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Extrapolating the figures from a previous study on FSHD in a province of The Netherlands to the entire Dutch population suggests that at present a nearly complete overview is obtained of all symptomatic kindred. In 139 families, dominant inheritance was observed in 97, a pattern compatible with germline mosaicism in 6, while sporadic cases were found in 36 families. A mutation frequency of 9.6% was calculated. Mental retardation and severe retinal vasculopathy were reported in low frequencies (1%). Early onset was seen more frequently in sporadic cases. Chromosome 4 linkage appeared excluded in 3 of 22 autosomal-dominant families. The clinical pictures in the linked and nonlinked families were identical. © 1995 John Wiley & Sons, Inc.

Key words: facioscapulohumeral muscular dystrophy • population study • mutation frequency • genetic heterogeneity

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FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY IN THE DUTCH POPULATION

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Facioscapulohumeral muscular dystrophy (FSHD) has generally been described as an autosomal-dominant myopathy with a variable age of onset and a mildly progressive course.⁴ Therefore, early onset, a rapid course, and extramuscular involvement such as hearing loss and retinal vascular pathology have been considered extraordinary manifestations and indications of clinical and by consequence genetic heterogeneity.⁶ Incidental observations contributed to a rather wide picture of FSHD, and only after several large studies of completely examined families, was it possible to recognize cardiac involvement, extensive contractures, ptosis, and extraocular muscle weakness as not being part of autosomal-dominant FSHD.⁵ For such cases, the term "FSH syndrome" came into use.⁷

The discussion about possible genetic heterogeneity of FSHD was not easily solved as pedigrees without clearly autosomal-dominant patterns con-

tinued to be observed. New insights in mechanisms of heredity such as germline mosaicism offered explanations for multiple cases in a sibship without the parents being affected. The demonstration of the locus for FSHD on the tip of chromosome 4q was thought to be compatible with the suspected high mutation rate.^{8,11} But when all genetic problems seemed to be reduced to one single locus, families with classical FSHD were reported in which this locus had been excluded.³ Thus it became important to have some idea about the frequencies of new mutations and locus heterogeneity of FSHD in the population. Although it is felt that a population study of FSHD will never be complete, this is a first attempt to give some general figures, as it is our impression that we have a fairly complete overview of the symptomatic FSHD population in The Netherlands.

PATIENTS AND METHODS

Probands of 19 autosomal-dominant FSHD families were seen at the University Hospitals of Amsterdam and Leiden from 1970 to 1979, and their families were extensively studied in 1980–1981. Ten of these families participated in the genetic studies of 1990–1994.^{8,10,11} Probands of 30 other dominant families were seen at the University Hospital in Leiden from 1986 to 1993 and during several field studies. These families were not studied completely. At least all probands underwent EMG

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and muscle biopsy. DNA was collected in 22 of these 49 families. Forty-eight probands of dominant families were seen in other neuromuscular centers at the University Hospitals during the last 15 years. Their pedigrees were constructed by patients' information only.

Also, 6 probands and their families were studied for possible germline mosaicism. In 3 families both parents, in 2 families only 1 parent, and in 1 family none of the parents were examined. We were able to analyze DNA of 3 families.

Finally, from 1980 to 1993 we saw 28 sporadic cases and their families. DNA was sampled in 17 cases and in 14 instances blood of both parents could be collected. Eight additional cases were seen at other neuromuscular centers.

DNA was extracted as reported previously, and 4q35 markers including p13E-11 were studied as described.^{10,11}

RESULTS

After the ascertainment of 50 patients from 12 autosomal-dominant families in the province of North-Holland, The Netherlands, in what was felt to be a thorough study in 1980, a prevalence of 1 patient per 46,000 was calculated.⁴ Based on the observation that no second probands were found in this apparently exhaustive study, the probability of ascertaining a kindred with FSHD was estimated to be lower than 45%, yielding an estimated prevalence of at least 1 patient per 21,000, which is a figure close to the one reported by Becker for the Baden-Baden population in Germany.^{1,4} Extending these figures to the general population of The Netherlands it was estimated that this country contains approximately 714 patients. If indeed a percentage of 30% of asymptomatic patients, as found in the first study,⁴ could be extrapolated to the general population, approximately 500 living symptomatic patients are to be expected in the Dutch population. Our first study⁴ was aimed at the larger families because we were interested in doing linkage studies. These families contained, on average, 5.05 symptomatic patients (Table 1). In the second series families not all affected sibs were studied personally, and these families were not ex-

