U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Burnett JR, Hooper AJ, Hegele RA. Chylomicron Retention Disease. 2022 Mar 24. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Chylomicron Retention Disease

Synonym: Anderson Disease

John R Burnett, MB ChB, MD, PhD, FRCPA,[1] Amanda J Hooper, PhD,[1] and Robert A Hegele, MD, FRCPC, FACP[2]

Created: March 24, 2022.

Summary

Clinical characteristics

Chylomicron retention disease (CMRD), characterized by the inability to secrete chylomicrons from the enterocytes following the ingestion of fat, typically presents in infancy with failure to thrive, diarrhea, vomiting, abdominal distention, and malabsorption of fat. This leads to steatorrhea – the severity of which relates to the fat content of the diet – and in some cases, hepatomegaly. Organ systems outside of the gastrointestinal tract may also be affected (often due to malnutrition and deficiencies of fat-soluble vitamins), including neuromuscular abnormalities (typically in the first or second decade of life) secondary to vitamin E deficiency, poor bone mineralization and delayed bone maturation due to vitamin D deficiency, prolonged international normalized ratio (INR) due to vitamin K deficiency, mild ophthalmologic issues (e.g., micronystagmus, delayed dark adaptation, abnormal visual evoked potentials, and abnormal scotopic electroretinograms), and (in a small proportion of adults) cardiomyopathy with decreased ejection fraction. Affected individuals typically have marked hypocholesterolemia, low plasma apolipoprotein B levels, normal-to-low plasma triglyceride levels, and low serum concentrations of fat-soluble vitamins (A, D, E, and K). Endoscopy typically demonstrates a *gelée blanche* ("white hoar frosting") appearance of the duodenal mucosa.

Diagnosis/testing

The molecular diagnosis of CMRD is established in a proband with suggestive findings and biallelic pathogenic variants in *SAR1B* identified by molecular genetic testing.

Management

Treatment of manifestations: Ensure adequate caloric intake with a low-fat diet (<30% of total calories from fat) enriched in essential fatty acids with or without medium-chain triglycerides; high-dose oral fat-soluble vitamins,

Author Affiliations: 1 Department of Clinical Biochemistry Royal Perth Hospital & Fiona Stanley Hospital Network PathWest Laboratory Medicine WA; Faculty of Health & Medical Sciences School of Medicine University of Western Australia Perth, Australia; Email: john.burnett@health.wa.gov.au; Email: amanda.hooper@health.wa.gov.au. 2 Departments of Medicine and Biochemistry Schulich School of Medicine and Robarts Research Institute Western University London, Ontario, Canada; Email: hegele@robarts.ca.

including vitamin E (hydrosoluble form) 50 IU/kg/d, vitamin A 15,000 IU/d, vitamin K 15 mg/week, and vitamin D 800-1200 IU/d; consider adding IV vitamin supplementation if an individual is late to be diagnosed with neurologic complications, although benefit is not proven in this situation; standard treatment for deficits in night vision and/or color vision, ataxia, and cardiomyopathy.

Surveillance: Annually: measurement of growth parameters; evaluation of digestive and neurologic symptoms; assessment of dietary fat content/compliance; and measurement of lipid profile, liver function tests, complete blood count, INR, and vitamins A, D, and E. Every three years after age ten: liver ultrasound, neurologic exam with serum creatine kinase and electromyography, ophthalmologic evaluation, and DXA scan. Every three to five years in adults: echocardiogram with assessment of ejection fraction.

Agents/circumstances to avoid: Avoidance of fatty foods, particularly those rich in long-chain fatty acids.

Pregnancy management: Vitamin A excess can be harmful to the developing fetus. Therefore, women who are pregnant or who are planning to become pregnant should reduce their vitamin A supplement dose by 50%. Additionally, close monitoring of serum vitamin A levels throughout pregnancy is recommended.

Genetic counseling

CMRD is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *SAR1B* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants. Once the *SAR1B* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for chylomicron retention disease (CMRD) have been published.

Suggestive Findings

CMRD **should be suspected** in individuals with the following clinical, supportive laboratory, and endoscopic findings.

