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LTBP4-Related Cutis Laxa

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

Bert L Callewaert, MD, PhD
Center for Medical Genetics
Ghent University Hospital
Ghent, Belgium
Bert.Callewaert@UGent.be

Zsolt Urban, PhD
Department of Human Genetics
University of Pittsburgh Graduate School of Public Health
Pittsburgh, Pennsylvania
urbanz@pitt.edu

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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 disorder such as inguinal hernias and hollow visceral diverticula (e.g., intestine, bladder). Other manifestations can include diaphragmatic hernia, congenital heart disease, intestinal malrotation, and ectopic kidneys. Of the 17 affected individuals (from 13 families) reported to date, cutis laxa was evident from birth in most and pulmonary emphysema was present in all. Pulmonary emphysema is clinically evident during the first months of life, is often severe, and is the most common cause of death. Bladder diverticula and hydronephrosis are common.

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: routine treatment of pulmonary emphysema (inhaled corticosteroids, atropine, and selective β2-adrenergic bronchodilation, and supplemental oxygen as needed) and gastroesophageal reflux; education on complete bladder emptying when voiding; and treatment of clinically relevant pulmonary artery stenosis and pulmonary hypertension.

Prevention of secondary complications: Routine immunizations against respiratory infections.

Surveillance: Routine 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); isometric exercise and contact sports or activities that increase the risk for blunt abdominal trauma and/or joint injury or pain; exposure to people with respiratory infections.

Genetic counseling. *LTBP4*-related cutis laxa is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has 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. Carrier testing for at-risk relatives and prenatal testing or preimplantation genetic diagnosis for pregnancies at increased risk are possible if the *LTBP4* pathogenic variants in the family are known.

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 loose redundant skin folds (cutis laxa) and various internal organ involvement including pulmonary emphysema and gastrointestinal and/or urinary tract diverticula.

The following major clinical findings and the rest of this *GeneReview* are based on the three reports published on *LTBP4*-related cutis laxa [Urban et al 2009, Callewaert et al 2013, Su et al 2015]:

Skin

- Loose redundant skin folds, mainly on the trunk and limbs with variable involvement of the facial skin resulting in a droopy and puffy face giving a prematurely aged appearance. Rarely, the skin can be mainly hyperextensible instead of lax.
- Thin skin with prominent veins

Pulmonary

- Emphysema: variable but is mostly congenital or early-onset and progressive. May clinically manifest as respiratory distress or hypoxia; may be evident on routine x-rays or lung CT
- Laryngomalacia, tracheomalacia, bronchomalacia
- Bronchiolitis: may be severe and result in progression of emphysematous lesions

Gastrointestinal

- Diverticula throughout the gastrointestinal tract
- Gastrointestinal tract dilatations
- Elongated gastrointestinal tract resulting in tortuosity
- Perforation of the stomach or intestine
- Gastroesophageal reflux
- Rectal prolapse
- Pyloric stenosis

Genitourinary

- Bladder diverticula and rupture
- Hydronephrosis
- Urinary tract infections (secondary to anatomical abnormalities of the urinary tract)

Cardiovascular

- Peripheral pulmonary artery stenosis
- Atrial septal defects and atrial septal aneurysms
- Cardiac valve insufficiency (mitral, tricuspid, aortic)
- Pulmonary and aortic valve stenosis
- Pulmonary hypertension

Craniofacial

- Sagging skin with prominent sagging cheeks
- Sparse hair, especially temporally
- Sloping forehead
- Narrow forehead
- Periorbital fullness
- Epicanthus
- Depressed nasal bridge
- Anteverted nares
- Long philtrum
- Micrognathia
- Large ears

Other

- Inguinal and umbilical hernias
- Sliding and diaphragmatic hernias or diaphragmatic eventration
- Muscular hypotonia
- Joint laxity

Establishing the Diagnosis

The diagnosis of *LTBP4*-related cutis laxa **is established** in a proband with cutis laxa and biallelic pathogenic variants in *LTBP4* (see Table 1).

