin; chorea-athetosis |
| | ARCL2B (OMIM 612940) | AR | + | – | – | +++ | – | Translucent skin |
| *RIN2* | *RIN2*-related cutis laxa (MACS syndrome) (OMIM 613075) | AR | + | – | – | ± | Unknown | Very characteristic facial gestalt [7]; alopecia; mild cutis laxa, mostly manifest as redundant, stretchable facial skin |
| *SLC2A10* | Arterial tortuosity syndrome | AR | + | – | + | – | – | Affected persons may display droopy facial appearance similar to other forms of cutis laxa [8] & 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. Beyens et al [2019]
2. Verlee et al [2021]
3. Adamo et al [2022]
4. McKenzie et al [2021]
5. Pottie et al [2021]
6. Sousa et al [2014], Piard et al [2018]
7. Basel-Vanagaite et al [2009]
8. Karakurt et al [2012]

# Management

No clinical practice guidelines for *LTBP4*-related cutis laxa have been published.

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *LTBP4*-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 *LTBP4*-Related Cutis Laxa

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Pulmonary emphysema** | Assessment of lung function | Incl oxygen saturation, spirometry, lung volumes & diffusion capacity |
| | • Chest radiograph or high-resolution CT scan<br>• Bronchoscopy if clinically indicated | |
| **Gastrointestinal concerns** | Eval by a pediatric gastroenterologist | • Visualization of GI tract by gastrographin ingestion or enema may be needed.<br>• Diaphragmatic hernia should be excluded. |
| **Genitourinary tract concerns** | Complete ultrasound of urinary tract. | Incl detailed eval of bladder for bladder diverticula. |
| | A voiding cystoureterogram may be needed to complement bladder ultrasound. | Due to potential presence of urethral diverticula, catheterization should be done carefully; intravenous pyelogram may be an alternative. |
| **Cardiovascular abnormality** | Pediatric cardiology eval incl echocardiography | Other evals as directed by cardiologist |
| **Hypotonia/ Hyperlaxity** | Physiotherapeutic eval | |
| **Genetic counseling** | By genetics professionals [1] | To inform affected persons & their families re nature, MOI, & implications of *LTBP4*-related cutis laxa in order to facilitate medical & personal decision making |
| **Family support & resources** | Assess need for:<br>• Community or online resources such as Parent to Parent;<br>• Social work involvement for parental support;<br>• Home nursing referral to stimulate motor development & assist w/potential feeding difficulties &/or oxygen supplementation. | |

MOI = mode of inheritance
*1.* Medical geneticist, certified genetic counselor, certified advanced genetic nurse

## Treatment of Manifestations

Experience in treating individuals with *LTBP4*-related cutis laxa is very limited. Treatment is largely symptomatic. A reasonable approach to treatment could include the following.

**Table 5.** Treatment of Manifestations in Individuals with *LTBP4*-Related Cutis Laxa

| Manifestation/ Concern | Treatment | Considerations/Other |
|---|---|---|
| **Pulmonary emphysema** | • Symptomatic treatment w/inhaled corticosteroids, atropine & selective β2-adrenergic bronchodilation<br>• Oxygen supplementation if necessary | |
| | Immunize against respiratory infections (influenza, *Streptococcus pneumonia, Haemophilus influenza*). | Consider passive immunization for RSV w/palivizumab during RSV season. |

*Table 5. continued from previous page.*

| Manifestation/ Concern | Treatment | Considerations/Other |
|---|---|---|
| **Gastrointestinal issues** | • Surgical treatment of congenital diaphragmatic hernia or severe hiatal hernia<br>• Medical treatment of gastroesophageal reflux to ↓ discomfort & reactive bronchospasms<br>• Mother's milk in infants to maximize passive immunization<br>• Gastrostomy tube may be needed to ensure nutrition in infants w/severe feeding difficulty.<br>• Dietary advice, sufficient fluid intake & (if needed) osmotic laxatives to avoid chronic constipation | |
| **Genitourinary issues** | • Education on complete bladder emptying when voiding<br>• Antibiotic prophylaxis in case of incomplete voiding & recurrent urinary tract infections<br>• Pelvic floor strengthening by PT may help to prevent prolapse of pelvic organs. | |
| | Consider artificial bladder implantation. | Performed in 1 person |
| **Cardiovascular concerns** | Care by (pediatric) cardiologist w/experience in connective tissue pathology | |
| | Treatment of clinically relevant pulmonary artery stenosis | Treatment by catheterization preferred, as it is minimally invasive & needs shorter period of anesthesia |
| | Medical treatment of pulmonary hypertension (e.g., by sildenafil) | As directed by pediatric cardiologist |
| **Hypotonia/ Hyperlaxity** | PT for muscle strength & stability | |

