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De Novo Facioscapulohumeral Muscular Dystrophy: Frequent Somatic Mosaicism, Sex-Dependent Phenotype, and the Role of Mitotic Transchromosomal Repeat Interaction between Chromosomes 4 and 10

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Summary

Autosomal dominant facioscapulohumeral muscular dystrophy (FSHD) is caused by deletion of most copies of the 3.3-kb subtelomeric D4Z4 repeat array on chromosome 4q. The molecular mechanisms behind the deletion and the high proportion of new mutations have remained elusive. We surveyed 35 de novo FSHD families and found somatic mosaicism in 40% of cases, in either the patient or an asymptomatic parent. Mosaic males were typically affected; mosaic females were more often the unaffected parent of a nonmosaic de novo patient. A genotypic-severity score, composed of the residual repeat size and the degree of somatic mosaicism, yields a consistent relationship with severity and age at onset of disease. Mosaic females had a higher proportion of somatic mosaicism than did mosaic males. The repeat deletion is significantly enhanced by supernumerary homologous repeat arrays. In 10% of normal chromosomes, 4-type repeat arrays are present on chromosome 10. In mosaic individuals, 4-type repeats on chromosome 10 are almost five times more frequent. The reverse configuration, also 10% in normal chromosomes, was not found, indicating that mutations may arise from transchromosomal interaction, to which the increase in 4-type repeat clusters is a predisposing factor. The somatic mosaicism suggests a mainly mitotic origin; mitotic interchromosomal gene conversion or translocation between fully homologous 4-type repeat arrays may be a major mechanism for FSHD mutations.

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Introduction

Facioscapulohumeral muscular dystrophy (FSHD [MIM 158900]) is a neuromuscular disorder with an autosomal dominant pattern of inheritance. Clinically, the disease is characterized mainly by a progressive wasting of the facial, shoulder, and upper-arm muscles, and it displays substantial inter- and intrafamilial variation. FSHD has an incidence of 1/20,000 in the European population, and there is a relatively high proportion of new mutations (10%–30%) (Padberg 1982; Padberg et al. 1995; Zatz et al. 1995, 1998; Tawil et al. 1996; Lunt 1998).

All patients with a confirmed diagnosis and for whom detailed molecular studies have been performed carry a chromosomal rearrangement within the subtelomere of chromosome 4q (4q35). This subtelomere is composed mainly of a polymorphic repeat structure consisting of 3.3-kb repeated elements (D4Z4). The number of repeat units varies from 10 to >100 in the population, and, in FSHD patients, an allele of 1–10 residual units is observed because of the deletion of an integral number of these units (Wijmenga et al. 1992; van Deutekom et al. 1993).

A highly homologous polymorphic repeat array is located near the telomere of chromosome 10q (Bakker et al. 1995; Deidda et al. 1995), and a specific *Bln*I site within each chromosome 10–derived repeat unit allows discrimination between the arrays (Deidda et al. 1996). This *Bln*I site–dependent discrimination demonstrated the presence of 10-type repeats on chromosome 4 and, vice versa, 4-type repeats on chromosome 10, suggesting a dynamic exchange between these chromosomes. Of the 50 healthy control males studied, 5 : 100 chromosomes carried a 4-type repeat on chromosome 10, and 5 : 100 chromosomes carried a 10-type repeat on chromosome 4 (fig. 1) (van Deutekom et al. 1996). Hybrid repeat arrays consisting of clusters of both 4-type and 10-type repeat units are also found. Only short repeat arrays on chromosome 4 cause FSHD, irrespective of the type of