amined completely. These families contained, on average, 3.9 affected sibs. Overall, our families contained 4.3 symptomatic sibs. Based on these figures it was estimated to find 99–128 and, on average, 116 autosomal-dominant families in The Netherlands. At present we are aware of 97 dominant families (Table 1). Families not referred to any of the neuromuscular centers at the university hospitals would be lost to inclusion. An easy access to the university hospitals, an intensive contact with primary care physicians, and a well-informed public in this tiny country suggests that only a small percentage of families have not been referred to these neuromuscular centers. Also, the chance of a family consisting entirely of asymptomatic patients is so small that it can be left out of the analysis. In conclusion, it appears that we have an almost complete overview of all families with autosomal-dominant FSHD and, following the same reasoning, also probably of all sporadic cases of FSHD in The Netherlands.

Mutation Frequency. From these figures a mutation frequency can be calculated. We have studied personally 28 sporadic cases and have been informed of 8 additional cases at other university hospitals. In our own autosomal-dominant families we know of 4 new mutations (i.e., top of the pedigree). In the 48 reported dominant families we assume a similar number of new mutations. Moreover, we know of 6 pedigrees with strong indications of germline mosaicism of which at least 4 of the mutated individuals are alive. Therefore, we assume 48 instances of new FSHD mutations among an estimated number of 500 symptomatic living FSHD patients in The Netherlands, suggesting a mutation frequency of 9.6% or 1 mutation per 320,000 live births as the Dutch population at present contains 15.4 million individuals.

Patterns of Inheritance. The family data presently known to us make it possible to estimate frequencies of mechanisms of inheritance in FSHD (Table 2). An autosomal-dominant pattern occurred in 97 families (69.7%). Germline mosaicism was the most likely explanation for the heredity pattern in 6

Table 1. Alive symptomatic patients in dominant FSHD families.

	Families	Patients	Males	Females	Pat./fam.
Families extensively studied	19	96	53	43	5.05
Families partially studied	30	117	57	60	3.9
Families studied by others	48				
Total	97	213	110	103	4.3

Table 2. Pattern of inheritance in 139 families.

Autosomal dominant	97	69.7%
Germline mosaicism	6	4.3%
Sporadic cases	36	25.9%
Total	139	

families (4.3%). New mutations were not infrequent and involved 38 sporadic cases or 25.9% of all families with FSHD patients (Table 2).

Sex Differences. As there has been a long-standing impression that males were more frequently and more severely affected with FSHD, we looked at this matter in our 1980 study.⁴ In that study, the reported age at onset between males (15.8 years) and females (19.0 years) was statistically not significant. The difference in number of asymptomatic males (i.e., 13; 22%) and females (i.e., 21; 44%) was statistically not significant. Also, the differences in numbers of affected males and females were not significant in 1980 and even less so in the present survey (Table 1). However, the difference between male (15) and female (4) probands were statistically significant ($P = 0.016$; chi-square test) in the 1980 study.⁴ The probands that we have studied personally so far (Table 3) again show a statistically significant ($P = 0.023$; chi-square test) difference between males and females.

Early Onset. Early onset of FSHD, defined as symptomatic before the age of 10 and/or signs before the age of 5, was observed in 9 (4.2%) of 241 personally examined cases of autosomal-dominant inheritance. Ten (36%) sporadic cases were of early onset.

Extramuscular Involvement. The present survey was not intended to study extramuscular involvement in FSHD. Estimation of hearing loss in sporadic (71%) and dominant (62%) cases are presented elsewhere.⁶ In the same article, a retinal vasculopathy is reported to occur in 50% of all patients with no differences between chromosome

Table 3. Proband analysis in 83 FSHD families.

