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Geleophysic Dysplasia

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Summary

Clinical characteristics

Geleophysic dysplasia, a progressive condition resembling a lysosomal storage disorder, is characterized by short stature, short hands and feet, progressive joint limitation and contractures, distinctive facial features, progressive cardiac valvular disease, and thickened skin. Intellect is normal. The characteristic clinical findings are likely to be present in the first year of life. Cardiac, airway, and pulmonary involvement result in death before age five years in approximately 33% of individuals.

Diagnosis/testing

The clinical diagnosis of geleophysic dysplasia can be established in a proband with characteristic clinical and radiographic findings; the molecular diagnosis of geleophysic dysplasia is established in a proband with characteristic clinical and radiographic findings and one of the following on molecular genetic testing: biallelic pathogenic variants in *ADAMTSL2* or a heterozygous pathogenic variant in either *FBN1* or *LTBP3*.

Management

Treatment of manifestations: Ongoing physiotherapy to prevent joint limitation; treatment of hip dysplasia, osteochondritis, and carpal tunnel syndrome per orthopedist; cardiac valve replacement in those with severe stenosis or insufficiency; management of cardiac septal defect per cardiologist and cardiac surgeon; tracheostomy as needed for severe tracheal stenosis; treatment of restrictive lung disease, obstructive sleep apnea, and/or asthma per pulmonologist; standard treatments for hearing loss and recurrent otitis media; treatment of ophthalmologic manifestations per ophthalmologist.

Surveillance: Frequent assessments in infancy and early childhood of growth, motor and speech development, frequency of ear infections, respiratory compromise, cardiac and pulmonary examination, and liver size; annual clinical assessments after age three years. Intermittent evaluation with clinical genetics and genetic counseling. Annual orthopedic evaluation until age 18 years, then every two years. EMG for carpal tunnel syndrome every two years beginning at age 11 years. Evaluation with cardiologist (including EKG and echocardiogram),

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pulmonologist, ENT specialist, and audiologist annually from birth until age three years, then at specific intervals. Thoracic CT examination at age six years; polysomnography as needed. Ophthalmology and funduscopic examination at specific intervals.

Genetic counseling

Geleophysic dysplasia caused by biallelic pathogenic variants in *ADAMTSL2* is inherited in an autosomal recessive manner. Geleophysic dysplasia caused by a heterozygous pathogenic variant in either *FBN1* or *LTBP3* is inherited in an autosomal dominant manner.

Autosomal recessive inheritance: If both parents are known to be heterozygous for an *ADAMTSL2* 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. Carrier testing for at-risk relatives requires prior identification of the *ADAMTSL2* pathogenic variants in the family.

Autosomal dominant inheritance: All probands reported to date with *FBN1*- or *LTBP3*-related geleophysic dysplasia whose parents have undergone molecular genetic testing have had the disorder as the result of a *de novo* pathogenic variant. If a molecular diagnosis has been established in the proband and the pathogenic variant identified in the proband is not identified in either parent, the recurrence risk to sibs is estimated to be 1% because of the possibility of parental germline mosaicism.

Once the geleophysic dysplasia-related pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for geleophysic dysplasia have been published.

Suggestive Findings

Geleophysic dysplasia **should be suspected** in individuals with the following clinical and radiographic findings.

Clinical findings

- Proportionate short stature
- Very short hands and feet
- Progressive joint limitation and contractures
- Distinctive facial features: round, full face; small nose with anteverted nares; broad nasal bridge; thin vermilion of the upper lip with a flat philtrum [Allali et al 2011]
- Thickened skin
- Progressive cardiac valvular disease diagnosed on echocardiography
- Normal intellect
- Hepatomegaly
- Tracheal stenosis
- Recurrent respiratory and middle ear infections

Radiographic findings

- Delayed bone age
- Broad proximal phalanges
- Cone-shaped phalangeal epiphyses
- Shortened long tubular bones
- Small capital femoral epiphyses

Establishing the Diagnosis

Clinical Diagnosis

The clinical diagnosis of geleophysic dysplasia **can be established** in a proband with characteristic clinical and radiographic findings (see Suggestive Findings).

