Updating the spectrum of *ARSB* mutations suspected of causing Maroteaux-Lamy (MPS VI) to enable genetic prevalence estimation and improve diagnostics

P319

Alice Piller[1], Sara L. Pulit[1], Emanuela Izzo[1], Sherif Khattab[1], Rob Power[1], Rachel Moore[2], Melissa Spear[2], Melisa Chuong[2], Vincent Plagnol[2], Christian Beetz[3], Mandy Radefeldt[3]

[1]BioMarin Pharmaceutical Inc., San Rafael, CA, USA; [2]Genomics Ltd, London, UK; 3CENTOGENE GmbH, Rostock, Germany

Background

Mucopolysaccharidosis VI (MPS VI) is a rare lysosomal storage disorder[1]

MPS VI
- Also known as Maroteaux-Lamy syndrome, MPS VI is caused by mutations in *ARSB*[1,2]
- OMIM 253200

Heterogeneous onset and severity[1,2]
- Symptom onset can be as early as the first year of life or as late as the second decade[2,3]
- Common signs and symptoms include short stature, skeletal abnormalities, cardiac and respiratory dysfunction, and corneal clouding[1]

Life expectancy from 10 to 30 years[2]
- **Early diagnosis allows access to the most appropriate multidisciplinary care and enzyme replacement therapy, and potentially improves survival[1,4]**

Prevalence varies widely between countries

- A full understanding of the prevalence of MPS VI is limited by its complex presenting symptoms,[1] a lack of newborn screening programs, and the high number of mutations that cause MPS VI[5]
- **Our aim was to improve understanding of regional prevalence and causative *ARSB* variants to support diagnosis**

Methods

- To undertake prevalence modeling and variant of unknown significance (VUS) reclassification, we collated disease mutations from a variety of sources in **(Figure 1)**

Figure 1. Variant curation, model prevalence and reclassification workflow. *No longer available. MAF, minor allele frequency; P/LP, pathogenic / likely pathogenic.c.

1. Curate *ARSB* variants

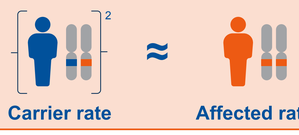
Data source (all public domain)
PubMed
ClinVar
Leiden Open Variation Database (LOVD)
The MPS VI database*

Extract P/LP variants

Extract VUSs

2. Model prevalence

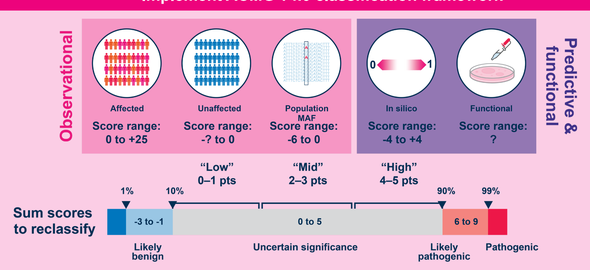
- Commercial collaborators added P/LP variants
  - Human Gene Mutation Database (HGMD) "damaging" variants
  - Putative loss-of-function variants (annotated in biobanks)
  - Internal P/LP variants (based on genetic testing information)
- Estimated genetic prevalence in 629,151 unaffected individuals from 68 countries



3. Reclassify VUSs

Collect additional patient data
ClinVar (updated weekly), sponsored and commercially available testing data

Implement ACMG v4.0 classification framework

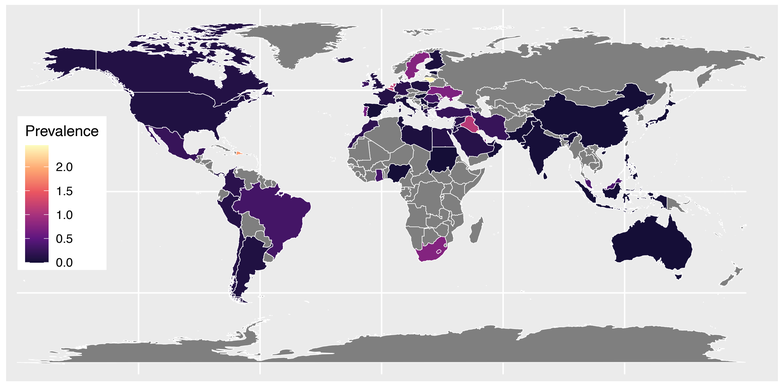


Results

Mean genetic birth prevalence of MPS VI across 68 countries was estimated at 0.09 per 100,000

- Prevalence was highest in Kuwait (2.45 per 100,000 [95% CI: 0.72–8.25]) and Lithuania (2.40 per 100,000 [95% CI: 0.36–15.72]) **(Figure 2)**

Figure 2. Genetic prevalence estimates of MPS VI



Our model underestimated prevalence in most countries for which epidemiological data were available

