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Abetalipoproteinemia

Synonym: Bassen-Kornzweig Syndrome

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Summary

Clinical characteristics

Abetalipoproteinemia typically presents in infancy with failure to thrive, diarrhea, vomiting, and malabsorption of fat. Hematologic manifestations may include acanthocytosis (irregularly spiculated erythrocytes), anemia, reticulocytosis, and hemolysis with resultant hyperbilirubinemia. Malabsorption of fat-soluble vitamins (A, D, E, and K) can result in an increased international normalized ratio (INR). Untreated individuals may develop atypical pigmentation of the retina that may present with progressive loss of night vision and/or color vision in adulthood. Neuromuscular findings in untreated individuals including progressive loss of deep tendon reflexes, vibratory sense, and proprioception; muscle weakness; dysarthria; and ataxia typically manifest in the first or second decades of life.

Diagnosis/testing

The diagnosis of abetalipoproteinemia is established in a proband with absent or extremely low LDL-cholesterol, triglyceride, and apolipoprotein (apo) B levels and biallelic pathogenic variants in *MTTP* identified by molecular genetic testing.

Management

Treatment of manifestations: Adequate caloric intake to alleviate growth deficiency; low-fat diet (10%-20% of total calories from fat); oral essential fatty acid supplementation (up to 1 teaspoon per day of oils rich in polyunsaturated fatty acids, as tolerated); supplementation with vitamin A (100-400 IU/kg/day), vitamin D (800-1,200 IU/day), vitamin E (100-300 IU/kg/day), and vitamin K (5-35 mg/week). Mild anemia rarely requires treatment, although occasionally vitamin B_{12} or iron therapy may be considered. Dysarthria, ataxia, and hypothyroidism are treated in the standard fashion.

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Prevention of primary manifestations: Most complications can be prevented through institution of a low-fat diet with supplementation of fat-soluble vitamins (A, D, E, and K).

Surveillance: Assessment of growth parameters at each visit. Complete blood count, INR, reticulocyte count, liver function tests (AST, ALT, GGT, total and direct bilirubin, alkaline phosphatase, and albumin), fat-soluble vitamin levels (vitamin A [retinol], 25-OH vitamin D, and plasma or red blood cell vitamin E concentrations), serum calcium, serum phosphate, serum uric acid, and TSH levels annually. Lipid profile (total cholesterol, triglyceride concentration, LDL-cholesterol, HDL-cholesterol, apo B, and apo A-I) every several years. Ultrasound of the liver every three years. Ophthalmology and neurology evaluations every six to 12 months.

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

Evaluation of relatives at risk: Sibs of a proband should undergo a full lipid profile and apolipoprotein (apo) B determination to allow for early diagnosis and treatment of findings. If the pathogenic *MTTP* variants in the family are known, molecular genetic testing may also be used to determine the genetic status of at-risk sibs. In classic abetalipoproteinemia, affected sibs will present shortly after birth with failure to thrive, diarrhea, vomiting, and malabsorption of fat.

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 beta carotene levels throughout pregnancy is recommended. Because vitamin A is an essential vitamin, vitamin A supplementation should not be discontinued during pregnancy.

Genetic counseling

Abetalipoproteinemia 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. Carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible if the pathogenic *MTTP* variants in the family are known.

Diagnosis

No formal clinical diagnostic criteria for abetalipoproteinemia have been published.

Suggestive Findings

Classic abetalipoproteinemia presents from birth with failure to thrive, severe diarrhea and vomiting, and malabsorption of fat. Abetalipoproteinemia **should be suspected** in children with the following clinical and supportive laboratory findings [Lee & Hegele 2014].

