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Squalene Synthase Deficiency

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Summary

Clinical characteristics

Squalene synthase deficiency (SQSD) is a rare inborn error of cholesterol biosynthesis with multisystem clinical manifestations similar to Smith-Lemli-Optiz syndrome. Key clinical features include facial dysmorphism, a generalized seizure disorder presenting in the neonatal period, nonspecific structural brain malformations, cortical visual impairment, optic nerve hypoplasia, profound developmental delay / intellectual disability, dry skin with photosensitivity, and genital malformations in males.

Diagnosis/testing

Individuals with SQSD have a unique urine metabolic profile with increased saturated and unsaturated branched-chain dicarboxylic acids and glucuronides derived from farnesol. The diagnosis of squalene synthase deficiency is established in a proband with characteristic urine metabolites on urine organic acids analysis or by the identification of biallelic pathogenic variants in *FDFT1* by molecular genetic testing.

Management

Treatment of manifestations: Currently there are no specific disease-modifying treatments. Standard treatment for epilepsy, congenital heart defects, constipation, cryptorchidism, hypospadias, spasticity, and developmental delay / intellectual disability is appropriate. Feeding therapy may be useful, although placement of a gastrostomy tube is recommended for those with dysphagia and/or poor growth. In those with visual impairment, early

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intervention may help to stimulate visual development. In those with sleep disturbance, a trial of melatonin may be considered.

Surveillance: At each visit: assess for new manifestations such as seizures, changes in tone, and movement disorder; monitor developmental progress, educational needs, and behavior; assess for evidence of aspiration or respiratory insufficiency; assess for evidence of sleep disorder; monitor growth, nutritional status, and signs and symptoms of constipation. Ophthalmology evaluation annually or as clinically indicated.

Agents/circumstances to avoid: Sun and UV light exposure; skin photosensitivity has produced clinically significant UV-related sunburns within ten minutes of direct sunlight exposure.

Genetic counseling

SQSD is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% change of being affected, a 50% change of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the *FDFT1* pathogenic variants in the family are known.

Diagnosis

Formal clinical diagnostic criteria for squalene synthase deficiency (SQSD) have not been established. However, the urine metabolic profile with increased saturated and unsaturated branched-chain dicarboxylic acids and glucuronides derived from farnesol in the appropriate clinical setting is specific for SQSD.

Suggestive Findings

Squalene synthase deficiency **should be suspected** in individuals with clinical manifestations similar to Smith-Lemli-Optiz syndrome and the following clinical, laboratory, and brain MRI findings.

Clinical findings

- Dysmorphic features (See Clinical Description, **Dysmorphic features**.)
- Neonatal generalized seizure disorder
- Profound developmental delay
- Cortical visual impairment
- Genital malformations in males
- Dry skin with photosensitivity

Laboratory findings. Gas chromatography-mass spectroscopy (GC-MS) and nuclear magnetic resonance spectroscopy (NMRS) of urine metabolites are listed in Table 1.

Table 1. Typical Urine Metabolite Profile in Squalene Synthase Deficiency

Testing Technique	Elevated Metabolites
Urine organic acid GC-MS	• Methylsuccinic acid • Mevalonic lactone • 3-methylhex-2-enedioic acid • 2,6-dimethylhept-2-enedioic acid • 3,7-dimethyl-2,6-dienedioic
NMRS profiles	• 3-methylhex-2,4-dienedioic acid • 3-methylhex-3,4-dienedioic acid

GC-MS = gas chromatography-mass spectroscopy; NMRS = nuclear magnetic resonance spectroscopy

Note: A similar metabolite profile is also found in the urine of humans treated with pharmacologic inhibitors of squalene synthase or those who have taken farnesol [Jemal & Ouyang 1998, Coman et al 2018]:

- Increased plasma farnesol levels
- Plasma squalene levels that are either reduced or normal
- Fasting cholesterol studies demonstrating:
  - Low normal total cholesterol level
  - Reduced low-density lipoprotein cholesterol level

Brain MRI findings

- Hypoplastic corpus callosum
- Reduced white matter volume
- Polymicrogyria involving the frontal, parietal, and temporal lobes
- Optic nerve hypoplasia

Establishing the Diagnosis

The diagnosis of SQSD **is established** in a proband with gas chromatography-mass spectroscopy (GC-MS) or nuclear magnetic resonance spectroscopy (NMRS) of urine metabolites showing the characteristic profile of SQSD (see Table 1) OR confirmed by identification of biallelic pathogenic (or likely pathogenic) variants in *FDFT1* by molecular genetic testing (see Table 2).

