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Sitosterolemia

Synonyms: Beta-Sitosterolemia, Phytosterolæmia, Phytosterolemia, Sitosterolæmia

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Summary

Clinical characteristics

Sitosterolemia is characterized by:

- Hypercholesterolemia (especially in children) which (1) shows an unexpected significant lowering of plasma cholesterol level in response to low-fat diet modification or to bile acid sequestrant therapy; or (2) does not respond to statin therapy;
- Tendon xanthomas or tuberous (i.e., planar) xanthomas that can occur in childhood and in unusual locations (heels, knees, elbows, and buttocks);
- Premature atherosclerosis, which can lead to angina, aortic valve involvement, myocardial infarction, and sudden death;
- Hemolytic anemia, abnormally shaped erythrocytes (stomatocytes), and large platelets (macrothrombocytopenia).

On occasion, the abnormal hematologic findings may be the initial presentation or the only clinical feature of this disorder. Arthritis, arthralgias, and splenomegaly may sometimes be seen and one study has concluded that "idiopathic" liver disease could be undiagnosed sitosterolemia. The clinical spectrum of sitosterolemia is probably not fully appreciated due to underdiagnosis and the fact that the phenotype in infants is likely to be highly dependent on diet.

Diagnosis/testing

In an individual with sitosterolemia, increased plasma concentrations of plant sterols (especially sitosterol, campesterol, and stigmasterol) are observed – if the diet includes plant-derived food, which contain plant sterols – once the plant sterols have accumulated in the body. The diagnosis of sitosterolemia is established in a proband with greatly increased plant sterol concentrations in plasma and/or by identification of biallelic pathogenic (or likely pathogenic) variants in *ABCG5* and/or *ABCG8*.

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Management

Treatment of manifestations: Treatment should begin at the time of diagnosis, though there is little experience treating children younger than age two years. Treatment can decrease plasma concentrations of cholesterol and sitosterol by 10% to 50%. Often existing xanthomas regress. Treatment recommendations include a diet low in shellfish sterols and plant sterols (vegetable oils, margarine, nuts, seeds, avocados, and chocolate) and use of the sterol absorption inhibitor, ezetimibe. In those with an incomplete response to ezetimibe, use of a bile acid sequestrant such as cholestryramine may be considered. Partial ileal bypass surgery may be considered as a last resort for those with poor response to maximal therapies. If arthritis, arthralgias, anemia, thrombocytopenia, and/or splenomegaly require treatment, the first step is management of the sitosterolemia, followed by routine symptomatic management.

Surveillance: Begin monitoring at the time of diagnosis on an annual basis: plasma concentrations of plant sterols (primarily beta-sitosterol and campesterol) and cholesterol; the size, number, and distribution of xanthomas; and CBC and platelet count, and liver transaminases (for elevation). In persons with long-standing untreated sitosterolemia, noninvasive imaging is used to exclude coronary and carotid plaque as well as valvular atherosclerotic manifestations.

Agents/circumstances to avoid: Margarines and other products containing stanols (e.g., campestanol and sitostanol) that are recommended for use by persons with hypercholesterolemia are contraindicated as they can exacerbate plant stanol accumulation.

Evaluation of relatives at risk: Early diagnosis of at-risk relatives either through measurement of plasma concentrations of plant sterols or through molecular genetic testing (if the family-specific pathogenic variants are known) allows early institution of treatment and surveillance to optimize outcome.

Pregnancy management: There are no adequate and well-controlled studies of ezetimibe in pregnant women; ezetimibe can be used during pregnancy only if the potential benefits justifiy the risk to the fetus. Since no studies have been published on the fetal effects of ezetimibe, it should be used with caution during pregnancy.

Genetic counseling

Sitosterolemia is inherited in an autosomal recessive manner. 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 but may occasionally have a mildly elevated concentration of sitosterol. Once the sitosterolemia-causing pathogenic variants have been identified in an affected family member, carrier testing for at-risk family members, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Formal diagnostic criteria for sitosterolemia have not been established.

