



## Byler Disease

### Service Description

#### 1 Background

Byler disease or Progressive Familial Intrahepatic Cholestasis type 1 (PFIC1: OMIM #211600: ATP8B1 gene) is a chronic autosomal recessive disorder causing hepatic fibrosis and end-stage liver disease. Defects in bile secretion and/or absorption, causing hepatic and systemic accumulation of bile acids with reduced enteric bile acid availability underlie PFIC. Clinical symptoms include history of neonatal diarrhoea, sepsis and intermittent jaundice becoming permanent. Intractable pruritus (itch) and growth retardation is also seen (Bourke *et al*, Arch Dis Child 1996 75:223-227). (The formation of bile is a vital function, and its impairment by drugs or infectious, autoimmune, metabolic, or genetic disorders results in the syndrome commonly known as cholestasis).

Benign Recurrent Intrahepatic Cholestasis (BRIC1: OMIM #243300: ATP8B1 gene) is an allelic disorder to PFIC and is characterised by intermittent episodes of cholestasis without extrahepatic bile duct obstruction.

Byler disease causing mutations in the ATP8B1 gene on chromosome 18 (formerly known as FIC1), are heterogenous. A unique seven base pair deletion c.3622\_3628delGCCTACG (p.Ala1208fs) in the ATP8B1 gene has been found in the Irish Traveller population (Klomp *et al*, Hepatology 2004 40:27-38). Children from the Travelling community with Byler disease are homozygous for this seven base pair deletion and testing for Byler disease (ATP8B1 gene) at the NCMG is only for this specific pathogenic mutation in this population.

PFIC is a genetically heterogenous disorder and other genes such as ABCB11 (PFIC2) and the ABCB4 gene (PFIC3) are known to be involved and are also caused by defects in the transport of bile acids.

#### 2 Standard service

##### A Essential referral information

In addition to supplying standard patient identification and referral information (see Section I below), the following should be clearly indicated:

1. Patient's symptoms.
2. Any family history, including names, dates of birth, relationship, and genetic test results of relatives with Byler disease if available.
3. Whether the patient is a member of the Irish Travelling community and whether their parents are from a consanguineous marriage.

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Dublin, Ireland  
**Division of Molecular Genetics**

It is the responsibility of the referring clinician to ensure consent has been obtained for testing and storage.

***B Samples required***

Generally 5-10ml of EDTA blood (FBC bottle) is required. Sample identification policy is detailed at (see Section I below).

Blood specimens must be appropriately packaged (see Section I), and preferably sent by courier to arrive as soon as possible. Do not freeze prior or during postage.

Please note that extracted DNA is stored from patient's samples at the National Centre for Medical Genetics, and kept indefinitely unless a written request for its disposal is received from the patient or their parent/guardian.

***C Restrictions on testing***

Samples for diagnostic testing are generally only accepted from a consultant gastroenterologist/paediatrician or consultant clinical geneticist.

Carrier or prenatal testing is only performed in conjunction with a counselling programme from a clinical genetics service such as offered by the National Centre for Medical Genetics.

Carrier testing is limited to adults over the age of 16 where there is a family history of, or where a family member has been found to be a carrier of the c.3622\_3628delGCCTACG ATP8B1 pathogenic mutation.

***D Tests offered***

**Diagnostic Test**

Diagnostic tests are available for patients with a clinical diagnosis or clinical symptoms suggestive of Byler disease. As the c.3622\_3628delGCCTACG ATP8B1 pathogenic mutation is unique to the Irish Travelling population, a family history of Byler disease is highly likely and/or consanguineous marriage.

**Carrier Test**

Carrier testing is offered to individuals over the age of 16 with a family history of Byler disease and/or a partner with the same.

**Prenatal Test**

Prenatal testing is available where the c.3622\_3628delGCCTACG ATP8B1 pathogenic mutation has been confirmed in both parents. Prenatal testing must be arranged in advance with the laboratory. Prenatal testing is only performed in conjunction with a counselling programme from a clinical genetics service such as offered by the National Centre for Medical Genetics.

**Test method**

Testing is by bi-directional DNA Sanger sequencing encompassing the c.3622\_3628del GCCTACG ATP8B1 pathogenic mutation.

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## National Centre for Medical Genetics

Dublin, Ireland

### Division of Molecular Genetics

#### **E Diagnostic Sensitivity of tests**

This test is 100% sensitive for the specific Irish Traveller c.3622\_3628delGCCTACG ATP8B1 pathogenic mutation only.

Please note that there >50 distinct Byler disease (PFIC/BRIC) pathogenic mutations (Klomp et al, 2004) in the ATP8B1 gene and that this test does not detect (is not sensitive for) these other mutations.

#### **F Interpretation**

Results are given in the form of a written interpretative report to the referring clinician. They are based on the clinical indications at referral and whether or not the c.3622\_3628delGCCTACG ATP8B1 pathogenic mutation has been detected or not.

#### **G Target reporting time**

As reporting times are constantly evolving, please refer to [www.genetics.ie/molecular](http://www.genetics.ie/molecular), or contact the molecular genetics laboratory, to receive up-to-date information on anticipated reporting times for your referral.

- Please contact the laboratory if you have not received a report within a week of your patient being due back in clinic.
- Please note it is our policy not to issue verbal results.
- Request for copies of reports on the day that your patient is in clinic cannot normally be accommodated. We usually require 24 hours notice in which to fax a copy of a report.

#### **H Further tests**

As Byler disease (PFIC/BRIC) is genetically heterogenous and in-house testing is sensitive for only one of >50 pathogenic mutations in the ATP8B1 gene, further mutation testing of the ATP8B1 gene or other PFIC genes (ABCB11) is available from external referral laboratories. Please contact the laboratory to enquire about the availability and cost of these tests.

#### **I Web Links to Related Documents**

Standard referral information/NCMG request form  
Sample/Patient identification policy  
Packaging of specimens for transport

[http://www.genetics.ie/pir/2006\\_NCMG\\_Referral\\_Form.pdf](http://www.genetics.ie/pir/2006_NCMG_Referral_Form.pdf)  
<http://www.genetics.ie/pir/SampleIdentificationPolicyWeb.pdf>  
[http://www.genetics.ie/pir/sending\\_samples.pdf](http://www.genetics.ie/pir/sending_samples.pdf)

Please note that hard copies of the above documents may be requested from:

*Division of Molecular Genetics, National Centre for Medical Genetics, Our Lady's Children's Hospital, Crumlin, Dublin 12. Tel: 01 4096733; Fax: 01 4096971*

*The NCMG Molecular Genetics laboratory participates in external QA schemes run by the UK NEQAS for Molecular Genetics, the European Molecular Genetics Quality Network (EMQN), and the Cystic Fibrosis European Network. Results of assessments are available for inspection upon request.*

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