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FBLN5-Related Cutis Laxa

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Summary

Clinical characteristics

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 viscus diverticula (e.g., intestine, bladder). Occasionally, supravalvar aortic stenosis is observed. Intrafamilial variability in age of onset is observed. Cardiorespiratory failure from complications of pulmonary emphysema (respiratory or cardiac insufficiency) is the most common cause of death.

Diagnosis/testing

The diagnosis of *FBLN5*-related cutis laxa is established in a proband with the characteristic clinical features and biallelic pathogenic variants in *FBLN5* (autosomal recessive *FBLN5*-related cutis laxa) or a heterozygous pathogenic variant in *FBLN5* (autosomal dominant *FBLN5*-related cutis laxa) identified by molecular genetic testing.

Management

Treatment of manifestations: Symptomatic treatment of pulmonary emphysema; antibiotics for urinary tract infections; routine repair of inguinal hernias; repeat plastic surgery of the face and trunk as needed.

Prevention of secondary complications: Attention to respiratory function prior to surgery; prophylactic antibiotics as needed for vesicoureteral reflux; immunizations against respiratory viruses.

Surveillance: Routine surveillance of the urinary tract for evidence of bladder diverticula and/or vesicoureteral reflux.

Agents/circumstances to avoid: Smoking; 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 respiratory infections.

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Genetic counseling

FBLN5-related cutis laxa can be inherited in an autosomal recessive or (less commonly) autosomal dominant manner.

- **Autosomal recessive inheritance.** 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.
- **Autosomal dominant inheritance.** Each child of an individual with autosomal dominant cutis laxa has a 50% chance of inheriting the pathogenic variant.

Prenatal testing is possible for a pregnancy at increased risk in families in which the pathogenic variant(s) have been identified.

Diagnosis

Suggestive Findings

FBLN5-related cutis laxa **should be suspected** in individuals with the following clinical features:

- Cutis laxa
- Pulmonary emphysema
- Arterial involvement (e.g., peripheral pulmonary artery stenosis, supravalvar aortic stenosis)
- Inguinal hernias
- Hollow viscus diverticula (e.g., intestine, bladder)
- Pyloric stenosis

Establishing the Diagnosis

The diagnosis of *FBLN5*-related cutis laxa **is established** in a proband with the above Suggestive Findings and biallelic pathogenic (or likely pathogenic) variants in *FBLN5* (autosomal recessive *FBLN5*-related cutis laxa) or a heterozygous pathogenic (or likely pathogenic) variant in *FBLN5* (autosomal dominant *FBLN5*-related cutis laxa) 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 a variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *FBLN5*-related cutis laxa is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of *FBLN5*-related cutis laxa has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of *FBLN5*-related cutis laxa molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *FBLN5* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected.

  Perform sequence analysis first. If only one or no pathogenic variant is found perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

- **A multigene panel** that includes *FBLN5* 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.

Option 2

When the diagnosis of *FBLN5*-related cutis laxa is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **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 *FBLN5*-Related Cutis Laxa

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
FBLN5	Sequence analysis [3]	6 families [4]
	Gene-targeted deletion/duplication analysis [5]	See footnote 6.

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Loeys et al [2002], Claus et al [2008], Callewaert et al [2013], Kantaputra et al [2014]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Duplication reported in one individual with autosomal dominant inheritance [Markova et al 2003]; see Table 5. No exon or whole-gene deletions or duplications are known to cause the autosomal recessive form of the disease.

Clinical Characteristics

Clinical Description

Autosomal Recessive *FBLN5*-Related Cutis Laxa

To date, six families with autosomal recessive *FBLN5*-related cutis laxa have been described [Van Maldergem et al 1988, Karakurt et al 2001, Loeys et al 2002, Pour-Jafari & Sahiri 2004, Claus et al 2008, Callewaert et al 2013, Kantaputra et al 2014]. Intrafamilial variability in age of onset is observed.