Clinical features

- Failure to thrive, with diarrhea and vomiting
- Fat malabsorption with steatorrhea
- Hepatomegaly
- Loss of night and/or color vision
- Acquired atypical pigmentation of the retina
- Spinocerebellar ataxia and myopathy

Supportive laboratory findings

- Marked hypocholesterolemia (total cholesterol ~1 mmol/L [~40 mg/dL])
- Plasma LDL-cholesterol (measured or calculated) absent or extremely low
- Plasma apo B absent or very low

- Plasma triglyceride very low
- Plasma HDL-cholesterol at a low to average level
- Acanthocytosis
- Abnormal liver transaminases (AST and ALT 1-1.5 times the upper reference limit)
- Prolonged international normalized ratio (INR)
- Low serum concentrations of fat-soluble vitamins (A, D, E, and K)

Establishing the Diagnosis

The diagnosis of abetalipoproteinemia **is established** in a proband with absent or extremely low LDL-cholesterol, triglyceride, and apo B levels and biallelic pathogenic (or likely pathogenic) variants in *MTTP* identified by molecular genetic testing (see Table 1).

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

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

- **Single-gene testing.** Sequence analysis of *MTTP* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected.

  Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

- **A multigene panel** that includes *MTTP* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Abetalipoproteinemia

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
MTTP	Sequence analysis [3]	59/60
	Gene-targeted deletion/duplication analysis [4]	1/60 [5]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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. 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.
5. R Hegele, personal observation

Clinical Characteristics

Clinical Description

Abetalipoproteinemia typically presents in infancy with failure to thrive, diarrhea, vomiting, and malabsorption of fat. The absence of apo B-containing lipoproteins and resulting deficiency of fat-soluble vitamins lead to multisystem manifestations as the affected individual ages.

Gastrointestinal. Steatorrhea is the primary gastrointestinal manifestation. The severity relates to the fat content of the diet.

- As affected individuals age they learn to avoid dietary fat, which improves steatorrhea [Kane & Havel 2001].
- Hepatic involvement as identified on laboratory studies is frequently stable over many years and may not evolve to be clinically significant [Lee & Hegele 2014].
- Hepatomegaly and hepatic steatosis can be observed, which rarely may progress to steatohepatitis, fibrosis, and cirrhosis [Di Filippo et al 2014].
- On a typical diet (e.g., no dietary fat restriction), the intestinal mucosa may have a "gelee blanche" or "white hoar frosting" appearance on endoscopy.

  Biopsy of the intestinal epithelium may demonstrate lipid-laden intestinal epithelial cells.

Hematologic manifestations of abetalipoproteinemia include the following:

- Acanthocytosis, defined as irregularly spiculated erythrocytes
- Low erythrocyte sedimentation rate
- Anemia
- Reticulocytosis
- Hyperbilirubinemia
- Hemolysis
- Prolonged INR due to vitamin K deficiency [Kane & Havel 2001]

Ophthalmologic manifestations of abetalipoproteinemia are variable, with the most prominent being an atypical pigmentation of the retina [Cogan et al 1984].

- Many affected individuals are asymptomatic until adulthood, when they experience loss of night vision and/or color vision.
- As the disease progresses, affected individuals may experience progressively expanding scotomas.
- Without treatment, progression to complete visual loss may occur.
- Other rare, typically acquired, ophthalmologic findings include the following:
  - Ptosis
  - Ophthalmoplegia
  - Corneal ulcers

It is hypothesized that the possible cause of ptosis and ophthalmoplegia is vitamin E deficiency leading to cranial nerve demyelination. Corneal ulcers may be caused or exacerbated by vitamin A deficiency [Lee & Hegele 2014].

Neuromuscular. If untreated, neuromuscular manifestations of abetalipoproteinemia secondary to the deficiency of vitamin E typically begin in the first or second decade of life. Symptoms include the following:

- Progressive loss of deep tendon reflexes, vibratory sense, and proprioception
- Muscle weakness
- Dysarthria
- Eventually, a Friedrich's-like ataxia, with a broad base and high stepping gait, can develop in early adulthood in untreated individuals [Tanyel & Mancano 1997].

Cardiac. Although rare, cardiomegaly can occur after decades, with rare death related to cardiomyopathy reported.

Endocrinologic. Although rare, both subclinical and overt hypothyroidism have been reported in individuals with abetalipoproteinemia.

Prognosis. In the past, without high-dose fat-soluble vitamin supplementation, affected individuals would typically not survive past the third decade of life, dying with severe neuromyopathy and respiratory failure. With lifelong high-dose oral fat-soluble vitamin treatment, longevity into the seventh and eighth decade of life, with relatively minimal symptoms, has been reported.

