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Achondrogenesis Type 1B

Synonym: ACG1B, *SLC26A2*-Related Achondrogenesis

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Summary

Clinical characteristics

Clinical features of achondrogenesis type 1B (ACG1B) include extremely short limbs with short fingers and toes, hypoplasia of the thorax, protuberant abdomen, and hydropic fetal appearance caused by the abundance of soft tissue relative to the short skeleton. The face is flat, the neck is short, and the soft tissue of the neck may be thickened. Death occurs prenatally or shortly after birth.

Diagnosis/testing

The diagnosis of ACG1B is established in a proband with characteristic clinical, radiologic, and histopathologic features. Identification of biallelic pathogenic variants in *SLC26A2* on molecular genetic testing can confirm the diagnosis.

Management

Treatment of manifestations: Palliative care for live-born neonates.

Genetic counseling

ACG1B is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *SLC26A2* 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 inheriting neither of the familial *SLC26A2* pathogenic variants. Once the *SLC26A2* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

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Diagnosis

Achondrogenesis type 1B (ACG1B) is a perinatal-lethal disorder with death occurring prenatally or shortly after birth.

Suggestive Findings

ACG1B **should be suspected** in individuals with the following clinical and radiographic findings.

Clinical findings

- Extremely short limbs with short fingers and toes and clubfeet
- Hypoplasia of the thorax
- Protuberant abdomen
- Hydropic fetal appearance caused by the abundance of soft tissue relative to the short skeleton
- Flat face with micrognathia
- Short neck
- Thickened soft tissue of the neck

Radiographic findings. While the degree of ossification generally depends on gestational age, variability can be observed between radiographs taken at similar gestational ages; thus, no single feature should be considered obligatory.

- Disproportion between the nearly normal-sized skull and very short body length. The skull may have a normal appearance or be mildly abnormal (reduced ossification for age; lateral or superior extension of the orbits).
- Total lack of ossification of the vertebral bodies or only rudimentary calcification of the center. The vertebral lateral pedicles are usually ossified.
- Short and slightly thin (but usually not fractured) ribs
- Iliac bone ossification limited to the upper part, giving a crescent-shaped, "paraglider-like" appearance on x-ray. The ischium is usually not ossified.
- Shortening of the tubular bones such that no major axis can be recognized. Metaphyseal spurring gives the appearance of a "thorn apple" (or in hematologic terms, acanthocyte). The phalanges are poorly ossified and thus rarely identified on x-ray.
- Only mildly abnormal clavicles (somewhat shortened but normally shaped and ossified) and scapulae (small with irregular contours) [Superti-Furga 1996]

Establishing the Diagnosis

The diagnosis of ACG1B can be **established** in a proband with the characteristic clinical and radiographic findings described in Suggestive Findings and/or biallelic pathogenic (or likely pathogenic) variants in *SLC26A2* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *SLC26A2* variants of uncertain significance (or of one known *SLC26A2* pathogenic variant and one *SLC26A2* variant of uncertain significance) does not establish 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 and/or clinical context.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other skeletal dysplasias are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *SLC26A2* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants. Typically, if only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications; however, to date such variants have not been identified as a cause of this disorder.

A multigene panel that includes *SLC26A2* 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 phenotype is not clearly distinguishable from other skeletal dysplasias, **comprehensive genomic testing**, which does not require the clinician to determine which gene is 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 Achondrogenesis Type 1B

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SLC26A2	Sequence analysis [3]	>90% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants.
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. Sequence analysis identifies 90% of alleles in individuals with radiologic and histologic features of achondrogenesis type 1B [Rossi & Superti-Furga 2001].
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]

Other Testing

Histopathologic testing. In ACG1B, the histology of the cartilage shows a rarified cartilage matrix partially replaced by a larger number of cells. After hematoxylin-eosin staining, the matrix appears non-homogeneous with coarse collagen fibers. The fibers are denser around the chondrocytes, where they can form "collagen rings." After staining with cationic dyes (toluidine blue, alcian blue), which bind to the abundant polyanionic sulfated proteoglycans, normal cartilage matrix appears as a homogeneous deep blue or violet; in ACG1B, cartilage staining with these dyes is much less intense because of the defective sulfation of the proteoglycans.

Biochemical testing. The incorporation of sulfate into macromolecules can be studied in cultured chondrocytes and/or skin fibroblasts through double labeling with ^{3}H-glycine and ^{35}S-sodium sulfate. After incubation with these compounds and purification, the electrophoretic analysis of medium proteoglycans reveals a lack of sulfate incorporation [Superti-Furga 1994], which can be observed even in total macromolecules. The determination of sulfate uptake is possible but cumbersome and is not used for diagnostic purposes [Superti-Furga et al 1996a].

