Estimating the Prevalence of Late-Onset Fabry Disease in the United States in 2024

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Objective

- The primary aim of this study was to estimate the prevalence of Fabry disease in the US in 2024 by analysing selected *GLA* variants mostly associated with late-onset Fabry disease, projecting their allele frequencies to the US population, and applying penetrance data to determine the number of symptomatic carriers.

Introduction

- Fabry disease is a rare lysosomal storage condition in which sphingolipids build up to harmful levels in various bodily organs, eventually leading to life-threatening complications such as stroke and kidney failure.
- Fabry disease is caused by rare pathogenic alleles in the *GLA* gene on chromosome X and may present as the early (known as "classic") or late-onset form of the disease, depending on the identity of the causal allele and the severity of its effect on the gene product.
- Epidemiological studies have produced widely varying estimates for Fabry disease prevalence, with estimates based on reported clinical cases ranging from 1 in 40,000 to 1 in 170,000 individuals, and much higher recent estimates based on newborn screening ranging from 1 in 1,250 to 1 in 21,973 individuals.
- Table 1 shows the list of genetic variants selected for analysis in this study, taken from a previously published Fabry disease study in the UK Biobank [1].

Methods

- Allele frequencies were obtained from gnomAD v4.1 for all *GLA* variants displayed in Table 1.
- The size and demographic makeup of the US population in 2024 was obtained from the US Census Bureau. Demographic data in the US Census is broken down by self-reported race featuring 5 main groupings, which can be selected alone or in combination. gnomAD v4.1 ancestry groups were mapped to US Census groups. For Census groups encompassing multiple ancestry groups, mapping was done by using previously reported estimates of the ancestral composition of these Census groups.
- Carrier counts by sex and ethnic group were calculated by projecting the summed allele frequencies calculated to the US population using the Hardy-Weinberg equation and considering the X-linked mode of inheritance, assuming each individual can only carry 1 pathogenic variant.

Table 1. Analysed genetic variants

rsID	Variant	Consequence	Phenotype
rs28935197	c.644A>G	p.N215S	Later Onset
rs797044776	c.1087C>T	p.R363C	Later Onset
rs869312163	c.1067G>A	p.R356Q	Later Onset
rs372966991	c.335G>A	p.R112H	Later Onset
rs104894828	c.902G>A	p.R301Q	Both
rs727503950	c.593T>C	p.I198T	Later Onset
rs869312389	c.718_719del	p.K240fs	Classic
rs797044749	c.695T>C	p.I232T	Later Onset

Results

- Carrier frequencies by sex and ethnic group are shown in Figure 1. Ancestry groups who had no pathogenic alleles recorded in gnomAD v4.1 across the 8 included variants have been removed.
- Carrier counts by sex and ethnic and ancestry groups are shown in Table 2.
- Pathogenic alleles are found in the gnomAD v4.1 sample for all variants in the non-Finnish European ancestry group, for 2 variants in the South Asian ancestry group, and for 1 variant in the African/African American and East Asian ancestry groups.
- Results show the highest pathogenic allele carrier frequencies in the European (non-Finnish) ancestry group, followed by the South Asian, East Asian and African/African American ancestry groups.
- Using reported penetrance figures of 100% for males and 70% for females, the carrier and symptomatic populations of Fabry disease in the US in 2024 according to the 8 variants included for analysis in this study are:

