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Lathosterolosis

Synonyms: Sterol C-5 Desaturase Deficiency, Sterol-C5-Desaturase Deficiency, SC5D Deficiency

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Summary

Clinical characteristics

Lathosterolosis is characterized by global developmental delays, intellectual disability, microcephaly, characteristic facial features (bitemporal narrowing, sloping forehead, epicanthal folds, ptosis, downslanting palpebral fissures, anteverted nares, broad nasal tip, long philtrum, high-arched palate, and micrognathia), cataracts, digit anomalies (postaxial polydactyly, toe syndactyly), and liver disease. The severity of liver disease can range from asymptomatic elevation of liver enzymes to cirrhosis and liver failure.

Diagnosis/testing

The diagnosis of lathosterolosis is established in a proband by identification of elevated lathosterol on plasma sterol analysis and/or biallelic pathogenic variants in *SC5D* by molecular genetic testing.

Management

Treatment of manifestations: Potential targeted therapies include simvastatin (the safety and/or efficacy of simvastatin has not been proven in lathosterolosis) and liver transplantation. Supportive care includes developmental and educational support; treatment of cataracts per ophthalmologist; treatment of digit anomalies per orthopedist; management of liver disease per hepatologist; treatment of genitourinary anomalies per nephrologist and/or urologist; social work support and care coordination as needed.

Surveillance: Assess developmental milestones at each visit throughout childhood; neuropsychological testing and quality of life assessments as needed; annual ophthalmology evaluation; liver enzymes at each visit; liver imaging including ultrasound and FibroScan® every six months or per hepatologist; plasma sterol profile before initiating simvastatin and every one to two months while on therapy.

Agents/circumstances to avoid: Medications and chemicals that are hepatotoxic.

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Evaluation of relatives at risk: It is appropriate to clarify the status of at-risk relatives of an affected individual to identify as early as possible those who would benefit from initiation of potential treatment, surveillance, and awareness of agents and circumstances to avoid.

Genetic counseling

Lathosterolosis is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *SC5D* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *SC5D* pathogenic variants have been identified in an affected family member, molecular genetic carrier testing for relatives at risk, prenatal testing, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Lathosterolosis **should be suspected** in individuals with the following clinical, laboratory, imaging, and family history findings.

Clinical findings

- Global developmental delays
- Intellectual disability
- Microcephaly
- Characteristic facial features, including bitemporal narrowing, sloping forehead, epicanthal folds, ptosis, downslanting palpebral fissures, anteverted nares, broad nasal tip, long philtrum, high-arched palate, and micrognathia (similar to individuals with Smith-Lemli-Opitz syndrome)
- Cataracts
- Digit anomalies (postaxial polydactyly, toe syndactyly)
- Liver disease

Laboratory findings

- Elevated liver enzymes (alanine aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase)
- Elevated lathosterol level on plasma sterol analysis

Imaging findings. Liver fibrosis detected by liver FibroScan®

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of lathosterolosis **is established** in a proband with suggestive findings by identification of elevated lathosterol on plasma sterol analysis and/or biallelic pathogenic (or likely pathogenic) variants in *SC5D* on molecular genetic testing (see Table 1).

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 any likely pathogenic variants. (2) Identification of biallelic *SC5D* variants of uncertain significance (or of one known *SC5D* pathogenic variant and one *SC5D* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include **gene-targeted testing** (single-gene testing, multigene panel) or **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. 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 inherited disorders with congenital malformations, developmental delay, and liver disease are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *SC5D* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. 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 sterol disorders multigene panel that includes *SC5D* 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 indistinguishable from many other inherited disorders characterized by congenital malformations, developmental delay, and liver disease, **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 Lathosterolosis

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SC5D	Sequence analysis [3]	~100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include 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.
4. Yaplito-Lee et al [2020] and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

Clinical Characteristics

Clinical Description

Lathosterolosis is an ultra-rare disorder of cholesterol biosynthesis. To date, seven affected individuals have been reported [Brunetti-Pierri et al 2002, Krakowiak et al 2003, Rossi et al 2007, Ho et al 2014, Anderson et al 2019, Prasun et al 2019, Yaplito-Lee et al 2020]. Hence, the full phenotypic spectrum is unknown at present. However, developmental delay, intellectual disability, microcephaly, facial dysmorphisms, cataracts, digit anomalies, and liver involvement appear to be consistent features of this condition (see Table 2). The following description of the phenotypic features associated with this condition is based on the published case reports.

