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# Uncommon features in Cuban families affected with Friedreich ataxia

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ABSTRACT

This report describes two families who presented with autosomal recessive ataxia. By means of Polymerase Chain Reaction (PCR) molecular testing we identified expansions in the gene encoding Frataxin (FTX) that is diagnostic of Friedreich ataxia. A history of reproductive loss in the two families, prominent scoliosis deformity preceding the onset of ataxic gait, the presence of a sensitive axonal neuropathy, as well as the common origin of ancestors are unusual features of these families. These cases illustrate the importance of molecular diagnosis in patients with a recessive ataxia. The origin of the expanded gene and the GAA repeat size in the normal population are issues to be further investigated. The molecular diagnosis of Friedreich ataxia is now established in Cuba.



Friedreich ataxia (FRDA) is considered the most common hereditary neurodegenerative disorder and the most frequent hereditary ataxia in the Caucasian population [16,31,39]. About 96% of the affected individuals are homozygous for a GAA triplet-repeat expansion in intron 1 of the FRDA gene, located at 9q13-q21.1. [23].

Clinically this condition is characterized by onset before 25 years of age, progressive limb and gait ataxia, dysarthria, absent reflexes in the lower limbs and altered vibration sense [23].

Although frequent, scoliosis is not a constant sign. Harding in 1981 did not consider it as a clinical feature [11]. Pascale found it in 73 out of 92 patients (79%) [26] and Milbrandt [22] developed a study in two institutions reporting a prevalence of 63% among patients affected by Friedreich ataxia. According to Cady [2] the prevalence of scoliosis in FRDA patients approaches 100%. Geoffroy considered scoliosis in 1976 as secondary criteria for the clinical diagnosis [9].

More than 20% of FRDA patients develop type II diabetes (T2D) and 10% have milder disturbances in their glucose metabolism, suggesting an increased susceptibility to T2D in these individuals [14].

Some authors found linkage of T2D with the locus harboring the human frataxin gene in different populations worldwide [10,17,19,25], suggesting a role in the pathogenesis of common T2D. Disruption of the frataxin gene selectively in pancreatic B-cells causes a progressive Diabetes Mellitus paralleled by impaired insulin secretion due to decreased B-cell mass and accumulation of reactive oxygen species [28,30].

Frataxins are small essential proteins whose deficiency causes a range of metabolic disturbances, which include oxidative stress [24]. It is known that mitochondrial [Fe-S] cluster levels are decreased in FRDA, but it is not clear whether this is due to the sensitivity of these moieties to oxidative stress [32] or the possible role of frataxin in [Fe-S] synthesis [45].

It was a belief that continuous oxidative damage resulting from hampered superoxidedismutases signaling participated in the mitochondrial deficiency and ultimately the neuronal and cardiac cell death. This was further supported by the findings that, the antioxidant Idebenone can reduce myocardial hypertrophy and decrease markers of oxidative stress in patients with FRDA [12,34,37].

Nevertheless Seznec in 2005 [38] demonstrated that in FRDA, mitochondrial iron accumulation does not induce oxidative stress nor the antioxidants attenuate the disease and proposed that, contrary to the general assumption, FRDA is a neurodegenerative disease not associated with oxidative damage.

Cuba reports the highest worldwide prevalence of Spinocerebellar ataxia type 2 (SCA2). In contrast, little is known about the

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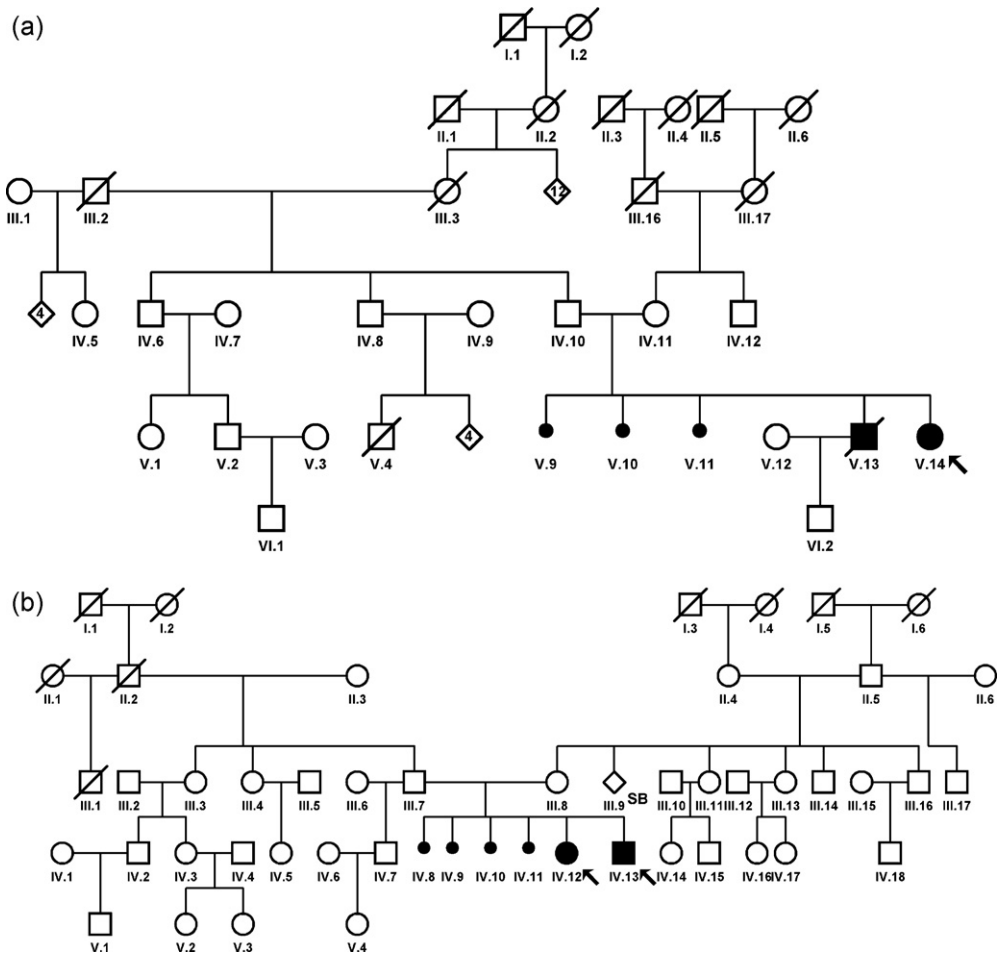


