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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Progressive familial intrahepatic cholestasis type 1

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

1. Progressive familial intrahepatic cholestasis type 1 (PFIC1).
2. FIC1 deficiency.

Initially reported under the names:

3. Byler disease.
4. Greenland familial cholestasis.

Byler syndrome refers to normal gamma-glutamyltransferase (GGT) level chronic intrahepatic cholestasis observed in children usually during the first year of life.[1] Later, PFIC1 (Byler disease) and PFIC2 were identified.[2–4] The term PFIC1 or FIC1 deficiency should be used preferentially.

1.2 OMIM# of the disease

211600.

1.3 Name of the analysed genes or DNA/chromosome segments

ATPase class I type 8B member 1 or *ATP8B1*.

Chromosome 18q21–q22 (g.55470326–55313658).

1.4 OMIM# of the gene(s)

602397.

1.5 Mutational spectrum

Over 80 mutations in *ATP8B1* have been described: not only point mutations (missense, nonsense and splicing) located throughout the gene's 27 exons but also small deletions and duplications. Large deletions and genomic rearrangements are also reported (10%).[3,5–8]

The majority of mutations are 'private' to specific families or ethnic communities.[5]

Mutations of *ATP8B1* can be found in the NHLBI ESP Exome Variant Server database (http://evs.gs.washington.edu/EVS/).

1.6 Analytical methods

Bidirectional sequencing of all coding exons and short adjacent intronic sequences (RefSeq accession number NM_005603.3).

When the analysis fails to identify both mutant alleles, a search for (partial) gene deletion or duplication by multiplex ligation-dependant probe identification (MLPA) may be considered.

1.7 Analytical validation

Independent sequencing of both strands of DNA (forward and reverse).

When heterozygosity for two mutations is found, testing of the patient's parents is recommended to confirm that the defect is biallelic.

In case of newly identified variation, a polymorphism has to be excluded by testing a set of at least 100 control chromosomes of the same ethnic origin. Pathogenicity of such novel variations has to be tested by *in silico* prediction methods. Moreover, protein stability and trafficking may be studied in cell lines on a research basis.[9] Concerning splice site variants, their pathogenic nature should be studied by cDNA analysis.

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)

The population prevalence of PFIC1 is unknown.

However, incidence can be estimated around 1/100.000 to 1/1.000.000 births.

Population prevalence is unknown but PFIC1 exists world-wide.

Byler disease was first described in an Amish kindred.[2]

PFIC1 was also reported as 'Greenland familial cholestasis' in 16 Inuit children from Greenland.[10]

1.9 Diagnostic setting

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

Comment:

PFIC1 is due to mutations in the *ATP8B1* gene encoding the FIC1 protein expressed at the canalicular membrane of hepatocytes as well as in other epithelia. FIC1 is a flippase translocating phosphatidylserine from the outer to the inner leaflet of the membrane.[11] PFIC1 is a chronic form of cholestasis causing hepatic fibrosis and end-stage liver disease. Transmission is autosomal recessive. PFIC1 should be

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suspected in children with a clinical history of cholestasis of unknown origin after exclusion of other main causes of cholestasis presenting with normal serum gamma-GT activity and high serum bile acid concentration. Usually, serum alpha-fetoprotein level is normal and alanine aminotransferase values are under fivefold the upper limit of normal.[7]

Extrahepatic features have been reported including persistent short stature, watery diarrhoea, pancreatitis and sensorineural deafness.[7,12] In some patients with PFIC1, abnormal sweat test results have been reported.[8] Liver ultrasonography is usually normal but may reveal a huge gallbladder. Liver histology reveals canalicular cholestasis and the absence of true ductular proliferation with only periportal biliary metaplasia of hepatocytes. When performed, cholangiography shows a normal biliary tree and allows bile collection. Biliary lipid analysis reveals mildly decreased biliary bile salt concentration.[7]

Benign recurrent intrahepatic cholestasis (BRIC1, OMIM 243300) is also due to biallelic mutations in the *ATP8B1* gene but has a less severe phenotype, characterized by intermittent cholestasis without liver scarring.[5]

Monoallelic mutation of ATP8B1, predisposes to drug-induced cholestasis (DIC), intrahepatic cholestasis of pregnancy type 1 (ICP1, OMIM 147480) and transient neonatal cholestasis (TNC).[13,14] Specialized medical follow-up should also be offered to heterozygous patients (mainly those who are symptomatic).

