Facioscapulohumeral disease

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Chapter 4

Facioscapulohumeral disease: personal observations

4.1. Introduction

The general clinical picture of FSHD is fairly well established but the extent and the limits of the disease are not clearly defined. Moreover, several issues, such as possible differences between males and females, the possibility of environmental influences on the manifestation of the disease, the problem of genetic heterogeneity and others, are still unsettled.

In order to study the various aspects of FSHD we started with the probands of 19 families. The terms family and kindred will be used as synonyms in this study. The probands of the families B,C,D,E,F,G,J,K,M,N,P,R and S were all known at the Muscle Research Center of the University of Amsterdam (Head Prof. Dr. J. Bethlem). The probands of the kindreds H,I,L, were seen regularly at the Neuromuscular Clinic of the University Hospital of Leiden (Head Dr. A.R. Wintzen). The probands of the families O and Q were known at the Neurological out-patient Department of the University of Amsterdam (Head Dr. J. van Manen). The Department of Human Genetics of the Free University of Amsterdam (Chairman Prof. Dr. A.W. Eriksson) referred the proband of family A to us. This patient was subsequently studied at the Muscle Research Center of the University of Amsterdam.

We reconstructed the pedigrees from anamnestic data, checking and expanding this information through the records of the registrar's office, to which our genealogist (Mr. L.P. Kuijt) had easy access. As many members of the families as possible were visited by the author at their homes and examined as extensively as possible, this being the only available method by which to determine whether someone is affected or not (Walton and Gardner-Medwin 1981). The persons examined are indicated in the pedigrees.

The support of the family doctors involved in this study was uniformly very positive. The patients varied in their degree of cooperation: only a few refused to be visited, most patients being eager to talk about the disease and about their families. The information regarding others, and especially more distant relatives, proved to be quite unreliable and confirmed earlier experiences of authors such as Tyler and Stephens (1950). Several patients refused a complete physical examination, the reasons for such refusal varying. However, all these patients could be persuaded to perform several tests of muscle function.

In a single visit it is impossible to assess what it means to each individual patient to have such a disease and, while examining the families, all kinds of reactions relating to the disease were observed. Some people were anxious to have confirmation that they were not affected, others sought the denial of an evident diagnosis. One unaffected person had made his family believe he had the same disease from which his father suffered, and he thought himself unfit to work. Many patients dissimulated their disabilities. It was interesting to note that a reluctance to a physical examination was never observed in the non-affected family members, while this reluctance was present in several of the asymptomatic patients. It was also impossible to know the real import of questions such as "Do I have the disease?" or "Is he or she affected?". On several occasions it was observed that the mechanisms of suppression and distortion of facts were quite strong. Also depressions and forced cheerfulness testified to the impact of this disease on the patients' existence.

4.2. The patients

One hundred and ninety individuals in 19 kindreds were examined at their homes (Table 4.1.). One hundred and seven gene carriers were identified. One hundred and eighty-nine persons are indicated in the pedigrees. The one person, that is not shown, is the mother of patient H V 20.

Table 4.1. All persons examined in 19 kindreds with FSHD.

	Affected	Possibly Affected	Not Affected	Total
Completely examined: males	46	3	41	90
females	28	2	31	61
Partially examined: males	13		2	15
females	20		4	24
	107	5	78	190

"Completely examined" means that the strength of all muscles or muscle groups described in Table 4.12. was graded. "Partially examined" indicates that not all muscles could be graded properly. This group includes severely affected patients, who refused a complete physical examination, but also obviously affected persons who refused to take off their clothes. Their muscles could be tested to a variable extent. All but one of these 33 patients had definite facial weakness. Testing of the facial muscles was never refused. The one patient without facial weakness was among a group of patients who were examined completely but in whom the grade of muscle strength was not recorded; therefore they were included in the group of "partially examined" patients. Six partially examined persons refused to take off some of their clothes, but they could be examined sufficiently so as to convince the examiner that they were not affected.

Three males (A IV 13, K V 23, K V 24) and two females (K V 2, P II 1) were considered "possibly affected". Physical examination did not reveal muscular weakness or a distinct

atrophy, but the history (patient P II 1, see section 4.22.) or the habitus of the patients (for instance an increased lumbar lordosis, a protruding belly, sloping shoulders, protruding scapulae or an increased distance between the medial borders of the scapulae with endorotation of the arms) was sufficient to raise the examiner's suspicion.

Table 4.2. gives all "possibly affected" persons in the kindreds. Persons not examined or deceased were designated "possibly affected" if the several sources of information within the families were not conforming.

Table 4.3. shows the number of all known patients. The not examined and the deceased patients all were recognisably affected.

Table 4.2. All "possibly affected" persons in 19 kindreds with FSHD.

	Examined	Not Examined	Deceased	Total
Males	3	2	5	10
Females	2	6	8	16
	5	8	13	26

Table 4.3. All affected persons in 19 kindreds with FSHD

	Examined	Not Examined	Deceased	Total
Males	59	7	29	95
Females	48	16	22	86
	107	23	51	181

Figure 4.1. represents the ages of the examined 107 patients. Table 4.4. gives the numbers of patients per age-decade.

The average duration of the disease at the time of examination (27.9 years) is based on anamnestic data of the 73 symptomatic patients and represented in Figure 4.2.. The average duration in males was 27.8 years and in females 29.9 years.

FIGURE 4.1: AGES IN YEARS OF 107 PATIENTS WITH FSHD (59 MALES, 48 FEMALES)

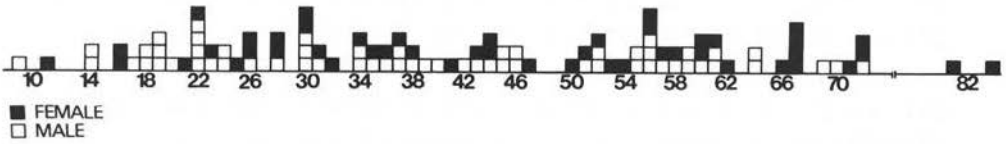


FIGURE 4.2: DURATION OF THE DEASE IN YEARS (46 MALES, 27 FEMALES)

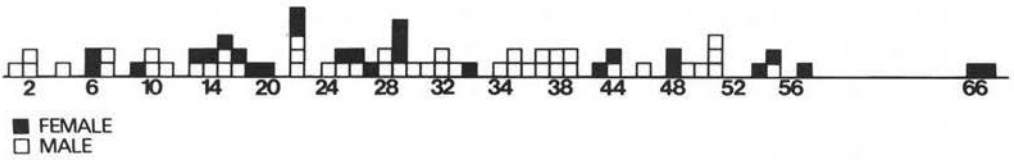


Table 4.4. Number of patients per age-decade.

Decade	1	2	3	4	5	6	7	8	9	Total
Males	1	8	10	12	8	12	6	2	0	59
Females	0	3	8	9	5	9	9	3	2	48
	1	11	18	21	13	21	15	5	2	107

In order to study phenomena such as penetrance and age of onset, we considered separately those sibships of which it could be reasonably assumed that all affected individuals had been identified. All these sibships had one definitely affected parent, with the exception of sibship P III. P II 1 must possess the abnormal gene, but she was completely healthy, when examined at the age of 68 years. The sibships were examined as extensively as possible. Because several authors (Tyler and Stephens 1950, Becker 1953) claimed that it was impossible to make the diagnosis before the age of seven, sibships consisting entirely of children in their first decade were excluded, with the exception of patient J VI 3, who was a nine-year old asymptomatic case. The sibships involved, indicated by their eldest representative, were A III 1, A V 4, A V 8, A V 14, B III 1, B IV 1, C III 1, D III 10, E III 1, E IV 1, E V 1, F IV 1, G III 17, H IV 3, H V 7, H V

16, H V 20, H VI 1, I V 6, I V 25, I VI 10, I VI 21, J III 1, J IV 1, J IV 27, J IV 38, J V 6, J V 15, J V 19, J V 23, J VI 3, K III 12, K III 18, K IV 1, K IV 15, L IV 8, L IV 40, L V 6, L V 10, L V 14, L V 83, M III 8, N IV 14, O III 6, P III 1, P IV 1, Q III 1, S III 1 and S IV 4. Only kindred R yielded no useful sibships as no sibship could be examined entirely. Sibship O III 6 consisted of the proband only. Also the probands in the other sibships (eleven males and four females) have to be excluded because of the bias of ascertainment. The same bias is present in the affected parents and grandparents of the probands as they are obligatory gene carriers. The numbers of individuals in these 49 sibships are shown in Table 4.5..

Table 4.5. Forty-nine sibships with FSHD in 17 kindreds.

	Males	Females	Total
Probands	10	4	14
Obligatory gene carriers	3	3	6
Affected sibs	44	41	85
Not affected sibs	37	43	80
	94	91	185

Figure 4.3. gives the distribution of the ages of all sibs involved, without the probands and the obligatory gene carriers. The ages recorded are the ages at the time of this study if they were alive, or the ages at their death.

FIGURE 4.3: AGES IN YEARS AT EXAMINATION OR OF DEATH OF 165 SIBS (81 MALES, 84 FEMALES) IN 49 SIBHIPS (17 KINDREDS) (PROBANDS AND OBLIGATORY GENE CARRIERS EXCLUDED)

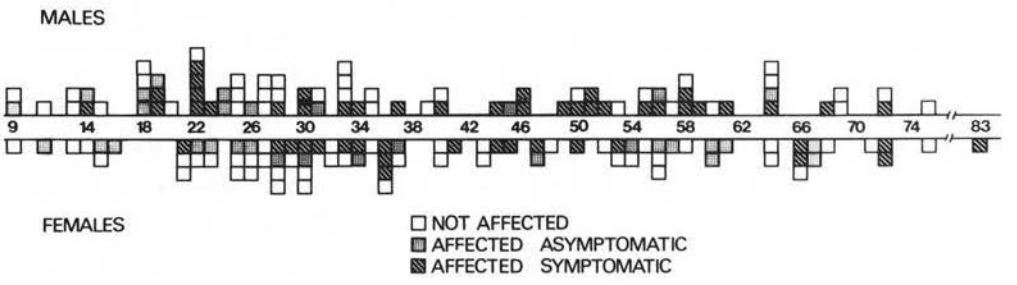


Table 4.6. Number of sibs per age-decade
(probands and obligatory gene carriers excluded)

Decade	Males				Females				Both sexes			
	Affected		Not Affected	Total	Affected		Not Affected	Total	Affected		Not Affected	Total
	sympto matic	asympto matic			sympto matic	asympto matic			sympto matic	asympto matic		
1	0	1	1	2	0	0	1	1	0	1	2	3
2	3	4	6	13	0	3	3	6	3	7	9	19
3	6	3	10	19	3	5	13	21	9	8	23	40
4	5	1	7	13	7	3	8	18	12	4	15	31
5	5	1	1	7	4	1	5	10	9	2	6	17
6	9	1	5	15	2	3	7	12	11	4	12	27
7	3	1	5	9	2	5	4	11	5	6	9	20
8	1	0	2	3	2	0	2	4	3	0	4	7
Total	32	12	37	81	20	20	43	83	52	32	80	164

Table 4.6. gives the numbers of the patients with symptoms, of those without symptoms, and the numbers of the unaffected sibs per age-decade. Joint and muscle pains and inability to whistle were not accepted as diagnostic symptoms. Inability to whistle was never a spontaneous complaint. Only patients without complaints related to muscle weakness are included in the asymptomatic group. There was only one affected female in the ninth decade: she is not considered in this table because the information is too limited to draw any conclusions for this decade.

The relative frequencies of the symptomatic, the asymptomatic, and the not affected sibs are given in the Figures 4.4. and 4.5.. These diagrams will be referred to later in the text.

FIGURE 4.4: PERCENTAGE OF AFFECTED AND NON-AFFECTED SIBS PER AGE GROUP (164 SIBS, BOTH SEXES)

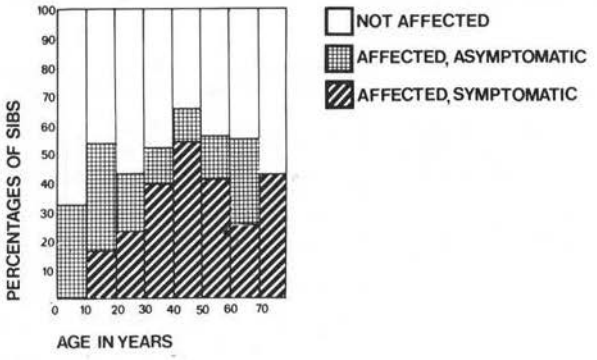
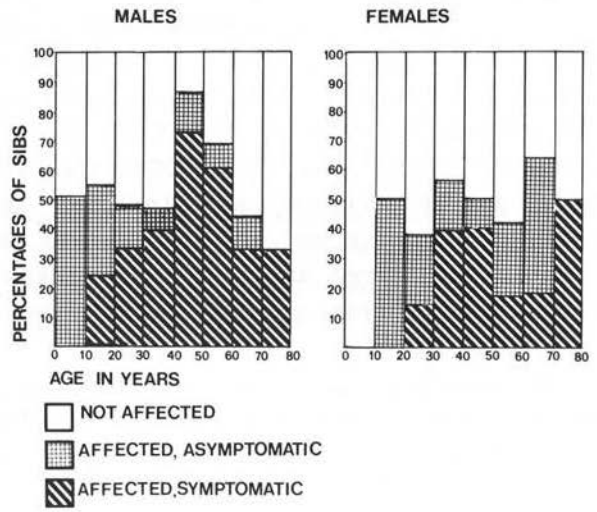


FIGURE 4.5: PERCENTAGES OF AFFECTED AND NON-AFFECTED SIBS PER AGE GROUP (164 SIBS: 81 MALES, 83 FEMALES)



4.3. The kindreds

The pedigrees are shown in the following pages. Details about the ancestors and other parts of the family, not studied by us, will be mentioned briefly if relevant. The living members of the families will be discussed only if they demonstrated remarkable features.