It is appropriate to perform molecular analysis of *LTBP4* in individuals with the following:

- Cutis laxa or hyperextensible skin
  AND
- Pulmonary emphysema
  AND
- Gastrointestinal and/or bladder diverticula

Molecular genetic testing approaches can include:

- Sequence analysis of *LTBP4* followed by deletion/duplication analysis if only one or no pathogenic variant is found. Note: To date, no large intragenic deletions have been reported in affected individuals.
- Use of a multi-gene panel that includes *LTBP4* and other genes of interest (see Differential Diagnosis). Note: The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and over time.

Table 1.

Summary of Molecular Genetic Testing Used in *LTBP4*-Related Cutis Laxa

Gene [1]	Test Method	Proportion of Probands with Pathogenic Variants [2] Detectable by This Method
LTBP4	Sequence analysis [3]	17/17 [4]
	Gene-targeted deletion/duplication analysis [4]	Unknown; none reported to date

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Urban et al [2009], Callewaert et al [2013], Su et al [2015]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods that may be used include: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Genetically Related (Allelic) Disorders

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

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 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 21 individuals from 17 families [Urban et al 2009, Callewaert et al 2013, Su et al 2015]. In most, cutis laxa was evident from birth. Pulmonary emphysema was present in all.

The overall prognosis is poor, with a mortality rate of 76% (13/17 probands). Mean age at death was 2.4 years and median age was six months (range 1 month to 13 years). The four surviving patients were all female, ages 7-23 years at the time of reporting. In addition to pulmonary emphysema, brain abscess and gastric perforation were each reported once as a cause of death.

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 giving 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 becomes clinically manifest during the first months of life, is often severe, and is the most common cause of death.

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

In the 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 (3/21 patients).

Diaphragmatic involvement includes sliding hernias, congenital hernias, hiatal hernia and diaphragmatic eventration (11/21 patients). 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 and rupture, which was the cause of death in three sibs homozygous for the c.4238dupC pathogenic variant (see also Genotype-Phenotype Correlations).

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 dilation 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 (one 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 one individual [Su et al 2015]

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 is mostly evident from birth and may be followed by motor development delay.

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

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.

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.

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.

Manifesting heterozygotes. Generally, heterozygotes do not show manifestations of *LTBP4*-related cutis laxa.

Genotype-Phenotype Correlations

No clear genotype-phenotype correlations have been established.

Of note, while most pathogenic variants result in nonsense-mediated decay of the mRNA, one family was shown to harbor a c.4238dupC pathogenic variant that partially escaped nonsense-mediated decay resulting in a truncated protein [Callewaert et al 2013]. Immunostaining for fibrillin-1, LTBP1 and LTBP4 on fibroblasts derived from patients showed thickened and wavy microfibrils. This family showed a more aggressive gastrointestinal phenotype with gastric and bowel perforations in several individuals.

Prevalence

The prevalence is unknown; the disorder is expected to be very rare (<1:1,000,000) with only 17 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.

Differential Diagnosis

Disorders to consider in the differential diagnosis of *LTBP4*-related cutis laxa are summarized in Table 2 and discussed below.

Table 2.

