Full Title: Impact of *GLA* variant classification on the estimated prevalence of Fabry disease: a systematic review and meta-analysis of screening studies

Short Title: Prevalence of Fabry disease

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Abstract

Background: The diagnosis of Fabry disease (FD) has relevant implications related to the management. Thus, a clear assignment of *GLA* variant pathogenicity is crucial. This systematic review and meta-analysis aimed to investigate the prevalence of FD in high-risk populations and newborns and evaluate the impact of different *GLA* variant classifications on the estimated prevalence of FD.

Methods: We searched the EMBASE and Pubmed databases on February 21, 2023. Observational studies evaluating the prevalence of FD and reporting the identified *GLA* variants were included. *GLA* variants were re-evaluated for their pathogenicity significance using the American College of American Genetics and Genomics (ACMG) criteria and the ClinVar database. Pooled prevalence of FD among different settings was calculated. The study was registered on PROSPERO (CRD42023401663) and followed the PRISMA guidelines.

Results: Of 3,941 studies identified, 110 met the inclusion criteria. The pooled prevalence of FD was significantly different according to the clinical setting and criteria used for the pathogenicity assessment. Using the ACMG criteria, the pooled prevalence was 1.2% in patients with left ventricular hypertrophy/hypertrophic cardiomyopathy (26 studies, 10,080 patients screened), 0.3% in end-stage renal disease/chronic kidney disease (38 studies, 62,050 patients screened), 0.7% in stroke (25 studies, 15,295 patients screened), 0.7% in cardiac conduction disturbance requiring pacemaker (3 studies, 1,033 patients screened), 1.0% in small-fiber neuropathy (3 studies, 904 patients screened), and 0.01% in newborns (15 studies, 1,1108,793 newborns screened). The pooled prevalence was different if the *GLA* variants were assessed using the ClinVar database, and most patients with a discrepancy in the pathogenicity assignment carried one of the following variants: p.A143T; p.D313Y; and p.E66Q.

Conclusions: This systematic review and meta-analysis describe the prevalence of FD among newborns and high-risk populations, highlighting the need for a periodic reassessment of the *GLA* variants in the context of recent clinical, biochemical, and histological data.

Keywords: Fabry disease; prevalence; screening; *GLA* variants.

Nonstandard Abbreviations and Acronyms

α-Gal A, α-galactosidase A

ACMG, American College of Medical Genetics and Genomics

AVB, atrioventricular block

CKD, chronic kidney disease

ERT, enzyme replacement therapy

ESRD, end-stage renal disease

FD, Fabry disease

Gb3, globotriaosylceramide

HCM, hypertrophic cardiomyopathy

LVH, left ventricular hypertrophy

P/LP, pathogenic / likely pathogenic

PMK, pacemaker

SND, sinus node disease

VUS, variant of uncertain significance

Background

Fabry disease (FD) is an X-linked lysosomal disorder caused by pathogenic variants in the *GLA* gene that result in reduced α-galactosidase A (α-Gal A) enzyme activity[1]. This leads to an accumulation of lysosomal globotriaosylceramide (Gb_3) in organs and tissues throughout the body[1]. Following the introduction of enzyme replacement therapy (ERT), early recognition of FD has become crucial to prevent disease progression and irreversible organ damage[2] and screening programs in newborns and high-risk populations have been implemented.

Previous systematic reviews and meta-analyses of screening studies evaluating the prevalence of FD[3–5] have utilized as inclusion criteria patients tested for α-Gal A deficiency using dried blood spots, plasma and/or leucocyte enzyme assays alone, or confirmed by *GLA* variants analyses. The main limitations of previous meta-analyses included the lack of genetic confirmation and/or interpretation[3] and data limited to specific high-risk populations[4,5]. Since then, the pathogenetic significance of different *GLA* variants has been re-evaluated, with a potential impact on FD prevalence.

Given the significant management implications related to the diagnosis of FD, after the identification of a *GLA* variant in an affected proband, the clear assignment of variant pathogenicity is crucial. Furthermore, since the pathogenicity assignment of variants can evolve over time, it is recommended that they undergo periodic re-evaluation[6,7].

Guidelines from the American College of Medical Genetics and Genomics (ACMG) provided criteria for the assignment of pathogenicity of genetic variants[8]. These criteria represent the gold standard for variant interpretation. However, several web-based databases are used by physicians to interpret the significance of genetic variants. One such, ClinVar, has been recently incorporated into recent guidelines of variant interpretation[9,10].

