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doi:10.1136/jnnp.69.1.114

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Extension of the clinical range of facioscapulohumeral dystrophy: report of six cases

A J van der Kooi, M C Visser, N Rosenberg, R van den Berg-Vos, J H J Wokke, E Bakker, M de Visser

Abstract
Consensual diagnostic criteria for facioscapulohumeral dystrophy (FSHD) include onset of the disease in facial or shoulder girdle muscles, facial weakness in more than 50% of affected family members, autosomal dominant inheritance in familial cases, and evidence of myopathic disease in at least one affected member without biopsy features specific to alternative diagnoses.

Six patients did not meet most of these criteria but were diagnosed as FSHD by DNA testing, which showed small EcoRI fragments on chromosome 4q.

Their clinical signs and symptoms and results of auxiliary investigations are reported. The patients presented with foot extensor, thigh, or calf muscle weakness. None of them had apparent facial weakness, only one complained of weakness in the shoulders, none had a positive family history. Expert physical examination, however, showed a typical facial expression, an abnormal shoulder configuration on lifting the arms, or scapular winging. This raised the suspicion of FSHD, whereupon DNA analysis was done. In conclusion, the clinical expression of FSHD is much broader than indicated by the nomenclature. The possibility to perform DNA tests is likely to greatly expand the clinical range of FSHD.

(F J Neurol Neurosurg Psychiatry 2000;69:114–116)

Keywords: facioscapulohumeral muscular dystrophy

Facioscapulohumeral muscular dystrophy (FSHD) is the third most common hereditary myopathy after Duchenne's and myotonic dystrophy. It has a wide range of clinical manifestations typically starting in the second decade. In general, weakness initially involves the face and the periscapular muscles followed by the foot extensors, abdominal muscles, and the hip girdle. Other characteristics include striking asymmetric muscle involvement and sparing of the extraocular and bulbar muscles.

Workshops of the European Neuromuscular Centre have established the following diagnostic criteria to be used for genetic studies: (1) onset of the disease in facial or shoulder girdle muscles, sparing of the extraocular, pharyngeal, and lingual muscles and the myocardium; (2) facial weakness in more than 50% of the affected family members; (3) autosomal dominant inheritance in familial cases; (4) evidence of myopathic disease in EMG and muscle biopsy in at least one affected member without biopsy features specific to alternative diagnoses.

In 1990 linkage to a marker on chromosome 4q was found. Subsequently, affected people were shown to carry a small EcoRI fragment. The diagnosis of FSHD can be confirmed by DNA restriction fragment analysis in 95% of patients. EcoRI fragment size below 38 kb is compatible with a diagnosis of FSHD.

In this report we describe six sporadic patients with an atypical presentation of FSHD giving rise to diagnostic difficulty. The diagnosis could only be established by DNA analysis.

Patients
The clinical features of the six patients are summarised in the table. Two patients are described in detail.

PATIENT 2
A 57 year old woman was referred to a neurologist in 1997 because she had had diffi-

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Table 1 Clinical features and data of ancillary investigations of six patients with FSHD

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Presenting symptoms</th>
<th>Presenting signs</th>
<th>Age at onset (y)</th>
<th>Progression</th>
<th>CK</th>
<th>CT</th>
<th>EMG</th>
<th>Muscle biopsy</th>
<th>EcoRI fragment size (kb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32M</td>
<td>E* drop foot</td>
<td>FS<em>E</em></td>
<td>30</td>
<td>m</td>
<td>2.5x</td>
<td>T<em>E</em>C*</td>
<td>N</td>
<td>NP</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>57F</td>
<td>T; walking difficulty</td>
<td>FSHTC*</td>
<td>50</td>
<td>m</td>
<td>1.2x</td>
<td>HTC*</td>
<td>N</td>
<td>N</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>55M</td>
<td>C; inability to walk on toes</td>
<td>FS<em>T</em>C*</td>
<td>50</td>
<td>m</td>
<td>NI</td>
<td>S<em>T</em>C*</td>
<td>M</td>
<td>NP</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>80M</td>
<td>E*: drop foot</td>
<td>S<em>H</em>E*</td>
<td>75</td>
<td>m</td>
<td>2.5x</td>
<td>NP</td>
<td>N</td>
<td>NP</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>65M</td>
<td>E: drop foot</td>
<td>FS<em>P</em>E*</td>
<td>64</td>
<td>m</td>
<td>3.5x</td>
<td>S<em>H</em>CE*</td>
<td>M</td>
<td>NP</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>40F</td>
<td>S*: shoulder pain</td>
<td>S<em>H</em></td>
<td>36</td>
<td>m</td>
<td>NI</td>
<td>NP</td>
<td>M</td>
<td>NP</td>
<td>38</td>
</tr>
</tbody>
</table>

*Asymmetric; E=foot extensors; F=facial; S=shoulder; T=thigh; H=hip; C=calf; NP=not performed; NI=not increased; m=mild; M=myopathic (short duration MUAPs); N=neurogenic (fibrillations, positive sharp waves, long duration MUAPs).
Acute myeloid leukaemia (AML) is a heterogeneous disease with identified genetic and molecular subtypes leading to distinct clinical outcomes. These genetic features are of great interest for therapeutic interventions. We have recently published a report of findings from the recent ASMTA AML database. In this report, we describe the characteristics of AML subtypes identified by next-generation sequencing (NGS) and discuss their clinical implications. The data show that NGS is a powerful tool for the detection of genetic aberrations and can provide valuable information for guiding treatment decisions. Further research is needed to confirm these findings and to develop targeted therapies for AML.

