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CLINICAL UTILITY GENE CARD UPDATE

Clinical utility gene card for: Abetalipoproteinaemia – Update 2014

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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 variants in *MTTP* associated with abetaliopoproteinaemia have been described, mostly missense, nonsense and splicing variants located throughout the gene's 18 exons.[1–6] The majority of variants associated with abetalipoproteinaemia 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 cannot be excluded or *MTTP* variant(s) cannot be identified, the *APOB* gene should be screened as homozygous familial hypobetalipoproteinaemia can give a similar biochemical and clinical phenotype to abetalipoproteinaemia.

1.7 Analytical validation
Where a variant is identified using bi-directional DNA sequencing, the test is repeated from a fresh dilution of DNA for confirmation. When heterozygosity for two variants is found, testing of the patient's parents is recommended to confirm that the two variants are present in trans (ie, 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 to confirmatory diagnosis in a subject suspected to be affected, rather than other applications such as predictive testing or prenatal 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%.

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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 from plasma together with systemic clinical manifestations. All reported patients have fat malabsorption, acanthocytosis, marked hypocholesterolaemia and deficiency of plasma apoB and its associated lipoproteins; 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, abetalipoproteinaemia or homozygous familial hypobetalipoproteinaemia. Family screening is useful in differentiating between these conditions as obligate heterozygote parents of homozygous familial hypobetalipoproteinaemia patients have approximately one-third plasma concentrations of LDL cholesterol and apoB, whereas obligate heterozygous 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 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 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 hypolipidaemia (due to homozygous variants in angiopoietin-like protein 3, *ANGPTL3*) that present with extremely low (but not absent) levels of apoB-containing lipoproteins, but no systemic manifestations.[4] In familial combined hypolipidaemia, high-density lipoprotein (HDL) cholesterol levels are also very low. 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) diagnostics: 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

Abetalipoproteinaemia 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 aminotransferases due to hepatic steatosis, acanthocytosis and fat-soluble vitamin deficiency are found. 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 fat restriction with replacement of fat-soluble vitamins (A, D, E and K).[1,4,5,7,8] A low-fat diet (<30% of total calories) will eliminate steatorrhoea 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 E supplementation (100–300 mg/kg/day) is recommended to halt the progression of neurological disease; however, serum levels do not normalise.[5,9] Supplementation with high-dose vitamin E and A is effective in reducing retinal degeneration. Although vitamin D and K deficiencies are inconsistent findings in abetalipoproteinaemia, oral replacement should be considered, along with other supplementary nutrients such as iron and folate. There is a need for novel therapeutic approaches to abetalipoproteinaemia as fat-soluble vitamin therapy alone fails to completely control or cure this disease.
	Prognosis (please describe)	The impact of age at diagnosis, commencement of a low-fat diet and fat-soluble vitamin supplementation, and the findings from *MTTP* genomic sequencing in abetalipoproteinaemia are variable. Early treament with high-dose oral vitamin E and A can reduce the potential severity of neuropathy and retinopathy.[5,10] A relative paucity of data makes it difficult to predict clinical outcomes based on *MTTP* genotype. The long-term outcome of hepatic steatosis in abtealipoproteinaemia is unknown but associations with hepatic steatohepatitis and cirrhosis have been reported.[11]

Management (please describe)	The clinical follow-up and management of abetalipoproteinaemia focuses on evaluating symptoms and monitoring growth in children, detecting and preventing complications, and monitoring compliance with therapy by providing specialised dietary advice and fat-soluble vitamin therapeutic regimens.[8]

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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