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.

Over 95%.

In few patients with a PFIC1 phenotype, none or only one disease-causing mutation has been identified.[5,7] A chaperone protein, CDC50A, may be required for normal trafficking and function of the product of *ATP8B1*.[15] No data are available concerning molecular study of the gene encoding CDC50A in patient with a PFIC1 phenotype. So whether mutation of CDC50A may be implicated in patients with a PFIC1 phenotype remains an open question.

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
(lifetime risk to develop the disease if the test is positive)
There is no case report of an asymptomatic person harbouring two predictedly pathogenic mutations in the biallelic state. In case of known disease-causing mutations, virtually 100% of affected individuals develop cholestasis. However, PFIC1 constitute the severe side of the clinical spectrum of FIC1 deficiency and some patients may suffer from BRIC1. In approximately half patients with PFIC1, liver transplantation is required before adulthood.

2.6 Negative clinical predictive value
(probability not to develop the disease if the test is negative)
Assume an increased risk on the basis of family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.

Index case in that family had been tested:
Practically 100%.
Index case in that family had not been tested:
Practically 100%.

3. CLINICAL UTILITY

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

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

No	☐ (continue with 3.1.4)	
Yes	☒	
	Clinically	☐
	Imaging	☐
	Endoscopy	☐
	Biochemistry	☐
	Electrophysiology	☒
	Other (please describe)	see below

3.1.2 Describe the burden of alternative diagnostic methods to the patient.
A combined clinical, biochemical, radiological and histological approach associated with liver immunostaining and biliary lipid analysis can allow a PFIC1 diagnosis. However, the use of genetic study to confirm clinicopathologic diagnoses – made through the study of clinical, biochemical, imaging-study, and histopathologic findings, with immunostaining and ultrastructural evaluation – is generally prudent.

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

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

No	☐	
Yes	☒	
	Therapy (please describe)	So far no specific treatment is available. Ursodeoxycholic acid (UDCA) therapy should be initiated in all patients to prevent liver damage but is not fully efficient.[16] Rifampicin is helpful to control pruritus. In some patients, biliary diversion may decrease cholestasis.[17] Nasobiliary drainage may help to select potential responders to biliary diversion. Treatment with 4-phenylbutyrate as chaperone drug might restore *in vitro* the aberrant folding caused by some missense mutations.[9] These results led to new therapeutic approach strategy such as tailored mutation-specific pharmacotherapy.[18] In the future, cell, gene or targeted mutation-specific pharmacological therapies might be useful tools for the management of patients with all types of PFIC.
	Prognosis (please describe)	However, because of severe cholestasis, half patients are ultimately candidates for liver transplantation (LT).[7] One should note that LT does not prevent from extrahepatic evolution of the disease and does not allow to catch up stature growth.[19] After LT, diarrhoea often worsens and severe steatohepatitis of the liver graft has been reported.[18] Treatment with bile adsorptive resin may improve diarrhoea. Biliary diversion (performed after LT) may prevent or decrease steatofibrosis of liver graft and improve diarrhoea.[20] Nevertheless, in some cases, liver retransplantation is required because of steatofibrosis.
	Management (please describe)	Life-long medical specialized follow-up is mandatory. Extrahepatic features of the disease should be looked at including deafness and pancreatic insufficiency.

3.2 Predictive setting: the tested person is clinically unaffected but carries an increased risk on the basis of 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).

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 performed (please describe)?

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?
If the two disease-causing mutations have been identified in the diseased person, family members with a negative test are not at risk for being affected.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
Yes: in case of a known familial mutation, carriership can be confirmed or excluded.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
As FIC1 deficiency at a heterozygous status predisposes to develop ICP1, DIC and TNC, a predictive test can be offered to family members.

In asymptomatic relatives with monoallelic mutation, information regarding the particular risks should be given. Specialized medical care (including UDCA treatment) and follow-up should be offered to symptomatic relatives with monoallelic mutation.

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?
Prenatal diagnosis can be proposed if a mutation has been identified in each parent.

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)

Genetic counselling is always useful for the family.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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