Molecular Diagnosis

The molecular diagnosis of geleophysic dysplasia **is established** in a proband with characteristic clinical and radiographic findings and one of the following on molecular genetic testing (see Table 1):

- Biallelic pathogenic (or likely pathogenic) variants in *ADAMTSL2* (~50% of affected individuals) [Le Goff & Cormier-Daire 2009, Cheng et al 2018]
- A heterozygous pathogenic (or likely pathogenic) variant in *FBN1* (~50% of affected individuals) [Le Goff & Cormier-Daire 2009, Cheng et al 2018]
- A heterozygous pathogenic (or likely pathogenic) variant in *LTBP3* (~<1% of affected individuals) [McInerney-Leo et al 2016]

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) The identification of 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** (serial single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the family history and/or phenotype. Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Single-gene testing. Sequence analysis detects missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected.

1. Perform *ADAMTSL2* sequence analysis first if autosomal recessive inheritance is suspected or there is known consanguinity.
2. If no pathogenic variant is found, perform *FBN1* sequence analysis.
3. If no pathogenic variant is found, perform *LTBP3* sequence analysis.

A multigene panel that includes *ADAMTSL2*, *FBN1*, *LTBP3*, 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 geleophysic dysplasia is not considered, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

Table 1. Molecular Genetic Testing Used in Geleophysic Dysplasia

Gene [1, 2]	Proportion of Geleophysic Dysplasia Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Identified by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
ADAMTSL2	~50% [6]	~99%	See footnote 7.
FBN1	~50% [6]	~99%	None reported
LTBP3	<1% [8]	~99%	None reported

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
7. A 30-bp deletion affecting the N glycan-rich module has been described that would likely be identified with sequence analysis [Allali et al 2011, Marzin et al 2021].

Clinical Characteristics

Clinical Description

Geleophysic dysplasia is a progressive disorder resembling a lysosomal storage disorder, involving bones and joints, cardiac valves, and skin. To date about 100 individuals have been reported: 51 affected individuals in two large cohorts [Allali et al 2011, Marzin et al 2021] and 55 in case reports [Vanace et al 1960, Spranger et al 1971, Koiffmann et al 1984, Spranger et al 1984a, Spranger et al 1984b, Peters et al 1985, Lipson et al 1987, Shohat et al 1990, Wraith et al 1990, Lipson et al 1991, Rosser et al 1995, Figuera 1996, Hennekam et al 1996, Pontz et al 1996, Rennie et al 1997, Santolaya et al 1997, Titomanlio et al 1999, Keret et al 2002, Matsui et al 2002, Zhang et al 2004, Panagopoulos et al 2005, Scott et al 2005, Giray et al 2008, Ben-Salem et al 2013, Lee et al 2013, Porayette et al 2014, Elhoury et al 2015, García-Ortiz et al 2015, Mackenroth et al 2016, McInerney-Leo et al 2016, Li et al 2017, Cheng et al 2018, Shan et al 2021, Tao et al 2021, Li et al 2022].

Table 2. Geleophysic Dysplasia: Frequency of Select Features

Feature		% of Persons w/ Feature	Comment
Skeletal	Characteristic skeletal manifestations	100%	Short stature, short hands & feet, joint limitations
	Additional orthopedic manifestations	30%-40%	Osteochondritis, carpal tunnel syndrome

Table 2. continued from previous page.

Feature		% of Persons w/ Feature	Comment
Cardiac manifestations		70%	Valvulopathy (progressive in half of affected persons); atrioventricular septal defect in <20% of individuals
Pulmonary hypertension		40%	
Respiratory/ ENT	Respiratory manifestations	50%	Asthma, restrictive lung disease
	Multilevel airway obstruction	30%	Airway stenosis &/or malacia
	Hearing loss	40%	Conductive hearing loss
Ophthalmologic manifestations		45%	Refractive errors, papillary edema
Hepatomegaly		40%	Related to right heart valve defect in some persons

Onset. The majority of characteristic clinical findings are likely to be present in the first year of life.