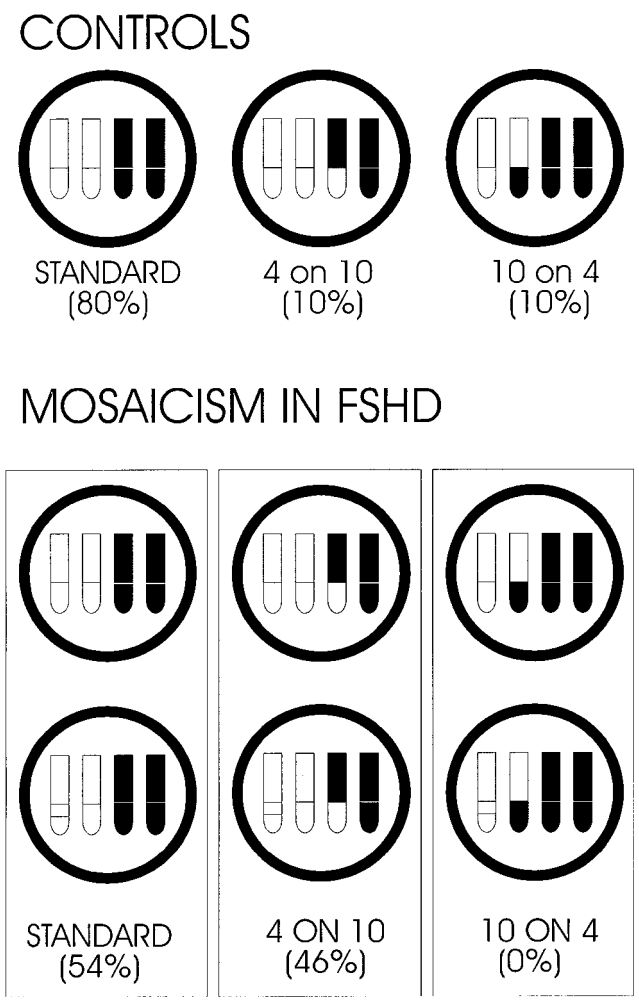

Figure 1 Subtelomeric repeat-array constitutions on chromosomes 4 and 10 in the Dutch control and FSHD population. Chromosomes 4 are shaded, whereas chromosomes 10 are blackened. *Top,* in the control population, 80% of the individuals carry a standard configuration, with 4-type repeats on chromosome 4 and 10-type repeats on chromosome 10. In 10%, a 4-type repeat is also present on one of the chromosomes 10 ("4 on 10"), and 10% carry a 10-type repeat on chromosome 4 ("10 on 4"). *Bottom,* the repeat-array constitutions of mosaic individuals from de novo FSHD families. The deletion is indicated by an open bar. These individuals carry two cell populations indicated within a box. In the original population, no FSHD-associated rearrangement is present, whereas, in the other population, a deletion has occurred on chromosome 4. In mosaic individuals, 54% carry a standard allele configuration, and 46% carry a "4 on 10" allele configuration.

repeat units. Small repeat arrays on chromosome 10 are nonpathogenic (Cacurri et al. 1998; Lemmers et al. 1998).

To understand the molecular basis of FSHD, the repeat array and adjacent regions have been scrutinized for expressed sequences (Hewitt et al. 1994; Lee et al. 1995). Also, the severity and age at onset of the disease have been correlated with the size of the residual repeat array on chromosome 4 (Lunt et al. 1995; Tawil et al. 1996). However, this has not yet clarified the genetic mechanisms underlying the deletion event, nor have the relatively high mutation frequency and the inter- and intrafamilial variation in clinical expression of the disease been explained. To elucidate the deletion process and the clinical variability of the disease, we have focused our attention on the repeat constitutions of de novo patients and their parents. The high degree of somatic mosaicism described here implies that the deletion is mainly mitotic. Furthermore, we find a distinct and as yet unexplained relationship between sex and affection status in mosaic carriers. Finally, we find that the numerical excess of 4-type repeats on chromosome 10 is a significant if not the major predisposing factor for the occurrence of the FSHD-type deletion.

Subjects and Methods

Patients and Controls

After informed consent, DNA isolated from peripheral blood lymphocytes (PBLs) of 35 sporadic FSHD patients and their parents were obtained via one of the Dutch Neuromuscular Centers. All patients had clinical diagnoses of FSHD. In all cases, diagnosis was confirmed by the presence of a short (<35 kb) D4Z4-repeat array. The repeat-array constitutions of 50 healthy control males has been described elsewhere (van Deutekom et al. 1996).

Clinical manifestations.—The age at onset of the various stages of FSHD was established in 12 mosaic individuals. Clinical severity scores were based on the age at onset of the initial clinical symptoms: 0 (no signs, no symptoms), 1 (facial weakness, no symptoms), 2 (onset of symptoms at age ⩾20 years), 3 (onset of symptoms at age 15–19 years), 4 (onset of symptoms at age 10–14 years), and 5 (onset of symptoms at age <10 years).

