Limb-girdle type muscular dystrophy in a large family with distal myopathy: homozygous manifestation of a dominant gene?

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Abstract

A family study was carried out to clarify the problem of two separate muscle disease phenotypes in a large consanguineous pedigree. These were a severe limb-girdle type muscular dystrophy and a mild late onset distal myopathy. Thirty-two first degree and 14 other relatives of 18 previously examined index patients were available for clinical examination. Twenty-three subjects underwent computed tomography of the lower leg muscles. No new cases of limb-girdle type muscular dystrophy were found. Distal myopathy was diagnosed in 14 subjects, 10 first degree relatives and four other relatives. Segregation analysis showed that the corrected proportion of affected with the severe proximal type was 0·246 and the proportion of affected with the distal myopathy was 0·58. Pedigree analysis is compatible with the possibility that the mild, late onset distal myopathy is caused by a dominant gene and that the limb-girdle type may be expressed in homozygotes.

Despite the recent achievements in the molecular genetics of X linked[1] and FSH[2] muscular dystrophies, there is still much confusion regarding the concept of limb-girdle muscular dystrophies.[3–6] Hereditary distal myopathy has been described in Sweden[7] and appeared to be a homogeneous entity. Subsequent reports suggest a wide range of manifestations in the group of distal myopathies.[8–15]

The observation of both these phenotypes in a large inbred family was recently reported by us.[16] Eight patients suffered from a severely disabling proximal muscle weakness and atrophy compatible with the limb-girdle type of muscular dystrophy. Ten patients had a late onset distal myopathy, usually confined to the lower leg muscles and with anterior tibial muscle weakness as the characteristic feature. There were dystrophic changes without specific findings in the muscles in both the proximal and the distal myopathy. Imaging methods showed vast end stage changes of fatty involvement of the proximal muscles in the first group. Unexpected large patchy lesions of fatty involvement were also discovered in asymptomatic muscles in patients with distal myopathy.

Clinical examination of all known symptomatic patients in the family did not provide sufficient evidence to decide whether there were two different muscle disorders in the family or one mutant gene with variable expression. The aim of this study was to obtain more information about the mode of inheritance through examination of subjectively healthy members of the family.

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Patients and methods

FAMILY STUDIES

The reconstruction of the pedigree was initiated when the first patients with proximal muscular dystrophy were diagnosed nine years before the present study. The family history of these and all subsequent patients with myopathy originating from Larsmo rural district was studied with the help of the local state church administration, which keeps the parish records of all citizens, even if they belong to other religious groups. Reliable data are available of persons living in the year 1720 onwards.

CLINICAL STUDIES

Clinical examination was carried out in 32 out of 41 asymptomatic first degree relatives of the previously examined 18 patients. Five of them were living abroad and four were not available for examination for other reasons. Clinical examination was also performed in another group, consisting of all nine more distant relatives with high serum CK values and in five other more distant than first degree relatives over 35 years. The age limit was chosen because the late onset distal myopathy appeared only after the age of 35 years. Characteristic features of the two separate phenotypes are shown in table 1.

Serum creatine kinase (CK) activity levels were determined in all 32 first degree relatives examined and in 48 other family members. Fifteen of these relatives had also had their serum CK levels measured six years earlier. The method used for serum CK measurement was the same on both occasions with an upper normal limit of 270 U/I for males and 150 U/I for females. Serum CK levels are shown in relation to the upper normal limit in tables 2 and 3.

CT scanning of the lower leg muscles was carried out in 23 clinically examined subjects. This was performed with a CT 8800 machine (General Electric, USA) making 10 mm thick transsections at the thickest part of the calf muscles. Additional CT sections of the thighs, hip, upper arms, and neck were obtained in two subjects.

Table 1 Main features of the two separate phenotypes.