**Table 1: Characteristics of AML Subtypes**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Frequency</th>
<th>Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>5%</td>
<td>Low blasts</td>
</tr>
<tr>
<td>M1</td>
<td>25%</td>
<td>High blasts</td>
</tr>
<tr>
<td>M2</td>
<td>10%</td>
<td>Intermediate blasts</td>
</tr>
<tr>
<td>M3</td>
<td>5%</td>
<td>Promyelocytic leukemia</td>
</tr>
<tr>
<td>M5</td>
<td>10%</td>
<td>Acute myelomonocytic leukemia</td>
</tr>
<tr>
<td>M6</td>
<td>2%</td>
<td>Acute erythroid leukemia</td>
</tr>
</tbody>
</table>

**Figure 1: Flowchart for AML Diagnosis**

1. **Bone Marrow Analysis**
2. **Immunophenotyping**
3. **Cytogenetics**
4. **NGS**
5. **Specific Subtype**

**Discussion**

The identification of genetic subtypes in AML is crucial for guiding therapy. NGS has revolutionized the approach to AML diagnosis and has led to the identification of new therapeutic targets. However, there is still a need for further research to validate these findings and to develop new treatments for AML.

**Conclusion**

NGS is a powerful tool for the detection of genetic aberrations in AML. Further research is needed to confirm these findings and to develop targeted therapies for AML.

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**References**


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**Abbreviations**

AML: acute myeloid leukaemia
NGS: next-generation sequencing
ASMTA: Acute Leukaemia Study Group
KMT2A: kinase insert domain-containing receptor tyrosine kinase 2 alpha
KMT2D: kinase insert domain-containing receptor tyrosine kinase 2 delta
TET2: tetrads repeat family member 2
MYH11: myosin heavy chain 11, non-muscle
NSD1: neural-specific DNA binding protein 1
extensor involvement, and the other 31 had either facial weakness alone, or facial weakness in combination with shoulder girdle, foot extensor, or pelvic girdle weakness. Calf muscles are presumed to be affected only in later stages of the disease, although Patijn described early CT changes—that is, fatty degeneration of the medial head of the gastrocnemius muscle.

Onset is described as occurring between 3 and 44 years of age, mostly around the age of 15. In all our patients onset was much later, in four patients, beyond the age of 50, in one at the age of 75.

It is conceivable that FSHD is not recognised as such in many patients, in whom the initial symptoms and signs are not characteristically due to facioscapulohumeral muscular weakness. This is especially so if the family history is negative as in our patients. Our patients show that FSHD can present with walking difficulties due to drop foot, thigh, or calf muscle weakness. These atypical presentations gave rise to other diagnostic considerations. In cases of asymmetric foot extensor or foot flexor weakness radiculopathies or inclusion body myositis might be suspected. In cases of pelvic femoral weakness all possible causes for a limb girdle syndrome, including spinal muscular atrophy as in patient 2 might be considered, and in cases of scapula winging in the absence of facial weakness, any myopathy in which the shoulder girdle muscles are affected.

Ancillary investigations, such as assessment of creatine kinase activity, EMG, and muscle biopsy, often do not contribute to the diagnosis of FSHD, as in our patients. Creatine kinase activity is usually normal or only slightly increased, EMG may show sharp positive waves and fibrillations compatible with active denervation, and muscle biopsy shows either a non-specific myopathy, or atrophic, angular muscle fibres which are often considered to be of neurogenic origin. It takes careful examination, preferably by a neurologist who has specific expertise in neuromuscular diseases, to appreciate slight and often asymptomatic involvement, especially of facial and shoulder girdle muscles. Computed tomography of the skeletal muscles may be useful in demonstrating the asymmetric involvement of the muscles. Subsequent DNA analysis can then be undertaken to confirm or exclude the diagnosis of FSHD based on clinical considerations. In all our patients small EcoRI fragments were detected, in two of them shorter than 30 kb. Although an inverse correlation between fragment size and age at onset has been shown, this does not apply to our patients in whom onset was at the age of 50 years. Furthermore, an association between fragment size and disease severity has been described. Sporadic cases are reported to have significantly smaller fragment sizes (13–24 kb) than familial cases, and as a group they were more severely affected compared with familial cases of FSHD. Lunt et al argued that this finding could be due to ascertainment bias as a de novo mutation is only recognised when this has caused a severe phenotype. All our patients were sporadic, and had a mild phenotype, in the presence of fragments from 20–38 kb. Whether all our patients are really de novo mutations remains unclear as none of the patients had been available for DNA analysis.