PFGE.—Five micrograms of DNA was double digested with *Eco*RI/*Hin*dIII (E/H) or double digested by *Eco*RI/*Bln*I (E/B) according to the manufacturer's instructions. DNA was separated by PFGE. In brief, DNA was loaded on a 0.8% agarose gel (Boehringer MP agarose) in 0.5 × TBE and separated by PFGE for 20 h at 8.5 V/cm (van Deutekom et al. 1996). After blotting to a Nytran+ membrane (Schleicher & Schuell), the DNA was hybridized sequentially with p13E-11 (D4F104S1) and 9B6A (D4Z4) (Wijmenga et al. 1992) as described elsewhere (Lemmers et al. 1998). After exposure to phosphorimager screens, repeat arrays were assigned to their chromosomal location on the basis of their *Bln*I sensitivity. Somatic mosaicism was defined as a fifth fragment hybridizing with p13E-11 in one individual. The proportion of cells carrying the mosaic alleles was estimated

Table 1

Repeat-Array Constitution of 35 Dutch De Novo FSHD Families

Family	D4Z4 Repeat Length (units)	Sex	Complete Allele Information	Presence of Mosaicism in			Inheritance	Allele Constitution in Mosaic Individuals
				Father	Mother	Patient		
1	2	M	+			+		4 on 10
2	5	M					Maternal	
3	4	M					Paternal	
4	2	F		+			Paternal	Standard
5	2	M				+		Standard
6	1	M	+			+		4 on 10[a]
7	4	M				+		Standard
8	3	M	+				Paternal	
9	1	M	+		+		Maternal	4 on 10[b]
10	3	F			+		Maternal	
11	5	M	+		+		Maternal	Standard
12	4	F	+			+		4 on 10
13	4	F				+		Standard
14	4	F					Maternal	
15	3	F					?	
16	4	F					?	
17	6	F					?	
18	3	F	+				Maternal	
19	4	F	+				Maternal	
20	4	F	+				Maternal	
21	4	M	+				Paternal	
22	3	M	+				?	
23[c]	3	M	+				Paternal	
24	3	M	+			+		Standard
25	4	F	+				Maternal	
26	2	M	+			+		Standard
27	4	F	+				?	
28	6	F	+				Paternal	
29	3	M	+				Maternal	
30	2	M	+				Paternal	
31	6	F	+				Maternal	
32	2	F	+				Paternal	
33	4	M	+				Maternal	
34	4/5[d]	M	+	+			Paternal	4 on 10
35	2/6[d]	M				+		

Note.—A plus sign (+) indicates presence, and a question mark (?) indicates unknown.

[a] This individual carries a hybrid allele on chromosome 10, consisting of both 4-type and 10-type repeat units.

[b] This individual carries only 4-type repeat arrays (fig. 3*B*).

[c] In this patient, the partial deletion of the D4Z4 repeat arrays includes the p13E-11 region.

[d] These individuals are mosaic for two short repeat arrays.

by comparison of the observed signal intensity with the expected intensity. Signal intensities of the various hybridizing fragments were obtained with the IMAGEQUANT program (Molecular Dynamics).

Statistical evaluation.—The allele constitutions in mosaic and control individuals were evaluated according to Fisher's exact test. D4Z4 repeat–array lengths in mosaic and control individuals were compared by means of the Mann-Whitney U test (one sided).

A relationship between the age at onset and the proportion of cells carrying the deleted allele was calculated by linear regression analysis. For this purpose, we constructed a composite genotypic-severity scale: (5 − remaining number of repeat units) × the fraction of cells showing that deletion. The number 5 is the largest repeat array observed in mosaic individuals in this study.

Results

Allele Identification by PFGE

The repeat-array constitutions of 35 Dutch sporadic FSHD patients (19 males and 16 females) and their parents were analyzed by PFGE (table 1). For all but two patients, DNA from the parents was studied. In 23 fam-

ilies we could determine the chromosomal origin and the size of each of the four repeat arrays (on chromosomes 4 and 10) in both patients and parents. In the 10 remaining families with incomplete information, the DNA quality of one of the individuals was not sufficient to assign all alleles.

