North Bristol NHS Trust

R333 Congenital / late-onset Central Hypoventilation Syndrome (CCHS/LO-CHS) Analysis of the *PHOX2B* gene

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Sample Required
See Sample requirements page at www.nbt.nhs.uk/genetics **for full details**

Adult: 5mls blood in EDTA
Paediatric: at least 1ml EDTA (preferably >2ml)

Prenatal testing MUST be arranged with the laboratory well in advance.

Samples should be accompanied by a FULLY completed request form (available as download at www.nbt.nhs.uk/genetics or from the laboratory).

Please include details of the test required, family history, address and POSTCODE, NHS number, referring clinician and centre.

Consent and Storage:
All genetic testing requires consent. **It is the responsibility of the referring clinician to ensure that appropriate consent has been obtained.**

DNA is stored from **ALL** patients undergoing DNA testing, unless consent for this is specifically denied.

Stored material from all referrals may be retained for quality assurance purposes and may be used anonymously for the development of new tests for the disorder in question.

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.
- Pathogenic variants 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 pathogenic variants in *PHOX2B* (these often associate with a severe respiratory phenotype, Hirschsprung's and a higher incidence of neural crest tumours).
- Pathogenic variants are inherited in an autosomal dominant stable manner. The majority of *PHOX2B* pathogenic variants arise de novo; however >8% of parents of a CCHS proband are mosaic for the *PHOX2B* pathogenic variant. 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 pathogenic expansion variant. 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 accepted from Consultant Paediatricians, Consultants in Respiratory Medicine, and Clinical Geneticists.
- Referrals for familial pathogenic variant testing or prenatal diagnosis are accepted only with the involvement of Clinical Genetics. **Please forewarn the laboratory prior to the taking of any prenatal samples**.

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

Clinical Advice: If clinical discussion is required we would recommend contact with Dr Tom Hilliard, Clinical Lead for Paediatric Respiratory Medicine at Bristol Children's Hospital; Email: tom.hilliard@nhs.net; Tel: 0117 342 8329

Target reporting Times

	Urgent/Standard
Level 1: *PHOX2B* polyalanine tract size analysis by PCR	14 / 42 days
Level 2: *PHOX2B* gene screen by sequence analysis	21 / 42 days
Familial: PCR analysis for known polyalanine expansion	14 / 42 days
Sequence analysis for known mutation	21 / 42 days
Prenatal: Contact laboratory to discuss prenatal analysis	(3 days reporting time for PCR test).

Quality

This service has been approved under our UKAS- accredited scope for testing. There are no specific EQA schemes for CCHS. However, BGL participates in the EMQN sample swap scheme for this service.

References

(i) Amiel et al. 2003. Nature Genetics; 33(4):459-461, (ii) Sasaki et al. 2003. Human Genetics; 114: 22-26, (iii) Weese-Mayer et al. 2003. American Journal of Medical Genetics; 123A(3): 267-278, (iv) Matera et al. 2004. Journal of Medical Genetics; 41: 373-380. (v) Review: Weese-Mayer et al. 2009. Pediatric Pulmonology 44:521-535.

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