Note: It is often difficult to distinguish between the three different forms of achondrogenesis: ACG1A, ACG1B, and ACG2 (see Differential Diagnosis).

Clinical Characteristics

Clinical Description

Achondrogenesis type 1B (ACG1B), one of the most severe chondrodysplasias, is a perinatal-lethal disorder with death occurring prenatally or shortly after birth. The mechanism of the prenatal death is unknown. In the live-born neonate, death is secondary to respiratory failure and occurs shortly after birth.

Fetuses with ACG1B often present in breech position. Pregnancy complications as a result of polyhydramnios may occur (e.g., maternal breathing difficulties, preterm labor).

Infants with ACG1B appear hydropic with an abundance of soft tissue relative to the short skeleton. The face is flat and the neck is short with thickened soft tissue.

The limbs are extremely shortened, with inturning of the feet and toes (talipes equinovarus) and brachydactyly (short stubby fingers and toes).

The thorax is narrow and the abdomen protuberant. Frequently, umbilical or inguinal hernias are present.

Genotype-Phenotype Correlations

Genotype-phenotype correlations indicate that the amount of residual activity of the sulfate transporter modulates the phenotype in this spectrum of disorders that extends from lethal ACG1B to mild *SLC26A2*-related multiple epiphyseal dysplasia (*SLC26A2*-MED). Homozygosity or compound heterozygosity for pathogenic variants predicting stop codons or structural variants in transmembrane domains of the sulfate transporter are associated with ACG1B, while pathogenic variants located in extracellular loops, in the cytoplasmic tail of the protein, or in the regulatory 5'-flanking region of the gene result in less severe phenotypes [Superti-Furga et al 1996b, Karniski 2001].

Pathogenic variant p.Arg279Trp is the most common *SLC26A2* variant outside Finland (45% of alleles); it results in the mild *SLC26A2*-MED phenotype when homozygous and mostly in the diastrophic dysplasia (DTD) and *SLC26A2*-related atelosteogenesis phenotypes when in the compound heterozygous state [Barbosa et al 2011].

Variant p.Arg178Ter is the second most common pathogenic variant (9% of alleles) and is associated with a more severe DTD phenotype or even the perinatal-lethal *SLC26A2*-related atelosteogenesis phenotype, particularly when combined in *trans* with the p.Arg279Trp pathogenic variant. This variant has also been found in some individuals with the diagnostic label of *SLC26A2*-MED and ACG1B, making it one of only two pathogenic variants identified in all four *SLC26A2*-related dysplasias.

Variants p.Cys653Ser and c.-26+2T>C are the third most common pathogenic variants (8% of alleles for each).

- Variant p.Cys653Ser results in *SLC26A2*-MED when homozygous and in *SLC26A2*-MED or DTD when present in *trans* with other pathogenic variants.
- Variant c.-26+2T>C is sometimes referred to as the "Finnish" variant, because it is much more frequent in Finland than in the remainder of the world population. It produces low levels of correctly spliced mRNA and results in DTD when homozygous. c.-26+2T>C is the only other pathogenic variant that has been identified in all four *SLC26A2*-related dysplasias, in compound heterozygosity with mild (*SLC26A2*-MED and DTD) or severe (*SLC26A2*-related atelosteogenesis and ACG1B) alleles [Dwyer et al 2010].

The same pathogenic variants found in the ACG1B phenotype can also be found in the milder phenotypes (*SLC26A2*-related atelosteogenesis and DTD) if the second allele is a relatively mild pathogenic variant. Indeed, missense variants located outside the transmembrane domain of the sulfate transporter are often associated with a residual activity that can "rescue" the effect of a null allele [Rossi & Superti-Furga 2001].

Nomenclature

The term "achondrogenesis" (Greek for "not producing cartilage") was used by the pathologist Marco Fraccaro in 1952 to denote the condition observed in a stillborn with severe micromelia and marked histologic changes in cartilage. Subsequently, "achondrogenesis" was used to characterize the most severe forms of human chondrodysplasia, invariably lethal before or shortly after birth.

In the 1980s, a new classification of achondrogenesis (types I to IV) based on radiologic criteria was proposed; the classification did not prove helpful and was later abandoned. Currently, three types of achondrogenesis are recognized and are distinguishable by molecular genetic testing and radiographic findings: ACG1A (an autosomal recessive disorder associated with pathogenic variants in *TRIP11*), ACG1B (the topic of this *GeneReview*), and ACG2 (an autosomal dominant disorder associated with pathogenic variants in *COL2A1*).