All patients showed one *Bln*I-insensitive repeat array <35 kb (9 units), consistent with FSHD diagnosis (Bakker et al. 1996; Lunt 1998) (table 1). The lengths of these arrays varied from 8 kb (1 unit and flanking sequences) to 25 kb (6 units). One patient inherited a 6-unit repeat array from his clinically unaffected father.

Mosaicism

We observed 14 cases of somatic mosaicism (defined by a fifth band on PFGE; tables 1 and 2 and fig. 1). In 3 of the 23 fully informative families, we observed mosaicism for the disease allele in unaffected parents (2 mothers and 1 father), and in 5 more families the patients were mosaic (4 males and 1 female; tables 2 and 3). In the remaining 12 families, for which we did not have full information on all repeat lengths, we observed mosaicism in one father, one mother, and four patients (three males and one female; tables 2 and 3).

The IMAGEQUANT program was used to estimate the percentage of the cell population carrying the deleted allele in mosaic individuals; this varied from 15% to 95% (table 3). Where possible, the parental origin of the mosaic allele was determined, as well as the original repeat-array size and the size of the deletion (table 3). In 8/11 mosaic individuals, the smallest D4Z4 allele was reduced to an FSHD-sized repeat array. A genotypic-severity score composed of the size of the residual repeat array and the proportion of cells carrying this array could be established in 11 mosaic individuals (table 3).

The age at onset of the clinical manifestations was used for a clinical severity score for the mosaic individuals (table 3). A relationship could be established between the age at onset of the disease, on the one hand, and the fraction of cells carrying the deleted allele and the residual repeat-array length (fig. 2), on the other hand. Individuals with a large proportion of cells carrying the disease allele have an earlier age at onset of the disease ($P \approx .02$).

Repeat-Array Inheritance

To determine whether the presence of either 4-type repeat arrays on chromosome 10 or 10-type repeat arrays on chromosome 4 might play a role in the deletion mechanism, we analyzed the repeat-array constitutions in those mosaic individuals in which we could score all alleles (13/14). Of these 13, 6 carried one or more 4-type repeat arrays on chromosome 10 (fig. 1 and table 3). Typically, in these cases, PFGE analysis revealed the presence of five p13E-11 hybridizing fragments: three *Bln*I-insensitive (4-type) repeat arrays >35 kb; one *Bln*I-sensitive (10-type) repeat array; and the mosaic, truncated, disease- associated repeat array <35 kb (fig. 1 and 3A and table 2). In one of these six individuals, the "nonstandard" repeat array consisted of both 4-type and 10-type repeat units (data not shown). One mosaic individual even carried only 4-type repeat arrays (fig. 3B). According to the results of Fisher's exact test, the frequency of 4-type repeats on chromosome 10 in the mosaic individuals (6 [40%] of 13) differs significantly from the Dutch control population, previously determined at 10% (van Deutekom et al. 1996) ($P = .0125$). In contrast, 0/13 mosaic individuals showed the reverse configuration of three or more *Bln*I-sensitive arrays indicative of the presence of 10-type repeat units on chromosome 4.

Table 2

Repeat Allele Information for the 35 FSHD Families Studied

Type of FSHD and Characteristic	No. of Individuals
Familial ($n = 1$)	1
De novo ($n = 34$):	34
Mosaicism:	14[a]
Male carriers	2
Female carriers	3
Male affecteds	7
Female affecteds	2
Repeat-array constitution in mosaic individuals:[a]	
Standard	7
4 on 10	6
10 on 4	0

[a] Thirteen individuals with complete information on all alleles.

Discussion

Although the deletion of an integral proportion of D4Z4 repeat arrays has been well established as the causal mutation of FSHD, little is known about the mechanism by which the deletion arises. We recently found that highly homologous repeat units on chromosomes 4 and 10 may interact, resulting in exchanged repeat units on both chromosomes in 20% of the population (van Deutekom et al. 1996; Lemmers et al. 1998). Recently, we could confirm this finding in a larger sample of both males and females (van der Maarel, unpublished data). To obtain more insight into the deletion mechanism and the putative role of interchromosomal repeat interference, we studied the repeat-array constitution on chromosomes 4 and 10 in 35 de novo FSHD families ascertained via the Dutch neuromuscular centers. The results highlight several aspects of FSHD, not previously reported, that are relevant to the basic and clinical insight in FSHD etiology.