Clinical findings

- Failure to thrive, with diarrhea
- Fat malabsorption with steatorrhea
- Vomiting
- Abdominal distention

Supportive laboratory findings

- Marked hypocholesterolemia:
  - Plasma total cholesterol level ~60 mg/dL (1.5 mmol/L)
  - HDL cholesterol ~20 mg/dL (0.5 mmol/L)
  - LDL cholesterol ~30 mg/dL (0.7 mmol/L)
- Low plasma apolipoprotein B level (<0.5 g/L)
- Normal-to-low plasma triglyceride level
- Low serum concentrations of fat-soluble vitamins (A, D, and E) and prolonged international normalized ratio (due to vitamin K deficiency)
- High plasma creatine kinase (1.5 to 4x the upper reference limit)

Endoscopic findings. White appearance of the duodenal mucosa. Note: Endoscopy is not required to make the diagnosis of CMRD.

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 molecular diagnosis of CMRD **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *SAR1B* identified by 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 section is understood to include likely pathogenic variants. (2) Identification of biallelic *SAR1B* variants of uncertain significance (or identification of one known *SAR1B* pathogenic variant and one *SAR1B* variant of uncertain significance) does not establish or rule out the diagnosis of this disorder.

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

- **Single-gene testing.** Sequence analysis of *SAR1B* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected.

  If only one or no pathogenic variant is identified, consider gene-targeted deletion/duplication testing.

- **A hypocholesterolemia multigene panel** that includes *SAR1B* 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 incidental 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.

Table 1. Molecular Genetic Testing Used in Chylomicron Retention Disease

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SAR1B	Sequence analysis [3]	90% [4]
	Gene-targeted deletion/duplication analysis [5]	10% [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 small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Jones et al [2003], Charcosset et al [2008], Peretti et al [2010]
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.

Clinical Characteristics

Clinical Description

To date, approximately 40 individuals have been identified with biallelic pathogenic variants in *SAR1B* [Jones et al 2003, Charcosset et al 2008, Peretti et al 2010]. The following description of the phenotypic features associated with this condition is based on these reports.

Chylomicron retention disease (CMRD) typically presents in infancy as failure to thrive, diarrhea, vomiting, abdominal distention, and malabsorption of fat [Levy et al 2019, Sissaoui et al 2021]. Some of the extraintestinal manifestations (e.g., those affecting the eyes, neuromuscular system, and blood) are due to deficiencies of fat-soluble vitamins.

Table 2. Chylomicron Retention Disease: Frequency of Select Features in Untreated Individuals

Feature	Frequency		
	In nearly all	Common	Infrequent
Failure to thrive	●		
Deficiency in fat-soluble vitamins	●		
Steatorrhea/diarrhea	●		
Fat malabsorption	●		
No chylomicrons in response to oral fat load	●		
Abdominal distention		●	
Vomiting		●	
Hepatomegaly			●
Steatosis			●
Hypo-/areflexia			●

Gastrointestinal. Following an oral fat load, triglyceride levels fail to increase due to inability to export chylomicron particles. Steatorrhea is the primary gastrointestinal manifestation. It can be present starting in infancy and throughout childhood. The severity relates to the fat content of the diet.

- Malabsorptive diarrhea, with vomiting and abdominal distention, is often present.
  - As affected individuals age, they learn to avoid dietary fat, which improves steatorrhea. Symptoms often improve within days or weeks of initiating a low-fat diet (see Management) [Peretti et al 2010].
  - Global caloric deficiency is associated with delayed growth trajectory, with both height and weight typically below the tenth centile without intervention.
  - Fat-soluble vitamin malabsorption is severe and, if untreated, can lead to irreversible systemic features that affect the eyes (see **Ophthalmologic** in this section), nervous system (see **Neuromuscular** in this section), and bones (decreased bone mineral density).
- Hepatomegaly and steatosis may develop in late childhood in some affected individuals.

  Note: While hepatomegaly is present in about 20% of affected individuals, cirrhosis of the liver, which has been described in individuals with abetalipoproteinemia and *APOB*-related familial hypobetalipoproteinemia (see Differential Diagnosis), is not a complication of CMRD.

Endoscopic findings. On a typical diet (i.e., no dietary restriction) the duodenal mucosa may have a *gelée blanche* ("white hoar frosting") appearance on endoscopy. Histologic evaluation demonstrates vacuolization of enterocytes in intestinal villi of normal structure.

Hematologic finding are uncommon.