Suggestive Findings

Sitosterolemia **should be suspected** in individuals with the following:

- Hypercholesterolemia (especially in children) that shows unexpected significant response (i.e., lowering of plasma cholesterol level) to low-fat diet modification (e.g., low saturated fat/low cholesterol/low plant-derived foods) or to bile acid sequestrant (e.g. cholestyramine) therapy [Cobb et al 1996, Park et al 2014]
- Hypercholesterolemia that does not respond to statin therapy [Nguyen et al 1990, Cobb et al 1996]

- Tendon xanthomas or tuberous xanthomas, which may occur in childhood and in unusual locations (heels, knees, elbows, and buttocks) [Niu et al 2010]
- Premature atherosclerosis, which may lead to angina, myocardial infarction, and sudden death [Kidambi & Patel 2008]
- Hemolytic anemia usually associated with abnormally shaped erythrocytes (stomatocytes) and/or thrombocytopenia usually associated with large platelets (macrothrombocytopenia)

  Note: The hematologic abnormalities can be the initial presentation [Rees et al 2005, Su et al 2006] or the only clinical feature of the disorder [Wang et al 2011].

Note: The complete clinical spectrum of sitosterolemia is probably not fully appreciated due to underdiagnosis. Furthermore, the phenotype in infants is likely to be highly dependent on diet.

Establishing the Diagnosis

The diagnosis of sitosterolemia **is established** in a proband with greatly increased plant sterol concentrations in plasma and/or by identification of biallelic pathogenic (or likely pathogenic) variants one or both of the genes listed in Table 1.

Note: 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.

Measurement of plasma plant sterol concentrations. Individuals with sitosterolemia have greatly increased plant sterol concentrations (especially sitosterol, campesterol, and stigmasterol) in plasma. Shellfish sterols can also be elevated.

- Typical plant sterol concentrations in healthy individuals are 100 times lower than cholesterol (0.21 ± 0.7 mg/dL); thus, their contribution to the total sterol concentration is negligible. These plant sterols and shellfish sterols are not detected by standard laboratory methods of cholesterol measurement and require specialized analysis typically utilizing gas chromatography (GC), gas chromatography / mass spectrometry (GC/MS), high-pressure liquid chromatography (HPLC) or separation with tandem mass spectrometry (LC-MS/MS).
- In untreated individuals with sitosterolemia the sitosterol concentration can be 30- to 100-fold increased (i.e., as high as 10 to 65 mg/dL) [Kidambi & Patel 2008]. Plasma concentrations of sitosterol above 1 mg/dL are considered to be diagnostic of sitosterolemia (except in infants, in whom further testing may be necessary; see following Note).

  Note: (1) In individuals with sitosterolemia the plant sterol transporters sterolin-1 (encoded by *ABCG5*) and sterolin-2 (encoded by *ABCG8*) are abnormal at birth; however, the increase in the plasma concentration of sitosterol and other plant sterols does not occur until plant-derived foods (which contain plant sterols) are consumed and the plant sterols accumulate in the body. Thus, even using GC, GC/MS, HPLC, or LC-MS/MS to measure plasma sitosterol concentrations, the diagnosis of sitosterolemia cannot be excluded until the child is consuming foods that contain plant oils. Formula-fed infants with sitosterolemia may have high plasma concentrations of cholesterol and plant sterols. (2) Total parenteral nutrition with intralipid often contains plant sterols; caution is advised in interpreting diagnostic testing for sitosterolemia in this situation. (3) Breast-fed infants with sitosterolemia likely will not have increased concentrations of plant sterols until after weaning [Rios et al 2010]. Of note, one breastfed infant age three months with sitosterolemia had increased plasma concentrations of sitosterol [Niu et al 2010].