LEGENDA


Affected male ; sib number 2; generation number 3

Not affected female

Possibly affected male

Sex unknown

Two males

Childless marriage

Offspring not explored

Consanguineous marriage

Di - zygotic twins

Proband

S Single

A Asymptomatic

Completely examined by the author

Partially examined by the author

Examined by others

✳ Year of birth

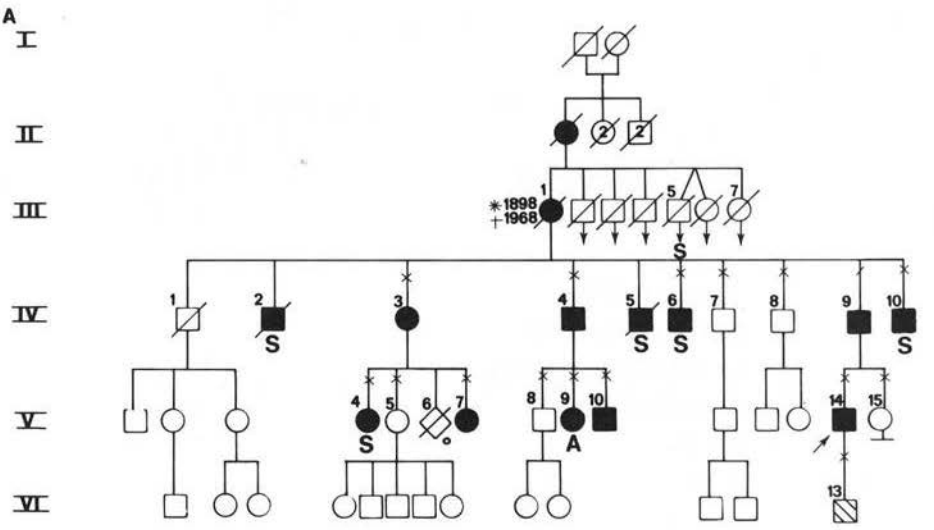
† Year of death

Male deceased at the age of 2 years

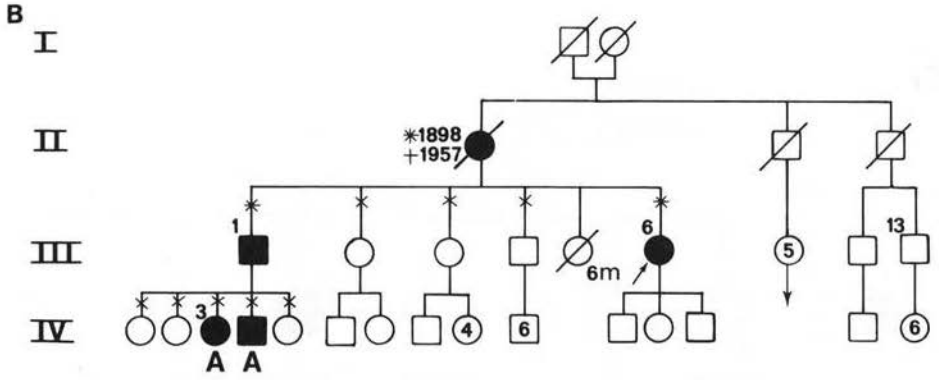
2m Male deceased at the age of 2 months

2d Male deceased at the age of 2 days

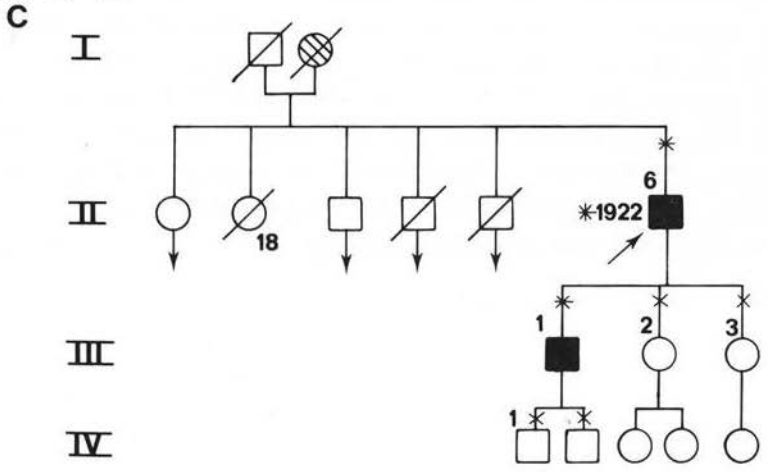
0 Male born dead



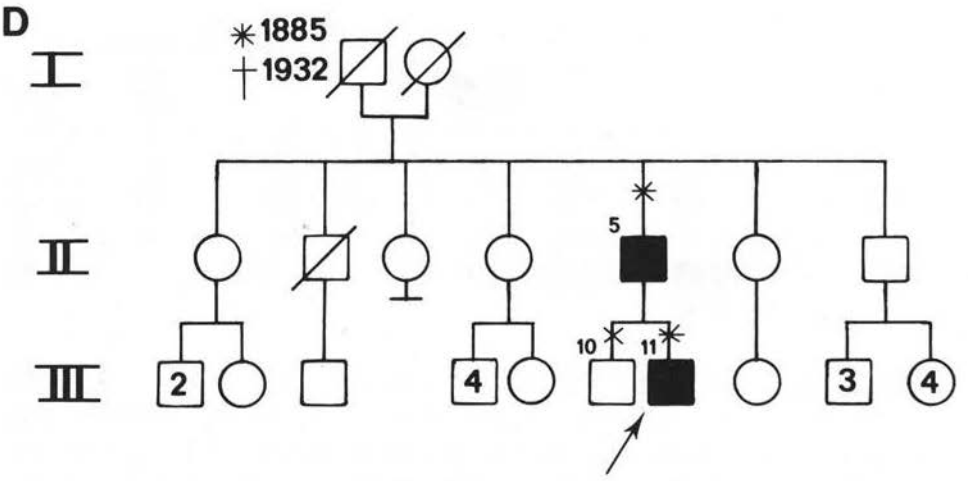
Kindred A: This kindred was ascertained through the proband V 14, who sought genetical advice. A definite diagnosis could not be made in his son (VI 13). II 1 was said to have had shoulder girdle weakness. Nothing is known about her two brothers and two sisters. III 1 suffered from severe pelvic girdle weakness. Her brother III 5 had died in his teens and her sister III 7 had emigrated to the USA: patient IV 3 thought they both had been affected. This could not be confirmed since no one else in the fourth generation had known these persons. Patient IV 10 was quite remarkable because he had severe neck extensor weakness; he could not keep his head constantly upright, which is definitely exceptional in FSHD. There was only one abortive case in his kindred (V 9).



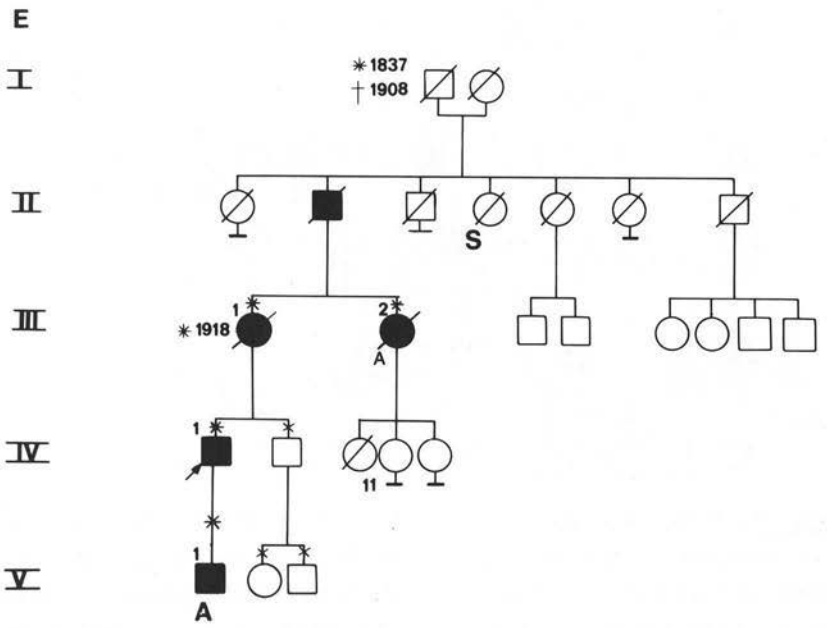
Kindred B: Patient II 1 died at the age of 59 after "a heart attack which was related to her thyroid disease". Details were not available. According to her children and to III 13, her two brothers and her parents were not affected. III 1 and III 6 had been examined ten years previously. At that time no facial weakness was noted; this was clearly present when they were examined by us.



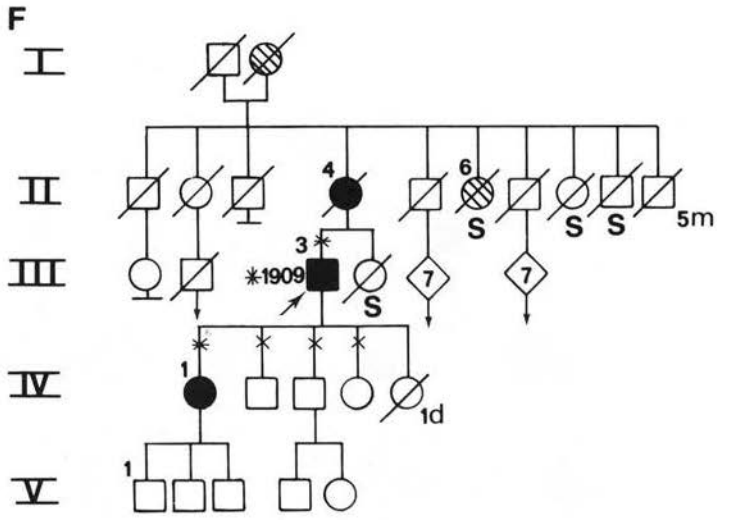
Kindred C: I 2 was an Indonesian woman. Nothing is known about her family. It was said she could not walk properly at advanced age, but II 6 was not sure she was affected. I 1 was a tall and strong professional soldier. The proband's brothers and sisters lived in Indonesia. Nothing is known about them regarding FSHD.



Kindred D: The proband's father (II 5) claimed to be the first one in his family with muscle disease. No one else of his generation could be examined. Biopsy of the right deltoid muscle of the proband (III 11) revealed no abnormalities. EMG of the shoulder girdle muscles showed a myopathic pattern in the left deltoid muscle only. II 5 had chronic heart failure, generalized atherosclerotic vascular disease, and anticoagulation therapy for an aorta bifurcation prosthesis. A muscle biopsy was not performed. The diagnosis in this family therefore, is largely based on clinical and genetic criteria.

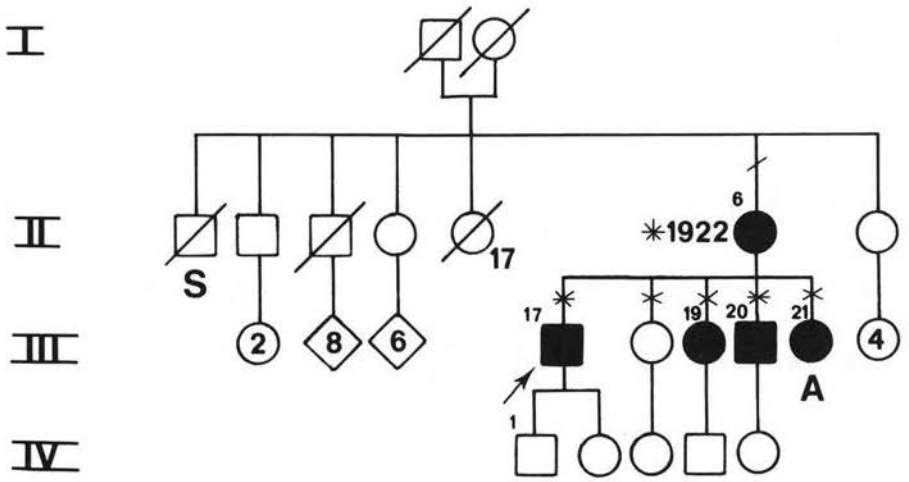


Kindred E: Patient II 2 was said to be the only one of his generation who was affected. His first symptoms became apparent around the age of 25 and were those of foot extensor weakness. His parents had no complaints of muscle weakness. His daughter (III 1) also noted symptoms of foot extensor weakness first. She was 38 years at that time and had never been able to whistle. Two years later she noted shoulder girdle weakness. Her sister had no symptoms but turned out to be affected. In her son (IV 1) the disease manifested by symptoms of shoulder girdle weakness at the age of 16 years.

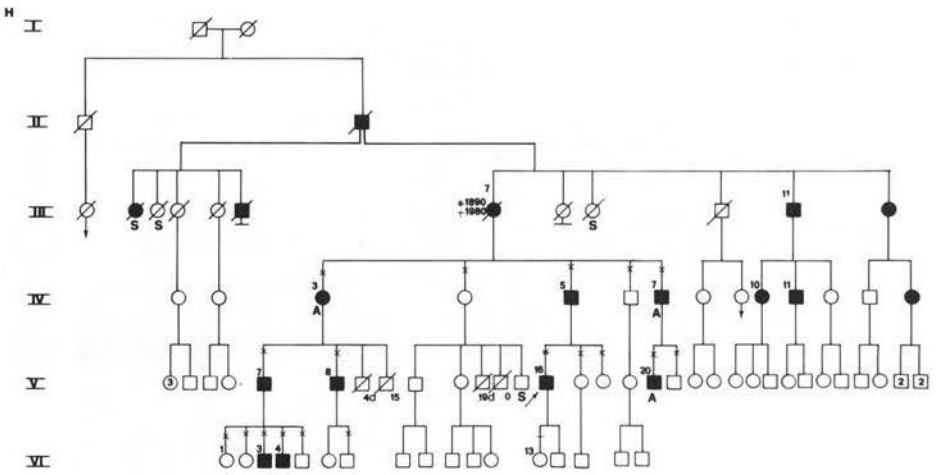


Kindred F: The information given in this pedigree is based on the family records of the probrand (III 3), and could not be checked, because the ancestors came from several small towns in Germany, close to the Dutch border. I 1 was said to have been a strong man, member of the German Imperial Guard. I 2 "missed a muscle in her shoulder" but details are lacking, nor is anything known about her sister and parents. II 4 also missed some muscles in her shoulder, which was noted on an examination for tuberculosis. She had difficulties walking when she became older. Her son is positive that she had the disease and suggested that II 6 was affected as well. The proband (III 3) had a slightly progressive costal gibbus and an impressive thoracic kyphoscoliosis. He could stand upright with an increased lumbar lordosis and flexed hip and knees, but he walked progressively bent forwards since his fifties. On examination he had a waddling gait with a bilateral foot drop and his upper trunk bent to an angle of 45 degrees. He had to hold on to chairs and tables in his house, and to a stick while outside. All his life he had ridden a bicycle and, when this became more difficult, he persuaded his wife to ride a tandem. This most remarkable man, who loved outdoor-life, still drove a car in his seventies and each year spent long summer holidays with his wife camping, sleeping in a tent, in the south of Europe.