**Fig. 1.** (a) Pedigree of the first family. Squares = men; circles = women; solid circles = affected; little solid circles = miscarriages; slash marks = deceased. (b) Pedigree of the second family. Squares = men; circles = women; solid circles = affected; little solid circles = miscarriages; slash marks = deceased; SB = Still birth.

neither incidence nor prevalence of sporadic or recessive ataxias, accounting for 2.38% and 9.16% among all forms of hereditary ataxias [44]. In this report, three clinically diagnosed cases are described as having FRDA. To date there have been no reports of other cases with FRDA confirmed by molecular testing in this country.

*Patient 1*: The proband (V.14 in Fig. 1a), a 30-year-old Cuban woman, was the product of a nonconsanguineous marriage. Her brother suffered frequent falls when running at 10 years, ataxic gait at 16, dysarthria at 19 and died at age 39 with a clinical diagnosis of FRDA.

Our patient was born at term after an uncomplicated delivery and grew up uneventfully. She developed scoliosis at 7 years of age, difficulty in running at age 16 and difficulty in walking at age 19, as well as nystagmus. Because of muscle weakness and truncal ataxia she was confined to a wheelchair by age 24 and 4 years later she developed dysarthria and cardiomyopathy.

*Patient 2*: The patient was an 18-year-old man (IV.13 in Fig. 1b), the product of a nonconsanguineous marriage. He presented with scoliosis at the age of 10 years, which has been markedly progressive. One year later he developed ataxia, limb weakness, as well as nystagmus and dysarthria. He remains ambulatory.

*Patient 3*: Patient 3, the sister of patient 2 (IV.12 in Fig. 1b), was the product of a normal pregnancy labour and delivery. Her early developmental milestones were normal. She was first seen at the age of 13 because of scoliosis. Her neurological examination was normal until she was 22 when ataxia was first noted. She remains ambulatory at 25 years of age although dysarthria, nystagmus and ataxia are clearly progressing.

*Family 1*: The mother of Case 1 had a history of three miscarriages prior to the birth of her first child. Her father and paternal grandfather had a history of Diabetes Mellitus. The paternal family comes from Pinar del Río province, in the western region of Cuba, and the maternal branch from Spain.

*Family 2*: The mother of Patients 2 and 3, had a history of four miscarriages, prior to the birth of her first child. Both parents were clinically unaffected, but gave a history of hypertension and the maternal grandmother suffered from Diabetes Mellitus. The family was also originally from Pinar del Río Province.

After informed consent was obtained patients were recruited at the Center for Research and Rehabilitation of Hereditary Ataxias for clinical examination. The International Cooperative Ataxia Rating Scale (ICARS) and the Scale for the Assessment and Rating of Ataxia (SARA) were used for the evaluation [36,42]. Laboratory tests included: haemogram, cholesterol level, blood sugar, glucose tolerance testing, and measurements of super oxide dismutase (SOD) and catalase. An echocardiogram and X-rays of chest and spine were also carried out together with neurophysiologic studies including motor nerve conduction studies in peroneal and median nerves, sensory nerve conduction studies in sural and median nerves and multimodal evoked potentials (visual, auditive and somatosensory in posterior tibial nerves).

Blood samples for molecular testing were collected with EDTA and genomic DNA was obtained by extraction from leukocytes. PCR for FRDA gene was carried out using standard protocols [6], which included the primers GAA-104F and GAA-629R, together with the Elongase enzyme (Invitrogen). Gel electrophoresis was performed