[redacted]

Genetics Report

Full Name	[redacted]				
Date of Birth	[redacted]	Sample ID	[redacted]	Sample Type	[redacted]
Sex	[redacted]	CG No		Received	[redacted]
Postcode	[redacted]	External ID	[redacted]	Activated	[redacted]
NHS Number	[redacted]	Hospital No	[redacted]	Authorised	[redacted]

Clinical Summary: For genetic confirmation of FSHD diagnosis.

Report

Probe/Enzyme	Fragment 1 (kb)	Fragment 2 (kb)	Fragment 3 (kb)	Fragment 4 (kb)
P13E11 EcoRI	[redacted]	[redacted]		
P13E11 EcoRI BlnI	[redacted]			

Single and double digests of the DNA from this patient show that he has a BlnI-resistant fragment measuring approximately [redacted] This fragment is estimated to contain [redacted] D4Z4 repeat units[4].

As this patient is presenting with classical FSHD symptoms, this is likely to represent a pathogenic gene rearrangement at 4q35 consistent with a diagnosis of FSHD1 in this patient.

Any offspring of this patient has a 50% risk of inheriting the [redacted] kb BlnI-resistant fragment, and therefore would have a high risk of developing FSHD1. We would recommend referral of this patient to Clinical Genetics if not already undertaken. At-risk family members can be tested following appropriate genetic counselling.

This patient also has a BlnI-sensitive fragment measuring approximately [redacted]. This is likely to be a typical chromosome 10 type repeat, not involved in clinical symptoms (Lemmers *et al.*, 2001. Ann Neurol. 50:816-9).

A registry exists for UK patients with FSHD. If this patient is interested, refer to www.fshd-registry.org/uk.

Notes:

1. National Genomics Test Directory clinical indication R74: Facioscapulohumeral muscular dystrophy. FSHD1 is characterised by a partial deletion of the polymorphic D4Z4 subtelomeric repeat region at 4q35. In affected patients, these fragments are generally <39 kb. Fragments between 39 kb and 42 kb can be associated with a milder phenotype. Non-penetrance and variable expressivity has been reported in FSHD1 families.
2. The D4Z4 region is delineated by EcoRI sites and detected by linear Southern blot using the probe p13E-11. The probe also hybridises to a similar repeat unit at 10q26; in 10% of the population, these are shorter than 35 kb. Restriction analysis using BlnI reduces the 4q35 fragment by 3 kb and completely digests the 10q26 fragment.
3. The inheritance pattern of FSHD1 is autosomal dominant. However, *de novo* contraction mutations of the D4Z4 locus account for 10-30% of FSHD1 cases (Lemmers *et al.*, 2012. Neuromuscul Disord. 22:463-70). *De novo* contractions may be found in a mosaic form in either the individual affected with FSHD1 or one of their parents (Van der Maarel *et al.*, 2000. Am J Hum Genet. 66:26-35). Somatic mosaicism may go undetected using the standard diagnostic technique of Southern analysis after linear gel electrophoresis. Mosaicism, if present, may alter the severity of the phenotype and the reproductive risks.
4. The sensitivity of this assay is approx. 95%, specificity is 94% (Deutekom *et al.*, 1996. Hum Mol Genet. 5:1997-2003). Fragments can be difficult to size, and inter-assay variability is +/-3 kb. EcoRI fragment size to D4Z4 repeat unit conversion from Genotyping: Methods and Protocols, Methods in Molecular Biology, 2017, vol. 1492, chapter 7, table 1.
5. Two distinct haplotypes (4qA and 4qB) are present in the region distal to the D4Z4 repeat. FSHD is only associated with the 4qA haplotype.

[redacted] [redacted]

Printed: 29 Sep 22
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[redacted]

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Digestion with HindIII results in D4Z4 fragments 6 kb larger than those with EcoRI (Lemmers *et al*., 2002. Nat Genet. 32:235-6). Not all 4qA fragments within the diagnostic size range are associated with FSHD; further testing may be poss ble to identify the three SSLP permissive haplotypes (4A161, 4A159, 4A168) identified in patients with pathogenic FSHD fragments (Richards *et al*., 2012. Hum Genet. 131:325-40).

6. Any remaining DNA is currently retained in long-term storage and may be used anonymously for quality control of this assay.

[redacted]

[redacted]