Neurological Case Reports

Research Article
Published: 03 Nov, 2018

About the Facioscapuloperoneal Muscular Dystrophy in the Famous K Kindred First Described by Oransky (1927), With Further Re-Examination by Davidenkov and Kulkova (1938), Kazakov (1969) and Kazakov et al. (1993)

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Abstract

Additional study of the K kindred examined previously by Oransky in 1927 and further by Davidenkov and Kulkova in 1938 and then by Kazakov in 1969 (published in 1975, 1976) was carried out. Seventeen members of the K kindred including 5 of them, earlier described by Oransky (1927) and Davidenkov, Kulkova (1938), were re-examined (VK) in 1969, and in total 25 were re-examined (VK) in 1993. In 15 members from Vth and VIth generations the 4q35 p13E-11 EcoRI/BlnI DNA analysis was carried out. The disease in the K kindred has been inherited as an autosomal dominant type for six generations. We could find the phenomena reverse of the progressing hereditary (we did not see the increase of the severity of the disease from pedigree to pedigree) and did not observe the phenomena of anticipation. In the patient who had developed the disease the (facio) scapulo peroneal phenotype was evident in the clinical picture during their first 12 to 16 years of life. The posterior thigh muscles, gluteus maximus, abdomen and not always biceps brachii were successively involved later. The muscular dystrophy in K kindred is the special type which we prefer to call "Facio Scapulo Limb Muscular Dystrophy, type 2 (FSLD2), a descending with a "jump", with initial (facio) scapulo peroneal phenotype". The (facio) scapulo peroneal phenotype constitutes merely a stage in the development of the FSLD2 in some members of the K kindred.

Keywords: Facio scapulo humeral dystrophy; Facio scapulo limb dystrophy; Scapulo peroneal dystrophy; Clinical heterogeneity

Introduction

We were able to reproduce the genealogy of the K kindred in which a muscular dystrophy has been transmitted as an autosomal dominant type over six generations yet with variations in the clinical picture. The K kindred were studied by different authors who did not agree that the nature of the disease was kindred. Oransky considered it to be a peculiar form of the progressive muscular dystrophy [1]. Davidenkov and Kulkova classified this disorder in K kindred as the scapulo peroneal amyotrophy which was an independent form which approached mostly the myopathy Landouzy Dejerine [2]. Welander characterized the disease in the K kindred as a common proximal muscular dystrophy [3]. Seitz related those patients to Erb's shoulder-girdle form of muscular dystrophy [4]. Hausmanova-Petrusewicz and Zielinska and Feigenbaum and Munsat thought that the patients described by Oransky in 1927 had a neural scapulo peroneal syndrome. However, in 1971 Hausmanova-Petrusewicz suggested that the syndrome was a form of the facio-scapulo-humeral muscular dystrophy [5-7]. Kaeser believed this syndrome in K kindred to be of a spinal origin [8]. Ricker and Mertens related the disease in the K kindred to the facio scapulo humeral dystrophy [9]. Zellweger and McCormick thought that a special scapulo peroneal form of muscular dystrophy having an intermediate place between Landouzy-Dejerine facio scapulo humeral form (Erb's shoulder-girdle variant) and Welander's distal one was inherited in the K kindred. Serratrice et al., [10-13] and Munsat, Serratrice believed that the patients described by Oransky had probably an unusual form of facio scapulo humeral dystrophy with peroneal group muscles involvement or facio scapulo peroneal muscular dystrophy. Kazakov et al., [13-15] considered the muscular dystrophy in the K kindred to be one of the forms (namely, a descending type with a "jump") of the facio scapulo limb muscular dystrophy. Walton and Gardner-Medwin suggested that the patients from K kindred

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Received Date: *18 Sep 2018*
Accepted Date: *31 Oct 2018*
Published Date: *03 Nov 2018*

Citation:
Kazakov V, Skorometz A, Rudenko D, Kolynin V, Stuchevskaya T. About the Facioscapuloperoneal Muscular Dystrophy in the Famous K Kindred First Described by Oransky (1927), With Further Re-Examination by Davidenkov and Kulkova (1938), Kazakov (1969) and Kazakov et al. (1993). Neurol Case Rep. 2018; 1(1): 1004.

