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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Abetalipoproteinaemia

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)
Abetalipoproteinaemia (Bassen–Kornzweig syndrome).

1.2 OMIM# of the disease
200100.

1.3 Name of the analysed genes or DNA/chromosome segments
MTTP.

1.4 OMIM# of the gene(s)
157147.

1.5 Mutational spectrum
Over 30 mutations in *MTTP* have been described, mostly small point mutations (missense, nonsense and splicing) located throughout the gene's 18 exons.[1–6] The majority of mutations are 'private' to specific families or ethnic communities.

1.6 Analytical methods
DNA sequencing of genomic-exonic DNA with at least 20 bp of flanking intronic sequence. In patients where autosomal co-dominant inheritance can not be excluded or *MTTP* mutation(s) not identified, the *APOB* gene should be screened; homozygous familial hypobetalipoproteinaemia can give a similar biochemical and clinical phenotype to abetalipoproteinaemia.

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. When heterozygosity for two mutations is found, testing of the patient's parents is recommended, to confirm that the two mutations are present in trans (that is, on opposite chromosomes).

1.8 Estimated frequency of the disease
(incidence at birth ('birth prevalence') or population prevalence)
Estimated at <1 in 1 000 000.[1]

1.9 If applicable, prevalence in the ethnic group of investigated person
Not applicable.

1.10 Diagnostic setting

	Yes.	No.
A. (Differential) diagnostics	☒	☐
B. Predictive testing	☐	☒
C. Risk assessment in relatives	☐	☒
D. Prenatal	☐	☒

Comment:
Use of genetic testing is essentially limited for confirmatory diagnosis in a subject suspected to be affected, rather than other applications such as predictive testing or pre-natal diagnosis.

2. TEST CHARACTERISTICS

	Genotype or disease		A: True positives B: False positives	C: False negative D: True negative
	Present	Absent		
Test				
Positive	A	B	Sensitivity:	A/(A+C)
			Specificity:	D/(D+B)
Negative	C	D	Positive predictive value:	A/(A+B)
			Negative predictive 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 should be given, even if a quantification can only be made case by case.

Abetalipoproteinaemia is clinically characterised by the absence of apolipoprotein (apo) B-containing lipoproteins together with systemic clinical manifestations. All reported patients have fat malabsorption,

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acanthocytosis, marked hypocholesterolaemia and deficiency of plasma apoB and its associated lipoproteins, such as chylomicrons, very low-density lipoprotein and low-density lipoprotein (LDL).[1] Most cases are complicated by retinitis pigmentosa, spinocerebellar ataxia and myopathy. Should this constellation of findings be present, there are two possibilities, namely, abetalipoproteinaemia or homozygous familial hypobetalipoproteinaemia caused by mutations in *APOB*. Family screening is useful in differentiating between these conditions, as obligate heterozygote parents of homozygous familial hypobetalipoproteinamia patients have one-quarter to one-third the absolute plasma concentration of LDL cholesterol and apoB, whereas obligate heterozygote parents of abetalipoproteinaemia patients have normal plasma lipid profiles.

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 of developing the disease if the test is positive)
100%.

2.6 Negative clinical predictive value
(probability of not developing 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 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	☐ (continue with 3.1.4)	
Yes	☒	
	Clinically	☐
	Imaging	☐
	Endoscopy	☐
	Biochemistry	☒
	Electrophysiology	☐
	Other (please describe)	

3.1.2 Describe the burden of alternative diagnostic methods to the patient
Abetalipoproteinemia is characterised by the absence of plasma apoB-containing lipoproteins with marked hypocholesterolaemia, absence of LDL cholesterol and apoB and low triglyceride concentrations.[1,4–5] In addition, increased serum transaminases due to hepatic steatosis, acanthocytosis and fat-soluble vitamin deficiency are found. Typically, abetalipoproteinaemia cannot be distinguished from homozygous familial hypobetalipoproteinaemia 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 abetalipoproteinaemia is dietary modification and replacement of fat-soluble vitamins.[1,4,5,7] A low-fat diet has been shown to improve steatorrhoea 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.[5,8] Vitamin D deficiency is not a consistent finding; however, vitamin D replacement should be considered in abetalipoproteinaemia patients, along with other supplementary nutrients such as iron and folate. There is a need for novel therapeutic approaches to abetalipoproteinaemia as vitamin therapy alone fails to completely control or cure this disease.
	Prognosis (please describe)	The impact on prognosis of age at diagnosis, commencement of a low-fat diet and vitamin replacement therapy, and MTTP genotype is variable. Early treament with high oral doses of vitamin E and A can reduce the potential severity of neuropathy and retinopathy.[5,9] A relative paucity of data makes it difficult to predict clinical outcomes based on MTTP genotype.
	Management (please describe)	Patients need to be followed regularly for evaluation of symptoms and complications, and to monitor compliance with therapy.

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?

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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