Title page

Fabry disease in the haemodialysis population: Outcome of a UK screening study (SoFAH)

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Abstract

Background and hypothesis

Fabry disease (FD) is an X-linked inherited disorder with an estimated prevalence among the end-stage kidney disease (ESKD) population of 0.3% in men and 0.1% in women [1]. Due to its non-specific manifestations, FD (especially the later-onset variant) is often underdiagnosed [2]. We aimed to estimate its prevalence in a large haemodialysis (HD) population in the UK.

Methods

This is a cross-sectional, multicentre study of eight renal centres in the UK. All male participants were tested via dried blood spot alpha-galactosidase A (AG) enzyme and globotriaosylsphingosine (Lyso-Gb3) assays. If either the AG (≤ 2.8 µmol/L/H) or Lyso-Gb3 (≥ 3.5 ng/mL) level was abnormal, genetic testing for *GLA* variant was performed. All females had AG, Lyso-GB3 and genetic tests.

Results

In total, 1325 consented to participate in the study. The mean age of the participants was 64 (SD 15) years, 67% were male, 64% were of white ethnicity, the duration of dialysis was 32 (IQR 56) months, and 32% underwent renal biopsy. Diabetic nephropathy (28%) was the most common cause of ESKD, whereas 21% had an unknown aetiology. A total of 1,295 had both AG and Lyso-Gb3 tests, whereas 573 had *GLA* genetic tests. Among the 14% (n=186) with an AG level≤ 2.8 µmol/L/H, 48 were female and 138 were male, all of whom had Lyso-Gb3< 3.5 ng/mL. Only 3 (0.2%) had abnormal Lyso-Gb3 but all had normal AG and negative

genetic tests. Two females were found to have likely benign, non-pathogenic *GLA* variants: heterozygous c.937G>T (p.(Asp313Tyr) and heterozygous c.1102G>A (p.(Ala368Thr)).

Conclusions

Despite the implementation of stringent screening criteria, we did not identify any new confirmed cases of Fabry disease in this large UK haemodialysis population.

Keywords: alpha-galactosidase A, Fabry disease, *GLA* variant, hemodialysis, Lyso-Gb3

Introduction

Fabry disease (FD) is an X-linked inherited lysosomal storage disorder [1]. Pathological variant of the GLA leads to deficiency of a lysosomal hydrolase enzyme, alpha-galactosidase A (AG), which causes progressive accumulation of glycophospholipids, predominantly globotriaosylceramide 3 (Gb3), resulting in multisystem pathology and premature death [2]. Patients may present with either the classic form, which has a severe clinical phenotype, or an atypical variant, which presents later in the 3rd to 7th decade of life [3, 4]. Although FD is an X-linked disorder that predominantly affects men, heterozygous women may also experience significant clinical manifestations due to random X-inactivation [5].

Owing to its non-specific manifestations, FD (especially the later-onset variant) is often underdiagnosed or delayed [3]. The worldwide estimated prevalence of FD varies from 1 in 40,000 to 1 in 117,000 live births for the classical form [6, 7]. However, several large genetic screening programs for male newborns reported a much greater incidence of α-galactosidase A deficiency between 1 in 1,250 and 1 in 7,800, with most cases having genetic variants associated with later-onset phenotypes [8-11], and a proportion with genetic variants of uncertain clinical significance requiring further characterisation [12, 13]. The screening of high-risk groups is therefore important for case finding and subsequent investigation and management.

Renal manifestations in FD are well described, with ESKD being a key contributor to morbidities and mortalities associated with the disorder [14]. Linthorst et al reported an estimated prevalence of FD among the ESKD population of 0.3% in men and 0.1% in women

in 2010 [15]. More recently, a reanalysis of FD screening in high-risk clinics, excluding benign or likely benign variants, concluded the revised prevalence estimates were 0.21% in males and 0.15% among the haemodialysis (HD) population with a predominantly classic phenotype (60%) [16]. In the UK, screening is not routinely performed in HD patients. Although a previous UK-based screening study of 155 males with HD did not identify any new cases of Fabry disease, it was limited by its small sample size [17]. We aimed to estimate its prevalence in a large HD population in both males and females in the UK.

