Atypical Phenotypes in Patients With Facioscapulohumeral Muscular Dystrophy 4q35 Deletion

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Background: Facioscapulohumeral muscular dystrophy (FSHD) is associated with a deletion on chromosome 4q35. Recent studies have shown that this deletion is found in patients with other phenotypes in addition to those with the classic Landouzy-Dejerine FSHD phenotype.

Objective: To examine patients with atypical phenotypes and an FSHD deletion on chromosome 4q35.

Design: Clinical characterization and genotype-phenotype correlation.

Setting: University hospital.

Patients: Forty-one symptomatic subjects with deletions on chromosome 4q35.

Results: We found 6 patients with atypical FSHD. Three (from a single family with FSHD) had additional symptoms of chronic progressive external ophthalmoplegia (4q35 EcoRI/BlnI fragment size, 20 kilobase [kb]), and 3 patients (1 with sporadic disease and 2 from a single family) had facial-sparing scapulohumeral dystrophy (4q35 EcoRI/BlnI fragment size, 30 and 34 kb, respectively).

Conclusions: The clinical presentations in patients with FSHD-associated short fragments on chromosome 4q35 are not restricted to the classic FSHD form, but constitute a variety of clinical manifestations. There seems to be no clear correlation between the atypical subtype and the DNA fragment size due to the deletion.

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Facioscapulohumeral muscular dystrophy (FSHD) is one of the most common forms of familial muscular dystrophy, with an estimated incidence of 1:20000.¹ The classic description of Landouzy and Dejerine² from 1884 still constitutes the fundamental FSHD clinical diagnostic criteria.³

The onset of symptoms in FSHD varies from infancy to middle age. The degree of involvement ranges from minimal facial weakness to severe generalized palsies. Facioscapulohumeral muscular dystrophy initially affects the facial and scapular muscles and upper-arm and foot dorsiflexion, and later affects the proximal hip muscles. The course usually progresses slowly; approximately 20% of patients eventually become wheelchair dependent.¹

Facioscapulohumeral muscular dystrophy is an autosomal dominant inherited disorder and is linked in 95% of cases to chromosome 4q35. A deletion of multiple copies of a tandem repeat consisting of 3.3-kilobase (kb) units (D4Z4) is associated with the disease. Restriction enzyme cleavage with EcoRI alone and EcoRI/BlnI allows the distinction of the 4q35 locus from a homologous locus on chromosome 10q26 in most individuals. The EcoRI/BlnI fragments in the range of 10 to 35 kb on chromosome 4q35 are assumed to be disease associated and can be detected by probe p13E-11 with a test sensitivity of 95% and a specificity approaching 100% at the 34-kb level.⁴ Sporadic cases can occur and are presumably the result of new mutations.⁵

Recent studies have shown that the 4q35 deletion is found in patients with the classic form of FSHD and in patients with phenotypes such as the facial-sparing form of FSHD (SHD),⁶ limb-girdle muscular dystrophy,⁷ distal myopathy,⁸ or asymmetric brachial weakness.⁹ The present study describes 6 patients from 3 unrelated families with atypical FSHD and partially undescribed phenotypes.

Methods

The 6 patients described in this report were selected from 41 consecutive symptomatic patients in whom the FSHD deletion could be demonstrated. We extracted DNA from the...
peripheral blood leukocytes by means of standard procedures. For detection of 4q35 deletions, DNA was cleaved with EcoRI and EcoRI/BlnI and electrophoretically separated on 0.7% agarose gels in 1/1003 TAE (Tris–acetic acid–EDTA) buffer for 40 hours at 1.2 V/cm. DNA cut with HindIII or XhoI and marker 19 (MBI Fermentas GmbH, St Leon–Roth, Germany) were used as size markers. The DNA was transferred to membranes (Hybond N+; Amersham Biosciences, Freiburg, Germany) and hybridized with radioactively labeled probe p13E-11 (D4F104S1). Bands were then visualized by means of autoradiography. To rule out a deletion on chromosome 4q35, the BglII/BlnI dosage test was performed as described previously.9

The clinical symptoms of all 41 patients were analyzed and classified as typical or atypical on the basis of the FSHD diagnostic criteria of the European Neuromuscular Centre.3

RESULTS

Of 41 patients with FSHD with typical deletions, we identified 6 (2 from 1 family, 3 from 1 family, and 1 sporadic case) with atypical (no Landouzy-Dejerine phenotype) clinical features (Table). These atypical phenotypes could be classified into subgroups.

FSHD WITH CHRONIC PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA

Three patients from a single family (F1) showed the typical FSHD phenotype associated with additional chronic progressive external ophthalmoplegia (CPEO).