G

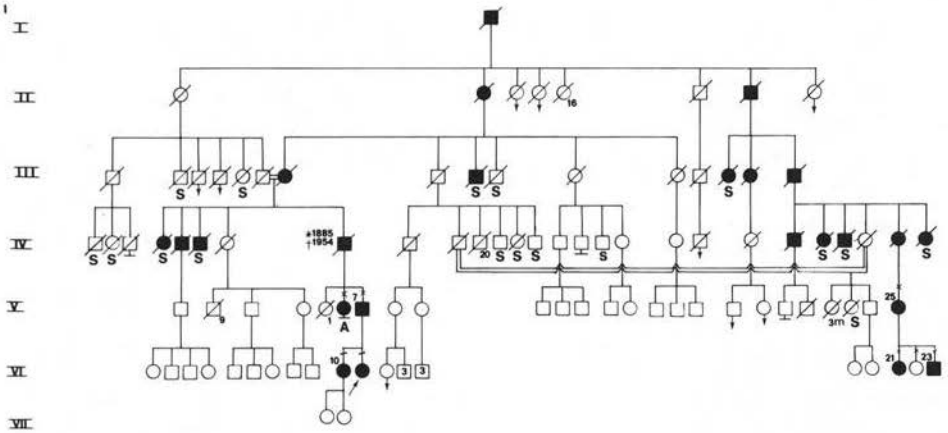


Kindred G: I 1 was a Belgian male who changed his name after his emigration to Indonesia. I 2 was an Indonesian orphan. The family is divided about her being affected or not. The largest part of the family still lives in Indonesia or Malaysia. They are all said to be without complaints. Patient II 6 was reluctant to be examined. She had facial weakness and was unable to raise her arms more than 90 degrees, also showing a right-sided foot extensor weakness.

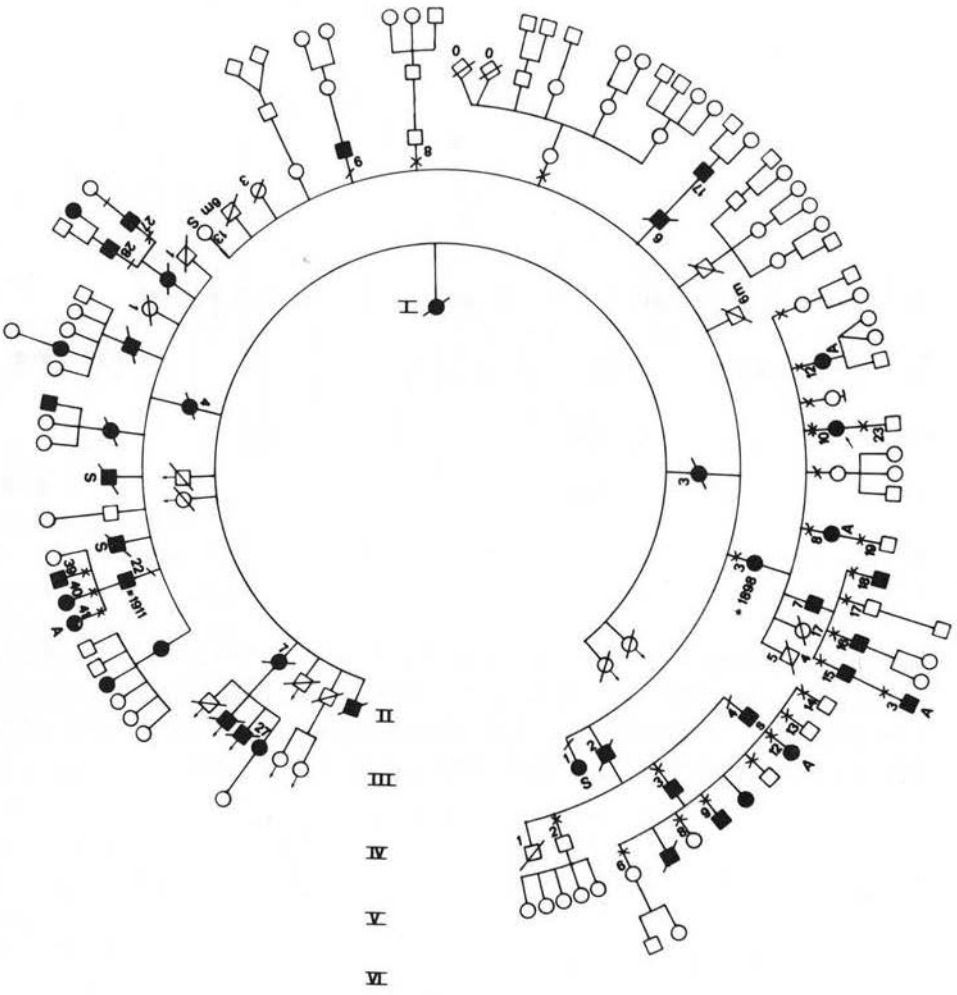


Kindred H: Only the proband (V 16) was so severely affected that he had sought referral to a neurologist. As a child of eight years he was unable to raise his arms above his head. He noted foot extensor weakness at the age of 20 and pelvic girdle weakness when 24 years old. His father (IV 5) developed shoulder girdle weakness at the age of 15. This progressed till he was 21 years old. Then the progression stopped, and on examination at the age of 61 he still had only shoulder girdle and upper arm weakness. There were several abortive cases in this family. IV 7 was minimally affected and will be discussed in detail in section 4.22. V 8 had suffered from a radicular S1 syndrome on the left due to slipped disc, which left him with a distinct paresis and atrophy of the left triceps surae muscle.

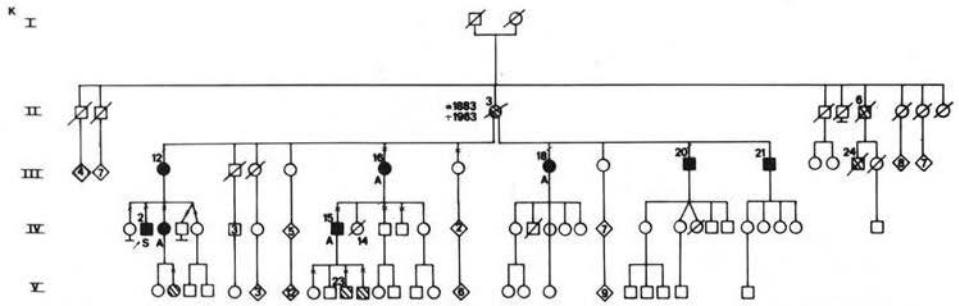
Remarkably, in this family facial weakness was generally minimal. IV 5, IV 7 and V 8 had no facial weakness at all. That this was not a rule without exception was demonstrated by III 11 whom we met but who was not examined by us: he showed severe facial weakness.



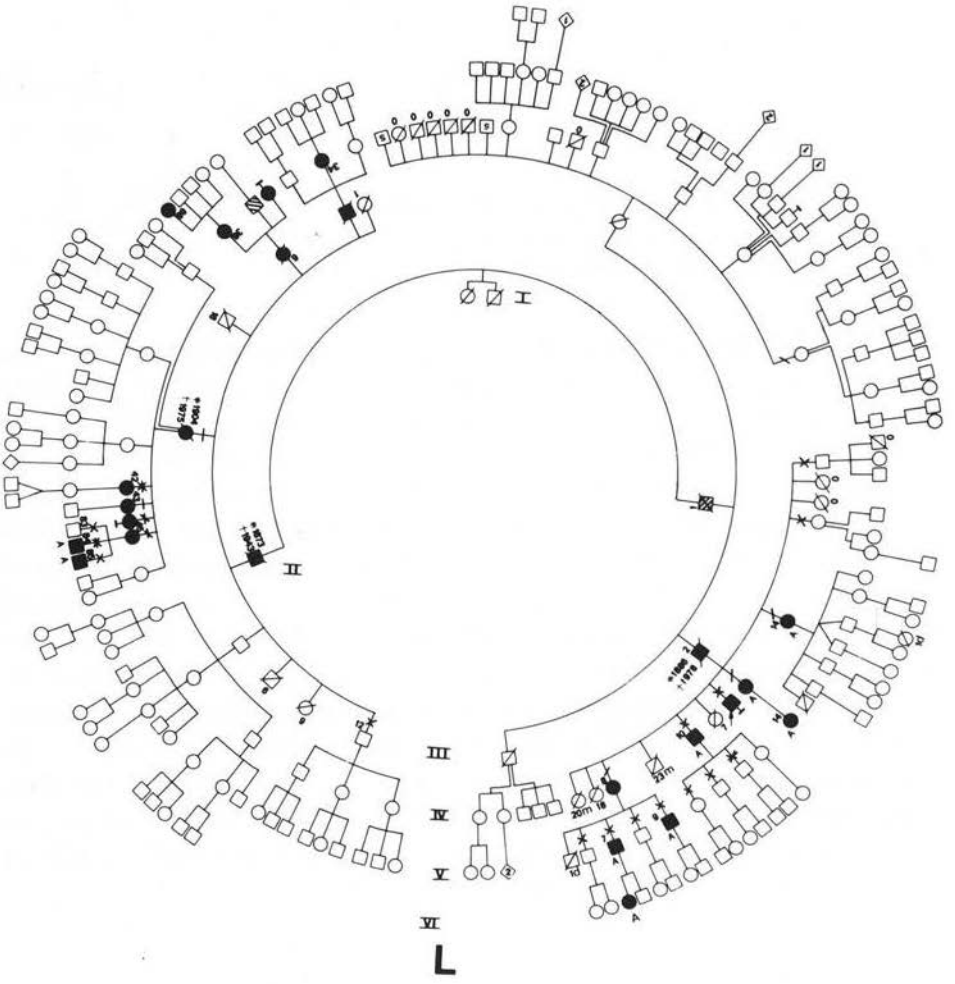
Kindred I: Many members of this family had been rose-growers living in the same village for centuries. Various degrees of severity were reported in the descendants of I 1. Among the members examined, one abortive case (V 6) was found.



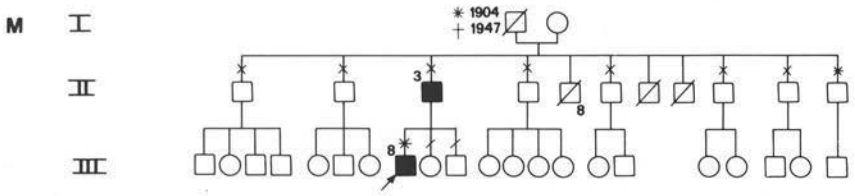
Kindred J: Several members of this kindred have been seen by other physicians in the past. Within this family large differences in the degree of involvement were noted. Asymptomatic patients of older age (IV 8, 54 years; IV 12, 47 years) and young, severely affected persons such as V 18 (22 years) have been seen.



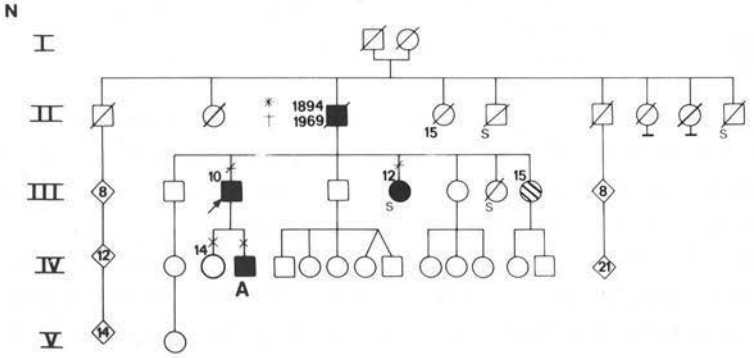
Kindred K: The proband (IV 2) told, when examined in the neuromuscular clinic, that only his half-uncle (III 20) was said to suffer from the same disorder. When visited at his home, his mother was found hanging out the clothes to dry on very low line, walking with a waddling gait and bilateral footdrop. For years she considered herself to suffer from rheumatism. Her sister (III 16) and her sister's son (IV 15) had no complaints and were minimally affected. III 20 refused a complete physical examination since he was very disappointed in his physicians for various reasons. His sister III 18 denied the obvious signs of her weakness and explained the weakness of her arms by fatigue. Neither would cooperate by permitting their children to be examined. All but one of the children of II 3 were definite that their mother was not affected. III 20 and III 19 said that III 24 had suffered from the same disease. They were not sure about II 6.



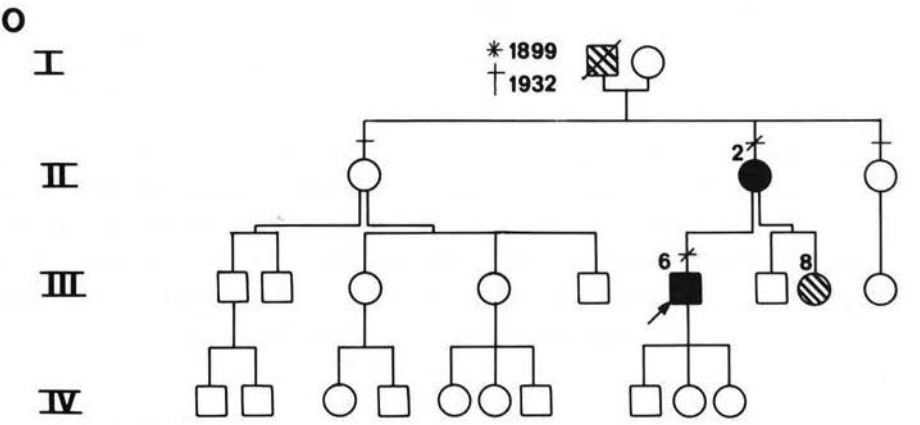
Kindred L: Descendants of I 1 were living in the same town. Their relationship was confirmed by tracing their common ancestor through the records of the registrar's office. The family was uncertain if II 1 was affected. There were many abortive cases in his offspring. Only III 2, IV 8 and IV 12 were symptomatic. Some of the descendants of II 2 could be examined. IV 42, IV 44 and IV 45 were notable because of the presence of ankle contractures.