In this systematic review and meta-analysis, we aimed to investigate the prevalence of FD in high-risk populations and newborns and evaluate the impact of different *GLA* variant classifications on the estimated prevalence of FD.

Methods

We performed a systematic review and meta-analysis of studies enrolling patients screened for FD. The aims and analyses to be performed were pre-specified, and the study was registered on

PROSPERO (CRD42023401663). The findings are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[11]. The authors declare that all supporting data are available within the article and its online supplementary files. The systematic review and meta-analysis did not involve accessing or otherwise processing patient-identifiable information and hence did not require ethical approval. A full description of the methods used in this study is available in the **Supplemental Material**.

Results

Among the 3,941 studies identified from the initial database search, 110 met the inclusion criteria and were analyzed for the systematic review and meta-analysis (**Figure 1, Supplemental Table I**). Among the included studies, 26 reports screened LVH/HCM patients[12–37], 38 ESRD/CKD patients[38–74], 25 stroke patients[75–99], 15 newborns[100–114], 3 small-fiber neuropathy patients[115–117], and 3 patients with AVB or SND requiring PMK implantation[118–120] (**Figure 2**).

Hypertrophic cardiomyopathy/left ventricular hypertrophy

Twenty-six studies performing screening in patients with HCM/LVH met the inclusion criteria[12–37], providing data on the prevalence of FD in 10,080 screened individuals.

The characteristics and the risk of bias of the studies, the screening methodology, and the *GLA* variants identified are described in **Supplemental Table II-V**.

The pooled prevalence of FD varies according to the screening methodology and the inclusion criteria **(Table 1)**. Considering all the studies describing the prevalence of FD among HCM/LVH patients, among 10,080 patients screened, 94 were diagnosed with FD, with a pooled prevalence of 1.4% (95%CI 0.9-2.1) according to the variant classification at the time of publication (as reported in published articles).

After re-classification of variants according to the ACMG criteria, 8 variants were downgraded from P/LP to VUS/LB/B (n= 5, n= 2, n= 1, respectively) while 4 variants were upgraded from VUS/LB/B to P/LP (n=2, n= 2, respectively), leading to re-classification of 34 patients, 24 as not having FD and 10 as having FD, respectively. Thus, according to the ACMG criteria, the pooled prevalence of FD among patients with HCM/LVH was 1.2% (95%CI 0.8-1.8) (**Figure 2**).

However, if the *GLA* variants were classified using the ClinVar database, of 80 patients diagnosed according to the ACMG criteria, 23 patients (29%) would have been categorized as not having FD due to re-classification from P/LP variants to variants with debated pathogenicity (n=8 with p.A143T; n=7 with p.E66Q; n=6 with p.D313Y; n=1 with p.R301G, and n=1 with p.A143P),

resulting in a pooled prevalence of FD among patients with HCM/LVH of 0.9% (95%CI 0.6-1.5) **(Figure 3)**. Continent-specific sub-analysis is shown in **Figure 4**.

End-stage renal disease/chronic kidney disease

Thirty-eight studies performing screening in patients with ESRD/CKD met the inclusion criteria[38–74], providing data on the prevalence of FD among 62,050 patients screened.

The characteristics and the risk of bias of the studies, the screening methodology, and the *GLA* variants identified are described in **Supplemental Table II-V**. The pooled prevalence of FD varies according to the screening methodology and the inclusion criteria **(Table 1)**.

Considering all the studies describing the prevalence of FD among ESRD/CKD patients, among 62,050 patients screened, 116 were diagnosed with FD, with a pooled prevalence of 0.2% (95%CI 0.2-0.4) according to the variant classification at the time of publication (as reported in published articles).

After re-classification of variants according to the ACMG criteria, 13 were downgraded from P/LP to VUS/LB (n= 9, n= 4, respectively) while 5 variants were upgraded from VUS/LB/B to P/LP (n=2, n= 3, respectively), leading to re-classification of 103 patients, 21 as not having FD and 82 as having FD, respectively. Thus, according to the ACMG criteria, the pooled prevalence of FD among patients with ESRD/CKD was 0.3% (95%CI 0.2-0.4) (**Figure 2**).

However, if the *GLA* variants were classified using the ClinVar database, among 177 patients diagnosed according to the ACMG criteria, 99 patients (56%) would have been categorized as not having FD due to re-classification from P/LP variants to variants with a conflicting of pathogenicity or VUS (n=43 with p.D313Y; n=40 with p.E66Q; n=8 with p.A143T; n=3 with p.A352G; n=2 with p.R220Q; n=1 with p.V199M; n=1 with p.A211P; n=1 with p.Y134D), resulting in a pooled prevalence of FD among patients with ESRD/CKD of 0.2% (95%CI 0.1-0.2) **(Figure 3)**.