In the 2023 revised Nosology of Genetic Skeletal Disorders [Unger et al 2023], ACG1B is referred to as *SLC26A2*-related achondrogenesis and included in the sulfation disorders group.

Prevalence

No data on the prevalence of ACG1B are available.

Genetically Related (Allelic) Disorders

Achondrogenesis type 1B (ACG1B) is the most severe phenotype in the spectrum of *SLC26A2*-related autosomal recessive skeletal disorders (Table 2).

Table 2. *SLC26A2* Skeletal Disorder Spectrum

Disorder	Comment
Achondrogenesis type 1B	Topic of this *GeneReview*
SLC26A2-related atelosteogenesis	• Commonly lethal in perinatal period • Presents around birth or before • Chondrodysplasia w/clinical & histologic characteristics resembling those of DTD but more pronounced
Diastrophic dysplasia (DTD)	• Short limb type of dwarfism assoc w/clubfeet & other joint restrictions incl "hitchhiker thumbs" • Progressive scoliosis in childhood
SLC26A2-related multiple epiphyseal dysplasia	• Joint pain (usually in hips & knees), deformities of hands, feet, & knees, scoliosis • Abnormal finding at birth (e.g., clubfoot, cleft palate, or cystic ear swelling) in ~50% of persons • Median height in adulthood at 10th %ile • Usually considered as a differential diagnosis of DTD in toddlers or school-age children

Differential Diagnosis

Achondrogenesis type 1B (ACG1B) should be distinguished from other lethal chondrodysplasias and severe osteochondrodysplasias (Table 3).

Table 3. Selected Disorders in the Differential Diagnosis of Achondrogenesis Type 1B

Gene	MOI	Disorder	Key Features
Achondrogenesis [1]			
TRIP11	AR	ACG1A (Houston-Harris type) (OMIM 200600)	Rib fractures & absence of ossification of vertebral pedicles may suggest ACG1A. Hands & fingers are less markedly shortened than in ACG1B. Cartilage matrix is normal & inclusions are present in chondrocytes.
COL2A1	AD	ACG2 (Langer-Saldino type) (See Type II Collagen Disorders Overview.)	Hands & fingers can be almost normal. ACG2 shows more severe underossification of vertebral bodies than ACG1B, & typical configuration of iliac bones w/concave medial & inferior borders, & nonossification of ischial & pubic bones. Cartilage is hypervascular & hypercellular w/↓ matrix & vacuoles ("Swiss cheese-like") but has roughly normal staining properties.
Osteochondrodysplasia			
COL1A1 *COL1A2*	AD	Perinatally lethal osteogenesis imperfecta (OI) & progressively deforming OI (See *COL1A1/2* OI.)	Typical signs: soft undermineralized skull & blue sclerae. Bones are bowed but not as short as in ACG. Multiple fractures are present.
FGFR3	AD	Thanatophoric dysplasia (TD)	The limbs are longer than in ACG & the thorax is narrow but elongated. Cloverleaf skull deformity is common in TD type II.

Table 3. continued from previous page.

Gene	MOI	Disorder	Key Features
>20 genes [2]	AR	Short-rib polydactyly syndromes (SRPS)	Extremely short limbs & ribs (severe narrow rib cage). Polydactyly is usually present; when absent, SRPS may be confused w/TD.
ESCO2	AR	Roberts syndrome (See *ESCO2* Spectrum Disorder.)	Severe limb shortening w/only mildly affected axial skeleton may suggest Roberts syndrome.
COL11A1 *COL11A2*	AR AD	Fibrochondrogenesis (OMIM PS228520)	Distinguishing radiographic features: marked metaphyseal flaring of long bones & clefts of vertebral bodies

ACG = achondrogenesis; AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance
1. Within the achondrogenesis group, clinical and radiologic distinction between ACG1A, ACG1B, and ACG2 is not always possible.
2. See OMIM Phenotypic Series: Short-Rib Thoracic Dysplasia.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with achondrogenesis type 1B (ACG1B), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Achondrogenesis Type 1B

System/Concern	Evaluation	Comment
Musculoskeletal	Complete skeletal survey	Babygram is preferable to radiographs of isolated elements
Respiratory	Eval of respiratory status in live-born infants	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of ACG1B to facilitate medical & personal decision making

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

Treatment of Manifestations

Provide palliative care for live-born neonate.

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 access to information on clinical studies for a wide range of diseases and conditions.

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

Achondrogenesis type 1B (ACG1B) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *SLC26A2* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *SLC26A2* 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 have normal stature. No evidence suggests that carriers are at increased risk of developing degenerative joint disease.