Genotype-Phenotype Correlations

Due to the small number of individuals with abetalipoproteinemia reported in the literature, reliable data on genotype-phenotype correlations are lacking.

Penetrance

While 100% of individuals either homozygous or compound heterozygous for pathogenic *MTTP* variants will have a biochemical diagnosis of abetalipoproteinemia, the penetrance of clinical symptoms is variable, increases with age, and may be incomplete [Paquette et al 2016]. The disorder affects males and females equally.

Nomenclature

Abetalipoproteinemia was initially named Bassen-Kornzweig syndrome.

Prevalence

Abetalipoproteinemia is rare; fewer than 100 individuals have been described in the literature.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of Abetalipoproteinemia

Differential Disorder	Gene	MOI	Clinical Features of Differential Disorder	
			Overlapping w/ abetalipoproteinemia	Distinguishing from abetalipoproteinemia
Homozygous hypobetalipoproteinemia (See *APOB*-Related Familial Hypobetalipoproteinemia.)	*APOB*	AR	Clinical features are indistinguishable.	Only distinguishing feature: lipid levels in heterozygotes. Obligate heterozygote parents have: • Normal lipid levels in abetalipoproteinemia; • LDL-cholesterol levels <50% of normal in hypobetalipoproteinemia.
Chylomicron retention disease	*SAR1B*	AR	May be clinically similar (failure to thrive, steatorrhea)	In chylomicron retention disease, LDL-cholesterol & apoB levels are low but not absent; triglyceride is normal & creatine kinase is high (1.5-5x upper reference limit); affected persons do not typically develop pigmentary retinopathy or acanthocytosis.
McLeod neuroacanthocytosis syndrome (MLS)	*XK*	XL	• Acanthocytosis • Peripheral neuropathy	MLS is X-linked; affected persons have normal lipid profiles & no manifestations of fat-soluble vitamin deficiency (e.g., retinal disease, bone abnormalities, coagulopathy).
Friedreich ataxia	*FXN*	AR	• Broad-based, high stepping gait • Loss of proprioception • Loss of deep tendon reflexes	Affected persons have normal lipid profiles & no manifestations of fat-soluble vitamin deficiency (e.g., retinal disease, bone abnormalities, coagulopathy).

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with abetalipoproteinemia, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

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

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

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Gastrointestinal	• Fecal fat • Serum lipid profile (LDL, HDL, & total cholesterol; triglyceride; ApoB; Apo-A-I) • Serum concentrations of fat-soluble vitamins (A, D, E, K) • Liver transaminases & bilirubin levels	
	Referral to nutritionist	To provide dietary advice about low-fat diet
	Abdominal ultrasound	To evaluate for steatohepatitis, fibrosis, &/or cirrhosis
Hematologic	Complete blood count	To evaluate for anemia &/or hemolysis
	INR	To evaluate for ↑ risk of bleeding
Ophthalmologic	Referral to ophthalmologist	For eval of visual acuity & pigmentary retinopathy
Neurologic	Referral to neurologist	If evidence of neurologic abnormality (e.g., ataxia, loss of deep tendon reflexes)
Endocrinologic	Thyroid stimulating hormone (TSH)	While thyroid function is not typically abnormal, TSH should be evaluated at least once.
Other	Consultation w/clinical geneticist &/or genetic counselor	

HDL = high-density lipoprotein; INR = international normalized ratio; LDL = low-density lipoprotein

Treatment of Manifestations

The following treatment is recommended for abetalipoproteinemia to address symptoms and prevent complications [Lee & Hegele 2014].