Stroke

Twenty-five studies performing screening in patients with stroke met the inclusion criteria[75–99], providing data on the prevalence of FD among 15,295 patients screened.

The characteristics and the risk of bias of the studies, the screening methodology, and the *GLA* variants identified are described in **Supplemental Table II-V**. The pooled prevalence of FD varies according to the screening methodology and the inclusion criteria **(Table 1)**.

Considering all the studies describing the prevalence of FD among stroke patients, among 15,295 patients screened, 77 were diagnosed with FD, with a pooled prevalence of 0.6% (95%CI 0.4-0.9) according to the variant classification at the time of publication (as reported in published articles).

After re-classification of variants according to the ACMG criteria, 10 variants were downgraded from P/LP to VUS/LB/B (n= 6, n= 3, n=1, respectively) while 5 variants were upgraded from VUS/LB/B to P/LP (n=2, n= 3, respectively), leading to re-classification of 53 patients, 22 has not having FD and 31 has having FD, respectively. Thus, according to the ACMG criteria, the pooled prevalence of FD among patients with stroke was 0.7% (95%CI 0.5-1.0) (**Figure 2**).
However, if the *GLA* variants were classified using the ClinVar database, among 86 patients diagnosed according to the ACMG criteria, 75 patients (87%) would have been categorized as not having FD due to re-classification from P/LP variants to variants with a conflicting of pathogenicity or VUS (n=50 with p.D313Y; n=14 with p.E66Q; n=8 with p.A143T; n=1 with p.G325S; n=1 with p.V199A; n=1 with p.R38G), resulting in a pooled prevalence of FD among patients with stroke of 0.3% (95%CI 0.1-0.5) **(Figure 3)**.

AVB/SND requiring PMK implantation and small-fiber neuropathy

Three studies performing screening in patients with AVB or SND requiring PMK implantation[118–120] and three studies in patients with small-fiber neuropathy met the inclusion criteria[115–117], providing data for 1,033 and 903 patients, respectively. The characteristics and the risk of bias of the studies, the screening methodology, and the *GLA* variants identified are described in **Supplemental Table II-V**. The pooled prevalence according to the variant classification at the time of publication varied significantly after variant reclassification using the ACMG criteria or the Clinvar database **(Figure 2,3)**.

Newborn screening

Fifteen studies performing screening in newborns met the inclusion criteria[100–114], providing data on the prevalence of FD among 1,108,793 newborns screened.
The characteristics and the risk of bias of the studies, the screening methodology, and the *GLA* variants identified are described in **Supplemental Table II-V**.
Among 1,108,793 newborns screened, 248 were diagnosed with FD, with a pooled prevalence of 0.01% (95%CI 0.001-0.067) according to the variant classification at the time of publication (as reported in published articles).
After re-classification of variants according to the ACMG criteria, 8 variants were downgraded from P/LP to VUS/LB (n= 5, n= 3, respectively) while 6 variants were upgraded from VUS/LB/B to P/LP (n=2, n= 4, respectively), leading to re-classification of 195 patients, 172 has not having FD and 23 has having FD, respectively. Thus, according to the ACMG criteria, the pooled prevalence of FD among newborns was 0.01% (95%CI 0.002-0.079) (**Figure 2**).

However, if the *GLA* variants were classified using the ClinVar database, among 99 patients diagnosed according to the ACMG criteria, 45 patients (45%) would have been categorized as not having FD due to re-classification from P/LP variants to variants with a conflicting of pathogenicity or VUS (n=18 with p.A143T; n = 8 with p.G80D; n = 6 with p.R356Q; n = 4 with p.E66Q; n = 4 with p.D313Y; n = 2 with p.V199M, n = 1 with p.R220Q; n = 1 with p.P60L; n = 1 with p.M290L), resulting in a pooled prevalence of FD among newborns of 0.005% (95%CI 0.001-0.025) **(Figure 3)**.