PT = physical therapist/therapy; RSV = respiratory syncytial virus

## Surveillance

**Table 6.** Recommended Surveillance for Individuals with *LTBP4*-Related Cutis Laxa

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Pulmonary emphysema** | Oxygen saturation | Daily; can be monitored at home in younger children |
| | Pulmonary function & oxygenation | Annually; more frequently if clinically indicated |
| | Low threshold for in-hospital observation if respiratory infections | On an ongoing basis |
| **Gastrointestinal tract** | Repeat imaging | Case by case as determined by specialist involved in care |
| **Genitourinary** | | |
| **Cardiovascular** | | Annually; more frequently if clinically indicated |
| **Hypovitaminoses** [1] | 25-hydroxyvitamin D level | Annually |

*1.* Due to avoidance of sunlight; see Agents/Circumstances to Avoid.

## Agents/Circumstances to Avoid

Avoid the following:

- Positive pressure ventilation unless needed to treat life-threatening conditions
- People with respiratory infections

- Tobacco smoking, which can result in rapid, severe loss of lung function in persons with *LTBP4*-related cutis laxa
- Isometric exercise and 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 any residual skin elasticity

## Evaluation of Relatives at Risk

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

## Pregnancy Management

Pregnancy has been observed in one affected female with an unaffected fetus. The pregnancy was uneventful, but delivery was induced because of elevated maternal blood pressure. Delivery was vaginal with normal healing and no signs of prolapse. Two years after delivery both the mother and her son were doing well.

Despite evidence for the possibility of relatively normal pregnancy, a risk of aggravation of cardiopulmonary manifestations, worsening of diaphragmatic hernia, and increased risk of both uterine rupture and exacerbation of pelvic floor/organ insufficiency including uterine, bladder, and rectal prolapse cannot be excluded based on this single case. Therefore, it is recommended that follow up of pregnancy and the postnatal period be done in a high-risk obstetric care unit with experience in connective tissue disorders.

## 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

*LTBP4*-related cutis laxa is inherited in an autosomal recessive manner.

## Risk to Family Members

**Parents of a proband**

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *LTBP4* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *LTBP4* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
    - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].

- Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- 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 *LTBP4* 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.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

**Offspring of a proband.** The offspring of an individual with *LTBP4*-related cutis laxa are obligate heterozygotes (carriers) for a pathogenic variant in *LTBP4*. (To date, pregnancy has been observed in one affected female with an unaffected fetus.)

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of an *LTBP4* pathogenic variant.

## Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *LTBP4* pathogenic variants in the family.

## 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 carriers or are at risk of being carriers.

## Prenatal Testing and Preimplantation Genetic Testing

Once the *LTBP4* pathogenic variants have 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.** LTBP4-Related Cutis Laxa: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *LTBP4* | 19q13.2 | Latent-transforming growth factor beta-binding protein 4 | LTBP4 database | LTBP4 | LTBP4 |

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 LTBP4-Related Cutis Laxa (View All in OMIM)

| | |
|---|---|
| 604710 | LATENT TRANSFORMING GROWTH FACTOR-BETA-BINDING PROTEIN 4; LTBP4 |
| 613177 | CUTIS LAXA, AUTOSOMAL RECESSIVE, TYPE IC; ARCL1C |

## Molecular Pathogenesis

Latent-transforming growth factor β-binding protein 4 (LTBP4) belongs to a family of four extracellular matrix proteins that are structurally related to fibrillins. LTBP4 has multiple isoforms with the long (LTBP4L) and short (LTBP4S) being the major isoforms. The third 8-cys domain of LTBP4 covalently binds the small latent complex consisting of the homodimer TGFβ1 and its propeptide (also known as latency-associated peptide). This interaction allows LTBP4 to sequester TGFβ1 and control its activation. However, the in vivo significance of this function has been called into question by the normal phenotype of mice with variants that prevent the binding of TGFβ1 to LTBP4 [Dabovic et al 2015].