False positive results have been observed:

- Normal infants ingesting commercial infant formula (which contains plant sterols) may have a transient increase in plasma plant sterols, probably due to immature transporters [Mellies et al 1976, Steiner 2011].
- Patients with cholestasis or liver disease receiving parenteral nutrition (which often contains plant sterols in intralipids) may be unable to effectively clear the plant sterols [Bindl et al 2000, Llop et al 2008, Kurvinen et al 2011]. Infants without obvious cholestasis or liver disease receiving parenteral nutrition who do not have sitosterolemia may also exhibit elevation of plasma plant sterols.
- Heterozygotes (carriers of one *ABCG5* or *ABCG8* pathogenic variant) may occasionally have mildly elevated concentration of sitosterol [Lee et al 2001], which can be exacerbated with plant sterols [Myrie et al 2012]. (Note, however, that plasma concentrations of sitosterol are usually normal in carriers [Kwiterovich et al 2003]).

False negative results can be observed in:

- Individuals using ezetimibe or ezetimibe combinations, or bile acid-binding resin;

  AND/OR

- Individuals on a diet low in plant-derived foods.

Note: (1) In general plasma cholesterol concentration is not diagnostic because it can be normal in individuals with sitosterolemia, and elevations of plasma cholesterol concentration can be seen in numerous common disorders. (2) In sitosterolemia, plasma concentrations of cholesterol in children can be high, even in the range seen in homozygous familial hypercholesterolemia [Togo et al 2009, Niu et al 2010, Rios et al 2010, Renner et al 2016].

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, 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 in whom the diagnosis of sitosterolemia 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 sitosterolemia, the molecular genetic testing approach is use of a **multigene panel**. A panel that includes *ABCG5* or *ABCG8* 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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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 sitosterolemia is not considered because an individual has atypical phenotypic features or laboratory results, **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.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that may not be detected by sequence analysis.

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 Sitosterolemia

Gene [1, 2]	Proportion of Sitosterolemia Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
ABCG5	42%	>95% [6]	None reported [7, 8]
ABCG8	58%	>95% [6]	None reported [7, 8]

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on allelic variants detected in these genes.
4. 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.
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. From 40 publications [Berge et al 2000, Hubacek et al 2001, Lu et al 2001, Heimerl et al 2002, Sehayek et al 2004, Wang et al 2004, Wilund et al 2004, Rees et al 2005, Solcà et al 2005, Su et al 2006, Kratz et al 2007, Mannucci et al 2007, Togo et al 2009, Niu et al 2010, Rios et al 2010, Tsubakio-Yamamoto et al 2010, Keller et al 2011, Wang et al 2011, Chong et al 2012, Horenstein et al 2013, Colima Fausto et al 2016, Rodriguez et al 2016, Tada et al 2016, Bardawil et al 2017, Bastida et al 2017, Buonuomo et al 2017, Jamwal et al 2017, Ono et al 2017, Yagasaki et al 2017, Brinton et al 2018, Fang et al 2018, Kawamura et al 2018, Martin et al 2018, Tada et al 2018, Huang et al 2019, Su et al 2019, Tada et al 2019, Veit et al 2019, Wang et al 2019, Sun et al 2020]
7. No data on detection rate of gene-targeted deletion/duplication analysis are available.
8. Although no deletions or duplications of *ABCG5 or ABCG8* have been reported to cause sitosterolemia, the identification of only one *ABCG5 or ABCG8* pathogenic variant in affected individuals could theoretically be explained by deletion of the other allele [Lu et al 2001].

Clinical Characteristics

Clinical Description

To date, approximately 110 individuals with biallelic pathogenic variants in *ABCG5* and/or *ABCG8* have been reported [Berge et al 2000, Hubacek et al 2001, Lu et al 2001, Heimerl et al 2002, Sehayek et al 2004, Wang et al 2004, Wilund et al 2004, Rees et al 2005, Solcà et al 2005, Su et al 2006, Kratz et al 2007, Mannucci et al 2007, Togo et al 2009, Niu et al 2010, Rios et al 2010, Tsubakio-Yamamoto et al 2010, Keller et al 2011, Wang et al 2011, Chong et al 2012, Horenstein et al 2013, Colima Fausto et al 2016, Rodriguez et al 2016, Tada et al 2016, Bardawil et al 2017, Bastida et al 2017, Buonuomo et al 2017, Jamwal et al 2017, Ono et al 2017, Yagasaki et al 2017, Brinton et al 2018, Fang et al 2018, Kawamura et al 2018, Martin et al 2018, Tada et al 2018, Huang et al 2019, Su et al 2019, Tada et al 2019, Veit et al 2019, Wang et al 2019, Sun et al 2020]. The following description of the phenotypic features associated with this condition is based on these reports.

