Original Research Article

Screening for Fabry Disease among Dialysis Patients in Brazil: Findings from the First 18 months of a Nationwide Study

Aims: To estimate the frequency of Fabry disease (FD) among kidney failure patients on dialysis in Brazil using an algorithm designed to track FD-suspected patients.
Study Design: Cross-sectional study.
Place and Duration of Study: Dialysis Centers in Brazil, from July, 2013 to December, 2014.
Methodology: A total of 25,223 dialysis patients from 188 dialysis centers spread all over the country were analyzed. All collected data were entered in a database created and maintained by DataGenno Interactive Research®. An algorithm was created to sort dialysis patients into three main groups: FD-suspected patients, FD-non suspected patients, and patients for medical analysis. Further up, FD-suspected patients were submitted to *GLA* gene sequencing.
Results: Out of 25,223 patients, 2,956 (11.72%) were considered FD-suspected. From FD-suspected patients, 109 (3.7%; 2.4% female, 1.3% male) were diagnosed with FD. FD-positive patients represented 0.4% (0.3% female, 0.1% male) of all analyzed patients. Mean age of FD-positive patients: 37.9 years (±17.4) and of FD-negative patients: 45.0 years (±11.6).

Eighteen different mutations were found in FD-positive patients. Missense mutations R118C, A368T, M290I and S126G were the most frequent (77.1%). A368T and S126G were highly frequent (32.5% and 20%, respectively) among 40 patients with depression. Six female patients had cerebrovascular disease; four of them (66.7%) had A368T. R118C was found in seven (36.8%) of the patients with heart disease. Six patients out of 15 with angiokeratoma had M290I (40%) and four had S126G (26.7%). Angiokeratoma frequency (13.8%) was higher than in previous findings in the Brazilian population.
Conclusion: The natural history and frequency of FD among Brazilian dialysis patients were, in general, according to literature. Four missense mutations were highly frequent among FD-positive patients; none of them were directly related to end-stage renal disease caused by FD. The algorithm used can be a helpful tool to identify FD.

Keywords: Fabry disease, lysosomal storage disorders, end-stage renal disease, dialysis, screening, mutation.

1. INTRODUCTION

Fabry disease (MIM: 301500), an X-linked lysosomal storage disorder, with an estimated incidence of 1:40,000–170,000, is caused by a deficiency of the alpha-galactosidase A (α-Gal A) enzyme, resulting in storage of globotriaosylceramide (Gb3/GL3) and related glycosphingolipids in the plasma and cellular lysosomes [1-3]. Currently, 845 variants in the galactosidase, alpha gene (*GLA,* MIM: 300644) have been described [4], most in single families [1]. Fabry disease (FD) is a chronic progressive condition, clinically heterogeneous with symptoms such as chronic neuropathic pain, acute pain crises, heat and cold intolerance, and fatigue often beginning in childhood. The average presentation age is: 6–8 years (y) (males) and 9y (females), although it may vary from individual to individual even within the same family [2,3,5,6]. The storage of Gb3/GL3 can result in: angiokeratoma, tinnitus, hearing loss, corneal whorls, vertigo, transient ischemic attacks, stroke, cardiomyopathy, left ventricular hypertrophy, cardiac arrhythmias and valve insufficiency, chronic alternating diarrhea and constipation, obstructive pulmonary disease, proteinuria, progressive renal disease, panic attacks, depression, and adaptive function disorders [2,3,5,6]. Heterozygous women may also be affected, with more variable phenotype [7-9]. Life expectancy is diminished, more apparent in men [10].

FD manifestations tend to be non-specific and often unrecognized. Patients are therefore frequently misdiagnosed or diagnosed lately [2,3,5,6]. Screening of FD patients among high-risk populations allows the diagnostic investigation and confirmation, the identification of

asymptomatic/oligosymptomatic affected relatives and genetic counseling for couples at risk [1,11]. An increasing number of screening studies in high-risk populations and newborn screening studies have been performed since enzyme replacement therapy became available [1,11,12]. The interest of nephrologists in FD increased after the description of the "renal variant" [13]. Large-scale screening efforts of end-stage renal disease (ESRD) populations in dialysis treatment have been carried out [1,11,14], as ESRD is an important outcome in FD. Currently, Brazil has around 90,000 patients with ESRD being treated in 692 dialysis centers (Ministry of Health; Figure 1) [15]. Considering a FD prevalence from 0.12-0.94% in dialysis centers [14], the estimative of FD patients in Brazil would be from 108–846. This number can increase since FD may be characterized as a family trait disorder [2,16].

The main objective of this study was to estimate the frequency of FD among Brazilian dialysis patients using an algorithm designed for screening FD-suspects.

2. METHODOLOGY

2.1 Study population

A cross-sectional study was undertaken from July 2013 to December 2014, with kidney failure patients from dialysis centers in Brazil. It's part of a large ongoing study that aims to assess around 90,000 kidney failure patients in order to track FD-suspected patients. Inclusion criteria: kidney failure patients on hemodialysis or peritoneal dialysis from dialysis centers throughout Brazil (Figure 1), both sexes, having or not underlying causes of chronic kidney disease – CKD: high blood pressure (HBP), diabetes mellitus (DM), obesity, rheumatoid arthritis, polycystic kidney disease, and Berger's disease [14,15]. Exclusion criteria: patients with confirmed laboratory and/or clinical diagnosis of underlying causes of CKD ruling out the possibility of FD.

2.2 Ethics, consent and permissions

The study protocol was approved by the Research Ethics Committee of Campos Medical School (legal opinion #305·988; 06/28/2013). Patients invited to participate were informed about the study purposes and each subject freely signed an individual consent form

agreeing to participate. Patients and the health care team involved had their anonymity fully preserved according to Resolution no. 196/96 of the National Board of Health, 1988 Medical Ethics Code and 1964 Declaration of Helsinki.

Figure 1. Map of the dialysis centers in Brazil.

2.3 Screening strategy

The screening strategy started with an invitation letter sent to all Brazilian dialysis centers. After the Ethics Committee's approval and formal acceptance by the head of the dialysis center, clinical questionnaires were sent to be answered by dialysis patients. Dialysis centers' healthcare staffs, mainly nurses, were trained to apply the questionnaire. Questionnaires with filling inconsistencies were sent back to be reapplied. The results were analyzed by a team of medical specialists (MPC, MGR). It should be clear that this study did not actively request the participant dialysis centers to run FD tests or send FD test results they have decided to run by their own. However, the dialysis centers kindly sent FD test results of the FD-suspected patients to the study investigators. The flowchart is in Figure 2.

2.3.1 Clinical questionnaire

The clinical questionnaire (Figure 3) contained a list of questions about FD signs and symptoms [2,3,5,6] that were divided in seven groups: 1, nefrological; 2, cardiological; 3, rheumatological; 4, neurological; 5, gastrointestinal/otorhinolaryngological; 6, dermatological; 7,

ophthalmological. The questionnaire also contained questions about underlying causes of CKD [17,18].

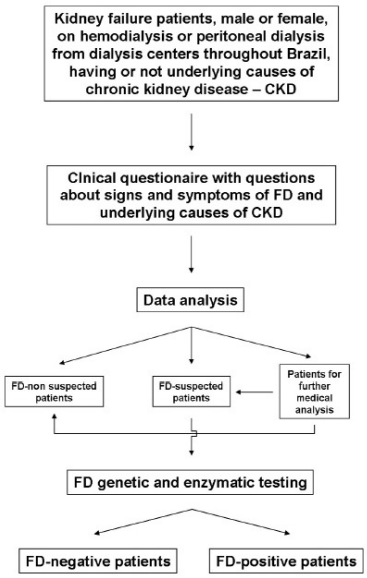
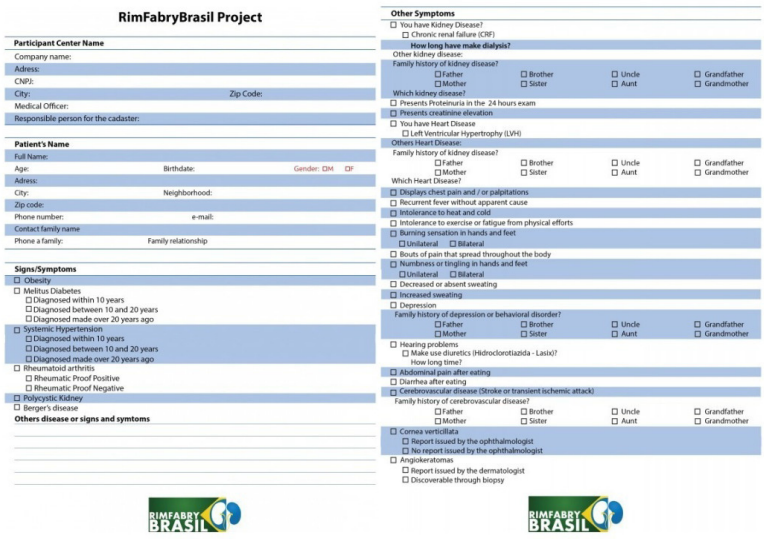


Figure 2. Flowchart depicting a method of screening for FD detection in Brazilian dialysis patients.