Patient F1-1

A 50-year-old man was referred for bilateral arm and shoulder girdle weakness since 25 years of age and slowly progressive ptosis without double vision throughout his lifetime. The family history was remarkable for leg weakness in his grandfather. His parents and grandparents were dead, and his only relatives were 2 children. In both children, ptosis and impaired ocular movements were observed (patients F1-2 and F1-3). The neurological examination revealed facial weakness, bilateral ptosis, oculomotor impairment (restricted upward gaze with the right eyeball, deviation to nasal, and minimal restricted right eyelid abduction), symmetric-predominant proximal arm and shoulder girdle paresis and atrophy, bilateral scapular winging, lumbar hyperlordosis, prominent foot drop, and moderate hip flexor paresis (Figure 1). The serum creatine kinase (CK) level was elevated (320 U/L; reference range, <80 U/L). Cranial magnetic resonance imaging findings were normal. Serum lactate level was within the reference range at rest and upon bicycle exercise. Electromyography findings showed reduced amplitude and duration of motor unit action potentials (MUAPs). Results of a muscle biopsy demonstrated prominent myopathic changes without ragged red fibers and histopathological features of other neuromuscular diseases. There were no singular or multiple deletions of mitochondrial DNA. The EcoRI restriction fragment of 23 kb was reduced to 20 kb by additional cleavage with BlnI. The BglII/BlnI dosage

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**Clinical Presentations in 6 Patients With Non–Landouzy-Dejerine Phenotype**

<table>
<thead>
<tr>
<th>Subtype, Patient No.</th>
<th>Sex/Age, y</th>
<th>EcoRI/BlnI Fragment Length, kb</th>
<th>Typical Presentations</th>
<th>Atypical Presentations</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSHD with CPEO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-1</td>
<td>M/50</td>
<td>20</td>
<td>FSHD</td>
<td>CPEO</td>
</tr>
<tr>
<td>F1-2</td>
<td>M/15</td>
<td>20</td>
<td>Winged scapula; lumbar hyperlordosis</td>
<td>CPEO</td>
</tr>
<tr>
<td>F1-3</td>
<td>F/15</td>
<td>20</td>
<td>Winged scapula; lumbar hyperlordosis</td>
<td>CPEO</td>
</tr>
<tr>
<td>SHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F2-1</td>
<td>F/61</td>
<td>34</td>
<td>SHD</td>
<td>No facies myopathica</td>
</tr>
<tr>
<td>F2-2</td>
<td>F/60</td>
<td>34</td>
<td>SHD</td>
<td>No facies myopathica; severe myalgia</td>
</tr>
<tr>
<td>S1</td>
<td>M/29</td>
<td>30</td>
<td>SHD</td>
<td>No facies myopathica; severe myalgia</td>
</tr>
</tbody>
</table>

Abbreviations: CPEO, chronic progressive external ophthalmoplegia; F1, family 1; F2, family 2; FSHD, facioscapulohumeral muscular dystrophy; kb, kilobase; S1, sporadic case; SHD, facial-sparing scapulohumeral dystrophy.

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**Figure 1.** Photograph of patients 1 and 2 from family 1 shows bilateral scapular winging.
test revealed 2 chromosome 4q35–type and 2 chromosome 10q26-type fragments.

**Patient F1-2**

The 15-year-old boy was delivered by cesarean section. Since infancy, he had noticed progressive bilateral ptosis. Motor development was delayed (reduced crawling, walking at 18 months of age). At 7 years of age, the patient underwent surgical correction of prominent strabismus. The neurological examination revealed bilateral ptosis, divergent strabismus, asymmetrically restricted eye movements with up gaze worse in the right than the left eye and down gaze worse in the left than in the right eye, slightly limited horizontal movement of both eyes, no facial weakness, minimal bilateral scapular winging, and lumbar hyperlordosis (Figure 1 and Figure 2). The serum CK level was within the reference range. Electromyography findings showed reduced amplitude and duration of MUAPs. Results of bicycle exercise testing were normal. A muscle biopsy specimen demonstrated minimal myopathic changes without ragged red fibers. Molecular analysis revealed an *EcoRI/BlnI* restriction fragment, as could be seen in his father.