Skeletal manifestations. About 40% of individuals present with a birth length below the 5th percentile; a skeletal disorder is usually suspected in the first months of life because of short stature and short hands and feet. The final height is between three and six standard deviations (SD) below the mean. Normal head growth results in relative macrocephaly. The progressive joint limitation and skin thickening interfere with normal joint function, leading to toe walking, contractures of the large joints, and limitation of wrist and hand movement. Other orthopedic manifestations include hip dysplasia, osteochondritis, and carpal tunnel syndrome.

Cardiac findings are likely to become evident in the first year of life. Postnatal cardiac valve thickening can include pulmonary stenosis, mitral insufficiency, mitral stenosis (5/15), or aortic stenosis. Fewer than 20% of individuals have atrioventricular septal defect [Allali et al 2011, Marzin et al 2021]. The cardiac disease is progressive in half of affected individuals, mostly in those with valvulopathy detected in the first year of life. Among those with valvular thickening, 40% of affected children underwent valve replacement.

Pulmonary arterial hypertension. Forty percent of individuals present with chronic or acute multifactorial pulmonary arterial hypertension related to mitral valve disease, interstitial lung disease, and/or airway obstruction.

Respiratory manifestations. Asthma is present in 30%-40% of individuals, ranging from mild to severe. Some individuals have restrictive lung disease, which can be related to cardiac valve defect or is unexplained.

Multilevel airway obstruction was identified in 30% of individuals, most often detected in the first year of life, including laryngeal stenosis, tracheal stenosis, tracheomalacia, laryngomalacia, and bronchomalacia. Airway obstruction in those with geleophysic dysplasia is often progressive.

Hearing loss. Intermittent conductive hearing loss from recurrent ear infections and adenoid hypertrophy is common.

Ophthalmologic features include refractive errors (hypermetropia, myopia, and astigmatism) in 40% of individuals during childhood. Some individuals were diagnosed with papilledema not related to intracranial hypertension. Two individuals developed glaucoma [Saricaoglu et al 2013; Authors, personal data].

Hepatomegaly has been reported but is not associated with liver disease. It is related to heart insufficiency in some but not all individuals.

Other. Two individuals were reported to have hypothyroidism.

Prognosis. About one third of children died before age five years [Allali et al 2011, Marzin et al 2021]; a combination of cardiac, airway, and pulmonary manifestations were reported.

The oldest living affected individual is age 62 years. In addition to progressive cardiac valvular thickening, survivors have short stature (height more than three SD below the mean), progressive joint contractures (limited range of motion of the fingers, toes, wrists, and elbows) with toe walking, thickened skin, and intermittent pulmonary hypertension.

Pathophysiology. Histologic examination of skin, liver, trachea, and heart shows lysosomal-like PAS-positive vacuoles, suggestive of glycoprotein and a storage disorder. In one study, histopathologic analysis of cardiac mitral valve revealed collagen accumulation responsible for severe fibrosis in which chordae tendineae were contained, without glycosaminoglycan deposition [Marzin et al 2021].

Phenotype Correlations by Gene

The clinical features of *ADAMTSL2*- and *FBN1*-related geleophysic dysplasia are indistinguishable.

Individuals with *LTPB3*-related geleophysic dysplasia to date have not had cardiac valvular involvement. While the absence of cardiac valvular thickening in contrast to the severity of the lung involvement may be a distinctive clinical feature for *LTPB3*-related geleophysic dysplasia [McInerney-Leo et al 2016], confirmation awaits additional data.

Genotype-Phenotype Correlations

ADMTSL2. To date, no individuals with biallelic nonsense variants have been reported, suggesting embryonic lethality.

