Prader-Willi Syndrome

Contact details

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Samples required

- 5ml venous blood in plastic EDTA bottles (>1ml from neonates)
- Prenatal testing must be arranged in advance, through a Clinical Genetics department if possible.
- Amniotic fluid or CV samples should be sent to Cytogenetics for dissecting and culturing, with instructions to forward the sample to the Regional Molecular Genetics laboratory for analysis
- A completed DNA request card should accompany all samples

Patient details

To facilitate accurate testing and reporting please provide patient demographic details (full name, date of birth, address and ethnic origin), details of any relevant family history and full contact details for the referring clinician

Introduction

Prader-Willi syndrome (PWS) (MIM 176270), occurring in 1/15000 - 1/20000 individuals, is characterised by diminished fetal activity, obesity, muscular hypotonia, developmental delay, short stature, hypogonadotropic hypogonadism, and small hands and feet. The PWS phenotype results from the lack of a paternal contribution at 15q11-q13. This can be caused by a deletion (~70%), maternal uniparental disomy (UPD) (25-30%) and rarely due to mutations in the imprinting centre (IC) that cause abnormal methylation at exon alpha of the SNRPN locus. These mutations are all detected by disrupted methylation. Deletions and UPD are usually de novo events, associated with low recurrence risks, although it is important to determine whether either parent of an affected child has a predisposing chromosome translocation. There is a recurrence risk of up to 50% in families with confirmed PWS who do not have a deletion or UPD and are therefore likely to have an IC mutation.

Referrals

- Confirmation of clinically suspected PWS in children/adults.
- Investigation of the molecular defect in confirmed PWS cases, distinguishing between UPD, deletion and IC mutations (parental samples required).
- Carrier testing in adult relatives of confirmed PWS patients who are suspected of having an IC mutation (samples from appropriate family members are required).

Prenatal testing

Prenatal diagnosis is available to couples where PWS has been confirmed in the family and to couples at risk of having a child affected with PWS due to a balanced chromosomal rearrangement involving chromosome 15 in one of the parents. Please contact the laboratory to discuss each case prior to sending prenatal samples to the laboratory.

Service offered

Confirmation of a PWS diagnosis by methylation analysis and microsatellite analysis to determinate the molecular defect in confirmed cases (requires samples from appropriate family members).

Technical

For diagnostic referrals the initial test is to determine the methylation status of exon alpha of the SNRPN gene. Methylation analysis is undertaken by methylation specific PCR following bisulphite modification of genomic DNA. Normal individuals yield a 313bp maternally derived fragment and a 221bp paternally derived fragment. Patients with Prader-Willi syndrome show a single 313bp maternal fragment only.
Positive results are confirmed by either MS-MLPA or aCGH analysis. Chromosome 15 microsatellite markers from within and flanking the commonly deleted region can also be used to characterise the mechanism in patients shown to have abnormal methylation. Cytogenetic analysis is also helpful in identifying deletions and predisposing parental translocations. **NB. A similar testing process is undertaken for Angelman syndrome.**

Target reporting time

Routine analysis - the initial methylation test takes up to 4 weeks. Microsatellite marker analysis takes 8 weeks from receipt of parental samples. Please contact the laboratory for urgent cases.