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

Finding	**Disorder**								
	ARCL1A	**ARCL1B**	**ARCL1C**	**ADCL**	**ARCL2A ARCL2B**	**ARCL3A ARCL3B**	**Progeroid ADCL**	**XLCL**	**ATS**
Gene	*FBLN5*	*EFEMP2*	*LTBP4*	*ELN*	*ATP6V0A2 PYCR1*	*ALDH18A1 PYCR1 ALDH18A1*	*ALDH18A1*	*ATP7A*	*SLC2A10*
Skin	Redundant	Hyper-extensible > redundant	Redundant	Redundant > hyper-extensible	Wrinkled > redundant	Wrinkled, thin	Wrinkled, thin	Wrinkeld	Hyper-extensible > redundant
Emphysema	+++	+	+++	++	No	No	No	No	No
Cardiovascular	Arterial stenoses	**Arterial tortuosity/ aneurysms**	Arterial stenosis, septal defects	ARD	-	Arterial stenoses, ICA malform.	ICA tortuosity	ICA tortuosity	**Arterial tortuosity**
Hiatal / diaphragmatic hernias	+	+	+++	+	+	No	No	+	++
Bladder diverticula	++	+	+++	+	+	No	No	+++	+
GI diverticula	No	No	+++	No	No	No	No	No	No
IUGR	No	No	+	No	++	+++	++	No	No
Postnatal growth delay	+	++	++	No	+++	+++	++	+	No
Congenital hip dislocation	No	+	No	No	+++	++	++	No	No
Osteoporosis, bone fragility	No	++	No	No	N/A	N/A	N/A	++	No
Scoliosis	No	+	No	No	++	++	++	++	++
Delayed anterior fontanel	No	No	+	No	+++	++	++	++	No

Finding	Disorder								
	ARCL1A	**ARCL1B**	**ARCL1C**	**ADCL**	**ARCL2A ARCL2B**	**ARCL3A ARCL3B**	**Progeroid ADCL**	**XLCL**	**ATS**
closure									
Microcephaly	No	No	No	No	+++	+++	++	+	No
Intellectual disability	No	No	No	No	++	+++	++	++	No
Brain malformations	No	No	No	No	Cobblestone gyri (*ATP6V0A2*) CCA (*PYCR1*)	**CCA**	+	No	No
Athetoid movements	No	No	No	No	No	+++	+	No	No
Corneal opacification / cataract	No	No	No	No	No	+++	+++	No	No
Other					**Glycosylation defects**		**Brisk reflexes**	**Bony exostoses (>Occipital)**	

Features characteristic for the cutis laxa subtype are shown in **bold**.

+ ++ = common finding

+ + = multiple case reports

+ = rare case reports

No = not present

Only one individual reported

ADCL = autosomal dominant cutis laxa

ARCL = autosomal recessive cutis laxa

ARD = aortic root dilatation

ATS = arterial tortuosity syndrome

CCA = corpus callosum agenesis

CV = cardiovascular

ICA = intracranial arteries

IUGR = intrauterine growth restriction

XLCL = X-linked cutis laxa

Autosomal recessive cutis laxa type 1A (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 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.

Autosomal recessive cutis laxa type 1B (ARCL1B, *EFEMP2* (*FBLN4*)-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.

Autosomal dominant cutis laxa type 1 (ADCL1) presents with generalized cutis laxa of variable severity. Aortic root dilatation and emphysema may occur and are currently only reported in adults, unlike the severe emphysema seen in *LTBP4*-related cutis laxa. ADCL1 is caused by *ELN* pathogenic variants that result in an elongated protein [Szabo et al 2006, Callewaert et al 2011,

Hadj-Rabia et al 2013].

Autosomal recessive cutis laxa type 2A (ARCL2A, *ATP6V0A2*-related cutis laxa). The phenotypic spectrum of *ATP6V0A2*-related cutis laxa includes Debré-type cutis laxa at the severe end and wrinkly skin syndrome at the mild end. Affected individuals have furrowing and premature wrinkling of the skin of the entire body that improves with time. In most (not all) affected individuals, microcephaly and cortical and cerebellar malformations are present and are associated with variable developmental delay, seizures, and/or neurologic regression [Kornak et al 2008, Fischer et al 2012].

Autosomal recessive cutis laxa type 2B and 3B (ARCL2B and ARCL3B) (OMIM 612940 and 614438). Although individuals with ARCL2B may have findings similar to ARCL2A, they often have a more progeroid appearance with a triangular face and corpus callosum agenesis. Patients who additionally have corneal clouding due to ruptures in Descemet's membrane or cataracts are considered to have ARCL3B (de Barsy syndrome B) [Reversade et al 2009, Dimopoulou et al 2013]. ARCL2B and ARCL3B are caused by mutation of *PYCR1*.