RimFabryBrasil Project

Participant Center Name
Company name:
Adress:
CNPJ:
City: Zip Code:
Medical Officer:
Responsible person for the cadaster:

Patient's Name
Full Name:
Age: Birthdate: Gender: ☐M ☐F
Adress:
City: Neighborhood:
Zip code:
Phone number: e-mail:
Contact family name
Phone a family: Family relationship

Signs/Symptoms
☐ Obesity
☐ Melitus Diabetes
☐ Diagnosed within 10 years
☐ Diagnosed between 10 and 20 years
☐ Diagnosed made over 20 years ago
☐ Systemic Hypertension
☐ Diagnosed within 10 years
☐ Diagnosed between 10 and 20 years
☐ Diagnosed made over 20 years ago
☐ Rheumatoid arthritis
☐ Rheumatic Proof Positive
☐ Rheumatic Proof Negative
☐ Polycystic Kidney
☐ Berger's disease
Others disease or signs and symtoms

Other Symptoms
☐ You have Kidney Disease?
☐ Chronic renal failure (CRF)
How long have make dialysis?
Other kidney disease:
Family history of kidney disease?
☐ Father ☐ Brother ☐ Uncle ☐ Grandfather
☐ Mother ☐ Sister ☐ Aunt ☐ Grandmother
Which kidney disease?
☐ Presents Proteinuria in the 24 hours exam
☐ Presents creatinine elevation
☐ You have Heart Disease
☐ Left Ventricular Hypertrophy (LVH)
Others Heart Disease:
Family history of kidney disease?
☐ Father ☐ Brother ☐ Uncle ☐ Grandfather
☐ Mother ☐ Sister ☐ Aunt ☐ Grandmother
Which Heart Disease?
☐ Displays chest pain and / or palpitations
☐ Recurrent fever without apparent cause
☐ Intolerance to heat and cold
☐ Intolerance to exercise or fatigue from physical efforts
☐ Burning sensation in hands and feet
☐ Unilateral ☐ Bilateral
☐ Bouts of pain that spread throughout the body
☐ Numbness or tingling in hands and feet
☐ Unilateral ☐ Bilateral
☐ Decreased or absent sweating
☐ Increased sweating
☐ Depression
Family history of depression or behavioral disorder?
☐ Father ☐ Brother ☐ Uncle ☐ Grandfather
☐ Mother ☐ Sister ☐ Aunt ☐ Grandmother
☐ Hearing problems
☐ Make use diuretics (Hidroclorotiazida - Lasix)?
How long time?
☐ Abdominal pain after eating
☐ Diarrhea after eating
☐ Cerebrovascular disease (Stroke or transient ischemic attack)
Family history of cerebrovascular disease?
☐ Father ☐ Brother ☐ Uncle ☐ Grandfather
☐ Mother ☐ Sister ☐ Aunt ☐ Grandmother
☐ Cornea verticillata
☐ Report issued by the ophthalmologist
☐ No report issued by the ophthalmologist
☐ Angiokeratomas
☐ Report issued by the dermatologist
☐ Discoverable through biopsy

Figure 3. The clinical questionnaire used for interviewing the patients.

2.3.2 Data analysis

All collected data were entered in a database created and maintained by DataGenno Interactive Research® [19]. An algorithm (Figure 4) was created by DataGenno to sort dialysis patients into three main groups: FD-suspected patients, FD-non suspected patients, and patients for further medical analysis.

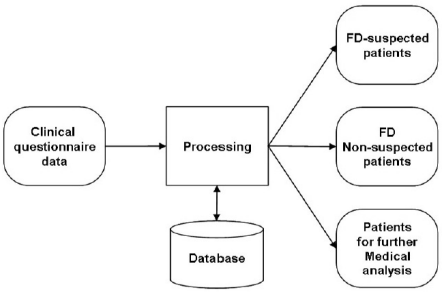


Figure 4. Algorithm for detection of FD-suspected in Brazilian dialysis patients.

The algorithm is based on combinations of FD signs and symptoms and patient's gender and age (Tables 1, 2). Patients for further medical analysis were clinically evaluated by a team of medical specialists (MPC and MGR) in order to decide if they could be included either in FD-suspected or FD-non suspected patient groups (Figure 2). Statistical analysis by frequency distribution, measures of central tendency, dispersion, and the chi-square test. The results were sent back to the dialysis centers which were entirely responsible for moving forward and order or not FD diagnostic tests for FD-suspected patients.

Table 1. Groups of FD signs and symptoms

Group	FD signs and symptoms	
1 Nefrological	1.1 Family history of kidney disease	1.2 Kidney disease
	1.3 Proteinuria in the 24 hours exam	1.4 Creatinine elevation
2 Cardiological	2.1 Family history of heart disease	2.2 Heart Disease

Group	FD signs and symptoms	
	2.3 Chest pain and/or palpitations	
3 Rheumatological	3.1 Recurrent fever without apparent cause	
	3.2 Heat and cold intolerance	
	3.3 Exercise intolerance or fatigue from physical efforts	
	3.4 Burning sensation in hands and feet	
	3.5 Bouts of pain that spread throughout the body	
	3.6 Numbness or tingling in hands and feet	
	3.7 Sweating decrease or absence	3.8 Sweating increase
4 Neurological	4.1 Family history of cerebrovascular disease	
	4.2 Cerebrovascular disease (stroke/transient ischemic attack)	
	4.3 Family history of depression/behavioral disorder	
	4.4 Depression	
Gastrointestinal / Otorhinolaryngological	5.1 Hearing problems	5.2 Abdominal pain (after eating)
	5.3 Diarrhea (after eating)	
6 Dermatological	6.1 Angiokeratomas	
7 Ophthalmological	7.1 Cornea verticillata	

Table 2. Combinations of FD signs and symptoms and patient's gender and age used to sort dialysis patients into three groups.

	Combinations of FD signs and symptoms, gender or age	Group of patients
A	1+ 2+3 (with four or more FD signs and symptoms of Group 3, without sweating increase)	FD-suspected

	Combinations of FD signs and symptoms, gender or age	Group of patients
B	Male patient >60y with 1+2+3 (with four or more FD signs and symptoms of Group 3, without sweating increase)	Analysis
C	1+1.1+3 (with three or more FD signs and symptoms of Group 3, without sweating increase)	FD-suspected
D	Male patient >60y with 1+1.1+3 (with three or more FD signs and symptoms of Group 3, without sweating increase)	Analysis
E	1+2+ 2.1+3 (with three or more FD signs and symptoms of Group 3, without sweating increase)	FD-suspected
F	Male patient >60y with 1+2+2.1+3 (with three or more FD signs and symptoms of Group 3, without sweating increase)	Analysis
G	Combinations A, B or C where Group 3 of FD signs and symptoms includes sweating increase	Analysis
H	Male patient >60y with combinations of signs and symptoms A,C or E where Group 3 of FD signs and symptoms includes sweating increase	FD-non suspected
I	Male patient with 1.1 and/or 2.1 whose father has 1.1 and/or 2.1 (healthy mother)	Analysis
J	1+2+7 (one or more FD signs and symptoms of Group 7)	FD-suspected
K	Patient with polycystic kidney disease, excluding FD signs and symptoms of Groups 5 and/or 6	Analysis
L	1+5	FD-suspected
M	1+6	FD-suspected
N	1	Analysis
O	1+5	FD-suspected

	Combinations of FD signs and symptoms, gender or age	Group of patients
P	1+6	FD-suspected
Q	1+2+3 (four or more FD signs and symptoms of Group 3)	Analysis
R	1+1.1+3 (three or more FD signs and symptoms of Group 3)	Analysis
S	1+2+2.1+3 (three or more FD signs and symptoms of Group 3)	Analysis
T	1+3 (three or more FD signs and symptoms of Group 3) +4 or 5	Analysis
U	Male patient >60y with combinations of signs and symptoms R,S or T where the FD signs and symptoms of Group 3 includes sweating increase	FD-non suspected
V	Patients with confirmed laboratory and/or clinical diagnosis of underlying causes of CKD ruling out the possibility of FD	FD-non suspected

A to V – combinations of FD signs/symptoms, gender or age used to define three main groups of patients: FD-suspected, FD-non suspected, and analysis.

1 to 7 – groups of FD signs/symptoms: 1, nefrological; 2, cardiological; 3, rheumatological; 4, neurological; 5, gastrointestinal/otorhinolaryngological; 6, dermatological; 7, ophthalmological.

2.3.3 FD laboratory testing

Male FD-positive patients: positive enzymatic test (low/undetectable α-Gal A activity) and/or presence of pathogenic mutation in the *GLA* gene. Female FD-positive patients: pathogenic mutation in the *GLA* gene. FD genetic and enzymatic tests were run independently by the participant dialysis centers.

2.3.4 Searches in human mutation databases

Searches for *GLA* gene mutations were performed at the Human Gene Mutation Database – HGMD [4], Leiden Open-source Variation Database – LOVD platform [20], available at Zhejiang University Center for Genetic and Genomic Medicine website [21], and at NCBI's ClinVar [22].