Inter-rater agreement and risk of bias

It was observed a strong agreement between reviewers in the two phases of study screening. In particular, among the 1,981 articles screened for title and abstract, agreement was observed in 1,948 cases (98.3%) and disagreement in 33 (1.7%; Cohen's κ 0.90 [95%CI 0.86-0.94], p-value <0.001). In addition, among the 167 articles screened for full-text, agreement was observed in 160 cases (95.8%) and disagreement in 7 (4.2%; Cohen's κ 0.91 [95%CI 0.84-0.98], p-value <0.001). The risk of bias was low in 76 studies (69.1%), moderate in 33 (30.0%), and high in 1 (0.9%).
The risk of bias of included studies is reported in **Supplemental Table V** and shown in **Figure 5**. Agreement between reviewers in the assessment of the risk of bias was observed in 93 cases (84.5%) and disagreement in 17 (15.5%; Cohen's κ 0.71 [95%CI 0.58-0.84], p-value <0.001).

Discussion

This systematic review and meta-analysis describe the prevalence of FD in the general population (estimated through newborn screening) and in patients considered at high-risk for having the disease.
The main findings of the review are:

- FD is a rare disease with an estimated prevalence of 0.01% in the general population. Its prevalence is significantly higher in high-risk populations (ranging from 0.3% in patients with ESRD or CKD to 1.2% in patients with HCM);
- During the last decades, several *GLA* variants initially described as P/LP were reclassified as VUS or B/LB variants and vice-versa, leading to a significant re-evaluation of the prevalence of FD in the different clinical settings;
- There is a significant discrepancy in the pathogenicity significance of the *GLA* variants when assessed using the ACMG criteria (the current gold standard for the pathogenicity assignment) and ClinVar (a public database commonly used in clinical practice).

Prevalence of Fabry disease in newborns

With the introduction of ERT and the demonstration of its efficacy in slowing the progression of the disease and the occurrence of adverse outcomes[2], efforts have been directed to develop screening methods to identify FD patients. Studies reporting the prevalence of FD among newborns undergoing metabolic screening started in 2006, when Spada et al. screened 37,104 consecutive Italian male neonates by determination of α-Gal A activities in DBS, observing a prevalence of 1 in 3,100 newborns. Since then, screening programs in different countries[100–114] reported a prevalence ranging between 1 in 1,250[101] and 1 in 18,436[112], according to the ethnicity, gender, and predicted disease phenotype. In the present study, we showed that variable assignment of *GLA* variant pathogenicity has an impact on the estimated prevalence. We observed a pooled prevalence of 1 in 10.000 patients, with a higher prevalence among males (1 in 3,125 newborns) than in females (1 in 100,000 newborns). This difference is likely related to the screening methodology adopted in many studies, based on the determination of α-Gal A activity, often normal in affected female patients[1], rather than genetic screening.

Prevalence of Fabry disease in high-risk populations

Patients with FD exhibit a large variability in age of onset and phenotype, ranging from patients with a classic multi-organ presentation to those with a mild presentation with single organ affected. Patients with later-onset disease usually present with HCM. However, due to the variable expression of any genetic disease even patients with classic FD may occasionally manifest with isolated AVB/SND, CKD, stroke, peripheral neuropathy, or a combination thereof [1,2,121]. Thus, screening studies mainly included patients with these clinical features, focusing on those with a single clinical manifestation. Among these high-risk populations, we observed that the pooled prevalence of FD was low, ranging from 0.30% in patients with ESRD to 1.20% in patients with LVH/HCM. Moreover, after the re-evaluation of *GLA* variants using the ClinVar database, the pooled prevalence of FD is some high-risk populations, such as those with stroke or cardiac conduction disease requiring PMK implantation, was significantly lower than that initially estimated. This study suggests that these conditions should not necessarily be considered high-risk conditions.

However, it should be observed that while the pooled prevalence of FD in patients with myocardial hypertrophy, kidney disease, and stroke was estimated from different studies including thousands of patients, only three studies were available for patients with cardiac conduction disease or small-fiber neuropathy, limiting the accuracy of the results.

As we sought to encompass all published screening studies, the original articles we included had varying inclusion criteria and screening methods for the diagnosis of FD, which may explain the high degree of observed heterogeneity in certain settings. Nonetheless, our results are likely generalizable, considering that we incorporated data from diverse large populations across numerous countries. In addition, no significant publication bias was observed.

Clinical significance of GLA variants

In this review, we re-assessed the clinical significance of *GLA* variants and classified them according to the ACMG criteria. Thus, patients with P/LP variants were considered to have FD and represented the numerator used for the evaluation of the prevalence of the disease. We found a significant difference in the prevalence of FD among newborns and high-risk populations compared to the prevalence described in the original articles, as previously reported[7].