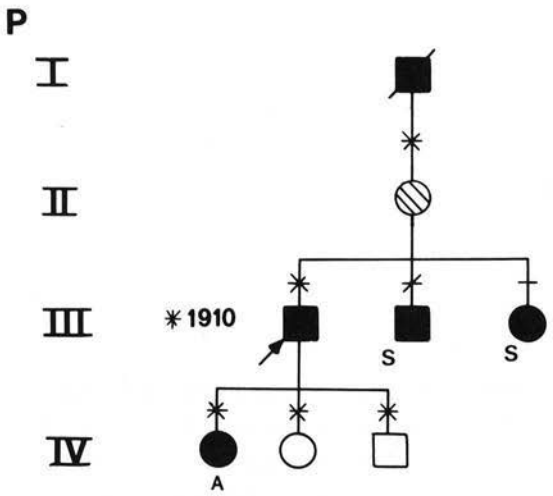
Kindred M: The proband of this kindred will be discussed in detail in section 4.19. on the infantile onset of FSHD. His father (II 3) demonstrated the normal pattern of FSHD. All his uncles appeared healthy. His grandmother (I 2) could not be examined, but was said to be without symptoms relating to FSHD. No muscular disease was known in his mother's family.



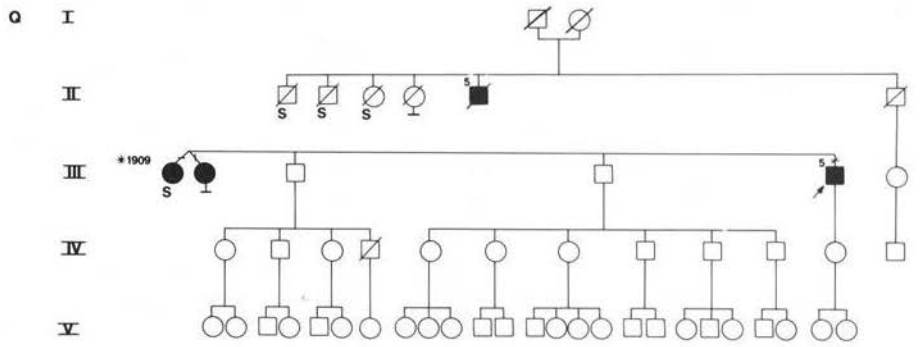
Kindred N: The proband (III 10) of this kindred demonstrated two notable features. Firstly, his calf muscles were rather bulky and slightly paretic (grade 4). Although he had been very muscular when he was young the question of pseudohypertrophy was raised. This will be discussed later. Fasciculations had been noted in the shoulder girdle muscles on a previous examination. We observed no myotonia nor fasciculations. Secondly, a biopsy of the left biceps muscle revealed a great variation in fibre diameter, more than 20% central nuclei, many ring fibres and sarcoplasmic masses, and many moth-eaten fibres. Patient III 12 was a more usual case of FSHD with no special features. A muscle biopsy in this case revealed no abnormalities. III 15 was said to be probably affected. IV 15 was affected but he had no complaints.



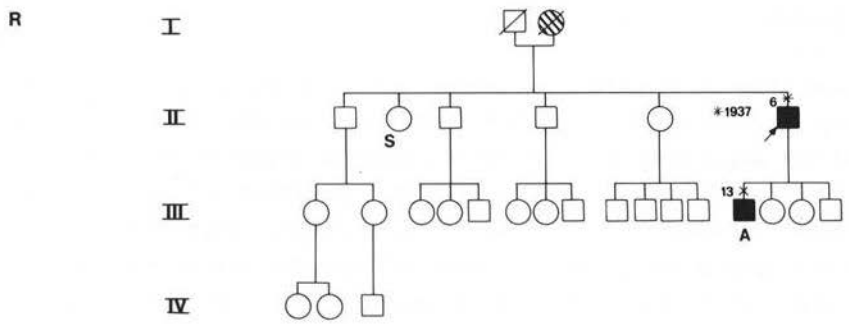
Kindred O: Proband III 6 had had a muscle biopsy. This biopsy could not be reviewed but was said to have demonstrated myopathic features. His half-sister III 8 had a wry mouth. She could not be examined. II 2 demonstrated facial weakness on a photograph at the age of three. It was suggested by the patient that the facial weakness might have been congenital but this could not be substantiated. She developed shoulder girdle weakness at the age of 14 and foot extensor weakness when 24 years old. Subsequently, ankle contractures became apparent and, at the time of examination, she was moderately affected. Her father (I 1) had died at the age of 34 of pneumonia. The family was not sure whether he was affected or not, but his sister had had "a wry face" and his mother a "crooked shoulder". No details on other relatives were available.



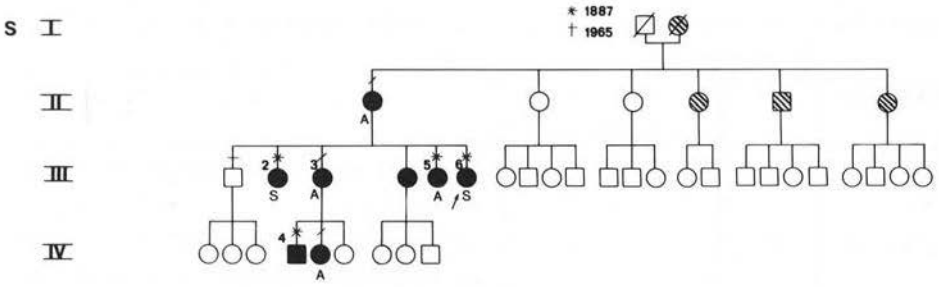
Kindred P: This kindred was particular in that II 1 was asymptomatic and without unequivocal physical findings suggestive of FSHD. She will be discussed in detail in the section on penetrance. Her father was known to have had a muscle disease. She is considered a carrier of the gene, which has not come to expression (yet). III 2 and IV 1 had no facial weakness, while the proband (III 1) had facial weakness with a protruding, immobile upper lip. III 1 showed myopathic features on EMG: he had normal motor nerve conduction velocities. Biopsy of his right biceps revealed small angulated fibres and type 2 predominance. III 2 showed neurogenic features on EMG: biopsy of the right deltoid muscle revealed no abnormalities.



Kindred Q: Proband III 5 was seen at the age of four at the neurological clinic because of shoulder girdle weakness. In his twenties or thirties he developed foot extensor weakness, but no further extension was noted on examination at the age of 52. At that time he had minimal facial weakness. Sensory examination had always been normal in the past. Diabetes mellitus was noted when he was 43 years old. Several years later, at the age of 50, he developed a mixed polyneuropathy. EMG of the lower legs, with slowing of the nerve conduction velocities, supported this diagnosis. EMG of the proximal arm muscles revealed a myopathic pattern. A muscle biopsy was refused. His sister (III 1) was noted to have facial weakness at the age of five. She developed shoulder girdle weakness when eight years old and was unable to walk unsupported at the age of 21. Her non-identical twin sister, III 2, noted shoulder girdle weakness when 20 years old and foot extensor weakness at the age of 48. When she was examined at the age of 72, she was unable to walk outside but she walked unaided at home. In both, sensory examination revealed no abnormalities. Both sisters refused a muscle biopsy. The father of these patients (II 5) had clearly been affected. He was said to have been able to walk for hours at the age of 60 years. He lived to be 86 years old and only in the last years of his life he was unable to stand up by himself. This family has been included in this study largely on the basis of clinical criteria like facial onset, the pattern of weakness on examination, and the course of the disease, and on the basis of the genetic criterion of autosomal dominant inheritance.



Kindred R: Proband II 6 was said to be the only one in his family with muscle disease. Only one of his four children, III 13, was examined: he was asymptomatic but physical examination demonstrated shoulder girdle weakness and atrophy. The facial muscles were not involved in this case. Photographs of the proband's mother were suggestive of facial weakness.



Kindred S: This pedigree is characterized by a considerable number of asymptomatic cases. The proband III 6 and her eldest sister III 2 both had slight ankle contractures and a rather severe facial weakness. A visit at home revealed that their mother (II 1) had facial weakness as well: she could not be examined in detail. A photograph of I 2 also suggested facial weakness. III 2, an intelligent woman and good observer, suggested on relevant grounds that other members of the family might be affected as well. These persons could not be examined.

4.4. Symptoms

Among the 107 affected persons, 73 were symptomatic (46 males and 27 females). The presenting symptoms are given in Table 4.7.. It is important to note that symptoms suggestive of pelvic girdle onset were not observed. In the majority of cases (82%) the presenting symptoms were those of shoulder girdle weakness. Only seven patients (10%) remembered events indicating early facial weakness (Table 4.8.). Most people could not answer

Table 4.7. Presenting symptoms in 73 symptomatic cases of FSHD.

	Facial weakness	Shoulder girdle weakness	Foot extensor weakness	Total
Males	2 (4%)	42 (91%)	2 (4%)	46 (100%)
Females	5 (18%)	18 (67%)	4 (15%)	27 (100%)
	7 (10%)	60 (82%)	6 (8%)	73 (100%)

Table 4.8. Observations indicating facial weakness being the presenting symptom of FSHD.

Patient	Sex	Age of observation	
F IV 1	F	7	Noticed mouth asymmetry in mirror herself.
I VI 11	F	6	Orbicularis oculi weakness noted by ophthalmologist consulted for spectacles.
I VI 21	F	6	Unable to blow up balloons.
J V 16	M	5	Unable to blow up a balloon in a competition.
K IV 2	M	6	unable to close his eyes while asleep.
O. II 2	F	3	Weakness of the orbicularis oris noted by family.
Q III 1	F	5	Her teacher observed that "she could not really smile".

questions about blowing up balloons or drinking through a straw because, as they said, they had never tried it. Inability to whistle is probably strongly suggestive of facial weakness, but the precise significance of this symptom is not clear. We observed inability to whistle in several elderly non-neurological patients who had no facial paresis and who could pout their lips. On the other hand, all medical students in a class of 50 and all unaffected persons in the families studied could whistle. Twenty-seven males (59%) and 18 females (67%) i.e. 45 (62%) symptomatic patients had never been able to whistle (Table 4.9.). At the time of examination 33 males (72%) and 23 (85%) females i.e. 56 (77%) symptomatic patients were unable to whistle. Ten other males and four females could whistle softly and with a twisted, asymmetric mouth. When the asymptomatic patients were asked about these symptoms it was found that one out of 13 males (8%) and eight out of 21 females (38%) had never been able to whistle. Although the average age of the symptomatic patients (45.3 years) was slightly higher than that of the asymptomatic patients (36.3 years), no conclusions can be drawn from these figures about the onset and progression of the disease in the asymptomatic cases since both are quite variable and independent of each other, as can be concluded from the symptomatic cases. Still it is noted that 54 of 107 patients (51%) never had been able to whistle, and that 67 of the 107 patients (63%) were unable to whistle at the time of examination. Although inability to whistle as a symptom

Table 4.9. Inability to whistle as a symptom of facial weakness.

	Symptomatic patients			Asymptomatic patients		
	Males	Females	Total	Males	Females	Total
Never been able to whistle	27	18	45	1	8	9
Lost the ability to whistle	6	5	11	0	2	2
Could whistle with:						
moderate facial weakness	4	2	6	2	5	7
mild facial weakness	6	2	8	8	5	13
no facial weakness	3	0	3	2	1	3
Total	46	27	73	13	21	34

of facial weakness may yield false positive findings and a substantial number of false negative findings it still may give an important hint as to who might be affected. Another, though rarer, symptom which we found more reliable is the inability to close the eyes completely while asleep: this always indicates weakness of the orbicularis oculi muscles. We never observed false positive findings.

Initial complaints relating to shoulder girdle weakness were inability to keep the arms sustained above shoulder level in various tasks. Pain in the shoulder region was not accepted as a diagnostic symptom of FSHD because it did not appear specific for it. However 21 symptomatic patients (28%) and three asymptomatic patients (9%) i.e. a total of 24 patients (22%), had suffered episodes of shoulder pains. One asymptomatic patient (L V 9) related pains in his right shoulder to his heavy work in the harbour of Rotterdam. The right shoulder girdle was more affected than the left on physical examination. In another asymptomatic patient (H IV 3) the pains in her left shoulder had been diagnosed as "frozen shoulder". She indeed had slight limitation of passive movement in the shoulder joint. The third asymptomatic patient (H V 20) had noted several episodes of shoulder pains, lasting hours. In four patients (D II 5, F IV 1, G III 19, S IV 4) the pains were thought to be related to the onset of the disease. Three patients(E III 1, I VI 23, J IV 27) had noticed episodes of shoulder pains lasting several days, followed by an exacerbation of the shoulder girdle weakness. Nine patients (A V 10, B III 6, C III 1, I VI 10, I VI 11, L IV 45, L V 80, N III 10, S III 2) were positive about a relation between shoulder pains and physical exertion in which the arms are used. Two patients (K III 12 and Q III 2) frequently had muscle and joint pains not clearly related to exercise. Three patients of old age (J III 1, J III 3, Q III 1), wheelchair-bound and dependent on nursing care, complained of severe muscle and joint pains upon being turned in bed, dressed, or lifted. Only in the last cases the explanation offered by Ketenjian (1978), who claims that stretching of tendons and weakened muscles causes pain, seems appropriate.

Six patients (Table 4.7.) presented symptoms related to the lower legs. Two men (B III 1, L IV 12) and one woman (E III 1) claimed they had foot extensor weakness only: they were not examined at that time. The son of E III 1 is positive that his mother had shoulder girdle weakness as well at that time, but she denied this. Three other women (L IV 42, L IV 44, S III 6) had both ankle contractures and foot extensor weakness at the time of first complaints. The ankle contractures contributed strongly to an early referral. When examined they all demonstrated shoulder girdle weakness as well.

4.5. Precipitating factors

Specific events precipitating the onset of the disease were not reported, nor was it possible to identify any. One patient (J VI 4) strongly believed that heavy labour and the preferred use of his right arm resulted in the severe atrophy and paresis of the right arm which was distinctly more seriously affected than the left.

Two patients (A V 14, F III 3) confirmed to notion that immobilisation in plaster casts has an adverse affect on the progression of the disease. Both had sustained a humerus fracture, and on mobilisation they noted a loss of muscle mass and strength in the upper arm that could not be regained by exercise. It is conceivable that immobilisation could elicit a first sign of the disease.

