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SHORT REPORT

Friedreich Ataxia: Diagnostic Yield and Minimal Frequency in South Brazil

Helena Fussiger[1] · Maria Luiza Saraiva-Pereira[2,3,4] · Sandra Leistner-Segal[1,4] · Laura Bannach Jardim[1,3,4,5]

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Abstract

Friedreich ataxia (FRDA) is an autosomal recessive disorder due to mutations in the *FXN* gene. FRDA is characterized by the classical triad of ataxia, absent reflexes, and Babinski sign, but atypical presentations might also occur. Our aims were to describe the proportion of FRDA diagnoses in suspected families living in Rio Grande do Sul, South Brazil, and to estimate a minimum frequency of symptomatic subjects. Subjects that were evaluated by molecular analysis for FRDA at the Hospital de Clínicas de Porto Alegre were identified in our files. Patients' clinical manifestation and phenotypes were described and compared. The number of FRDA subjects alive in the last 5 years was determined. One hundred fifty-six index cases (families) were submitted to evaluation of GAA repeats at *FXN* since 1997: 27 were confirmed as FRDA patients. Therefore, the diagnostic yield was 17.3%. Proportion of classical, late onset, and retained reflexes subphenotypes were similar to those described by other studies. A minimum prevalence was estimated as 0.20:100.000 inhabitants. In conclusion, we verified that this FRDA population displayed the usual clinical characteristics, but with a lower period prevalence than those obtained in populations from Europe.

Keywords Friedreich ataxia · FRDA · *FXN* · Prevalence · Diagnostic yield

Introduction

Friedreich ataxia (FRDA) is an autosomal recessive disease caused by loss of function of the frataxin protein, as a consequence of mutations at *FXN*, in the majority of cases represented by an intronic expansion of a GAA repeat [1]. Usually referred as the most frequent autosomal recessive ataxia [2], FRDA is characterized by the classical triad of ataxia, areflexia, and Babinski sign, starting before puberty. Bone deformities, diabetes mellitus (DM), and cardiomyopathy are additional common findings [3]. Atypical presentations include FRDA starting after 25 years—the late onset FRDA (called LOFA)—and FRDA cases with retained reflexes or even with hyperreflexia (called FARR) [2], among others.

Prevalence varies from more than 1:50,000 to 0.13:100,000 in populations from Europe or with European ancestry [4]. In Asian [5, 6] and Latin American [7, 8] countries, FRDA frequencies seem to be much lower than those reported above. For instance, the estimated prevalence of FRDA in Cuba was 0.045:100,000 [7]. To date, there are no published reports on FRDA frequency in Brazil.

The aims of this report were to describe the proportion of molecular diagnosis of FRDA among ataxic subjects from South Brazil, to report their clinical findings, and to estimate the minimal prevalence of FRDA in this region.

Methods

A cross-sectional study was performed reviewing medical records of all ataxic patients who underwent molecular testing for FRDA at the Hospital de Clínicas de Porto Alegre (HCPA) from 1997 to 2017. Our institution is the regional reference

✉ Laura Bannach Jardim
ljardim@hcpa.edu.br

[1] Programa de Pós-Graduação em Saúde da Criança e do Adolescente, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos, 2400, sala 220, Porto Alegre 90035-003, Brazil

[2] Departamento de Bioquímica, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos, 2600-Prédio Anexo, Porto Alegre 90035-003, Brazil

[3] Laboratório de Identificação Genética, Centro de Pesquisa Experimental, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos 2350, Porto Alegre 90035-003, Brazil

[4] Serviço de Genética Médica, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos 2350, Porto Alegre 90035-003, Brazil

[5] Departamento de Medicina Interna, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos 2350, Porto Alegre 90035-003, Brazil

center for rare diseases and performs molecular diagnosis for FRDA not only for the Brazilian Public Health System (SUS) but also for private subjects. Molecular analyses were performed based on PCR amplification of region of interest using specific primers for detecting alleles within normal range. If just one allele was present or no amplification was observed, sample was further analyzed by triplet repeat primed PCR (TP-PCR) using fluorescently labeled primers, followed by capillary electrophoresis in an ABI3130xl detection system.