Furthermore, we found a significant discrepancy in the pathogenicity assignment when the variants were evaluated using the ACMG criteria and when assessed using the ClinVar database. Specifically, 29% to 87% of patients with a diagnosis of FD according to the ACMG criteria would have been reclassified as not having FD using the ClinVar database. Most patients showing a discrepancy in the pathogenicity assignment carried one of three variants: p.E66Q; p.A143T; and p.D313Y.

The p.E66Q *GLA* variant was first described as the cause of later-onset FD phenotype in many patients[74,122]. However, studies revealed that patients with p.E66Q *GLA* variant showed high residual enzyme activity, no Gb_3 accumulation in culture fibroblasts neither increased plasma Lyso-Gb_3 levels, suggesting that this variant is more likely a functional polymorphism rather than a disease-causing mutation[123].

The pathogenicity of the p.A143T *GLA* variant has been questioned as the phenotype of affected patients varied from the classic FD to asymptomatic unaffected individuals with normal α-Gal A activity[124]. Thus, according to the latest ClinVar variant classification, it has been described as having conflicting interpretations regarding pathogenicity. Recently, extensive clinical, biochemical, imaging, and histological data were suggestive for FD-related cardiomyopathy in a Finnish family with HCM and the p.A143T *GLA* variant[125]. It was concluded that the p.A143T *GLA* variant is very likely to be a later-onset FD-causing variant with incomplete age- and sex-related penetrance and predominantly cardiac manifestations[125].

Finally, the p.D313Y *GLA* variant has been described as a pseudo-deficiency allele with reduced α-Gal A activity and enzyme instability at neutral pH[126]. Recently, a systematic review and meta-analysis of studies reporting p.D313Y as the single occurring variant in *GLA* showed that the

prevalence of p.D313Y variant was higher than in general population and that patients carried this variant had a mild phenotype with predominantly neurological manifestations. The authors concluded that p.D313Y *GLA* variant seems to be associated with a later-onset phenotype with predominantly neurological manifestation. However, while histological findings seem to support the pathogenicity of p.A143T variant, so far, no convincing histological evidence of Gb_3 accumulation in tissues of patients carrying the p.D313Y variant has been provided. Indeed, a careful examination of the allele frequencies published in the GnomAD database disclosed a prevalence of 0.45% in the non-Finnish European populations in favor of benignity of the p.D313Y variant. In this systematic review, the p.D313Y variant was mainly observed in patients experiencing a stroke, and its reclassification using the ClinVar database was responsible for the significant difference observed in the pooled prevalence of FD.

In most cases of ClinVar reclassification of *GLA* variants, the invasive histological assessment of Gb_3 storage in target tissues and circulating levels of lyso-Gb_3 represented the main factors concurring to define variant pathogenicity since they are not considered in the ACMG criteria. The erroneous interpretation of a *GLA* variant may have devastating socio-economic effects on patients, families, and the health system, particularly if the variant has been identified in the newborn screening setting. Indeed, the classification of the *GLA* variant as pathogenic will be responsible for periodic multi-specialistic evaluations, lifelong ERT infusions, family screening, and devastating psychological consequences for patients and families. In addition, the indiscriminate availability of dried-blood spots and genetic testing in less experienced centers during the latest years led to the identification of an increasing number of patients carrying a *GLA* variant of uncertain significance or incorrectly interpreted as disease-causing.

This study reinforces the need for international or national networks providing guidance for variant interpretation and multi-parametric assessment of the *GLA* variant pathogenicity. In the setting of newborn screening, the evaluation of α-Gal A enzyme activity and lyso-Gb_3 circulating levels should be integrated with genetic testing. At the same time, in adult patients, the pathogenicity assessment of a novel *GLA* variant should be carefully interpreted considering the clinical features, the lyso-Gb_3 circulating levels, the α-Gal A activity, and, in select cases, the histological assessment of affected tissues (**Figure 6**).

Clinical Implications

FD is a multi-systemic disease characterized by progressive Gb_3 and lyso-Gb_3 accumulation, potentially affecting any organ or tissue. However, in relation to specific genotypes, it is common to observe in clinical practice a heterogeneous presentation, with severe multiorgan phenotype on one

extreme or later-onset disease, characterized by a milder and often single-organ presentation on the other extreme[127]. In addition, newborn metabolic screening, including assessing the α-Gal A activity, is becoming a common practice in several countries. As a result, an increasing number of individuals carrying a *GLA* variant disease have been identified.

In this context, the clinical interpretation of *GLA* variants is crucial for patient diagnosis, management, and therapy, including ERT, chaperone therapy, and new advanced therapies in development (i.e., gene therapy)[128]. Therefore, the clinical message of this study is to highlight the necessity of interpreting the pathogenicity of *GLA* variants in the context of updated clinical, biochemical, and histological data in referral centers with a multidisciplinary team of experts in FD, including a medical geneticist (**Figure 6**). Moreover, promoting educational programs and multicenter networks has become essential to enhance physicians' awareness of FD.

