Congenital/late-onset Central Hypoventilation Syndrome (CCHS/LO-ChS) Analysis of the PHOX2B gene

Clinical Background and Genetics

- CCHS (OMIM 209880) is a rare autosomal dominant disease of the autonomic nervous system, characterised by abnormal control of respiration.
- Affected individuals have an inadequate response to hypercapnia and hypoxemia, resulting in hypoventilation. Patients usually require lifelong ventilation during sleep.
- CCHS can be associated with other symptoms reflecting dysfunction of the autonomic nervous system, such as Hirschsprung disease.
- Mutations in the paired-like homeobox gene, PHOX2B are associated with CCHS (see references below).
- Approximately 90% of CCHS patients have a heterozygous expansion of the 20 residue polyalanine tract encoded within exon 3 of PHOX2B. The largest reported expansion is 13 alanines (33-residue tract). The remainder have heterozygous missense, nonsense or frameshift mutations in PHOX2B (these often associate with a severe respiratory phenotype, Hirschsprung’s and a higher incidence of neural crest tumours).
- Mutations are inherited in an autosomal dominant stable manner. The majority of PHOX2B mutations arise de novo; however >8% of parents of a CCHS proband are mosaic for the PHOX2B mutation. Variable penetrance has been observed.


Service offered

- PHOX2B polyalanine tract size analysis by PCR
  First-line or exclusion test for patients with a possible or firm clinical diagnosis of CCHS or LO-ChS. Also for familial testing for a known expansion mutation. If a polyalanine expansion is detected, the repeat tract will be confirmed and accurately sized by sequence analysis.
  - PHOX2B gene screen by sequence analysis
    For patients with a firm clinical diagnosis of CCHS or LO-ChS and negative for a polyalanine expansion.

Referrals

- Diagnostic referrals are welcomed from Consultant Paediatricians, Consultants in Respiratory Medicine, and Clinical Geneticists.
- Referrals for familial mutation testing or prenatal diagnosis are accepted only with the involvement of Clinical Genetics.

Please ensure that clinical history details are provided on the referral form.

Target reporting Time and Indicative Cost

- **Level 1:** PHOX2B polyalanine tract size analysis by PCR
  14 / 28 days

- **Level 2:** PHOX2B gene screen by sequence analysis
  56 days

- **Familial:** PCR analysis for known polyalanine expansion
  Sequence analysis for known mutation
  28 days
  14 / 28 days

Contact laboratory to discuss prenatal analysis (3 days reporting time for PCR test).

Please contact the laboratory for up-to-date prices

Quality

- This is a UKGTN approved service, There are no specific EQA schemes for this service. BGL participates in the EMQN scheme for DNA sequencing.

Clinical Advice

If clinical discussion is required we would recommend contact with Prof. Peter Fleming, Bristol Children’s Hospital Peter.Fleming@bristol.ac.uk