Table 3

Mosaic Individuals in De Novo FSHD Families

Family	Sex	Repeat Length	Affection Status	Percentage of PBLs Carrying Allele (Size, in kb)		Inheritance	Rearranged Allele[a]	Δ[b] (kb)	Allele Constitution	Age (in years) at Onset of Weakness[c]			Severity Score	
				Original	Disease					Shoulder	Foot Extensor	Pelvic	Clinical	Genotypic
1	M	2	Affected	50 (70)	50 (12)	Paternal	Small	58	4 on 10	15	19	40	3	1.50
5	M	2	Affected	80 (96)	20 (12)	Paternal	Small	84	Standard	18	23	−	3	.60
6	M	1	Affected	66 (230)	34 (8)	Paternal	Large	222	4 on 10	4	4	4	5	1.36
7	M	4	Affected	73 (65)	27 (18)	Maternal	Small	47	Standard	18	?	34	3	.27
12	F	4	Affected	5 (80)	95 (18)	Maternal	Large	62	4 on 10	12	7	12	5	.95
13	F	4	Affected	35 (62)	65 (17)	?	Small	45	Standard	14	?	?	4	.65
24	M	3	Affected	55 (40)	45 (15)	Maternal	Small	25	Standard	14	30	30	4	.90
26	M	2	Affected	60 (130)	40 (12)	Maternal	Large	118	Standard	13	11	18	4	1.20
35	M	2/6	Affected						4 on 10	73	48	72	2	
4	M	2	Carrier	67 (40)	33 (12)		Small	28	Standard	?	?	?		
34	M	4/5	Carrier	60 (22)	40 (19)		Small	3	4 on 10	−	−	−	0	.00
9	F	1	Carrier	85 (110)	15 (10)			100	4 on both 10	−[d]	−	−	1	.60
10	F	3	Carrier							?	?	?		
11	F	4	Carrier	62 (48)	38 (21)		Small	27	Standard	−	−	−	0	.38

[a] Smallest or largest chromosome 4 allele rearranged.

[b] Size of the deletion.

[c] A minus sign (−) indicates that the individual is not affected; a question mark (?) indicates onset unknown.

[d] This individual has a mild facial weakness.

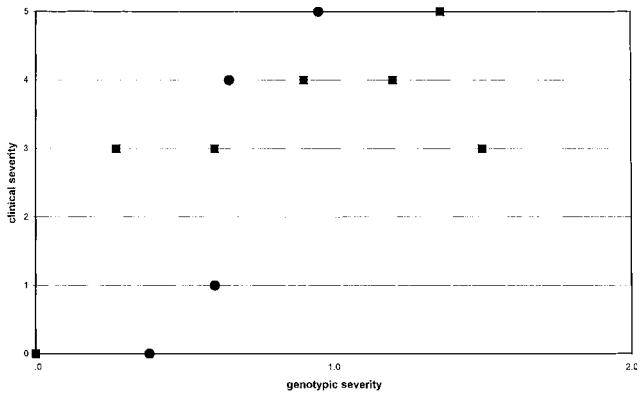

Figure 2 Relationship between clinical and genotypic severity in mosaic individuals. The clinical severity is on the Y axis, whereas the genotypic severity, calculated by [(5 − number of remaining repeat units) × fraction of cells with that deletion] is on the X axis. Males are represented by blackened squares, whereas females are represented by blackened circles.

Mitosis or Meiosis

We identified somatic mosaicism in 40% of our de novo families. Mosaicism has previously been reported for several human X-linked and autosomal dominant diseases, including Duchenne muscular dystrophy and hemophilia A (Bakker et al. 1987; Passos-Bueno et al. 1992; Becker et al. 1996). Also, for several tumor-prone syndromes, such as neurofibromatosis type 2 and retinoblastoma, mosaicism has been reported (Evans et al. 1998; Sippel et al. 1998). However, the high proportion of mosaicism identified in FSHD, as reported here, is unprecedented. Considering that we had full allele information on only 23/35 de novo families and that PFGE reveals only a significant degree of mosaicism, we estimate that ⩾40%, and possibly much more, of de novo families carry somatic mosaicism for the disease allele. Therefore, we propose that the FSHD rearrangement is predominantly mitotic.

