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Familial Combined Hypolipidemia

Synonyms: Angiopoietin-Like Protein 3 (ANGPTL3) Deficiency, Familial Combined Hypobetalipoproteinemia Type 2 (FHBL2)

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Summary

Clinical characteristics

Familial combined hypolipidemia is not associated with any pathologic signs or symptoms; diagnosis is suggested by low plasma concentrations of lipids. The lipid profile is one of hypocholesterolemia with low plasma low-density lipoprotein (LDL) cholesterol, low plasma high-density lipoprotein (HDL) cholesterol, low plasma triglycerides, and low plasma apolipoprotein (apo) B and apo A-I levels.

Diagnosis/testing

The molecular diagnosis of familial combined hypolipidemia is established in a proband with suggestive laboratory findings and biallelic pathogenic variants in *ANGPTL3* identified by molecular genetic testing.

Management

No specific evaluation, management, or surveillance is required for individuals who have familial combined hypolipidemia; however, consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and lack of specific clinical implications of familial combined hypolipidemia should be considered.

Genetic counseling

Familial combined hypolipidemia is inherited in an autosomal recessive manner. At conception, each sib of a person with FCH has a 25% chance of also having FCH, a 50% chance of being a heterozygous carrier, and a 25%

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chance of being unaffected and not a carrier. Heterozygotes for *ANGPTL3* loss-of-function pathogenic variants have mildly reduced LDL cholesterol and triglyceride levels, and protection against atherosclerotic cardiovascular disease. Carrier testing for at-risk relatives is possible if the pathogenic *ANGPTL3* pathogenic variants in the family are known. Prenatal and preimplantation genetic testing are also possible, but given the lack of clinical symptoms in most individuals who have FCH, this is not commonly pursued.

Diagnosis

Suggestive Findings

Familial combined hypolipidemia **should be suspected** in individuals with the following laboratory findings and family history.

Laboratory findings *

- Hypocholesterolemia with a total cholesterol of 1.9 ± 0.5 mmol/L (1.3-2.8)
- Low plasma low-density lipoprotein (LDL) cholesterol of 1.3 ± 0.6 mmol/L (0.5-1.4)
- Low plasma high-density lipoprotein (HDL) cholesterol of 0.6 ± 1.3 mmol/L (0.3-1.2)
- Low plasma triglycerides of 0.4 ± 0.1 mmol/L (0.2-0.7)
- Low plasma apolipoprotein (apo) B of 0.5 ± 0.1 g/L (0.3-0.7)
- Low plasma apo A-I of 0.7 ± 0.2 mmol/L (0.4-1.1)

* Data reported are mean ± standard deviation (range) [Minicocci et al 2013].

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.

Note: Heterozygous individuals who have one *ANGPTL3* pathogenic variant ("carriers") often have lipid profiles that are intermediate between the general population and individuals with biallelic pathogenic variants in *ANGPTL3*.

Establishing the Diagnosis

The molecular diagnosis of familial combined hypolipidemia **is established** in a proband with suggestive laboratory findings and biallelic pathogenic (or likely pathogenic) variants in *ANGPTL3* 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 *ANGPTL3* variants of uncertain significance (or of one known *ANGPTL3* pathogenic variant and one *ANGPTL3* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) 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 laboratory findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with abnormal lipid profiles are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the lipid laboratory findings suggest the diagnosis of familial combined hypolipidemia, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *ANGPTL3* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A hypolipidemia, dyslipidemia, or lipoprotein disorders multigene panel** that includes *ANGPTL3* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

When the diagnosis of familial combined hypolipidemia has not been considered because an individual has atypical laboratory findings, then genomic testing may be considered.

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Familial Combined Hypolipidemia

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
ANGPTL3	Sequence analysis [3]	>99% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]

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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

To date, approximately 30 individuals from a small number of families have been identified with biallelic pathogenic variants in *ANGPTL3* [Musunuru et al 2010, Minicocci et al 2012, Noto et al 2012, Pisciotta et al 2012, Minicocci et al 2016, Tikkanen et al 2019]. The following description of the phenotypic features associated with this condition is based on these reports.

Familial combined hypolipidemia is not associated with any pathologic signs or symptoms, and diagnosis is suggested by low plasma concentrations of lipids. Using a mendelian randomization approach, familial combined hypolipidemia has been associated with a reduced risk of atherosclerotic cardiovascular disease [Dewey et al 2017, Stitziel et al 2017]; however, the effect of functionally deficient ANGPTL3 protein on atherosclerosis burden has not been systematically investigated. In contrast to *APOB*-related familial hypobetalipoproteinemia, the prevalence of hepatic steatosis in familial combined hypolipidemia does not differ from that of the general population [Di Costanzo et al 2017].

Genotype-Phenotype Correlations

No genotype-phenotype correlations for familial combined hypolipidemia have been identified.

Prevalence

The prevalence of familial combined hypolipidemia is not known, but it appears to be very rare; approximately 30 individuals have been reported in the literature. However, the condition is probably underdiagnosed, as in the absence of a clinical phenotype, many clinicians fail to follow up on low plasma lipid levels.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ANGPTL3*.