FBN1. Pathogenic variants in *FBN1* are localized in exons 41-42 encoding the TGFβ-binding protein-like domain 5 (TB5) characterized by eight cysteine residues, which are involved in fibrillin-1 folding via intradomain disulfide linkage. Pathogenic variants eliminating a cysteine are associated with a severe phenotype with life-threatening complications.

LTBP3. The small number of individuals with *LTBP3* pathogenic variants limits any genotype-phenotype correlation.

Prevalence

Geleophysic dysplasia is rare; about 100 individuals have been reported to date.

Genetically Related (Allelic) Disorders

Other phenotypes associated with pathogenic variants in *ADAMTSL2*, *FBN1*, and *LTBP3* are summarized in Table 3 and Table 4. Disorders included in Table 3 have overlapping phenotypic features with geleophysic dysplasia and should be considered in the differential diagnosis.

Table 3. Allelic Disorders to Consider in the Differential Diagnosis of Geleophysic Dysplasia

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/geleophysic dysplasia	Distinguishing from geleophysic dysplasia
ADAMTSL2	Dysplastic cortical hyperostosis, Al-Gazali type [1]	AR	• Moderate IUGR • Relative macrocephaly • Short limbs, w/very short hands • Stiff joints	• More severe: lethal during neonatal period • Hypertrichosis • Large anterior fontanelle • Short neck • Generalized bone sclerosis • Mild platyspondyly

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/geleophysic dysplasia	Distinguishing from geleophysic dysplasia
FBN1 *LTBP3*	*FBN1*-related acromicric dysplasia (OMIM 102370) & *LTBP3*-related acromicric dysplasia [2, 3]	AD	• Short stature • Short hands • Stiff joints • Delayed bone age • Cone-shaped phalangeal epiphyses • Thickened skin • Heart disease	• Less severe outcome • Absence of progressive cardiac valvular thickening • Absence of distinctive facial features • Absence of hepatomegaly • See footnote 4.
FBN1	*FBN1*-related Weill-Marchesani syndrome, dominant (See Weill-Marchesani Syndrome.)	AD [4]		Abnormalities of the lens of the eye (typically recognized in childhood) incl: • Microspherophakia (small spherical lens) • Myopia secondary to abnormal shape of the lens • Ectopia lentis (abnormal position of the lens) • Glaucoma (can lead to blindness) Absence of hepatomegaly

AD = autosomal dominant; AR = autosomal recessive; IUGR = intrauterine growth restriction; MOI = mode of inheritance
1. Batkovskyte et al [2023]
2. McInerney-Leo et al [2016]
3. Moore-Federman syndrome is probably the same as acromicric dysplasia.
4. Additional clinical findings in 22 individuals with acromicric dysplasia from 15 families include: frequent ear, tracheal, and respiratory complications; non-progressive heart disease (4/22; 2 with bicuspid aortic valve, 2 with atrial septal defect); and myopia (8/20) [Author, personal observations].

Table 4. Other Allelic Disorders

Gene	Phenotype
FBN1	*FBN1*-related Marfan syndrome
	Marfan lipodystrophy syndrome (OMIM 616914)
	Isolated ectopia lentis (OMIM 129600)
	MASS syndrome (OMIM 604308)
	Nonsyndromic heritable thoracic aortic disease (See Heritable Thoracic Aortic Disease Overview.)
	Stiff skin syndrome (OMIM 184900)
LTBP3	Dental anomalies and short stature (OMIM 601216)

Differential Diagnosis

The acromelic dysplasia group includes four rare disorders with striking clinical overlap: geleophysic dysplasia, Weill-Marchesani syndrome, acromicric dysplasia, and Myhre syndrome. Overlapping and distinguishing clinical features are summarized in Table 5. Hepatomegaly and early mortality are encountered only in the most severe forms of geleophysic dysplasia.