Interchromosomal Repeat Interference

In 6 (46%) of 13 of the mosaic individuals in whom we could score all alleles, we observed one or more 4-type repeat arrays on chromosome 10. In the Dutch population, this type of repeat-array configuration is present in only 10% of the individuals (van Deutekom et al. 1996). The reverse configuration, equally present in 10% of controls, was never found in association with mosaicism. This provides strong support for the causal involvement of the extra 4-type repeat in the partial deletion of one of them and, in the case of chromosome 4, leading to FSHD. Studies of minisatellite repeat structures and a similar megasatellite repeat (*RNU2*) in the human genome indicate that intrachromosomal recombination, such as unequal sister-chromatid exchange (USCE) or intrachromatid gene conversion, dominates over interchromosomal recombination processes (Jeffreys et al. 1994; Liao et al. 1997). A high rate of intrachromosomal recombination effects homogenization and hence concerted evolution of repetitive multigene families, which is thought to maintain the integrity of each repeated gene (Liao 1999). In FSHD, a similar process might well play a role in the partial deletion of the D4Z4 repeat–array rearrangements. Since USCE should result in a reciprocal allele in the mosaics, which we have never observed, these deletions may arise by gene conversion.

On the other hand, the numerical excess of 4-type repeats on chromosome 10 in mosaic individuals indicates that supernumerary 4-type repeats may physically facilitate the partial deletion on either chromosome 4 or chromosome 10 (which would go undetected). In this model, the deletion arises independent of its inter- or intrachromosomal nature. Since recombination depends highly on the homology between both alleles (Lambert et al. 1999), normal 10-type repeat units may have diverged sufficiently to suppress their contribution to D4Z4 repeat deletions. For rDNA repeat arrays, recombination between nonhomologous chromosomes has been reported and was attributed to the close proximity of these repeat alleles in the nucleolus (Arnheim et al. 1980).

Allele Sizes

In most of the mosaic individuals, the original allele from which the disease allele has arisen could be identified by the lower hybridization intensity. Strikingly, in most of the cases (8/11), it was the shortest D4Z4 repeat allele that was reduced to an FSHD-sized repeat array. This finding may be due to ascertainment bias wherein mosaicism of relatively large alleles remains unnoticed, since they will not be reduced to arrays smaller than 35 kb. Indeed, the size distribution of the original alleles was significantly smaller than the size distribution of 78 standard chromosome 4 alleles in the control population ($P < .05$). This may indicate that deletions from relatively large alleles may in general have no pathological consequences.

As already observed by Zatz et al. (1998), the FSHD allele in asymptomatic mosaic individuals is relatively short. The average repeat length in mosaic individuals in this study is 3.1 units, whereas nonmosaic patients