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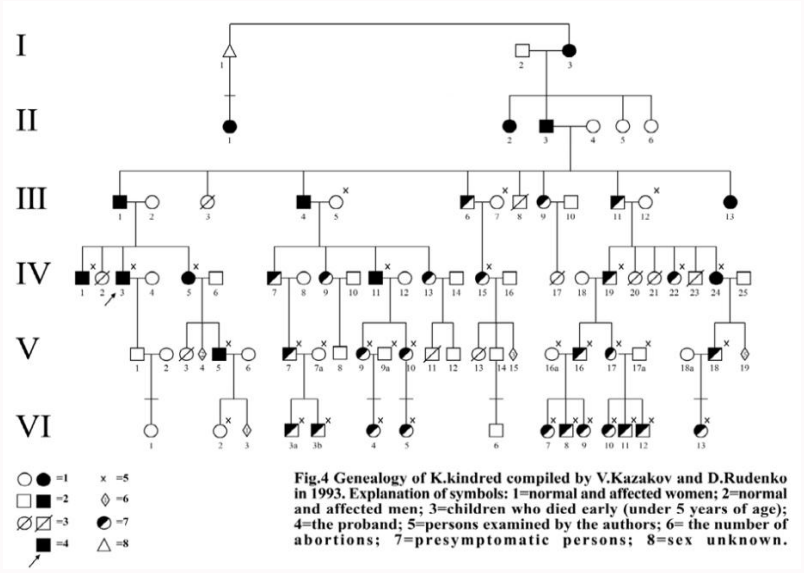

Figure 1: Genealogy of K. kindred compiled by Kazakov and Rudenko in 1993.

had "incomplete" or abortive forms of the facio scapulo humeral muscular dystrophy in which a facial weakness was a late and a mild feature in many cases [16,17]. Padberg wrote that in 1927 Oransky described the patients with clinical picture identical to FSHD with minimal facial weakness [18,19].

Subjects and Methods

In 1927 Oransky observed in K kindred the 4 members from generation III (III- 4, 9,11,13) and 4 men of one family from generation IV (IV-1,3,5,7) (altogether 8 members) (Figure 1). In 1938 Davidenkov and Kulkova re-examined in K kindred the 3 members from generation III (III - 4,11,13) and 3 members from generation IV (IV-1,3,5), earlier described by Oransky in 1927 and they examined some other new 8 members of generation IV (altogether 14 members) [1,2] (Figure 1). Kazakov in 1969 (published in 1975,1976) observed the following members of the K kindred: IV-3, IV-5, IV-11, IV-15, IV-19, IV-22, IV-24, V-5, V-9, V-10, V-16, V-17, V-18, VI-2 as well as III-5, III-7, III-12 (altogether 17 members) and including 5 patients from IV generation (IV-1,3,5,11,19) who were examined earlier by Oransky in 1927 and Davidenkov, Kulkova in 1938. Our proband was IV-3. IV-1 was observed by Bogorodinsky in 1953 (Figures 1) [13-15]. In 1993 (Figures 1) we could have reexamined (VK) the 7 patients in K kindred since 1969 (IV-24, V-5, V-9, V-10, V-16, V-17, V-18) after 24 years and IV-11 after 8 years and we also observed some new members of V and especially of VI generations (V-7, VI-3a, VI-3b, VI-4, VI-5, VI-7, VI-8, VI-9, VI-10, VI-11, VI-12, VI-13 as well as V-7a, V-9a, V-16a, V-17a, V-18a) who have never been examined earlier (altogether 25 members) [20,21]. In 15 patients (IV-24, V-5, V-7, V-9, V-10, V-16, V-17, V-18, VI-3a, VI-7, VI-8, VI-9, VI-10, VI-11 and VI-13) the DNA analysis was carried out. The molecular genetic analysis of the isolated DNA from peripheral blood lymphocytes was performed by EcoRI/BLnI double digestion using the probe p13E-11 (D4F104S) and other 4q35 markers (D4S139, D4S153) in Department of Neuromuscular Research, National Institute of Neuroscience, NCNP, Tokyo, Japan [22]. Muscle strength was measured manually by Daniels et al., [23,24] the trophic and function of the muscles was studied by Kendall H and Kendall F. Mimic muscle strength, the severity of the disease and the daily-life work disability in FSLD2 patients were assessed according to the criteria defined by Kazakov et al., [21]. The diagnosis of muscular dystrophy was supported by myopathic needle EMG and normal motor and sensory nerves conduction velocity ("Viking IV", Nicolet, USA) and myopathic changes at the supraspinatus muscle biopsy stained by hematoxylin and eosin (in one patient). Clinical phenotypes of the members of the K kindred described at different times by Oransky (1927), Davidenkov and Kulkova (1938), Kazakov (1969), published in 1975, 1976 and Kazakov and Rudenko (1993) (Table 1).