3. RESULTS

3.1 Patient demographics

A total of 25,223 dialysis patients from 188 dialysis centers were analyzed. Five percent of the invited dialysis centers did not adhere to the study (nine centers). Male patients were 59.3% (14,957) and female, 40.7% (10,266) (Figure 5A). FD-suspected patients were 2,956 (11.7%). The total of FD-positive patients was 109, most female (72 {66.1%} female; 37 {33.9%} male) (Figure 5C). Female predominance in FD-positives was significant (χ^2 = 9.67; *P* = 0.0018). FD-positive patients represented 3.7% (2.4% female, 1.3% male) of all FD-suspected patients and 0.4% (0.3% female, 0.1% male) of all participant dialysis patients. FD-negatives were 2,847 (Figure 5B), both sexes in similar proportions (49.6%;50.4%).

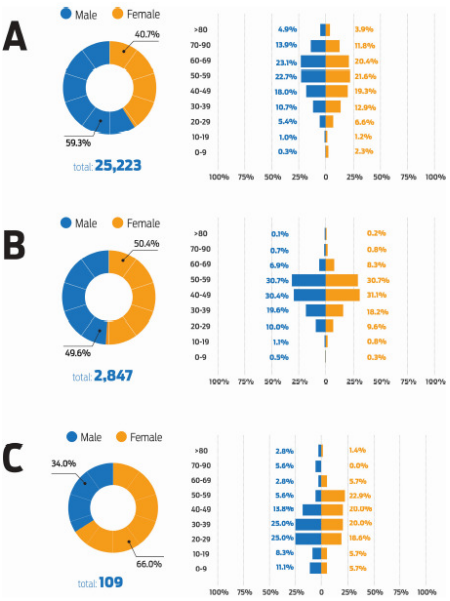


Figure 5. Distribution of the Brazilian dialysis patients by gender, age group, and FD diagnosis. **A)** Total; **B)** FD-negatives; **C)** FD-positives.

The mean age of FD-positive patients was 37.9y (±17.4); for FD-negative patients it was 45.0y (±11.6). FD-positive patients showed lower mean age (male: 35.7±19.4; female:

39.0±16.0) when compared to FD-negatives (male: 44.8±11.6; female: 45.2±11.6). It is possible to see a sharp decline in the number of FD-positive male patients from 40y (Figure 5C) while the decline in the number of FD-positive female patients becomes more significant from 60y. The distribution of FD-negative patients by gender and age was also different from the total of analyzed patients (Figure 5B,5A). In FD-negative patients, both genders, a sharp decline in the number of patients is only seen from 60y (Figure 5B) and in the total of analyzed patients that happens from 70y (Figure 5A).

3.2 *GLA* gene mutation analysis

A total of 18 different mutations were found in FD-positive patients' *GLA* gene (Table 3). Four mutations were highly frequent (77.1%): R118C, S126G, M290I, and A368T. Mutations 194+1G>A, 370-1G>T and 801+36G>A were located in intronic regions of the *GLA* gene.

Table 3. Mutations found in FD-positive patients' *GLA* gene

Mutation No.	*GLA* gene nucleotide change	Location	Mutation	Number of patients with the mutation
M1	c.194+1G>A	intron	unknown	3
M2	c.370-1G>T	intron	splice acceptor variant	1
M3	c.801+36G>A	intron	unknown	1
M4	c.337T>C	exon 2	p.Phe113Leu (F113L)	3
M5	c.352C>T	exon 2	p.Arg118Cys (R118C)	18
M6	c.376A>G	exon 3	p.Ser126Gly (S126G)	22
M7	c.413delG	exon 3	p.Gly138Glufs (G138E)	1
M8	c.427G>A	exon 3	p.Ala143Thr (A143T)	1
M9	c.679C>T	exon 5	p.Arg227X (R227X)	4
M10	c.803T>C	exon 6	p.Leu268Ser (L268S)	1

Mutation No.	*GLA* gene nucleotide change	Location	Mutation	Number of patients with the mutation
M11	c.870G>A	exon 6	p. Met290Ile (M290I)	5
M12	c.870G>C	exon 6	p.Met290Ile (M290I)	20
M13	c.877C>T	exon 6	p.Pro293Ser (P293S)	2
M14	c.937G>T	exon 6	p.Asp313Tyr (D313Y)	4
M15	c.1025G>A	exon 7	p.Arg342Gln (R342Q)	4
M16	c.1067G>A	exon 7	p. Arg356Gln (R356Q)	1
M17	c.1102G>A	exon 7	p.Ala368Thr (A368T)	19
M18	c.1117G>A	exon 7	p.Gly373Ser (G373S)	1

Nineteen patients (17.4%; 11 female, eight male) had heart disease or family history of heart disease: R118C mutation, seven patients; R342Q, two; A368T, two; R227X, two; M290I, F113L, R356Q, 801+36G, P293S and A143T, one patient each. Six female (5.5%) had cerebrovascular disease: A368T, four; R118C and M290I, one each. Forty patients (36.7%; 23 female, 17 male) had depression: A368T, 13; S126G, eight; R118C, four; M2901, three; R342Q, 194+1G>A, R227X and D313Y, two each; R356Q, 370-1G>T, L268S and P293S, one each. Fifteen patients (13.8%; 10 female, 5 male) had angiokeratoma: M290I, six; S126G, four; A368T, P293S, R118C, R342Q,D313Y, R227X and F113L, one each. A total of 10 FD-positive had cornea verticillata (9.2%; 6 female, 4 male); no mutation was significantly prevalent.

3.3 Frequency of FD symptoms

Heart, neurological, rheumatologic, dermatological and gastrointestinal/otorhinolaryngologic symptoms were more frequent in FD-positive patients below 39y (Figure 6B), unlike what was observed in FD-negative patients (Figure 6A). This became even more evident when the comparison is made with FD-positive male patients (Figure 6C).

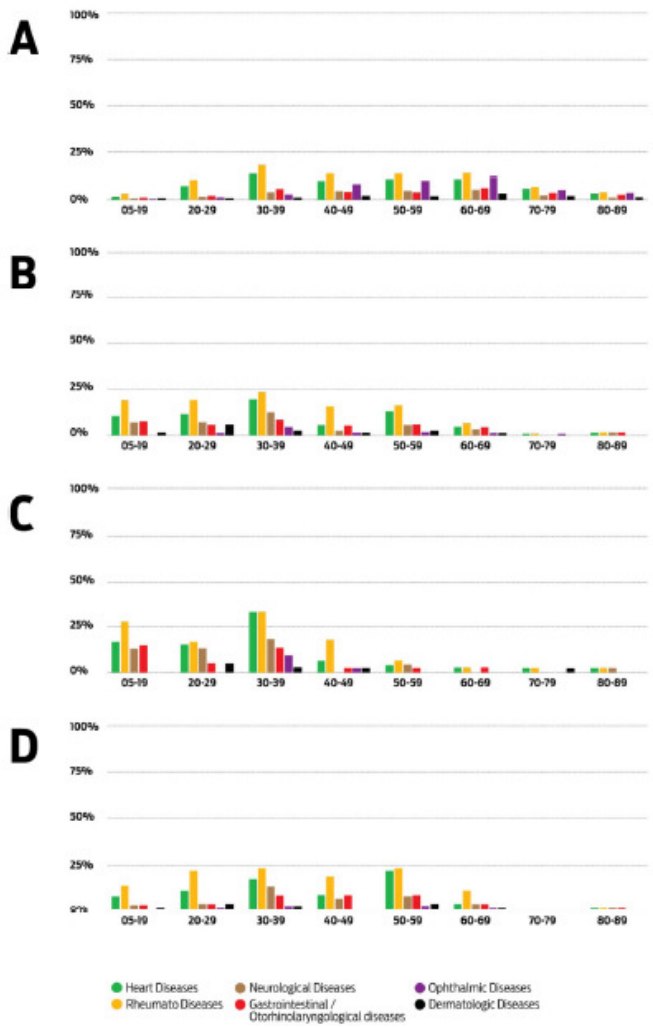


Figure 6. Frequency of FD symptoms by gender, age group, and FD diagnosis. **A)** FD-negative; **B)** FD-positive; **C)** FD-positive male; **D)** FD-positive female.

3.4 Frequency of underlying causes of CKD

HBP (80.0%) and DM (33.0%) were highly frequent underlying causes of CKD in FD-negative patients (Figure 7), followed by obesity (9.6%), rheumatoid arthritis (9.2%), and polycystic kidney disease (6.8%). However, underlying causes of CKD were way less frequent (23; 21.1%) and equally distributed by gender (11 male, 12 female) in FD-positive patients (Figure 7). HBP was the most frequent (17.4%) followed by rheumatoid arthritis (4.6%). DM together with obesity were the third most frequent (2.7% each).

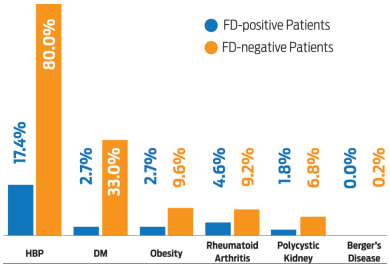


Figure 7. Frequency of underlying causes of CKD in FD-positive and negative patients.

Most of the FD-negative patients with HBP were males (60.0%; Figure 8B). In FD-positive individuals only a small part (19; 17.4%) of the patients had HBP, most of them were female (57.9%) (Figure 8A).