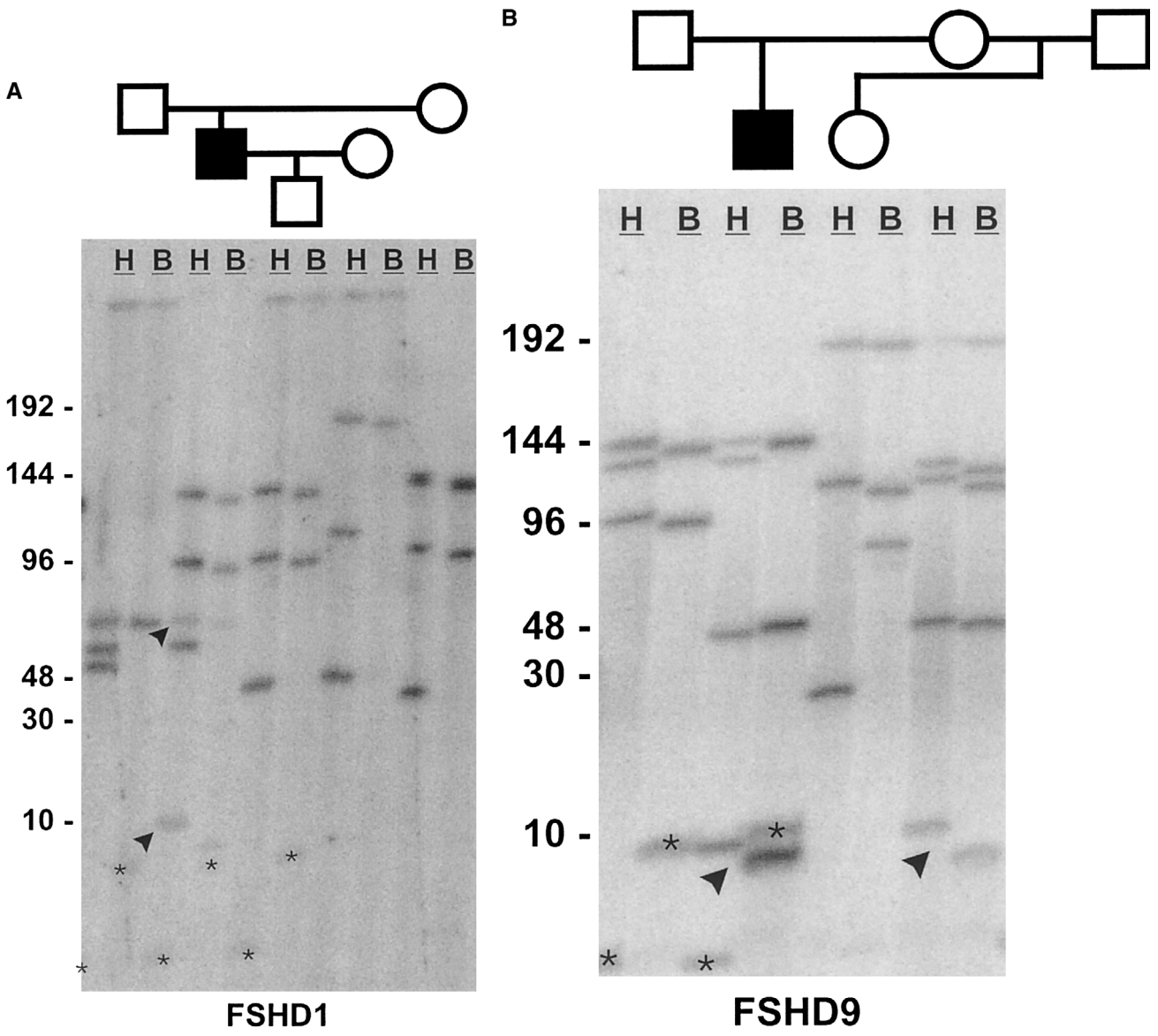

Figure 3 *A*, Somatic mosaicism in a de novo FSHD patient (FSHD1). DNA, digested by *Eco*RI/*Hin*dIII (H) or *Eco*RI/*Bln*I (B) and separated by PFGE, was visualized with probe p13E-11. The patient inherited a 65-kb 4-type repeat array from his father, which is reduced in 50% of his PBLs to the FSHD range of 10 kb (both alleles have a reduced intensity [arrows]). Note that this patient inherited from his mother two 4-type repeat arrays and, therefore, has a 4 on 10 repeat-array configuration. Y alleles are marked with an asterisk (*). The son of this patient inherited both grandmaternal alleles and is therefore not affected. *B*, Somatic mosaicism in a female carrier of a de novo FSHD kindred (FSHD9). DNA, digested by *Eco*RI/*Hin*dIII (H) or *Eco*RI/*Bln*I (B) and separated by PFGE, was visualized with probe p13E-11. The patient carries a short *Bln*I-insensitive repeat array of 10 kb (arrow), indicating FSHD. This allele (arrow) is also weakly present in the mother, who carries on chromosomes 4 and 10 four-type repeat arrays, identified on the basis of their *Bln*I insensitivity. The Y chromosomal cohybridizing fragment is marked with an asterisk (*).

carry, on average, 3.9 units. This may be explained in part by the association between the residual repeat size and severity and age at onset of the disease. In general, small alleles result in a more severe phenotype (Lunt et al. 1995; Tawil et al. 1996), and it may well be that, in mosaic individuals, the tolerance for short alleles is smaller than that for larger FSHD alleles. In this scenario, high proportions of cells carrying larger FSHD alleles may be required, to elicit a disease phenotype. The resulting low proportion of original alleles may go undetected by PFGE.