Results and Discussion

Clinical peculiarities of muscular dystrophy in K kindred

In 1927 Oransky had reported on an unusual type of the muscular dystrophy in the K kindred in which the shoulder girdle and peroneal group muscles were severely involved, *i.e.,* the scapulo peroneal phenotype of muscle affection predominated by the clinical picture in the patients (III-1, III-4, III-13, IV-1, IV-3) (Figure 1 and Table 1) whereas some facial muscles were slightly involved [1]. Only in III-13 the muscle atrophy and weakness spread to the posterior thigh muscles, glutei and upper arm muscles. The patients did not complain of a muscle dysfunction for a long period of time and some of them did not suspect of having a muscle disease. In 1938 Davidenkov and Kulkova re-examined and published those K kindred after 10 years again [2]. At that point the attention of Davidenkov & Kulkova was drawn by a substantial dissimilarity of the phenotypes in the K kindred between those showing distinct scapulo peroneal dystrophy with minimal affection of the some facial muscles (IV-1, IV-3, IV-5) and the cases resembling, in their opinion, of FSHD (III-4, III-13, IV-11) (Figure 1 and Table 1) In 1969, 42 years after the first examination performed by Oransky in 1927, we reexamined and published data on the K kindred (Figure 1 and Table 1) [13-15]. At that period of time we investigated the people of approximately the same age with the developed form of the disease, as a result of this investigation a considerable resemblance in the topography and the order of development of the muscle weakness and atrophies in the patient of the K kindred was noted. According to the extension of the atrophies (involvement of the shoulder girdle and peroneal group muscles) at the early stages of the disease one can isolate in all the patients a more

or less distinct scapulo peroneal phenotype with a slight involvement of some muscle of the face (frequently that of orbicularis oris or orbicularis oculi or zygomaticus). Hereafter the deepening of the atrophies in the muscles of the scapulo peroneal region, the atrophy and weakness of the muscles of the thigh (posterior group of the muscles), pelvic girdle (gluteus maximus), abdomen and upper arm (biceps brachii) was also developed. Thus, we could see that the sharp dissimilarity of the phenotypes in the K kindred between (facio) scapulo peroneal muscular dystrophy (IV-1, IV-3) and the cases resembling unusual type of FSHD (III-4, III-13, IV-11) pointed out by Davidenkov, Kulkova at the early stages of the disease shifting to their considerable similarity at a later period [2] (Figure 1 and Table 1). However, it should be noted that in all these patients (III-4, III-13, IV-1, IV-3, IV-11) having the same final (facio)-scapulo-peroneal-femoro (posterior thigh muscles)-gluteo (gluteus maximus)- humeral (biceps brachii) phenotype of the disease (excluding III-4 and IV-11 in who biceps brachii muscles strength was preserve) the muscles of scapulo peroneal region were more severely affected. Thus, the scapulo peroneal localization of muscle weakness predominated in clinical picture in these patients throughout their lifetime whereas some facial muscles (orbicularis oris, mainly) were slightly/minimally involved. The affected persons preserved the ability for manual labor and walking for a long time. The patients from IV generation did not complain of a muscle dysfunction for a long period of time and some of them did not suspect of having a muscle disease. In 1993 we reexamined and published the K kindred again (Figure 1 and Table 1). Between the patients from IV, V and VI generations we did not encounter the persons with a developed form of the muscular dystrophy, although the age of the patients of IV and V generations whom we reexamined after 24 years exceeded 34 years [20,21]. Likewise we did not receive any information from the relatives of the Family K. about the development of any motor disturbances between the persons of IV and V generations in January 2010. Thus, we could see in K kindred the phenomena reverse of the progressing heredity, which means that we could not see increase of the severity of the disease from pedigree to pedigree. The disease in patients with developed disease from generations III and IV on an average begins at the age of 18 to 21. The true age of onset of the disease in the patients who probably were Pre-symptomatic (Pr) (IV-7 and his sisters IV-9, IV-13 and III-6 and his daughter IV-15 as well as III-9, III-11 and his children IV-19, IV-22) as well as in Pr members from generations V and VI was rather difficult to determine (Figure 1 and Table 1). The onset of the disease at an earlier age in the members from V and VI generations was due to the fact that they came under thorough medical observation at a more early age than the persons from III and IV generations. These findings on the onset of the disease do not allow us to draw the conclusion that it affects the later generations at an earlier age. In other words, we did not find the phenomenon of anticipation in the K kindred. We are more inclined to consider the disease to be homocronic in the patients who have the developed disease, which was also the opinion of Oransky in 1927 [1].