Table 4. Treatment of Manifestations in Individuals with Abetalipoproteinemia

Manifestation/ Concern	Treatment	Considerations/ Other
Growth deficiency	Ensure adequate caloric intake. [1]	Consider referral to nutritionist.
Steatorrhea	Low-fat diet (10%-20% of total calories) [2]	Total fat intake of >20% is not likely to be tolerated.
	Oral essential fatty acid supplementation	≤1 tsp/day of oils rich in polyunsaturated fatty acids (e.g., soybean or olive oil) as tolerated
Steatotic liver w/o fibrosis	Restriction of dietary fat	Because fatty liver develops w/o active inflammation, no need for anti-inflammatory treatment
Hepatic fibrosis &/or cirrhosis	Liver transplantation may be considered. [3]	A very rare complication, esp w/early diagnosis & treatment
Deficiency of fat-soluble vitamins	• Vitamin A (100-400 IU/kg/day) [4, 5, 6] • Vitamin D (800-1,200 IU/day) • Vitamin E (100-300 IU/kg/day) [7] • Vitamin K (5-35 mg/wk)	Supplemental vitamins should be given orally; IV administration of fat-soluble vitamins is not necessary.
Anemia	Mild anemia typically requires no treatment; occasionally vitamin B_{12} or iron is given in addition to fat-soluble vitamins.	
Increased INR	Vitamin K supplementation (See above.)	

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/ Other
Abnormal visual acuity	Vitamin A supplementation can arrest progression of visual impairment & prevent development of eye complications.	
Dysarthria	Speech & language therapy	W/early vitamin E supplementation dysarthria is rare.
Ataxia	• Intensive rehab (or coordinative physiotherapy) • Canes/walkers to prevent falls • Home modifications to accommodate motorized chairs as needed • Weighted eating utensils & dressing hooks • Weight control, as obesity can exacerbate problems w/ambulation & mobility	Treatment best provided by a multidisciplinary team comprising a neurologist, physiatrist, PT, & OT
Hypothyroidism	Standard treatment w/thyroid hormone replacement	

INR = international normalized ratio; OT = occupational therapist; PT = physical therapist
1. With proper treatment, a normal growth velocity can be achieved in affected persons; however, affected persons may not meet their full growth potential, even after treatment [Lee & Hegele 2014].
2. Long-chain fatty acids should be avoided (see Agents/Circumstances to Avoid).
3. Black et al [1991]
4. Vitamin A dosing should be titrated to serum beta-carotene concentrations (see Surveillance).
5. While vitamin A toxicity is unlikely, it has been reported in one affected person with a normal serum vitamin A level who initiated vitamin A supplementation [Bishara et al 1982].
6. The target goal for vitamin A levels should be low normal to avoid hepatotoxicity.
7. Despite supplementation, an affected person will always have low vitamin E levels.

Prevention of Primary Manifestations

Early treatment with vitamin E (100-300 IU/kg/day) may delay or prevent the development of neurologic dysfunction [Zamel et al 2008].

Vitamin E supplementation may also delay or prevent the development of ophthalmoplegia and/or ptosis.

Vitamin A supplementation (100-400 IU/kg/day) may help to prevent corneal ulcers from developing.

See Treatment of Manifestations.

Prevention of Secondary Complications

See Treatment of Manifestations.

Surveillance

Clinical evaluation every six to 12 months, including assessment of diet and any gastrointestinal or neurologic symptoms, is recommended. The following evaluations are also recommended for abetalipoproteinemia [Lee & Hegele 2014] (see Table 5).

Table 5. Recommended Surveillance for Individuals with Abetalipoproteinemia

System/Concern	Evaluation	Frequency
General	Assessment of growth parameters	At every visit

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Gastrointestinal	Lipid profile [1]	Every several yrs [2]
	• Liver function tests [3] • Fat-soluble vitamin levels [4, 5]	Annually
	Liver ultrasound	Every 3 yrs [6]
Hematologic	• Complete blood count • INR • Reticulocyte count	Annually
Endocrinologic	• Serum calcium, phosphate, & uric acid • Serum TSH	
Eyes	Ophthalmologic eval	Every 6-12 mos [6]
Neurologic	Neurologic exam	

INR = international normalized ratio; TSH = thyroid stimulating hormone
1. Lipid profile typically includes total cholesterol, triglyceride concentration, LDL-cholesterol, HDL-cholesterol, apo B, and apo A-I.
2. Annual lipid profile evaluation is not absolutely necessary, as lipid levels often remain stable over long periods of time.
3. AST, ALT, GGT, total and direct bilirubin, alkaline phosphatase, and albumin
4. Vitamin A (retinol), 25-OH vitamin D, and plasma or red blood cell (RBC) vitamin E
5. Vitamin A dosing should be titrated to serum beta-carotene concentrations.
6. In affected persons age >10 years

Agents/Circumstances to Avoid

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

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger sibs of a proband 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 and apo B determination;
- Molecular genetic testing if the pathogenic variants in the family are known.