Sibs of a proband

- If both parents are known to be heterozygous for an *SLC26A2* 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 inheriting neither of the familial *SLC26A2* pathogenic variants.
- Heterozygotes (carriers) are asymptomatic and have normal stature. No evidence suggests that carriers are at increased risk of developing degenerative joint disease.

Offspring of a proband. ACG1B is a perinatal-lethal condition; affected individuals do not reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *SLC26A2* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SLC26A2* pathogenic variants in the family. (See also **Family planning**.)

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.
- Carrier detection for the reproductive partner of a heterozygous individual is possible using *SLC26A2* molecular genetic testing (see Table 1).

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

High-Risk Pregnancies

Molecular genetic testing. Once the *SLC26A2* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Ultrasound examination. All fetuses with ACG1B will have ultrasound-detectable anomalies. However, this should not be relied on as a diagnostic method to exclude a recurrence.

Low-Risk Pregnancies

Routine prenatal ultrasound examination may identify very short fetal limbs ± polyhydramnios ± small thorax and raise the possibility of achondrogenesis in a fetus not known to be at risk. Subtle ultrasound findings may be recognizable in the first trimester, but in low-risk pregnancies the diagnosis of a skeletal dysplasia is usually not made until the second trimester. DNA extracted from cells obtained by amniocentesis can be theoretically analyzed to try to make a molecular diagnosis prenatally. However, the differential diagnosis in such a setting is very broad (see Differential Diagnosis).

Molecular genetic testing. Molecular analysis for suspicion of ACG1B in the prenatal context should be done via a comprehensive skeletal dysplasia panel, exome sequencing, or genome sequencing.

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.

- **MedlinePlus**
  Achondrogenesis
- **Compassionate Friends**
  Supporting Family After a Child Dies
  Phone: 877-969-0010
  compassionatefriends.org
- **Helping After Neonatal Death (HAND)**
  PO Box 341
  Los Gatos CA 95031
  Phone: 888-908-HAND (4263)
  www.handonline.org
- **UCLA International Skeletal Dysplasia Registry (ISDR)**
  Phone: 310-825-8998
  International Skeletal Dysplasia Registry

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. Achondrogenesis Type 1B: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
SLC26A2	5q32	Sulfate transporter	SLC26A2	SLC26A2

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 Achondrogenesis Type 1B (View All in OMIM)

600972	ACHONDROGENESIS, TYPE IB; ACG1B
606718	SOLUTE CARRIER FAMILY 26 (SULFATE TRANSPORTER), MEMBER 2; SLC26A2

Molecular Pathogenesis

SLC26A2 encodes a sulfate transporter protein [Hästbacka et al 1994]. This protein transports sulfate into chondrocytes to maintain adequate sulfation of proteoglycans. The sulfate transporter protein belongs to the family of sulfate permeases. *SLC26A2* is expressed in developing cartilage in human fetuses but also in a wide variety of other tissues [Haila et al 2001].

Impaired activity of the sulfate transporter in chondrocytes and fibroblasts results in the synthesis of proteoglycans, which are either not sulfated or insufficiently sulfated [Rossi et al 1998, Satoh et al 1998], most probably because of intracellular sulfate depletion [Rossi et al 1996]. Undersulfation of proteoglycans affects the composition of the extracellular matrix and leads to impairment of proteoglycan deposition, which is necessary for proper endochondral bone formation [Corsi et al 2001, Forlino et al 2005].

Loss of SLC26A2 sulfate transporter activity is associated with several skeletal disorders (see Genetically Related Disorders) [Rossi & Superti-Furga 2001].

Mechanism of disease causation. Loss of function. The predicted residual activity of the sulfate transporter correlates with phenotypic severity [Rossi et al 1997, Cai et al 1998, Rossi & Superti-Furga 2001, Karniski 2004, Maeda et al 2006].

Table 5. Notable *SLC26A2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_000112.3	c.-26+2T>C (IVS1+2T>C)	--	Founder variant in Finnish population [2]

Table 5. continued from previous page.

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_000112.3 NP_000103.2	c.532C>T	p.Arg178Ter	Common pathogenic variant [2]
	c.835C>T	p.Arg279Trp	Most common pathogenic variant outside of Finland [2]
	c.1724delA (1751delA)	p.Lys575SerfsTer10	Recurrent pathogenic variant in persons w/ ACG1B
	c.1535C>A	p.Thr512Lys	Second-most common pathogenic variant in the Finnish population [Bonafé et al 2008]
	c.1020_1022del	p.Val341del	Recurrent pathogenic variant in persons w/ ACG1B
	c.1957T>A	p.Cys653Ser	See footnote 2.

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. See Genotype-Phenotype Correlations for severity.

Chapter Notes

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