Table 2. Lathosterolosis: Frequency of Select Features

Feature	Proportion of Persons w/Feature [1]	Comment
Global developmental delay / intellectual disability	6/6	Mild to severe
Microcephaly	6/6	
Hypotonia	5/6	
Dysmorphic facial features	6/6	Bitemporal narrowing, sloping forehead, epicanthal folds, ptosis, downslanting palpebral fissures, anteverted nares, broad nasal tip, long philtrum, high-arched palate, & micrognathia
Cataracts	6/6	
Digit anomalies	6/6	Postaxial polydactyly, toe syndactyly, &/or clinodactyly
Liver disease	6/6	

1. Seven individuals with lathosterolosis have been described in the literature thus far. However, diagnosis was established based on histopathologic and molecular studies of a fetus aborted at 21 weeks' gestation [Rossi et al 2007]. The full clinical phenotype of this fetus is unknown, and therefore, this fetus was not included in the denominator.

Neurologic features. Hypotonia has been described in all individuals with lathosterolosis except one who had a milder phenotype [Yaplito-Lee et al 2020]. All individuals had global developmental delays. The severity of

developmental delays / intellectual disability is most often moderate to severe. However, in one individual developmental delay was reported to be mild and accompanied by features of autism spectrum disorder [Anderson et al 2019]. Microcephaly has been reported in all affected individuals. Microcephaly appears to be prenatal in onset and progressive in nature.

Dysmorphic facial features. The most common facial features described in individuals with lathosterolosis are bitemporal narrowing, sloping forehead, epicanthal folds, ptosis, downslanting palpebral fissures, anteverted nares, broad nasal tip, long philtrum, high-arched palate, and micrognathia. Facial features are similar to individuals with Smith-Lemli-Optiz syndrome. Facial features may be subtle in individuals with a milder phenotype [Anderson et al 2019, Yaplito-Lee et al 2020]. The craniofacial phenotype may evolve over time [Rossi et al 2007].

Ocular manifestations. Cataracts have been reported in all individuals to date. They are often bilateral. They may be present at birth, but they usually appear in early childhood and progress with age [Parnes et al 1990, Cavallini et al 2009]. Cataracts are usually described as posterior and subcapsular. In one individual, cataracts were present as small dot opacities without vision impairment [Ho et al 2014]. In another individual, corneal clouding was reported [Parnes et al 1990].

Digit anomalies. Postaxial polydactyly and 2-3 toe syndactyly are the most common digit anomalies. Interdigital polydactyly and 2-4 toe syndactyly were reported in one individual [Rossi et al 2007]. Clinodactyly was the only observed digit anomaly in another individual reported to have a milder phenotype [Anderson et al 2019].

Liver disease is common in individuals with lathosterolosis. The severity is variable and ranges from asymptomatic elevation of liver enzymes to cirrhosis and liver failure [Prasun et al 2019]. Liver enzymes, including alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT), may be elevated. However, two individuals had normal liver enzymes. In these individuals, liver involvement was very subtle, manifesting as increased liver echogenicity on MRI suggestive of fibrosis in one individual [Ho et al 2014] and elevated prothrombin time in the second individual [Anderson et al 2019].

Intrahepatic cholestasis caused by abnormal bile acids lead to hepatocellular and biliary damage and subsequent progression to fibrosis, cirrhosis, portal hypertension, and liver failure. There are no characteristic biopsy findings; intrahepatic cholestasis, portal and lobular hepatitis, and portal, focal, and bridging fibrosis have been described [Rossi et al 2005, Prasun et al 2019].

Genitourinary anomalies. Horseshoe kidney was reported in two individuals [Brunetti-Pierri et al 2002, Yaplito-Lee et al 2020]. Penoscrotal hypospadias was present in one individual [Parnes et al 1990].

Hematologic findings. Macroplatelets, acanthocytosis, schistocytosis, and vacuolated monocytes have been reported on peripheral blood smear examination [Rossi et al 2007, Yaplito-Lee et al 2020].

Rarely, features of a storage disorder may be present. One individual with lathosterolosis was described with poor weight gain, global developmental delay, progressive hepatosplenomegaly, corneal clouding, gingival hypertrophy, and death at 18 weeks of life. Autopsy showed widespread storage of mucopolysaccharides [Parnes et al 1990]. In addition, lamellar bodies suggestive of intracellular storage defect have been described in the cultured skin fibroblasts of two individuals [Rossi et al 2007, Herman & Kratz 2012].