Presentation. The clinical presentation of sitosterolemia varies from xanthomas and atherosclerosis and its complications to a milder phenotype with few to no specific symptoms and signs [Kidambi & Patel 2008].

Hypercholesterolemia. Individuals with sitosterolemia show an unexpected significant lowering of plasma cholesterol level in response to low-fat or low plant-derived food diet modification or to bile acid sequestrant therapy, and do not respond to statin therapy.

There is evidence of an age-related change in sterol homeostasis in sitosterolemia, where plasma concentrations of cholesterol in children with sitosterolemia can be in the hypercholesterolemia range and decrease to normal cholesterol levels by adulthood [Mymin et al 2018].

Tendon or tuberous xanthomas. Although the tuberous xanthomas are more typically seen in adults, they may appear at any age, even in children. Children may have xanthomas in unusual locations such as the buttocks, heels, elbows, and knees. Xanthomas have been reported in children as young as ages one to two years [Shulman et al 1976, Hubacek et al 2001, Niu et al 2010], four years [Togo et al 2009], and six years [Salen et al 2006, Mannucci et al 2007]. A child age ten years with tendon xanthomas was reported [Solcà et al 2005].

Premature atherosclerosis. Ten individuals with sitosterolemia with early-onset (age 5-33 years) atherosclerosis with or without sudden death have been reported [Miettinen 1980, Kwiterovich et al 1981, Salen et al 1985, Watts & Mitchell 1992, Kolovou et al 1996, Heimerl et al 2002, Katayama et al 2003, Mymin et al 2003, Salen et al 2006, Tsubakio-Yamamoto et al 2010].

- Assessment for premature atherosclerosis should include noninvasive imaging to exclude coronary and carotid plaque as well as atherosclerotic manifestations (e.g. heart murmurs and vascular bruits).
- Because of the limited number of reports, the incidence of coronary artery disease is not known.

Hematologic abnormality. Hemolytic anemia and/or thrombocytopenia can be the initial presentation [Rees et al 2005, Su et al 2006] or the only clinical feature of the disorder [Wang et al 2011, Zheng et al 2019]. The hemolytic anemia may be associated with low hemoglobin levels of 76 to 109 g/L and the thrombocytopenia has been reported with platelet counts as low as 12 to 82 x 10^9/L [Wang et al 2014, Zheng et al 2019].

Other findings

- On occasion arthritis, arthralgias, and splenomegaly are also seen.
- Miettinen et al [2006] described an individual with chronic non-A non-B hepatitis and cirrhosis in whom the diagnosis of sitosterolemia was serendipitously made by plasma analysis of sitosterol, and further confirmed by the finding of the biallelic *ABCG8* pathogenic variants. Following liver transplantation, the sitosterolemia unexpectedly resolved and plant sterol levels fell to the same levels seen in unaffected individuals. Although it is unknown if the liver problem was initially due to the sitosterolemia, the findings suggest that "idiopathic" liver disease could indeed be undiagnosed sitosterolemia. The authors concluded that an unaffected liver can overcome the intestinal transport defect in clearing the plant sterols from the circulation.

Intrafamilial variability has been reported in two consanguineous families:

- In one family, phenotypic variablilty was seen in three affected sibs and one affected first cousin with the same genotype [Wang et al 2004]. One child had abdominal pain, anemia, xanthomas, and early cardiac death; the others had high plasma concentrations of cholesterol and plant sterols but no other symptoms.
- In another family the mother and brother of the proband were homozygous for the same nucleotide change in *ABCG5*. All had increased concentrations of plasma sitosterol; however, only the proband (age 6 years) had xanthomas. The mother and brother, who had no evidence of xanthomas, had much lower cholesterol concentrations [Mannucci et al 2007].