Conclusion

Reviewing 110 studies including more than one million patients, this systematic review and meta-analysis describes the prevalence of FD among newborns and high-risk populations. Our findings highlight the need for a periodic reassessment of the *GLA* variants, to discriminate affected patients from those carrying benign variants, and the importance to interpretate pathogenicity in the context of recent clinical, biochemical, and histological data.

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Supplemental Material

Supplemental Methods

Supplemental Table I-V

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Table 1. Prevalence of Fabry disease in screening studies, according to population screened, inclusion criteria, and screening strategies.

Abbreviations: ACMG, American College of Medical Genetics and Genomics; AVB, atrioventricular block; CKD, chronic kidney disease; ESRD, end-stage renal disease; FD, Fabry disease; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; PMK, pacemaker; SND, sinus node dysfunction.

Population Screened	**Screening Strategies**	**Sex**	**Studies n[ref]**	**Participants, n**	**Pooled Prevalence**								
					Original, % (95%CI)	I^2	*Egger's Test, t-value; p-value*	*ACMG, % (95%CI)*	I^2	*Egger's Test, t-value; p-value*	*Clinvar, % (95%CI)*	I^2	*Egger's Test, t-value; p-value*
HCM/LVH	All	All	24[12–37]	10,080	1.4 (0.9-2.1)	73	0.035; 0.973	1.2 (0.8-1.8)	67	0.024; 0.981	0.9 (0.6-1.5)	64	0.789; 0.438
		M	21 [12,13,13,15–18,20–22,24–31,33–37]	6,565	1.3 (0.8-2.1)	67	1.568; 0.132	1.1 (0.7-1.8)	64	1.541; 0.138	0.9 (0.5-1.5)	55	2.074; 0.051
		F	18 [13–20,22,25,27,28,30,31,33–37]	2,306	1.6 (0.9-2.9)	51	1.021; 0.322	1.4 (0.9-2.3)	20	0.421; 0.679	1.2 (0.7-2.2)	29	0.743; 0.469
	Enzyme and DNA	All	13[12–14,17,20,21,24–26,31,33,34,37]	4,922	1.5 (0.8-2.6)	73	0.702; 0.497	1.2 (0.7-2.2)	70	1.330; 0.211	1.0 (0.5-1.9)	68	1.891; 0.085
		M	15[12,13,17,20–22,24–27,29,31,33,34,37]	4,822	1.3 (0.8-2.2)	69	2.293; 0.039	1.0 (0.6-1.8)	66	2.120; 0.046	0.8 (0.4-1.5)	59	2.786; 0.015
		F	8[14,17,20,25,31,33,34,37]	875	1.3 (0.4-4.2)	65	3.484; 0.014	1.3 (0.4-3.7)	52	2.938; 0.026	1.3 (0.4-3.7)	52	2.938; 0.026
	DNA	All	10[15,16,18,19,23,28,30,32,35,36]	4,033	1.5 (0.7-3.0)	72	0.988; 0.352	1.2 (0.7-2.3)	65	1.731; 0.121	1.0 (0.5-1.8)	49	1.664; 0.134