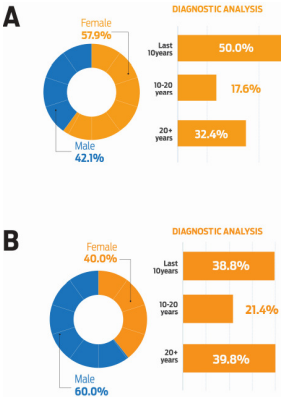


Figure 8. Diagnosis time and distribution of HBP by gender in FD patients. **A)** FD-positive; **B)** FD-negative.

HBP in FD-negative patients was observed in all age groups, in about the same proportion in both sexes (Figure 9A), and starts to become more common from 30y. In FD-positive female patients, the number of individuals with HBP increased significantly from 30y (Figure 9B) while in FD-positive men the number of individuals with HBP was quite high in the age group of 20-29y but significantly drops from 50-69y.

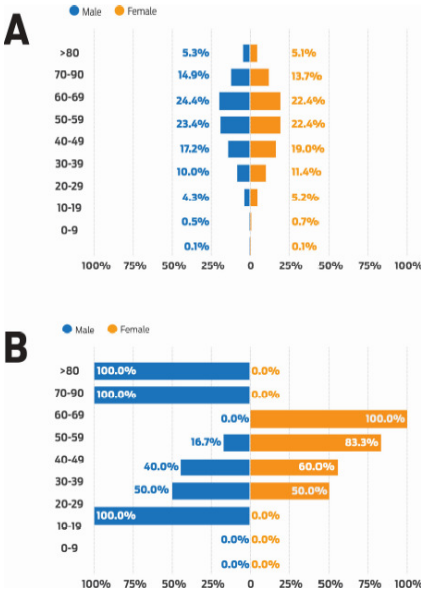


Figure 9. Frequency of HBP by gender and age group in FD patients. **A)** FD-negative; **B)** FD-positive.

In FD-negative patients, DM is observed in both sexes and in all age groups, but it starts to become more common above 40-49y. However, the number of FD-positive patients with DM was very small (three), prevailing female patients (67.0%). DM was detected in FD-positive patients above 50-59y in both sexes.

Comparing FD-negative and positive patients regarding to underlying causes of CKD, HBP and DM, FD-negative patients showed higher frequencies (χ^2 = 301.57; 214.24 and 41.50 respectively; $P < 0.0001$ for all). The distribution of underlying causes of CKD according to age group revealed that the highest prevalence occurs between 30-59y for both FD-positive/negative patients (69.5 and 51.35% respectively), but FD-negative patients showed higher frequency after 60y (43.4% *versus* 17.5% in FD-positive patients), (χ^2 = 7.64; degrees of freedom = 2; P = 0.02). Similar findings occurred with HBP (χ^2 = 6.03; degrees of freedom = 2; P = 0.04). The small number of FD-positive patients with DM prevented this analysis.

4. DISCUSSION

As far as we know, this is the first study with such a large sample carried out in a continental multiethnic country like Brazil, in order to identify FD patients among dialysis patients enrolled in dialysis centers from all over the country. FD exhibits a vast phenotypic spectrum, lacking a clear genotype-phenotype correlation [4,6,11]. Thus, an algorithm based on combinations of signs and symptoms, age and gender (Figure 4, Table 2) was used to screen for FD-suspected patients in a population of 25,223 dialysis patients. The algorithm was efficient since it allowed to reduce by 88.3% the number of dialysis patients for FD enzymatic and genetic testing. The prevalence of 0.4% (0.3% female, 0.1% male) is in line with previous studies carried out in hemodialysis centers. Porsch *et al*. (2008) [23] evaluated 558 southern Brazilian male patients with ESRD and only two had low α-Gal A activity and were diagnosed with FD (0.36%). Other FD screening studies performed in Brazilian patients with CKD undergoing hemodialysis in Paraná and in patients on dialysis treatment in Rio de Janeiro found a prevalence of 0.24% [24,25]. In Latin American countries, FD prevalence in Peru was 0.3% and in Colombia, 0.4% [26,27]. A review encompassing all screening studies [14] showed 55 patients (44 males/11 females) detected in a total of 18,837 hemodialysis patients; mean prevalence of 0.29% (0.23% female/0.06% male).

The sharp decline in the life expectancy observed in FD-positive patients (Figure 5), not associated to underlying causes of CKD, reinforces previous findings that FD is a devastating disorder [2,3,10]. The life expectancy (35.7y male; 39.0y female) was diminished to about the half of the average in the Brazilian general population (74.9y) [28]. These numbers are much lower than the observed in the United States Fabry Registry (58.2y male; 75.4y female) and other countries [10]. Lack of diagnosis may have contributed to the early deaths due to FD in Brazilian dialysis patients, since FD progress quickly and kidney failure may occur by the third or fourth decade of life [2,10].

Rheumatologic symptoms were the most frequent in general (Figure 6A,6B). However, the frequency was much higher in FD-positives as these symptoms are common in FD since

childhood [2,3,29].

Four mutations (R118C, A368T, M290I, S126G) were highly frequent in FD-positive patients (Table 3). However, no mutation previously confirmed with manifestation confined to the kidney or heart [13,30] was found in this study. Depression was the second most frequent symptom amongst FD-positive patients and mutations A368T and S126G were frequent (32.5%;20%, respectively). Dementia, cognitive impairment, and depression occur in patients with FD [31,32]. However, additional studies are needed to establish a direct link of these morbidities to FD. An analysis of a large cohort of 2,446 patients in the Fabry Registry (Fabryregistry.com) reported that stroke occurs in 6.9% of men and 4.3% of women [33]. Six female patients (5.5%) had cerebrovascular disease, four had A368T mutation, making it highly prevalent; mutation that was previously reported in Brazilian hemodialysis patients [34,35]. Nevertheless, it is not considered a disease causing mutation by HMGD [4]. On the other hand, mutations S126G and A143T are associated with a stroke-only phenotype in FD [36, 37].

Heart diseases were the third most prevalent amongst FD-positive patients. Mutation R118C was found in seven of these patients with heart disease (36.8%). This same mutation was previously found in Italian male neonates [38]. It was frequent in unrelated hemodialysis patients in Spain [39] and in young Portuguese patients with stroke [40]. Historically, Brazil has received large numbers of Italian, Spanish, and Portuguese immigrants; the country itself was a colony of Portugal which may explain the high frequency of this mutation among Brazilian FD patients. This mutation has been described in Brazilian families suspected of FD [41]. R118C is considered by HMGD a disease causing mutation since it has been found in young adults with stroke, in a patient with apical left ventricular hypertrophy, and may be a cardiomyopathy phenotype modifier thought not to cause classic FD phenotype in a Medelian fashion [40,42-44].

Angiokeratoma, a classic sign of FD was frequent among FD-positive patients (13.8%). It's not

directly related to kidney failure [2]. A previous study carried out in Brazil found 6.7% of FD patients after reviewing angiokeratomas' biopsies [45]. Another Brazilian study about FD patients' registry identified angiokeratomas in 8.7% of FD patients [46]. Despite of different methodologies, the percentage of FD patients with angiokeratomas in this study was higher. Six of the patients with angiokeratoma had M290I and four, S126G (prevalence of these mutations: 40% and 26.7% respectively). Mutation M290I was originally identified as causing FD classic phenotype in 66 unrelated families [47]. On the other hand, cornea verticillata, the main ocular finding in FD [48], was present in only 9.2% of the patients. Its prevalence in FD ranges from 44% to 94.5% in men and 88.0% in women [49]. The striking low incidence found in this study may be explained due to the need of a more specific evaluation by an ophthalmologist to a more precise diagnosis.

Although the intronic mutations found in this study (Table 3) have been found in FD patients before [9,22], their effects on the *GLA* gene expression or in alpha-galactosidase protein remain unknown.

HBP and DM were highly prevalent in FD-negative patients while FD-positive patients presented much less underlying causes of CKD (Figure 7). These results reinforce previous findings [50] that FD is the main cause of kidney failure in FD patients.

The algorithm (Figure 4, Table 2) used in the present study to track FD-suspected allowed to reduce significantly (by 88.3%) the number of dialysis patients for genetic and enzymatic testing. The natural history and frequency of FD among dialysis patients in this study were in line with literature. This indicates the algorithm can be a helpful tool in screening studies set to identify FD patients among large numbers of dialysis patients.

5. CONCLUSION

The initial findings of this large long-term study ongoing in Brazil emphasize the importance of early diagnosis in order to detect and treat FD before it may causes irreversible renal, cardiac, and/or neurologic damages. Although the algorithm used for screening of FD-suspected patients has been an invaluable tool, it still needs to be statistically validated

(sensitivity, specificity, predictive value). The encouraging results obtained from this first 18 months abet us to move forward with this country-wide study since it will allow us to have a better understanding of FD natural history in Brazil. More important, it will contribute to the development of an optimized diagnosis strategy which can save resources from public health system and provide early disease identification for an appropriate timely treatment.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this study. The patients invited to participate were informed about the study purposes and each subject freely signed an individual consent form agreeing to participate in

the study. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

ETHICAL APPROVAL

The study protocol was approved by the Research Ethics Committee of Campos Medical School (legal opinion #305·988; 06/28/2013). Patients and the health care team involved had their anonymity fully preserved according to Resolution no. 196/96 of the National Board of Health, 1988 Medical Ethics Code and 1964 Declaration of Helsinki.