Table 5. Disorders to Consider in the Differential Diagnosis of Geleophysic Dysplasia

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/geleophysic dysplasia	Distinguishing from geleophysic dysplasia
ADAMTS10 *ADAMTS17* *FBN1* *LTBP2*	Weill-Marchesani syndrome	AD AR [1]	See Table 2.	See Table 2.
ADAMTSL2	Dysplastic cortical hyperostosis, Al-Gazali type	AR		
FBN1 *LTBP3*	Acromicric dysplasia	AD		
SMAD4	Myhre syndrome	AD	• IUGR • Short stature • Short hands & feet • Progressive joint limitation & contractures • Thickened skin • Heart involvement	• Characteristic facial features w/prognathism • Calvarial thickening • Variable degree of cognitive impairment • Mixed conductive & sensorineural deafness

AD = autosomal dominant; AR = autosomal recessive; IUGR = intrauterine growth restriction; MOI = mode of inheritance
1. FBN1-related Weill-Marchesani syndrome (WMS) is inherited in an autosomal dominant manner. *ADAMTS10*-, *ADAMTS17*-, and *LTPBP2*-related WMS are inherited in an autosomal recessive manner.

Management

Clinical practice guidelines have been published (see Supplementary Data in Marzin et al [2021]).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with geleophysic dysplasia, the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6. Geleophysic Dysplasia: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Skeletal	• Assessment of growth • Assessment of joint range of motion by an orthopedist/physiotherapist • Radiographs for hip dysplasia	
Cardiac	Eval by cardiologist incl EKG & echocardiography to evaluate for cardiac valve defect, septal defect, & pulmonary hypertension	
Pulmonary	Eval by pulmonologist to assess for obstructive or restrictive lung disease, obstructive sleep apnea, & asthma	
	Polysomnography	As needed
ENT	Flexible endoscopy (w/rigid endoscopy as needed) to assess for upper airway obstruction & adenoidal hypertrophy	
Hearing	Hearing assessment	

Table 6. continued from previous page.

System/Concern	Evaluation	Comment
Eyes	• Eye exam for refractive error (incl astigmatism) & corneal thickening • Funduscopic exam for papilledema	
Hepatic	Assessment of liver size by clinical assessment &/or ultrasound exam	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of geleophysic dysplasia to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

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

Treatment of Manifestations

There is no cure for geleophysic dysplasia. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 7).

Table 7. Geleophysic Dysplasia: Treatment of Manifestations

Manifestation/Concern	Treatment
Joint manifestations	Ongoing physiotherapy to prevent joint limitation
Other orthopedic manifestations	Treatment per orthopedist for hip dysplasia, osteochondritis, & carpal tunnel syndrome
Cardiac manifestations	• Cardiac valve replacement in those w/severe stenosis or insufficiency
	• Mgmt of cardiac septal defect per cardiologist & cardiac surgeon
Tracheal stenosis	Tracheostomy as needed for severe tracheal stenosis
Pulmonary disease	Treatment of restrictive lung disease, obstructive sleep apnea, &/or asthma per pulmonologist
Hearing	Standard treatment for hearing loss & recurrent otitis media
Ophthalmologic manifestations	Treatment per ophthalmologist

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 8 are recommended according to published guidelines [Marzin et al 2021].