24,845 female carriers, of whom 17,392 will develop symptoms

12,024 male carriers, all of whom will develop symptoms

Figure 1. Carrier frequencies by sex and ethnic group

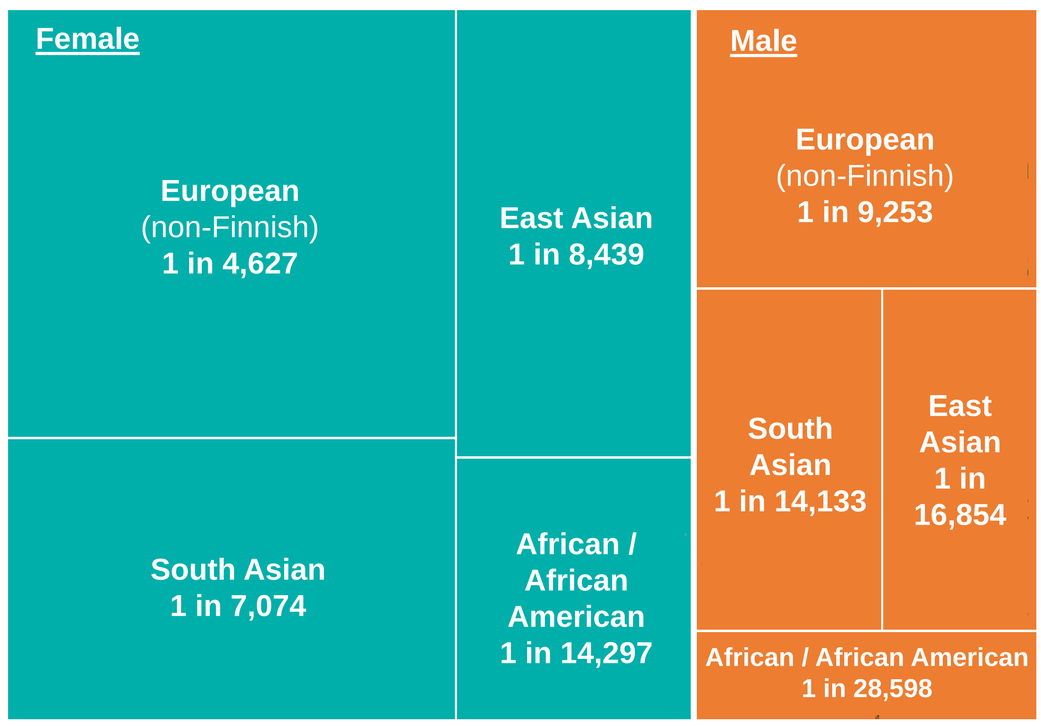

Table 2. Carrier counts by sex and ethnic group

		Women		Men	
US Census Group	**gnomAD Ancestry Group**	**Population**	**Carriers**	**Population**	**Carriers**
Non-Hispanic White	**European (non-Finnish)**	99,323,629	21,468	96,816,526	10,463
	Ashkenazi Jewish	1,549,423	0	1,510,313	0
	Middle Eastern	1,252,647	0	1,221,028	0
	European (Finnish)	242,756	0	236,628	0
	Amish	149,877	0	146,094	0
Non-Hispanic Black or African American	**African / African American**	23,444,050	1,640	21,666,883	758
Non-Hispanic American Indian or Alaska Native	**Admixed American**	1,792,091	0	1,717,738	0
Non-Hispanic Asian	**East Asian**	9,069,665	1,075	8,282,936	491
	South Asian	2,789,207	394	2,547,263	180
Non-Hispanic Hawaiian or Pacific Islander	**East Asian**	480,735	57	484,688	29
Hispanic White	**Admixed American**	29,599,652	0	30,276,587	0
Hispanic Black or African American	**African / African American**	1,918,233	134	1,869,445	65
Hispanic American Indian or Alaska Native	**Admixed American**	1,124,555	0	1,194,295	0
Hispanic Asian	**East Asian**	361,902	43	356,675	21
	South Asian	111,296	16	109,689	8
Hispanic Hawaiian or Pacific Islander	**East Asian**	155,438	18	162,506	10
All	**All**	**173,365,156**	**24,845**	**168,599,294**	**12,024**

Conclusions

- Prevalence figures presented in this study are significantly higher than those based on reported clinical cases and are in line with those presented more recently based on newborn screening studies and in the UK Biobank analysis [1].
- The US National Institute of Health reports Fabry disease prevalence at around 1 in 50,000 males (which would correspond to 1 in 25,000 females).
- Analysing just 8 of the hundreds of potential causal variants within the *GLA* gene, this study suggests Fabry disease may be over 3 times as prevalent as is currently believed.
- This work highlights the vast potential of large genetic databases to analyse rare genetic diseases, which will only increase as these datasets include more data, improving their power and diversity.

Poster presented at the 2024 World Orphan Drug Congress Europe, October 23–25 (Barcelona)
References: [1] Gilchrist et al. J Med Genet 2023, PMID 35977816
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