REFERENCES

1. van der Tol L, Smid BE, Poorthuis BJHM, Biegstraaten M, Lekanne Deprez RH, Linthorst GE, et al. A systematic review on screening for Fabry disease: prevalence of individuals with genetic variants of unknown significance. J. Med. Genet. [Internet]. 2013;51:1–9.

2. Germain DP. Fabry disease. Orphanet J. Rare Dis. [Internet]. BioMed Central Ltd; 2010;5:1–49.

3. Zarate YA, Hopkin RJ. Fabry's disease. Lancet[Internet]. Elsevier Ltd; 2008;372:1427–35.

4. Stenson PD, Mort M, Ball E V, Shaw K, Phillips AD, Cooper DN. The Human Gene Mutation Database: Building a comprehensive mutation repository for clinical and molecular genetics, diagnostic testing and personalized genomic medicine. Hum.Genet. 2014;133:1–9.

5. Desnick RJ, Brady R, Barranger J, Collins AJ, Germain DP, Goldman M, et al. Fabry disease, an under-recognized multisystemic disorder: Expert recommendations for diagnosis, management, and enzyme replacement therapy. Ann. Intern. Med. [Internet]. 2003;138:338–46. Available from: http://annals.org/article.aspx?doi=10.7326/0003-4819-138-4-200302180-00014

6. Laney DA, Bennett RL, Clarke V, Fox A, Hopkin RJ, Johnson J, et al. Fabry disease practice guidelines: Recommendations of the national society of genetic counselors. J. Genet. Couns. 2013;22:555–64.

7. Deegan PB, Baehner AF, Barba Romero M, Hughes DA, Kampmann C, Beck M. Natural history of Fabry disease in females in the Fabry Outcome Survey. J. Med. Genet. 2006;43:347–52.

8. Wilcox WR, Oliveira JP, Hopkin RJ, Ortiz A, Banikazemi M, Feldt-Rasmussen U, et al. Females with Fabry disease frequently have major organ involvement: Lessons from the Fabry Registry. Mol. Genet. Metab. 2008;93:112–28.

9. Echevarria L, Benistan K, Toussaint A, Dubourg O, Hagege AA, Eladari D, et al. X-chromosome inactivation in female patients with Fabry disease. Clin. Genet. 2016;89:44–54.

10. Waldek S, Patel MR, Banikazemi M, Lemay R, Lee P. Life expectancy and cause of death in males and females with Fabry disease: Findings from the Fabry Registry. Genet. Med. [Internet]. 2009;11:790–6.

11. Linthorst GE, Bouwman MG, Wijburg FA, Aerts JMFG, Poorthuis BJHM, Hollak CEM. Screening for Fabry disease in high-risk populations: a systematic review. J. Med. Genet. 2010;47:217–22.

12. Rombach SM, Smid BE, Linthorst GE, Dijkgraaf MGW, Hollak CEM. Natural course of Fabry disease and the effectiveness of enzyme replacement therapy: A systematic review and meta-analysis: Effectiveness of ERT in different disease stages. J. Inherit. Metab. Dis. 2014;37:341–52.

13. Nakao S, Kodama C, Takenaka T, Tanaka A, Yasumoto Y, Yoshida A, et al. Fabry disease: Detection of undiagnosed hemodialysis patients and identification of a “renal variant” phenotype. Kidney Int. 2003;64:801–7.

14. Okur I, Ezgu F, Biberoglu G, Tumer L, Erten Y, Isitman M, et al. Screening for Fabry disease in patients undergoing dialysis for chronic renal failure in Turkey: Identification of new case with novel mutation. Gene [Internet]. Elsevier B.V.; 2013;527:42–7.

15. Brasil - Ministério da Saúde. 2014. Saúde amplia tratamento para doentes renais crônicos. http://www.brasil.gov.br/saude/2014/03/saude-amplia-tratamento-para-doentes-renais-cronicos. Last access: July/2016.

16. Gutiérrez-Amavizca BE, Orozco-Castellanos R, R. Padilla-Gutiérrez J, Valle Y, Figuera LE. Pedigree analysis of Mexican families with Fabry disease as a powerful tool for identification of heterozygous females. Genet. Mol. Res. [Internet]. 2014;13:6752–8.

17. Snyder S, Pendergraph B. Detection and evaluation of chronic kidney disease. Am. Fam. Physician. 2005;72:1723–34.

18. Levey AS, Coresh J. Chronic kidney disease. Lancet [Internet]. Elsevier Ltd; 2012;379:165–80.

19. Costa F, Costa F, Foly L, Coutinho M. DataGenno: building a new tool to bridge molecular and clinical genetics. Appl. Clin. Genet. 2011;4:45–54.

20. Fokkema IFAC, Taschner PEM, Schaafsma GCP, Celli J, Laros JFJ, den Dunnen JT. LOVD v.2.0: The next generation in gene variant databases. Hum. Mutat. 2011;32:557–63.

21. http://www.genomed.org/lovd2/home.php?select_db=GLA. Last access: July/2016.

22. Landrum MJ, Lee JM, Riley GR, Jang W, Rubinstein WS, Church DM, et al. ClinVar: Public archive of relationships among sequence variation and human phenotype. Nucleic Acids Res. 2014;42:980–5.

23. Porsch DB, Nunes ACF, Milani V, Rossato LB, Mattos CB, Tsao M, et al. Fabry disease in hemodialysis patients in southern Brazil: prevalence study and clinical report. Ren. Fail. 2008;30:825–30.

24. Biagini G *et al*. Prevalence of Fabry disease in patients with chronic renal insufficiency undergoing hemodialysis in the State of Paraná—Brazil. World Congress of Nephrology, abstract, 2007.

25. Delgado V *et al*. Fabry disease epidemiology in Rio de Janeiro State: Partial outcome of screening in patients on dialysis treatment. World Congress of Nephrology, abstract, 2007.

26. Prevalence in Peru of Fabry disease among males with chronic renal insufficiency. X Latin American Symposium in Lysosomal Storage Disease, abstract, 2005.

27. Martínez JA, Ardila ME, Gamarra G, *et al*. Prevalence of Fabry disease in Colombia—preliminary report. Book of Abstracts. San Jose, Costa Rica: X Latin American Symposium in Lysosomal Storage Disease 2005; 237.

28.http://www.ibge.gov.br/home/estatistica/populacao/tabuadevida/2013/defaulttab_pdf.shtm Last access: July/2016.

29. Ellaway C. Paediatric Fabry disease. Transl Pediatr. 2016;5:37–42.

30. Nakao S, Takenaka T, Maeda M, Kodama C, Tanaka A, Tahara M, et al. An atypical variant of Fabry's disease in men with left ventricular hypertrophy. N. Engl. J. Med. 1995;333:288–93.

31. Schermuly I, Müller MJ, Müller KM, Albrecht J, Keller I, Yakushev I, et al. Neuropsychiatric symptoms and brain structural alterations in Fabry disease. Eur. J. Neurol. 2011;18:347–53.

32. Cole AL, Lee PJ, Hughes DA, Deegan PB, Waldek S, Lachmann RH. Depression in adults with Fabry disease: A common and under-diagnosed problem. J. Inherit. Metab. Dis. 2007;30:943–51.

33. Sims K, Politei J, Banikazemi M, Lee P. Stroke in Fabry disease frequently occurs before diagnosis and in the absence of other clinical events: Natural history data from the Fabry Registry. Stroke. 2009;40:788–94.

34. Pereira EM, do Monte SJH, do Nascimento FF, de Castro JAF, Sousa JLM, Filho HCSALC, et al. Lysosome-associated protein 1 (LAMP-1) and Lysosome-associated protein 2 (LAMP-2) in a larger family carrier of Fabry disease. Gene [Internet]. Elsevier B.V.; 2014;536:118–22.

35. Silva, C. A. B., Barreto, F. C., dos Reis, M. A., Junior, J. A. M., & Cruz, C. M. S. (2016, May). Family Screening for Fabry Disease based on Male Index Cases with End-Stage Renal Disease. In *Nephrology Dialysis Transplantation* (Vol. 31, pp. 357-357). GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND: OXFORD UNIV PRESS.

36. Brouns R, Thijs V, Eyskens F, Van Den Broeck M, Belachew S, Van Broeckhoven C, et al. Belgian Fabry study: Prevalence of Fabry disease in a cohort of 1000 young patients with cerebrovascular disease. Stroke. 2010;41:863–8.

37. Rolfs A, Fazekas F, Grittner U, Dichgans M, Martus P, Holzhausen M, et al. Acute cerebrovascular disease in the young: The stroke in young Fabry patients study. Stroke. 2013;44:340–9.

38. Spada M, Pagliardini S, Yasuda M, Tukel T, Thiagarajan G, Sakuraba H, et al. High incidence of later-onset fabry disease revealed by newborn screening. Am. J. Hum. Genet. [Internet]. 2006;79:31–40.