4.6. Presenting signs

Records on the clinical conditions made within a couple of years after the onset of symptoms were available only in a few cases. We saw only four patients (all males) within five years after the onset of their symptoms (Figure 4.2.). Assuming that sooner or later, with progression of the disease, the asymptomatic patients might become symptomatic, it was felt that

studying the signs in the asymptomatic patients could provide insight into the presentation of FSHD. Knowledge of the presentation is important in the discussion of the differential diagnosis. Table 4.10. shows the signs in the 34 asymptomatic patients. Facial weakness was the only sign in eight patients but in three women the shoulder girdle muscles could not be inspected for atrophy. Facial weakness was absent in two males and one female, i.e. in approximately 9% of the asymptomatic cases, which suggests that the majority of patients with FSHD will have facial weakness at the time of first symptoms.

Any combination of shoulder girdle weakness with facial, foot extensor or pelvic girdle weakness was observed. Foot extensor weakness was invariably minimal. Otherwise, obviously it would have led to complaints. Pelvic girdle weakness was present in two cases. Although unlikely, it is conceivable that pelvic girdle weakness could give rise to presenting symptoms in FSHD. In those cases, shoulder girdle weakness might be expected as well, but the correct diagnosis might be difficult if the family history is lacking. The frequency (12%) of pelvifemoral onset among the 95 cases of Chung and Morton (1959) is inconceivably high and raises suspicion that other disorders, such as spinal muscular atrophies, might have been included in their material, which could account for their remarks on genetical heterogeneity of the disorder under study.

table 4.10. The signs in 34 asymptomatic patients with FSHD.

	F	S	FS	SE	FSE	FSP	FSEP	Total
Males	1	1	7	1	2		1	13
Females	7	1	7	0	5	1		21
	8	2	14	1	7	1	1	34

F: Facial weakness; S: shoulder girdle weakness; E: foot extensor weakness; P: Pelvic girdle weakness.

4.7. The facial muscles

The facial muscles were examined as suggested by Kendall et al. (1971). No grading system was used for facial weakness. Facial weakness was the sole finding in eight cases (Table 4.10.), and was present in 101 (94%) out of the 107 patients. This percentage is higher than Becker's 81% (1953) and Chung and Morton's 83% (1959). Facial weakness was absent in three of the 34 asymptomatic cases (9%) and in three of the 73 symptomatic patients (4%). These percentages suggest that facial weakness can arise later in the course of the disease and are not contrary to the observation that B III 1 and B III 6 had no facial weakness ten years ago (according to their physician at that time) but did, when examined by us.

A remarkable finding is the frequent asymmetric involvement of the facial muscles (Table 4.11.). Occasionally, the orbicularis oculi muscle was weaker on one side and the orbicularis oris muscle weaker on the opposite side: this is referred to as "crossed asymmetry" in Table 4.11. Fifty-four patients had facial asymmetry which is 57% of all patients in whom the symmetry was judged and recorded. There was no preference for the right or left side, nor for males or females. It is not clear why and how facial asymmetry should develop. The jaws are often used asymmetrically in chewing and biting but these muscles are spared in FSHD. Several facial expressions require an asymmetric use of muscles but it is hard to understand how this could lead to asymmetric weakness and atrophy.

Table 4.11. Facial weakness in 101 patients with FSHD.

	Predominantly right-sided weakness	Predominantly left-sided weakness	Asymmetry crossed or not specified	Symmetric weakness	Weakness not specified	Total
Males	13 (24%)	11 (20%)	6 (11%)	18 (33%)	6 (11%)	54 (100%)
Females	9 (19%)	7 (15%)	8 (17%)	22 (47%)	1 (2%)	47 (100%)
	22 (22%)	18 (18%)	14 (14%)	40 (40%)	7 (7%)	101 (100%)

Three or more generations of abortive cases do occur (Pamboukis, 1931; our family S) but facial weakness without a clear autosomal dominant pattern of inheritance is not enough to make the diagnosis FSHD. We observed, in two years time, five (two males, three females) unrelated persons with weakness of the orbicularis oris muscle, who were referred to us for neurological problems not related to neuromuscular diseases. Both the men were aware of it because they never could whistle well, and they claimed it had not been progressive since their early youth. However, one of the males claimed his sister had a similar paresis. Neuromuscular disorders in any of the five families were reportedly not present, but these families could not be studied. Speculations that these five patients might be part of a large source of asymptomatic families with FSHD cannot be denied with certainty, although another explanation, such as congenital aplasia of the orbicularis oris muscle, seems more appropriate in these patients, as is properly illustrated in Mumenthaler's Atlas (1982).

4.8. The shoulder girdle, pelvic girdle and limb muscles

In 74 patients (46 males and 28 females; see Table 4.1) all muscles, indicated in Table 4.12., could be examined using methods as described by Kendall et al. (1971) and as published in the Medical Research Council (MRC) memorandum No. 45. All muscles were graded for their strength from 0 to 5 according to the MRC scale. The gradings of each muscle for all patients were added. The maximum score that could be reached for each pair of the same muscles on the right and on the left side was 740. Table 12 shows the percentages of the maximum score observed for each muscle pair. It is appreciated that grading of muscles around the shoulder joint may be difficult if the fixation of the scapula has weakened or is lost. In those instances, fixation was attempted by the examiner's hand. The teres major muscle was tested in two ways, by adduction of the upper arms and by having the arms internally rotated. Both tests are combined effort of

several muscles and the total score has to be interpreted with caution.

The group of 33 partially examined patients (see Table 1) included several seriously affected persons. The scores in Table 12, therefore, do not reflect the severity of the disease in the total group of patients. Four patients with facial weakness only were included in the group of completely examined patients.

The muscles were arranged in an ascending order of their scores. The truncal muscles could not be graded according to the MRC system. Their place in Table 12 will be discussed in section 4.9. Assuming a steady progression of the muscular weakness once a muscle has become affected, this transverse section gives a rough estimate regarding the order in which the muscles become involved in FSHD. The individual differences which are known to occur, are expected to level out in this large sample. Therefore, one should not adhere to this order rigidly, but it should be noted that the sequence of this transverse section is in agreement with the general picture of spread of disease based on anamnestic data (longitudinal section). Since we did not perform a longitudinal study, these data are the best available.

For the purpose of this study the muscles were grouped. Each group suggests a stage in the course of this disease. Each stage is marked by the onset of recognisable symptoms and signs. It is suggested in Table 4.12., that the scapular fixators, the latissimus dorsi, and the pectoralis major muscles are among the first to become affected. Involvement of these muscles and involvement of the facial muscles constitute the first stage of the disease. The onset of the second stage is marked by the involvement of the anterior tibial muscles. The peroneal muscles become affected later in this stage. In the shoulder region other muscles such as the infraspinatus, the supraspinatus, the teres major and, finally, also the deltoid muscles become involved. In the upper arms the triceps appears to be involved first, followed by the biceps. The lower arm muscles are notably spared in this stage. The brachioradialis muscles become involved in the third stage of the disease in this material, which is in contrast to the findings of Tyler and Stephens (1950), who noted an

Table 4.12. Mean scores of strength of muscles in 74 patients with FSHD (scores in percentages of the maximum score obtainable).

	Rhomboids	55
	Lower trapezius	59
Stage 1	Pectoralis major (sternocostal head)	63
	Serratus anterior	65
	Pectoralis major (clavicular head)	68
	Latissimus dorsi	74
	Abdominal Muscle Weakness	not scored
	Tibialis anterior	74
	Infraspinatus	76
	Triceps brachii	77
	Supraspinatus	78
	Teres major	79
Stage 2	Peroneus longus and brevis	79
	Extensor hallucis longus	80
	Extensor digitorum longus	81
	Extensor digitorum brevis	82
	Biceps brachii	83
	Deltoid (medial belly)	86
	Deltoid (anterior belly)	86
	Hyperlordosis	not scored
	Iliopsoas	89
	Brachioradialis	91
	Glutaeus medius and minimums	91
	Quadriceps femoris	92
Stage 3	Upper trapezius	93
	Adductors	93
+	Wrist extensors	93
	Neck flexors	94
	Glutaeus maximus	94
Stage 4	Hamstring muscles	94
	Sternocleidomastoid	96
	Finger extensors	96
	Triceps surae	97
	Wrist flexors	97
	Finger flexors	97
	Intrinsic hand muscles	98
	Neck extensors	99
Stage 5	Ambulatory indoors, unable to climb stairs. In wheelchair while outside.	
Stage 6	In wheelchair indoors. Dependent on nursing care.	

early involvement of these muscles in their patients

The third stage of the disease is marked by the start of involvement of the pelvic girdle and thigh muscles. Late in this stage the upper trapezius muscles, the neck flexors and the wrist extensors become involved. The relatively late involvement of the neck flexors in these patients is in agreement with observations made by Van Wijngaarden and Bethlem (1973).

The fourth stage is essentially characterized by progressive pelvic girdle weakness, leading to progressive disability. We would like to mark the onset of stage 4 with the loss of ability to climb stairs. Also in this stage there is further extension of the disease to the lower arms. Finally, the triceps surae and the neck extensors become involved.

We marked the onset of the fifth stage at the moment the patient became dependent on a wheelchair for all outdoor activities. The last stage, stage 6, covers the period a patient is wheelchair-ridden at home too; this always implies dependence on nursing care.

In our material the deltoid muscle did not appear so uniformly spared as is suggested in the literature (Brooke 1977). Table 4.13. shows that 40 patients of the 74 that could be examined completely, demonstrated weakness of the deltoid muscles. Distinct atrophy was present in 25 patients (34%). The pattern of atrophy was quite different from patient to patient, and different patterns were found within families. There is no good explanation for the partial atrophy of this muscle. Hypertrophy of the deltoid muscle was never observed.

Recent publications about thoracoscapular fusion (Copeland and Howard, 1978) and scapular fixation (Ketenjian, 1978) in FSHD have directed special interest towards the deltoid muscles. We repeatedly observed in mildly affected patients that the scapulae rose higher if abduction of the arms was resisted by the examiner. This suggests that the rise of the scapulae into the normal position of the trapezius muscles on abduction of the arms is, indeed, the result of the relatively strong deltoid muscles, pulling on the scapulae that have lost their muscular fixation to the chest.

There was only one patient in this material in whom scapular fixation was attempted (K IV 2). The sutures broke after several months. He was not operated upon again.

4.13. Deltoid muscle involvement in 74 patients with FSHD.

	Whole muscle atrophy	Proximal atrophy all bellies	Anterior belly atrophy	Posterior belly atrophy	Paresis no atrophy	No atrophy normal function	Total
Males	4	8	0	2	8	24	46
Females	1	5	1	4	7	10	28
	5 (7%)	13 (18%)	1 (1%)	6 (8%)	15 (20%)	34 (46%)	74 (100%)

4.9. The truncal muscles

The MRC scale does not provide adequate grading for the truncal muscles. The only test for the abdominal muscles used in this study consisted of asking the patient to try to come to a sitting position, while lying supine, without the use of the arms. Table 4.14. shows that 43 patients (58%) had abdominal muscle weakness. Seven patients had abdominal muscle weakness without foot extensor weakness, while the opposite was found in two patients. Abdominal muscle weakness thus appears to be a fairly early sign in FSHD. Under the same conditions as applied for the interpretation of Table 4.12., abdominal muscle weakness might be placed on the border between the first and second stage. A protruding abdomen, which is a rather subjective finding on the examiner's part, was scored separately. Forty-one patients with abdominal muscle weakness on the test had a protruding abdomen. Two patients with a protruding abdomen had no abdominal muscle weakness while tested.

Lumbar hyperlordosis is also a rather subjective finding. Since it probably reflects a compensatory mechanism for the pelvic tilt due to both an increasing abdominal muscle weakness and a hip extensor weakness, one might expect to note an

increased lumbar lordosis at the beginning of the third stage when a certain degree of abdominal weakness has developed and pelvic girdle weakness becomes apparent (Table 4.14.). It is possible that the strength of the iliopsoas muscle was recorded lower in a few cases because an increase of the lumbar lordosis, due to a lack of compensatory mechanisms of the abdominal muscles, was not taken into account. Still it is felt that this would not have a great influence on the sequence of muscle involvement, as suggested in Table 12.

Table 4.14. Involvement of truncal muscles as compared to pelvic girdle and foot extensor involvement in 74 patients with FSHD.

	Abdominal muscle weakness	Foot extensor weakness	Pelvic girdle weakness	Lumbar hyper-lordosis	All patients
Males	29	23	19	18	46
Females	14	15	10	9	28
	43 (58%)	38 (51%)	29 (39%)	27 (36%)	74 (100%)

4.10. Asymmetry of muscle involvement

Becker (1953) noted that the shoulder girdle muscles on the right side were significantly (P2 = 0.03 sign test) more severely affected than those on the left side in his patients. We considered asymmetry to be present if the strength of similar muscles on the right and left side differed one degree or more on the MRC scale, if either side was graded 4+ and the other 4- on the MRC scale, or if there was a distinct difference in muscle atrophy. A preference for right-sided shoulder girdle or arm weakness was observed in 39 patients (Table 4.15.). In 17 the left side was more involved. Twelve patients had some muscles on the right side and others on the left side that were more involved than the corresponding muscles on the opposite side. The preference for the right shoulder or arm was statistically significant (P1 = 0.005 sign test). No such preference was found

in 72 patients with pelvic girdle or lower extremity involvement. In 13 of these patients the right leg or the right side of the pelvis showed more involvements and 16 patients were more affected on the left side. An alternating picture was present in one patient, 19 patients had a symmetrical clinical picture, and in 23 patients definite data on laterality were lacking.

Table 4.15. Preference of side of shoulder girdle involvement in 107 patients with FSHD.

	Right side	Left side	Alter-nating	Symmet-rical	Facial weakness only	Limited data	Total
Males	24	10	8	8	1	8	59
Females	15	7	4	9	4	9	48
	39	17	12	17	5	17	107

We scored arbitrarily right arm and left leg preference each + 1, and left arm and right leg preference each - 1. Symmetric involvement, no involvement or alternating involvement of several corresponding muscles on similar girdles or extremities were scored 0. Adequate data for scoring were present in 77 patients (see Table 4.16.). The total score of all individuals was +22, which proved to be statistically significant when compared to the

Table 4.16. Scores of laterality of muscle involvement in 77 patients

		Arms			
Scores		-1	0	+1	
L	-1	1	5	7	13
E	0	11	16	21	48
G	+1	3	7	6	16
S					
		15	28	34	77

variance of scores between the individuals (P2 = 0.01 Student's

test), indicating that the preference of involvement of the right shoulder and upper extremity was not related to a preference for the right side of the body.