Cutis laxa. The most common finding in *FBLN5*-related cutis laxa is described as furrowing of the skin of the whole body that is particularly obvious in the neck, axillae, and groin. The face has a "droopy" appearance with eyelid ptosis and drooping cheeks. When one tries to extend the skin, it does not display hyperelasticity as in the Ehlers-Danlos syndromes, but rather keeps its consistency.

Pulmonary emphysema. Most affected individuals have early childhood-onset pulmonary emphysema, and some individuals have presented with emphysema during the neonatal period. Two affected sibs reported by Van Maldergem et al [1988] had recurrent pneumonias.

Arterial involvement. Peripheral pulmonary artery stenosis appears to be specific for this disorder. Peripheral pulmonary artery stenosis leads to ventricular dilatation and contributes to progressive heart failure. Supravalvar aortic stenosis was reported in two related children from Iran who died at ages two years and 14 years [Elahi et al 2006]. Aortic valve dysplasia (stenosis and regurgitation) was reported in one affected child of Lebanese ancestry [Callewaert et al 2013].

Other evidence of a generalized connective disorder including inguinal hernias and hollow viscus diverticula (e.g., intestine, bladder). In one individual, the bladder was described on voiding cystoureterogram as having an unusual "cauliflower" shape secondary to the presence of multiple diverticula. In a Lebanese family, all three affected sibs homozygous for missense variant c.649T>C underwent surgery in the first months of life for pyloric stenosis [Callewaert et al 2013].

Infections secondary to vesicoureteral reflux (e.g., pyelonephritis) are observed. Urinary tract candidiasis with "fungus balls" have been observed on renal ultrasound [Author, personal communication].

Prognosis. Pulmonary artery stenosis, congenital heart disease, and/or hollow viscus diverticula are likely to cause early death, with cardiorespiratory failure from complications of pulmonary emphysema (respiratory or cardiac insufficiency) being the most common cause of death. For those who survive early childhood, pulmonary emphysema, cor pulmonale, and multiple surgeries are the rule. Prolonged survival is exceptional; the oldest known person with this disorder was a high-functioning young woman who died at age 21 years from cor pulmonale.

Hip dislocation is not observed in *FBLN5*-related cutis laxa.

Intelligence is normal [Van Maldergem et al 1988].

Note: To date, no heterozygous carriers for autosomal recessive *FBLN5*-related cutis laxa have developed age-related macular degeneration.

Skin histology. Skin biopsy with orcein staining on paraffin-embedded samples on light microscopy shows normal or mild fragmentation and paucity/absence of elastic fibers.

Electron microscopy (EM) shows paucity of elastic fibers with accumulation of elastin (ELN) globules, reflecting lack of assembly of the primary components of elastic fibers [Ledoux-Corbusier 1983]. These findings are in contrast to those of Debré-type cutis laxa (see *ATP6V0A2*-Related Cutis Laxa) and De Barsy syndrome (see

Differential Diagnosis), in which a sparse elastic network, but not defective assembly of ELN fibers, is observed. Because deficiency of other proteins or cofactors involved in the process of elastic fiber assembly could potentially give the same ultrastructural picture, it is not known whether this feature is specific for *FBLN5*-related cutis laxa. EM studies require a high level of expertise and are only available in specialized centers.

Autosomal Dominant *FBLN5*-Related Cutis Laxa

Based on the description of the only family reported to date to have demonstrated autosomal dominant inheritance, this form appears to be milder in clinical presentation with less internal organ involvement than the autosomal recessive form [Markova et al 2003].

Genotype-Phenotype Correlations

Due to the small number of individuals with *FBLN5*-related cutis laxa reported in the literature, reliable data on genotype-phenotype correlations are lacking.

Of note, one individual who was heterozygous for an inherited *FBLN5* allele (p.Gly202Arg) and compound heterozygous for *ELN* alleles has been reported. It was hypothesized that the *FBLN5* allele modified the phenotype caused by the *ELN* pathogenic variants in the context of inflammatory destruction of elastic fibers in an acquired form of cutis laxa [Hu et al 2006].

