



Osteogenesis Imperfecta Type VIII (LEPRE1/P3H1 gene)

Service Description

1 Background

Osteogenesis imperfecta (OI) is a group of heterogeneous conditions characterised by a varying degree of bone fragility, susceptibility to fracture, short stature, bowing of the long bones and other clinical features. OI is usually caused by a heterozygous mutation in either of the type I collagen genes and it is inherited in an autosomal dominant fashion. The collagen genes COL1A1 and COL1A2 encode the $\alpha 1$ and the $\alpha 2$ chain of type 1 collagen. Type 1 (pro) collagen is the major extracellular matrix protein of bone and skin.

The existence of recessive forms of lethal/severe OI has long been suspected since the original 1979 Sillence classification. However, a recent study has identified a number of genes that cause recessive OI including the genes CRTAP (encodes the protein cartilage-associated protein, CRTAP) and LEPRE1 (which encodes prolyl-3-hydroxylase-1 (PH31)) which are involved in type 1 collagen formation. A unique loss of function mutation c.232delC in the LEPRE1/P3H1 gene (OMIM #601905) was identified in the Irish Traveller population (Cabral *et al*, Nature Genetics 2007 39(3) 359-365).

Type VIII OI caused by pathogenic mutations the LEPRE1/P3H1 gene has a variable phenotype from perinatal lethal to surviving phenotypes. It is clinically and radiographically comparable to OI Type II/III. In the perinatal period, it is very difficult to distinguish radiographically severe OI due to LEPRE1 mutations from severe OI caused by COL1A1 or COL1A2. However with increasing age there are some distinctive clinical and radiological characteristics.

Children from the Travelling community with OI Type VIII are homozygous for this c.232delC LEPRE1/P3H1 deletion and it is testing for this specific pathogenic mutation that forms the basis of the service offered.

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 OI Type VIII if available.
3. Whether the patient is a member of the Irish Travelling community and whether their parents are from a consanguineous marriage.

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

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National Centre for Medical Genetics

Dublin, Ireland

Division of Molecular Genetics

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 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.232delC LEPRE1/P3H1 pathogenic mutation.

D Tests offered

Diagnostic Test

Diagnostic tests are available for patients with a clinical diagnosis or clinical symptoms suggestive of OI Type VIII. As the c.232delC LEPRE1/P3H1 pathogenic mutation is unique to the Irish Travelling population, a family history of OI Type VIII 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 OI Type VIII and/or a partner with the same.

Prenatal Test

Prenatal testing is available where the c.232delC LEPRE1/P3H1 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.232delC LEPRE1/P3H1 pathogenic mutation

E Diagnostic Sensitivity of tests

This test is 100% sensitive for the specific Irish Traveller c.232delC LEPRE1/P3H1 pathogenic mutation only.

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Please note that there are numerous distinct OI Type VIII pathogenic mutations (Baldrige *et al*, Human Mutation 2008 0, 1-8) in the LEPRE1/P3H1 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.232delC LEPRE1/P3H1 pathogenic mutation has been detected or not.

G Target reporting time

As reporting times are constantly evolving, please refer to 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 Osteogenesis Imperfecta is extremely genetically heterogeneous (autosomal dominant and recessive forms) and in-house testing is sensitive for only one of several pathogenic mutations in the LEPRE1/P3H1 gene (recessive form), further mutation testing for (many) other genes involved in OI may be available from external referral laboratories. Please contact the laboratory to enquire about the clinical suitability, 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/SampleIdentificationPolicyWeb.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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