Incidence and prevalence of newborn, paediatric and adolescent patients with Fabry disease: a targeted literature review

Ian Keyzor,[1] Simon Shohet,[1] Teresa Morris-Spicer,[2] Klara Belzar[2]

[1]Amicus Therapeutics UK Ltd., Marlow, England; [2]Prescript Communications Ltd., Letchworth, England

ICIEM 2021

BACKGROUND

- Fabry disease is an X-linked, multisystemic disorder caused by *GLA* gene variants resulting in α-galactosidase A (α-Gal A) deficiency.[1] Insufficient enzyme activity leads to the lysosomal accumulation of globotriaosylceramide (GL3) and other products[1,2]
  - These products begin to accumulate in kidney cells in utero, and continue to accumulate throughout childhood and adulthood[3]
  - Over time, this accumulation damages cells, leading to progressive and irreversible damage to multi-organ systems, such as the cardiovascular, renal and nervous system.[1,2,4–6]
- Classically affected hemizygous males, with no or very low residual α-Gal A activity, may display all of the characteristic multisystemic signs of the disease.[1]
- The estimated prevalence of classic Fabry disease in newborn males has historically been estimated at 1:40,000–1:60,000.[7]
- However, newborn screening studies in Italy, Taiwan, Japan, Spain and the United States found a prevalence of *GLA* gene and α-Gal A variants in both males and females of 1:2445–1:7800,[8] which is much higher than the historical estimated prevalence of classic Fabry disease[7]
  - For newborn males reported in some of those studies, the prevalence of *GLA* gene and α-Gal A variants was as high as 1:3100–1:7575[8]
  - However, not all *GLA* gene and α-Gal A variants detected by screening lead to symptomatic Fabry disease in all people with those variants.[3]

OBJECTIVE

- To better understand the incidence and prevalence of Fabry disease and associated *GLA* gene and α-Gal A variants in newborn, paediatric and adolescent populations.

METHODS

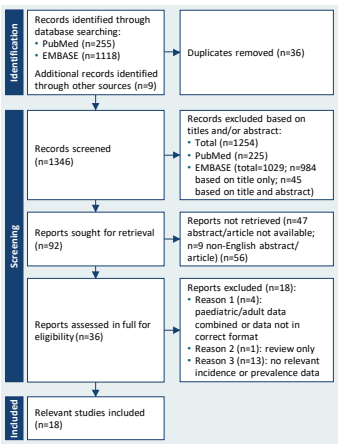
- A literature search was conducted on data published between 1974 and 2020 (last access date: 27 August 2020) using MEDLINE/PubMed and EMBASE databases to identify epidemiology data relevant to paediatric and/or adolescent patients with Fabry disease.
  - **Table 1** details the study eligibility criteria.

Table 1. Eligibility criteria for identification of relevant studies

Population	Newborn, paediatric and/or adolescent patients (aged 0–<18 years) with Fabry disease
Intervention	Any interventions (or none)
Comparators	Any comparators (or none)
Outcomes	Includes Fabry disease incidence and/or prevalence
Study design	Randomised clinical trial, clinical trial, systematic review, and real-world observation studies (case, cohort or cross-sectional)
Other	• Studies undertaken from 1974 to 2020 • Studies published in English language • Conference abstracts were eligible for inclusion

- The search string used the terms: 'Fabry disease', 'paediatric' or 'pediatric', 'adolescent', 'children', 'infant' and/or 'enzyme replacement therapy' in the title and/or abstract only.
- This broad search strategy was performed to identify as many relevant articles as possible, assessed through manual screening by two independent reviewers.
- The search resulted in 1346 possibly relevant articles that underwent manual title/abstract review. Of these, 92 articles were reviewed in full for eligibility, with 18 final articles identified with relevant data (**Figure 1**).

Figure 1. PRISMA flow diagram



RESULTS

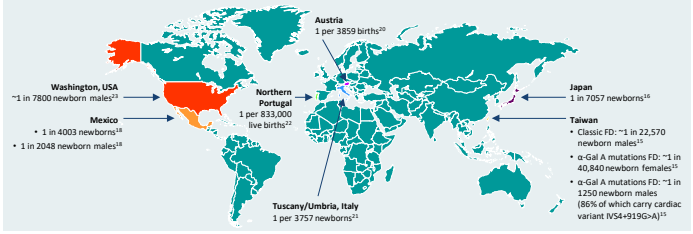
- Results are shown in **Table 2**.
- 18 eligible studies were included:
  - 16 studies were retrieved from EMBASE: 14 newborn screening studies with relevant incidence/prevalence data, and 2 studies that estimated prevalence based on the number of cases that had been diagnosed in a given period and the birth rate over that period
  - 2 additional studies were retrieved from PubMed: 1 newborn screening study and 1 relevant prevalence study in an adolescent/paediatric cohort.
- The prevalence of Fabry disease *GLA* and α-Gal A variants in newborn screening data was found to vary by country (**Figure 2**).
- Overall, our prevalence estimates, based on *GLA* and α-Gal A variants detected in newborns, tended to be higher than historical classic male Fabry disease prevalence estimates.[7]