39. Gaspar P, Herrera J, Rodrigues D, Cerezo S, Delgado R, Andrade CF, et al. Frequency of Fabry disease in male and female haemodialysis patients in Spain. BMC Med. Genet. [Internet]. 2010;11:19.

40. Baptista MV, Ferreira S, Pinho-E-Melo T, Carvalho M, Cruz VT, Carmona C, et al. Mutations of the GLA Gene in Young Patients with Stroke: The PORTYSTROKE Study-Screening Genetic Conditions in PORTuguese Young STROKE Patients. Stroke. 2010;41:431–6.

41. Turaça LT, Pessoa JG, Motta FL, Muñoz Rojas MV, Müller KB, Lourenço CM, et al. New mutations in the GLA gene in Brazilian families with Fabry disease. J. Hum. Genet. [Internet]. 2012;57:347–51.

42. Caetano F, Botelho A, Mota P, Silva J, Marques AL. Fabry disease presenting as apical left ventricular hypertrophy in a patient carrying the missense mutation R118C. Rev. Port. Cardiol. [Internet]. Sociedade Portuguesa de Cardiologia; 2014;33:183.e1–183.e5.

43. Golbus JR, Puckelwartz MJ, Dellefave-Castillo L, Fahrenbach JP, Nelakuditi V, Pesce LL, et al. Targeted analysis of whole genome sequence data to diagnose genetic cardiomyopathy. Circ. Cardiovasc. Genet. 2014;7:751–9.

44. Ferreira S, Ortiz A, Germain DP, Viana-Baptista M, Caldeira-Gomes A, Camprecios M, et al. The alpha-galactosidase A p.Arg118Cys variant does not cause a Fabry disease

phenotype: Data from individual patients and family studies. Mol. Genet. Metab. [Internet]. Elsevier Inc.; 2015;114:248–58.

45. Kelmann SV, Quaio CRDC, Honjo RS, Bertola DR, Rosa Neto NS, Lourenço CM, et al. Multicentric study on the diagnosis of Fabry's disease using angiokeratoma biopsy registries. Int. J. Dermatol. [Internet]. 2014;54:1–3.

46. Martins AM, Kyosen SO, Garrote J, Marques FM V, Guilhem JG, Macedo E, et al. Demographic characterization of Brazilian patients enrolled in the Fabry Registry. Genet. Mol. Res. 2013;12:136–42.

47. Shabbeer J, Yasuda M, Benson SD, Desnick RJ. Fabry disease: identification of 50 novel alpha-galactosidase A mutations causing the classic phenotype and three-dimensional structural analysis of 29 missense mutations. Hum. Genomics. 2006;2:297–309.

48. Pitz S, Kalkum G, Arash L, Karabul N, Sodi A, Larroque S, et al. Ocular Signs Correlate Well with Disease Severity and Genotype in Fabry Disease. PLoS One [Internet]. 2015;10:1–13.

49. Nguyen TT, Gin T, Nicholls K, Low M, Galanos J, Crawford A. Ophthalmological manifestations of Fabry disease: a survey of patients at the Royal Melbourne Fabry Disease Treatment Centre. Clin. Experiment. Ophthalmol. [Internet]. 2005;33:164–8.

50. Branton M, Schiffmann R, Kopp JB. Natural history and treatment of renal involvement in Fabry disease. J. Am. Soc. Nephrol. 2002;13 Suppl 2:S139–43.

DEFINITIONS, ACRONYMS, ABBREVIATIONS

α-Gal A: Alpha-galactosidase A

CKD: chronic kidney disease

DM: diabetes mellitus

ESRD: end-stage renal disease

FD: Fabry disease

Gb3/**GL3:** globotriaosylceramide

GLA: galactosidase, alpha gene

HBP: high blood pressure

HGMD: Human Gene Mutation Database

LOVD: Leiden Open-source Variation Database

MGR: Márcia Gonçalves Ribeiro

MPC: Marcelo Paula Coutinho

APPENDIX

Table X. Gender, age, laboratory findings and FD signs and symptoms of FD-positive patients.

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P1	F	5	c.1102G>A (het)		Kidney disease, Abdominal pain after eating
P2	M	10	c.1102G>A (hemi)	3,2 μmol/l/h	Kidney disease, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Decrease or absence of sweating, Depression, Diarrhea after eating
P3	M	11	c.1102G>A (hemi)	3,7 μmol/l/h	Kidney disease, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Decrease or absence of sweating, Depression, Diarrhea after eating

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P4	F	11	c.376A>G (het) c.870G>C (het)		Famíly history of kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Burning sensation in hands and feet, Numbness or tingling in hands and feet, Angiokeratomas
P5	M	13	c.870G>C (het)	1,1 µmol/l/h	Famíly history of kidney disease, Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Recurrent fever without apparent cause, Numbness or tingling in hands and feet

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P6	M	14	c.352C>T (hemi)	1,9 µmol/l/h	Heart disease, Decrease or absence of sweating, HBP, Recurrent fever without apparent cause, Diarrhea after eating
P7	F	14	c.870G>C (het)		Famíly history of kidney disease, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Recurrent fever without apparent cause, Numbness or tingling in hands and feet

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P8	M	14	c.376A>G (hemi)	1,0 µmol/l/h	Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Numbness or tingling in hands and feet, Depression
P9	M	16	c.352C>T (hemi)	1,5 µmol/l/h	Displays chest pain and /or palpitations, Decrease or absence of sweating, Abdominal pain after eating, Diarrhea

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P10	F	16	c.870G>C (het)		Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Numbness or tingling in hands and feet
P11	F	16	c.352C>T (het)		Proteinuria, Heart disease, Decrease or absence of sweating, HBP, Bouts of pain that spread throughout the body, Recurrent fever without apparent cause, Diarrhea after eating, Numbness or tingling in hands and feet

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P12	F	16	c.870G>C (het)		Famíly history of kidney disease, Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Recurrent fever without apparent cause, Numbness or tingling in hands and feet
P13	M	17	c.1117G>A (hemi)	0,58 µmol/l/h	Famíly history of kidney disease, Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Burning sensation in hands and feet, Numbness or tingling in hands and feet

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P14	F	17	c.1102G>A (het)		Kidney disease, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Decrease or absence of sweating, Depression, Diarrhea after eating
P15	M	17	c.352C>T (hemi)	2,0 µmol/l/h	Famíly history of kidney disease, Kidney disease, Presents proteinuria in the 24 hours exam, Bouts of pain that spread throughout the body Presents creatinine elevation, Numbness or tingling in hands and feet, Depression

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P16	M	18	c.1102G>A	4,8 µmol/l/h	Proteinuria, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Decrease or absence of sweating, Diarrhea after eating
P17	F	18	c.194+1G>A (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Numbness or tingling in hands and feet, Depression
P18	F	19	c.376A>G (het)		Kidney disease, Presents creatinine elevation, Recurrent fever without apparent cause, Decrease or absence of sweating

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P19	F	19	c.194+1G>A (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Numbness or tingling in hands and feet, Depression
P20	F	20	c.870G>C		Famíly history of kidney disease, Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Burning sensation in hands and feet, Numbness or tingling in hands and feet, Cornea verticillata

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P21	M	21	c.376A>G (hemi)	2,7 µmol/l/h	Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Intolerance to heat and cold, Numbness or tingling in hands and feet, Depression, Angiokeratomas
P22	M	22	c.376A>G (hemi)	4,0 µmol/l/h	Family history of Fabry disease, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Numbness or tingling in hands and feet, Depression

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P23	F	25	c.376A>G (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and/or palpitations, Decrease or absence of sweating, Diarrhea after eating
P24	F	25	c.870G>C (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Intolerance to heat and cold, Numbness or tingling in hands and feet, Angiokeratomas

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P25	F	25	c.352 C>T (het)		Kidney disease, Heart disease, Decrease or absence of sweating, HBP, Recurrent fever without apparent cause, Diarrhea after eating, Numbness or tingling in hands and feet
P26	M	25	c.870G>C (hemi)	0,7 µmol/l/h	Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Recurrent fever without apparent cause, Numbness or tingling in hands and feet, Depression

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P27	F	25	c.376A>G (het), c.870G>C (het)		Famíly history of kidney disease, Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Burning sensation in hands and feet, Numbness or tingling in hands and feet, Angiokeratomas
P28	F	25	c.1102G>A (het)		Famíly history of kidney disease, Kidney disease, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Depression, Numbness or tingling in hands and feet

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P29	F	25	c.870G>C (het)		Famíly history of kidney disease, Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Recurrent fever without apparent cause, Numbness or tingling in hands and feet
P30	F	26	c.376A>G (het)		Famíly history of kidney disease, Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Numbness or tingling in hands and feet

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P31	F	26	c.1102G>A (het)		Kidney disease, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Decrease or absence of sweating, Depression, Diarrhea after eating, Angiokeratoma
P32	F	26	c.376A>G (het)		Famíly history of kidney disease, Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Numbness or tingling in hands and feet
P33	F	28	c.352C>T (het)		Kidney disease, Presents creatinine elevation, Intolerance to heat and cold, Decrease or absence of sweating,

