Bristol Genetics Laboratory

North Bristol NHS Trust

Smith-Lemli-Opitz (SLOS) / *DHCR7* Mutation analysis

Contact details:
Bristol Genetics Laboratory
Southmead Hospital
Bristol, BS10 5NB
Enquiries: 0117 4146168
FAX: 0117 4146464

Head of Department:
Eileen Roberts FRCPath

Consultant Lead for Molecular Genetics:
Maggie Williams FRCPath

Service Lead:
Rebecca Whittington
Email: Rebecca.whittington@nbt.nhs.uk

Sample Required:
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 test, family history, address and POSTCODE, NHS number, referring clinician and unit/hospital.

Consent and DNA 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 unless consent for this is specifically denied.

Stored samples may be used for quality assurance purposes and may be used anonymously for the development of new tests for the disorder in question.

Clinical Background and Genetics
- Smith-Lemli-Opitz (SLO) is an autosomal recessive metabolic congenital multiple malformation syndrome resulting from deficiency of 7-dehydrocholesterol reductase (DHCR7) which catalyses the last step of endogenous cholesterol synthesis.
- There is a continuum of clinical severity in SLOS varying from intrauterine lethality or severe congenital malformation through severe neonatal presentation to mild dysmorphism/physical anomaly and moderate/mild mental impairment.
- Biochemically SLO patients have low cholesterol [<5 mmol/L] and high 7-dehydrocholesterol (7-DHC)* levels.
- The gene involved is 7-dehydrocholesterol reductase (***DHCR7***). There are 9 exons of which only exons 3-9 are coding. >125 different point and small insertion or deletion mutations in *DHCR7* have been described to date.

*The biochemical levels given are those used locally in Bristol. Different levels may be used elsewhere.

Service offered
- Screening of coding exons 3-9 by direct sequence analysis (clinical sensitivity~96%) in affected and equivocal patients and parents (see below).
- Partners of known *DHCR7* mutation carriers are tested for exon 9, which covers the common *DHCR7* mutation (c.964-1G>C) and other common *DHCR7* mutations; this analysis accounts for approx. 57% of affected alleles in the UK.
- Testing for known familial *DHCR7* mutations in adult relatives.

Referrals
Diagnostic: (referrals are accepted from Consultant Clinical Geneticists and Consultant Metabolic Disease Specialists).
1) Patient with **raised 7DHC*** [>20umol/L] and clinical diagnosis of SLOS, including 2 or more features listed on the UKGTN proforma (see overleaf).
2) **Normal (7DHC <2.5umol/L) or atypical biochemistry*** [7DHC 2.5umol/L to 20umol/L] but characteristic facial dysmorphology and 3 or more other clinical features of SLOS (see overleaf).

Carrier Testing (referrals are accepted from Consultant Clinical Geneticists):
- Parent of child or foetus diagnosed with SLOS clinically and on biochemistry.
- Parent of offspring or foetus suspected to have SLOS on post-mortem **from typical facial dysmorphology** and 3 or more other features from list overleaf.
- Parent of pregnancy where USS and biochemical results indicate SLOS abnormal biochemistry levels [(7DHC: cholesterol ratio) x1000 > 3.1]* on amniocentesis or chorionic villus sampling.
- Adult with close family history of SLOS and known *DHCR7* mutation(s) in relative(s).
- Partners of known *DHCR7* mutation carriers will be tested for exon 9 which includes the common *DHCR7* mutation (c.964-1G>C).

Prenatal Testing: Prenatal diagnosis can be offered, after prior arrangement for couples with confirmed mutations.

A UKGTN service proforma should be completed for all referrals (see overleaf) and be accompanied by the biochemical results and interpretation.

Target reporting Time:

	TAT
Diagnostic screen:	56 days
Urgent parental screen for SLOS on USS	Contact Lab
Familial mutation analysis	28 days
Common mutation analysis	28 days
Prenatal/urgent:	3 working days

For up-to-date prices please contact the laboratory

Quality
This laboratory participates in the following external quality assurance schemes which cover the technique and strategies used for this service: EMQN Sanger DNA sequencing scheme (since the pilot scheme was introduced in 2002) and UKNEQAS Pathogenicity of sequence variants interpretation only scheme (pilot scheme introduced in 2012).

Clinical Advice
If clinical discussion is required we would recommend contact with Dr Ruth Newbury-Ecob Consultant Clinical Geneticist, St Michael's Hospital, Bristol (Tel: 0117 928 5107).

Laboratory contact: For enquiries/requesting contact:
Alison.Hills2@nbt.nhs.uk or Rebecca.Whittington@nbt.nhs.uk

CPA
Accredited Medical Laboratory
Reference No: 2907

Exceptional healthcare, personally delivered

UKGTN Testing criteria for disease:

Patient name:
Patient postcode:
Name of referring clinician:
Title/Position:

A

Name of Disease/test: Smith-Lemli-Opitz (*DHCR7* mutation testing)

B

Referrals will only be accepted from one of the following:

Referring clinician	Tick if this refers to you
Clinical Geneticist	
Consultant Metabolic Disease Specialist	

C

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:

Criteria	Tick if this patient meets criteria
Patient with raised 7DHC* [>20umol/L] and clinical diagnosis of SLOS, including 2 or more of: ▪ Microcephaly ▪ Cleft palate ▪ Characteristic facial dysmorphology (e.g. ptosis, epicanthic folds, short nose with anteverted nares, broad alveolar ridges) ▪ Cardiac anomaly ▪ Hypospadias or Ambiguous genitalia in males (or 46,XY phenotypic females) ▪ 2/3 toe syndactyly ▪ Short thumb ▪ Post-axial polydactyly	
Normal (7DHC <2.5umol/L) or atypical biochemistry* **[7DHC 2.5umol/L to 20umol/L]** but **characteristic facial dysmorphology** and 3 or more other clinical features of SLOS (see above list)	
Parent of child or foetus diagnosed with SLOS clinically and on biochemistry	
Parent of offspring or foetus suspected to have SLOS on post-mortem **from typical facial dysmorphology** and 3 or more other features from above list.	
Parent of pregnancy where USS and biochemical results indicate SLOS abnormal biochemistry levels [(7DHC:cholesterol ratio)x1000 > 3.1]* on amniocentesis.	
Adult with close family history of SLOS and known *DHCR7* mutation(s) in relative(s)	
Partners of known *DHCR7* mutation carriers will be tested for the common DHCR7 mutation (c.964-1G>C).	

*These are based on local reference ranges at the Biochemical Genetics Unit, Southmead Hospital, Bristol; reference ranges used in other laboratories may vary.

If the sample does not fulfil these criteria and you still feel that testing should be performed please contact the Bristol Genetics Laboratory (Tel: 0117 414 6143/6175) to discuss testing of the sample.

Approved by: Rebecca Whittington