- Mild acanthocytosis, defined as irregularly speculated erythrocytes, has only rarely been reported.
- Prolonged international normalized ratio due to vitamin K deficiency may occur.

Ophthalmologic. Unlike individuals with abetalipoproteinemia and *APOB*-related familial hypobetalipoproteinemia (see Differential Diagnosis), individuals with CMRD do not typically develop pigmentary retinopathy. Ophthalmologic manifestations are generally mild but may include:

- Micronystagmus;
- Delayed dark adaptation;
- Abnormal visual evoked potentials;
- Abnormal scotopic electroretinograms.

Neuromuscular. If untreated, neuromuscular abnormalities secondary to the deficiency of vitamin E typically begin in the first or second decade of life and include:

- Progressive loss of deep tendon reflexes, vibratory sense, and proprioception;
- Electromyographic abnormalities;
- Muscle pain and cramps.

Ataxia, myopathy, and sensory neuropathy may be seen in adults. The neuromuscular manifestations can be arrested (but not reversed) with vitamin supplementation, and can be averted altogether with early diagnosis and treatment.

Cardiac. Cardiomyopathy with decreased ejection fraction has only rarely been described in adults; the prevalence of this finding is unknown [Silvain et al 2008]. Cardiomyopathy was not a feature before age 23.5 years in a Canadian cohort, with normal echocardiography reported [Peretti et al 2010]. Neither the underlying pathogenesis nor possible response to treatment of cardiomyopathy in this condition is well understood.

Endocrinologic. Poor bone mineralization and bone maturation, likely due to a combination of malabsorption, malnutrition, and vitamin D deficiency, can be seen. When commenced early, vitamin D therapy has been shown to prevent osteoporosis [Peretti et al 2010].

Prognosis. Early diagnosis combined with appropriate lifelong vitamin supplementation help prevent the neurologic and retinal manifestations of CMRD with favorable long-term prognosis.

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *SAR1B* have been identified.

Prevalence

CMRD is very rare; approximately 40 individuals have been reported in the literature.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SAR1B*.

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of Chylomicron Retention Disease

Gene	DiffDx Disorder	MOI	Features of DIffDx Disorder	
			Overlapping w/CMRD	Distinguishing from CMRD
ANGPTL3	Familial combined hypolipidemia	AR	Low plasma levels of LDL & HDL cholesterol	Familial combined hypolipidemia is not assoc w/any clinical symptoms (i.e., no failure to thrive or steatorrhea), & plasma triglyceride levels are very low.
APOB	Biallelic *APOB*-related familial hypobetalipoproteinemia (FHBL)	AR	May be clinically similar (failure to thrive, steatorrhea)	In biallelic *APOB*-related FBHL, LDL cholesterol is absent & triglyceride is very low to absent.
MTTP	Abetalipoproteinemia	AR	May be clinically similar (failure to thrive, steatorrhea)	In abetalipoproteinemia, LDL cholesterol is absent & triglyceride is very low to absent; ophthalmologic manifestations are variable; most prominent is acquired atypical pigmentation of retina.
PCSK9	Hypocholesterolemia w/↓ LDL cholesterol (OMIM 607786)	AD	Low plasma levels of LDL cholesterol	In PCSK9 deficiency, hypocholesterolemia is not assoc w/any clinical signs or symptoms.

AD = autosomal dominant; AR = autosomal recessive; CMRD = chylomicron retention disease; DiffDx = differential diagnosis; MOI = mode of inheritance

Management

Clinical practice guidelines for chylomicron retention disease (CMRD) have been published based primarily on expert opinion [Peretti et al 2010].

Evaluations Following Initial Diagnosis

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

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Chylomicron Retention Disease

System/Concern	Evaluation	Comment
General	Growth parameters	To assess for poor growth

