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

North Bristol NHS Trust

Cystinuria (R256)
(Slice of Nephrocalcinosis/nephrolithiasis panel)

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

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

Please include details of test, 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

Cystinuria is due to defective transport of Cystine and other "dibasic" amino acids through the lining cells of the proximal renal tubule and gastrointestinal tract. The high concentration of poorly soluble Cystine in the urine results in the formation of kidney stones, causing pain, obstruction, infections, and, if left untreated, kidney damage and eventual kidney failure. It is associated with variants in 2 genes in ~92% of cases.

- **Type A Cystinuria** is associated with pathogenic variants in *SLC3A1* (Solute Carrier Family 3 Member 1) at 2p21 and is recessive with two variants required for the phenotype.
- **Type B Cystinuria** is associated with pathogenic variants in *SLC7A9* (Solute Carrier Family 7 glycoprotein-associated amino acid transported light chain, bo,+system Member 9) at 19q13.11 and although two variants are associated with the phenotype, about 85% of carriers have raised urine cystine levels with 5% with very high levels and an increased risk of stone formation.

Cystinuria is therefore considered as a recessive, dominant and digenic condition, with allelism of the two genes responsible for the subtypes.

Service offered

- **Genomic test directory reference R256:** Two-gene cystinuria slice of the nephrocalcinosis next generation sequencing (NGS) panel).
- All coding regions and intron/exon boundaries of *SLC3A1* (10 exons) and *SLC7A9* (13 exons; exon 1 being non-coding) detects missense, frameshift, nonsense and splicing variants, i.e. approx. 90% variants in UK population and copy number changes (10%) variants.
- Familial tests are available for known variants using Sanger sequencing or MLPA

Referrals

Referrals meeting NHSE testing eligibility criteria are accepted nationally. Please refer to: https://www.england.nhs.uk/publication/national-genomic-test-directories/

Quality

BGL participates in the EMQN scheme for DNA sequencing and GENQA for variant interpretation and renal disorders.

Target reporting Time (costs available on request)

- NGS 2-gene panel: 42 days (6 weeks)
- Familial Testing*: 14-42 days (2-6 weeks)*
- Urgent: Contact laboratory

Clinical Advice: If clinical discussion is required we would recommend contact with: Dr Richard Coward FRCP Consultant Paediatric Nephrologist (email: Richard.Coward@bristol.ac.uk). to enrol patients onto the Cystinuria registry on RaDaR (http://rarerenal.org/radar-registry/).

References

- Dello Strogolo *et al* (2002). Comparison between SLC3A1 and SLC7A9 Cystinuria patients and carriers: A need for a new classification. *J Am Soc Nephrol*; 13: 2547-2553
- Chillaron *et al* (2010). Pathophysiology and treatment of Cystinuria. *Nat. Rev. Nephrol*; 6: 424-434.