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) Identification of biallelic *FDFT1* variants of uncertain significance (or of one known *FDFT1* pathogenic variant and one *FDFT1* 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).

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

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of squalene synthase deficiency molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *FDFT1* detects missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, gene-targeted deletion/duplication analysis should be performed to evaluate for larger intragenic deletions or duplications.
- **A multigene panel** that includes *FDFT1* and other genes of interest (see Differential Diagnosis) is 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 this disorder, a multigene panel that also includes deletion/duplication analysis is recommended (see Table 2).

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 squalene synthase deficiency is not considered because the phenotypic association with SQSD was not recognized or an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **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 2. Molecular Genetic Testing Used in Squalene Synthase Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
FDFT1	Sequence analysis [3]	2/3 [4, 5]
	Gene-targeted deletion/duplication analysis [6]	1/3 [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. Coman et al [2018]
5. Note that of the three described disease-associated variants to date, one – c.-75+131_-75+146del – is outside of the exon and intron/exon boundary regions typically sequenced; therefore, analysis may need to be extended into the 5'UTR to detect this variant.
6. 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. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Coman et al [2018]) may not be detected by these methods.

Clinical Characteristics

Clinical Description

Squalene synthase deficiency (SQSD) is a rare inborn error of cholesterol biosynthesis with multisystem clinical manifestations similar to Smith-Lemli-Optiz syndrome. Key clinical features include facial dysmorphism, a generalized seizure disorder, structural brain malformations, cortical visual impairment, optic nerve hypoplasia, profound developmental delay, dry skin with photosensitivity, and genital malformations. The following information is based on three known affected individuals, two of whom are sibs [Coman et al 2018].

Neonates may present with the following features:

- Small for gestational age, including one individual with a birth weight at the tenth centile and another with an occipital frontal circumference at birth at the tenth centile
- Generalized seizures, typically presenting in the first week of life
- Neonatal hepatitis consisting of unconjugated hyperbilirubinemia and elevated liver function enzymes with normal hepatic synthetic function

Dysmorphic features may include the following (see Coman et al [2018], Figure 2):

- Coarse facial features
- Narrow forehead
- Epicanthus
- Depressed nasal bridge
- Low-set and posteriorly rotated ears
- Squared nasal tip
- Micrognathia and retrognathia
- 2-3 toe syndactyly

Neurologic findings may include the following:

- Generalized tonic-colonic seizures that present in the neonatal period
- Profound developmental delay. The limited number of affected individuals identified to date have been:
  - Able to sit independently
  - Nonambulatory
  - Nonverbal
  - Not able to perform any self-care

  Affected individuals have varying degrees of nonverbal social communication skills ranging from no meaningful nonverbal communication/interactions to use of eye contact.
- Autistic features
- Habitual eye poking
- Irritability
- Central hypotonia, typically present at birth
- Hyperreflexia, typically present at birth
- Hypersalivation

Brain MRI findings are often nonspecific but may include the following:

- Hypoplastic corpus callosum in two sibs
- Reduced white matter volume
- Polymicrogyria involving the frontal, parietal, and temporal lobes in one affected individual

Ophthalmology. Optic nerve hypoplasia was found in two affected sibs but was absent in one unrelated affected individual. However, all three affected individuals had cortical visual impairment.

Cardiac. Bicuspid aortic valve has been described in one affected individual. It is unclear if this is a finding within the spectrum of squalene synthase deficiency or an unrelated co-occurrence.

Sleep. All three affected individuals have been described as having delayed sleep initiation. One affected individual also had poor nocturnal sleep maintenance.

Gastrointestinal. All three affected individuals had postnatal failure to thrive and required placement of a gastrostomy tube to address dysphagia and poor growth. All three also had constipation, possibly secondary to hypotonia.

Genitourinary. One affected male had bilateral cryptorchidism and the other had hypospadias without cryptorchidism. The third affected individual is female without any known genitourinary anomalies.

Musculoskeletal. Skeletal radiographs demonstrated:

- Thin gracile bones in two sibs
- Reduced bone mineralization in two sibs
- Fixed flexion joint contractures at the knees in two sibs and of the elbows in one unrelated affected individual

Skin. All three affected individuals have dry skin with photosensitivity. The two sibs both had lack of hair pigmentation on microscopy.

Biochemical findings include the following:

- Plasma total cholesterol is mildly decreased.
- Plasma HDL- and LDL-cholesterol levels are decreased or low normal range.
- Plasma total farnesol levels (the sum of free farnesol and farnesyl-pyrophosphate) are significantly increased.
- Plasma squalene levels are reduced or normal.
- Pathognomonic urine metabolic profile (See Suggestive Findings, **Laboratory findings**.)