	Severe proximal muscular dystrophy	Mild late onset distal myopathy
Age of onset	First to third decade	Fourth to seventh decade
Initial symptoms	Weakness in proximal limb muscles	Reduced foot dorsiflexion
Progression	Severe disability in 20 years	Slow change without disability, no weakness of hand or arm muscles
Muscle involvement	All proximal muscles severely affected, distal muscles less, and facial muscles not affected	Usually only long foot extensors affected clinically; patchy lesions in other muscles seen with EMG and imaging methods
Neurophysiology	Myopathy, no neurogenic change	Myopathy, no neurogenic change
Muscle pathology	Dystrophic findings with end stage pathology in most biopsied muscles; no rimmed vacuoles	Severe dystrophic changes in clinically affected muscles and mild myopathy in unaffected muscles; no rimmed vacuoles
Serum CK activity	Normal or moderately raised	Normal or moderately raised
Sex distribution	Both sexes	Both sexes
Occurrence in generations	No parents affected with the same phenotype. One father affected with mild distal myopathy	Same phenotype in consecutive generations
Distribution within nuclear families	3 nuclear families with this phenotype	4 families with only this type
	Both phenotypes represented in one nuclear family	

Table 2 Asymptomatic first degree relatives examined.

Subject	Age	SCK level		Subjective weakness	Walking ability	Wasting of muscles	Foot dorsiflexion	CT findings of myopathy
		Present	6 years ago					
Affected with distal myopathy								
IX.13	75	×5·0	×1·3	0	N	T (l)	Reduced	T (b)
X.54	39	×1·5		+/−	N	T (b)	Reduced	T (l), P (r)
X.26	47	×2·0	N	0	N	T (b)	Reduced	T (b)
IX.35	72	×1·1		0	N	0	Lost	NE
X.6	71	N	×1·7	0	N	0	N	C (l)
X.9	67	N	N	0	Clumsy	T (b)	Lost	NE
X.20	54	N		0	N	T (b)	Reduced	T (b)
IX.19	69	N		0	N	+/−T	Reduced	T (b)
IX.20	68	N		0	N	+/−T	Reduced	T (b)
IX.53	50	N		0	N	0	Reduced	T (b)
Unaffected								
IX.4	90		N	?	Wheelchair	+/−	?	NE
IX.10	82		N	?	Bedridden	+/−	?	NE
IX.23	55	N		0	N	0	N	NE
IX.24	52	N		0	N	0	N	NE
X.7	69	N		0	N	0	N	NE
X.10	63	N	×1·8	0	N	0	N	0
X.39	43	N		0	N	0	N	NE
X.52	42	N		0	N	0	N	NE
X.55	35	N		0	N	0	N	NE
XI.8	28	N		0	N	0	N	NE
XI.9	26	N		0	N	0	N	NE
XI.10	13	N		0	N	0	N	NE
XI.11	24	N		0	N	0	N	NE
XI.12	21	×2·0		0	N	0	N	0
XI.35	20	N		0	N	0	N	NE
XI.36	17	×1·0		0	N	0	N	0
XI.37	17	N		0	N	0	N	NE
XI.38	14	N		0	N	0	N	NE
XI.39	12	N		0	N	0	N	NE
XI.56	34	N		0	N	0	N	NE
XI.57	31	N		0	N	0	N	NE
XI.58	27	N		0	N	0	N	NE

N = normal. NE = not examined. SCK: × = times the upper normal limit of activity. Muscle findings: T = tibial muscles, C = calf muscles, P = pelvic muscles, (l) = left, (r) = right, (b) = bilateral, 0 = not present, +/− = possible.

Table 3 More distant relatives with high SCK value or age over 35 years.

Subject	Age	SCK level		Subjective weakness	Walking ability	Wasting of muscles	Foot dorsiflexion	CT findings of myopathy
		Present	6 years ago					
Affected with distal myopathy								
X.4	62	×1·5	×1·7	0	N	T (b)	Reduced	T (b)
X.28	53	N	×5·7	0	N	0	N	T (r)
XI.21	21	×14·4		0	N	0	N	+/−T (l)
X.35	44	N		0	N	0	Reduced	+/−T (l)
Unaffected								
X.37	41	×1·4		0	N	0	N	0
XI.18	26	×1·2		0	N	0	N	0
XI.23	16	×1·1		0	N	0	N	0
XI.26	23	×1·2		0	N	0	N	0
XI.27	20	×1·0		0	N	0	N	0
X.26+	52	×1·4		0	N	0	N	0
X.36	50	N	N	0	N	0	Reduced	T (l)
X.43	55	N		+/−	N	0	Reduced	0
X.29	62	N		0	N	0	N	NE
X.30	50	N		0	N	0	N	NE