Variance analysis of the score per kindred demonstrated a significant influence of the kindred on the score (P = 0.02 Fisher's F-test) and no significant influence of the individuals (P = 0.2 Fisher's F-test).

The results so far were rather surprising and we had no information on handedness of the patients at the end of our investigation. Therefore, we sent questionnaires to all patients, asking them if they considered themselves right- or left-handed. In addition we asked them which hand was used for writing, throwing a ball, dealing cards, brushing teeth, and eating soup. Forty-three patients of the 56 patients with asymmetry of shoulder girdle or arm involvement responded (Table 4.17.). All patients had a clear preference for one arm: no ambidexterity was reported. The association between the side of most involvement and handedness was tested in a four-fold contingency table yielding a one-sided tail probability of 0.01.

Table 4.17. Preferred side of shoulder and arm weakness and handedness in 43 patients.

		Preferred side		Total
		Left	Right	
Handedness	Left	3	1	4
	Right	8	31	39
Total		11	32	43

Because we used several statistical tests on the item of laterality, a correction had to be made for the critical level of the tail probabilities. The main factor determining this level for a total of mutually independent tests is the number of tests involved. We therefore fixed our probability of an error of the first kind at 0.0125 for each of the four tests performed. This requirement was not met by the test on the influence of the kindreds only. We therefore would like to conclude that the right

shoulder girdle and arm were significantly more often more seriously involved than the left; this asymmetry was not related to body side but was associated significantly with handedness.

4.11. Reflexes

The myotatic reflexes were spared in all cases with the disease limited to the shoulder girdle muscles (stage 1). With further spread the myotatic reflexes were lower and ultimately absent. Absent myotatic reflexes were not necessarily related to severe involvement. Asymmetry in myotatic reflexes was often but not always related to asymmetry of muscle involvement.

The myotatic reflexes of the legs tended to be spared longer than those of the upper arms. The Achilles' tendon reflex disappeared in several cases without signs of involvement of the calf muscles, while the opposite, i.e. foot flexor weakness with positive ankle jerks, was never observed. The knee jerk was often preserved till late in the course of the disease, but any suggestion of an order of disappearance of the myotatic reflexes was opposed by numerous observations to the contrary. The plantar responses never were pathological.

4.12. Muscle contractures

Muscle contractures were indeed quite rare in our material, with the exception of ankle contractures, which were found in ten patients (one male, nine females) out of 102 (10%) that could be examined for this feature. In three female patients (L IV 42, L IV 44, S III 6) ankle contractures gave rise to the first symptoms. In three other females (L IV 45, O II 6, S III 2) ankle contractures developed in the course of lower leg involvement. The male patient (M III 8) and three females (E III 1, J III 3, Q III 1) were all in an advanced stage of the disease and completely dependent on wheelchairs. Achilles' tendon elongation has been performed in two patients (L IV 44, Q III 1), both with

poor results and no subjective improvement of the patients' conditions.

A pronation contracture of both lower arms was present in E III 1. Patient M III 8 had a flexion contracture of his right arm, limitations of movement of both wrists, and flexion contractures of both hips and knees, in addition to the abovementioned ankle contractures.

The left sternocleidomastoid muscle was transected in patient L IV 42 at the age of 12 years because of a progressive torticollis. At the time of examination she was unable to bend her head completely laterally to the right. The left sternocleidomastoid muscle was absent, but the left trapezius and scaleni muscles appeared tight and contracted. Rotation to the right was minimally impaired. Anteflexion and retroflexion of her head were unimpaired.

4.13. Hypertrophy of muscles

Hypertrophy of muscles was rarely observed. One patient (M II 3) had hypertrophy of the infraspinatus muscles. Two patients (A V 10 and S III 6) had a remarkable hypertrophy of the extensor digitorum brevis muscles as described by Brooke (1977). These muscles tend to be spared for a long time and were found to be absent only in the severely affected patients confined to bed and wheelchair. Hypertrophy of these muscles apeared to be a transient phenomenon in the course of FSHD in some patients and a compensatory mechanism for a footdrop.

Hypertrophy of the calf muscles was observed in two male patients (M III 8 and N III 10). In the former, the calf muscles were firm on palpation and severely paretic (grade 2). This patient will be discussed in detail in the section on the infantile form of FSHD. The latter had been a very muscular man, as could be judged from photographs, and in contrast to the foot extensors the calf muscles were very well developed, but slightly paretic (grade 4) at the time of examination. In both instances hypertrophy of the calf muscles was not present in other patients

in these families. Both cases meet the requirements of the clinical definition of pseudohypertrophy of muscles i.e. hypertrophy with weakness.

4.14. Skeletal abnormalities

In 81 patients (49 males and 32 females) the backs could be examined properly. A scoliosis was observed in 18 males (37%) and eight (25%) females, i.e. in 26 (32%) patients. Only one patient (M III 8) had a severe and progressive kyphoscoliosis that compromised respiratory functions. He had several other notable findings and his case will be discussed in section 4.19 on the infantile form of FSHD. In all other patients the scoliosis was quite mild and most patients were not aware of it. An increased thoracic kyphosis was present in five males (10%) and in four females (12.5%) i.e. in nine (11%) out of 81 patients.

A progressive costal gibbus was present in the patient with severe scoliosis mentioned above (M III 8) and in another male patient with a mild scoliosis (F III 3). Both had an increased thoracic kyphosis. The latter patient had no respiratory complaints.

Pectus excavatum was not observed as frequently as reported by Tyler and Stephens (1950). We observed this in four patients (three males, D II 5, D III 11, J V 18, and one female, L IV 42). Foot deformities have never been observed.

4.15. The cardiac muscle

Cardiac complaints were very rare in the patients under study. Patient C II 6 had angina pextoris and suffered a myocardial infarction at the age of 47 years. In another patient (J III 3) chronic heart failure was diagnosed at the age of 78 years. She suffered a small myocardial infarction when 81 years old. A third patient (D II 5) had coronary and peripheral atherosclerotic disease and chronic heart failure. An aorta

bifurcation prosthesis had been implanted and he was treated with diuretics, digoxine and acenocoumarol. Patient G III 19 had a congenital valvular disease and underwent a commissurotomy at the age of 14: she was free of symptoms at the time of examination. One patient (L IV 44) underwent a cardiologic examination in the course of establishing the diagnosis. The electrocardiogram and phonocardiogram were within normal limits. Two of the deceased patients (B II 1, J III 6) were said to have died from a heart attack.

It appears that cardiac disease in these patients with FSHD was rather a result of a vascular disorder than of a cardiomyopathy.

4.16. Concomitant diseases

Concomitant diseases in our material appeared to be a matter of coincidence. Strumectomy had been performed in one patient. Another deceased patient was said to have suffered from thyroid disease. Other operations, not mentioned in Table 4.18, were gastrectomy (1), appendectomy (2), hysterectomy (1), cholecytectomy (1), scapular fixation (1), and Achilles' tendon elongation (2). The patient with late onset hydrocephalus underwent ventricular drainage. The eye was removed in the patient with the retinoblastoma. A brother of this patient had a retinoblastoma as well; he had no muscular weakness. Retinitis pigmentosa was present in two sisters with FSHD. A third sister with FSHD was ophthalmologically normal.

Intermittent low back pain as a sole symptom was present in four patients. None of them had a severe hyperlordosis. An episode of sciatic pain was reported in two patients.

Psoriasis was found in three patients with FSHD in one family, but it was also present in non-affected members.

Severe depressions were reported in three instances. Two patients related their depressions to the neuromuscular disease. The third patient was an asymptomatic case.

Psychotic episodes have been reported in two patients.

Mental retardation has not been observed in this patient-material.

Table 4.18. Concomitant diseases in 107 patients with FSHD.

Transient ischaemic attack	1
Stroke	1
Hypertension	2
Varicose veins	2
Diabetes	1
Strumectomy	1
Hydrocephalus	1
Retinoblastoma	1
Retinitis pigmentosa	2
Low back pain	4
Sciatica	2
Psoriasis	3
Depression	3
Psychosis	2

4.17. The age of onset

The problem of the age of onset has been discussed in Chapter 2. We divided the patients in symptomatic and asymptomatic ones (abortive cases). The symptomatic patients could give more or less precise information on the onset of muscle weakness. Most of the asymptomatic patients were not aware having the disease. A few of them (E V 1, L V 84, P IV 1) were brought to the attention of a physician by their concerned parents and were made aware of their condition. A similar problem is observed regarding facial weakness. Most patients were not aware of it at the time of examination. Questions about the inability to whistle suggest that facial weakness might be the earliest symptom in the majority of cases. Reporting facial onset depends to a great extent upon an attentive family.

The ages of onset in the symptomatic group of patients are

presented in Figures 4.6. and 4.7.. The mean age of onset of the disease was 17.0 years, if all symptoms were considered (Table 4.19.). The differences between the onset in males (15.8 years) and females (19.0 years) was statistically not significant (P2 = 0.1 Student's t-test). As facial weakness remained unnoticed in the majority of cases, the age of first complaints of any muscle, other than the facial muscles, probably is a more comparable situation in the course of this disease. If symptoms of facial weakness were excluded, the mean age of first symptoms was 17.8 years for all patients. Then the difference between males (16.1 years) and females (20.6 years) was statistically significant (P2 = 0.02 Student's t-test). The last figures do not reflect an early stage of detection.

FIGURE 4.6: AGES AT ONSET OF SYMPTOMS IN 73 PATIENTS (46 MALES, 27 FEMALES)

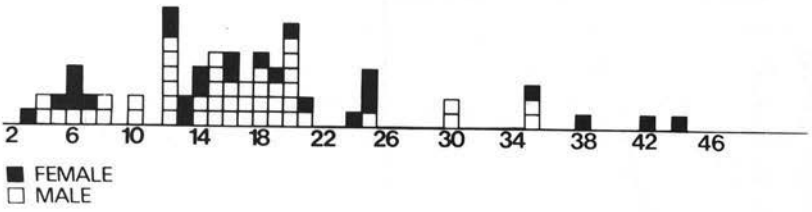


FIGURE 4.7: AGE AT ONSET OF SYMPTOMS (FACIAL SYMPTOMS EXCLUDED) IN 46 MALES, 27 FEMALES

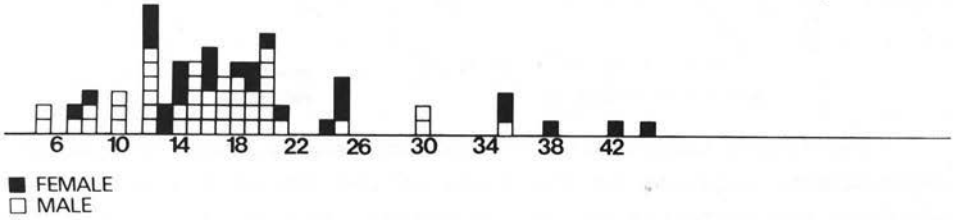
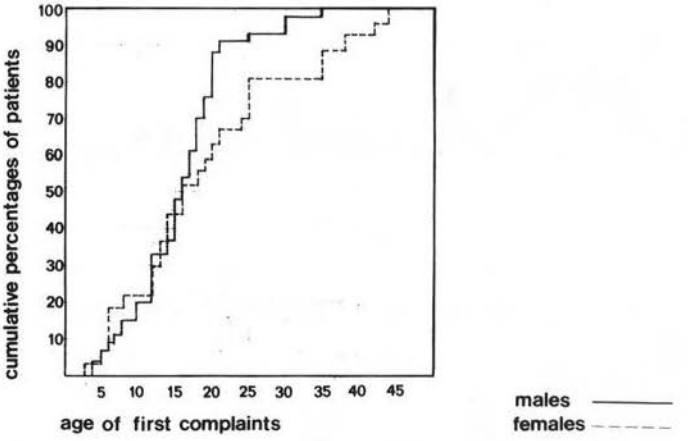


Table 4.19. Mean age at onset in 73 symptomatic patients

	Males	Females	All patients
Facial symptoms included	15.8 (SD6.5)	19.0 (SD11.6)	17.0 (SD8.8)
Facial symptoms excluded	16.1 (SD6.2)	20.6 (SD10.2)	17.8 (SD8.1)

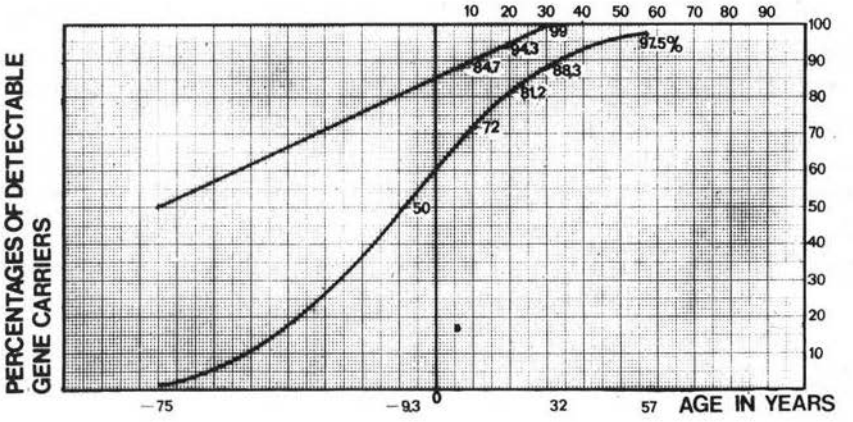
The age of first complaints of all symptomatic patients, given in cumulative percentages, is represented in Figure 4.8.. It shows that at the age of 20 years at least 89% of the males and 63% of the females, that will be symptomatic, can be diagnosed. At the age of 30 years, these percentages are 98 and 81 respectively. For genetic counseling one is particularly interested in the asymptomatic cases. Figure 4.5, which reports only the 49 extensively studied sibships, suggests that in all decades but the first, the expected 50% affected persons can be diagnosed by clinical examination; however, the standard error in the estimated probability of missing a gene carrier in the second decade is rather large (0.229), due to the limited number of observations, so that no firm conclusions can be drawn.