Materials and methods

The Screening for Fabry Disease in Haemodialysis Population (SoFAH) study is a cross-sectional, multicentre screening study. Adult HD patients at eight renal centres in the Midlands, UK, with a total HD population of 2,452, were invited to participate in the study. Patients who were unable to provide written informed consent or who had a known diagnosis of FD were excluded from the study. All the participants provided informed consent prior to inclusion.

Demographic and clinical data, including age, sex, ethnicity, renal diagnosis, previous renal biopsy, dialysis vintage and cardiovascular disease, were collected. All participants were also asked to complete the EQ-5D-5L questionnaire and a symptom survey, developed for the study (see supplementary). All consented male participants were tested via the dried blood spot (DBS) AG enzyme and Lyso-Gb3 assays. If either the AG enzyme (≤2.8 μmol/L/H) or the Lyso-Gb3 (≥ 3.5 ng/mL) level was abnormal, genetic testing for *GLA* variant was performed. All consented female participants had AG enzyme, Lyso-GB3 and genetic tests (Figure 1). All

blood samples were taken prior to the start of the HD session and sent for analysis to Archimed Laboratories, Vienna, Austria, Europe.

Continuous variables are summarised by mean and standard deviation (SD), or median and interquartile range (IQR). Categorical variables are summarised as N (%). All analyses were conducted in SPSS v27.

Results

Among the 2,452 HD patients in the eight centres, 1325 consented to participate in the study from August 2022 to August 2023. The mean age of the participants was 64 (SD 15) years, and 67% were male. There were 64% (n=848) White, 21% (n=278) Asian, 11% (n=146) Black or Afro-Caribbean and 4% (n=53) mixed or other ethnicities. The median duration of dialysis was 32 (IQR 56) months. Diabetic nephropathy (28%, n=371) was the most common cause of ESKD; 17% (n=225) had glomerulonephritis, 9% (n=119) had ischaemic nephropathy, and 21% had an unclear cause of ESKD. Overall, 32% (n=419) had kidney biopsies. The majority had a history of cardiovascular disease (85%, n=1130), including 12% (n=158) with coronary artery disease and 10% (n=132) with heart failure.

Based on the symptom survey, 27% (n=359) self-reported burning pain in the extremities, 25% (n=335) had heat intolerance, 25% (n=335) had gastrointestinal symptoms without a cause, 22% (n=288) had a family history of renal disease, and 41% (n=541) had a family history of heart disease or stroke.

In total, 1295 participants had DBS AG enzymes and Lyso-Gb3 tested (Figure 2). Six patients withdrew from the study prior to blood sampling, whereas the other patients did not complete the study due to clinical deterioration (n=7), changes in modality (n=5), no blood being sampled (n=5), moving out of area (n=2) or death (n=1). Four patients did not have AG enzyme and Lyso-Gb3 tested due to poor sample quality, but all had *GLA* genetic tests, which were negative. The median AG enzyme level was 4.3 (IQR 2.2) µmol/L/H. Among the 14% (n=186) with AG enzyme levels ≤ 2.8 µmol/L/H, 48 were female and 138 were male. All (n=186) had Lyso-Gb3 < 3.5 ng/mL, 185 had negative *GLA* genetic tests, and 1 did not have a genetic test performed because of a sample issue. The false positive rates of the DBS AG enzyme test for FD in our study were 11% in females and 16% in males. The median Lyso-GB3 level was 1.4 (IQR 0.7) ng/mL. Only three (0.2%), 1 female and 2 males, had abnormal Lyso-Gb3, but all had normal enzyme levels and negative *GLA* genetics. Therefore, the false positive rate of Lyso-Gb3 for FD in our study was 0.2% for males and 0.2% for females.

Of the 1295 participants, 573 (44%) had a *GLA* genetic test, of whom 150 were male and 423 were female. Only two participants, both female, were found to have *GLA* variants (Table 1). The first participant was a 33-year-old woman of white ethnicity with presumed diabetic nephropathy due to type 1 diabetes. Her dialysis duration was 5 months. There was no history of cardiovascular disease. Both her AG (5.7 µmol/L/H) and Lyso-Gb3 levels (0.8 ng/mL) were within the normal range. The *GLA* genetic test identified a heterozygous c.937G>T (p.(Asp313Tyr)) variant, which was deemed to be a likely benign, non-pathogenic variant. The second participant was a 57-year-old woman of black ethnicity with ESKD of uncertain aetiology. Her dialysis vintage was 8 years and 4 months. She had a history of hypertension. In addition, she had left ventricular hypertrophy and atrioventricular block,