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Gastrointestinal	Plasma lipid profile: • Total cholesterol • LDL cholesterol • HDL cholesterol • Triglyceride • Apo B • Apo A-I	Normal TG levels are characteristic, while other lipid/lipoprotein variables are usually depressed.
	Serum concentration of fat-soluble vitamins (A, D, & E) & INR	
	Liver transaminases (AST & ALT), GGT, total bilirubin, & alkaline phosphatase	
	Abdominal ultrasound, typically after age 10 yrs	To evaluate for hepatomegaly & steatosis
	Referral to nutritionist	To provide dietary advice re low-fat diet
Hematologic	INR	Prolongation of INR may result from vitamin K deficiency.
	Consider CBC.	Anemia & mild acanthocytosis has only rarely been reported.
Ophthalmologic	Consider referral to ophthalmologist, typically after age 10 yrs, unless there are clinical signs/symptoms before age 10 yrs.	• To evaluate visual acuity & for baseline fundus exam • Consider visual evoked potential & electroretinography in those w/concerning symptoms.
Neuromuscular	Plasma CK	Usually after age 10 yrs
	Referral to neurologist	If evidence of neurologic abnormality (e.g., loss of deep tendon reflexes, loss of vibratory sense, loss of proprioception, ataxia)
Cardiac	Echocardiogram in adults [1]	• To evaluate cardiac function & assess ejection fraction • Cardiomyopathy is uncommon. • Consider referral to cardiologist.
Endocrinologic	DXA scan in those age >10 yrs	• To evaluate bone density • Consider referral to endocrinologist if abnormal.
Genetic counseling	By genetics professionals [2]	To inform affected persons & families re nature, MOI, & implications of CMRD to facilitate medical & personal decision making

ALT = alanine aminotransferase; Apo = apolipoprotein; AST = aspartate aminotransferase; CBC = complete blood count; CK = creatine kinase; CMRD = chylomicron retention disease; DXA = dual-energy x-ray absorptiometry; GGT = gamma-glutamyl transferase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; INR = international normalized ratio; MOI = mode of inheritance

1. Cardiomyopathy and decreased ejection fraction has not been reported in those younger than age 20 years [Peretti et al 2010].

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There are no specific recommendations for the treatment of CMRD, with therapeutic regimens currently based on those recommended for abetalipoproteinemia, namely, a low-fat diet supplemented with essential fatty acids

[Peretti et al 2010]. Vitamin deficiencies are variable in severity among affected individuals, but respond well over time to oral supplementation.

Table 5. Treatment of Manifestations in Individuals with Chylomicron Retention Disease

Manifestation/Concern	Treatment	Considerations/Other
Poor growth	Ensure adequate caloric intake on a low-fat diet.	Working w/nutritionist may be helpful for practical strategies to ↓ fat content but maintain adequate caloric intake.
Steatorrhea	Low-fat diet (<30% of total calories) enriched in essential fatty acids (appropriate amount & ratio of n-6 to n-3) ± medium-chain triglycerides [1]	Will eliminate steatorrhea & allow absorption of other nutrients essential for growth & development.
Fat-soluble vitamin deficiencies	High-dose oral fat-soluble vitamins: [2] • Vitamin E (hydrosoluble form [3]): 50 IU/kg/d • Vitamin A: 15,000 IU/d (adjust according to serum levels) • Vitamin D: 800-1200 IU/d OR 100,000 IU every 2 mos if age <5 yrs; 600,000 IU every 2 mos if age ≥5 yrs • Vitamin K: 15 mg/wk (adjust per INR & plasma levels)	Serum vitamin levels can be monitored approximately yearly as index of adequacy of supplementation (see Surveillance).
Fat-soluble vitamin deficiencies in those w/delayed diagnosis & neurologic complications	In addition to oral fat-soluble vitamin recommendations, IV replacement may be considered: [4] • Intralipid 20%: 2 g/kg as single infusion 1x/mo • Vitamin E: 4-6 mg/kg as single infusion 1x/mo • Vitamin A: 500 IU/kg as single infusion 1x/mo	Such therapy can be continued until there is clear clinical improvement or stabilization & should be done in conjunction w/at least annual serum vitamin level monitoring to ensure adequacy of supplementation (see Surveillance).
Loss of night &/or color vision	Standard treatment per ophthalmologist	May incl optical aids
Ataxia	Assistance for coordination problems through established methods of rehab medicine & OT/PT	
Cardiomyopathy	Standard treatment per cardiologist	
Decreased bone mineral density	Vitamin D supplementation	See **Fat-soluble vitamin deficiencies** in this table.

INR = international normalized ratio; IV = intravenous; OT = occupational therapy; PT = physical therapy

1. For young children, milk preparations that contain medium-chain triglycerides can correct malnutrition and improve diarrhea, although some affected individuals do not tolerate this. In older children, a regimen low in long-chain fatty acids is often sufficient to improve symptoms [Peretti et al 2010].