Genetic peculiarities of the muscular dystrophy in K kindred

The interpretation of the molecular genetic data received is very difficult. Analysis of the muscular status in III-11, taking into account the data of III-12, IV-19 and IV-22 and the opinions of Oransky, Davidenkov and Kulkova, allows to suggest that in III-11 the muscular dystrophy gene did not show full penetrance (Figure 1 and Table 1) [1,2]. This finding substantiates the fact that in his grand-daughter (V-17) and great-grandchild (VI-10) a 4q35 deletion 33/30 kb (double digestion) was found. The similar data was found in some other published families in which the individuals related to FSHD patients who carried a deleted EcoRI fragment remained asymptomatic or minimally affected [25-27]. The existence of non-penetrance gene patients suggests the hypothesis of the epigenetic mechanisms (or modifier genes) protecting individuals from FSHD deleterious effect of the FSHD allele [28-30]. We suppose that the patients from generation V (V-7, V-9, V-10, V-16, V-17 and V-18) are Pr with a minimal (facio) scapular and (facio)-scapulo-peroneal (tibial) phenotypes as well as members of the generation VI (VI-3a, aged 8; VI-3b, aged 7; VI- 4, aged 7; VI- 5, aged 8; VI- 7, aged 20; VI-8, aged 16; VI-9, aged 9; VI-10, aged 16; VI-11, aged 13; VI-12, aged 7; VI-13, aged 12) although the age of generation VI patients varied from 7 to 20 years old (Figure 1 and Table 1). It is well known that the penetrance of the FSHD gene increases with years: 21% for those aged 5 to 9 years, 58% for those aged 10 to 14 years, 86% for those aged 15 to 19 years and 95% for those aged 20 and above [31]. Thus, between 13 clinical pre-symptomatic members from V and VI generations (see above) and in 2 symptomatic patients IV-24 and V-5 with slight (facio)scapulo peroneal(tibial) phenotype, who underwent the DNA analysis (altogether 15 men), only in third Pr members (V-10, aged 34, V-17, aged 39 and VI-10, aged 16) the 4q35 deletions less than 35 kb (24/21 kb, 33/30 kb and 33/30 kb) were found (Figure 1 in Table 1). In all the other examined Pr members (12 men) the DFS was more than 50 kb although they had a definite phenotype of muscle weakness which was typical of the initial phase of the muscular dystrophy which was transmitted in K kindred, and in IV-24, V-5, V-18 and VI-8 there were myogenic changes on needle EMG and myopathic changes on muscle biopsy (in V-5). It is believed that the accuracy and reliability of the molecular diagnosis is closely linked to the molecular diagnostic technique for FSHD [32,33]. In cases where the origin of the allele could not be confirmed or the FSHD EcoRI fragment could not be sized through standard electrophoresis, Pulsed Field Gel Electrophoresis (PFGE) using additional chromosome-specific probes should be performed [33]. Unfortunately, we could not use a PFGE to determine the size of the fragments (fragments of >50 kb) in the clinically pre-symptomatic persons. The examination of K kindred revealed 13 clinical affected patients and 15 Pr persons in total (given the exclusion of 11 Pr children from VI generation at the age of 7 to 20) i.e. 53.5% members who were more than 33 years old, except of IV-7 (24 years old) and IV-9 (23 years old) were Pr. Padberg reported on 34 (32%) asymptomatic FSHD patients among 107 studied [18]. Other authors revealed that over 30% of subjects carrying the FSHD molecular defect were asymptomatic. However, the percentage of asymptomatic carriers was 38% in carriers at the age of 41 to 50 and 22% at the age of 61 to 71 and in some families in which two deleted alleles segregate the asymptomatic subjects increased to 44% [34]. According to Arashiro et al., [30] in some pedigrees there seem to concentrate more asymptomatic cases. These authors reported on a large genealogy which included 16 individuals with FSHD among them only 3 were clinically affected and 13 (81.2%) persons were asymptomatic or minimal affected. The authors suggest that in this pedigree and some other similar ones modifier genes that would protect some individuals from the deleterious effect of FSHD may be segregating [30]. At present we can confirm our point of view earlier expressed by us that in the K kindred one of the variants (namely, as a descending type with a "jump") of the Facio-Scapulo-Limb Muscular Dystrophy (FSLD) is transmitted from generation to generation which we refer to as "the Facio Scapulo Limb Muscular