**Patient F1-3**

The 15-year-old girl was delivered by cesarean section. Since infancy, she had noticed progressive bilateral ptosis. Her motor development was delayed (very reduced crawling, walking at 18 months of age). At 7 years of age, she underwent surgical correction of a prominent strabismus. At 2 and 7 years of age, ptosis was corrected. The neurological examination revealed bilateral ptosis, divergent strabismus, downward and horizontal bilaterally restricted eye movements, left eye deviation without conjugation, no facial weakness, minimal bilateral scapular winging, and lumbar hyperlordosis. The serum CK level was within the reference range. Electromyography findings showed reduced amplitude and duration of MUAPs. Results of molecular analysis revealed an *EcoRI/BlnI* restriction fragment, as could be seen in her father.

**FACIAL-SPARING FORM**

Three patients (2 from family 2 [F2]) had SHD with otherwise typical FSHD features. One patient had only scapulohumeral dystrophy, whereas 2 had SHD and additional prominent myalgia.

**Patient F2-1**

This 61-year-old woman was referred for symptoms of progressive limb muscle weakness. At 40 years of age, she first noticed difficulties in climbing stairs and slowly progressive leg weakness. Her mother exhibited different thickness of the legs, and her sister had muscle pain. The mother of the patient was dead, and no other relatives were available. She had no facial weakness, but atrophy of the dorsal trunk muscles and bilateral infraspinatus and supraspinatus muscles, slight muscular atrophy of the right extremities, scapular winging that was worse on the right than on the left, bilateral paresis of arm retroversion, foot drop, minimal proximal leg and pelvic girdle weakness, striking Gothic palate, thoracic scoliosis, and lumbar hyperlordosis were seen. The serum CK level was elevated (360 U/L). Results of a muscle biopsy demonstrated moderate myopathic changes. The molecular genetic test revealed an *EcoRI/BlnI* restriction fragment of 34 kb. The *BglII/BlnI* dosage test revealed 2 chromosome 4q35– and 2 chromosome 10q26-type copies.

**Patient F2-2**

The 60-year-old sister of patient F2-1 was referred for chronic muscle pain. Throughout her life, the patient had noticed bilateral, nearly permanent pains in the shoulder girdle and upper arm muscles without joint problems. The pain was described as a continuous ache without exacerbation on exercise; however, spontaneous irregular worsening was described as sharp and stabbing pain. Results of the rheumatological and orthopedic investigations, including labor tests and radiography of shoulder and elbow joints, were normal. The neurological examination revealed no facial weakness, but revealed moderate calf atrophy that was worse on the right than on the left, minimal hip flexor paresis, thoracic hyperkyphosis, and scoliosis. Tendon reflexes were normal. Results of the sensory examination were unremarkable. The serum CK level was elevated (390 U/L). Electromyography findings showed reduced amplitude and duration of MUAPs. A muscle biopsy was not performed. An *EcoRI/BlnI* fragment of 34 kb could be seen in this patient, as in patient F2-1.

**Sporadic Case**

A 29-year-old man was referred for chronic generalized muscle pain since 19 years of age. Pain was described as a continuous diffuse aching in all muscle groups, including trunk musculature, with no worsening on exercises. The patient had no joint problems. Rheumatological investigation, including labor tests and spine radiography, revealed no rheumatological disease. There was no

![Figure 2. Photograph of patient 2 from family 1 shows bilateral ptosis and ocular movement disorders.](image-url)
family history of neuromuscular disease and no local muscle weakness. The neurological examination re-
vealed a well-muscled man with no facial weakness, mini-
mal scapular winging that was worse on the right than
on the left, minimal right pectoralis major atrophy, and
a distinct right quadriceps femoris atrophy. Tendon re-
flexes and results of sensory examinations were normal.
The serum CK level was elevated (387 U/L). Electromy-
graphy findings showed reduced amplitude and dura-
tion of MUAPs. Results of a muscle biopsy demon-
strated moderate myopathic changes. Molecular genetic
examination demonstrated a 30-kb EcoRI/Blnl frag-
ment. The BglII/Blnl dosage test revealed 3 chromo-
some 4q35–type and 1 chromosome 10q26–type frag-
ments.

Our study findings are consistent with those of recent
publications,5,6 which show that not all patients with the
FSHD 4q35 deletion present with the classic FSHD phe-
notype described by Landouzy and Dejerine.2 Six (15%)
of our 41 patients or 3 (11%) of 28 unrelated families
with FSHD-typical genetic defects on chromosome 4q35
did not fulfill the clinical criteria of the European Neu-
romuscular Centre for Landouzy-Dejerine FSHD.3 How-
ever, the underlying gene defect for FSHD has not been
identified. Molecular genetic studies test only for an as-
sociation of a deletion of copies of tandem repeats on chro-
mosome 4q35 with the disease. The test is highly spe-
cific, but false-positive or false-negative results cannot
be excluded. In contrast to previous studies about atypi-
cal FSHD,5–8,10 we performed the BglII/Blnl dosage test,
which helps identify translocations between 4q35 and
10q26.9 The BglII/Blnl dosage test revealed 2 chromo-
some 4q35–type and 2 chromosome 10q26–type copies
in our 2 families. These data support an origin of the 20-kb
(F1) and the 34-kb EcoRI/Blnl fragments (F2) from 4q35
in these families. In our sporadic case, this test revealed
3 chromosome 4q35–type fragments, but only 1 chro-
mosome 10q26–type fragment. That means that 1 chro-
mosome 4q35–type fragment is localized on chromo-
some 10, and this fragment could be the short (30-kb)
EcoRI/Blnl fragment. However, a concrete statement can-
not be made in these patients.