requiring pacemaker insertion prior to starting dialysis. In the symptoms survey, the patient self-reported acroparesthesia and a family history of cardiovascular disease. Both her alpha-galactosidase A (3 µmol/L/H) and Lyso-GB3 levels (1.7 ng/mL) were within range, but she was found to be heterozygous for the *GLA* genetic variant c.1102G>A (p.(Ala368THR)). This participant was assessed at the FD specialist unit in Birmingham, UK. Her echocardiogram showed concentric hypertrophy likely related to hypertension, and ophthalmological examination was normal. Based on these clinical details and the ClinVar database, suggesting c.1102G>A (p.Ala368Thr) is of conflicting germline classifications of pathogenicity [18], it was deemed that the variant is likely benign and that the participant did not have FD.

Discussion

This comprehensive screening study of FD using the AG enzyme, Lyso-GB3 assays and confirmatory *GLA* genetic tests in a maintenance HD population in the UK identified two female participants with non-pathogenic, likely benign *GLA* variants. There was not a single patient of FD identified in this largest screening study for FD in the HD population in the UK to date.

Fabry disease is the most common lysosomal storage disease. Due to a pathological variant of the *GLA* located on the X chromosome (Xq22.1), resulting in a deficiency or a reduction in lysosomal AG enzyme activity and an accumulation of Gb3, patients with FD often experience a wide range of clinical symptoms, including acroparesthesia, hypohidrosis, heat intolerance, cutaneous angiokeratoma, gastrointestinal problems, progressive multiorgan dysfunction and premature death. Renal failure, cardiomyopathy, arrhythmia and cerebrovascular events are the major complications.

To date, more than 900 variants in the *GLA* have been described, with the majority associated with the classical phenotype, whereas others are associated with the late-onset phenotype or variants of unknown significance [19]. This classification and definition of phenotype is often based on residual enzyme activity and the presence of characteristic FD symptoms [20]. Owing to random X-chromosomal inactivation in females, enzyme analysis may be inconclusive and requires *GLA* genetic testing. Although patients with the classical form often present early with characteristic manifestations, there has been increasing recognition and understanding of the natural course of those with late-onset or late-onset phenotypes [20]. Late-onset FD is usually caused by missense changes in the *GLA* that lower but do not abolish enzyme activity [21]. Unsurprisingly, the disease course of patients with classical FD differs from that of patients with late-onset FD; it also differs from that of men and women [20]. Using a merged database of 596 FD patients, Arends et al demonstrated that males with classical FD were at the highest risk of renal, cardiac and cerebral events, with a median event-free survival of 50 years, whereas females with classical FD resembled males with late-onset FD, with comparatively better event-free survival [20]. Females with late-onset FD had the mildest disease course [20].

With the increasing availability and wider application of *GLA* genetic screening, especially in high-risk populations, a growing number of *GLA* variants have been identified. While early diagnosis of FD is crucial to provide support and treatment, it is equally important to avoid misdiagnosis among those who do not, and most likely will not, develop the clinical phenotype of FD [22]. As an X-linked metabolic disorder, which is highly variable in disease penetration in females and with the *GLA* known to have considerable missense variation

[21, 23], careful clinical evaluation of the pathogenicity of each genetic variant is paramount to establish a diagnosis of FD. In 2015, the American College of Medical Genetics and Genomics published the guidelines for classifying variants, which represent the gold standards for the interpretation of sequence variants [24]. More recently, ClinVar, a free, web-based, public archive of human genetic variants, has also been increasingly used to support variants interpretation [25]. Interestingly, a systematic review and meta-analysis of 38 screening studies, which examined the impact of GLA variant classification on the estimated prevalence of Fabry disease reported a pooled prevalence of 0.3% based on ACMG criteria, in contrast to the 0.2% based on ClinVar database, among patients with ESKD or chronic kidney disease [26].