2. Peretti et al [2010]

3. To prevent neurologic complications, alpha-tocopherol in either lipid or aqueous form is the most effective formulation [Peretti et al 2010].

4. The use of IV vitamin supplementation in those who are late to diagnosis with neurologic complications has not been proven to be beneficial.

Prevention of Primary Manifestations

As outlined in Table 5, adoption of a low-fat diet (<30% of total calories) and high-dose oral fat-soluble vitamin supplementation may ameliorate or prevent clinical features of CMRD.

Surveillance

Table 6. Recommended Surveillance for Individuals with Chylomicron Retention Disease

Frequency	Evaluation [1]
Every 12 mos	• Measurement of growth parameters • Eval of digestive & neurologic symptoms • Eval of dietary fat content & compliance
	Laboratory investigations: • Lipid profile [2] • Liver function tests (AST, ALT, GGT, total bilirubin, alkaline phosphatase) • Vitamins A, D, & E; INR • CBC
Every 3 yrs after age 10 yrs	• Liver ultrasound • Neurologic: clinical exam, creatine kinase, electromyography • Ophthalmologic: eval of fundus, assessment of color vision, visual evoked potentials, & electroretinography • DXA scan (whole-body bone mineral content)
Every 3-5 yrs in adults	Echocardiography (ejection fraction)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; DXA = dual-energy x-ray absorptiometry; GGT = gamma-glutamyl transferase; INR = international normalized ratio

1. Surveillance of CMRD is based on that recommended for abetalipoproteinemia [Peretti et al 2010].

2. To include total, LDL, and HDL cholesterol levels and measurement of triglycerides

Agents/Circumstances to Avoid

Avoid fatty foods, particularly those rich in long-chain fatty acids.

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 prompt initiation of treatment and preventive measures. Evaluations can include:

- A full lipid profile, including apolipoprotein B and apolipoprotein A-I concentrations;
- Molecular genetic testing for the *SAR1B* pathogenic variants identified in the proband, if known.

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

Pregnancy Management

Vitamin A excess can be harmful to the developing fetus. Therefore, affected women who are pregnant or who are planning to become pregnant should reduce their vitamin A supplement dose by 50%. Additionally, close monitoring of serum vitamin A levels throughout pregnancy is recommended, since its absorption is impaired as a fundamental feature of the condition.

However, because vitamin A is an essential vitamin, vitamin A supplementation for affected women should not be discontinued during pregnancy. Vitamin A deficiency can lead to maternal morbidity.

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. 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

Chylomicron retention disease (CMRD) 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 a *SAR1B* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *SAR1B* 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, additional possibilities to consider include the following:
  - A large deletion (i.e., a copy number variation) in the proband was not detected by sequence analysis and resulted in the artifactual appearance of homozygosity.
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant 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 a *SAR1B* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with CMRD are obligate heterozygotes (carriers) for a pathogenic variant in *SAR1B* (carriers are asymptomatic and not at risk of developing the disorder). Unless an individual with CMRD has children with an affected individual or a carrier, the individual's offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *SAR1B*. Note: The rarity of the condition makes it unlikely that an unrelated reproductive partner of the proband whose ancestors do not come from a confined geographic area will be a carrier (see Table 7 for information about founder variants in French Canadians).

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *SAR1B* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SAR1B* pathogenic variants in the family.

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 affected, 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).

Prenatal Testing and Preimplantation Genetic Testing

Once the *SAR1B* 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. 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.

- **MedlinePlus**
  Chylomicron retention disease

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. Chylomicron Retention Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

SAR1B	5q31.1	GTP-binding protein SAR1b	SAR1B database	SAR1B	SAR1B

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 Chylomicron Retention Disease (View All in OMIM)

246700	CHYLOMICRON RETENTION DISEASE; CMRD
607690	SECRETION-ASSOCIATED RAS-RELATED GTPase 1B; SAR1B

Molecular Pathogenesis

Chylomicron retention disease (CMRD) is caused by biallelic pathogenic variants in *SAR1B* [Jones et al 2003], which encodes Sar1b (secretion-associated RAS-related GTPase 1B), a member of the Sar1-ADP-ribosylation factor family of small GTPases that control the intracellular trafficking of proteins. SAR1B is needed to transport immature chylomicrons to the Golgi apparatus, allowing chylomicrons to be secreted from enterocytes [Levy et al 2021]. Loss-of-function *SAR1B* variants result in the inability to secrete chylomicrons, leading to the accumulation of lipid droplets within the enterocytes and the selective absence of chylomicrons from plasma. The fat malabsorption is associated with diarrhea and failure to thrive, with deficiencies in the fat-soluble vitamins. Synthesis and secretion of triglyceride-rich lipoproteins of hepatic origin are relatively spared in this condition.