Table 8. Geleophysic Dysplasia: Recommended Surveillance

System/ Concern/ Specialty	Evaluation	Frequency by Age			
		Birth-3 yrs	3-10 yrs	11-18 yrs	>18 yrs
General / Primary care	• Assessment of growth & motor & speech development • Assessment for recurrent ear infections, serous otitis media, obstructive sleep apnea, & asthma • Clinical examination incl heart, lungs, & liver size	• Age ≤6 mos: monthly • Age 6 mos-2 yrs: every 3 mos • Age 2-3 yrs: every 6 mos	Yearly		
Clinical genetics	• Clinical exam w/clinical geneticist • Genetic counseling incl information re support organizations	Every 6 mos	Yearly	At ages 11, 13, & 17 yrs	Every 2-3 yrs
Skeletal	• Orthopedic/physiotherapy eval for joint limitation • Radiographs for hip dysplasia	Yearly			Every 2 yrs
Neurologic	EMG to assess for carpal tunnel syndrome	--		Every 2 yrs	
Cardiology	Eval w/cardiologist incl EKG & echocardiography to assess for valvular valve defects & pulmonary hypertension	Yearly	At ages 6 & 9 yrs	At ages 11, 13, & 17 yrs	Every 5 yrs
Pulmonary	Eval w/pulmonologist for restrictive lung disease, obstructive sleep apnea, & asthma	Yearly	At ages 6 & 9 yrs	At ages 11, 13, & 17 yrs	Every 5 yrs
	Thoracic CT scan	--	At age 6 yrs	--	
	Polysomnography	As needed			
ENT	• Flexible endoscopy (w/rigid endoscopy as needed) to assess for upper airway obstruction & adenoidal hypertrophy • Audiogram for conductive deafness	Yearly	At age 6 yrs	At ages 11 & 13 yrs	Every 5 yrs
Eyes	• Ophthalmology exam for refractive error (incl astigmatism) & corneal thickening • Funduscopic exam for papilledema	At ages 9 mos & 2 yrs	At age 6 yrs	As needed	

Evaluation of Relatives at Risk

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

Pregnancy Management

The management of a pregnant woman is complicated due to the small pelvis, cardiac anomalies, and tracheal stenosis. It is recommended that women considering a pregnancy be evaluated prior to pregnancy and followed during pregnancy in a high-risk perinatal center.

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

Geleophysic dysplasia caused by biallelic pathogenic variants in *ADAMTSL2* is inherited in an autosomal recessive manner. Geleophysic dysplasia caused by a heterozygous pathogenic variant in either *FBN1* or *LTBP3* is inherited in an autosomal dominant manner.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *ADAMTSL2* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *ADAMTSL2* 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, it is possible that 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]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that 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 *ADAMTSL2* 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 *ADAMTSL2*-related geleophysic dysplasia are obligate heterozygotes (carriers) for a pathogenic variant in *ADAMTSL2*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ADAMTSL2* pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the *ADAMTSL2* pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- All probands reported to date with *FBN1*- or *LTBP3*-related geleophysic dysplasia whose parents have undergone molecular genetic testing have had the disorder as the result of a *de novo* pathogenic variant.
- If the proband appears to be the only affected family member (i.e., a simplex case), recommendations for the evaluation of the parents of the proband include physical examination for manifestations of geleophysic dysplasia* (e.g., proportionate short stature, joint limitations, short hands and feet, and distinctive facial features) and – if a molecular diagnosis has been established in the proband – molecular genetic testing for the *FBN1* or *LTBP3* pathogenic variant identified in the proband.

  * Reduced penetrance has not been reported to date in *FBN1*- or *LTBP3*-related geleophysic dysplasia.
- If a molecular diagnosis has been established in the proband, the pathogenic variant identified in the proband is not identified in either parent, and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.

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 molecular diagnosis has been established in the proband and the pathogenic variant identified in the proband is not identified in either parent, the recurrence risk to sibs is estimated to be 1% because of the possibility of parental germline mosaicism [Rahbari et al 2016].
- If the genetic status of the parents is unknown but neither parent has manifestations of geleophysic dysplasia on physical examination, 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 geleophysic dysplasia because of the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant geleophysic dysplasia has a 50% chance of inheriting the geleophysic dysplasia-related pathogenic variant.

Other family members. Given that all probands with *FBN1*- or *LTBP3*-related geleophysic dysplasia reported to date have the disorder as a result of a *de novo* pathogenic variant, the risk to other family members is presumed to be low.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected with geleophysic dysplasia or are at risk of being a carrier of an *ADAMTSL2* pathogenic variant.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the geleophysic dysplasia-related pathogenic variant(s) 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.

