Research Article

Determination of Contraction of D4Z4 Repeats on Chromosome 4q35 in Iranian Facioscapulohumeral Muscular Dystrophy Patients

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Abstract

Facioscapulohumeral Muscular Dystrophy (FSHD)is characterized by weakness of the facial, scapular muscles and the dorsiflexors of the foot. Severity in this disorder is highly variable. Approximately 95% of individuals with FSHD phenotype have type 1 FSHD, with D4Z4 allele of between one and ten repeat units and about 5% have type 2 FSHD with mutations in the chromatin modifier SMCHD1gene which causes the chromatin relaxation at D4Z4. We studied 49 Iranian patients with clinical findings of FSHD, and detected contraction of the D4Z4 repeats located at 4q35 in 40, confirming FSHD type I in 40.

Key words: Facioscapulohumeral Muscular Dystrophy; FSHD; D4Z4

Introduction

Facioscapulohumeral muscular dystrophy (FSHD) also called Landouzy-Dejerine disease is an autosomal dominant inherited form of muscular dystrophy that initially affects the skeletal muscular of the face (facio), Scapula (Scapulo) and upper arms (humeral) (1).

FSHD is the third most common muscular dystrophy after Duchenne muscular dystrophy (OMIM: 310200) and myotonic dystrophy (OMIM: 160900) and is associated with a typical pattern of muscle weakness. It has two types, type one (OMIM: 158900) is found in more than 95% of individuals which have depleted repeat between one to ten in D4Z4 allele and FSHD type 2 (OMIM: 158901), with mutation in SMCHD1 (2). FSHD type 1is caused by inappropriate expression of the double homeobox-containing gene DUX4 in muscle cells, which results in contraction of the critical numbers of D4Z4 repeat in a macrosatellite repeat array on chromosome 4q35. The contraction causes loss of DNA methylation and heterochromatin markers in the 4q35 D4Z4 region, leading to relaxation of the chromatin structure and release of DUX4 repression (3). Majority of patients with FSHD have a large deletion in the polymorphic D4Z4 with 1-10 repeats, whereas normal individuals have 11-150 repeats (2). About 20% of the general population possess both chromosome 4q35-type D4Z4 repeat array on chromosome 10 and a D4Z4 array that consists of 4q35- and 10q26-type sequence repeats on chromosome 4q35. Translocated arrays on chromosome 10q are non-permissive to FSHD, whereas the contractions on the hybrid arrays on chromosome 4q35 leads to FSHD (4).

Orphan.net lists the prevalence of FSHD as 4/100.000 (5). FSHD shows the earliest and most severe weakness in facial and shoulder girdle muscles. The facial weakness is characterized by inability to close the eyes completely during sleep, extra-ocular muscle weakness, inability to bury eyelashes and sometimes inability to whistle.

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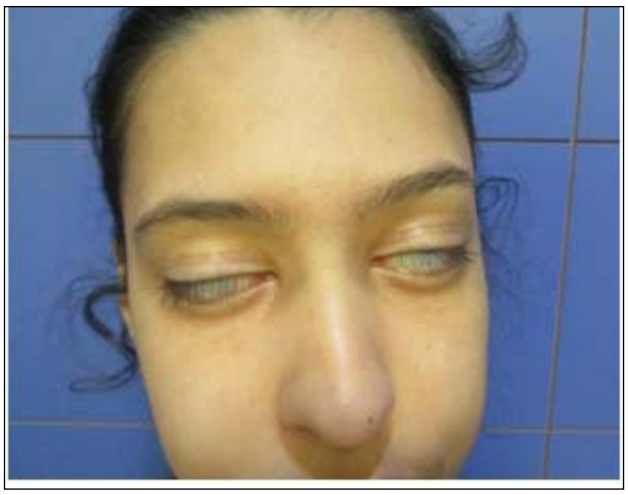

Figure 1: Inability to close eyes completely and bury eyelashes

Scapular winging is prominent, even in infants. Flattening or even concavity of the deltoid contour is seen, and the biceps and triceps brachii muscles are wasted and weak. Muscles of the hip girdle and thighs also eventually lose strength and undergo atrophy, and Gowers sign and a Trendelenburg gait appear. Contractions are rare. Finger and wrist weakness occasionally are the first symptoms. Weakness of the anterior tibial and peroneal muscles may lead to foot drop; this complication usually occurs only in advanced cases with severe weakness. Lumbar lordosis and kyphoscoliosis are common complications of axial muscle involvement.

