Bristol Genetics Laboratory is a UKAS accredited medical laboratory No.9307.

Cantú Syndrome

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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 >2mls).

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

- Cantú syndrome (OMIM 239850) is a rare autosomal dominant disorder characterized by congenital hypertrichosis, distinctive facial appearance, osteochondrodysplasia and cardiac features. To date 50 cases have been reported in the literature.
- Cantú syndrome is an autosomal dominant/sporadic disorder with mutations in *ABCC9* (OMIM *601439 also known as *SUR2*) identified in approximately 88% of patients with a clinical diagnosis. The ABCC9 protein is part of an ATP-sensitive potassium channel complex with pathogenic variants disturbing channel function.
- The *ABCC9* gene encodes two transcripts *SUR2A* (cardiac and skeletal muscle) and *SUR2B* (vascular smooth muscle and hair follicles) which are identical except for the use of an alternative final exon (exon 38). Pathogenic variants in exon 38 of *SUR2A* have been associated with dilated cardiomyopathy and atrial fibrillation.
- 70% of pathogenic variants identified in *ABCC9* in patients with Cantú syndrome reside in exons 24-27 which encode the second transmembrane domain. There have been no *ABCC9* copy number variants reported in the literature to date.

Service Offered

- **1st Tier:** Bidirectional sequence analysis of exons 24-27 of *ABCC9* (expected detection rate of 70%). The sensitivity of the sanger sequencing assay is 99%.
- **2nd Tier:** The whole of the *ABCC9* gene can be screened using a Next Generation Sequencing approach (bespoke design Twist probeset with Illumina Nextera DNA flex library prep). Please contact the laboratory to discuss.
- **3rd Tier:** Familial testing (Cascade or Segregation): **Cascade:** Offered where a known pathogenic variant identified in the proband. **Segregation:** To ascertain whether a VUS is associated with disease in a family.
- **4th Tier:** Confirmation of pathogenic variants detected in research settings e.g. DDD, 100K.

Referrals

- **Diagnostic Testing**: Referrals meeting genetic testing criteria (congenital hypertrichosis and characteristic facial appearance) accepted from Consultant Clinical Geneticists.
- **Familial Testing:** Accepted from Consultant Clinical Geneticists. Please provide details of affected patient and known pathogenic variant.

Target reporting Times

Test	Turn around Time (Calendar days)
Diagnostic screen	42 days
Familial testing for known pathogenic variants	42 days
Urgent Testing (prenatal)	3 days

Quality

- BGL participates in the external quality assurance EMQN sequencing QA schemes (since the pilot scheme was introduced in 2002) and UKNEQAS Unclassified Variant interpretation scheme (pilot scheme introduced in 2012).

Clinical Advice

- We recommend contact with **Dr Ingrid Scurr or Dr Sarah Smithson** Consultant Clinical Geneticists, Level B St Michael's Hospital, Bristol BS2 8EG (Tel: 0117 342 5653; e-mail Ingrid.Scurr@UHBristol.nhs.uk).

References

1) Harakalova, M. et al. (2012) **Dominant missense mutations in *ABCC9* cause Cantu syndrome.** *Nature Genet*. 44: 793-796.
2) van Bon, B. W. M. et. al. (2012) **Cantu syndrome is caused by mutations in *ABCC9*.** *Am. J. Hum. Genet.* 90: 1094-1101, 2012.
3) Scurr, I. et al. (2011) **Cantu syndrome: report of nine new cases and expansion of the phenotype.** *Am. J. Med. Genet*. 155A: 508-518.
4) Brownstein, CA *et. al.* (2013**) Mutation of KCNJ8 in a patient with Cantu Syndrome with unique cardiovascular abnormalities: support for the role of k(ATP) channels in this condition**. *Europ J Med Genet*. 56: 678-682.
5) Cooper PE *et al.* (2014) **Cantu Syndrome resulting from activating mutation in the KCNJ8 gene.** *Hum Mutat* 35: 809-13.