- **American Heart Association**
  Phone: 800-242-8721
  Congenital Heart Defects
- **MAGIC Foundation**
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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. Geleophysic Dysplasia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ADAMTSL2	9q34.2	ADAMTS-like protein 2	ADAMTSL2 database	ADAMTSL2	ADAMTSL2
FBN1	15q21.1	Fibrillin-1	FBN1 @ LOVD	FBN1	FBN1
LTBP3	11q13.1	Latent-transforming growth factor beta-binding protein 3	LTBP3 database	LTBP3	LTBP3

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 Geleophysic Dysplasia (View All in OMIM)

134797	FIBRILLIN 1; FBN1
231050	GELEOPHYSIC DYSPLASIA 1; GPHYSD1
602090	LATENT TRANSFORMING GROWTH FACTOR-BETA-BINDING PROTEIN 3; LTBP3
612277	ADAMTS-LIKE PROTEIN 2; ADAMTSL2
614185	GELEOPHYSIC DYSPLASIA 2; GPHYSD2
617809	GELEOPHYSIC DYSPLASIA 3; GPHYSD3

Molecular Pathogenesis

ADAMTSL2, *FBN1*, and *LTBP3* encode proteins involved in the microfibrillar network, a key component of the extracellular matrix (ECM) with an important role in its mechanical function and the bioavailability and activity of the transforming growth factor beta (TGFβ) superfamily. Alterations of the microfibrillar network and enhanced TGFβ bioavailability have been shown in acromelic dysplasia [Marzin et al 2021].

ADAMTSL2 encodes ADAMTS-like protein 2 (ADAMTSL2), a glycoprotein lacking enzymatic activity whose function is unknown. Latent TGFβ-binding protein 1 (LTBP1) was identified as an ADAMTSL2 partner [Le Goff et al 2008]. LTBP1 plays a major role in the storage of latent TGFβ in the ECM and regulates its availability [Isogai et al 2003]. In individuals with geleophysic dysplasia, a tenfold higher level of TGFβ was found in the culture medium of fibroblasts compared to controls. Active TGFβ represented 85% and 92% of total TGFβ in culture medium of individuals with geleophysic dysplasia, whereas active TGFβ represented only 7% of total TGFβ in control medium [Le Goff et al 2008]. This suggests that ADAMTSL2 may be involved in the microfibrillar network and in TGFβ bioavailability. TGFβ is a growth factor that regulates cell proliferation, migration, differentiation, and survival in a context-dependent fashion; its activity is tightly regulated through the ECM [Isogai et al 2003].

The functional consequences of *ADAMTSL2* pathogenic variants have been tested using a myc-tagged wild type and an *ADAMTSL2* mutated construct in parallel transfections of HEK293F cells. Western blot analyses after 48 hours of transfection confirmed that wild type ADAMTSL2 protein was secreted into the medium. Mutated proteins were also secreted at normal intracellular level, but at reduced extracellular levels. Thus, the mutated proteins are likely to be synthesized, but it is possible that they are misfolded, which may interfere with their efficient secretion. An increased turnover of mutated protein or altered function of secreted mutated protein could also explain these data [Le Goff et al 2008].

FBN1 encodes fibrillin 1 (FBN1). Fibrillins are large glycoproteins (350 kd) ubiquitously expressed. They give rise to filamentous assemblies (microfibrils) with an average diameter of 10 nm. They are grouped together with LTBPs and fibulins into a structurally related family of ECM proteins. Fibrillins have a specific modular structure that consists of 46/47 epidermal growth factor (EGF)-like domains (42/43 of which are of the calcium-binding type) interspersed with seven 8-cysteine-containing modules (TB/8-Cys). The modules with 8-Cys are specific to fibrillins and LTBPs. Fibrillins also contain a specific binding sequence to integrin receptors α5β1, αvβ3, and vβ6. Fibrillin assemblies thus constitute the non-collagenous architectural elements of soft- and hard-tissue matrices. The importance of fibrillin deposition for the proper storage, distribution, release, and activation of locally produced TGFβ and bone morphogenic protein (BMP) has been demonstrated.

