**NE THAMES REGIONAL MOLECULAR GENETICS SERVICE**

**Interferon Regulatory Factor 6 (IRF6) gene mutation disorders**
*(Popliteal Pterygium syndrome / Van der Woude syndrome)*

**Contact details**

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**Introduction**

Van der Woude syndrome (VWS; MIM) and Popliteal Pterygium syndrome (PPS) are allelic autosomal dominant disorders caused by mutations in the interferon regulatory factor 6 gene (IRF6; MIM *607199). VWS is the most common form of cleft lip and/or palate accounting for 1-2% of cases. Lip pits and/or sinuses are cardinal features of the syndrome present in 70-80% of patients. PPS combines the symptoms of VWS with popliteal webs, unusual nails, syndactyly, ankyloblepharon and genital abnormalities.

It has been proposed that orofacial development is affected in VWS as a result of haploinsufficiency with protein truncating mutations commonly identified throughout the IRF6 gene. The features of PPS are thought to result from dominant negative mutations (generally missense) in the DNA binding domain of the protein. Confirmation of diagnosis enables prenatal testing for PPS and clarification of recurrence risk for VWS (50% as opposed to 3-5% for isolated cleft/lip palate families).

The IRF6 gene (1q32-q41) has 9 exons (exons 1 and 2 are non-coding). c.250C>T (p.Arg84Cys) and c.251G>A (p.Arg84His) are recurrent mutations identified in PPS patients. A variety of point mutations and small deletions have been identified in VWS located throughout the IRF6 gene.

**Samples required**

5ml venous blood in plastic EDTA bottles (>1ml from neonates)

Prenatals must be arranged in advance, through a Clinical Genetics department if possible. Amniotic fluid or CV samples for genetic testing should be sent to Cytogenetics for dissecting and culturing, with instructions to forward the sample to the Regional Molecular Genetics laboratory for analysis. Prenatal detection can also be undertaken by biochemical analysis.

A completed DNA request card should accompany all samples.

**Referrals**

- Referrals will only be accepted via a Clinical Geneticist or cleft surgeon.
- Testing of other family members will be possible upon identification of a causative mutation in the index case.

**Prenatal testing for PPS**

Prenatal testing is available for families in whom mutations causing PPS have been identified or in whom appropriate family studies have been undertaken. Please contact the laboratory to discuss.

**Service offered**

- Direct sequencing of all coding exons (3-9) and intron-exon boundaries.
- Testing for known mutations in relatives of patients with confirmed PPS / VWS mutations by sequencing.

**Target reporting time**

2 months for routine mutation screen in index case. 2 weeks for carrier testing. For urgent samples please contact the laboratory.

**Contact details for Consultant Cleft Geneticist at Great Ormond Street Hospital:**

Dr M Lees, Clinical Genetics, Great Ormond Street Hospital, Level 4 York House, 37 Queen Square, London WC1N 3BH

**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.