N = normal. NE = not examined. SCK: × = times the upper normal limit of activity. Muscle findings: T = tibial muscles, (l) = left, (r) = right, (b) = bilateral, 0 = not present, +/− = possible.

SEGREGATION ANALYSIS

Segregation analysis of the pedigree was performed combining the information from previously examined patients with new data from the present family study. Criteria for considering a person affected with distal myopathy were weakness and atrophy of the long extensors in the lower leg muscles or degenerative changes of the lower leg muscles discovered by CT scan. The direct a priori method[17] was used for correcting the segregation ratio of the limb-girdle type muscular dystrophy.

Results

FAMILY STUDIES (FIG 1)

All known generations of the family have lived on Eugmo island in the Larsmo archipelago, which lies off the coast half way down Finland in the Gulf of Bothnia (fig 2). The archipelago was probably not inhabited until the 13th century. The origin of the founders of the island population is not known. The ancestor I.2 was born in 1659, and the gene(s) concerned probably came from either one of the ancestor parents I.1 or I.2. The wife (II.1) of their son (II.2) came from another kindred living on the island with no offspring with muscle disease.

Consanguinity is present in 14 out of the total 17 pairs of parents. In the remaining three couples the fathers could not be linked to the pedigree, but they were born on the same island.

CLINICAL FINDINGS

Among 32 first degree relatives examined, 10 were considered to have the mild distal myopathy (table 2). Nine of them showed the characteristic weakness in the anterior tibial muscles. Diagnosis was made on clinical grounds in only two subjects and was confirmed by CT scan of the lower leg muscles in seven. One had only CT changes. CT showed myopathic changes of fatty involvement in the anterior tibial muscles in seven subjects, and patches of fatty involvement in the calf muscle and pelvic muscle in one case each. Two aged first degree relatives, an 82 year old bedridden woman with senile dementia and a 90 year old woman confined to wheelchair, also showed some distal muscle atrophy. As clinical examination was inconclusive and CT could not be performed, they were classified as unaffected.

In the group of 14 more distant relatives examined, four subjects were considered to be affected with distal myopathy (table 3). One subject (X.36) had fatty involvement of his left anterior tibial muscle on CT scan, but was not classified as affected because of a defect in the same muscle after a chainsaw accident.

PEDIGREE ANALYSIS (FIG 3)

Pedigree 1. Parents VIII.1 and VIII.2 were fifth cousins, known to be healthy. The father died at 85 and the mother at 81 years of age. They had seven girls and four boys, of whom two males (IX.12 and IX.16) were affected with severe proximal muscular dystrophy and one female (IX.13) had distal myopathy. She had two children and her daughter (X.35) was classified as affected with distal myopathy. Another dead female (IX.1) was considered to have had distal myopathy by history, and her son (X.4) showed typical distal myopathy.

Parents IX.8 and IX.9 were fifth cousins. The mother was also a child of parents VIII.1 and VIII.2 and known to be healthy, whereas the father showed distal myopathy on examination. The mother was 76 years when she died. They had two girls and five boys. One of the boys died young. Two males (X.18 and X.24) and one female (X.19) suffered from severe proximal muscular dystrophy. Two males (X.20 and X.21) and one female (X.26) had distal myopathy on examination.

Pedigree 4. Parents VIII.14 and VIII.15 were first cousins. The father died when he was 52 years old and the mother at the age of 80 years without signs of muscular weakness, according to the affected daughter. Their first three children died very young and one daughter (IX.44) of the five living children suffered from severe proximal muscular dystrophy. The other sibs were not available for examination.