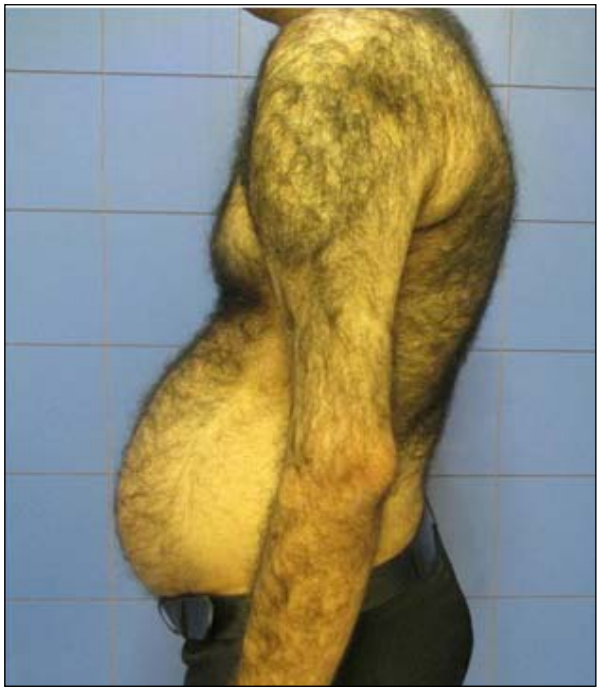

Figure 2: Note hyperlordosis

Calf pseudohypertrophy is not a feature. Clinical manifestations may be expressed in teenage and middle adult age. Unlike most other muscular dystrophies asymmetry of weakness is common (6). Life expectancy can be threatened by respiratory insufficiency and about 1% of them require ventilatory support (7). Nearly 20% of affected patients become severely disabled, needing special strollers and also wheel chair (7).

FSHD type 2 (OMIM: 158901) is clinically indistinguishable from FSHD type1, but it is not associated with contraction of the D4Z4 microsatellite repeat.

Mutation in SMCHD1 on chromosome 18 reduce SMCHD1 protein levels and causes FSHD2. FSHD type 2 is inherited in a digenic manner (8). Serum levels of CK and other enzymes vary greatly, ranging from normal or near normal to elevation of several thousands (6). EMG reveals nonspecific myopathic muscle potentials (6). Molecular testing for both types is diagnostic (6).

Material & Methods

According to the medical ethics, informed consents were obtained from all patients who had been referred to Kariminejad-Najmabadi Pathology & Genetics Center with FSHD clinical diagnosis. Clinical examination and assessment of the families' pedigree were conducted for all 49 affected individuals (Table 1).

Thirty four (70%) of our patients were male versus fifteen (30%) female. The age range was 12y to 72y. Age of onset was 8y the lowest and surprisingly 68y, the highest. Eight of patients 16% did not have facial weakness but two of them had positive FSHD test.

Nearly all of our patients had shoulder girdle weakness. An 18-year-old girl without shoulder weakness which is about 2% of all, had a positive test. Seven out of forty nine patients, approximately 14% did not have pelvic girdle weakness and also eight (16%) of patients did not show any sign of lordosis. Four of the patients (8%) did not have scapular winging and twenty four (49%) had asymmetric clinical findings.