Prevalence

The prevalence is unknown, with only six families reported to date.

Genetically Related (Allelic) Disorders

The two phenotypes other than those discussed in this *GeneReview* that are known to be associated with heterozygous pathogenic variants in *FBLN5* are age-related macular degeneration (OMIM 608895) and hereditary neuropathy with or without age-related macular degeneration (OMIM 608895).

Differential Diagnosis

Other disorders characterized by cutis laxa are summarized in Table 2.

***EFEMP2*-related cutis laxa (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. Severity ranges from perinatal lethality as a result of cardiopulmonary failure to manifestations limited to the vascular and craniofacial systems. The cutis laxa and emphysema are similar in *FBLN4*- or *FBLN5*-related cutis laxa; however, to date, the diaphragmatic changes and arterial aneurysms seem more predominant in *EFEMP2*-related cutis laxa.

***ATP6V0A2*-related cutis laxa (ARCL2A)** spans a phenotypic spectrum that includes Debré-type cutis laxa at the severe end and wrinkly skin syndrome at the mild end. Affected individuals have furrowing of the skin of the whole body that improves with time. They may have other evidence of a generalized connective disorder, including enlarged anterior fontanelle in infancy, congenital dislocation of the hips, inguinal hernias, and high myopia. In most, but not all, affected individuals, cortical and cerebellar malformations are present and are associated with severe developmental delays, seizures, and neurologic regression. Clinical features that distinguish *FBLN5*-related cutis laxa from ARCL2A are absence of intellectual disability, hip dislocation, and delayed closure of the fontanelle. In individuals with ARCL2A, EM findings of skin biopsy, rarefaction of ELN fibers composed of ELN and elastofibrils, and abnormal serum transferrin isoelectrofocusing may help confirm the diagnosis.

***ELN*-related cutis laxa (ADCL1)** was historically considered a strictly cutaneous disorder without systemic involvement; however, it is now known that persons with *ELN* pathogenic variants can also have aortic aneurysms that require aortic root replacement or lead to aortic rupture in early adulthood. The aortic pathology of these aneurysms (so-called cystic media degeneration) is indistinguishable from that of Marfan syndrome. It remains to be seen whether pathogenic variants in *ELN* are associated with heritable thoracic aortic disease (HTAD).

***EMILIN1*-related cutis laxa** is characterized by cutis laxa and systemic involvement, including arterial tortuosity, aneurysms, bone fragility, and congenital anomalies of kidney and urinary tract [Adamo et al 2022].

Gerodermia osteodysplastica (GO). Onset occurs in infancy or early childhood [Nanda et al 2008]. Children appear older than their age as a result of sagging cheeks and jaw hypoplasia. Skin wrinkling is less severe and is confined to the dorsum of the hands and feet and to the abdomen when in the sitting position. A generalized connective tissue weakness leads to frequent hip dislocation and hernias. GO can be distinguished from other types of cutis laxa by the presence of osteopenia/osteoporosis and fractures, most commonly vertebral compression fractures, but also fractures of the long bones. Mental development is in the normal range. In contrast to Debré-type cutis laxa, fontanelle size and closure are normal, positioning of the palpebral fissures is normal, and disease manifestations do not become milder with age. Pathogenic variants in *GORAB* are causative [Hennies et al 2008].

Cutis laxa, autosomal recessive, type IIIA (or de Barsy syndrome A) is characterized by a progeroid appearance, pre- and postnatal growth restriction, moderate to severe intellectual disability, corneal clouding or cataracts, and generalized cutis laxa [Guerra et al 2004]. The progeroid appearance is not caused by skin sagging, but rather by a hypoplasia of the dermis. Joint hyperlaxity, pseudoathetoid movements, and hyperreflexia are observed. Inheritance is autosomal recessive, with the exception of *PYCR1* (pathogenic variants in which account for a small percentage of this syndrome). Further molecular characterization is needed.