In our study, the *GLA* variant c.937G>T (p.(Asp313Tyr)) was identified in one of the participants. This variant is now recognised to be relatively common and likely to be benign. In a study of FD in a cerebrovascular disease cohort, Marquardt et al regarded it as *GLA* polymorphism and not pathogenic [27], which was supported by the fact that male patients with this variant do not accumulate glycosphingolipids in organs, plasma or urine [28]. With respect to the c.1102G>A (p.(Ala368THR)) variant, there have been conflicting interpretations of pathogenicity. While some reported the variant as likely benign, others suggested uncertain significance [18]. Owing to the increasing challenges and complexity in interpreting clinical sequence variance, the ACMG strongly recommended the involvement of clinical geneticists or the equivalent for such cases [24]. Following further assessment at the FD specialist clinic, our patient who was heterozygous for the *GLA* genetic variant c.1102G>A (p.(Ala368THR)) was deemed to not to have FD and the variant was considered to be likely benign.

Overall, our study did not identify any new cases of FD despite screening 1,299 patients on maintenance haemodialysis. Our results are consistent with recent screening studies of 526 dialysis patients in Australia and 227 dialysis patients in Japan, both of which also did not identify any confirmed FD cases [29, 30]. Compared with the previously estimated prevalence of 0.1% in females and 0.3% in males by Linthorst et al [15]; or 0.15% and 0.21%, respectively, for females and males by Doheny et al (after excluding benign or likely benign variants) [16], the findings of our study were significantly different. There are several plausible explanations for our findings.

First, in our study, only 21% of the patients had an unclear cause of ESKD, and up to 32% of the patients had a renal biopsy. The European Renal Best Practice group has recommended screening for FD in CKD patients with unexplained aetiology [31]. Although dual pathology is not uncommon, as hypertension and diabetes can often co-exist in patients with various other renal conditions, our study's broad inclusion criteria were likely to contribute to the lower yield than those of other screening studies. For example, in a screening study for FD in 897 patients with chronic kidney disease (CKD) or on dialysis in Korea, only patients with CKD with albuminuria were included, whereas patients with confirmed aetiology on kidney biopsy or those who were considered to have typical diabetic nephropathy were excluded [32]. This study reported only one patient with a pathogenic *GLA* variant, giving a prevalence of 0.1%. Likewise, another screening study of 1,079 patients on hemodialysis in Brazil included only patients with hypertension, glomerulosclerosis, and/or diabetes with inexplicable pain or other FD signs but excluded those with polycystic kidney disease or another renal aetiology [33]. Second, according to the global Fabry Registry, the median

ages at diagnosis were 13 and 32 years for males and females, respectively [34]. A large screening study of 5,572 dialysis patients in Russia reported a median age of 43 years among 20 new FD cases (19 males and 1 female) [35]. However, our study population had a mean age of 64 years, with only 18% under the age of 50 years and 37% under the age of 60 years. Third, although FD is known to affect all ethnicities, a 2002 study based on the United States Renal Disease System database revealed that patients with FD on dialysis were younger and more likely to be male and Caucasian than the overall US ESKD population [36]. A large screening study of 2,924 haemodialysis patients in Chiba, Japan only identified one male case, giving a much lower estimated prevalence of 0.03% and suggesting potential variation of FD prevalence based on ethnicity or geographical differences [37]. As 33% of our study population was of non-white ethnicity, this might have partially reduced the likelihood of undiagnosed FD cases. Fourth, since the publication of the 'renal variant' phenotype by Nakao et al. in 2003, there has been growing awareness of FD amongst the clinician [38]. With increasing availability of biomarkers or genetic testing for rare diseases embedded in day-to-day clinical practice in England, which facilitates earlier diagnosis of rare diseases, such a positive change in the clinical landscape might also potentially reduce the number of undiagnosed cases in our study. A study by Prats et al., which screened 3,470 incident or prevalent HD patients in Madrid, similarly did not identify any FD patients but reported eight cases of non-pathogenic *GLA* variants [39]. In contrast to our study, in which we performed genetic testing on 44% of the study participants, only 2.5% had *GLA* genotyping in the study by Prats et al., as only males with decreased enzyme activity and females with either decreased enzyme activity or increased lyso-Gb3 or both would proceed to genetic testing.