Only subjects living in the southernmost state of Brazil, Rio Grande do Sul, were included. The exclusion criteria were inheritance other than recessive or sporadic; congenital cases; cerebral imaging suggesting other specific diagnosis; presence of ocular apraxia; and carrier status testing. Data on disease duration, age at onset, year of molecular diagnosis, neuroimaging findings; and presence of areflexia, hyperreflexia, Babinski sign, DM, and cardiomyopathy by the time of diagnosis were obtained. Cardiomyopathy was defined by transthoracic or transesophageal echocardiogram criteria: left ventricular concentric hypertrophy, increased thickness of the interventricular septum, and dilated cardiomyopathy. According to the similarity of subjects to FRDA phenotype, individuals were divided

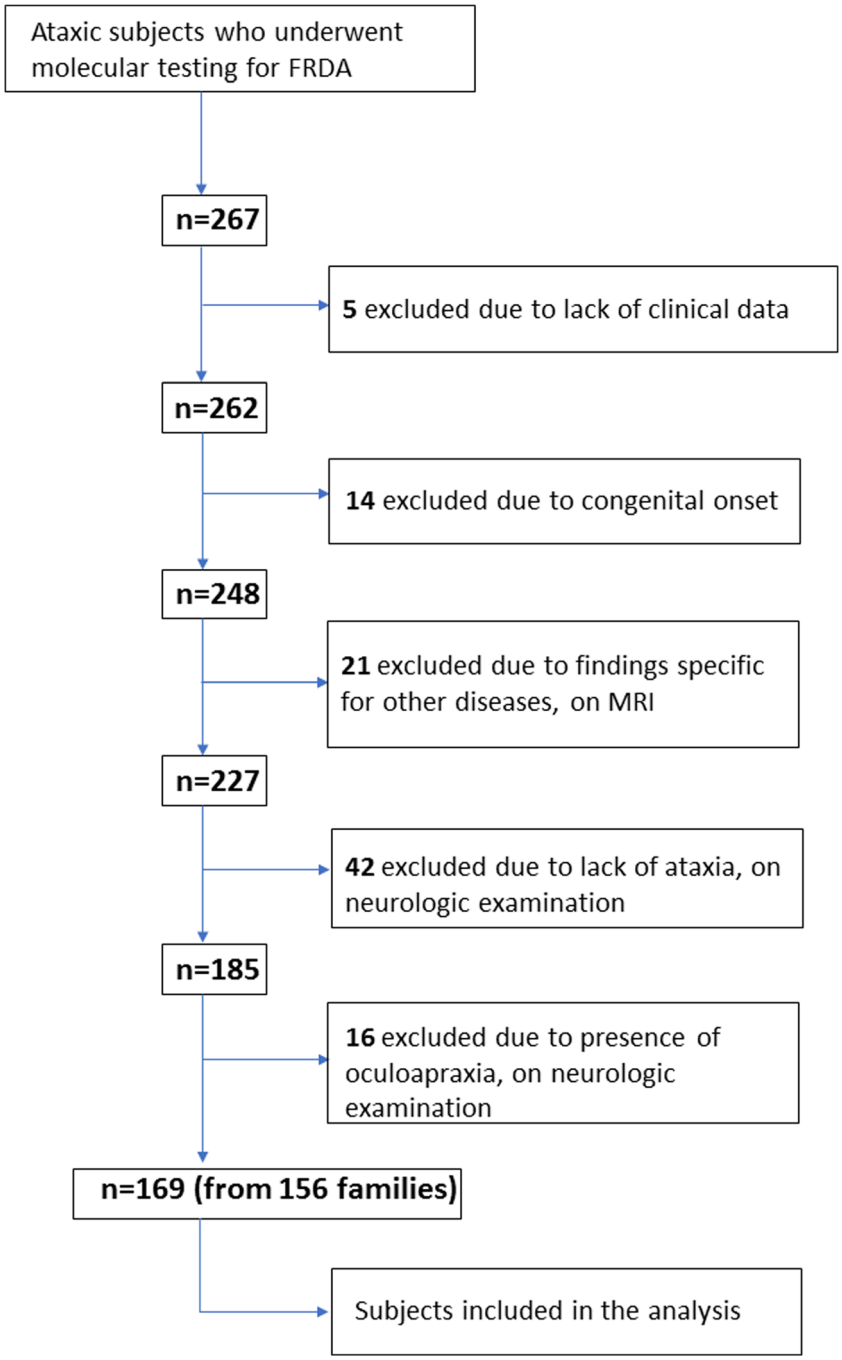

Fig. 1 Workflow description of the study, showing the number of subjects screened, exclusion criteria, and number of subjects included in the analysis

into four categories: "partial phenotype," if at least two features of the classical triad were present, starting at any age, and less than 10 years of disease duration; "classical phenotype," if the classical triad was present and if disease started before 25 years of age; "LOFA or FARR"; and "no phenotype," if the clinical characteristics did not fit into any of the former categories.

A survey was then made by telephone calls between June and August 2017 in order to get information about living status of all subjects identified by the medical records search as well as of other affected relatives. The total number of FRDA subjects alive between September 2013 and September 2017 (5 years), in Rio Grande do Sul, was compared to the overall population in order to estimate the minimal period prevalence of FRDA in that state.