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *ABCG5* and *ABCG8* have been identified.

Nomenclature

The disorder was named β-sitosterolemia by the investigators who first described it [Bhattacharyya & Connor 1974].

Prevalence

To date, about 110 individuals with molecularly confirmed sitosterolemia have been reported worldwide [Tada et al 2018].

Because the usual clinical test for plasma concentration of cholesterol does not measure plant sterols, sitosterolemia is likely to be underdiagnosed. In a population-based study, the data suggest a much higher prevalence than that indicated by the small number of known cases [Wilund et al 2004]; these researchers identified one individual with sitosterolemia out of 2542 persons in whom plasma concentration of plant sterols was analyzed, data that support a prevalence of 1/384 to 1/48,076 (95% confidence interval).

Sitosterolemia has been described in persons of Hutterite, Amish, Japanese, and Chinese ancestry as well as in other populations [Lu et al 2001]. Populations that show a high prevalence include:

- The Old Order Amish. Carrier frequency up to 4%
- North American Hutterites. Carrier frequency 8% [Chong et al 2012]
- The inhabitants of Kosrae (Micronesia). Adult carrier frequency 13% [Sehayek et al 2004]

A founder effect is evident in certain populations [Lu et al 2001]:

- Northern Europeans / individuals of northern European heritage more frequently have pathogenic variants in *ABCG8*.
- Chinese, Japanese, and Indian individuals tend to have pathogenic variants in *ABCG5*.

Genetically Related (Allelic) Disorders

No phenotypes other than those described in this *GeneReview* are known to be associated with biallelic pathogenic variants in *ABCG5* or *ABCG8*.

Differential Diagnosis

Hereditary Disorders in the Differential Diagnosis of Sitosterolemia

Table 2. Genes of Interest in the Differential Diagnosis of Sitosterolemia

Gene(s)	DiffDx Disorder	MOI	Features of DiffDx Disorder	
			Overlapping w/sitosterolemia	Distinguishing from sitosterolemia
ABCA1	Tangier disease (analphalipoproteinemia)	AR	Stomatocytosis	• Extreme ↓ circulating HDL-C levels (<1-2 mg/dL) • Extreme hypercholesterolemia

Table 2. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Features of DiffDx Disorder	
			Overlapping w/sitosterolemia	Distinguishing from sitosterolemia
APOB *LDLR* *PCSK9*	Familial hypercholesterolemia [1] (also called heterozygous FH)	AD	Xanthomas in children	• Extreme hypercholesterolemia: LDL-C levels >190 mg/dL in untreated adults • LDL-C levels >130 mg/dL in untreated children/adolescents • Not assoc w/macro-thrombocytopenia
	Homozygous FH [2]	AD	Xanthomas in children	• Both parents of affected child have hypercholesterolemia. • LDL-C levels are generally >500 mg/dL in untreated adults (levels can be lower in children). • Not assoc w/macro-thrombocytopenia
CYP27A1	Cerebrotendinous xanthomatosis	AR	Xanthomas in children	• ↑ concentrations of plasma cholestanol, childhood-onset protracted diarrhea, & cataracts • Typically, neurologic involvment in affected adults
LCAT	Lecithin-cholesterol aceyl transferase (LCAT) deficiency (OMIM 245900)	AR	Stomatocytosis	• Extreme ↓ circulating HDL-C levels (<10 mg/dL) • ↑ VLDL-C & triglycerides

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MOI = mode of inheritance; VLDL-C = very low-density lipoprotein cholesterol

1. FH results from a heterozygous pathogenic variant in *APOB*, *LDLR*, or *PCSK9*.

2. Homozygous FH results from biallelic (homozygous or compound heterozygous) pathogenic variants in *APOB*, *LDLR*, or *PCSK9*.