Table 1: Clinical phenotypes of the members of the K. kindred described at different times by Oransky (1927), Davidenkov and Kulkova (1938), Kazakov (1969, published in 1975, 1976) and Kazakov and Rudenko (1993).
The number of the described members of K. kindred is given on genealogy compiled by Kazakov and Rudenko in 1993 (Figure 1). The proband was IV-3. Data about the patients from I-III generations was received from Oransky and Davidenkov, Kulkova as well as from some healthy members (III-5, III-7, III-12) and one patient IV-5 by Kazakov [1,2,13].

N of generation, N of patient in generation (see Figure 1) Profession	Disease Onset (years)	Age of exam patient	Signs and phenotypes	Age at death	DNA fragment size	EMG needle / CV
I-3, the proband's grand-grandmother on his father's side			She was affected and had a waddling gait (data received by Oransky from anamnesis)			
II-1, the first grandmother of the proband on his father's side			She was affected and could not walk and could hardly raise her hand to her mouth (data received by Oransky from anamnesis)			
II-2, the second grandmother of the proband on his father's side			She was affected and had lordosis and stepping gait (data received by Oransky from anamnesis)	60		
II-3, the grandfather of the proband on his father's side			He was affected and had lordosis and stepping gait (data received by Oransky from anamnesis)	55		
II-5 and II-6 the third and forth grandmothers of the proband's side			They were healthy (data received by Oransky from anamnesis in 1927 [1])			
III-1, the proband's father; a wood turner	20-30		He had severe (facio)-scapulo-peroneal phenotype (data received by Oransky from IV 1 in 1927 [1])	41 Typhoid fever		
III-4, the proband's uncle; a fitter	18-21	43-53	He had a (facio)-scapulo-peroneal phenotype which turned into severe (facio)-scapulo-peroneal-femoro-gluteal phenotype [1,2]	57 Alimentary dystrophy		
III-6, the proband's uncle			He was affected and had a "sunken" chest (data received by Oransky from anamnesis in 1927) [1]	33 Pneumonia		
III-9, the proband's aunt; a worker		36	She had an "abortive" form of the disease [1]	49 Perished		
III-11, the proband's uncle; a fitter		35,45	He had an "abortive" form of the disease with the "deformities" in the shoulder girdle. He was possibly affected [1,2]	51 Alimentary dystrophy		
III-13, the proband's aunt	18	28,39	She had a severe facio-scapulo-peroneal-femoro-gluteo- humeral phenotype. She had the same phenotype [1,2]	62 Cancer		
IV-1, the proband's elder brother; an military engineer	20	27,36,52	He had a pure (facio)-scapulo-peroneal phenotype which turned into the final (facio)scapulo-peroneal-femoro-gluteo-humeral phenotype [1,2,15]	54 Myocardium infarction		
IV-3, the proband; pensioner	18.5	20,30,60,68	He had a pure slight scapulo-peroneal phenotype which turned into the (facio)-scapulo-peroneal-humeral one and then - into severe final (facio)-scapulo-peroneal-humero-femoro-gluteal phenotype [1,2,13,14]	70 Myocardium imfarction		Myo/ normal
IV-5, the proband's sister; a pensioner	18-25	18,28,61,68	She was healthy; She was Pr with minimal (facio)-scapulo-peroneal phenotype and later she was minimally affected with slight (facio)-scapulo-peroneal (tibial) phenotype [1,2,13,14]	69		Myo/ normal
IV-7, a proband's cousin; an electrician		14,24	He had "high hold of shoulders" He was Pr with minimal (facio)-scapular phenotype with protrusion of the lower lip and some abnormalities of interscapular muscles [1,2]			
IV-9, a proband's cousin; a worker		23	Probably Pr with minimal (facio)-scapular phenotype with slight weakness of some facial muscles and could highly raise her shoulders [2]	27 Perished		
IV-11, a proband's cousin; metalworker	18	20,53,69	He had a (facio)-scapular phenotype which turned into moderate (facio)-scapulo-peroneal-(femoro-gluteal) phenotype [2,20].	77 Cancer of prostate		Myo/ normal
IV-13, a proband' cousin		16	He was probably Pr with minimal (facio)-scapular phenotype with slight involvement of facial muscles and stooping shoulders [2]	20 Alimentary dystro-phy		
IV-15, a proband's cousin; an accountant		18,53	She was healthy She was Pr with minimal (facio)-scapulo-peroneal (tibial) phenotype [2,13]			
IV-19, a proband's cousin; a turner		11,19,53	He was healthy He was probably Pr with minimal changes in face and biceps and gastrocnemius muscles He was Pr. with minimal (facio)-scapulo-peroneal phenotype [1,2,13,20]	64 Myocardium infarction		
IV-22, a proband's cousin; a designer		11monts, 9,43	She was healthy. She was probably Pr with stooping shoulders and sunken chest. She was Pr with minimal (facio)-scapulo-peroneal (tibial) phenotype [1,2,13,20]	53 Cancer of pancreas		
IV-24, a proband's cousin	School years	38, 62	She was Pr with minimal (facio)-scapulo-peroneal (tibial) phenotype. She was minimally affected with slight facio-scapulo-peroneal phenotype [13,20]		>50	Myo/ normal
V-5, a proband's nephew; a turner	20	38,53	He was Pr with minimal (facio)-scapulo-peroneal (tibial) phenotype, He was minimal affected with the same phenotype [13,20]		>50	Myo/ normal Biopsy/ Myo
V-7, a first cousin once removed of the proband; an engineer		35	He was Pr with minimal (facio)-scapular phenotype with atrophy of the left half of the upper lip, "round" back and moderate weakness of trapezius muscles [20]		>50	