Pedigree 6. Parents VIII.18 and VIII.19 were not known to be related but they came from the same island. The father died at the age of 54 years of coronary heart disease and the mother died at 81 years. Neither had symptoms of muscle weakness. Their daughter (IX.53) had distal myopathy on examination while both their sons (IX.54 and IX.55) had severe proximal muscular dystrophy.

SEGREGATION ANALYSIS

The severe proximal muscular dystrophy in four sibships did not show vertical transmission. In one sibship the father was affected with the mild distal type. All the other parents were dead. The proportion of affected, six males and two females, was 0·246 when corrected for complete ascertainment. In three sibships there were also subjects with the milder phenotype.

The mild distal phenotype showed vertical transmission in six families. In the other three families, at least one of the parents was dead and thus could not be examined. The sex distribution of the affected was 14 males and 16 females. The proportion of sibs affected was 0·48, when 41 dead sibs and six sibs who were not examined, were removed from the total of 94 sibs. Excluding sibs younger than 35 years, which was the youngest age of onset of clinical symptoms, raised the proportion of affected to 0·58. The eight patients with severe proximal muscular dystrophy were also excluded, since simultaneous mild distal myopathy could not be distinguished in these patients. The proportion of affected is therefore 0·71.

Discussion

Most inherited muscle diseases are defined by the clinical pattern, the type of histopatholo-