Table 2. Eligible studies reporting the incidence and/or prevalence of Fabry disease or associated *GLA* gene and α-Gal A variants in newborn, paediatric and/or adolescent populations

Study	Study design	Geographical location	Population	Screening method	Prevalence	Incidence
Gonçalves *et al* 2017[9]	Observational cohort	Portugal	Children with juvenile idiopathic arthritis (N=292)	G	Late-onset FD-associated variant (R118C): 0.34% (1 in 292)	
Burlina *et al* 2018[10]	Newborn screening	Italy (North East)	Newborns (N=44,411)	EA + G		FD: 1 in 8882
Burton *et al* 2017[11]	Newborn screening	USA (Chicago)	Newborns (N=219,793)	EA + G		FD: 1 in 8454
Chien *et al* 2020[12]	Newborn screening	Taiwan	Newborns (N=73,743)	EA + G		FD: 1 in 18,436
Colon *et al* 2017[8]	Newborn screening	Spain (North West)	Newborns (N=14,600)	EA + G	FD: 1 in 7575 newborn males	
Hopkins *et al* 2018[13]	Newborn screening	USA (Missouri)	Newborns (N=~308,000)	EA + G		FD: 1 in 3277
Hult *et al* 2014[14]	Retrospective	Sweden	N=23 cases*	EA		FD: 1 in 90,000 births
Hwu *et al* 2009[15]	Newborn screening	Taiwan	Consecutive newborns (N=171,977)	EA + G	• Classic FD: ~1 in 22,570 newborn males • FD: ~1 in 40,840 newborn females • FD: ~1 in 1250 newborn males (86% of which carry cardiac variant IVS4+919G>A)	
Inoue *et al* 2013[16]	Newborn screening	Japan	Newborns (N=21,170)	EA + G	FD: 1 in 7057 newborns	
Navarrete *et al* 2015[17]	Newborn screening	Mexico	Newborns (N=10,853)	NR	FD: 1 in 2713 newborns	
Navarrete-Martínez *et al* 2017[18]	Newborn screening	Mexico	Newborns (N=20,018)	EA + G	FD: 1 in 4003 newborns; 1 in 2048 newborn males	
Lin *et al* 2009[19]	Newborn screening	Taiwan-Chinese population	Newborns (N=110,027)	EA + G	• FD: 1 in 1368 newborn males • Cardiac variant IVS4+919G>A: ~1 in 1600 newborn males	
Mechtler *et al* 2012[20]	Newborn screening	Austria	Consecutive newborns (N=34,736)	EA + G	Variants characteristic of FD: 1 per 3859 births	
Pasquini *et al* 2017[21]	Newborn screening	Italy (Tuscany/ Umbria)	Newborns (N=52,592)	EA + G	FD: 1 per 3757 newborns	
Pinto *et al* 2004[22]	Retrospective	Portugal (Northern)	N=1 case*	EA + G	FD: ~1 per 833,000 live births	
Scott *et al* 2013[23]	Newborn screening	USA (Washington)	Newborn males (N=~54,800)	EA + G	FD: 1 in 7800 newborn males	
Spada *et al* 2006[24]	Newborn screening	Italy (North West)	Consecutive newborn males (N=37,104)	EA + G	• Late-onset FD: ~1 in 3100 newborn males • Classic FD: ~1 in 37,000 newborn males	
Van der Tol *et al* 2014[25]	Systematic review	Various	Newborns (N=397,271)	Mostly EA	• Pooled *GLA* variants: 1 in 2597 newborns†	

*Extrapolated using the number of live births in the ascertainment period; †calculated but not reported in paper *per se*. α-Gal A, α-galactosidase A; EA, α-Gal A enzyme activity; FD, Fabry disease; G, genetic; NR, not reported.