Mechanism of disease causation. Loss of function

Table 7. Notable *SAR1B* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001033503.3 NP_001028675.1	c.409G>A	p.Asp137Asn	Found in French Canadians [Charcosset et al 2008, Peretti et al 2009]
	c.537T>A	p.Ser179Arg	

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

Acknowledgments

RAH is supported by the Jacob J Wolfe Distinguished Medical Research Chair, the Edith Schulich Vinet Research Chair, and the Martha G Blackburn Chair in Cardiovascular Research. RAH holds operating grants from the Canadian Institutes of Health Research (Foundation award), the Heart and Stroke Foundation of Ontario (G-21-0031455).

Revision History

- 24 March 2022 (ma) Review posted live
- 27 September 2021 (jrb) Original submission

References

Literature Cited

Charcosset M, Sassolas A, Peretti N, Roy CC, Deslandres C, Sinnett D, Levy E, Lachaux A. Anderson or chylomicron retention disease: molecular impact of five mutations in the SAR1B gene on the structure and the functionality of Sar1b protein. Mol Genet Metab. 2008;93:74-84. PubMed PMID: 17945526.

Jones B, Jones EL, Bonney SA, Patel HN, Mesenkamp AR, Eichenbaum-Voline S, Rudling M, Myrdal U, Annesi G, Naik S, Meadows N, Quattrone A, Islam SA, Naoumova RP, Angelin B, Infante R, Levy E, Roy CC, Freemont PS, Scott J, Shoulders CC. Mutations in Sar1 GTPase of COPII vesicles are associated with lipid absorption disorders. Nat Genet. 2003;34:29-31. PubMed PMID: 12692552.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519-22. PubMed PMID: 28959963.

Levy E, Beaulieu JF, Spahis S. From congenital disorders of fat malabsorption to understanding intra-enterocyte mechanisms behind chylomicron assembly and secretion. Front Physiol. 2021;12:629222. PubMed PMID: 33584351.

Levy E, Poinsot P, Spahis S. Chylomicron retention disease: genetics, biochemistry, and clinical spectrum. Curr Opin Lipidol. 2019;30:134-39. PubMed PMID: 30640893.

Peretti N, Roy CC, Sassolas A, Deslandres C, Drouin E, Rasquin A, Seidman E, Brochu P, Vohl MC, Labarge S, Bouvier R, Samson-Bouma ME, Charcosset M, Lachaux A, Levy E. Chylomicron retention disease: a long-term study of two cohorts. Mol Genet Metab. 2009;97:136-42. PubMed PMID: 19285442.

Peretti N, Sassolis A, Roy CC, Deslandres C, Charcosset M, Castagnetti J, Pugnet-Chardon L, Moulin P, Labarge S, Bouthillier L, Lachaux A, Levy E. Guidelines for the diagnosis and management of chylomicron retention disease based on a review of the literature and the experience of two centers. Orphanet J Rare Dis. 2010;5:24. PubMed PMID: 20920215.

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.

Silvain M, Bligny D, Aparicio T, Laforêt P, Grodet A, Peretti N, Ménard D, Djouadi F, Jardel C, Bégué JM, Walker F, Schmitz J, Lachaux A, Aggerbeck LP, Samson-Bouma ME. Anderson's disease (chylomicron retention disease): a new mutation in the SARA2 gene associated with muscular and cardiac abnormalities. Clin Genet. 2008;74:546-52. PubMed PMID: 18786134.

Sissaoui S, Cochet M, Poinsot P, Bordat C, Collardeau-Frachon S, Lachaux A, Lacaille F, Peretti N. Lipids responsible for intestinal or hepatic disorder--when to suspect a familial intestinal hypocholesterolemia? J Pediatr Gastroenterol Nutr. 2021;73:4-8. PubMed PMID: 33853111.

License