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P34	M	28	c.877C>T	0,3 µmol/l/h	Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Left ventricular hypertrophy, Displays chest pain and /or palpitations, Recurrent fever without apparent cause, Intolerance to heat and cold, Decrease or absence of sweating, Depression, Abdominal pain after eating, Angiokeratomas
P35	M	28	c.870G>C (hemi)	0,5 µmol/l/h	Kidney disease, Presents creatinine elevation, Recurrent fever without apparent cause, Decrease or absence of sweating

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P36	M	28	c.1102G>A (hemi)	0,9 µmol/l/h	Kidney disease, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Decrease or absence of sweating, Diarrhea after eating
P37	F	28	c.376A>G (het)		Famíly history of kidney disease, Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Numbness or tingling in hands and feet, Depression

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P38	F	30	c.337T>C (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Recurrent fever without apparent cause, Bouts of pain that spread throughout the body, Decrease or absence of sweating, Abdominal pain after eating, Diarrhea after eating
P39	M	30	c.1102G>A (hemi)	3,7 µmol/l/h	Kidney disease, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Decrease or absence of sweating, Depression, Diarrhea after eating
P40	M	31	c. 870G>C (hemi)	0,7 µmol/l/h	Depression, Famíly history of kidney disease, Family history of heart disease

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P41	F	32	c.803T>C (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Bouts of pain that spread throughout the body, Displays chest pain and /or palpitations, Intolerance to heat and cold, Numbness or tingling in hands and feet, Depression
P42	F	33	c.1102G>A (het)		Kidney disease, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Decrease or absence of sweating, Depression, Diarrhea after eating

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P43	M	33	c.870G>A (hemi)	0,5 µmol/l/h	Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Recurrent fever without apparent cause, Numbness or tingling in hands and feet, Cornea verticillata
P44	F	33	c.376A>G (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Bouts of pain that spread throughout the body, Displays chest pain and /or palpitations, Intolerance to heat and cold, Numbness or tingling in hands and feet, Depression

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P45	F	34	c.352C>T (het)		Kidney disease, Cerebrovascular disease (Stroke or transient ischemic attack)
P46	M	34	c.352 T>C	1,44 µmol/l/h	Kidney disease, Heart disease, Recurrent fever without apparent cause, Burning sensation in hands and feet, Numbness or tingling in hands and feet, Increase of sweating, Diarrhea after eating, Cornea verticillata, Angiokeratomas
P47	F	35	c.937G>T (het)		Kidney disease, Displays chest pain and /or palpitations, Intolerance to exercise or fatigue from physical efforts, Decrease or absence of sweating, Depression

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P48	F	35	c.937G>T (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Decrease or absence of sweating
P49	F	35	c.1102G>A (het)		Kidney disease, Bouts of pain that spread throughout the body, Decrease or absence of sweating, Depression, Diarrhea after eating

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P50	F	35	c.1025G>A (het)		Kidney disease, Heart disease, Recurrent fever without apparent cause, Burning sensation in hands and feet, Numbness or tingling in hands and feet, Increase of sweating, Diarrhea after eating, Cornea verticillata, Angiokeratomas
P51	F	35	c.352C>T (het)		Kidney disease, Heart disease, Decrease or absence of sweating, HBP, Recurrent fever without apparent cause, Diarrhea after eating, Numbness or tingling in hands and feet

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P52	M	36	c.337T>C (hemi)	0,3 µmol/l/h	Famíly history of kidney disease, Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Heart disease, Burning sensation in hands and feet, Numbness or tingling in hands and feet, Cornea verticillata
P53	F	36	c.352C>T (het)		Intolerance to heat and cold, Burning sensation in hands and feet, Bouts of pain that spread throughout the body, Numbness or tingling in hands and feet, Depression

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P54	M	36	c.679C>T (hemi)	0,2 µmol/l/h	Famíly history of kidney disease, Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Heart disease, Burning sensation in hands and feet, Numbness or tingling in hands and feet, Depression
P55	F	36	c.376A>G (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Numbness or tingling in hands and feet,

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P56	F	37	c.937G>T		Famíly history of kidney disease, Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Burning sensation in hands and feet, Numbness or tingling in hands and feet, Cornea verticillata Angiokeratomas
P57	F	37	c.376A>G (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Numbness or tingling in hands and feet

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P58	M	37	c.376A>G (hemi)	1,6 µmol/l/h	Famíly history of kidney disease, Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Numbness or tingling in hands and feet, Depression
P59	F	37	c.376A>G (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Bouts of pain that spread throughout the body, Displays chest pain and /or palpitations, Intolerance to heat and cold, Numbness or tingling in hands and feet, Depression

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P60	M	38	c.1067G>A (hemi)	0,3 µmol/l/h	Kidney disease, Heart disease, Numbness or tingling in hands and feet, Decrease or absence of sweating, Depression, Abdominal pain after eating, Diarrhea after eating
P61	M	38	c.679C>T (hemi)	0,2 µmol/l/h	Famíly history of kidney disease, Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Heart disease, Burning sensation in hands and feet, Numbness or tingling in hands and feet

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P62	M	38	c.870G>C (hemi)	0,9 µmol/l/h	Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Recurrent fever without apparent cause, Numbness or tingling in hands and feet
P63	M	39	c.1025 G>A	0,8 µmol/l/h	Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Recurrent fever without apparent cause, Intolerance to heat and cold, Depression, Abdominal pain after eating

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P64	F	40	c.376A>G (het)		Kidney disease, Presents creatinine elevation, Displays chest pain and /or palpitations, Recurrent fever without apparent cause, Bouts of pain that spread throughout the body, Abdominal pain after eating
P65	F	40	c.352 C>T		Kidney disease, Intolerance to heat and cold
P66	F	41	c.376A>G (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Decrease or absence of sweating

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P67	M	41	c.870G>C (hemi)	0,9 µmol/l/h	Famíly history of kidney disease, Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Burning sensation in hands and feet, Numbness or tingling in hands and feet, Cornea verticillata, Angiokeratomas
P68	F	41	c.1025G>A (het)		Kidney disease, Heart disease, Recurrent fever without apparent cause, Burning sensation in hands and feet, Numbness or tingling in hands and feet, Diarrhea after eating,

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P69	F	41	c.1102G>A (het)		Kidney disease, Displays chest pain and /or palpitations, HBP, Cerebrovascular disease (Stroke or transient ischemic attack) Bouts of pain that spread throughout the body, Decrease or absence of sweating, Depression, Diarrhea after eating,
P70	F	43	c.352C>T (het)		Kidney disease, Intolerance to heat and cold, Intolerance to physical exercises, Numbness or tingling in hands and feet, Diabetes mellitus, HBP

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P71	F	43	c.1102G>A (het)		Kidney disease, Displays chest pain and /or palpitations, HBP, Cerebrovascular disease (Stroke or transient ischemic attack) Bouts of pain that spread throughout the body, Decrease or absence of sweating
P72	F	44	c.376A>G (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Intolerance to heat and cold, Decrease or absence of sweating, HBP, Hearing problems

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P73	M	45	c.194+1G>A (hemi)	0,2 µmol/l/h	Kidney disease, Presents creatinine elevation, Displays chest pain and /or palpitations, Recurrent fever without apparent cause, Decrease or absence of sweating, Abdominal pain after eating
P74	M	45	c.870G>C	1,1 µmol/l/h	Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Recurrent fever without apparent cause, Numbness or tingling in hands and feet.

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P75	F	45	c.870G>C (het)		Famíly history of kidney disease, Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Cerebrovascular disease (Stroke or transient ischemic attack), Bouts of pain that spread throughout the body, Intolerance to heat and cold, Recurrent fever without apparent cause, Numbness or tingling in hands and feet
P76	M	46	c.352C>T (hemi)	1,4 µmol/l/h	Kidney disease, Heart disease, Decrease or absence of sweating, HBP, Rheumatoid arthritis: Absence of rheumatic activity, Hepatitis C, Right shoulder tendinitis

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P77	F	46	c.1102G>A (het)		Kidney disease, Heart disease, Displays chest pain and /or palpitations, Intolerance to heat and cold, Decrease or absence of sweating, Hearing problems, Cerebrovascular disease (Stroke or transient ischemic attack)
P78	M	48	c.870G>A (hemi)	0,5 µmol/l/h	Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Recurrent fever without apparent cause, Numbness or tingling in hands and feet

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P79	F	49	c.413delG (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Intolerance to heat and cold, Decrease or absence of sweating, Abdominal pain after eating, Diarrhea after eating, Hearing problems
P80	F	50	c.870G>C (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Intolerance to heat and cold, Decrease or absence of sweating, Abdominal pain after eating, Hearing problems
P81	F	50	c.870G>A (het)		Kidney disease, Angiokeratomas

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P82	F	50	c.370-1G>T (het)		Displays chest pain and /or palpitations, Intolerance to heat and cold, Intolerance to physical exercises, Burning sensation in hands and feet, Bouts of pain that spread throughout the body, Numbness or tingling in hands and feet, Increase of sweating, Depression, Abdominal pain after eating
P83	F	50	c.937G>T (het)		Kidney disease, Presents creatinine elevation, left ventricular hypertrophy, Angina, Displays chest pain and /or palpitations, Intolerance to heat and cold, Burning sensation in hands and feet, Depression, Abdominal pain after eating, Cornea verticillata