	Male	Female	Total
AD families extensively studied	15	4	19
AD families partially studied	17	13	30
Germline mosaicism	5	1	6
Sporadic cases	19	9	28
Total	56	27	83

4-linked and -non linked families; in the two chromosome 4-excluded families in which retinal angiograms were studied, patient RII6 revealed no abnormalities, while both patients of family KL showed retinal vascular changes. This study indicates that severe retinal vasculopathy, i.e., a Coats' disease-like picture is quite rare as we were able to find only 3 patients with Coats' disease of the 256 (1.2%) FSHD patients under survey. As such a severe complication is likely to come under the attention of specialists, the chance is that the true incidence of severe retinal vasculopathy is even lower.

Similarly, mental retardation occurs in a low frequency in FSHD. We know of 4 male cases in our survey of 256 patients, which might be the only cases in the entire symptomatic FSHD population. Three of these cases have been described elsewhere because of early onset,² while the fourth case is discussed as the first case of a severe retinal vasculopathy in the addendum of our article on retinal pathology.⁶ The percentage of male patients with mental retardation might not be different from the percentage of male mental retardation in the general population. Yet the combination of early onset (4 cases), hearing loss (3 cases), and severe retinal vascular changes (2 cases) suggest a special configuration. The 2 cases with autosomal-dominant inheritance had an affected parent with an usual pattern of involvement and average severity. The demonstration of chromosome 4 involvement in the dominant cases supports the concept that these cases represent the extreme of the clinical spectrum that on the other end consists of facial weakness only, or even more rarely, nonpenetrance.

Sporadic Cases. In this survey of 139 families, sporadic cases occurred in 36 instances (25.9%) and in 28 (11%) of all 256 patients seen by us personally. Onset below the age of 10 years occurred in 10 of 28 sporadic cases, while this was found in 3 of 15 cases of germline mosaicism and in 9 of 213 dominant cases. Fourteen sporadic cases showed a short fragment with p13E-11; in 10 instances, both parents could be studied and in 4 cases one parent and other sibs were examined, all showing no short fragment, suggesting that these 14 sporadic cases were 4q-associated new mutations. In 3 cases and their parents, a short fragment could not be demonstrated, and in 11 other cases no DNA was available for analysis.

Germline Mosaicism. Among 139 pedigrees studied we found 6 with multiple cases in the same

sibship and apparently nonaffected parents. Both parents had been studied in 4 families (nos. 1–4). In family 5, one parent and in family 6 both parents were diseased. In family 3, the patients revealed a short fragment with p13E-11, while no such fragment could be found in family 4. Also in family 5, only the patient had a short fragment. From families 1, 2, and 6 no DNA was available.

Autosomal-Dominant Inheritance. In this study, we obtained information on 97 families with autosomal-dominant FSHD. Ten of the original 19 extensively studied families participated in the linkage studies leading to the location of the gene.⁸ One small family is probably not linked.¹¹ Later, 12 additional families were studied; in two small families, no short fragment with p13E-11 could be found and haplotyping suggested nonlinkage to 4q35. Thus, in 3 of 22 families (13.6%) linkage to 4q35 seemed excluded.

DISCUSSION

Population-based studies of FSHD always appear to be hazardous enterprises. With a large proportion of asymptomatic patients, and many patients familiar with the disorder through their parents and relatives, and therefore often not seeking medical attention, FSHD is a disorder prone to underestimation of its prevalence. Figures obtained in a small Dutch population⁴ turned out to be fairly accurate when extrapolated to the Dutch population at large. It seems that we have reached a near complete ascertainment of families and index cases, making possible a reliable estimate of the mutation rate for the first time. Our figure of 1 new mutation per 320,000 live births is again a rather conservative estimate. Strong arguments for germline mosaicism have been found which appear to occur in 4.6% of all families. This report clearly demonstrates that the linkage studies need to be extended to estimate the percentage of genetic heterogeneity of FSHD more accurately; our figures of non-4q linkage in sporadic cases (17.6%) and familial cases (13.6%) are presently not based on sufficiently large numbers of patients.

On the clinical side, this survey has given some information on the low frequency of mental retardation and severe retinal vasculopathy both occur-

ring in approximately 1% of the FSHD patients. Significant sex differences were not found with the exception of a male excess in the numbers of probands. This might be a cultural bias; we have no other convincing explanation for it. Also, the association of more severe cases, onset before the age of 10 in conjunction with new mutations, could be an ascertainment bias, but a final answer probably has to wait for the finding of the gene.

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