Facioscapulohumeral Muscular Dystrophy – FSHD 1 and 2

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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
- 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 EcoR1/BlnI/Apol 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).
- Of the remaining <5% of cases, approximately 2% are negative due to a proximal deletion including the p13E-11 probe region D4F104S1. These cases can be identified with a 1kB D4Z4 probe (which binds within the repeat array proper).
- 3% of cases are FSHD2 – exhibiting a normal D4Z4 length, hypomethylation and a mutation in SMCHD1 (18p11.32).

Services Offered
FSHD1
- Level 1: EcoR1/BlnI/Apol DNA digest and Southern blot with the p13E-11 probe.
  First-line test to identify patients with a D4Z4 contraction within the pathogenic size range.
- Level 2: HindIII DNA digest and Southern blot analysis using the 1kB D4Z4 probe. CLINICAL PROFORMA REQUIRED.
  Extended deletion analysis to identify clinically typical patients with a proximal deletion of the p13E-11 probe region.
- Level 3: HindIII DNA digest and Southern blot with probes 4qA and 4qB. 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.
- Level 4: HindIII DNA digest and Southern blot with the pH30 probe (D4S139).
  Where appropriate linkage analysis is available to support prenatal testing in families with two affected members; or for family studies where there is more than one potentially pathogenic fragment in a family.

FSHD2
- Clinical proforma and EXCLUSION OF FSHD1 (level 1 and 2 testing required).
  Quantification of methylation at D4Z4, hypomethylated patients will go on for sequencing of SMCHD1. (testing available from November 2013)

Referrals
- Diagnostic testing is available for FSHD or 7FSHD patients. Referrals are accepted from Consultant Neurologists or Clinical Geneticians accompanied by relevant clinical details. FSHD2 is only available after full 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 Geneticians 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
<table>
<thead>
<tr>
<th>Service Level</th>
<th>FSHD2</th>
<th>Routine</th>
<th>40 days</th>
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<tbody>
<tr>
<td>Level 1</td>
<td></td>
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<tr>
<td>Level 2, 3 and 4</td>
<td>Routine</td>
<td>40 days</td>
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<tr>
<td>Level 1 and 4</td>
<td>Urgent</td>
<td>10 days</td>
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Please contact the laboratory for up to date prices.