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P84	M	50	c.352C>T (hemi)	2,2 µmol/l/h	Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Intolerance to heat and cold, Numbness or tingling in hands and feet, Depression
P85	M	51	c.870G>C (hemi)	0,8 µmol/l/h	Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Intolerance to exercise or fatigue from physical efforts, Decrease or absence of sweating

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P86	F	51	c.870G>A (het)		Kidney disease, Displays chest pain and /or palpitations, Burning sensation in hands and feet, Bouts of pain that spread throughout the body, Numbness or tingling in hands and feet
P87	F	51	c.1102G>A (het)		Kidney disease, Heart disease, Intolerance to heat and cold, Intolerance to physical exercises, Bouts of pain that spread throughout the body, Decrease or absence of sweating, Abdominal pain after eating

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P88	F	51	c.1102G>A (het)		Famíly history of kidney disease, Kidney disease, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Decrease or absence of sweating, Depression, Diarrhea after eating
P89	F	52	c.870G>A (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Intolerance to heat and cold, Numbness or tingling in hands and feet, Decrease or absence of sweating, Depression, Angiokeratomas

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P90	F	52	c.870G>C (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Intolerance to heat and cold, Numbness or tingling in hands and feet
P91	M	52	c.376A>G (het)	1,4 µmol/l/h	Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Intolerance to heat and cold, Numbness or tingling in hands and feet, Depression

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P92	F	54	c.801+36G>A (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Heart disease, Displays chest pain and /or palpitations, Recurrent fever without apparent cause, Intolerance to heat and cold, Bouts of pain that spread throughout the body, Decrease or absence of sweating

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P93	F	54	c.877C>T (het)		Kidney disease, Heart disease, Displays chest pain and /or palpitations, Recurrent fever without apparent cause, Intolerance to heat and cold, Intolerance to physical exercises, Burning sensation in hands and feet, Bouts of pain that spread throughout the body, Decrease or absence of sweating
P94	F	55	c.1102G>A (het)		Kidney disease, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Decrease or absence of sweating, Depression, Diarrhea after eating

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P95	F	55	c.376A>G (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Numbness or tingling in hands and feet
P96	F	58	c.352 C>T (het)		Kidney disease, Presents creatinine elevation, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Decrease or absence of sweating, Cornea verticillata
P97	F	59	c.679C>T (het)		Kidney disease, Angiokeratomas diagnosed after biopsy

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P98	F	59	c.352C>T (het)		Kidney disease, Burning sensation in hands and feet, HBP
P99	M	60	c.352 C>T	0,3 µmol/l/h	Kidney disease, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Diarrhea after eating, Numbness or tingling in hands and feet
P100	F	61	c.427G>A (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Heart disease, Burning sensation in hands and feet, Numbness or tingling in hands and feet, Abdominal pain after eating, Cornea verticillata

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P101	F	61	c.870G>C		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Numbness or tingling in hands and feet
P102	F	62	c.679C>T (het)		Famíly history of kidney disease, Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Burning sensation in hands and feet, Numbness or tingling in hands and feet, Depression

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P103	F	63	c.352C>T (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Heart disease, Displays chest pain and /or palpitations, Burning sensation in hands and feet, Bouts of pain that spread throughout the body, Depression, Obesity
P104	F	63	c.337T>C (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Intolerance to heat and cold, Intolerance to physical exercises, Diarrhea after eating, Angiokeratomas

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P105	F	63	c.1025G>A (het)		Kidney disease, Bouts of pain that spread throughout the body, Decrease or absence of sweating, Depression, Diarrhea after eating
P106	F	64	c.376A>G (het)		Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Recurrent fever without apparent cause, Burning sensation in hands and feet, Bouts of pain that spread throughout the body, Numbness or tingling in hands and feet

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P107	M	75	c.376A>G (hemi)	2,5 µmol/l/h	Famíly history of kidney disease, Kidney disease, Presents proteinuria in the 24 hours exam, Presents creatinine elevation, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Intolerance to heat and cold, Numbness or tingling in hands and feet, Angiokeratomas
P108	M	84	c.1102G>A (hemi)	1,1 µmol/l/h	Kidney disease, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Decrease or absence of sweating, Depression, Diarrhea after eating

Patient No.	Gender	Age	Mutation	α-Gal A activity on DBS	FD signs and symptoms
P109	F	84	c.1102G>A (het)		Kidney disease, Displays chest pain and /or palpitations, Bouts of pain that spread throughout the body, Cerebrovascular disease (Stroke or transient ischemic attack), Decrease or absence of sweating, Depression, Diarrhea after eating, Numbness or tingling in hands and feet

Termo de Consentimento Informado do Paciente

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO
(Conselho Nacional de Saúde, Resolução 196/96)

1.NOME DO PACIENTE.....

DOCUMENTO DE IDENTIDADE Nº : .....
DATA NASCIMENTO: ...../...../..... **SEXO** M ( ) F ( )
ENDEREÇO.....
Nª.....**APTO**:.....**BAIRRO**:.....
CIDADE.....**CEP**:__ __ __ __ __ - __ __ __
TELEFONE: DDD (.....) .....

2. RESPONSÁVEL LEGAL (SÓ PREENCHER ESSA PARTE SE HOUVER UM)

NATUREZA (grau de parentesco, tutor, curador etc.).....

DOCUMENTO DE IDENTIDADE .....**SEXO**: M ( ) F ( )

DATA NASCIMENTO: ...../...../.....

ENDEREÇO..... **Nº** .....

APTO: .....**BAIRRO**.....

CIDADE .....CEP:__ __ __ __ __ - __ __ __

TELEFONE: DDD (.....).....

O presente termo refere-se a um convite para participação do Sr.(a) _____ _____, ou sob a responsabilidade de seu representante legal Sr. (a) _____, a participar como sujeito de pesquisa intitulada: "QUESTIONARIO PARA ANÁLISE DOS SINAIS CLINICOS DA DOENÇA DE FABRY NOS PACIENTES DOS CENTROS DE DIALISE DO BRASIL (Rim-Fabry-Brasil)". A Doença de Fabry é uma doença, rara, genética, herdada na família, que é caracterizada pela falta ou diminuição da ação de uma enzima (proteína), (Alfagalactosidase A). A falta desta enzima provoca o acúmulo nas células de uma espécie de gordura (esfingolípides). Os pacientes, geralmente do sexo masculino, acometidos por tal doença ficam com as células do corpo "abarrotadas" com esta gordura e podem apresentar mau funcionamento de diversos órgãos como os rins, coração e cérebro, além de dores nas pernas e braços, manchas pelo corpo, diarréia e intolerância ao frio e calor. O **objetivo** deste trabalho é tentar saber se você tem ou não essa doença, chamada Doença de Fabry.

Eu, _____, RG_____, fui devidamente esclarecido (a) do Projeto de Pesquisa acima citado e aceito o convite para participar.

_____, _____ de _____ de 20____

_____

Assinatura do sujeito da pesquisa ou responsável legal

FACULDADE DE MEDICINA DE CAMPOS/FUNDAÇÃO BENEDITO PEREIRA NUNES

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ANÁLISE CLÍNICA E EPIDEMIOLÓGICA DA DOENÇA DE FABRY NOS CENTROS DE DIÁLISE DO BRASIL

Pesquisador: MARCELO PAULA COUTINHO

Área Temática:

Versão: 1

CAAE: 18029513.0.0000.5244

Instituição Proponente: Faculdade de Medicina de Campos/Fundação Benedito Pereira Nunes

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 305.988

Data da Relatoria: 28/06/2013

Apresentação do Projeto:

Projeto apresenta delineamento adequado e capaz de responder os objetivos da pesquisa

Objetivo da Pesquisa:

Objetivo claro e preciso que se insere adequadamente no desenvolvimento do projeto de pesquisa.

Avaliação dos Riscos e Benefícios:

Contribuirá para uma investigação diagnóstica mais otimizada, com a redução do tempo e do custo da confirmação diagnóstica laboratorial, maior conhecimento da história natural da DF e uma avaliação detalhada nos familiares do paciente facilitando a identificação precoce da DF em parentes sintomáticos ou não

Comentários e Considerações sobre a Pesquisa:

Nenhum comentário ou considerações a fazer.

Considerações sobre os Termos de apresentação obrigatória:

O projeto de pesquisa apresentou todos os requisitos exigidos e de acordo com as resoluções nº

Endereço: Avenida Dr. Alberto Torres, 217
Bairro: Centro **CEP:** 28.035-580
UF: RJ **Município:** CAMPOS DOS GOYTACAZES
Telefone: (22)2101-2948 **Fax:** (22)2101-2929 **E-mail:** cepfmc@fmc.br

196/96 e novas normatizações da Plataforma Brasil

Recomendações:

Nada a acrescentar

Conclusões ou Pendências e Lista de Inadequações:

Como resultado desta análise e com base nas resoluções n° 196/96 e n° 340/2004, o projeto de pesquisa foi aprovado por seus próprios fundamentos.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

CAMPOS DOS GOYTACAZES, 16 de Junho de 2013

Assinador por:
ISRAEL NUNES ALECRIN
(Coordenador)

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