Early-Onset Ataxia with Cardiomyopathy and Retained Tendon Reflexes Maps to the Friedreich's Ataxia Locus on Chromosome 9q

Francisco Palau, MD, PhD,* Giuseppe De Michele, MD,† Juan J. Vilchez, MD, PhD,‡§ Massimo Pandolfo, MD,‖ Eugènia Monrós, MSc,* Sergio Cocozza, MD,¶ Patricia Smeyers, MD,*# José Lopez-Arlandis, MD, PhD,** Giuseppe Campanella, MD,† Stefano Di Donato, MD,¶ and Alessandro Filla, MD†

Absence of lower limb tendon reflexes has been considered an essential diagnostic criterion for Friedreich's ataxia (FA). However, preservation of knee and ankle jerks has been reported in a few patients. Linkage analysis to FA locus (FRDA) on chromosome 9q13–21.1 was performed in 11 patients from 6 families with FA phenotype, including cardiomyopathy, but retained reflexes (FARR). A maximal lod score of 3.38 at recombination fraction theta equal to 0.00 was obtained demonstrating that FARR maps to the FRDA locus. These results suggest that FARR is a variant phenotype of FA.

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Friedreich's ataxia (FA) is the most frequent form of hereditary ataxia in large series [1, 2]. Geoffroy and associates [3] and Harding [4] proposed strict clinical diagnostic criteria that include early age of onset, before 20 years and 25 years, respectively, autosomal recessive inheritance, progressive ataxia of limbs and gait, and absence of lower limb tendon reflexes. However, in spite of its autosomal recessive pattern, FA shows clinical variability, particularly in terms of onset age, progression, and cardiomyopathy. Intrafamilial correlation of onset age suggested genetic heterogeneity [5], but no definite evidence was found.

Linkage studies [6, 7] mapped the FA locus (FRDA) to chromosome 9q13–21.1. Chamberlain and colleagues [8] demonstrated genetic homogeneity, in all families, that satisfied strict diagnostic criteria. Studies in other populations confirmed linkage to this chromosomal region [9–11]. Even patients with milder or late-onset variants showed linkage to FRDA locus [12–14].

Few patients with FA phenotype but preserved lower limb tendon reflexes have been reported [15–17]. The diagnosis of these patients is difficult, especially when they present as isolated cases. Genetic linkage analysis was carried out in 6 families with such patients to test the hypothesis of whether the mutation causing FA with retained lower limb tendon reflexes (FARR) maps to FRDA locus.

Patients and Methods

Patient Ascertainment

Patients were from the La Fe University Hospital (LF) of Valencia, Spain, the Department of Neurology of the University of Naples (UN), and the C Besta Neurological Institute (CB) of Milan, Italy. Six families with 11 patients were ascertained (Fig). Eight patients had FARR phenotype and 3 "typical" FA. Two families, UN-B and UN-C, have previously been reported [15]. FARR patients fulfilled Harding's essential diagnostic criteria for FA [4] except absence of knee and ankle jerks: autosomal recessive inheritance, onset before age 25, progressive unremitting ataxia of limbs and gait, and sensory axonal neuropathy at neurophysiological tests. Moreover, we considered an essential criterion the presence of cardiomyopathy detected by electrocardiogram (ECG) and/or echocardiogram.

From the Departments of *Genetics, ‡Neurology, and #Clinical Neurophysiology, Hospital Universitari La Fe, and §Department of Medicine, University of Valencia, Valencia, Spain; Departments of †Neurology and ¶Cellular Biology and Pathology and CEOS (CNR), Federico II University, Naples, Italy; ‖Department of Genetics and Biochemistry, C Besta Neurological Institute, Milan, Italy; and **Neurology Unit, Department of Internal Medicine, Hospital "Verge dels Lliris," Alcoi, Spain.