In the systematic review by Linthorst et al., almost half of the screening studies for FD in high-risk populations examined only men and did so primarily via an enzymatic test [15]. Even among screening studies that included women, the vast majority were also performed using enzymatic activity as the primary method; hence, likely to result in 40% false-negative results and subsequent missed diagnoses. Linthorst et al noted that the AG enzyme activity level threshold for positive screening varied from <10% to <60% in 20 screening studies of FD in high-risk populations [15], highlighting the uncertainty in the correlation between such biomarkers and FD diagnosis. We employed an enzymatic activity cut-off of ≤2.8 μmol/L/H using the DBS and reported false positive rates of 16% and 11% in men and women, respectively. There is no direct conversion between the different units used, for instance, % and μmol/L/H, when comparing the threshold of AG enzyme activity for FD screening. While DBS was known to yield more false-positive results (4.2%, 95% CI 1.2-7.1%), relative to plasma (1.0%) or leucocytes (1.3%) [15], our finding was significantly higher than expected, suggesting that the AG enzyme cut-off we applied in our study might be too low, especially for male patients.

Lyso-Gb3 is considered, in general, a more sensitive biomarker for the screening and diagnosis of FD [40]. In FD, accumulated Gb3 in the endothelium is a hallmark of FD and results in characteristic end-organ damage. As the accumulated Gb3 is converted by acid ceramidase within the tissue and released into the circulation, measuring lyso-Gb3 in biological fluid was identified as a valuable biomarker for assessing disease burden with promising clinical utility [41]. As a biomarker for screening, it has also been shown to be elevated in patients with late-onset FD, despite normal AG enzyme levels [42]. As a biomarker for assessing organ damage and prognosis, each 10 mmol/L increase in Lyso-Gb3

316 was reported to be associated with an additional 0.34 ml/min/1.73m^2 decrease in the eGFR
317 and a 20% increase in the left ventricular mass among males with late-onset FD and females
318 with FD [20]. Moreover, as it has been shown to decrease with enzyme replacement
319 treatment for FD, Lyso-Gb3 is also used for therapeutic monitoring [40]. Of note, the
320 AG/lyso-Gb3 ratio was recently postulated as a novel parameter for diagnosing women with
321 FD [43]. Overall, using a lyso-Gb3 threshold of ≥ 3.5 ng/ml, we reported a false-positive rate
322 of 0.2% in both men and women in our study, which was considerably lower than that of the
323 AG enzyme.
324
325 In summary, despite implementing stringent screening in both men and women, we did not
326 identify any confirmed case of FD, but found two cases of non-pathogenic GLA variants, in a
327 large HD population in the UK. This suggests a lower prevalence of Fabry disease among HD
328 patients than previously reported but might be influenced by our cohort's demographic and
329 clinical background. The AG enzyme was below the normal range among 14% and Lyso-Gb3
330 level was above the normal range among 0.2% of our study cohort. However, both were
331 falsely positive for FD diagnosis given the negative *GLA* genetic test. Symptoms commonly
332 associated with FD were non-specific and self-reported in almost a quarter of the
333 participants.
334
335 **Declarations:**
336 **Ethics approval and consent to participate**
337 The study was approved by the UK Health Research Authority (REC reference no. 281233)
338 and was prospectively registered (ISRCTN44751506). Written informed consent was

obtained from all participants. The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki.

Availability of data and materials

The dataset used and analysed during the current study is available from the corresponding author upon reasonable request.

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Authors' contributions: KN wrote the first draft; ID and TG edited and amended the first draft and contributed to subsequent drafts; MS, DB, TD, JB, LC, RH, KS, MM, JN, SR, and TG critically reviewed and approved the final draft.