Genotype-Phenotype Correlations

Thus far, pathogenic variants have included a contiguous gene deletion, a splice acceptor site variant, and an intronic deletion in three individuals with similar features. Therefore, no clear genotype-phenotype correlations exist.

Prevalence

The prevalence is unknown. Currently three affected individuals from two kindreds have been described [Coman et al 2018]. Both families are of European descent.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *FDFT1*.

Differential Diagnosis

Currently, ten mendelian disorders of cholesterol biosynthesis have been characterized. Of these, four overlap clinically with squalene synthase deficiency (SQSD): lanosterol synthase deficiency, lathosterolosis, Smith-Lemli-Opitz syndrome, and desmosterolosis (see Table 3). SQSD is differentiated from these disorders by the abnormal urine GC-MS and NMRS of complex, farnesol-derived dicarboxylic acids.

Table 3. Cholesterol Biosynthesis Disordersof Interest in the Differential Diagnosis of Squalene Synthase Deficiency

Gene	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/SQSD	Distinguishing from SQSD
DHCR24	Desmosterolosis (OMIM 602398)	AR	• Facial dysmorphism • Congenital heart defects • Microcephaly • DD & ID • Structural brain malformations	• ↑ desmosterol • Normal urine organic acids
DHCR7	Smith-Lemli-Opitz syndrome	AR	• 2-3 toe syndactyly • DD & ID • Facial dysmorphism • Genital abnormalities • Structural brain malformations • Congenital heart defects • Dry skin / photosensitivity • Autism • Low-normal plasma TC levels	• ↑ 7-dehydrocholesterol • Normal urine organic acids
LSS	Lanosterol synthase deficiency [1]	AR	• Seizures • DD & ID • Structural brain malformations	• Congenital cataracts • Hypotrichosis simplex • Normal urine organic acids
SC5D	Lathosterolosis	AR	• Microcephaly • DD & ID • Structural brain malformations • Genital abnormalities	• Cataracts • Normal urine organic acids

AR = autosomal recessive; DD = developmental delay; DiffDx = differential diagnosis; GC-MS = gas chromatography-mass spectrometry; ID = intellectual disability; MOI = mode of inheritance; NMRS = nuclear magnetic resonance spectroscopy; SQSD = squalene synthase deficiency; TC = total cholesterol

1. Besnard et al [2019]

Management

Evaluations Following Initial Diagnosis

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

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Squalene Synthase Deficiency

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	• To incl brain MRI • Consider EEG if seizures are a concern.
Development	Developmental assessment	• To incl motor, adaptive, cognitive & speech-language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	In persons age >12 mos: screen for presence of behavior issues incl sleep disturbances &/or findings suggestive of ASD.
Eyes	Ophthalmologic eval	To assess for ↓ vision & optic nerve hypoplasia
Hearing	Audiologic eval	To assess for hearing loss [1]

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Cardiovascular	Clinical cardiac eval, w/consideration of echocardiogram	To assess for congenital structural cardiac lesions
Respiratory	Consider sleep study.	If sleep initiation & maintenance are an issue
Gastrointestinal/ Feeding	Assess for neonatal hepatitis incl bilirubin concentrations (total, conjugated & unconjugated) & liver enzymes.	In neonates
	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk, nutritional status, & for constipation • Consider eval for gastrostomy tube placement in those w/ failure to thrive, dysphagia, &/or aspiration risk.
Genitourinary	Genitourinary eval for cryptorchidism & hypospadias in males	Consider US to assess for structural renal defects if external anomalies of the genitalia are present. [2]
Musculoskeletal	Orthopedics / physical medicine & rehab / PT/OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures • Mobility & activities of daily living & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Integument	Complete skin eval	Assess for history of photosensitivity & sunburn when exposed to UV light.
Endocrine	Endocrine assessment	Consider investigating anterior & posterior pituitary function if optic nerve hypoplasia is present.
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling
	Family supports & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.

ASD = autism spectrum disorder; OT = occupational therapy; PT = physical therapy; US = ultrasound
1. Hearing loss has not been described as a primary feature in this condition; however, this recommendation is based on the fact that the affected individuals have intellectual impairment, which makes clinical assessment for hearing loss difficult.
2. No structural renal anomalies have as yet been described in affected individuals.

Treatment of Manifestations

There are currently no specific disease modifying treatments for SQSD.