Other Disorders in the Differential Diagnosis of Sitosterolemia

The combination of **hemolysis and thrombocytopenia** can occur in the following conditions (in which large platelets are not observed):

- Liver disease
- Thrombotic thrombocytopenic purpura
- Systemic lupus erythematosus (SLE)

Stomatocytosis can be associated with Rh_{null} condition.

Management

Evaluations Following Initial Diagnosis

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Sitosterolemia

System/Concern	Evaluation	Comment
Plant sterol levels	Measure plasma concentrations of plant sterols (primarily beta-sitosterol & campesterol) & cholesterol.	

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Xanthomas	Determine size, number, & distribution of xanthomas (tendon & tuberous).	
Heart	Cardiology consultation to evaluate for atherosclerosis & cardiac valve abnormalities	Consider use of coronary artery calcium score (from cardiac CT) or coronary arteriography as needed.
Hematologic abnormalities	• CBC w/smear to look for platelet abnormalities &/or thrombocytopenia • Eval for possible hemolysis/ hemolytic anemia	
Liver	Baseline liver function (albumin, ALT, AST, ALP, bilirubin)	
Spleen	Evaluate for splenomegaly.	If present, consultation w/hematologist & gastroenterologist
Joints	Evaluate for arthralgias &/or arthritis.	
Genetic counseling	By genetics professionals [1]	To inform individuals & families re nature, MOI, & implications of sitosterolemia in order to facilitate medical & personal decision making

CBC = complete blood count; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Treatment should begin at the time of diagnosis, though there is little experience treating children younger than age two years. Treatment can decrease the plasma concentrations of cholesterol and sitosterol by 10% to 50%. Existing xanthomas often regress.

Arthritis, arthralgias, anemia, thromobocytopenia, and/or splenomegaly require treatment, the first step being management of the sitosterolemia, followed by routine management of the finding (by the appropriate consultants) as needed.

Note: Sitosterolemia does not respond to standard statin treatment.

Table 4. Treatment of Manifestations in Individuals with Sitosterolemia

Manifestation	Treatment	Considerations/Other
Elevated plant sterol levels	• Diet low in shellfish sterols & plant sterols (i.e., avoidance of vegetable oils, margarine, nuts, seeds, avocados, chocolate, & shellfish) • Treatment w/sterol absorption inhibitor ezetimibe (10 mg/day in adults) • Bile acid sequestrants such as cholestryramine (8-15 g/day) may be considered in those w/incomplete response to ezetimibe.	
	Partial ileal bypass surgery (i.e., shortening of the ileum) has been used to ↑ intestinal bile acid loss.	Partial or complete ileal bypass surgery in persons w/sitosterolemia has resulted in ≥50% ↓ of plasma & cellular sterol & stanol levels but should be used only as a last resort now that ezetimibe is available.

Surveillance

Table 5. Recommended Annual Surveillance for Individuals with Sitosterolemia

System/Concern	Evaluation
Plant sterol levels	• Plasma concentrations of plant sterols (primarily beta-sitosterol & campesterol) & cholesterol • Evaluate size, number, & distribution of xanthomas.
Hematologic abnormalities	CBC & platelet count
Liver function	Liver transaminases
Atherosclerosis & coronary artery disease (esp in those w/longstanding untreated sitosterolemia)	Noninvasive imaging to exclude coronary & carotid plaque as well as valvular atherosclerotic manifestations

CBC = complete blood count

Agents/Circumstances to Avoid

Margarines and other products containing stanols (e.g., campestanol and sitostanol), which are recommended for use by persons with hypercholesterolemia, are contraindicated in those with sitosterolemia as they can exacerbate plant stanol accumulation [Connor et al 2005].

Note: Foods with high plant sterol content including shellfish, vegetable oils, margarine, nuts, avocados, and chocolate should be taken in moderation due to increased intestinal absorption of plant sterols in those with sitosterolemia [Bhattacharyya & Connor 1974].

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from early institution of treatment and surveillance. Evaluations include the following:

- Molecular genetic testing if the *ABCG5* or *ABCG8* pathogenic variants have been identified in an affected family member
- Measurement of plasma concentrations of plant sterols if the family-specific pathogenic variants are not known

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

Pregnancy Management

Guidelines for the management of women with sitosterolemia during pregnancy have not been established.