***LTBP4*-related cutis laxa** is characterized by a cutaneous phenotype similar to that of *FBLN5*-related cutis laxa and by severe multiple malformations including congenital heart disease, pulmonary arterial stenosis, and, interestingly, pulmonary hypertension. The latter appears to be a distinctive feature as it was observed in two individuals in the authors' series. Bladder diverticulae, noticeably absent in the other entities discussed in this section, have also been described.

Table 2. Disorders to Consider in the Differential Diagnosis of Cutis Laxa

Disease Name	Gene	MOI	Clinical Findings				
			Cutis laxa	Emphysema	Aneurysms	ID	GI & GU malformations
ARCL1A [1]	*FBLN5*	AR	+++	+++	–	–	+
ARCL1B	*EFEMP2*	AR	++	++	+++	–	–
EMILIN1-related cutis laxa [2]	*EMILIN1*	AR	+	–	+++	–	+
LTBP4-related cutis laxa	*LTBP4*	AR	++	+++	–	–	+++
ARCL2A	*ATP6V0A2*	AR	++	–	–	++	–
ARCL2B (OMIM 612940, 614438)	*PYCR1*	AR	++	+	–	++	–
ADCL1	*ELN*	AD	+	+	+	–	–
Geroderma osteodysplasticum (OMIM 231070)	*GORAB*	AR	++	–	–	–	–

Table 2. continued from previous page.

Disease Name	Gene	MOI	Clinical Findings				
			Cutis laxa	Emphysema	Aneurysms	ID	GI & GU malformations
Cutis laxa, autosomal recessive, type IIIA (de Barsy syndrome A) (OMIM 219150)	*PYCR1* [3]	AR	+	–	–	+++	–

AD = autosomal dominant; AR = autosomal recessive; GI = gastrointestinal; GU = genitourinary; ID = intellectual disability; MOI = mode of inheritance
1. The subject of this *GeneReview* chapter
2. Adamo et al [2022]
3. Pathogenic variants in *PYCR1* account for a small percentage of De Barsy syndrome.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *FBLN5*-related cutis laxa, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *FBLN5*-Related Cutis Laxa

System/Concern	Evaluation	Comment
Pulmonary	• Chest roentgenogram • Chest CT exam	To evaluate for pulmonary emphysema
	• Pulmonary function testing • Eval by pulmonologist	If clinical signs/symptoms of pulmonary disease
Cardiovascular	Echocardiogram	Consider pulmonary vessel angiogram if clinically indicated.
Renal	Kidney ultrasound exam	Consider voiding cystoureterogram, given potential presence of urethral diverticula; catheterization should be done carefully. IV pyelogram may be an alternative.
Gastrointestinal	Exam for inguinal hernia	Barium enema if clinically indicated
Other	Consultation w/clinical geneticist &/or genetic counselor	

IV = intravenous

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *FBLN5*-Related Cutis Laxa

Manifestation/Concern	Treatment
Pulmonary emphysema	• Symptomatic treatment w/inhaled corticosteroids, atropine, & selective β2-adrenergic bronchodilation • Oxygen supplementation if necessary
Arterial abnormalities	No treatment available
Urinary tract infections	Antibiotic therapy
Inguinal hernias	Surgical repair
Cutis laxa	Repeat plastic surgery of the face and trunk as needed

Prevention of Secondary Complications

The following are appropriate:

- Attention to respiratory function prior to surgery
- Prophylactic antibiotics (cotrimoxazole) in individuals with vesicoureteral reflux
- Immunization against respiratory infections (influenza, *Streptococcus pneumonia*, *Haemophilus influenza*)
- Consideration of passive immunization for respiratory syncytial virus (RSV) with palivizumab during the RSV season

Surveillance

Routine surveillance of the urinary tract for evidence of bladder diverticula and/or vesicoureteral reflux is indicated.