Autosomal recessive cutis laxa type 3A (ARCL3A, de Barsy syndrome A) (OMIM 219150) is similar to ARCL3B, but is usually situated at the most severe end of the type 3 recessive cutis laxa spectrum with severe IUGR, a progeroid appearance with a thin skin and visible veins, adducted thumbs, and corneal clouding and/or cataract. In addition, patients with ARCL3A can show choreoathetoid movements and arterial involvement, including aortic stenosis and intracranial aneurysms [Zampatti et al 2012, Fischer et al 2014]. ARCL3A is caused by mutation of *ALDH18A1*.

Central nervous system and ocular anomalies in the absence of severe emphysema distinguish these disorders from *LTBP4*-related cutis laxa.

Geroderma osteodysplasticum (GO) (OMIM 231070), an autosomal recessive disorder that resembles ARCL2, has some distinct craniofacial characteristics and severe skeletal manifestations (osteopenia and fractures). Lipodystrophy and periodontal disease may occur. Emphysema is usually absent. Both mutation of *GORAB* [Hennies et al 2008] and *PYCR1* [Yildirim et al 2011] have been described.

Occipital horn syndrome (OHS) (sometimes referred to as X-linked cutis laxa [XLCL]) is characterized by "occipital horns," distinctive wedge-shaped exostoses at the sites of attachment of the trapezius muscle and the sternocleidomastoid muscle to the occipital bone. Individuals with OHS also have lax skin and joints, bladder diverticula, inguinal hernias, and vascular tortuosity. Cutis laxa in OHS is often less severe and mostly involves wrinkling of the dorsum of the hands and feet. OHS is caused by mutation of *ATP7A* (encoding a copper transporter).

The skeletal abnormalities and abnormalities of the hair shaft (pili torti) seen in OHS and the absence of severe emphysema distinguish it from *LTBP4*-related cutis laxa.

Arterial tortuosity syndrome (ATS) is an autosomal recessive disorder characterized by:

- Severe and widespread arterial tortuosity of the aorta and middle-sized arteries (with an increased risk of aneurysms and dissections) and focal and widespread stenosis which can involve the aorta and/or pulmonary arteries. In addition, large veins may be dilated and valvular regurgitation and mitral valve prolapse can occur.
- Craniofacial involvement with characteristic facies and high palate with dental crowding;
- Soft/doughy skin and other evidence of a generalized connective tissue disorder including skeletal findings (scoliosis, pectus excavatum/carinatum, joint laxity, knee/elbow contractures, arachnodactyly, camptodactyly); inguinal/abdominal wall hernia; sliding hiatal or diaphragmatic hernia; hypotonia; and ocular involvement (myopia, keratoconus).

ATS is caused by mutation of *SLC2A10*. The absence of severe lung involvement and the presence of arterial tortuosity distinguish ATS from ARCL1C.

Macrocephaly, alopecia, cutis laxa, scoliosis (MACS) syndrome (also known as *RIN2* syndrome) (OMIM 613075) is an autosomal recessive disorder that includes the eponymous clinical manifestations as well as progressive facial coarsening, gingival hyperplasia, and skin and joint laxity. The skin phenotype has been described variably as cutis laxa [Basel-Vanagaite et al 2009] or hyperextensible [Syx et al 2010]. *RIN2* encodes a Ras and Rab interactor with guanine nucleotide exchange factor activity involved in endocytosis.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *LTBP4*-related cutis laxa, the following evaluations are recommended:

- Assessment of lung function, including oxygen saturation, spirometry, lung volumes, and diffusion capacity
- Chest x-ray or high-resolution CT scan

- Ultrasound examination of the genitourinary tract
- Bladder ultrasound examination to diagnose multiple bladder diverticula
- Echocardiography
- Physiotherapeutic evaluation (hypotonia, hyperlaxity)
- Consultation with a medical geneticist and/or genetic counselor

On clinical indication:

- Bronchoscopy
- Visualization of the gastrointestinal tract by gastrographin ingestion or enema
- Pulmonary vessel angiogram
- If necessary, bladder ultrasound can be complemented with a voiding cystoureterogram. Due to the potential presence of urethral diverticula, catheterization should be done carefully. Intravenous pyelogram may be an alternative.