All *FBN1* pathogenic variants identified to date in individuals with geleophysic dysplasia are missense variants clustered in exons 41-42 encoding the TGFβ-binding protein-like domain 5 (TB5) of FBN1, which contains eight cysteine residues linking four disulfide bonds. Half of the pathogenic variants created or removed a cysteine residue within this domain, which is characterized (as are the other TGFβ-binding domains) by eight cysteines directly involved in FBN1 folding via intradomain disulfide linkage. Functional analysis in fibroblasts

from affected individuals show a reduced number of microfibrils with complete microfibrillar network disorganization. *FBN1* pathogenic variants are also associated with enhanced TGFβ signaling.

Because *ADAMTSL2* pathogenic variants were previously identified in a subset of individuals with geleophysic dysplasia, a direct link between *FBN1* associated with acromicric dysplasia and geleophysic dysplasia and *ADAMTSL2* was hypothesized. A specific interaction between FBN1 and ADAMTSL2 may provide evidence that dysregulation of the FBN1/ADAMTSL2/TGFβ interrelationship is the underlying mechanism of the short stature phenotypes.

LTBP3 encodes latent TGBβ-binding protein 3 (LTBP3), which belongs to the LTBP family and comprises four proteins found in microfibrils of the ECM and structurally similar to fibrillins. LTBP3 is incorporated into the ECM through its interaction with FBN1 [Zilberberg et al 2012]. It contains 13 epidermal growth factor-like repeats and four TGFβ-binding domains (or 8-cysteine domains), which are specific to the LTBP-fibrillin superfamily. LTBP3 is involved in TGFβ secretion, trapping, and activation [Koli et al 2008]. TGFβ signaling is important in chondrogenesis and osteogenesis [Le Goff & Cormier-Daire 2015].

Table 9. Geleophysic Dysplasia: Mechanism of Disease Causation

Gene [1]	Mechanism of Disease Causation
ADAMTSL2	Loss of function
FBN1	Dominant negative
LTBP3	Not fully elucidated to date. Pathogenic variants assoc w/geleophysic dysplasia are responsible for a disorganized microfibrillar network. However, TGFβ signaling is not increased [McInerney-Leo et al 2016].

1. Genes from Table 1 in alphabetic order

Table 10. Geleophysic Dysplasia: Gene-Specific Laboratory Considerations

Gene [1]	Special Consideration
ADAMTSL2	To date, persons w/autosomal recessive *ADAMTSL2*-related geleophysic dysplasia have either biallelic missense variants or 1 missense & 1 nonsense variant. None have biallelic nonsense variants. Pathogenic variants are distributed throughout the gene [Marzin et al 2021].
FBN1	Mutational cluster in exons 41-42
LTBP3	None

1. Genes from Table 1 in alphabetic order

Chapter Notes

Author Notes

Pauline Marzin and Valérie Cormier-Daire (pauline.marzin@aphp.fr, valerie.cormier-daire@inserm.fr) are actively involved in clinical research regarding individuals with skeletal dysplasia, including geleophysic dysplasia. They would be happy to communicate with persons who have any questions regarding diagnosis of geleophysic dysplasia or other considerations.

Contact Pauline Marzin and Valérie Cormier-Daire to inquire about review of *FBN1*, *ADAMTSL2*, or *LTBP3* variants of uncertain significance.

Author History

Valérie Cormier-Daire, MD, PhD (2009-present)
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Revision History

- 28 March 2024 (sw) Comprehensive update posted live
- 11 October 2018 (bp) Comprehensive update posted live
- 19 April 2012 (me) Comprehensive update posted live
- 22 September 2009 (et) Review posted live
- 5 June 2009 (vcd) Original submission

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