FIGURE 4.8: cumulative percentages of ages of first complaints in 73 symptomatic patients (46 males, 27 females)



Regression analysis offers another way to also include the asymptomatic patients in the study of the age of onset. Such an analysis was performed on the segregation data of the cohort ages in 84 patients and 80 healthy sibs in 49 sibships (Table 4.6.). If it assumed that a linear relation exists between the age and percentage of affected cases, one finds that at the age of 32 years all cases can be diagnosed by clinical examination (Figure

FIGURE 4.9: PERCENTAGES DETECTABLE GENE CARRIERS AT DIFFERENT AGES, CALCULATED FROM REGRESSION ANALYSIS



4.9.). At the ages of ten, 20 and 30 years these percentages are 89.7, 94.3 and 99.0 respectively, with a standard error of 9.5%, 7.3% and 5.6% respectively. Fifty percent of the cases can be diagnosed at the age of -75 years. This would be the mean age at onset. The reason for this strange figure lies in the fact that already in the second decade all expected cases could be diagnosed. Clearly, such an analysis is a theoretical one and not much in agreement with reality.

If regression analysis is performed under the assumption that the relation between the age and percentage of affected cases is represented by an S-shaped curve or ogive, the mean age at onset is found to be -9.3 years (Figure 4.9.). This figure appears not to be in contradiction with the statement that a congenital manifestation is within the possibilities of FSHD. According to these calculations, it is possible to diagnose 72.0% of the cases at the age of ten years, 81.2% at the age of 20 and 88.3% at the age of 30 years, with a standard error of 38.3%, 16.9% and 18.1% respectively. The assumption of an ogive is probably more in agreement with the reality since the curves of the ages at onset based on symptoms (Figure 4.8.) appeared to be ogives. Regression analysis has not been performed for males and

females separately because the sex differences in this material were not statistically significant (see section 4.23. on sex-influences).

Variance analysis on the ages of onset revealed no significant correlation between the ages of onset among sibships (P = 0.2 Fisher's F-test) or among kindreds (P = 0.2 Fisher's F-test). These figures led to an intraclass correlation of individuals belonging to the same kindred of 0.06806 and to an intraclass correlation of individuals belonging to the same sibship of 0.24875. From these estimates non-genetic factors appear to play a large role in the age of onset of the disease.

4.18. Abortive cases

Abortive cases are defined as asymptomatic cases. The distinction between symptomatic and asymptomatic patients serves only the practical purpose of studying FSHD. Symptoms of shoulder pain were not accepted as specific for FSHD. Inability to whistle is a fairly reliable sign of facial weakness. It suggests early onset of the disease. But it was never brought out as a complaint, and since it could not help to establish the onset of the disease more precisely, it was disregarded as a criterion on which to base the decision whether a patient was symptomatic or not. It turned out that only a fair degree of girdle or extremity muscle weakness led to complaints. Patients with complaints constitute the symptomatic group and by reciprocity the patients without complaints of muscle weakness form the asymptomatic group.

There were 34 (32%) asymptomatic patients among 107 studied (Table 4.20.). The ages are presented in Figure 4.10.. If we consider the 49 sibships that were extensively studied, the percentage of abortive cases was 30%.

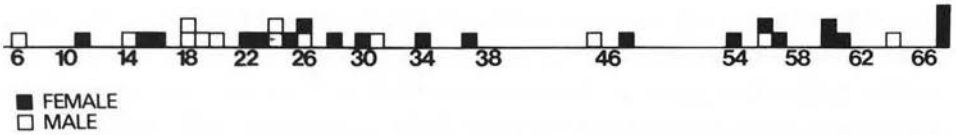
The differences between the absolute numbers of males and females was statistically not significant but, if percentages were considered, the difference between asymptomatic males and females among all patients studied was statistically significant

(P = 0.016 Student's t-test).

Table 4.20. Asymptomatic patients with FSHD.

	Males	Females	Total
All cases considered (107 cases in 19 kindreds)	13 (22%)	21 (44%)	34 (32%)
49 sibships considered (105 cases in 17 kindreds)	12 (21%)	20 (42%)	32 (30%)

FIGURE 4.10 AGES IN YEARS OF 34 ASYMTOMATIC PATIENTS (13 MALES, 21 FEMALES)



The differences between the percentages of males and females remained more or less the same for many years (Table 4.21.). Since the natural history of the asymptomatic cases is not known, one cannot conclude that such findings indicate that women tend to remain asymptomatic for a longer period of time than men.

Table 4.21. Percentages of asymptomatic patients at different ages.

	All cases	> 20 years	> 30 years
Males	22% (13/59)	16% (8/50)	10% (4/40)
Females	44% (21/48)	40% (18/45)	35% (13/37)
Total	32% (34/107)	27% (26/95)	22% (17/37)

Variance analysis of the cohort data of the 49 extensively studied sibships yielded no significant influence (P = 0.1 Fisher's F-test) of sex and no influence (P = 0.2 Fisher's F-test) of the decades on the frequency of abortive cases. Regression analysis demonstrated no significant (P > 0.05) decrease or increase of the number of abortive cases per decade.

There are two possible explanations for this finding: some patients will remain asymptomatic all their lives or, at each age, some previously asymptomatic patients may become symptomatic, while other gene carriers will develop the first detectable signs and will become asymptomatically affected. The latter mechanism is probably not of great importance, since at most decades the expected 50% of affected sibs could be found (Figure 4.4.).

It is important to note that asymptomatic patients may be found up to the seventh decade. It should be clear that one can never rely on family data if all cases in a family have to be detected.

The degree of muscle involvement in the asymptomatic cases was quite variable (see Table 4.10.). The clinical picture in these cases has been discussed in section 4.6. on the presenting syndromes. The impression existed that a certain, unquantifiable, degree of dissimulation was present in several cases. Denying seemed definitely present in the two cases with pelvic girdle weakness. The man (B IV 4) was unable to run properly and the woman (H IV 3) even refused to accept any other explanation than her mild obesity for her difficulties in climbing stairs.

4.19. Infantile onset and onset in early childhood

Infantile onset, i.e. onset within the first two years of life, was not observed in our patients. Also Möbius' syndrome was never mentioned. Patient O II 2 demonstrated a distinct asymmetry of the orbicularis oris muscle on a photograph taken at the age of three years. Her mother had said that this sign was present at birth but this could not be confirmed. In her case the disease was slowly progressive, with the onset of shoulder girdle weakness at the age of 14 years (see kindred O).

There were several patients in this study who had onset of the disease before the age of seven years (Table 8). Patient Q III 5 was presented at the neurological clinic of the "Wilhelmina Gasthuis" in Amsterdam at the age of four years. Shoulder girdle

weakness was noted several months earlier. In his case the disease ran a rather mild course which is reported in more detail in the description of his kindred. Patient Q III 1 was observed to have facial weakness at the age of five, and shoulder girdle weakness when eight years old.

Another patient that deserves particular attention is M III 8. His parents appeared unrelated. Pregnancy and delivery were unremarkable. His mother thought he was slow in motor development, yet he stood unsupported at 15 months and walked with 17 months. His facial expression was unobtrusive at that time. At the age of four years he was noted to have a waddling gait and to have difficulties in running. At the same time, shoulder girdle weakness became apparent. When he was examined at the age of nine years he had a mild to moderate facial weakness, but a severe paresis of the neck flexors, the shoulder girdle and the upper arm muscles, while the distal arm and intrinsic hand muscles were only minimally to mildly involved. He had pelvic girdle, quadriceps and foot extensor weakness. The quadriceps femoris and triceps surae appeared to be hypertrophic. Myotonia or fasciculations were not observed.

The disease progressed rapidly. He was completely dependent on an electric wheelchair since he was 11 years old. When he was examined at the age of 19 he had a moderate to severe facial weakness. The extraocular, the masseter, the temporalis, the lingual and the pharyngeal muscles were unaffected. His wheelchair was slightly tilted backwards to prevent head and truncal collapse. He had developed a rather severe thoracolumbar kyphoscoliosis and a pectus excavatum. The use of his right hand was very limited. He steered his wheelchair using the right wrist. With his left hand he controlled several electronical devices and a typewriter. His pelvic girdle and upper leg muscles were all graded 1 or 0. He had a severe paresis of his triceps surae muscles (grade 3), which still appeared to be hypertrophic amidst the general atrophy, and a bilateral foot extensor paralysis. Both extensor digitorum brevis muscles could be felt to contract without a visible movement. There was a generalized areflexia.

He had a flexion contracture of his right elbow. All

movements of both his wrists were limited and he had bilateral hip, knee and ankle flexion contractures.

At the age of nine years serum CK activity was 1265 U/L. EMG at that time demonstrated a myopathic pattern. The conduction velocity of the right peroneal nerve was 53 m/sec. Biopsy of the left quadriceps femoris muscle showed myopathic features only.

The father (M II 3) had never been able to whistle. When he was eight years old he developed a progressive shoulder girdle weakness. Foot extensor weakness was noted at the age of 20 years and pelvic girdle weakness at the age of 33 years. At the age of 43 he displayed an average case of FSHD in stage 3. All his brothers were examined and appeared unaffected. His mother could not be examined. She was said to have no muscle weakness. The mother of the proband had no symptoms and her family history was unremarkable.

The case of M III 8 is certainly unusual for FSHD. The hypertrophy of the calf muscles is rather exceptional. The high levels of CK activity might reflect the rate of progression of his disease and the contractures could have been the result of his confinement to bed and wheelchair. The facial weakness had initially been mild, which is different from the cases with the infantile form of FSHD described by Brooke (1977) who all had early and severe facial weakness. Most, but not all, of Brooke's patients had a parent who was minimally affected, which is also different from this case. Still there are no good grounds to reject this case as an unusual expression of a quite variable disease. Also the other patients described in this section testify to the variability of the expression of FSHD. These patients and the other patients mentioned in Table 8 demonstrate clearly that FSHD can manifest before the age of seven years, as was stated by Landouzy and Dejerine (1885) but denied by Tyler and Stephens (1950) and Becker (1953), and that an early manifestation does not necessarily imply the presence of the syndrome with severe facial weakness described by Brooke (1977).

4.20. The clinical course and disability

The course of the disease in our patients will be assessed in two ways. Firstly, we will look at the onset of symptoms. They certainly do not reflect early detectable weakness as is stated in 2.2., but they represent a kind of longitudinal section through our patient-material. Secondly, we will attempt a transverse section and describe the clinical picture at the time of examination.

Table 4.22. gives the onset of symptoms in 73 patients. The mean age of first symptoms, facial symptoms excluded (Table 4.19.), was 16.1 years in males and 20.6 years in females and 17.8 years for all patients. These figures are lower than the mean age of shoulder girdle weakness because a small group of patients first noted foot extensor weakness (group ESP). It is suggested that the shoulder girdle weakness in the ESP group was very slowly progressive, while the onset of foot extensor weakness did not differ significantly from the average for the whole group of patients: if these patients were examined early, they all showed shoulder girdle weakness as well. Symptoms of pelvic girdle weakness also developed quite late in the ESP group, so that this group of patients probably reflects a slow progression of the disease. The five patients in this group (B III 1, E III 1, L IV 12, L IV 42, L IV 44) came from three families. In two patients ankle contractures were present at the first examination. In all these families other patterns of spread of disease have been observed.

The last group, indicated with a question mark, represents all patients who could not give precise ages of the onset of all symptoms. One female (S III 6) had foot extensor weakness and tight heel cords at the age of 14. She noted shoulder girdle weakness when 19 years old but she was unable to tell when symptoms of pelvic girdle weakness were noted first. All other patients in this group had presented with shoulder girdle weakness. Two of them could indicate the onset of foot extensor weakness and five patients remembered the onset of pelvic girdle weakness. Most of these patients though could indicate the Table

4.22. Mean age of first symptoms in 73 patients.

Sequence of muscle involvement	Sex	Number of patients	Mean age at onset of symptoms			Mean age at time of examination
			S	E	P	
S	M	12	16.2			32.3
	F	3	18.7			30.3
	Total	15	16.7			31.9
SE	M	6	16.2	27		32.8
	F	4	23	32		41.5
	Total	10	18.7	29		36.3
SEP	M	15	14.9	22.8	33.4	47.5
	F	5	21	33.4	43.6	57.2
	Total	20	16.5	25.5	36.0	49.9
SP	M	2	17.5		34	47
	F	2	14		27	28.5
	Total	4	15.8		30.5	37.8
SPE	F	2	19	37	23	46
ESP	M	2	45	25	53.5	59
	F	3	41.7	33.7	45.7	52
	Total	5	43	30.2	48.8	54.8
?	M	9	15.8	?	43.7 (131/3)	50.2
	F	8	17.6	25 (75/3)	40.5 (81/2)	61.9
	Total	17	16.6		42.4 (212/5)	55.7
All groups	M	46	17	24.1	36.7	42.6
	F	27	21.7	32.0	38.3	49.7
	Total	73	18.7	27.5	37.3	45.3

S: shoulder girdle muscles; E: foot extensor muscles; P: pelvic girdle muscles; ?: sequence unknown (see text); M: males F: females.

sequence of muscle involvement.

Table 4.22. suggests that, for the group as a whole, foot extensor weakness might be present nine years after the onset of symptoms and that again ten years later symptoms of pelvic girdle weakness might be expected. Such global statements should be handled with extreme caution because the onset of symptoms of foot extensor weakness varied from 0 to 28 years and the onset of pelvic girdle weakness from 0 to 33 years after the onset of shoulder girdle weakness, and some patients even presented with foot extensor weakness. Moreover, other patients will never develop more than shoulder girdle weakness, and some will remain asymptomatic. Patients H IV 5 and I V 7 had been symptomatic for 46 and 39 years respectively. At the time of examination the disease was still limited to the upper extremities.

In order to compare the clinical pictures in our patients we staged their condition as outlined in Table 4.12. The stages were chosen so that all partially examined patients could be classified as well. Stage 1 also comprises patients with the disease limited to their facial muscles. The four patients with pelvic girdle weakness but no foot extensor weakness were classified in stage 3. The different stages reflect an increasing severity of the disease and the criteria for each stage are chosen so as to represent an increasing disability as well. Table 4.23. shows, as could be expected, an increasing severity with age. A similar tendency, although less distinct, is shown in Table 4.24 where the stage of the disease is compared to its duration in 73 symptomatic patients. A comparison of the two tables shows that the bulk of the patients of stage 1 in table 4.23. is formed by the 24 asymptomatic patients, of which eight patients had facial weakness only.