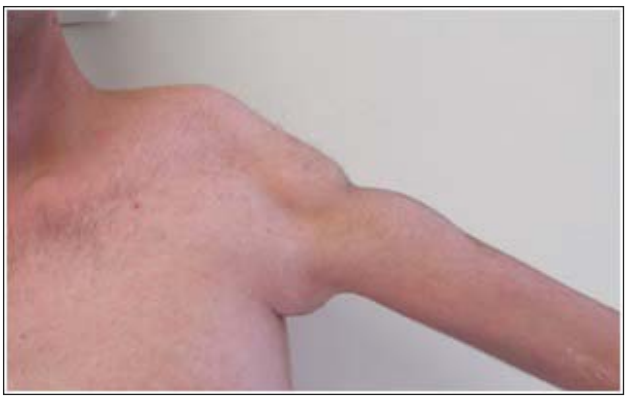

Figure 3: Terracing of shoulders on abduction, shoulder girdle muscle atrophy

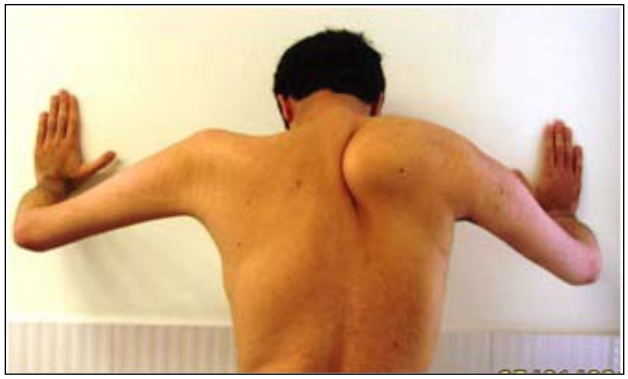

Figure 4: Asymmetrical scapular winging

According to laboratory test, sixteen patients (32%) had a high CK level and the rest had normal or near normal CK level. Thirty one of the patients had EMG results which showed typical myopathic pattern and the rest did not have their EMG results. Three of our patients had additional findings of sensory neural hearing loss which is about 6%. Twenty three of patients approximately 46% had a positive family history. DNA extraction was performed from the whole blood and sent for molecular diagnosis. Nine of our patients did not show contraction in D4Z4 but 40 patients' molecular tests, confirmed the diagnosis of FSHD type1.

Discussion

FSHD findings usually present in the in the teenage years, but age of onset could be variable, however more than 90% of affected patients show their symptoms by the age of 20 years.

Saylietal.et al (1984) (9) found at least 53 affected persons in a Turkish Kindred originating in the village of Cullar. Initial signs and symptoms seemed to appear early in infancy in 19 patients, while our patients did not develop any symptoms before the age of 8 years. Although, their patients reported symptoms since infancy but the mean age of them was 23.3 years versus our patients which is 17.7 years .

About 60% of patients with FSHD have an abnormal audiogram with high-tone sensorineural hearing loss and subclinical sensorineural hearing loss occurs approximately in 75% of affected ones (10,13).

The studies of Brouwer et al (1991) suggest that a change of hearing function is part of the disease and may lead to severe hearing loss in some patients (10). Abnormal audiogram with high-tone sensorineural hearing loss can be found in approximately 60% of patients while only 6.6% of our patients suffered from mild hearing loss (10,13). It could be that more of our patients have subclinical hearing loss but have not been clinically evaluated. Calf hypertrophy was absent in all patients, but has been reported by Reardon et al (1991) (11). Shield et al (2007) (12) noted that retinal telangiectasia can be an extra muscular manifestation of FSHD, but the most affected telangiectasia found at ocular screening after diagnosis of FSHD. We are planning to refer our patients to ophthalmologist for retinal examination after writing of this article.

Five percent of patients might have a predilection for atrial tachyarrhythmia, even though symptoms are rarely experienced(14-16); None of our patients suffered from atrial tachyarrhythmia.

In conclusion, in this study, we studied 49 patients with clinical manifestation of FSHD. Molecular analysis was performed for the diagnosis of this disorder which confirmed FSHD type 1 in 40 of patients by showing contraction in D4Z4, 9 of our patients did not show the contracture which need to send for SMCHD1 mutation in future.