Table 5. Treatment of Manifestations in Individuals with Squalene Synthase Deficiency

Manifestation/ Concern	Treatment	Considerations/Other
Epilepsy	Standardized treatment w/ASM	• To date, no one ASM has been demonstrated effective specifically for SQSD. • Education of parents/caregivers [1]
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Central visual impairment	No specific treatment, but early intervention may help stimulate visual development.	
Congenital heart defects	Standard treatment per cardiologist	
Sleep disturbance	Consider a trial of melatonin.	
Neonatal hepatitis	Supportive care	
Poor weight gain / Failure to thrive	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia
Bowel dysfunction	Stool softeners, prokinetics, osmotic agents or laxatives as needed	
Cryptorchidism or hypospadias	Standard surgical treatment per urologist	
Spasticity	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Photosensitivity	Avoidance of sun & UV light exposure	See Agents/Circumstances to Avoid.
Family/Community	Ensure appropriate social work involvement to connect families w/local resources, respite, & support.	Ongoing assessment of need for palliative care involvement &/or home nursing
	Care coordination to manage multiple subspecialty appointments, equipment, medications, & supplies	Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability; OT = occupational therapy; PT = physical therapy

1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States (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 and to support parents in maximizing quality of life. An IEP may be considered:

- An IEP provides specially designed instruction and related services to children who qualify.

- IEP services will be reviewed annually to determine if 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 and hearing 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 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.

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 by 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.

Social/Behavioral 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 is 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

The authors recommend general care as outlined in Table 6.

Table 6. Recommended Surveillance for Individuals with Squalene Synthase Deficiency

System/Concern	Evaluation	Frequency
Neurologic	Monitor those w/seizures as clinically indicated.	At each visit
	Assess for new manifestations incl seizures, changes in tone, movement disorders.	
Development	Monitor developmental progress & educational needs.	
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Eyes	Ophthalmology evaluation w/vision assessment	Annually or as clinically indicated
Respiratory	Assess for evidence of: • Aspiration or respiratory insufficiency; • Sleep disorder.	At each visit
Feeding	• Measurement of growth parameters • Evaluation of nutritional status & safety of oral intake	
Gastrointestinal	Monitor for constipation.	
Musculoskeletal	Assess need for physical medicine, OT/PT, self-help skills assistance.	
Miscellaneous/ Other	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

The skin photosensitivity has produced clinically significant UV-related sunburns within ten minutes of direct sunlight exposure. Skin care and UV protection is recommended (see Table 4).

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. 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

Squalene synthase deficiency (SQSD) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *FDFT1* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. To date, individuals with squalene synthase deficiency 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 a *FDFT1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *FDFT1* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to the parents of an affected child.

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 *FDFT1* pathogenic variants 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, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. 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.

- **Rare Voices Australia**
  PO Box 138
  Mentone Victoria 3194
  Australia
  Phone: 0497 003 104
  Email: info@rarevoices.com.au
  www.rarevoices.org.au
- **RDCRN Contact Registry for Sterol and Isoprenoid Research (STAIR) Consortium**
  RDCRN Patient Contact 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. Squalene Synthase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
FDFT1	8p23.1	Squalene synthase	FDFT1	FDFT1

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 Squalene Synthase Deficiency (View All in OMIM)

184420	FARNESYLDIPHOSPHATE FARNESYLTRANSFERASE 1; FDFT1
618156	SQUALENE SYNTHASE DEFICIENCY; SQSD

Molecular Pathogenesis

FDFT1 encodes for the enzyme squalene synthase (SS, farnesyl-pyrosphosphate farnesyl-transferase 1), which is ubiquitously expressed in human tissues [Shechter et al 1994, Tansey & Shechter 2000]. *FDFT1* exists in 11 different isoforms, encoding five different protein isoforms.

Mammalian SS is a conserved ~47-kd protein containing ~416 amino acids; it forms an alpha-helical structure which is located in the endoplasmic reticulum, where it is anchored by a C-terminal membrane-spanning domain, with the N-terminal catalytic domain facing the cytosol [Pandit et al 2000, Tansey & Shechter 2000, Do et al 2009]. SS catalyzes the conversion of two molecules of farnesyl-pyrophosphate (FPP) to pre-squalene diphosphate, which is then converted into squalene, a C30 isoprenoid, in a two-step reaction [Pandit et al 2000]. This is the first committed step in cholesterol biosynthesis. The protein is not predicted to be post-translationally modified, but is modulated both at the mRNA and at the protein level to regulate intracellular cholesterol levels [Robinson et al 1993].

Plasma total farnesol levels are elevated and plasma squalene levels may be reduced or normal. The accumulation of farnesyl pyrophosphate initiates a complex metabolic cascade involving glucuronidation, hydroxylation, and oxidation to shorter chain molecules [Coman et al 2018]. Farnesol and its products exhibit a wide variety of biologic activities, including cell growth inhibition, induction of apoptosis, and regulation of bile acid secretion [Joo & Jetten 2010]. Alternate splicing is an important mechanism for regulation in cholesterol biosynthesis and has been represented in SQSD [Coman et al 2018].

