Bristol Genetics Laboratory

North Bristol NHS Trust

Facioscapulohumeral Muscular Dystrophy – FSHD 1 and 2

Contact details:
Bristol Genetics Laboratory
Pathology Sciences and
Bristol Genetics
Southmead Hospital
Bristol, BS10 5NB
Enquiries: 0117 414 6168
FAX: 0117 414 6464
Email: nbn-tr.geneticsenquiries@nhs.net

Head of department:
Eileen Roberts FRCPath

Consultant Lead for Molecular Genetics:
Maggie Williams FRCPath

Service Lead:
Maggie Williams
Email: Maggie.williams@nbt.nhs.uk

Sample Required:
Adult: 5mls blood in EDTA
Paediatric: at least 1ml EDTA (preferably >2ml)
DNA requirements: at least 30µg DNA
If these requirements cannot be met please contact the laboratory for advice

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

- Autosomal dominant Facioscapulohumeral Muscular Dystrophy (OMIM 158900) is the third most common myopathy with an incidence of approximately 1 in 20,000.
- Affected individuals show progressive weakness and asymmetrical atrophy of facial, shoulder and upper arm musculature. There is wide clinical variability within and between families and non-penetrance has been reported. The disease mechanism has not been fully elucidated.
- The majority (~95%) of FSHD1 cases are associated with a contraction of D4Z4 tandem repeat units (3.3kb) in the subtelomere region 4q35. In FSHD patients the number of D4Z4 repeat units is reduced to 1-10 in comparison to 11-100 in normal individuals.
- 10-30% of FSHD cases are *de novo* D4Z4 deletions, a high proportion of which arise mitotically, leading to somatic mosaicism in either the affected patient, or in a mild or non-affected parent.
- Genetic diagnosis is complicated by the homologous polymorphic D4Z4 repeat array on chromosome 10 (10q26), contractions of which are not associated with the disease.
- Testing for FSHD1 is by linear gel electrophoresis using *EcoRI*/*BlnI*/*ApoI* digests and the probe p13E-11, which confirms the D4Z4 contraction size and chromosome of origin. In situations where the pathogenicity of a specific fragment is unclear, 4qA and 4qB haplotyping can be used to further characterise the fragment (see below).
- ~3-4% of cases are FSHD2 – exhibiting a normal D4Z4 length, hypomethylation and a mutation in *SMCHD1* (18p11.32).

Services Offered

FSHD1

- ***Eco*RI/*Bln*I/*Apo*I DNA digest as required and Southern blot with p13E-11 probe.** First-line test to identify patients with a D4Z4 contraction within the pathogenic size range.
- **Permissive haplotype analysis: *HindIII* DNA digest and Southern blot with probes 4qA and 4qB, plus SSLP analysis.**
  ***CLINICAL PROFORMA REQUIRED*.**
  To clarify pathogenicity:
  - when more than one short 4q35 fragment is detected.
  - of borderline/intermediate 4q35 fragments.
  - where clinical diagnosis is not compatible with test result i.e. exclusion test patients with a positive molecular test result.

FSHD2

- ***CLINICAL PROFORMA REQUIRED* plus negative FSHD1**. Quantification of methylation at D4Z4, hypomethylated patients will go on for sequencing of *SMCHD1*.

If clinically typical patients are negative for FSHD2 please contact the laboratory to discuss additional testing.

Referrals

- **Diagnostic testing** is available for FSHD or ?FSHD patients. Referrals are accepted from Consultant Neurologists or Clinical Geneticists accompanied by relevant clinical details. FSHD2 is only available after exclusion of FSHD1
- **Familial testing (predictive**) is available for patients where a molecular diagnosis of FSHD has been confirmed in the family and they themselves are at risk of developing FSHD. Requests are only accepted from Clinical Geneticists after appropriate genetic counselling.
- **Prenatal testing**: Prenatal diagnosis can be offered where one parent of the foetus has a confirmed molecular diagnosis of FSHD, and if possible where molecular diagnosis has been confirmed in a second affected relative. A partners sample is also required to assist in test work up.

Target reporting Time and Indicative Cost

FSHD1	Routine	56 days
FSHD1	Urgent	14 days
4qA/B +SSLP	Routine	56 days
FSHD2 methylation analysis	Routine	28 days
SMCHD1 sequencing	Routine	56 days

Please contact the laboratory for up to date prices.

EQA

No EQA scheme available. Collaboration with diagnostic and research laboratories in Leiden, Netherlands is in place for discussion of atypical results and an annual sample swap has been arranged with Leiden for FSHD1 and a laboratory in Wurzburg, Germany for FSHD2.

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