Categorical variables are presented as frequencies and compared using chi-square test, while continuous variables with normal distribution are described through means and standard deviations and compared using *t* test or Mann-Whitney. The *p* value for significance was 0.05. All statistical analysis was made using SPSS vs 20.0.

This study was approved by the local ethical committee under the registry number CAAE 79117317.2.0000.5327.

Results

One hundred sixty-nine subjects from 156 families were included (Fig. 1). Twenty-seven out of 156 index cases (17.3%) were diagnosed as FRDA. If the oculoapraxic patients were included, total number of cases would rise to 185 and the diagnostic percentage would be 14.5%. Twenty-six FRDA index cases were shown to present GAA expansions in both alleles, and one patient was a compound heterozygote for c.157del (p.Arg53Alafs*23)/GAA expansion. Therefore, 53 out of 54 FRDA alleles (98%) were due to GAA expansions.

In order to better characterize FRDA phenotypes in our region, all the affected siblings from the 156 families under study were included in the analysis; for instance, 27 FRDA families comprised 33 affected sibs. Results are summarized in Table 1. The majority of FRDA cases belonged to the classical phenotype (66%), followed by LOFA/FARR (18%) and partial phenotypic presentations (15%). Six out of 27 FRDA families had more than one affected sib: four sibships presented the classical phenotype, and two sibships presented LOFA/FARR (both starting after 25 years and with retained reflexes). The only intrafamiliar variability seemed to be time dependent: a kindred with the classical form in one sib and with a partial phenotypic presentation in another. DM was present in 6/27 (22%) and 7/98 (7.1%) subjects with and without FRDA (chi-square = 5.1, $p = 0.023$). Cardiomyopathy was also more frequent in FRDA (12/27 or 44.4%) than in subjects without FRDA (2/32 or 6.8%) (chi-square = 12, $p < 0.05$); in FRDA, it was associated with earlier disease onset. FRDA patients with and without DM or cardiomyopathy had similar duration of their diseases since first symptom (data not shown). Cerebellar atrophy was present in the magnetic resonance imaging in 1/12 FRDA carriers and in 70/142 individuals without FRDA (chi-square = 12, $p < 0.05$).

Table 1 Ataxic subjects from Rio Grande do Sul state, whose *FXN* alleles were analyzed from 1997 to 2017. Numbers of subjects with a positive diagnosis of Friedreich ataxia (FRDA) were compared to those of subjects with negative results (non-FRDA), according to the phenotype classification

	Ataxic subjects under study	
	Non-FRDA, *n* (%)	FRDA, *n* (%)
Partial phenotype	10 (7.3)	5 (15)
Classical phenotype	5 (3.6)	22 (66)
LOFA or FARR phenotypes	79 (58)	6 (18)
No phenotype	42 (30.8)	0 (0)
Total	136 (100)	33 (100)

Partial phenotype: at least two features of the classical triad were present, starting at any age, in a disease with less than 10 years of duration; classical phenotype: the classical triad of ataxia, areflexia, and Babinski sign was present and disease started before 25 years of age; LOFA: the classical triad with start after 26 years of age; FARR: ataxia, Babinski, and retained/brisk reflexes; no phenotype: the clinical characteristics did not fit into any of the former categories

Information obtained from the survey confirmed that there were 23 living FRDA subjects in the last 5 years, from 21 out of 27 FRDA families. Four subjects were deceased. Six subjects from six families, diagnosed between 2002 and 2009, were lost. Therefore, between 2014 and 2017, at least 23 FRDA subjects were alive in Rio Grande do Sul state, Brazil. As the total population in 2017 was 11,329,000 (http://www.fee.rs.gov.br/indicadores/populacao/estimativas-populacionais/), the minimum prevalence of FRDA was 0.20:100.000 inhabitants in this region.

Discussion

The present study found a low percentage of FRDA diagnosis—17.3%—among ataxic subjects tested in Rio Grande do Sul, Brazil. The proportion of phenotypes and clinical characteristics disclosed by the present FRDA series was very close to those reported in previous studies around the world [9]. These figures corresponded to a minimum period prevalence of 0.20:100.000 in the last 5 years in the same region.

The diagnostic yield of FRDA varies according to population of origin, ranging from 30 to 44.5% in European series [10], to 5.7 and 10.4% in reports from Mexico and Cuba [7, 11]. Our numbers—17.3%—are located in the middle of those figures. More than 150 ataxic subjects have been investigated in the last 20 years in our institution; quite a few of them—