Table 4.23. Stage of the disease related to age at examination in 107 patients.

Stage	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	Total
1	1	9	11	7	2	1	4			35
2		1	2	2	3	7	3			18
3			5	12	7	10	5	1		40
4					1		1	2		4
5						2	1	1		4
6		1				1	1	1	2	6
	1	11	18	21	13	21	15	5	2	107

Table 4.24. Stage of the disease related to its duration in 73 symptomatic patients

Stage	0-9	10-19	20-29	30-39	40-49	50-59	60-69	Total
1	5	2	2	1	1			11
2	2	3	3	1	1			10
3	3	9	12	8	6			38
4				2		2		4
5			1		2	1		4
6		1	1	1	1		2	6
	10	15	19	13	11	3	2	73

Stage 3 includes many patients with a clinical picture ranging from minimal pelvic girdle weakness, detectable only at examination, to such a degree of weakness that climbing stairs was just possible with extreme effort. The average duration of this stage is probably longer than the previous ones, since this stage involved the largest number of patients, but no adequate data were available to assess this problem.

It is clear though, that the majority of the symptomatic patients (81%) are within the first three stages of the disease, but table 4.23 demonstrates that six out of seven patients (86%) over 70 years of age are within stage 4 or even higher. Since, as will be demonstrated later, the age of death is probably not

affected by the disease, and since the average expected life span in the Dutch population is 72 years in men and 78 years in women, a distinct degree of disability might be anticipated at an older age. If disability is judged by complete inability to walk, only six patients qualified for this criterion. Ten patients (9%) needed a wheelchair when outside their houses. Four of six patients in stage 6 were in a nursing home. Two were nursed at their homes by their husbands with the aid of district-nurses. All patients in stage 1 to 5 were living with their families.

Fifty-two male patients were between the ages of 18 and 65 years. Five patients were still at school or university. Eleven of the 47 patients (23%) were unemployed. Their disabilities were the major reason for unemployment in all patients.

Table 4.25. shows the stage of the disease related to sex. None of the stages revealed a significant difference between the numbers or percentages of males and females. If we adopt Becker's (1953) criterion for severity, i.e. the presence of pelvic girdle involvement, we will find 31 males (53%) and 23 females (48%) severely affected.

We assigned a score 1 to each patient in stage 1 and score 2 to each patient in stage 2 and so on. All 107 patients were scored. All scores added per sex yielded no significant difference between the sexes (P2 = 0.6 Student's t-test). Also, if all patients in stage 4, 5 and 6 are considered together, no significant difference is found between the sexes (P2 = 0.124 Student's t-test).

Table 4.25. Stage of the disease related to sex in 107 patients.

Stage	1	2	3	4	5	6	Total
Males	18 (31%)	10 (17%)	26 (44%)	2 (3%)	1 (2%)	2 (3%)	59 (100%)
Females	17 (35%)	8 (17%)	14 (29%)	2 (4%)	3 (6%)	4 (8%)	48 (100%)
Total	35 (33%)	18 (17%)	40 (37%)	4 (4%)	4 (4%)	6 (6%)	107 (100%)

4.21. Death

The age at death of affected individuals with symptoms was known in 16 males and 12 females. The average age at death in males was 64.2 years. Affected women lived to an average age of 70.5 years. The majority of these patients lived the greatest part of their lives in the first half of this century and died after the second World War. The average year of death in males was 1963 and females 1957. According to the Dutch National Office of Statistics the average age at death in the Dutch population for males in 1963 was 65.5 years and for females in 1957 was 67.3 years. Table 4.6. shows that equal, though limited numbers of affected and healthy sibs, live up to old age and that there are no apparent differences between males and females. These findings suggest in different ways that there is a little or no influence of the disease on the age of death.

Only in a few instances were the precise causes of death known to the families. Two patients (one male, one female) had died of what was said to be a heart attack. Two patients had died of pneumonia. A relation between the disease and respiration was never suggested. Other causes mentioned were drowning (1), complications of alcohol abuse (2), uremia (1), and abdominal malignancy (1).

4.22. Penetrance

The penetrance of FSHD is said to be complete (Tyler and Stephens 1950; Becker 1953). Table 4.5. shows that 85 affected and 80 non-affected sibs are involved in the 49 extensively studied sibships after corrections have been made for the probands and the obligatory gene carriers. These numbers do not differ significantly from the expected 1 : 1 ratio and suggest complete penetrance.

Yet we made two observations that were of interest with regard to the problem of penetrance. Patient H IV 7 (56 years old) was judged a questionable case when first examined. He was restudied after his son H V 20 was found to be clearly affected. His scapulae were somewhat prominent but all shoulder girdle

muscles were found to be of good strength. He could whistle and had no facial weakness. His foot extensor muscles were graded 4+ and his extensor hallucis longus muscles 4. The remaining examination revealed no abnormalities. Because of this minimal foot extensor weakness, he was classified as an abortive case. His wife was examined as well. She revealed no abnormalities.

The other observation was made on P II 1 (68 years old). She claimed she never could whistle well. People had made remarks about her shoulders when she was young and she had never been able to ride a bicycle properly. Yet no definitely abnormal findings were present on physical examination. Her father was said to have suffered from muscular dystrophy and a photograph showed him walking with a steppage gait. Her children were clearly affected. She could not be classified as an asymptomatic case, because she demonstrated no abnormalities on physical examination. She is therefore classified as possibly affected. Still there is little doubt that she is a non-penetrant gene carrier.

Experiences like the ones above demonstrate the potential biases of the examiner. One wonders how these patients would have been classified if they had had no offspring or if their children were too young to show signs. It is known from the examination of children that there is a phase in the development of FSHD in which the diagnosis cannot be made with certainty and, since the decision on who is a gene carrier and who is not hinges on the physical examination, it is suggested that the penetrance of FSHD might not be complete, although it must be almost complete because of the observed 1 : 1 ratio.

The S-shaped curve for the age of onset calculated with regression analysis (Figure 4.9.) suggests that at the age of 57 years 2.5% of the gene carriers have not come to clinical expression yet. Although it is in the nature of such a curve never to cross the 100% line, calculations such as these support the suggestion that there is a chance that a small percentage of the gene carriers may not come to expression in a lifetime.

4.23. Sex-influences

Influences of the sex have been implicated concerning the severity of the disease (Becker, 1953) and the age of onset (Chung and Morton, 1959). We looked at several potentially important differences between the male and female patients.

1. Of the 19 probands, 15 were males and four females, a difference which was statistically significant (P2 = 0.0117 Student's t-test).
2. The mean age of onset, based on symptoms, was 15.8 years in males and 19.0 years in females. This difference was statistically not significant (P2 = 0.1 Student's t-test).
3. Twenty-two percent of the male patients and 44% of the female patients were abortive cases. This difference was statistically significant (P2 = 0.016 Student's t-test).
4. If the severity of the disease was judged by pelvic girdle involvement no important sex-difference was demonstrable. If patients in stage 4, 5 and 6 were considered together, the difference in scores of severity between males and females involved was statistically not significant (P2 = 0.124 Student's t-test).

If the issue of sex-influences on the disease as a whole is considered, we have to correct for the number of tests performed in order to fix our probability of an error of the first kind at 0.05. Since the main factor determining the critical level of the tail probabilities for the total of mutually independent tests is the number of tests involved, we required each of the four tests to have a P value smaller than 0.0125 in order to be significant. This requirement was only met by the test on the number of probands.

The differences between males and females were mostly found in those items that include an important subjective element. It is possible that men by their nature and professional tasks become aware of this disorder earlier than the female sex, and that for similar reasons they seek professional advice more easily.

4.24. Genetic heterogeneity

Several suggestions have been made in the literature that FSHD might be genetically heterogeneous (Chung and Morton, 1959; Kazakov et al. 1974). Regression analysis of the ages of affected sibs (figure 4.9), and anamnestic data of our patients suggested that congenital and infantile manifestation are very well within the possibilities of FSHD.

Kazakov et al. (1974) stated that the spread of muscle involvement to the lower extremities always occurred in a similar manner in one family i.e. either to the foot extensors first and then to the pelvic girdle muscles, or the other way round. We observed shoulder girdle weakness and pelvic girdle weakness without foot extensor weakness in six patients (A IV 4, F IV 1, G III 20, I VI 11, I VI 12, J V 16). Two other patients (J IV 10, L IV 45) were positive that the muscle weakness first had spread to the pelvic girdle and later to the foot extensors. The reverse sequence of spread was observed in other patients in all these families. Therefore we could not substantiate Kazakov's suggestion, based on the clinical course, that FSHD is genetically hetereogeneous.

Chung and Morton (1959) using 18 characters, calculated an interpedigree correlation of 0.747 for their patient-material collected from the literature. Such a figure suggests that multiple alleles or different loci are involved. The authors could not exclude a systematic bias of the various examiners in reporting the onset of symptoms. Also a pelvifemoral onset in 11.6% of their cases suggests heterogeneous material according to our experience. Variance analysis of the ages of onset in our patients (see section 4.17.) yielded an intraclass correlation of individuals belonging to the same sibship of 0.24875. Such a figure argues against heterogeneity.

In summary, no arguments for genetic heterogeneity were found in our patient-material.

4.25. Environmental influences

Influence of non-genetic factors on the expression of the disease could not be proven in our material. The presence of such factors affecting the age of onset has been suggested by finding an intraclass correlation of individuals belonging to the same sibship of 0.24875, but genetic factors leading to such a figure could not be excluded.

The asymmetry of muscle involvement (see section 4.10.) could very well be due to environmental factors, although again, genetic influences of some kind could not be excluded.

Studies of genetic markers showed that patients Q III 1 and Q III 2 were non-identical twins.

4.26. Fitness

To study fitness, we only considered those children of one affected parent, that were older than 25 years (see Table 4.26). Among 107 affected sibs 25 (23.4%) remained single, two were infertile and 80 fertile sibs had 255 children, which was an average of 3.19 children per sib. We also considered 65 non-affected sibs. Fourteen were single (21.5%), two were infertile and the 49 fertile sibs had 150 children, an average of 3.05 children per sib. The relative fitness in the patients with FSHD is therefore 1.04, which is a normal fitness compared to their non-affected sibs. Also the chances to remain single appeared not to be increased in the group of affected sibs, compared to their non-affected sibs.

If the fitness was normal in the past, one would expect to find some very large kindreds. These have not been identified and they were also not suggested by genealogical investigations. This apparent inconsistency is not well explained.

Table 4.26. Fitness in patients with FSHD.

	Single	Infertile	Fertile	No. of children	Average
Affected	25	2	80	255	3.19
Not affected	14	2	49	150	3.06

4.27. Genealogical examination

Extensive genealogical investigations were undertaken in all families described. Information obtained from family members was often of great help. Most of the data could be checked with the aid of the records of the registrar's office. In two of the families (I and L) these data also served to confirm the already suspected relation of various parts of the kindreds. Two families (C and G) were of Indonesian origin through the maternal line. There was little information on the paternal line in family C. The paternal line of family G came from Belgium and could not be traced further. According to both families, the disease was inherited through the maternal, Indonesian line. The ancestors of family F came from Germany. We obtained quite detailed information on the family from the proband but we were unable to confirm all his data. Six and occasionally seven generations of ancestors could be traced in the other 16 families. In general, the lists of ancestors were reconstructed until around 1800 AD. None of the 17 kindreds appeared to have a common ancestor. They also could not be traced to a common region. The chances that the families were related more distantly seemed small. Such findings suggest that mutations are the main factor in the emergence of new kindreds with FSHD. However, it should be realised that the first reported cases in a kindred are not necessarily de novo mutations. One or more generations of abortive cases do occur in FSHD (Pamboukis, 1931), the patients may have had ancestors with late onset of the disease and incomplete penetrance might play a role in some kindreds. The same arguments apply to all sporadic cases: only follow-up studies may elucidate whether they are non-

hereditary cases or mutations.

4.28. Prevalence

Figures about the prevalence of FSHD in the Netherlands cannot be more than a rough estimate. The pedigrees shown still might hide several cases. If approximately one-third of the patients are asymptomatic it is possible that asymptomatic families might be hidden in a population (Pamboukis, 1931). But even symptomatic patients often do not seek referral to a specialized centre. For instance in Family H only the proband (H V 16) was known to us.

Forty-three patients out of 11 kindreds living in the province of North-Holland are included in the present study. We know of another famiy in this area with at least seven affected members. All but one refused examination and are not discussed here. Genealogical examination, going back an average of 180 years, revealed no relation between these families, although they lived in a small area of 2600 square kilometers. At the end of this study, the population of the province of North-Holland was 2.299.175. This would yield a prevalence of approximately 1 patient per 46.000 individuals. Assuming similar prevalences in other parts of this country one would expect at least 300 cases of FSHD in the Netherlands. From the information of other neuromuscular clinics known to us, this figure is probably on the conservative side. No second proband was found in the 12 kindreds in North-Holland. If we assume that the chance for finding no second proband in 12 kindreds is greater than 0.05, than the chance for finding no second proband in one kindred is greater than 0.775, and the chance for finding a second proband in one kindred smaller than 0.225. According to the Poisson distribution the chance of finding a second proband in one kindred with this disease is about $\frac{1}{2}\lambda$, in which λ represents the probability of ascertaining a kindred. Therefore it is estimated that less than 45% of the kindreds in North-Holland have been found. The ascertainment probability (π) is estimated to be smaller than

0.108, which is in agreement with other reports (Morton et al., 1959). These estimates suggest that the true prevalence of FSHD is greater than 1 per 21.000 individuals in our population, a figure which is close to the one reported by Becker (1953).

Because several families had moved in recent times we were unable to estimate directly the number of new cases in a population within a certain period of time (incidence). Although the average Dutchman is expected to live 75.8 years in 1982, so that the average patient with FSHD in the province of North-Holland is expected to live approximately 59 years with this disease, we did not try to estimate the incidence indirectly since this involved too many uncertainties. Similarly, because several families had moved, because of possible illegitimacy, and because of reasons outlined in the previous section, we were unable to estimate reliably the number of mutations by the direct method (Morton et al., 1959). The indirect method appeared not applicable since we observed a normal fitness in our material. Even if we assume a reduced fitness of patients with FSHD, the estimation of the incidence rate is too uncertain to try to calculate a mutation rate.