Alternatively, in addition to the mosaic rearrangement described here, which exhibits relatively short arrays, an unidentified mutational mechanism may exist that re-

sults in relatively larger FSHD arrays. If such an alternative exists, the high proportion of severely affected patients among de novo cases may be explained by a mechanistic difference rather than by a clinical ascertainment bias.

Sex and Affection Status

Somatic mosaicism has been observed in 15%–20% of the unaffected parents of de novo FSHD patients. In these studies, a female predominance of mosaic carriers (15 females : 6 males) was reported and was then attributed to a higher mutation rate in females than in males (Kohler et al. 1996; Lunt 1998; Zatz et al. 1998). In agreement, we found parental mosaicism in 14% of our de novo families (three females and two males).

In addition to mosaicism in parents, we found a high frequency (26%) of somatic mosaicism in de novo FSHD patients who belong to different families as the mosaic carrier parents. In these mosaic patients we find, in contrast, an excess of mosaic males over mosaic females (7 : 2). The proportion of cells carrying the deletion allele varied from 15% to 95% on the basis of the signal intensities of the different alleles. Typically, in mosaic female patients, the proportion of the deleted allele was higher than in mosaic male patients (table 3). Combining the female excess among unaffected mosaic carrier parents with the male mosaic excess among the patients themselves, we propose that the female predominance of mosaic asymptomatic carriers is not due to a higher mutation rate in females, but rather to a higher clinical tolerance for mosaic disease alleles in females compared with males. Consistent with this proposal, males are more severely affected than females (Padberg 1982; Lunt et al. 1989; Padberg et al. 1995; Zatz et al. 1998).

Although the extent of somatic mosaicism depends on the timing of the deletion event and on tissue-specific selection, we established a relationship between the residual repeat size and the proportion of cells carrying this disease allele, on one hand, and the severity and age at onset on the other ($P \approx .02$). This suggests that the mutation may already occur early in embryogenesis, before the divergence of muscle and lymphocyte lineages. Nevertheless, it will be important to analyze the mosaicism in muscles of mosaic patients and parents.

Implications for FSHD Diagnosis

For autosomal dominant diseases, recurrence risks in parents of de novo patients are considered very low, whereas disease carriers have 50% probability of having affected offspring. Since we have detected somatic mosaicism in $\geq$40% of the de novo families, this is not necessarily true for de novo FSHD families. According to table 3, since asymptomatic mosaic carriers may have as much as 40% of cells carrying the disease allele, such carriers may have a $\leq$20% risk that their offspring will be affected. In contrast, the mosaic FSHD patient in family 5 may have as little as 10% risk of having affected offspring. Detailed analysis of somatic and germline mosaicism in de novo FSHD families will be required, to obtain more-accurate figures for genetic counseling.

In conclusion, we have shown (1) that the D4Z4 repeat reduction associated with FSHD arises in ~40% of the de novo cases, mitotically, in either parent or patient; (2) that the basic mechanism of the repeat reduction likely involves inter- or, possibly, intrachromosomal gene conversion; (3) that this is facilitated by the presence of D4Z4 repeat arrays on chromosome 10, which thus predisposes for the deletion; (4) that somatic mosaicism occurs in both males and females but that males are more often affected than females; therefore, the proposed sex difference in the occurrence of somatic mosaicism may in fact be a sex-dependent clinical threshold for the mosaic disease allele; and (5) that a relationship exists between, on one hand, a combination of the residual repeat size and proportion of cells carrying the disease allele and, on the other hand, the age at onset and the severity of the disease. This chromosomal copy number–dependent repeat interference may well turn out to be a basic mechanism for genome instability involving multicopy repetitive elements.

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Electronic-Database Information

Accession number and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for FSHD [MIM 158900])

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