Differential Diagnosis

Table 2. Genes of Interest in the Differential Diagnosis of Familial Combined Hypolipidemia

Gene	Disorder	MOI	Features of Differential Diagnosis	
			Overlapping w/FCH	Distinguishing from FCH
APOB	Biallelic *APOB*-related familial hypobetalipoproteinemia [1]	AR [2]	Low plasma levels of LDL cholesterol	• Assoc w/clinical symptoms (e.g. failure to thrive, steatorrhea) • HDL cholesterol levels are lower in FCH. [3]
MTTP	Abetalipoproteinemia	AR	Low plasma levels of LDL cholesterol	Assoc w/clinical symptoms (e.g. failure to thrive, steatorrhea)
PCSK9	Hypocholesterolemia w/↓ LDL cholesterol [4]	AD	• Not assoc w/any clinical symptoms • Low plasma levels of LDL cholesterol	Normal levels of plasma HDL cholesterol

Table 2. continued from previous page.

Gene	Disorder	MOI	Features of Differential Diagnosis	
			Overlapping w/FCH	Distinguishing from FCH
SAR1B	Chylomicron retention disease	AR	Low plasma levels of LDL & HDL cholesterol	• Assoc w/clinical symptoms (e.g. failure to thrive, steatorrhea) • Plasma triglycerides are not low.

AD = autosomal dominant; AR = autosomal recessive; FCH = familial combined hypolipidemia; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MOI = mode of inheritance

1. Individuals with a heterozygous, typically truncating pathogenic variant in *APOB* are usually asymptomatic with mild liver dysfunction and hepatic steatosis. However, about 5%-10% of individuals with heterozygous *APOB*-related familial hypobetalipoproteinemia (*APOB*-FHBL) develop relatively more severe non-alcoholic steatohepatitis requiring medical attention and occasionally progressing to cirrhosis.

2. APOB-FHBL due to a monoallelic, heterozygous pathogenic variant is inherited in an autosomal dominant fashion.

3. Di Costanzo et al [2017]

4. Cohen et al [2005]

Population- and clinic-based studies of individuals with marked hypocholesterolemia have shown that of those without a known monogenic cause, a significant proportion are genetically predisposed to low LDL cholesterol, suggesting a polygenic cause for hypocholesterolemia [Balder et al 2018, Blanco-Vaca et al 2019, Rimbert et al 2021, Cefalù et al 2022]. However, HDL cholesterol levels would generally be normal in this setting.

Acquired conditions that may present with laboratory findings similar to those of familial combined hypolipidemia include intestinal fat malabsorption disorders, severe liver disease, chronic pancreatitis, malnutrition, and hyperthyroidism.

Management

No clinical practice guidelines for familial combined hypolipidemia have been published.

No specific evaluation, management, or surveillance is required for individuals who have familial combined hypolipidemia [Bredefeld et al 2022].

Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and lack of specific clinical implications of familial combined hypolipidemia should be considered

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic

status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Familial combined hypolipidemia is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for an *ANGPTL3* pathogenic variant.
- Molecular genetic testing should be considered for the parents of the proband to confirm that both parents are heterozygous for an *ANGPTL3* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes for *ANGPTL3* loss-of-function pathogenic variants have mildly reduced LDL cholesterol and triglyceride levels, and protection against atherosclerotic cardiovascular disease [Stitziel et al 2017].

Sibs of a proband

- If both parents are known to be heterozygous for an *ANGPTL3* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Heterozygotes for *ANGPTL3* loss-of-function pathogenic variants have mildly reduced LDL cholesterol and triglyceride levels, and protection against atherosclerotic cardiovascular disease [Stitziel et al 2017].

Offspring of a proband. Unless an affected individual's reproductive partner also has familial combined hypolipidemia or is heterozygous for an *ANGPTL3* loss-of-function variant, offspring will be obligate heterozygotes for an *ANGPTL3* pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for an *ANGPTL3* pathogenic variant.

Heterozygote Detection

Heterozygote testing for at-risk relatives requires prior identification of the *ANGPTL3* pathogenic variants in the family.

Related Genetic Counseling Issues

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 heterozygotes, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ANGPTL3* 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**
  Familial hypobetalipoproteinemia

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. Familial Combined Hypolipidemia: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
ANGPTL3	1p31.3	Angiopoietin-related protein 3	ANGPTL3	ANGPTL3

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 Familial Combined Hypolipidemia (View All in OMIM)

604774	ANGIOPOIETIN-LIKE 3; ANGPTL3
605019	HYPOBETALIPOPROTEINEMIA, FAMILIAL, 2; FHBL2

Molecular Pathogenesis

Angiopoietin-related protein 3 (ANGPTL3) is a regulatory protein secreted by the liver that modulates plasma triglycerides [Kersten 2017]. It inhibits lipoprotein lipase, the enzyme responsible for the hydrolysis of triglycerides within circulating triglyceride-rich lipoproteins, namely, chylomicrons and very low-density lipoproteins. Homozygous or compound heterozygous loss-of-function *ANGPTL3* pathogenic variants are associated with higher lipoprotein lipase activity and mass, with the enhanced lipolysis associated with markedly reduced plasma LDL cholesterol, HDL cholesterol, and triglyceride concentrations [Tarugi et al 2019, Arca et al 2020, Bredefeld et al 2022]. Cell models have shown *ANGPTL3* silencing or deletion is associated with elevated LDL receptor expression and LDL uptake and reduced nascent apo B-100 secretion [Xu et al 2018].

A gene-dosage effect can be observed such that heterozygotes for *ANGPTL3* loss-of-function pathogenic variants have mildly reduced LDL cholesterol and triglyceride levels, and protection against atherosclerotic cardiovascular disease [Stitziel et al 2017].

Mechanism of disease causation. Loss of function

Chapter Notes

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