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Figures

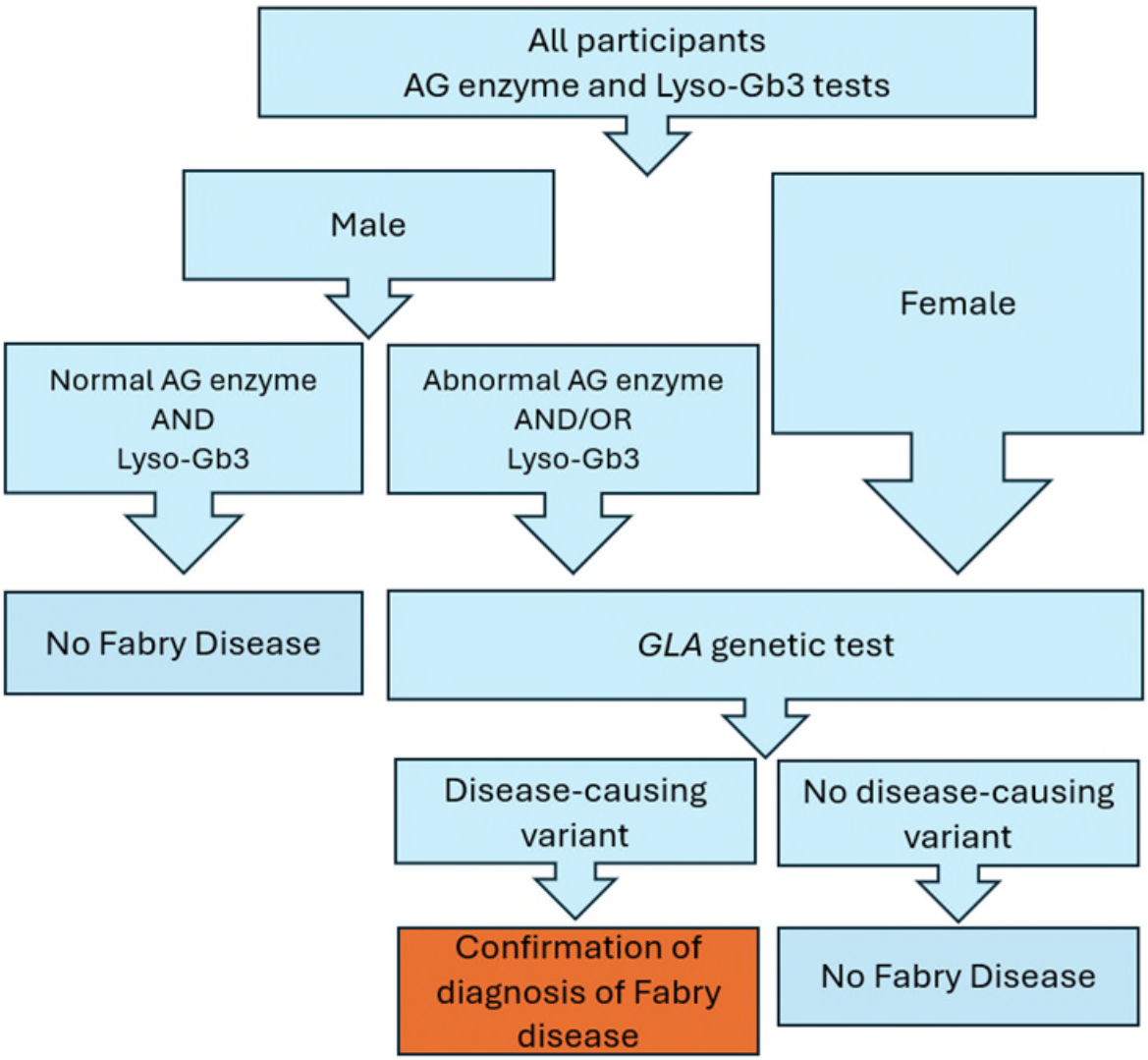

Figure 1: SoFAH study screening and diagnosis algorithm for Fabry disease

Abbreviations: alpha-Gal A: alpha-galactosidase A enzyme (dried blood spot); Lyso-GB3: globotriaosylsphingosine

NB: Abnormal alpha-Gal A was defined as ≤2.8 µmol/L/H. Abnormal Lyso-Gb3 was defined as ≥ 3.5 ng/mL.