V-9, a first cousin once removed of the proband; an engineer		13,37	Probably Pr with slight affection of trapezius muscles. She was Pr with minimal (facio)-scapular phenotype with asymmetry of the lips in puckering the lips to whistle [13,20]		>50	
V-10, a first cousin once removed of the proband; a subway worker		10,34	Probably Pr with slight weakness of trapezius muscles She was Pr with minimal (facio)-scapulo-peroneal (tibial) phenotype [13,20]		24/21	
V-14, a first cousin once removed of the proband		47	Not observed. He was on military service.			
V-16, a first cousin once removed of the proband; an engineer-technologist		22,44	Probably Pr with (facio)-scapular phenotype: thick lips, slight protrusion of the lower lip, wide shoulders and right shoulder showed displacement downwards. He was Pr with minimal (facio)-scapulo-peroneal (tibial) phenotype [13,20]		>50	
V-17, a first cousin once removed of the proband; a teacher		15,39	Probably Pr with (facio)-scapular phenotype: slight weakness of zygomaticus muscles, slight weakness and atrophy of the lower and middle parts of trapezius and slight weakness of serratus anterior muscles. She was Pr with minimal (facio)-scapulo-peroneal phenotype [13,20]		33/30	
V-18, a first cousin once removed of the proband; cinema operator		13,38	Probably Pr with (facio)-scapular phenotype) She was Pr with minimal (facio)-scapulo-peroneal (tibial) phenotype [13,20]		>50	Myo/ normal
VI-2, a proband's granddaughter		4	Healthy [13]			
VI-3a, a second cousin once removed of the proband		8	Probably Pr with minimal (facio)-scapular phenotype: asymmetry of the lips in puckering the lips in whistle, the right shoulder was widened and showed displacement downwards, a slight atrophy of the sternal parts of pectoralis major muscles, [20]		>50	
VI-3b, a second cousin once removed of the proband		7	Probably Pr with scapular phenotype [20]			
VI-4, a second cousin once removed of the proband		7	Probably Pr with minimal (facio)-scapulo-peroneal (tibial) phenotype. At attempting to stand up on the heels she could not extend the feet fully. The girl could not stand on the one heel [20]			
VI-5, a second cousin once removed of the proband		8	Probably Pr with minimal (facio)scapular phenotype [20]			
VI-7, a second cousin once removed of the proband; student		20	He was Pr with minimal (facio)-scapulo-peroneal (tibial) phenotype [20]		>50	
VI-8, a second cousin once removed of the proband; student		16	He was Pr with minimal (facio)-scapulo-peroneal (tibial) phenotype [20]		>50	Myo/ normal
VI-9, a second cousin once removed of the proband; a schoolgirl		9	Probably Pr with minimal (facio)-scapulo-peroneal phenotype [20]		>50	
VI-10, second cousin once removed of the proband; schoolgirl		16	She was Pr with minimal (facio)-scapulo-peroneal phenotype [20]		33/30	
VI-11,a second cousin once removed of the proband; schoolboy		13	Probably Pr with minimal (facio)-scapulo-peroneal (tibial) phenotype [20]		>50	
