

CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Familial Hypobetalipoproteinaemia (*APOB*)

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Familial hypobetalipoproteinaemia.

1.2 OMIM# of the disease

107730.

1.3 Name of the analysed genes or DNA/chromosome segments

APOB.

1.4 OMIM# of the gene(s)

107730.

1.5 Mutational spectrum

Over 60 mutations have been reported, mostly nonsense and frame-shift, occurring throughout the 29 exons of *APOB*.¹⁻³ Missense mutations affecting the amino terminal region of the protein have also been described in hypobetalipoproteinemia.⁴

1.6 Analytical methods

DNA sequencing of genomic-exonic DNA with at least 20-bp of flanking intronic sequence. Western blotting can be used to detect truncated apoB species that are >30% of full-length protein size, to estimate where the mutation occurs within *APOB*. If Western blotting is negative, sequencing of the 5' 30% of the gene (exons 1 through 25) is recommended. Where homozygous familial hypobetalipoproteinaemia is suspected and a mutation(s) in *APOB* cannot be found, consider *MTTP* sequencing.

1.7 Analytical validation

Where a mutation is identified using bi-directional DNA sequencing, the test is repeated from a fresh dilution of DNA for confirmation. For homozygous familial hypobetalipoproteinaemia, testing of the patient's parents is recommended, to confirm that the two mutations are present in trans (ie, on opposite chromosomes).

1.8 Estimated frequency of the disease

(Incidence at birth ('birth prevalence') or population prevalence)

1 in 3000 are estimated to carry apoB truncations (heterozygous familial hypobetalipoproteinaemia).⁵

1.9 If applicable, prevalence in the ethnic group of investigated person

Not applicable.

1.10 Diagnostic Setting

	Yes	No
A. (Differential) diagnostics	<input checked="" type="checkbox"/>	<input type="checkbox"/>
B. Predictive testing	<input type="checkbox"/>	<input checked="" type="checkbox"/>
C. Risk assessment in relatives	<input type="checkbox"/>	<input checked="" type="checkbox"/>
D. Prenatal	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Comment: Familial hypobetalipoproteinaemia is primarily a biochemical diagnosis; heterozygotes have apoB levels one-quarter to one-third of normal, whilst in homozygotes apoB is very low or undetectable.

2. TEST CHARACTERISTICS

Test	Genotype or disease		A: True positives	C: False negatives
	Present	Absent	B: False positives	D: True negatives
Positive	A	B	Sensitivity:	A/(A + C)
Negative	C	D	Specificity:	D/(D + B)
			Pos. predict. value:	A/(A + B)
			Neg. predict. value:	D/(C + D)

2.1 Analytical sensitivity

(proportion of positive tests if the genotype is present)

Approximately 100%.

2.2 Analytical specificity

(proportion of negative tests if the genotype is not present)

Approximately 100%.

2.3 Clinical sensitivity

(proportion of positive tests if the disease is present)

The clinical sensitivity can be dependent on variable factors such as age or family history. In such cases a general statement

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should be given, even if a quantification can only be made case by case.

Many factors, such as a strict vegan diet, illness, and high-dose statin therapy, can cause hypobetalipoproteinaemia. The more common secondary causes in the hospital setting include cachexia, malabsorption, malnutrition, severe liver disease and hyperthyroidism. Familial hypobetalipoproteinaemia is characterised by low levels (<5th percentile for age and sex) of plasma apoB-containing lipoproteins.^{1,2} It has been suggested that familial hypobetalipoproteinaemia might represent a longevity syndrome and be associated with cardiovascular protection due to resistance to atherosclerosis. Heterozygotes are usually asymptomatic with LDL cholesterol and apolipoprotein (apo) B concentrations approximately one-third of those in normal plasma.

Homozygous familial hypobetalipoproteinaemia is clinically characterised by the absence of apoB-containing lipoproteins and the clinical features resemble those of abetalipoproteinaemia; fat malabsorption, acanthocytosis, marked hypocholesterolaemia and deficiency of apoB. Most cases are complicated by retinitis pigmentosa, spinocerebellar ataxia and myopathy. Should this constellation of findings be present there are two possibilities, homozygous familial hypobetalipoproteinaemia or abetalipoproteinaemia caused by mutations in *MTTP*. Family screening is useful in delineating between these conditions, as while obligate heterozygote parents of abetalipoproteinaemia have normal plasma lipid profiles, obligate heterozygous parents of homozygous familial hypobetalipoproteinaemia have one-third plasma concentrations of LDL cholesterol and apoB.

The clinical sensitivity is also dependent on the type of mutation in *APOB* gene: (i) heterozygotes for apo B truncations shorter than apo B-48 may have fatty liver and a mild intestinal fat malabsorption following high fat intake; (ii) homozygotes for apo B truncations longer than apo B-48 may have a milder phenotype than homozygotes for shorter apo B truncations (whose clinical manifestations are similar to those of ABL); (iii) homozygotes for long truncations (eg, apo B-87) are asymptomatic or have fatty liver.

2.4 Clinical specificity

(proportion of negative tests if the disease is not present)

The clinical specificity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if a quantification can only be made case by case.

Approximately 100%.

2.5 Positive clinical predictive value

(life time risk to develop the disease if the test is positive)

100%.

2.6 Negative clinical predictive value

(Probability not to develop the disease if the test is negative)

Assume an increased risk based on family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.