Figure 2. Prevalence of Fabry disease-associated *GLA* gene and α-Gal A variants identified by newborn screening



- In Taiwanese and Chinese-Taiwanese populations, the incidence of a Fabry disease cardiac variant (IVS4+919G>A) was ~1 in 1460 to ~1 in 1600 newborn males.[15,19] However, further studies of the IVS4 later-onset phenotype are needed to understand its natural history.
- Classic male Fabry disease prevalence in Italy was consistent with previous reports of 1 per 22,000 to 1 per 40,000 in the general male population,[26] reported as 1 per 22,570 newborn males and 1 per 37,000 newborn males in Taiwan and Italy, respectively.[15,24]
- Lin and colleagues[19] acknowledged that detecting hotspot mutations is preferred to lymphocyte enzyme activity to screen females because enzyme activity fails to predict disease severity in a particular organ.[19]
- In our literature search, a single newborn screening study reported the prevalence of Fabry disease-associated *GLA* variants among newborn females specifically, showing a significantly lower incidence than male newborns.[15]

LIMITATIONS

- This review was limited to studies published in English language. It is possible that relevant studies published in other languages were not retrieved.
- Unlike a systematic literature review, the present literature search was not subjected to a critical appraisal of the risk of bias. However, a targeted review approach can still be considered a rigorous and transparent method to synthesise evidence and provide insight into the incidence and prevalence of Fabry disease in newborn, paediatric and adolescent populations.

DISCUSSION

- Overall, Fabry disease epidemiology estimates are extremely heterogeneous between different countries and, while data are emerging for newborns based on gene and enzyme variants, epidemiological studies are particularly lacking in paediatric and adolescent populations.
- There is also a risk that estimates of *GLA* variant prevalence in females may be being underestimated in screening programmes relying on α-Gal A enzyme assays.[27]

Acknowledgements

- This study was supported by Amicus Therapeutics, Inc.
- IK and SS are employees of Amicus Therapeutics UK Ltd.
- TMS and KB are employees of Prescript Communications Ltd.
- Third-party medical writing assistance was provided by Anna Campbell, PhD, CMPP, of Cence, supported by Amicus Therapeutics, Inc.

Presented at the 14th International Congress of Inborn Errors of Metabolism (ICIEM) Hybrid Congress; Sydney, Australia and virtually; 21–23 November 2021.

CONCLUSIONS

- Our findings support the importance of continued and wider implementation of newborn screening studies to better understand the epidemiology of Fabry disease-associated *GLA* variants
  - Care should be taken not to directly extrapolate the incidence and prevalence of *GLA* gene and α-Gal A variants to the clinical presentation of Fabry disease
  - Newborn screening results should therefore complement post-screening follow-up to ensure early symptoms are detected, enabling timely diagnosis and therapeutic intervention in the proportion who later present with symptomatic Fabry disease.
- Screening criteria for α-Gal A may need to be refined to ensure that females are not missed in newborn screening programmes.

References

1. Germain DP. *Orphanet J Rare Dis* 2010;5:30.
2. El-Abassi R *et al. J Neurol Sci* 2014;344:5–19.
3. Tondel C *et al. Nephron* 2015;129:16–21.
4. Eng CM *et al. J Inherit Metab Dis* 2007;30:184–92.
5. Arends M *et al. PLoS One* 2017;12:e0182379.
6. Bichet DG *et al. Genet Med* 2021;23:192–201.
7. Paulo Oliveira J & Ferreira S. *Appl Clin Genet* 2019;12:35–50.
8. Colon C *et al. Eur J Pediatr* 2017;176:1075–81.
9. Gonçalves MJ *et al. Front Med (Lausanne)* 2017;4:12.
10. Burlina AB *et al. J Inherit Metab Dis* 2018;41:209–19.
11. Burton BK *et al. J Pediatr* 2017;190:130–5.
12. Chien Y-H *et al. Orphanet J Rare Dis* 2020;15:38.
13. Hopkins PV *et al. JAMA Pediatr* 2018;172:696–7.
14. Hult M *et al. Acta Pediatr* 2014;103:1258–63.
15. Hwu W-L *et al. Hum Mutat* 2009;30:1397–405.
16. Inoue T *et al. J Hum Genet* 2013;58:548–52.
17. Navarrete JI *Blood* 2015;126:5581.
18. Navarrete-Martínez JI *et al. Mol Genet Metab* 2017;121:16–21.
19. Lin H-Y *et al Circ Cardiovasc Genet* 2009;2:450–6.
20. Mechtler TP *et al. Lancet* 2012; 379:335–41.
21. Pasquini E *et al. J Inborn Errors Metab Screen* 2017;5:doi:10.1177/2326409817722292 (Abstract 124).
22. Pinto R *et al. Eur J Hum Genet* 2004;12:87–92.
23. Scott CR *et al. J Paediatr* 2013;163:498–503.
24. Spada M *et al. Am J Hum Genet* 2006;79:31–40.
25. van der Tol L *et al. J Med Genet* 2014;51:1–9.
26. Bokhari SRA *et al.* Fabry Disease [Updated Jul 2021]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK435996/
27. Lu Y-H *et al. J Hum Genet* 2018;63:1–8.