The SHD (in both F2 patients and the patient with
sporadic disease) in genetically typical FSHD was already
described by Jardine et al10 and seems to be the most com-
mon atypical presentation of FSHD.7 The term facial-
sparing SHD should only be used for sporadic cases
and cases in families without facial muscle weakness in all fam-
ily members, as it could be shown in our F2 patients and
in our patient with sporadic disease.7,10 It is well known
that in some families with typical FSHD, a proportion of
clinically affected members may not have facial weak-
ness.11 According to the FSHD diagnostic criteria of the
European Neuromuscular Centre, our patients did not have
typical FSHD because facial weakness should be present
in more than 50% of the affected family members.7 Our
patient F2-2 with SHD and the patient with sporadic dis-
ease reported severe diffuse muscle pain as the most promi-
cent disabling symptom of their condition. Subjectively,
these patients had noticed no muscle weakness at all. In
contrast, patient F2-1 remembered no muscle pain, whereas
this was the only symptom of his sister (patient F2-2). Al-
though moderate shoulder girdle pain is not rare in pa-
ients with FSHD, clinical studies of typical FSHD rarely
report muscle pain as a significant feature or as the most
disabling aspect of the condition.12

All 3 F1 patients initially presented with progres-
sive ptosis and ocular movement disorder. Years later,
the classic FSHD distribution of muscle weakness devel-
oped in patient F1-1 (the father of patients F1-2 and F1-
3), in addition to the ocular symptoms. Other possible
neuromuscular disorders with extraocular muscle in-
volvement reviewed by Jones and North13 were clini-
cally, electrophysiologically, and histopathologically ex-
cluded. In particular the paternal inheritance, the absence
of ragged red fibers and other histopathological changes
in a muscle biopsy specimen, a normal result of bicycle
eexercise testing, and the absence of single or multiple de-
letions of mitochondrial DNA excluded the diagnosis of
a coincidental CPEO of mitochondrial origin. However,
the possibility of another coincidental cause of CPEO can-
not entirely be excluded. The classic FSHD distribution
of the muscle weakness in our patients, particularly promi-
nent scapular winging, and lumbar hyperlordosis were
never observed in patients with CPEO.14 A recent study
has shown that FSHD occurs only if the deletion is as-
sociated with 1 of 2 polymorphisms distal to the D4Z4
repeats.15 It is, however, unlikely that the nonpatho-
genic polymorphism is relevant in family 1 because pa-
tient F1-1 had all of the classic clinical features of the
Landouzy-Dejerine FSHD in addition to the ocular symp-
toms. In addition, both children already had minimal
scapular winging and lumbar hyperlordosis, whereas more
prominent FSHD symptoms developed in the father only
at 25 to 30 years of age.

It is conceivable that the diagnosis of FSHD is of-
ten missed in those patients who do not initially exhibit
the typical leading symptoms of the facioscapulo-
humeral muscular weakness. In none of our patients,
except patient F2-1, was FSHD primarily suspected, be-
cause clinical presentations in all these cases were
extremely different from the FSHD diagnostic criteria.3
Consistent with a previous study,7 there seems to be no
clear correlation between the atypical subtype and the
fragment size due to the deletion.

On the basis of our experience (Table) and those of
previous studies,6,8,10 the following atypical variants of
clinical presentations (atypical phenotypes) can be dis-
tinguished in patients with the FSHD genotype:

1. SHD or facial-sparing SHD with or without my-
algia (Felice et al,6 Felice and Moore,7 Jardine et al,10
and the present study)
2. FSHD with CPEO symptoms (present study)
3. Limb-girdle muscular dystrophy syndrome7
4. Distal myopathy7,8
5. Asymmetric brachial weakness.7

Because of the extreme variety of clinical pheno-
types in patients with an FSHD genotype, an atypical form
of FSHD should be considered in patients with obscure
and unclassified myopathies.
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