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

NHS Specialised Barth Syndrome Service R391

Contact details:
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Pathology Sciences
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Bristol, BS10 5NB
Enquiries: 0117 414 6168

Head of Department:
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Consultant Clinical Scientist

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or juliehoneychurch@nhs.net

Sample Required
See Sample requirements page at www.nbt.nhs.uk/genetics for full details

- **Adult:** 5 mls blood in EDTA
- **Paediatric:** at least 1 ml EDTA (Preferably >2mls)

Note: Please contact the Department of Biochemistry regarding samples for Cardiolipin analysis (see referrals for details).

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

- 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* 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* pathogenic variants have been reported in all exons. Hotspots exist in exons 2, 4 and 8.
- *TAZ* gene pathogenic variants 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* variants 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 sanger sequence analysis (sensitivity 99%).
- Tests for known familial pathogenic variants (including prenatal diagnosis).

Referrals

- **Please see link to the National Genomic test Directory eligibility criteria for Barth Syndrome, test code R391: https://www.england.nhs.uk/wp-content/uploads/2018/08/Rare_and_Inherited_Disease_Eligibility_Criteria_August_20-21.pdf**
- **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: Duty Metabolic Biochemist, Department of Biochemistry, Bristol Royal Infirmary, BS2 8WW (Tel 0117 342-1299) 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 disease causing variant 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 pathogenic variant 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).

Target reporting Times

Test	Turn around Time (Calendar days)
Diagnostic screen	42 days
Familial testing for known pathogenic variants	42 days
Prenatal Testing	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 would recommend contact with Dr Germaine Pierre and Dr Effie Chronopoulou, Metabolic Consultants, Bristol Royal Hospital for Children, Division of Women's and Children's services, Level 6, UBHT Education Centre, Upper Maudlin St, Bristol, BS2 8AE (Tel: 0117-342-1694), or Dr Ruth Newbury-Ecob, Consultant Clinical Geneticist, Department of Clinical Genetics, St Michael's Hospital, Southwell Street, Bristol, BS2 8EG (Tel: 0117-342-5316).

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Approved by: Rebecca Whittington

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North Bristol NHS Trust

NHS BARTH SYNDROME SERVICE R391: 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.

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 .....

.....

Name/Address for invoice.....

.....

Clinical details (circle as appropriate)

Cardiolipin test result .....

Heart problems -any of:

Cardiomyopathy (dilated/hypertrophic)/

Non-compaction of left ventricle/ Yes/No/Unknown

Endocardial fibroelastosis/other

(please specify) .....

Raised 3-Methylglutaconic acid Yes/No/Unknown

Idiopathic Neutropaenia Yes/No/Unknown

(chronic, cyclical or intermittent)

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.....

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

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Is Test for Barth Syndrome:

Diagnostic ☐

Exclusion ☐

Familial testing for pathogenic variant

(Provide details below):

Name of Index Case / Proband / Lab or Ref Number

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Relationship.....

Pathogenic Variant details.....

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

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