		M	8[15,16,18,19,28,30,35,36]	1,743	1.5 (0.5-4.2)	67	0.205; 0.844	1.5 (0.5-4.2)	67	0.205; 0.844	1.2 (0.5-3.1)	51	0.285; 0.785
		F	10[15,16,18,19,22,27,28,30,35,36]	1,431	1.6 (0.8-3.0)	31	0.935; 0.377	1.2 (0.7-2.0)	0	1.889; 0.096	0.9 (0.5-1.7)	0	1.931; 0.089
HCM (Unexplained LVH≥13 mm or ≥15 mm)	All	All	18[13–20,23,24,26–28,30,32,35–37]	6,497	1.7 (1.0-2.9)	78	0.514; 0.614	1.5 (0.9-2.5)	73	0.630; 0.538	1.2 (0.7-2.1)	68	0.556; 0.586
		M	15[13,15–20,24,26–28,30,35–37]	3,508	1.6 (0.9-2.9)	67	1.164; 0.265	1.6 (0.9-2.8)	66	1.361; 0.197	1.3 (0.7-2.2)	55	1.238; 0.237
		F	13[14–20,27,28,30,35–37]	1,780	1.7 (0.8-3.8)	61	0.604; 0.558	1.4 (0.8-2.7)	33	0.026; 0.980	1.3 (0.7-2.7)	39	0.171; 0.867
	Enzyme and DNA	All	8[13,14,17,20,24,26,27,37]	2,464	2.0 (0.9-4.4)	82	0.598; 0.571	1.7 (0.8-3.7)	77	0.493; 0.639	1.5 (0.7-3.3)	75	0.406; 0.699
		M	7[13,17,20,24,26,27,37]	1,765	1.8 (0.9-3.7)	71	1.952; 0.108	1.7 (0.8-3.5)	70	1.899; 0.116	1.4 (0.7-2.9)	61	1.679; 0.154
		F	4[14,17,20,37]	527	1.4 (0.2-9.4)	80	2.604; 0.176	1.4 (0.2-7.2)	72	1.739; 0.224	1.4 (0.2-7.2)	72	1.739; 0.224
	DNA	All	10[15,16,18,19,23,28,30,32,35,36]	4,033	1.5 (0.7-3.0)	72	0.988; 0.352	1.4 (0.7-2.6)	65	1.731; 0.122	1.0 (0.5-1.8)	49	1.664; 0.135
		M	8[15,16,18,19,28,30,35,36]	1,743	1.5 (0.5-4.2)	67	0.205; 0.844	1.5 (0.5-4.2)	67	0.205; 0.844	1.1 (0.4-2.9)	51	0.285; 0.785
		F	9[15,16,18,19,27,28,30,35,36]	1,253	1.6 (0.7-3.5)	38	1.008; 0.347	1.1 (0.6-1.9)	0	2.546; 0.038	1.0 (0.5-1.8)	0	2.922; 0.022
ESRD/CKD	All	All	38[38–74]	62,050	0.2 (0.2-0.3)	43	2.807; 0.008	0.3 (0.2-0.4)	60	2.646; 0.012	0.2 (0.1-0.2)	40	2.920; 0.006
		M	35[38–60,62–68,70,71,73,74]	37,359	0.3 (0.2-0.4)	38	2.404; 0.022	0.4 (0.0-0.5)	44	2.119; 0.042	0.2 (0.0-0.3)	42	2.804; 0.008
		F	23[39–44,46,49,51–55,58–60,62–64,66,70,73]	18,691	0.2 (0.1-0.3)	0	1.982; 0.061	0.2 (0.1-0.4)	52	4.191; <0.001	0.1 (0.1-0.2)	0	0.032; 0.975
	Enzyme and DNA	All	35[38–61,64–71,73,74]	59,319	0.2 (0.2-0.3)	46	2.825; 0.008	0.3 (0.2-0.4)	53	2.414; 0.022	0.2 (0.1-0.2)	42	2.968; 0.005

