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

North Bristol NHS Trust

Cystinuria UKGTN service (OMIM #220100)

Contact details:
Bristol Genetics Laboratory
Pathology Sciences
Southmead Hospital
Bristol, BS10 5NB
Enquiries: 0117 414 6168
FAX: 0117 414 6464

Head of Department:
Professor Rachel Butler, FRCPath
Consultant Clinical Scientist

Consultant Lead for Rare Disease:
Dr. Maggie Williams, FRCPath

Consultant Lead for Oncology:
Christopher Wragg, FRCPath

Renal Genetics Section Lead:
Elizabeth Watson, DipRCPath
Elizabeth.Watson@nhs.net
0117 414 6148

Cystinuria Service Lead:
Dr. Celia Duff-Farrier
Celia.duff-farrier@nhs.net

Renal Genetics contact details:
Nbn-tr.swglhrenalservice@nhs.net

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

- Screen by Sanger sequencing of 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.
- Quantitative MLPA assay to detect copy number changes in *SLC3A1* and *SLC7A9* (10% variants).
- Familial tests are available for known variants using Sanger sequencing or MLPA

Quality

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

Referrals

Referrals meeting UKGTN testing criteria are accepted nationally from Consultant Renal Physicians, Consultant Urologists, and Consultant Clinical Geneticists.

Target reporting Time (costs available on request)

- *Sequencing and MLPA: 42 days (6 weeks) , Familial Mutation: 42 days (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.