Treatment of Manifestations

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

Pulmonary

- Symptomatic treatment of pulmonary emphysema with inhaled corticosteroids, atropine, and selective β2-adrenergic bronchodilation
- Oxygen supplementation if necessary

Gastrointestinal

- Medical treatment of gastroesophageal reflux to reduce discomfort and reactive bronchospasms
- Feeding of mother's milk in infants to maximize passive immunization
- Dietary advice, sufficient fluid intake and, if necessary, osmotic laxatives to avoid chronic constipation

Genitourinary

- Education on complete bladder emptying when voiding
- Antibiotic prophylaxis in case of incomplete voiding and recurrent urinary tract infections
- Pelvic floor strengthening by physical therapy may help to prevent prolapse of pelvic organs
- Consideration of artificial bladder implantation (performed in 1 patient)

Cardiovascular

- Care by a (pediatric) cardiologist with experience in connective tissue pathology
- Treatment of clinically relevant pulmonary artery stenosis (preferably by catheterization which is minimally invasive and needs a shorter period of anesthesia)
- Medical treatment of pulmonary hypertension (e.g., by sildenafil)

Other

- Surgical treatment of congenital diaphragmatic hernia or severe hiatal hernia
- Caution in surgical treatment of cutis laxa and inguinal or umbilical hernia, as the risk of recurrence is likely to be high (i.e., similar to that observed in other cutis laxa syndromes) and mechanical ventilation used during the procedure may aggravate pulmonary emphysema
- Physical therapy for muscle strength and joint stability
- Psychosocial support

Prevention of Secondary Complications

Immunize against respiratory infections (influenza, *Streptococcus pneumonia, Haemophilus influenza*).

Passive immunization for respiratory syncytial virus (RSV) with palivizumab may be considered during the RSV season.

Surveillance

The following are appropriate:

- Routine assessment of pulmonary function and oxygenation, at least yearly, or more frequently if indicated clinically
- Repeat imaging of:
  - Gastrointestinal tract
  - Urinary tract
  - Cardiovascular system

Agents/Circumstances to Avoid

Avoid the folloiwng:

- Positive pressure ventilation unless needed to treat life-threatening conditions
- Isometric exercise and contact sports or activities that increase the risk for blunt abdominal trauma and/or joint injury or pain
- People with respiratory infections
- Sunbathing or tanning in order to preserve any residual skin elasticity
- Smoking, which can result in rapid, severe loss of lung function in persons with *LTBP4*-related cutis laxa

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes. In one family, recurrent spontaneous abortions have been noted.

Pregnancy Management

Affected mother. To date 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, 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.

Affected fetus

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

Therapies Under Investigation

Search ClinicalTrials.gov 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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face 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., carriers of one *LTBP4* pathogenic variant).
- Heterozygotes (carriers) are generally asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has 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 generally asymptomatic.

Offspring of a proband

- No individuals with *LTBP4*-related cutis laxa are known to have reproduced to date.
- The offspring of an individual with *LTBP4*-related cutis laxa would be obligate heterozygotes (carriers) for a pathogenic variant in *LTBP4*.

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

Heterozygote (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, clarification of carrier status, and discussion of the availability of prenatal 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.

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

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the *LTBP4* pathogenic variants have been identified in an affected family member, prenatal testing and preimplantation genetic diagnosis for a pregnancy at increased risk for *LTBP4*-related cutis laxa are possible options.