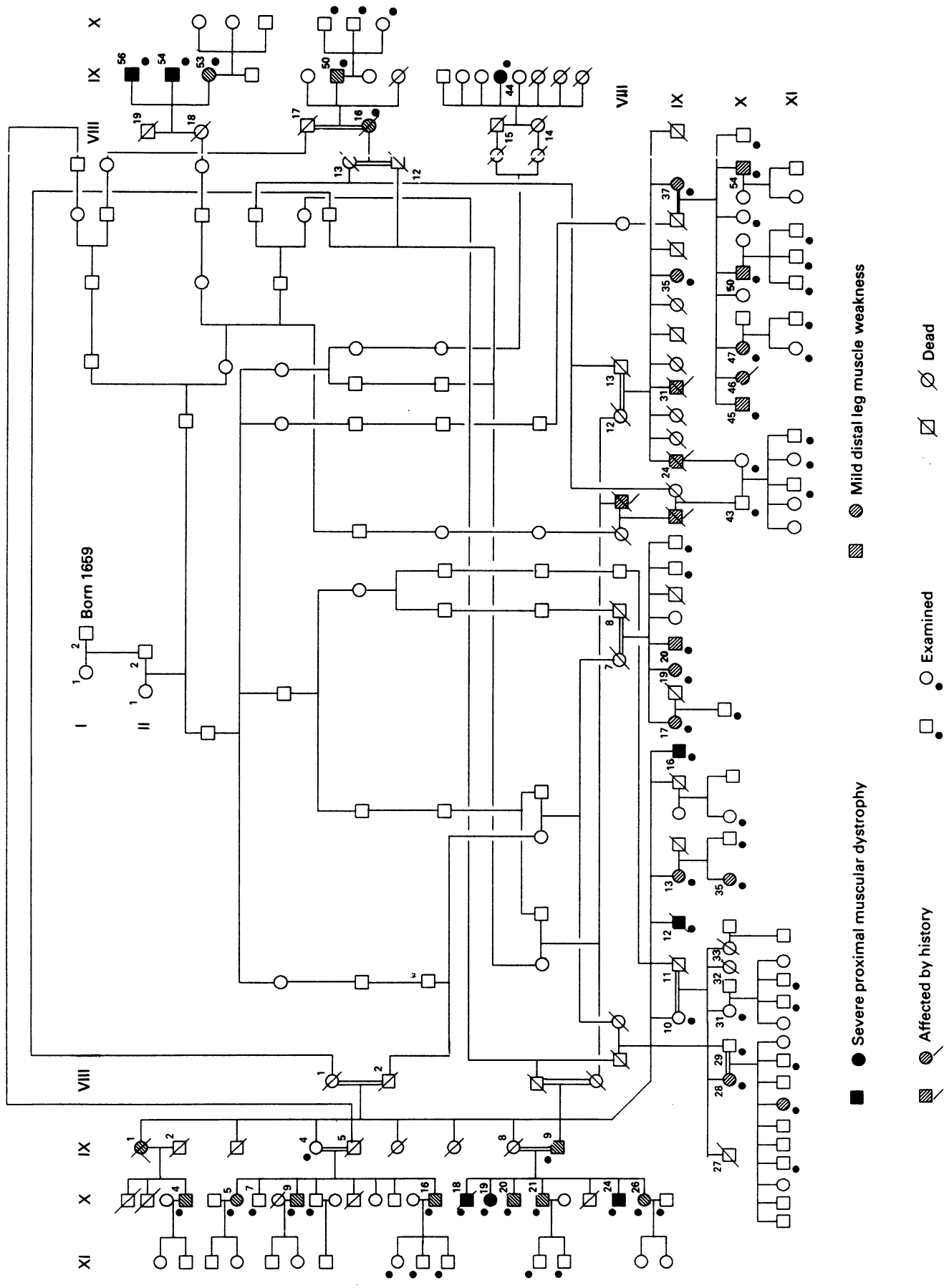

Figure 1 Pedigree data.

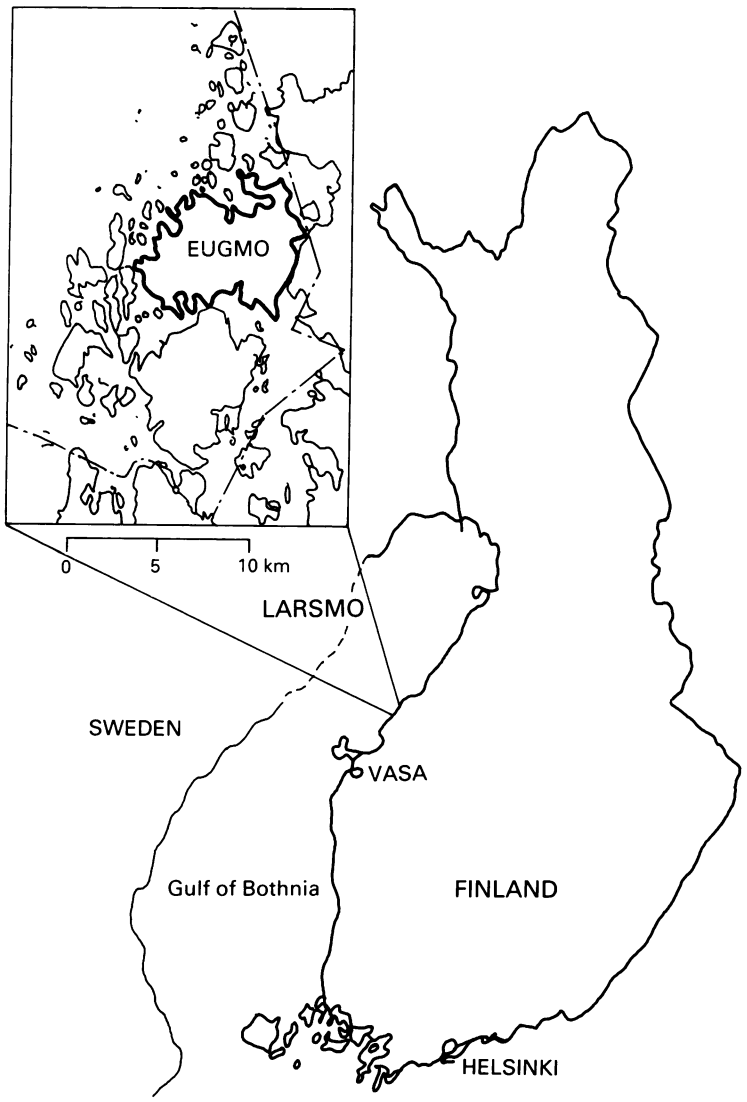

Figure 2 Geographical map of Finland. Larsmo rural district is an archipelago with about 3600 inhabitants; 1300 of them live on Eugmo island from where the family originates.

