Bristol Genetics Laboratory

North Bristol NHS Trust

NHS Specialised Barth Syndrome Service

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

Head of Department:
Eileen Roberts FRCPath

Consultant Lead for Molecular Genetics:
Maggie Williams FRCPath

Service Lead:
Julie Honeychurch
julie.honeychurch@nbt.nhs.uk

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 to 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

- Barth Syndrome (OMIM 302060) is a rare X-linked recessive disease with variable presentation and a high rate of infant mortality.
- Clinical features include dilated cardiomyopathy (DCM), neutropenia, 3-methylglutaconic aciduria, failure to thrive, abnormal mitochondria, skeletal myopathy and short stature. Clinical diagnosis may be difficult due to variability of presentation within patients. Therefore it has been reported that Barth Syndrome may be relatively under-diagnosed.
- The gene involved is *TAZ* (previously known as *G4.5*) located at Xq28.12. It is composed of 11 exons and the coding sequence spans 1.9kb.
- The protein tafazzin is thought to function as an acyltransferase in the remodeling of cardiolipin in the inner mitochondrial membrane.
- Over 100 different disease-causing *TAZ* mutations have been reported in all exons. Mutational hotspots exist in exons 2, 4 and 8.
- *TAZ* gene mutations have also been reported in X-linked endocardial fibroelastosis, severe X-linked dilated cardiomyopathy and isolated non-compaction of the left ventricular myocardium (INVM).
- A database of *TAZ* mutations plus other relevant information for professionals and Barth Syndrome patients and families can be found at http://www.barthsyndrome.org/. UK website: www.barthsyndrome.org.uk

Service offered

- Full *TAZ* gene screening by direct sequence analysis (sensitivity 99%).
- Tests for known familial mutations

Referrals

- **Diagnostic Testing**: Cardiolipin analysis (MLCL/CL ratio) must be undertaken on all diagnostic/exclusion referrals on male patients, **prior to *TAZ* full genetics screening**. In advance of sending a sample for cardiolipin analysis please contact: Dr Vicki Powers, Department of Biochemistry, Bristol Royal Infirmary (Tel 0117 342-2590) to discuss sample requirements.
- **All referrals should be accompanied by a completed Barth Syndrome testing proforma (see below).** Please provide clinical details of affected patient and family history.
- **Carrier Testing:** Once a mutation has been found in a patient, the laboratory can offer carrier testing for the mother and other at-risk relatives through local Clinical Genetics services. Please note that female carriers of a *TAZ* gene mutation appear to be healthy.
- **Females with a history of multiple still-births, foetal hydrops or foetal cardiomyopathy undergo a *TAZ* full gene screen** (Cardiolipin analysis is not able to distinguish between normal and carrier females).
- **Prenatal Testing**: Prenatal diagnosis can be offered for carrier females with an identified mutation by arrangement with the Laboratory

Target reporting Time & Cost

Diagnostic screen:	56 days
Known Mutation:	14 days
Prenatal/urgent:	3 days

Please Note: The service is provided free of charge for referring UK Clinicians meeting the criteria. Otherwise, please contact BGL for current prices.

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 would recommend contact with Dr Colin Steward (Clinical Lead NHS Specialised Barth Syndrome Service), Department of Paediatric Haematology/Oncology/BMT, Bristol Royal Hospital for Children, Upper Maudlin Street, Bristol, BS2 8BJ (Tel: 0117-342-0245) or Ruth Newbury-Ecob Consultant Clinical Geneticist, Level B St Michael's Hospital, Bristol (Tel: 0117-342-5107).

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CPA
Accredited Medical Laboratory
Reference No: 2907

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Bristol Genetics Laboratory

North Bristol NHS Trust

NHS BARTH SYNDROME SERVICE: GENETIC TESTING PROFORMA

This form must be completed prior to undertaking diagnostic molecular testing on any patient for Barth Syndrome.
Please return completed form to the address below FAO: Julie Honeychurch/Maggie Williams.

Patient Demographics

Surname .....

First Name.....

Date of Birth.....

Hospital No.....

Genetics No.....

NHS No.....

Postcode.....

Referring Clinician's Details

Clinician name .....

Telephone .....

Email address.....

Address for report .....

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Name/Address for invoice.....

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Clinical details (circle as appropriate)

Cardiolipin test result .....

Heart problems -any of:

Cardiomyopathy (dilated/hypertrophic)/ Non-compaction of left ventricle/ Endocardial fibroelastosis/other (please specify)	Yes/No/Unknown
Raised 3-Methylglutaconic acid	Yes/No/Unknown
Idiopathic Neutropaenia (chronic, cyclical or intermittent)	Yes/No/Unknown
Proximal Myopathy	Yes/No/Unknown
Positive Gower's sign or waddling gait	Yes/No/Unknown
Growth delay	Yes/No/Unknown
Motor delay	Yes/No/Unknown
Hypoglycaemia	Yes/No/Unknown
Lactic Acidosis	Yes/No/Unknown
Food fads	Yes/No/Unknown
Abnormal muscle biopsy	Yes/No/Unknown

Age of onset of 1st symptoms .....

Is Test for Barth Syndrome:

Diagnostic ☐

Exclusion ☐

Familial mutation test ☐
(provide details below)

Name of Index case/proband

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Relationship .....

Mutation details.....

.....

Family History (circle as appropriate)

Stillbirths	Yes/No/Unknown
Miscarriages	Yes/No/Unknown
Sudden death	Yes/No/Unknown

If answered yes to any of these questions please provide further details below, with pedigree (use reverse of form if needed).

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Other potentially clinically relevant details (use reverse of form if needed).

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Return completed form to: Bristol Genetics Laboratory, Pathology Sciences, Southmead Hospital, Bristol, BS10 5NB