



Prader-Willi Syndrome (PWS)

Service Description

1 Background

OMIM# 176270

Prader-Willi Syndrome is a neurological disorder characterised by neonatal hypotonia, hyperphagia with obesity, hypogonadism, mental and psychomotor retardation. The estimated prevalence is 1/15,000 to 1/30,000.

Several genes are believed to be involved in PWS and are located on chromosome 15 (15q11-q13). Normally these genes are only active (unmethylated) on the chromosome inherited from the father. In PWS, expression of these paternally active genes is lost resulting in abnormal methylation patterns.

Loss of the paternal allele arises by a de novo deletion of the critical region of the paternal chromosome in approximately 75% of PWS cases, or by inheritance of two maternal copies of chromosome 15 (maternal uniparental disomy - mUPD) in approximately 25% of cases. Both of these types of abnormality usually arise de novo and have a very low risk of recurrence.

In very rare cases, PWS may be caused by an imprinting defect – in these cases there can be up to 50% risk of recurrence.

Table 1: Molecular defects and recurrence risks in PWS.

Genetic defect	Proportion of cases	Recurrence risk
<i>De novo</i> deletion of 15q11-q13 on the paternal chromosome	75-80%	<1%
Maternal uniparental disomy (UPD) of chromosome 15	20-25%	<1%
Imprinting defects (with an imprinting centre deletion excluded)	≈1%	<1%
Imprinting centre deletion	≈ 10-15% of patients with an imprinting defect	Up to 50% (if present in father)

(Table taken from "Practice Guidelines for Molecular Analysis of Prader-Willi and Angelman Syndromes". CMGS/EMQN 2008)

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:

- Patient's symptoms.
- Any family history, including names, dates of birth, relationship and genetics test results if available.

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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 3-5ml 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:

Referrals on patients where obesity is the only clinical indication are not processed. There are no other particular restrictions on testing.

D Tests offered:

1. Diagnostic test – Methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) is used to detect copy number changes and analyse CpG island methylation patterns within the 15q11-q13 region (Prader-Willi/Angelman critical region). Absence of the paternal methylation pattern confirms a diagnosis of PWS.
2. Mechanism of inheritance – when a diagnosis of PWS is confirmed, the mechanism of inheritance (i.e. paternal deletion, mUPD or imprinting centre defect) is investigated in order to assess recurrence risks. MS-MLPA analysis can detect deletions of the 15q11-q13 critical region and can determine if the mechanism of inheritance is a paternal deletion. However if a deletion is not detected the mechanism could be either mUPD or an imprinting centre defect. MS-MLPA cannot distinguish between these. Further molecular analysis is necessary in order to investigate UPD. This requires parental samples in EDTA.

E Diagnostic sensitivity of tests

The diagnostic sensitivity of the genetic test is greater than 99%.

F Interpretation:

Results are given in the form of a written interpretative report to the referring clinician.

G Target reporting times:

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.

- The following are current target reporting times for each category of test offered (information correct as of 11/01/10):
 - Urgent samples (newborns): 2 weeks
 - Routine samples: 4-6 weeks

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- UPD: 3 months
- 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

- ? Imprinting centre (IC) defect: When a diagnosis of PWS is confirmed using MS-MLPA and both a deletion and UPD have been excluded as the mechanism of inheritance, further analysis can be performed in an external laboratory to confirm/exclude the presence of an IC deletion.

Please contact us to make arrangements for such testing, if required.

I Web Links to Related Documents

Standard referral information/NCMG request form

http://www.genetics.ie/pir/2006_NCMG_Referral_Form.pdf

Sample/Patient identification policy

<http://www.genetics.ie/pir/SampleIdentificationPolicyWeb.pdf>

Packaging of specimens for transport

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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