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Table 1: Clinical features of patients with FSHD presentation

Gender	Age	Age of onset	Facial weakness	Shoulder girdle weakness	Pelvic girdle weakness	Lordosis	Scapular winging	Asymmetry	EMG	CPK	Family history	SNHL	Molecular test
F	58y	21y	+	+	+	+	+	-	N/A	Normal	-	-	+
M	24y	16y	+	+	+	+	+	+	Myopathic	Increased	-	-	+
M	33y	13y	+	-	+	+	-	-	N/A	Normal	-	-	+
M	35y	26y	+	+	+	+	-	-	N/A	Normal	-	-	+
M	34y	8y	+	+	+	+	+	-	Myopathic	Increased	-	+	+
M	29y	8y	+	+	-	-	+	-	N/A	Normal	+	-	+
F	12y	8y	+	+	+	+	+	+	N/A	Normal	+	+	+
M	21y	12y	+	+	+	+	+	-	N/A	Normal	-	-	+
M	17y	13y	+	+	-	-	+	-	N/A	Normal	-	-	+
F	11y	7y	+	+	+	+	+	-	N/A	Normal	+	-	+
F	33y	21y	+	+	+	+	+	-	N/A	Normal	+	-	+
M	38y	23y	+	+	+	+	+	-	N/A	Normal	+	-	+
F	32y	14y	+	+	+	+	+	-	N/A	Normal	+	-	+
M	16y	11y	+	+	+	+	+	-	Myopathic	Normal	-	-	+
M	30y	20y	+	+	+	+	+	-	Myopathic	Increased	+	-	+
F	25y	19y	+	+	+	+	+	-	Myopathic	Increased	+	-	+
M	27y	12y	+	+	+	+	+	-	Myopathic	Increased	+	-	+
M	23y	7y	+	+	+	+	+	-	N/A	Normal	+	-	+
F	34y	10y	+	+	+	+	+	-	N/A	Normal	+	-	+
M	30y	28y	+	+	+	+	-	-	Myopathic	Normal	-	-	+
F	11y	5y	+	+	+	+	+	+	Myopathic	Normal	+	-	+
M	40y	27y	+	+	+	+	+	+	Myopathic	Normal	+	-	+
M	37y	18y	+	+	+	+	+	+	Myopathic	Normal	-	-	+
M	26y	14y	+	+	+	+	+	+	N/A	Normal	-	-	+
M	40y	32y	-	+	+	+	+	+	Myopathic	Normal	-	-	-
M	35y	20y	+	+	+	+	+	+	N/A	Normal	+	-	+
F	30y	22y	+	+	+	+	+	+	Myopathic	Normal	-	-	+
M	15y	13y	+	+	-	-	-	-	Myopathic	Normal	-	-	-
F	54y	52y	+	+	+	+	+	-	Myopathic	Normal	-	-	-
F	72y	58y	+	+	+	+	+	+	Myopathic	Normal	-	-	+
M	24y	14y	+	+	-	-	+	+	Myopathic	Increased	-	-	+
M	44y	18y	-	+	-	-	+	+	N/A	Normal	-	-	+
M	54y	15y	+	+	+	+	+	+	Myopathic	Normal	-	+	-
F	38y	16y	+	+	+	+	+	+	Myopathic	Normal	+	-	+
M	25y	10y	+	+	+	+	+	+	Myopathic	Normal	+	-	+
M	20y	19y	+	+	+	+	+	+	N/A	Normal	+	-	+
M	26y	21y	+	+	-	-	+	+	Myopathic	Normal	-	-	+
M	51y	10y	+	+	+	+	+	+	N/A	Normal	+	-	+
M	34y	18y	-	+	-	-	+	+	Myopathic	Increased	+	-	+
F	24y	10y	-	+	+	+	+	+	Myopathic	Increased	+	-	-
M	56y	30y	-	+	+	+	+	-	Myopathic	Increased	-	-	-
M	40y	10y	+	+	+	+	+	+	Myopathic	Increased	-	-	+
M	25y	18y	-	+	+	+	+	+	Myopathic	Increased	+	-	-
M	36y	12y	-	+	+	+	+	-	Myopathic	Increased	-	-	-
F	21y	13y	-	+	+	+	+	+	Myopathic	Increased	-	-	-
M	25y	17y	+	+	+	+	+	+	Myopathic	Normal	+	-	+
F	21y	19y	+	+	+	+	+	+	Myopathic	Normal	+	-	+
M	28y	27y	+	+	-	-	+	+	Myopathic	Increased	+	-	+
M	33y	17y	+	+	+	+	+	+	Myopathic	Increased	+	-	+

CPK, creatinine phosphokinase; EMG, electromyography; F,female; M,male; N/A,not available; SNHL, sensorineural hearing loss; y, years

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