gical findings, and the mode of inheritance. In this family the pedigree analysis was complicated. The kindred is highly consanguineous and there are two separate phenotypes involved. The distal myopathy is confined to the older age groups, and in the majority of the affected persons symptoms of muscle weakness were so insignificant that they were not recognised by them. Some subclinical cases might have remained unnoticed if diagnostic methods other than clinical examination had not been performed. Computed tomography of muscles proved effective in indicating abnormalities of skeletal muscle. Diagnostic changes compatible with fatty involvement in the lower leg muscles were also found in three subjects with normal findings on clinical examination.

The results of the present study of 14 affected relatives still leaves open the basic question of whether or not both phenotypes are caused by the same gene.

Marked consanguinity automatically leads to a high likelihood of different recessive genes and alleles to manifest. A pseudodominant recessive trait causing the distal myopathy is, however, unlikely. Practically every subject in the pedigree since the early 18th century should be a gene carrier, which would mean a very high prevalence of the mutant gene in the population and consequently more symptomatic patients on the island. Allelic compounds causing the two different phenotypes is yet another possibility, but would cause rather more variation of symptoms.

If there is only one major mutant gene involved, it is tempting to suggest that the recessive severe proximal phenotype represents a homozygous form of the mild distal phenotype. The proportions (0·174 unaffected, 0·58 affected with the mild phenotype, and 0·246 affected with the severe phenotype) among sibs over 35 years of age seem to fit. The theory is possible but difficult to prove without further studies and linkage analysis. The only parent alive (IX.9) of the patients with severe proximal muscular dystrophy has distal myopathy, and the same distal myopathy is found in sibs of his dead wife. The gene for distal myopathy is therefore present in the father and in the family of the dead mother. The parents in the other families were healthy by history, but this does not exclude the existence of distal myopathy, since the majority of the affected subjects were more or less unaware of their symptoms.

In the case of different genes for the two phenotypes, the severe proximal disease appears to follow autosomal recessive inheritance. Reportedly healthy parents had more than one affected offspring and both sexes were affected. The proportion (0·246) of affected sibs is fully in accordance with recessive inheritance. The proportion (0·71) of sibs affected with mild distal myopathy is very high but still compatible with autosomal dominant inheritance. The disease occurs in consecutive generations and equally in both sexes. A proportion of affected less than 0·50 might have been expected, as the symptoms in the mild phenotype appear late and can be difficult to recognise. The high proportion could be explained by marked consanguinity and the fact that there may be families where both parents have one mutant gene. Families with many symptomatic sibs may be overrepresented, and families with very few mildly affected members may have been unrecognised.

The existence of complete dominance in man, indicating that homozygotes do not differ clinically from heterozygotes, has even been questioned.[18] This has, however, been confirmed, at least in Huntington's disease,[19 20] and in familial amyloidosis with polyneuropathy.[21] A more serious clinical picture as a manifestation of homozygosity of a dominant gene (incomplete dominance) is reported only rarely. However, there are some well known and documented examples, like achondroplasia,[22] familial hypercholesterolaemia,[23] and hereditary haemorrhagic telangiectasia.[24]

In muscular disorders, severe myopathy resulting from homozygosity was also presumed in some patients by Welander[25] in her large study of distal myopathy in Sweden. Both parents of patients with rapidly progressing proximal muscular dystrophy had been