Evidence suggests that LTBP4 enhances elastogenesis by regulating the incorporation of elastin-fibulin-5 complexes into the microfibrillar bundles to form elastic fibers [Noda et al 2013, Dabovic et al 2015], a mechanism that provides an explanation for the significant phenotypic overlap of *LTBP4*- and *FBLN5*-related cutis laxas.

In addition to its function in TGFβ1 sequestration and elastic fiber formation, LTBP4 stabilized the TGFβ receptors TGFBR1 and TGFBR2 [Su et al 2015]. Loss of LTBP4 results in diminished TGFβ signaling in skin fibroblasts and mouse tissue caused by rapid degradation of the TGFBR1/TGFBR2 receptor complex, which is reversed by chemical inhibition of TGFBR1 kinase activity.

In mice and humans with LTBP4 deficiency, emphysema results from impaired terminal air sac septation [Sterner-Kock et al 2002, Urban et al 2009]. Of note, mice expressing the long form only (*Ltbp4S*$^{-/-}$) survive into adulthood and show late-onset emphysema only, indicating that interaction of LTBP4L and fibulin-4 is sufficient for survival [Bultmann-Mellin et al 2015, Bultmann-Mellin et al 2016]. The role of TGFβ signaling in the development of *LTBP4*-related emphysema is still poorly understood. Increased TGFβ signaling has been observed during embryologic stages in *Ltbp4*$^{-/-}$ knockout mice and, in this mouse model, impaired terminal sac septation could be counteracted in E18.5 (embryonic day 18.5) embryos by prenatal treatment with a TGFBR1

inhibitor or by elimination of TGFβ2 [Dabovic et al 2009]. In *Ltbp4*$^{-/-}$ mice, impaired elastogenesis, increased TGFβ activity, and reduced angiogenesis would contribute to impaired air sac septation [Bultmann-Mellin et al 2017]. However, lung development was normal in a *Ltbp4* knock-in mouse model expressing LTBP4 that was unable to bind TGFβ1 [Dabovic et al 2015]. Therefore, TGFβ dysregulation and perinatal failure of elastogenesis may act together in the pathophysiology of *LTBP4*-related pulmonary emphysema.

**Mechanism of disease causation.** Most of the currently described pathogenic variants are nonsense or frameshift variants resulting in a premature termination codon and nonsense-mediated decay. The mechanism causing *LTBP4*-related cutis laxa appears to be associated with the absence of LBTP4 protein causing failure of fibulin-5-elastin complexes to target the microfibrils, resulting in severely impaired elastic fiber formation [Urban et al 2009, Callewaert et al 2013, Dabovic et al 2015].

# 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 zebrafish and mouse models are used to gain insight into the pathogenesis of these 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 diseases. For more information, go to the Cutis Laxa Research Study website or email urbanz@pitt.edu.

Dr Callewaert (bert.callewaert@ugent.be) is actively involved in clinical research regarding individuals with *LTBP4*-related cutis laxa. He would be happy to communicate with persons who have any questions regarding diagnosis of *LTBP4*-related cutis laxa or other considerations.

Contact Dr Callewaert at bert.callewaert@ugent.be to inquire about the interpretation of *LTBP4* variants of uncertain significance.

Dr Callewaert (bert.callewaert@ugent.be) 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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## Revision History

- 23 February 2023 (aa) Revision: clarified age of onset of emphysema in *ELN*-related cutis laxa; added *EMILIN1*-related cutis laxa to Differential Diagnosis
- 14 July 2022 (blc) Revision: contact information for questions about *LTBP4*-related cutis laxa added to Author Notes
- 22 July 2021 (ha) Comprehensive update posted live
- 11 February 2016 (bp) Review posted live

- 1 December 2014 (zu) Original submission

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