Other. The following have each been identified in a single affected individual [Parnes et al 1990, Brunetti-Pierri et al 2002, Krakowiak et al 2003, Rossi et al 2007, Ho et al 2014, Prasun et al 2019, Yaplito-Lee et al 2020]:

- Chiari malformation
- Hydrocephalus ex vacuo
- Cerebral calcifications

- Lumbosacral meningocele
- Butterfly vertebra
- Bilobed gallbladder
- Severe food aversion leading to growth failure
- Single umbilical artery

Prognosis. Life span in lathosterolosis is related to the severity of liver involvement; individuals with mild liver disease or lacking liver disease completely may or may not have reduced life span. The individuals with milder liver involvement were reported to be alive in the early second decade of life [Anderson et al 2019, Yaplito-Lee et al 2020]. Thus, in the absence of severe liver involvement, survival into adulthood is possible. Since many adults with disabilities have not undergone comprehensive genomic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Prevalence

Lathosterolosis is extremely rare; only seven individuals have been reported thus far. However, it is possible that individuals with milder manifestations have not been identified.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SC5D*.

Differential Diagnosis

Another autosomal recessive disorder of cholesterol biosynthesis, Smith-Lemli-Opitz syndrome (SLOS), closely resembles lathosterolosis. Developmental delay, microcephaly, characteristic facial dysmorphism (epicanthal folds, ptosis, broad nasal tip, anteverted nostrils, and long philtrum), 2-3 toe syndactyly, and postaxial polydactyly are common in both conditions. Growth restriction is reported in most individuals with SLOS; other variably associated features include cleft palate, congenital heart defects, and external female genitalia in individuals with a 46,XY karyotype. Although cataract and liver disease are very common in lathosterolosis, they are relatively less common in SLOS [Ryan et al 1998, Rossi et al 2005].

Squalene synthase deficiency, lanosterol synthase deficiency, and desmosterolosis share common clinical features with lathosterolosis. All these conditions are due to defects in cholesterol biosynthesis [Platt et al 2014, Romano et al 2018]. A comprehensive plasma sterol panel should be performed when a disorder of cholesterol biosynthesis is suspected based on clinical features; if that testing is negative, consideration should be given for a multigene panel (see Table 3) or comprehensive genomic testing.

Table 3. Genes of Interest in the Differential Diagnosis of Lathosterolosis

Gene	Disorder
DHCR24	Desmosterolosis (OMIM 602398)
DHCR7	Smith-Lemli-Opitz syndrome
FDFT1	Squalene synthase deficiency
LSS	Lanosterol synthase deficiency [1]

1. Besnard et al [2019]

Management

No clinical practice guidelines for lathosterolosis have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with lathosterolosis, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Lathosterolosis: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Eyes	Ophthalmology eval	To assess visual acuity & for cataracts
Liver	• Liver enzymes: ALT, ALP, & GGT • Liver ultrasound • Liver FibroScan®	To assess liver function & for liver fibrosis
	Plasma sterol profile	Prior to starting simvastatin
Genitourinary anomalies	• Clinical exam for genitourinary anomalies • Renal ultrasound	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of lathosterolosis 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

ALP = alkaline phosphatase; ALT = alanine aminotransferase; GGT = gamma-glutamyl transferase; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no proven effective treatment or cure for lathosterolosis.

Potential targeted therapies

- **Simvastatin** inhibits the enzyme hydroxy methylglutaryl-coenzyme A (HMG-CoA) reductase, which converts HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. It has been used to treat at least three individuals with lathosterolosis [Ho et al 2014, Prasun et al 2019, Yaplito-Lee et al 2020]. A marked reduction in plasma lathosterol level was seen in all three individuals. In addition, reduction in plasma liver enzyme levels and reduced liver fibrosis was noted in one individual [Yaplito-Lee et al 2020], while in another, improvement in development was attributed to simvastatin [Ho et al 2014]. A dose of 0.2 mg/kg/day to 1 mg/kg/day was recommended. Safety and efficacy of simvastatin in individuals with lathosterolosis in large controlled clinical trials has not been established.
- **Liver transplantation.** One individual with lathosterolosis underwent liver transplantation at age seven years due to end-stage liver disease, which resulted in complete normalization of plasma lathosterol level

and liver function tests. In addition, it led to arrest of cognitive decline [Calvo et al 2014]. A second individual with liver cirrhosis and liver failure underwent liver transplant at age 13 years, leading to normalization of liver function tests and plasma lathosterol level. Her aggressive behavior, quality of life, and need for hospitalization during intercurrent illnesses have significantly improved. However, the follow-up duration is too short to determine neurologic outcome in this individual [P Prasun, personal observation].