Agents/Circumstances to Avoid

Avoid the following:

- Smoking; however, the limited life span of affected individuals makes this recommendation mostly theoretic.
- 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

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for 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

FBLN5-related cutis laxa can be inherited in an autosomal recessive or (less commonly) autosomal dominant manner.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *FBLN5* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

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 asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. To date, individuals with autosomal recessive *FBLN5*-related cutis laxa are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *FBLN5* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *FBLN5* pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Rare individuals diagnosed with autosomal dominant *FBLN5*-related cutis laxa have an affected parent.
- An individual diagnosed with autosomal dominant *FBLN5*-related cutis laxa may have the disorder as the result of a *de novo* pathogenic variant. The proportion of cases caused by a *de novo* pathogenic variant is unknown but is presumed to be high.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include a dermatologic examination and molecular genetic testing for the pathogenic variant identified in the proband.
- The family history of some individuals diagnosed with autosomal dominant *FBLN5*-related cutis laxa may appear to be negative because of reduced penetrance or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

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 an *FBLN5* pathogenic variant, the risk to the sibs is 50%.
- If the *FBLN5* pathogenic variant 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 *FBLN5* 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 *FBLN5*-related cutis laxa because of the possibility of reduced penetrance in a parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant cutis laxa has a 50% chance of inheriting the 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 *FBLN5* 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, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *FBLN5* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for *FBLN5*-related cutis laxa are possible.

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
- **Medline Plus**
  Emphysema

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. FBLN5-Related Cutis Laxa: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FBLN5	14q32.12	Fibulin-5	FBLN5 database	FBLN5	FBLN5

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 FBLN5-Related Cutis Laxa (View All in OMIM)

219100	CUTIS LAXA, AUTOSOMAL RECESSIVE, TYPE IA; ARCL1A
604580	FIBULIN 5; FBLN5
614434	CUTIS LAXA, AUTOSOMAL DOMINANT 2; ADCL2

Molecular Pathogenesis

Independent of the underlying molecular pathophysiology, all types of cutis laxa are characterized by alterations of elastic fibers, not collagen. In ultrastructural investigations elastic fibers are reduced in number and often appear fragmented.

The assembly of elastic fibers, a complex mechanism, takes place in the extracellular space. According to the currently accepted model, microfibrillar proteins like the fibrillins first form a lattice with fibulins into which secreted tropoelastin is deposited and then further processed [Kielty 2006]. Enzymes necessary for the conversion of tropoelastin into ELN are the lysyl oxidases, a group of copper-dependent enzymes (deficient in secondary cutis laxa associated with treatment with copper chelators like penicillamine) that form covalent crosslinks between ELN molecules. Elastic fibers not only increase the elasticity of the extracellular matrix, but also influence its architecture and regulate TGFβ-signaling.

When tropoelastin expression is insufficient, the generation of elastic fibers is disturbed. This explains why heterozygous loss-of-function *ELN* pathogenic variants cause alterations that primarily affect the vasculature (supravalvar aortic stenosis) and only minimally affect the skin. In autosomal dominant cutis laxa, *ELN* pathogenic variants are mostly confined to the 3' end of the gene [Metcalfe et al 2000]. These variants result in secretion of abnormal tropoelastin molecules that interfere with elastic fiber assembly in a dominant-negative fashion [Zhang et al 1999]. See *ELN*-Related Cutis Laxa.

Pathogenic variants in *FBLN5* can cause either dominant or recessive cutis laxa resulting from alterations of the microfibrillar component of the elastic fibers. The dominant pathogenic variants lead to an elongation of the protein that is stable and can act in a dominant-negative manner [Markova et al 2003], whereas the recessive pathogenic variants entail loss of function as a result of aberrant folding and intracellular retention [Loeys et al 2002, Hu et al 2006]. The same applies to recessive pathogenic variants in *FBLN4* (*EFEMP2*) [Hucthagowder et al 2006] (see *EFEMP2*-Related Cutis Laxa).