		M	34[38–60,63–68,70,71,73,74]	37,179	0.3 (0.2-0.4)	39	2.493; 0.018	0.4 (0.3-0.5)	46	2.184; 0.036	0.2 (0.2-0.3)	44	2.904; 0.007
		F	22[39–44,46,49,51–55,58–60,63,64,66,70,73]	18,570	0.2 (0.1-0.3)	0	2.160; 0.043	0.2 (0.1-0.4)	50	4.732; <0.001	0.1 (0.1-0.2)	0	0.158; 0.876
Stroke	All	All	25[75–99]	15,295	0.6 (0.4-0.9)	61	2.177; 0.040	0.7 (0.5-1.0)	37	1.167; 0.255	0.3 (0.1-0.5)	41	5.914; <0.001
		M	23[75–81,83–85,87–99]	6,565	0.6 (0.3-1.0)	45	3.842; <0.001	0.8 (0.6-1.2)	14	2.991; 0.007	0.4 (0.2-0.7)	21	5.887; <0.001
		F	21[75–77,79–81,83–85,87–98]	3,528	1.1 (0.7-1.8)	24	3.698; 0.001	1.4 (0.1-1.8)	0	1.970; 0.064	0.7 (0.4-1.2)	0	2.999; 0.007
	Enzyme and DNA	All	3[75,78,87]	715	0.6 (0.1-2.4)	27	0.044; 0.972	0.6 (0.2-1.7)	0	0.456; 0.727	0.5 (0.1-3.1)	36	1.823; 0.319
		M	13[75,77,78,80,81,85,87,92–94,96,97,99]	3,097	0.7 (0.4-1.2)	0	1.344; 0.206	0.9 (0.6-1.3)	0	0.986; 0.345	0.5 (0.2-1.0)	5	3.136; 0.009
	DNA	All	11[76,79,82–84,88–91,95,98]	10,568	0.4 (0.2-0.9)	77	1.679; 0.127	0.6 (0.3-1.0)	51	0.924; 0.380	0.1 (0.1-0.3)	29	4.573; 0.001
		M	10[76,79,83,84,88–91,95,98]	3,468	0.5 (0.2-0.4)	66	3.726; 0.006	0.6 (0.3-1.3)	47	3.691; 0.006	0.3 (0.1-0.8)	39	6.935; <0.001
		F	18[76,77,79–81,83–85,88–91,93–98]	3,345	1.1 (0.6-1.8)	34	3.660; 0.002	1.4 (1.0-1.9)	0	1.868; 0.080	0.6 (0.4-1.1)	7	3.340; 0.004
Newborn	Enzyme and DNA	All	15[100–114]	1,108,793	0.010 (0.001-0.067)	85	3.920; 0.002	0.011 (0.002-0.079)	81	0.387; 0.705	0.005 (0.001-0.025)	41	0.433; 0.672
		M	7[100–102,104,109,110,113]	303,061	0.032 (0.005-0.188)	86	2.355; 0.065	0.023 (0.003-0.143)	72	0.612; 0.567	0.010 (0.002-0.038)	0	0.474; 0.655
		F	6[101,102,104,109,110,113]	245,267	0.001 (0.001-0.010	0	0.515; 0.634	0.001 (0.000-0.156)	55	1.787; 0.148	0.001 (0.000-0.004)	0	1.042; 0.356
Small-Fibre Neuropathy	All	All	3[115–117]	904	0.7 (0.1-5.7)	65	1.356; 0.406	1.0 (0.3-3.4)	38	0.308; 0.810	0.50 (0.01-6.3)	68	3.034; 0.203

AVB/SND Requiring PMK Implantation	All	All	3[118–120]	1033	0.5 (0.2-1.5)	9	2.967; 0.207	0.7 (0.3-1.4)	0	0.769; 0.583	0.20 (0.01-0.80)	0	9.925; 0.064

Figure legends

Figure 1. *PRIMA flow-chart.*

The figure shows the flow of study identification and selection. Using the Embase and Medline databases, 3941 articles were identified. After the removal of articles fulling the exclusion criteria, 1981 were eligible for title and abstract screening. This phase of screening excluded 1814 records, and 167 articles underwent full-text screening. Among them, 110 studies fulfilled the inclusion criteria and were included in the review.

Figure 2. *Pooled prevalence of Fabry disease in high-risk population or using newborn screening.*

The pooled prevalence refers to that calculated using the re-evaluation of variants using the ACMG criteria.

Abbreviations: ACMG, American College of Medical Genetics and Genomics; AVB, atrioventricular block; CKD, chronic kidney disease; ESRD, end-stage renal disease; FD, Fabry disease; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; PMK, pacemaker; SND, sinus node dysfunction.

Figure 3. *Pooled prevalence of Fabry disease after the re-evaluation of variants using the ACMG criteria or the Clinvar database.* With the re-evaluation of the GLA variants, the pooled prevalence varied significantly compared with the original prevalence reported in the studies. Moreover, there was a large discrepancy in the variant assessment between the ACMG criteria and the Clinvar database.

Abbreviations: ACMG, American College of Medical Genetics and Genomics; AVB, atrioventricular block; CKD, chronic kidney disease; ESRD, end-stage renal disease; FD, Fabry disease; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; PMK, pacemaker; SND, sinus node dysfunction.

Figure 4. *Continent-specific sub-analysis.*

Continent-specific pooled prevalence of Fabry disease within each setting (red: Europe; green: Asia; blue: North America; grey: prevalence in these continents not available).

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy.

Figure 5. *Risk of bias.*

Risk of bias in studies assessing the prevalence of Fabry disease in high-risk populations or using newborn screening.

Abbreviations: AVB, atrioventricular block; CKD, chronic kidney disease; ESRD, end-stage renal disease; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; PMK, pacemaker; SND, sinus node dysfunction.

Figure 6. *Clinical interpretation of a GLA variant.*

The identification of a GLA variant should be followed by a multidisciplinary team evaluation to assess its clinical significance. In addition, in patients carrying GLA variants of uncertain significance, the periodic re-evaluation is required.

Abbreviations: α-Gal A, α-galactosidase A; B/LB, benign / likely benign; P/LP, pathogenic / likely pathogenic; VUS, variant of uncertain significance.