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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Sitosterolaemia

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)
Sitosterolaemia (phytosterolaemia; Mediterranean stomatocytosis/macrothrombocytopenia).

1.2 OMIM# of the disease
210250.

1.3 Name of the analysed genes or DNA/chromosome segments
ABCG5, *ABCG8*.

1.4 OMIM# of the gene(s)
605459, 605460.

1.5 Mutational spectrum
The sitosterolaemia genes *ABCG5* (NM_022436.2) and *ABCG8* (NM_022437.2) lie 'head to head' on chromosome 2.[1–3] They each contain 13 exons and encode a half-transporter (sterolin-1 and sterolin-2, respectively), with the C-terminus only containing 6 of the usual 12 transmembrane domains of the other ABC transporters.[3] Together they form a heterodimeric transporter responsible for sterol trafficking in the liver and intestine. Loss-of-function mutations associated with sitosterolaemia have been described throughout the *ABCG5* and *ABCG8* genes.

1.6 Analytical methods
Sequencing (Sanger or NGS). NGS approaches include using exome analysis or as part of a hypercholesterolaemia/cardiac gene panel.

1.7 Analytical validation
Where a mutation(s) can be identified using 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)
If known to be variable between ethnic groups, please report:

No published data are available on the prevalence of sitosterolaemia, an autosomal recessive disorder, although the condition appears to be mainly owing to *ABCG8* mutations in Caucasians, whereas in Chinese, Japanese and Indian patients with sitosterolaemia (20% of known cases), it is mainly owing to *ABCG5* mutations.[4] On the basis of allele frequencies of loss-of-function variants (frameshift, nonsense and splicing only; not missense) in the ExAC database, sitosterolaemia has a global prevalence of at least 1 in 2.6 million for *ABCG5* and 1 in 360 000 for *ABCG8*; the most common loss-of-function variant appears to be *ABCG8* c.1083G>A (p.(Trp361Ter)) (Exome Aggregation Consortium; http://exac.broadinstitute.org/)

1.9 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.

Sitosterolaemia is a phenotypically heterogeneous disorder that is clinically characterised by increased plasma concentrations of plant sterols, xanthomas, arthralgia and premature atherosclerotic cardiovascular disease.[5,6] In addition, some patients can present with haematological abnormalities including macrothrombocytopenia, stomatocytes, haemolytic anaemia and splenomegaly.[7,8] Very rare patients can present primarily with elevated plasma levels of low-density lipoprotein cholesterol and cutaneous xanthomas, expressing a phenotype that resembles heterozygous familial hypercholesterolaemia (FH),[9] and in severe cases, resembling homozygous FH, with coronary disease in childhood and adolescence.[10,11] The condition should be considered even when consumption of plant sterols has not commenced, as phytosterols can be found in breast milk.[12]

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:

Patients with sitosterolaemia can be clinically differentiated from patients with other childhood xanthomatoses, such as FH, by the inheritance pattern, or cerebrotendinous xanthomatosis, by the absence of neurological involvement or cataracts.

3. CLINICAL UTILITY

3.1 (Differential) diagnostics: The tested person is clinically affected
(To be answered if in 1.9 'A' was marked).

Sitosterolaemia should be considered in the differential diagnosis of severe hypercholesterolaemia, including apparent homozygous FH.

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

Very low. Patients with sitosterolaemia exhibit generalised hyperabsorption of dietary sterols including cholesterol, shellfish sterols and plant sterols (sitosterol, stigmasterol and campesterol), which, combined with impaired biliary excretion, leads to markedly elevated plasma levels of these plant sterols; >30-fold, with sitosterol being the most abundant species.[4,13] High levels of plant sterols in plasma are considered pathognomonic for sitosterolaemia, although elevations in plasma plant sterols may also be seen in primary biliary cirrhosis.[14] Cholesterol comprises only ~80% of the total plasma sterols in patients with sitosterolaemia. Some obligate heterozygotes have mildly increased plant sterol levels.[15,16] Mass spectrometry (GC and LC) plant sterol analysis of plasma is only available in specialist laboratories.

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)	A low plant sterol diet (avoidance of vegetable oils, margarine, nuts, seeds, avocados, chocolate), including restriction of algae-derived plant sterols found in shellfish and seaweed, can decrease plasma plant sterols levels, however, this is only partially effective as plant sterols are found in all plant-based foods. Ezetimibe (10 mg per day) is the pharmacotherapeutic agent of choice for the treatment of sitosterolaemia. Ezetimibe, which binds to the Niemann-Pick C1-like 1 sterol transporter in the proximal intestine, blocks the uptake of sterols leading to marked reductions in plasma sterol concentrations. Bile acid binding resins such as cholestyramine may be considered for use in those patients who fail to fully respond to ezetimibe, however, gastrointestinal side effects can limit its tolerability. Statins are minimally effective as HMG-CoA reductase is already maximally inhibited in patients with sitosterolaemia.[17–20]
	Prognosis (please describe)	Patients with sitosterolaemia show marked phenotypic heterogeneity. The patient's phenotype and prognosis depends on their age at diagnosis, the proportion of sterols they absorb (environmental and genetic variation dependent), and when they commenced a plant sterol-restricted diet and pharmacotherapy. Early treatment with ezetimibe leads to regression of xanthomas and atherosclerotic cardiovascular disease in patients with sitosterolaemia.[21] It has also been shown to normalise most haematological abnormalities.[22]
	Management (please describe)	The clinical follow-up and management of sitosterolaemia focuses on detecting and preventing complications, and monitoring compliance with diet and pharmacotherapy.

3.2 Predictive Setting: The tested person is clinically unaffected, but carries an increased risk based on family history
(To be answered if in 1.9 '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) Not applicable.
If the test result is negative (please describe) Not applicable.

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 1.9 '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 1.9 '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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