A more complex mechanism underlies autosomal recessive cutis laxa, Debré type (ARCL2A) (see *ATP6V0A2*-Related Cutis Laxa). Here, the loss-of-function variants do not affect an extracellular matrix protein, but a subunit of a v-type H^+-ATPase that resides in endosomes as well as in the Golgi compartment [Hurtado-Lorenzo et al 2006, Pietrement et al 2006]. Proton pumps are universally expressed and allow pH regulation in the extracellular space and in many subcellular compartments [Forgac 2007]. In addition, there are indications that a subunit of the proton pump complex is directly involved in vesicle fusion [Peters et al 2001]. The following two lines of evidence suggest that a defect of the secretory pathway is the basis of the elastic fiber defect in ARCL2A:

- Patients show a glycosylation defect, which can be detected by isoelectrofocusing (IEF) of serum transferrins [Morava et al 2005, Kornak et al 2008, Van Maldergem et al 2008].
- Patient cells display a delay of Golgi-to-ER trafficking. It is unknown whether the glycosylation defect impairs the function of a protein involved in the formation of elastic fibers or if it is just an epiphenomenon caused by a secretion defect also involving elastic fiber components.

Gene structure. *FBLN5* consists of 13 exons that are differentially combined in three major transcripts. The primary transcript is NM_006329.3. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. See Table 5. The only annotated nonsynonymous coding normal variant in *FBLN5* resides in exon 10 and leads to a p.Asp364Tyr change.

Pathogenic variants. See Table 5.

- Autosomal recessive *FBLN5*-related cutis laxa: p.Cys144Trp, p.Cys217Arg (in 2 families), p.Ser227Pro (in 2 likely related families), and p.Glu391Ter
- Autosomal dominant *FBLN5*-related cutis laxa: a 22,729-bp duplication (c.380-9061_873dup) spanning exons 5 to 8 and the first 9 bp of exon 9 [Markova et al 2003]

Table 5. *FBLN5* Variants Discussed in This *GeneReview*

Variant Classification	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
Benign	c.1090G>T [2]	p.Asp364Tyr [2]	NM_006329.3 NP_006320.2
Pathogenic	c.432C>G	p.Cys144Trp	
	c.604G>A [3]	p.Gly202Arg [3]	
	c.649T>C	p.Cys217Arg	
	c.679T>C [4] (T998C)	p.Ser227Pro	
	c.1171G>T	p.Glu391Ter	
	c.380-9061_873dup (380-9063_872dup22729) [5]	See footnote 6.	NM_006329.3

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. rs1802492

3. One of three variant alleles of different genes thought to result in an acquired form of cutis laxa [Hu et al 2006] (See Genotype/Phenotype Correlations.)

4. Variant nomenclature described in Elahi et al [2006]

5. Duplication of 22,729 nucleotides from intron 4 to exon 9 [Markova et al 2003]. The genomic coordinates are NG_008254.1:g.48570_71295dup22726.

6. Duplication results in a larger transcript with a tandem duplication of 483 nucleotides that translates to a tandem duplication of four cbEGF motifs in the protein product [Markova et al 2003]. This is the only pathogenic variant known to cause the autosomal dominant form of the disease.

Normal gene product. Fibulin-5, the protein encoded by *FBLN5*, is an extracellular matrix protein involved in the formation of the microfibrillar scaffold of the elastic fibers. It contains calcium-binding EGF-like repeats and an RGD-motif and is approximately 55 kd in size.

Abnormal gene product. Autosomal recessive variants in *FBLN5* result in intracellular retention of the misfolded protein [Hu et al 2006] and matrix deposition. Additionally, these pathogenic variants show decreased affinity for tropoelastin [Hu et al 2006]. The single known autosomal dominant variant leads to an elongation of the protein that is stable and can act in a dominant-negative manner [Markova et al 2003].

Chapter Notes

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Revision History

- 15 June 2023 (aa) Revision: added *EMILIN1*-related cutis laxa to Differential Diagnosis
- 16 August 2018 (sw) Comprehensive update posted live
- 13 March 2014 (me) Comprehensive update posted live

- 13 October 2011 (me) Comprehensive update posted live
- 19 March 2009 (et) Review posted live
- 10 September 2008 (lvm) Original submission

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