Index case in that family had been tested:

100%.

Index case in that family had not been tested:

Should the constellation of clinical findings be present in an index case, it is possible that they might have abetalipoproteinaemia, rather than homozygous familial hypobetalipoproteinaemia. Abetalipoproteinaemia patients receive similar treatment advice as homozygous familial hypobetalipoproteinaemia patients. Should the constellation of clinical findings be present in an index case, it is possible that they might have homozygous familial hypobetalipoproteinaemia, rather than

abetalipoproteinaemia. Homozygous familial hypobetalipoproteinaemia patients receive similar treatment advice as abetalipoproteinaemia patients. Also, there are even rarer conditions called homozygous proprotein convertase subtilisin/kexin type 9 (PCSK9) deficiency and familial combined hypolipidemia (due to homozygous mutations in angiopoietin-like protein 3, *ANGPTL3*) that present with extremely low (but not absent) levels of apoB-containing lipoproteins, but no systemic manifestations. To date, there are only a handful of families in the world reported with these latter two genetic conditions.

3. CLINICAL UTILITY

3.1 (Differential) diagnosis: The tested person is clinically affected

(To be answered if in 1.10 'A' was marked)

3.1.1 Can a diagnosis be made other than through a genetic test?

No	<input type="checkbox"/> (continue with 3.1.4)
Yes	<input checked="" type="checkbox"/>
	Clinically <input type="checkbox"/>
	Imaging <input type="checkbox"/>
	Endoscopy <input type="checkbox"/>
	Biochemistry <input checked="" type="checkbox"/>
	Electrophysiology <input type="checkbox"/>
	Other (please describe)

3.1.2 Describe the burden of alternative diagnostic methods to the patient

Heterozygotes for familial hypobetalipoproteinaemia are often asymptomatic, but have plasma LDL cholesterol and apoB concentrations that are one-third of normal. Most of them have increased serum transaminases due to hepatic steatosis and sometimes mild fat malabsorption.^{6,7} Homozygous familial hypobetalipoproteinaemia is characterised by the absence of plasma apoB-containing lipoproteins with marked hypocholesterolaemia, absence of LDL cholesterol and apoB and low triglyceride concentrations. In addition, increased serum transaminases due to hepatic steatosis, acanthocytosis and fat-soluble vitamin deficiency are found. Homozygous familial hypobetalipoproteinaemia cannot be distinguished from abetalipoproteinaemia clinically.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?

Not applicable.

3.1.4 Will disease management be influenced by the result of a genetic test?

No

Yes

Therapy
(please
describe)

The cornerstone of treatment for homozygous familial hypobetalipoproteinaemia is dietary modification and replacement of fat-soluble vitamins.^{1,2} A low-fat diet has been shown to improve steatorrhea associated with fat malabsorption and allow absorption of other nutrients essential for growth and development. High dose oral fat-soluble vitamins are thought to bypass the intestinal chylomicron assembly pathway via the portal circulation and are associated with improved clinical outcomes. High dose oral vitamin A, E and K are needed to correct the deficiencies. Vitamin E supplementation in heterozygous familial hypobetalipoproteinaemia has been recommended in those with low vitamin E concentrations to prevent neurological deficits,¹ however, more recently this advice has been called into question.⁸

Prognosis (please describe)	The impact of age at diagnosis, commencement of a low-fat diet and vitamin replacement therapy, and the findings from <i>APOB</i> genomic DNA sequencing in homozygous familial hypobetalipoproteinaemia are variable. Early treatment with high oral doses of vitamin E and A can reduce the potential severity of neuropathy and retinopathy. ^{1,9} A relative paucity of data makes it difficult to predict outcomes based on <i>APOB</i> genotype. The long-term outcome of hepatic steatosis in familial hypobetalipoproteinaemia is unknown, but associations with hepatic steatohepatitis, cirrhosis and hepatocarcinoma have been reported. ^{3,6,10,11}
Management (please describe)	Patients with homozygous familial hypobetalipoproteinaemia need to be followed regularly for evaluation of symptoms, complications, and to monitor compliance with therapy. Increased serum transaminases and hepatic steatosis are a common occurrence in heterozygous familial hypobeta-lipoproteinaemia, however, the long-term consequences are unknown. Therefore, it would seem prudent to monitor biochemically and by imaging techniques the livers of these individuals given a potential increased risk of progression to cirrhosis, particularly in the presence of known risk factors, such as alcohol, caloric excess, and liver injury.

3.2 Predictive setting: The tested person is clinically unaffected but carries an increased risk based on family history

(To be answered if in 1.10 'B' was marked)

3.2.1 Will the result of a genetic test influence lifestyle and prevention?

If the test result is positive (please describe).

If the test result is negative (please describe).

3.2.2 Which options in view of lifestyle and prevention does a person at-risk have if no genetic test has been done (please describe)?

Not applicable.

3.3 Genetic risk assessment in family members of a diseased person

(To be answered if in 1.10 'C' was marked)

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?

Not applicable.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?

Not applicable.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?

Not applicable.

3.4 Prenatal diagnosis

(To be answered if in 1.10 'D' was marked)

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnosis?

Not applicable.

4. IF APPLICABLE, FURTHER CONSEQUENCES OF TESTING

Please assume that the result of a genetic test has no immediate medical consequences. Is there any evidence that a genetic test is nevertheless useful for the patient or his/her relatives? (Please describe)

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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