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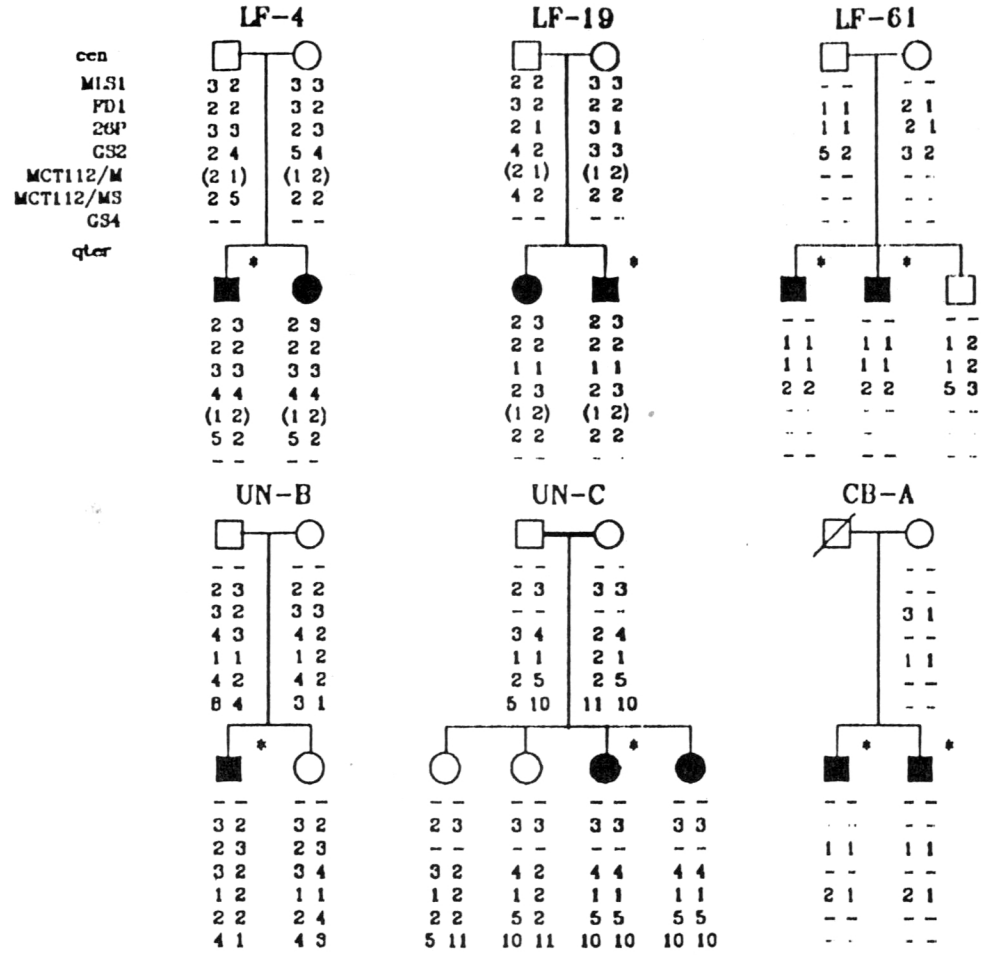
Address correspondence to Prof Filla, Clinica Neurologica, Università Federico II, via Pansini 5, 80131 Napoli, Italy.



Pedigrees of the 6 FARR families. Filled symbols indicate the patients; asterisks, FARR phenotypes. The haplotypes combine the information of 7 FRDA-linked polymorphisms. Numbers between brackets indicate that the segregation phase could not be established for the marker alleles. A first-degree cousin of the patient UN-B II-1, affected by "typical" FA, was not available for DNA studies. FARR = Friedreich's ataxia with retained lower limb tendon reflexes; FRDA = Friedreich's ataxia locus; FA = Friedreich's ataxia; UN = University of Naples; LF = La Fe University Hospital; CB = C Besta Neurological Institute.

Molecular Analysis

DNAs from patients and relatives were extracted by standard procedures. Several FRDA-linked markers were analyzed in each individual to construct extended haplotypes of the region. Markers included restriction fragment length polymorphisms MCT112/*Msp*I (D9S15) [18] and 26P/*Bst*XI (D9S5) [19], and short tandem repeats MLS1 (D9S202) [20], FD1 (X11) [21], GS2 (D9S110) [22], MCT112/MS (D9S15) [19, 23], and GS4 (D9S111) [22].

Restriction fragment length polymorphisms were analyzed by Southern blotting and short tandem repeats by polymerase chain reaction according to the procedures described for each marker.

Pairwise lod scores between FARR and the extended haplotypes across the FRDA linkage group were calculated using the Mlink program from the LINKAGE package version 5.1 [24].

Results

Seven patients were male and 4, female. Mean age of onset ± SD was 13.5 ± 5.5 years (range, 3–20 yr). Mean age at last examination was 25.0 ± 4.0 years (range, 19–30 yr). Inheritance appeared to be autosomal recessive in all families: in 5 families 2 siblings were affected, in the last one a first-degree cousin was affected but not available for the study (see Fig). Consanguinity was present in 1 family. All patients had progressive ataxia of gait, dysarthria, dysmetria, and skeletal deformities (scoliosis and/or pes cavus). Plantar response was extensor in all but 1 (UN-B II-1). Lower limb reflexes were absent in 3 (typical FA phenotype), increased in 4, and normal in 4 (FARR phenotype). Lower limb vibration and position sense was decreased in 8, normal in 3 (LF-19 II-1 and II-2, UN-C II-4). Diabetes mellitus was present in 1 (CB-A II-1). Neurophysiological tests showed severe mainly sensory axonal neuropathy in all. Repolarization abnormalities at ECG were evident in all patients. Two-dimensional echocardiogram, performed in all but the LF-4 family, showed hypertrophic cardiomyop-

athy in 7 and was normal in 1 FA (UN-C II-4) and 1 FARR patient (UN-B II-1). Vitamin E levels were in the normal range in all patients. Hexosaminidase A and B activities, detected in LF-19, UN-B, UN-C, and CB-A families, were normal.

Magnetic resonance imaging (MRI) was performed in either affected siblings from LF-4, LF-19, LF-61, and UN-C families and showed shrinkage of the upper cervical cord, associated with slight cerebellar atrophy in the last two.