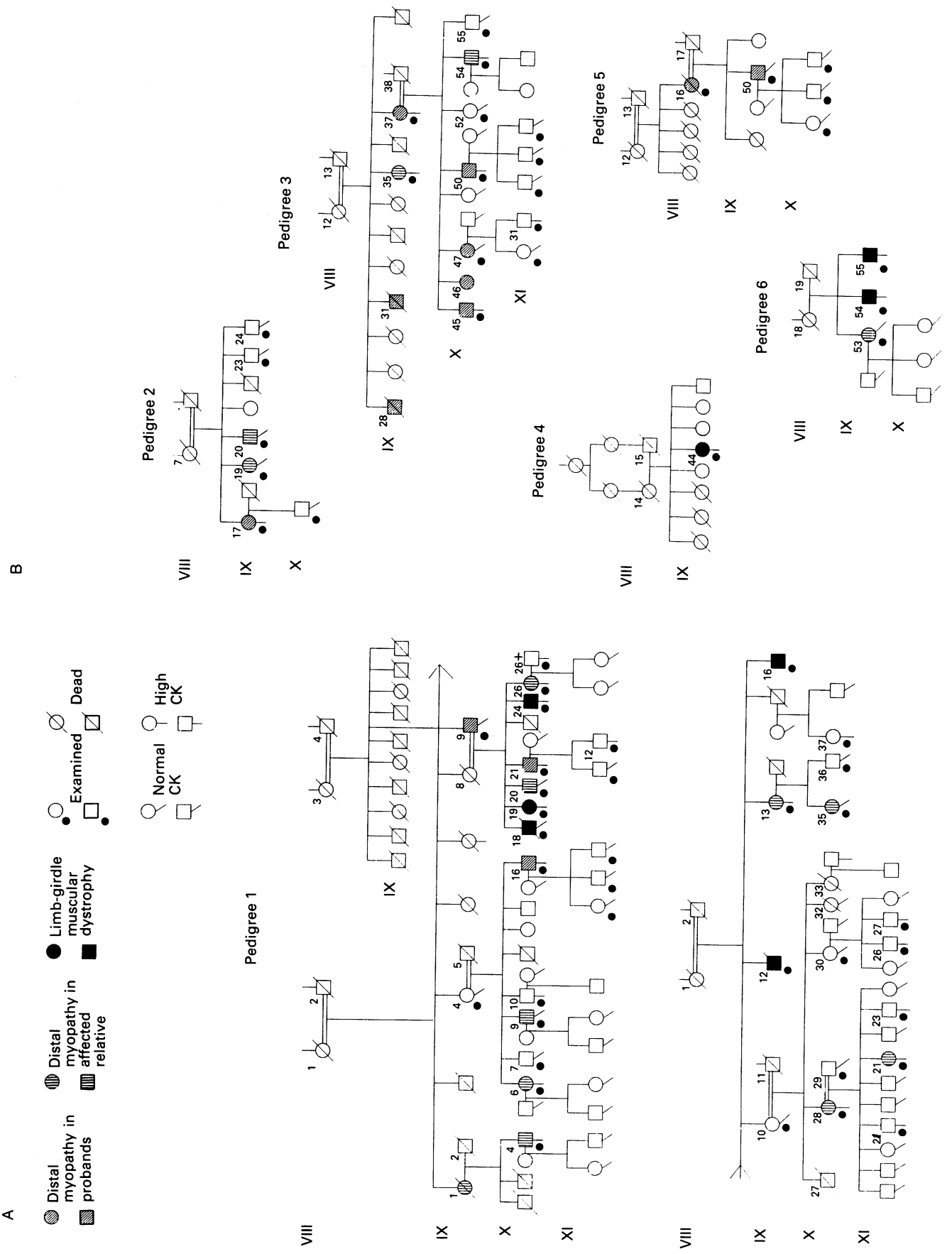

Figure 3 (A) Pedigree 1 showing distinction between probands and affected relatives with CK activity distribution. A part of the complete pedigree is shown in order to facilitate analysis. (B) Parts of the complete pedigree showing smaller subunits named pedigrees 2 to 6 with distinction between probands and affected relatives and with serum CK activity in family members.

diagnosed by her as affected with distal myopathy. This distal myopathy appeared predominantly in the upper extremities,[15] whereas patients with distal myopathy in the present families do not show changes in the upper limb muscles. The present pedigree may thus represent another example of a myopathy where a homozygous manifestation of a dominant gene is expressed in a different way with a more serious clinical picture.

Addendum

During the preparation of this manuscript, autosomal recessive limb-girdle muscular dystrophy has been linked to a locus on chromosome 15. This finding will have an impact on further linkage studies in the present family.

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