There are no adequate and well-controlled studies of ezetimibe in pregnant women; ezetimibe can be used during pregnancy only if the potential benefits justify the risk to the fetus (Ezetimibe drug monograph).

See MotherToBaby for further information on medication use during pregnancy.

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

Sitosterolemia 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., presumed to be carriers of one *ABCG5* or *ABCG8* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *ABCG5* or *ABCG8* pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic but may occasionally have a mildly elevated concentration of sitosterol [Lee et al 2001].

Sibs of a proband

- If both parents are known to be heterozygous for an *ABCG5* or *ABCG8* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of unaffected and not a carrier. A sib who inherits biallelic pathogenic variants may be more or less severely affected than the proband.
- Heterozygotes (carriers) are asymptomatic but may occasionally have a mildly elevated concentration of sitosterol.

Offspring of a proband. Unless an individual with sitosterolemia has children with an affected individual or a heterozygote (carrier) (see Prevalence and Population screening), his/her offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *ABCG5* or *ABCG8*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ABCG5* or *ABCG8* pathogenic variant.

Carrier Detection

Molecular genetic carrier testing for at-risk family members requires prior identification of the *ABCG5* or *ABCG8* pathogenic variants in the family.

Note: Carriers cannot be reliably detected by analyte testing.

Related Genetic Counseling Issues

See Evaluation 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, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

Population screening. Individuals of North American Hutterite or Amish ancestry may choose to have carrier testing for the *ABCG8* p.Ser107Ter founder variant or the *ABCG8* p.Gly574Arg founder variant, respectively.

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).

Prenatal Testing and Preimplantation Genetic Testing

Once the sitosterolemia-causing pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would regard use of prenatal testing to be a personal choice, 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.

- **Sitosterolemia Foundation**
  Email: sitosterolemiafoundation@gmail.com
  www.sitosterolemiafoundation.org
- **American Heart Association**
  Phone: 800-242-8721
  www.americanheart.org
- **Medline Plus**
  Atherosclerosis
- **RDCRN Sterol and Isoprenoid Research (STAIR) Consortium**
  STAIR Research Studies

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. Sitosterolemia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ABCG5	2p21	ATP-binding cassette sub-family G member 5	ABCG5 database	ABCG5	ABCG5

Table A. continued from previous page.

ABCG8	2p21	ATP-binding cassette sub-family G member 8	ABCG8 database	ABCG8	ABCG8

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 Sitosterolemia (View All in OMIM)

210250	SITOSTEROLEMIA 1; STSL1
605459	ATP-BINDING CASSETTE, SUBFAMILY G, MEMBER 5; ABCG5
605460	ATP-BINDING CASSETTE, SUBFAMILY G, MEMBER 8; ABCG8

Molecular Pathogenesis

Sterolin-1 (encoded by *ABCG5*) and sterolin-2 (encoded by *ABCG8*) are two ATP-binding cassette half-transporters that belong to the G family members. They function as heterodimers. The highest expression of sterolin-1 and sterolin-2 is in the intestines and liver, functioning to selectively remove plant sterols and resecrete them back into the intestinal lumen and from the liver into the bile [von Bergmann et al 2005].

Defective sterolin heterodimer transporter function increases cholesterol and sitosterol absorption and decreases sitosterol and cholesterol excretion into the bile.

Mechanism of disease causation. Loss of function

Table 6. Notable *ABCG8* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_022437.2 NP_071882.1	c.320C>G	p.Ser107Ter	Hutterite founder variant [Chong et al 2012, Triggs-Raine et al 2016]
	c.1720G>A	p.Gly574Arg	Amish founder variant [Solcà et al 2005. Horenstein et al 2013]

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.

Chapter Notes

Author Notes

Analyte clinical diagnostic testing for sitosterolemia is available here.

The authors conduct research studies on sitosterolemia as part of the Rare Diseases Clinical Research Network: Sterol & Isoprenoid Research Consortium.

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