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
- **Genodermatoses Network - Fondation René Touraine**
  The network on rare genetic skin diseases for professionals and patients
  France
  www.fondation-r-touraine.org/genodermatoses-Network-88
- **National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)**
  1 AMS Circle
  Bethesda MD 20892-3675
  Phone: 877-226-4267 (toll-free); 301-565-2966 (TTY)
  Fax: 301-718-6366
  Email: niamsinfo@mail.nih.gov
  www.niams.nih.gov

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	HGMD
LTBP4	19q13.2	Latent-transforming growth factor beta-binding protein 4	LTBP4 database	LTBP4

Data are compiled from the following standard references: gene from HGNC; chromosome locus, locus name, critical region, complementation group from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD) 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 Genetic 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. 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 mutated variants that prevent the binding of TGFβ1 to LTBP4 [Dabovic et al 2015].

Recent 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 highly overlapping phenotypes between *LTBP4*- and *FBLN5*-related cutis laxa.

In addition to its function in TGFβ1 sequestration and elastic fiber formation, LTBP4 was recently found to stabilize 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]. 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]. 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.

Gene structure. *LTBP4* consists of 33 exons that are differentially combined in three major protein coding transcript variants:

- A 5163-base pair mRNA transcript (NM_001042544.1) encoding 1624 amino acids (isoform a; NP_001036009.1);
- A 5052-bp mRNA transcript (NM_003573.2) encoding 1587 amino acids (isoform b; NP_003564.2)
- A 4979-bp mRNA product (NM_001042545.1) encoding 1557 amino acids (isoform c; NP_001036010.1).

NP_001036009.1 and NP_003564.2 are also known as long isoforms and NP_001036010.1 is known as the short isoform (LTBP4S). For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign allelic variants. Flanigan et al [2013] reported four *LTBP4* non-synonymous benign variants (p.Val194Ile, p.Thr787Ala, p.Thr820Ala, and p.Thr1140Met) which influence the timing of loss of ambulation in individuals with Duchenne muscular dystrophy. Individuals with Duchenne muscular dystrophy who had a homozygous genotype at the residues Ile194/Ala787/Ala820/Met1140 remained ambulatory significantly longer than those with a homozygous or heterozygous genotype of Val194/Thr787/Thr820/Thr1140 [Flanigan et al 2013]. Similar results were found in mice [Heydemann et al 2009].

Pathogenic allelic variants. See Table 3.

Table 3.

LTBP4 Variants Discussed in This *GeneReview*

Variant Classification	DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
Benign	c.580G>A	p.Val194Ile [1]	NM_001042544.1 NP_001036009.1
	c.2359A>G	p.Thr787Ala [1]	
	c.2458A>G	p.Thr820Ala [1]	
	c.3422C>T	p.Thr1141Met [1]	
Pathogenic	c.4238dupC	p.Arg1414AlafsTer27 [2]	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

ND = not determined

1. Flanigan et al [2013]
2. Callewaert et al [2013]

Normal gene product. Three LTBP-4 isoforms exist, with 1624, 1587, and 1557 amino acids (see **Gene structure**).

LTBP4, an extracellular protein that is closely related to fibrillins, consists of epidermal growth factor-like domains (that stabilize the linear structure of the protein) interspersed with four 8-cys domains (including a hybrid domain). The third 8-cys domain covalently binds the small latent TGFβ1 complex. A proline-rich hinge region provides flexibility to the protein. The N-terminus of LTBP4 binds to the microfibrillar structures.

Abnormal gene product. Most of the currently described pathogenic variants are nonsense or frameshift variants resulting in a premature termination codon and nonsense-mediated decay. In the absence of LBTP4 protein, fibulin-5-elastin complexes fail to target the microfibrils, resulting in severely impaired elastic fiber formation [Urban et al 2009, Callewaert et al 2013, Dabovic et al 2015]. One exception, the c.4238dupC pathogenic variant, was described to result in a shortened truncated protein, p.Arg1414AlafsTer27 [Callewaert et al 2013].

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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 in the pathogenesis of these disorders.

Center for Medical Genetics, Ghent University Hospital

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, identify the genetic causes and the underlying molecular mechanisms responsible for this group of diseases. For more information, go to the Cutis Laxa Research Study Web site or email urbanz@pitt.edu.

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