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 5).

Table 5. Lathosterolosis: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Cataracts	Treatment per ophthalmologist	Cataracts may appear after birth & progress gradually.
Digit anomalies	Treatment per orthopedist	
Liver disease	Treatment per hepatologist	Avoid hepatotoxic drugs.
Genitourinary anomalies	Treatment per nephrologist &/or urologist	
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the US; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.

    - Vision consultants should be a part of the child's IEP team to support access to academic material.
    - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
    - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Neurobehavioral/Psychiatric Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social,

and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. Lathosterolosis: Recommended Surveillance

Manifestation	Evaluation	Frequency/Comment
Developmental delay / Intellectual disability	Monitor developmental milestones	At each visit throughout childhood
	• Neuropsychological testing using age-appropriate standardized assessment batteries • Standardized quality of life assessment tools for affected persons & parents/caregivers	As needed
Cataracts	Ophthalmology eval	Annually or more frequently for severe presentation
Liver disease	Liver enzymes: ALT, ALP, & GGT	At each visit
	• Liver ultrasound • FibroScan®	Every 6 mos
	Plasma sterol profile	• Before initiating simvastatin treatment • Repeat every 1-2 mos while on simvastatin to optimize simvastatin dose

ALP = alkaline phosphatase; ALT = alanine aminotransferase; GGT = gamma-glutamyl transferase

Agents/Circumstances to Avoid

Avoid medications and chemicals that are hepatotoxic.

Evaluation of Relatives at Risk

It is appropriate to clarify the status of at-risk relatives of an affected individual to identify as early as possible those who would benefit from initiation of potential treatment, surveillance, and awareness of agents and circumstances to avoid. Evaluations can include:

- Molecular genetic testing if the pathogenic variants in the family are known;
- Plasma comprehensive sterol profile if the pathogenic variants in the family are not known.

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. 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

Lathosterolosis 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 *SC5D* 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 *SC5D* 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 *SC5D* 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. To date, individuals with lathosterolosis 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 *SC5D* pathogenic variant.

Carrier Detection

Molecular genetic carrier testing for at-risk relatives requires prior identification of the *SC5D* pathogenic variants in the family.

Note: The utility of plasma lathosterol level for carrier detection is unknown but is unlikely to be a sensitive or specific test.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.

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

Molecular genetic testing, Once the *SC5D* pathogenic variants have been identified in an affected family member, molecular genetic prenatal and preimplantation genetic testing are possible.

Note: The utility of amniotic fluid sterol profile in prenatal diagnosis is unknown. Lathosterol may be normally abundant in the amniotic fluid [Chevy et al 2005].

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.

- **Genetic and Rare Diseases Information Center (GARD)**
  Lathosterolosis

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. Lathosterolosis: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SC5D	11q23.3-q24.1	Lathosterol oxidase	SC5D database	SC5D	SC5D

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 Lathosterolosis (View All in OMIM)

602286	STEROL C5-DESATURASE; SC5D
607330	LATHOSTEROLOSIS; LATHOS

Molecular Pathogenesis

Lathosterolosis is a disorder of cholesterol biosynthesis. It is due to deficiency of the enzyme lathosterol oxidase (sterol-C5-desaturase), encoded by *SC5D*, which catalyzes conversion of lathosterol to 7-dehydrocholesterol, the second-to-last step in cholesterol biosynthesis. The molecular pathogenesis is unknown but considered to be either mediated by accumulation of lathosterol and/or decreased cholesterol [Cooper et al 2003]. An abnormal sterol profile may lead to a bile acid synthesis defect, causing cholestasis, and abnormal hedgehog signaling, leading to limb defects.

Mechanism of disease causation. Loss of function

Chapter Notes

Author Notes

Dr Pankaj Prasun is actively involved in clinical research regarding individuals with lathosterolosis and would be happy to communicate with persons who have any questions regarding diagnosis of lathosterolosis or other considerations.

Revision History

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