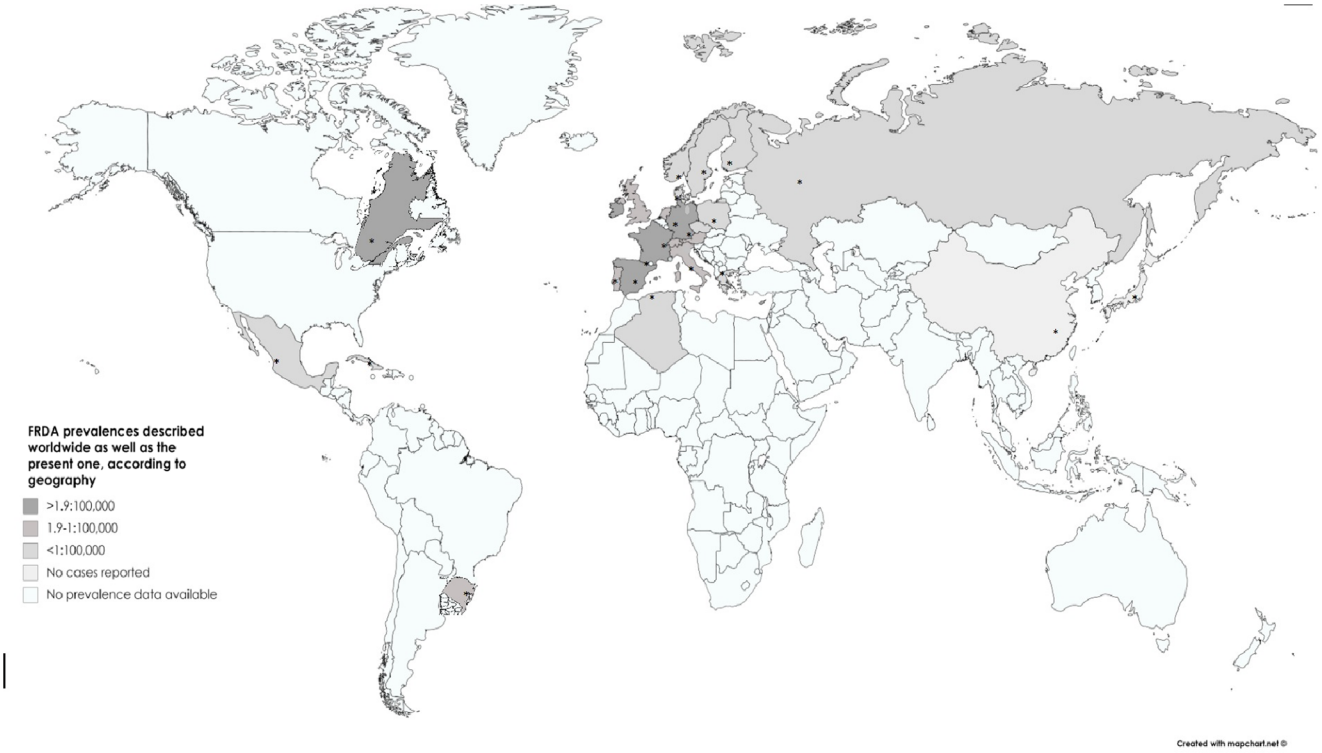

Fig. 2 FRDA prevalences described worldwide as well as the present one, according to geography [4–8, 13, 14]

42—presented the classical triad or at least two of the classical findings (Table 1), and fewer—33—were confirmed to carry FRDA. These figures sustain the argument of a low frequency of these diseases in our population.

The survey on living FRDA subjects in our region raised from cases diagnosed in a reference center and indeed, the present data did not constitute a truly population study on prevalence. This limitation will hardly be overcome in a near future, given the disease rarity. Thus, we believe that the minimum prevalence as reported here is a valuable information for health policies and for researchers in this field of knowledge.

FRDA has been proposed to emerge from at risk GAA alleles, prone to pathologic expansions, carried mostly by individuals of European ancestry; these at risk alleles would have appeared after the divergence of Indo-Europeans and Afro-Asiatics in the superior paleolithic [12]. This hypothesis would explain the diverse prevalence rates found worldwide (Fig. 2). In line with this assumption, FRDA carriers living in Mexico, a country of high Amerindian ancestry and very low incidence of FRDA, presented markers indicative of an European origin for their *FXN* expanded alleles [8]. Molecular studies performed in normal populations from South Brazil showed that general markers of European ancestry are present in about 75% of samples [15]. In other words, the impact of European ancestry in Rio Grande do Sul was high. Most European settlements arrived in the nineteenth century from Germany and Italy. Our minimum prevalence of 0.20:100.000 was close to the numbers found in Padua, Italy, of 0.60:100,000 [14] and quite lower than those found in Germany [10]. Future studies on ancestral origins of *FXN* alleles in South Brazil are required to clarify the reasons for these differences. Those studies will probably help to confirm the low frequency of FRDA in this population.

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Compliance with Ethical Standards

This study was approved by the local ethical committee under the registry number CAAE 79117317.2.0000.5327.

Conflict of Interest The authors declare that they have no conflict of interest.

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