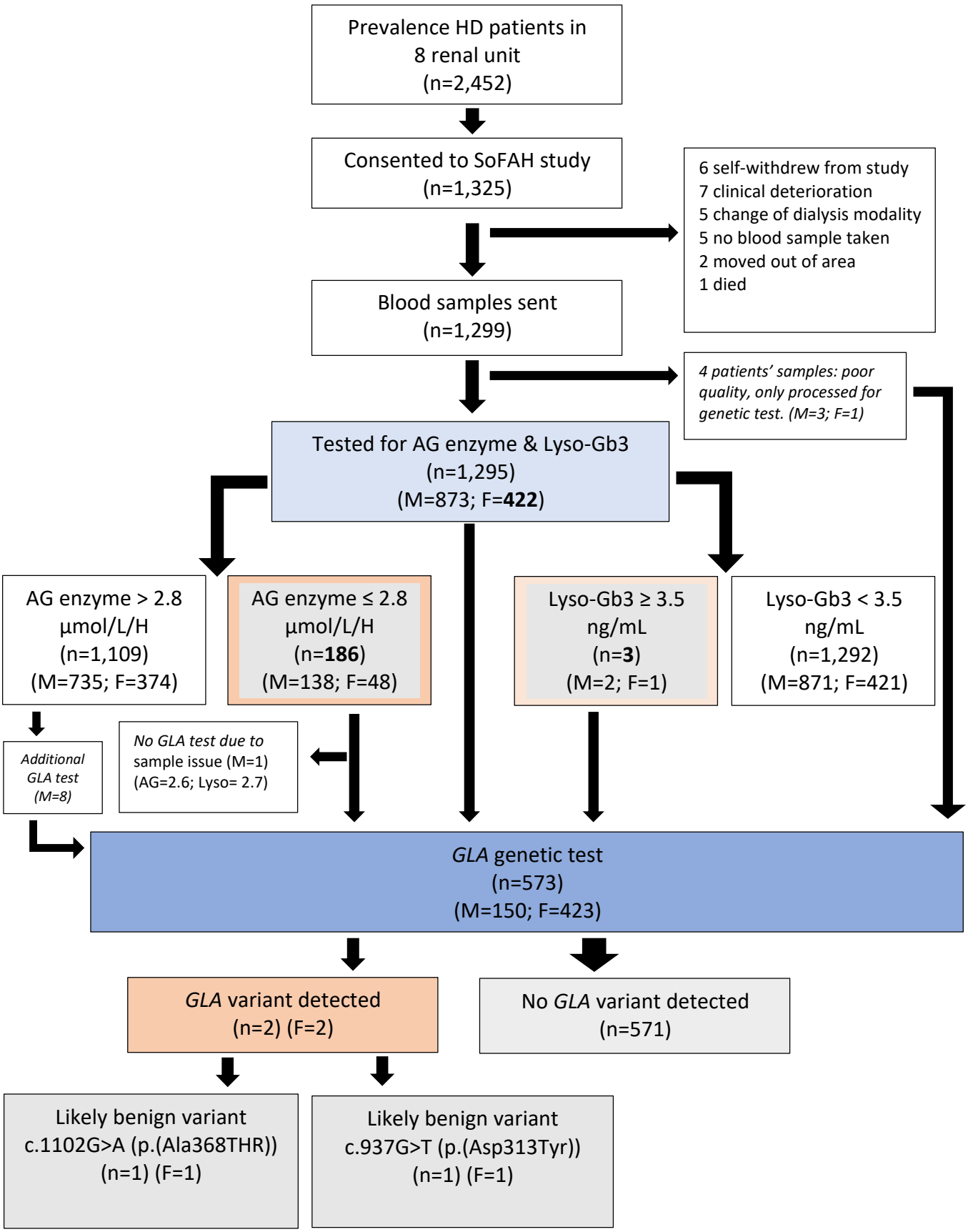

Figure 2: SoFAH study flow diagram

Abbreviations: AG: alpha-galactosidase A enzyme (dried blood spot); F: female; HD: hemodialysis; Lyso-GB3: globotriaosylsphingosine; M: male

Table

GLA variant	ACMG	ClinVar	AG level (µmol/L/H)	Lyso-GB3 (ng/mL)	Clinical phenotype
c.1102G>A (p.(Ala368THR))	Likely benign	COP: likely benign (n=3); uncertain significance (n=1)	3	1.7	57 years, female, black ethnicity HD duration: 8 years and 4 months PRD: uncertain aetiology History of CVD: atrioventricular block required pacemaker, left ventricular hypertrophy, no ophthalmic abnormalities.
c.937G>T (p.(Asp313Tyr))	Likely benign	COP: Benign (n=3); Likely benign (n=3); Uncertain significance (n=3)	5.7	0.8	33 years, female, white ethnicity HD duration: 5 months PRD: presume diabetic nephropathy due to type 1 diabetes. History of CVD: none

Table 1: GLA variants identified in SoFAH study, variant classification, alpha-galactosidase A enzyme level, Lyso-GB3 level and phenotype

Abbreviations: ACMG: American College of Medical Genetics and Genomics; AG: alpha-galactosidase A enzyme (dried blood spot); COP: conflicting classifications of pathogenicity; CVD: cardiovascular disease; HD: haemodialysis; Lyso-GB3: globotriaosylsphingosine; PRD: primary renal diagnosis.

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