Note: In classic abetalipoproteinemia, affected sibs will present shortly after birth with failure to thrive, diarrhea, vomiting, and malabsorption of fat.

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, 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 beta carotene levels throughout pregnancy is recommended [Lee & Hegele 2014].

Because vitamin A is an essential vitamin, however, 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 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

Abetalipoproteinemia 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 *MTTP* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic, have normal lipid profiles, 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. Unless an affected individual's reproductive partner also abetalipoproteinemia or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *MTTP*.

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

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *MTTP* 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, 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.

Prenatal Testing and Preimplantation Genetic Testing

Once the *MTTP* pathogenic variants have been identified in an affected family member, prenatal testing 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.

- **Genetic and Rare Diseases Information Center (GARD)**
  Abetalipoproteinemia
- **National Library of Medicine Genetics Home Reference**
  Abetalipoproteinemia
- **National Organization for Rare Disorders (NORD)**
  Abetalipoproteinemia

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. Abetalipoproteinemia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
MTTP	4q23	Microsomal triglyceride transfer protein large subunit	MTTP database	MTTP	MTTP

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 Abetalipoproteinemia (View All in OMIM)

157147	MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN; MTTP
200100	ABETALIPOPROTEINEMIA; ABL

Molecular Pathogenesis

The microsomal triglyceride transfer protein is an essential cofactor for the assembly and secretion of the apolipoprotein (apo) B-containing lipoproteins: chylomicrons from the intestine and very low-density lipoprotein from the liver. Active microsomal triglyceride transfer protein consists of two subunits, the unique MTTP subunit (encoded by *MTTP*) and a ubiquitously expressed protein disulfide isomerase (PDI) subunit (encoded by *P4HB*). PDI maintains the solubility of the heterodimeric complex. In individuals with abetalipoproteinemia, the biallelic pathogenic variants in *MTTP* result in the inability of apoB-containing lipoprotein particles to be secreted. The absence of apoB-containing lipoproteins and deficiency of fat-soluble vitamins in the circulation lead to a variety of clinical manifestations.

Gene structure. The longer transcript variant of *MTTP* (NM_000253.3) has 19 exons with the first being noncoding.

Pathogenic variants. Approximately 60 *MTTP* pathogenic variants have been identified; they are interspersed throughout the gene and are not found with increased prevalence in any specific ethnic group. The majority of these are inactivating variants (nonsense, splicing, and small indels). In vitro studies have shown that several pathogenic missense variants affect MTTP function (see **Abnormal gene product**).

Table 6. *MTTP* Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1304T>A	p.Leu435His	NM_000253.3 NP_000244.2
c.1619G>A	p.Arg540His	
c.1769G>T	p.Ser590Ile	
c.2237G>A	p.Gly746Glu	
c.2338A>T	p.Asn780Tyr	

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.

Normal gene product. MTTP consists of 894 amino acids with a signal peptide of 18 residues and three distinct structural regions: an amino-terminal β-barrel domain (amino acids 22-297), a central α-helical region (298-603), and a carboxyl-terminal domain (604-894).

Abnormal gene product. Null alleles and C-terminal truncations result in the inability to produce full-length functional MTTP. The functional consequences of several pathogenic missense variants have been described; p.Arg540His results in defective interaction with PDI, with the mutated MTTP remaining as an insoluble aggregate [Rehberg et al 1996], while p.Leu435His and p.Ser590Ile exhibit negligible lipid transfer activity [Di Filippo et al 2012, Khatun et al 2013]. Pathogenic variants p.Gly746Glu and p.Asn780Tyr are able to interact with PDI, but cannot transfer lipids [Ohashi et al 2000, Khatun et al 2013].

Chapter Notes

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