Mechanism of disease causation. Pathogenic variants in *FDFT1* cause SQSD by reduction of squalene synthase activity.

FDFT1 cDNA analysis using RNA isolates generated from fibroblasts of affected individuals found normally and misspliced *FDFT1* cDNA. Western blot analysis confirmed a marked reduction in SS protein [Coman et al 2018].

***FDFT1*-specific laboratory technical considerations.** One identified pathogenic variant, c.-75+131_-75+146del, is outside of the exon and intron/exon boundary regions typically included in sequencing analysis; therefore, analysis may need to be extended into the 5'UTR to detect this variant.

Table 7. Notable *FDFT1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001287742.1	c.-75+131_-75+146del	--	A deletion w/evidence for ↓ promoter activity [Coman et al 2018] [1]

NA = not applicable
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. FDFT1 has 11 isoforms, encoding five different protein isoforms. Annotation of the chromatic state for *FDFT1* indicates that the 16-bp deletion region is predicted to have promoter and/or enhancer effects (tested via a luciferase assay).

Chapter Notes

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- 6 February 2020 (ma) Review posted live
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References

Literature Cited

Besnard T, Sloboda N, Goldenberg A, Küry S, Cogné B, Breheret F, Trochu E, Conrad S, Vincent M, Deb W, Balguerie X, Barbarot S, Baujat G, Ben-Omran T, Bursztejn AC, Carmignac V, Datta AN, Delignières A, Faivre L, Gardie B, Guéant JL, Kuentz P, Lenglet M, Nassogne MC, Ramaekers V, Schnur RE, Si Y, Torti E, Thevenon J, Vabres P, Van Maldergem L, Wand D, Wiedemann A, Cariou B, Redon R, Lamazière A, Bézieau S, Feillet F, Isidor B. Biallelic pathogenic variants in the lanosterol synthase gene LSS involved in the cholesterol biosynthesis cause alopecia with intellectual disability, a rare recessive neuroectodermal syndrome. Genet Med. 2019;21:2025-35. PubMed PMID: 30723320.

Coman D, Vissers LELM, Riley LG, Kwint MP, Hauck R, Koster J, Geuer S, Hopkins S, Hallinan B, Sweetman L, Engelke UFH, Burrow TA, Cardinal J, McGill J, Inwood A, Gurnsey C, Waterham HR, Christodoulou J, Wevers RA, Pitt J. Squalene synthase deficiency: clinical, biochemical, and molecular characterization of a defect in cholesterol biosynthesis. Am J Hum Genet. 2018;103:125-30. PubMed PMID: 29909962.

Do R, Kiss RS, Gaudet D, Engert JC. Squalene synthase: a critical enzyme in the cholesterol biosynthesis pathway. Clin Genet. 2009;75:19–29. PubMed PMID: 19054015.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389-97. PubMed PMID: 35834113.

Jemal M, Ouyang Z. Gas chromatography-mass spectrometric method for quantitative determination in human urine of dicarboxylic (dioic) acids produced in the body as a consequence of cholesterol biosynthesis inhibition. J Chromatogr B Biomed Sci Appl. 1998;709:233–41. PubMed PMID: 9657220.

Joo JH, Jetten AM. Molecular mechanisms involved in farnesol-induced apoptosis. Cancer Lett. 2010;287:123–35. PubMed PMID: 19520495.

Pandit J, Danley DE, Schulte GK, Mazzalupo S, Pauly TA, Hayward CM, Hamanaka ES, Thompson JF, Harwood HJ Jr. Crystal structure of human squalene synthase. A key enzyme in cholesterol biosynthesis. J Biol Chem. 2000;275:30610–7. PubMed PMID: 10896663.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Robinson GW, Tsay YH, Kienzle BK, Smith-Monroy CA, Bishop RW. Conservation between human and fungal squalene synthetases: similarities in structure, function, and regulation. Mol Cell Biol. 1993;13: 2706–17. PubMed PMID: 8474436.

Shechter I, Conrad DG, Hart I, Berger RC, McKenzie TL, Bleskan J, Patterson D. Localization of the squalene synthase gene (FDFT1) to human chromosome 8p22-p23.1. Genomics. 1994;20:116-8. PubMed PMID: 8020937.

Tansey TR, Shechter I. Structure and regulation of mammalian squalene synthase. Biochim. Biophys. Acta. 2000;1529:49–62. PubMed PMID: 11111077.

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