The lod scores generated between the disease locus and the extended haplotypes are shown in the Table. No recombination event was observed (see Fig). The lod_{Max} was 3.38 at recombination fraction theta = 0.00, demonstrating linkage between FARR and FRDA locus. Analysis of FRDA-associated haplotypes showed no common haplotype.

Discussion

Autosomal recessive diseases usually show low inter- and intrafamilial clinical variability. In FA a variability higher than expected has been reported, concerning onset age, severity, and associated symptoms. Linkage analysis demonstrated linkage to FRDA locus in the "Acadian" variant with slower course and older age at death [12]. Klockgether and co-workers [13] suggested that late-onset FA is a variant phenotype that may result from a more benign mutation within FRDA locus. We demonstrated linkage to FRDA locus in 8 families with late-onset FA [14].

Friedreich reported absence of lower limb tendon reflexes in 4 of his patients after Erb's article on tendon reflexes, but further series of FA patients also included cases with preserved knee jerks [25]. Absence of knee and ankle jerks was included as an essential diagnostic criterion of FA by Geoffroy and colleagues [3] and Harding [4]. The latter author considered preservation of knee jerks as the distinguishing criterion between early-onset cerebellar ataxia with retained tendon reflexes (EOCA) and FA [26]. However, in the last few years, well-documented cases with FA but preserved or increased lower limb reflexes have been reported [15–17, 27, 28] and a small percentage (1–2%) of FA patients with retained knee jerks is present in large series [4, 15].

Coexistence in the same family of typical FA and FARR was reported, suggesting that preservation of lower limb reflexes may represent a FA variant phenotype [15]. In the present study we obtained a total lod_{Max} of 3.38 at recombination fraction theta = 0.00. The conditional probability that FARR maps to FRDA locus is 0.98. However, it should be noted that the individual lod scores for each family are quite small, as expected in autosomal recessive disorders. Affected children in families LF-61 and UN-C are homozygous for the extended haplotypes, which raises the possibility of an identical mutation in both paternal and maternal FRDA-carrying chromosomes. This hypothesis is the most likely in family UN-C where parental consanguinity occurs. On the other hand, two distinct allelic mutations might be segregating in patients from the remaining 4 families, which are heterozygous for FRDA-associated haplotypes. The absence of a common marker allele or haplotype among families suggests more than one mutation causing FARR phenotype.

Phenotypic variability could be explained by allelic heterogeneity; that is, different phenotypes are caused by different mutations at a single locus, as it occurs in G_{M1}- and G_{M2}-gangliosidoses [29]. On the other hand, phenotypic heterogeneity can be explained by the influence of additional genetic or environmental factors. The 6 families can be sorted out into two groups. In the first group there is coexistence of typical FA and FARR (LF-4, LF-19, UN-B, and UN-C). The second group includes families in which both affected sibs have FARR phenotype (LF-61 and CB-A). Intrafamilial differences could be attributed to modifier loci and/or epigenetic factors in the families of the first group. Conversely, allelic heterogeneity could account for the preservation of lower limb reflexes in the families of the second group.

The relationship between FARR and EOCA has to be clarified. EOCA differs from FA because of preservation of tendon reflexes, a better prognosis, and absence of optic atrophy, hypertrophic cardiomyopathy, diabetes mellitus, and severe skeletal deformities [26]. The absence of peripheral neuropathy at neurophysiological tests allows to exclude the diagnosis of FA in 61% of EOCA patients [30]. MRI showed that spinal atrophy is more frequent in FA, whereas cerebellar atrophy is more likely in EOCA [31]. EOCA is clinically and genetically heterogeneous [32] and it is not unlikely that some patients labeled as EOCA actually have FARR. The presence of severe peripheral neu-

Pairwise Lod Scores between Friedreich's Ataxia Locus–Linked Extended Haplotypes and FARR Families

	Recombination Fraction					
Family	0.00	0.05	0.10	0.20	0.30	0.40
LF-4	0.602	0.515	0.430	0.267	0.129	0.034
LF-19	0.602	0.515	0.430	0.267	0.129	0.034
LF-61	0.727	0.639	0.549	0.367	0.193	0.055
UN-B	0.125	0.086	0.056	0.018	0.004	0.000
UN-C	0.852	0.742	0.630	0.407	0.205	0.056
CB-A	0.477	0.405	0.335	0.205	0.098	0.026
Total	3.385	2.902	2.430	1.531	0.758	0.205

FARR = Friedreich's ataxia with retained lower limb tendon reflexes; LF = La Fe University Hospital; UN = University of Naples; CB = C Besta Neurological Institute.

ropathy and cardiomyopathy should suggest the diagnosis of FARR. All FARR patients in the present study had constant sensory neuropathy and ECG abnormalities. Echocardiographic evidence of hypertrophic cardiomyopathy was present in all but one.

In conclusion, FARR phenotype is an FA variant phenotype. It accounts for a small percentage of cases in FA large series, but the occurrence of FARR may be underestimated. This diagnosis should be considered in EOCA patients with severe sensory neuropathy and cardiomyopathy.

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