VI-12, a second cousin once removed of the proband; schoolboy		7	Probably Pr with minimal (facio)-scapular phenotype [20]			
VI-13, a second cousin once removed of the proband; student		12,17	Probably Pr with minimal (facio)-scapulo-peroneal (tibial) phenotype. The same Pr phenotype. In a standing position she could not fully extend her feet and toes. [20]		>50	

Myo/normal=EMG needle myogenic/CV: Conduction Velocity normal

Dystrophy, type 2 (FSLD2), a descending with a "jump" with initial (facio) scapulo peroneal phenotype, autosomal dominant (Erb, Landouzy-Dejerine)" [13-15,35]. The muscular dystrophy in K. kindred on the sequence of extension of muscle involvement which we have observed for many years differs a lot from the other variant of FSLD referred by us as "the facio scapulo limb MD, type 1 (FSLD1), a gradually descending with initial facio scapulo humeral phenotype, autosomal dominant (Duchenne de Boulogne)" [36-38].

Conclusion

We can suppose that the clinical picture of the FSLD2 may correspond to the ones of the FSHD1 and FSHD2 [although the pattern of the extension of the muscles weakness and atrophy from lower leg to thigh and pelvic girdle is different from Patberg's patients and may be SMCHD1 gene located on chromosome 18p which acts as an epigenetic modifier for the DUX4 gene in FSHD1 (or FSLD2) and causes the FSHD2]. This modifier gene influences the variation of the phenotypes, the onset age and the severity in FSHD1 (or FSLD2) and FSHD2 patients having a descending type with a "jump" of the developing disease with initial facioscapuloperoneal phenotype. However, the clinical picture of FSLD1, the gradually descending type of the development of the disease with initial facio scapulo humeral phenotype, does not correspond to the clinical picture of FSLD2 (or FSHD1/FSHD2). The FSLD1 was first described as a nosological entity by Duchenne in 1855 and later, under the name of FSHD, a descending type; it was described by many famous clinicians and was included in many old and modern handbooks on nervous diseases and handbooks on muscle diseases. In our opinion, FSLD1 is a very rare disease encountered in specific geographical regions only the same as distal types of muscular dystrophy described by Welander, Udd and Miyoshi, for example. It is quite possible that FSLD1 and FSLD2 are connected with the same mutation but the different phenotypes due to the action of the different modifier genes. However, it can be also suggested that FSLD1 is connected with the basic gene other than

FSLD2 and is not linked to the chromosome 4q35.

Acknowledgment

The authors are grateful to Drs. Arahata K, Sugita H and Ms. Goto K for molecular genetic testing of the DNA samples, and to the Japanese Research Fund and Japan Foundation for Aging and Health for the support of this study.

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