Waardenburg Syndrome types 1-4 (PAX3, MITF, SOX10 genes)

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
Waardenburg syndrome (WS) is an auditory-pigmentary disorder consisting of four clinical subtypes with an annual incidence of 1/270 000 births. WS comprises approximately 3% of congenitally deaf children. WS1 (MIM #193500) and WS3 (MIM #148820) are defined by deafness, depigmentation features and dysmorphology. WS3 individuals also have musculoskeletal abnormalities of the upper limbs.

The Paired Box Gene 3 (PAX3) on chromosome 2q35 is the only gene known to be associated with WS1 and WS3 with point mutations identified in more than 90% of affected individuals. No common mutations are known. Partial and total gene deletions have also been described and may represent 10% of cases without identified point mutations.

WS1 is autosomal dominant but may arise de novo and demonstrates variable expressivity. In WS3 homozygous and compound heterozygous (severe phenotype) or heterozygous (moderate phenotype) mutations are seen.

Waardenburg syndrome Type 2 (WS2) and Type 4 (WS4) are genetically heterogeneous disorders. Partial and full gene deletions of MITF have been reported in WS2 patients and in patients with Tietz syndrome, a severe WS2 phenotype characterised by uniform hypopigmentation. SOX10 deletions have been reported in patients with WS2 and WS4.

Referrals
- Patients with suspected WS1/WS3 for mutation screening and MLPA analysis of PAX3
- Adult relatives of patients with PAX3 mutations for carrier status.
- Patients with suspected WS2, WS4 or Tietz syndrome can also be screened for deletions in the MITF and SOX10 genes by MLPA.

Service offered
- Mutation screening of PAX3 gene. Dosage analysis by MLPA (PAX3, MITF, SOX10).
- Detection of known mutations in relatives of patients with PAX3 mutations. Sequence analysis of the MITF and SOX10 genes is not available.

Technical
- Direct Sanger sequencing analysis of PAX3 covering the 5’UTR and all ten exons present in the longest transcript. This analysis also covers the alternatively spliced 3’ end of the major isofrm.
- Large scale deletions detected in PAX3, MITF and SOX10 by MLPA.

Target reporting time
- Routine mutation screen in index case takes 8 weeks. Routine testing of specific mutations takes 2 weeks. For urgent samples please contact the laboratory.