- In nine countries with available literature, our modeled prevalences correlated poorly (Lin's r^2 = -0.01)
- In Turkey, Saudi Arabia, and the United Arab Emirates, published prevalence is >2.5 per 100,000[5–7]
- This may be driven by consanguinity, which was not captured in our model
- **Remodeling without data from Turkey, Saudi Arabia, or the United Arab Emirates increased correlation (Lin's r^2 = 0.53)**

We identified geographically restricted (founder) mutations

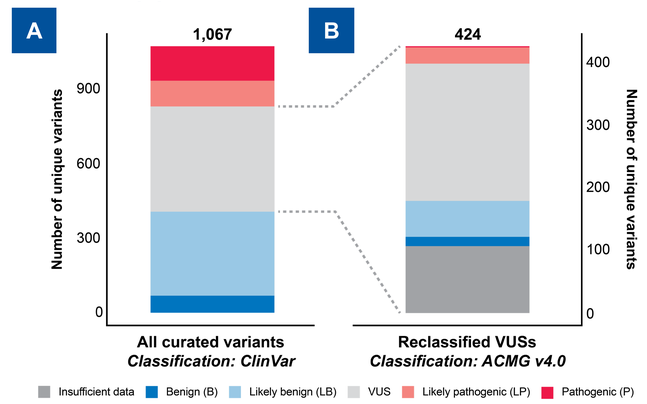
- In Mexico, NM_000046.5(ARSB): c.904_905delGGinsCC was reported in 16 carriers
- In global biobank (n=629,041) and gnomAD (n=806,999) data from individuals outside of Mexico, there were only four individuals heterozygous for NM_000046.5, indicating a likely recent founder event

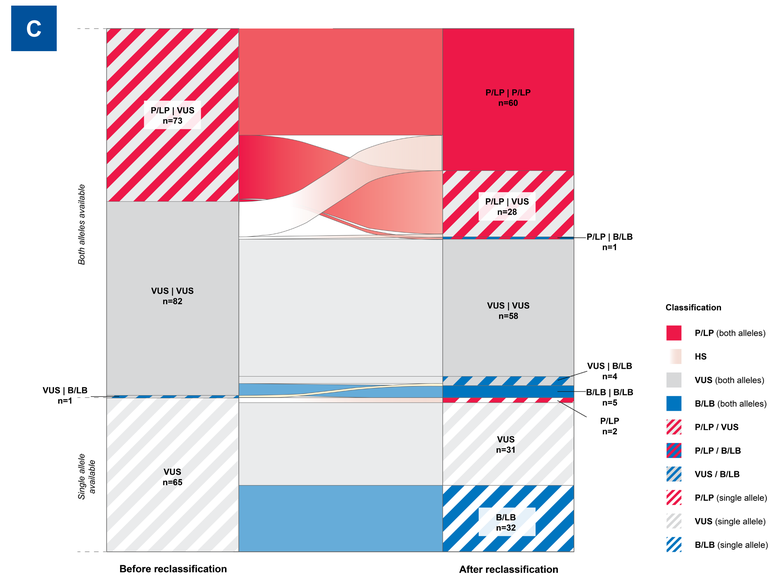
Reclassification of VUSs increased the number of patients with two P/LP alleles by 13.1%

- After curation of all data, 1,067 variants in *ARSB* were identified including 424 VUSs
- Twenty-eight (6.6%) of 424 VUSs were reclassified as P/LP using the ACMG framework **(Figure 3)**
- The number of patients with at least one VUS was reduced by 45.5%
- This increased global prevalence by one additional patient (0.000002 per 100,000)

To view a copy of this poster, scan this QR code.

Figure 3. A) Classification distribution of curated variants, based on ClinVar annotations. We defined VUSs as those variants listed as VUS or Conflicting in ClinVar, variants without a classification, or variants not found in ClinVar (novel variants). **(B) Distribution of VUS classifications, after applying the ACMG v4.0 classification pipeline.** Pathogenic (P) variants score ≥10 points, LP (likely pathogenic) variants score [6-10) points, VUS (variant of uncertain significance) score (-1,6) points, LB (likely benign) variants score (-4,-1] points, B (benign variants) score ≤ -4 points, and a small portion of variants (in grey) have insufficient data to be reclassified. **(C) Genotype classification changes of patients, after applying the ACMG v4.0 pipeline.**





Conclusions

- **Estimated mean genetic birth prevalence of MPS VI across 68 countries is low (0.09 per 100,000)**
- **Generating additional data through *in vitro* assays is a key route to reclassify further VUSs**
- **Aggregating *in vitro* data with biobank data could support continued elucidation of prevalence and improve patient identification**

References

1. Akyol MU, et al. *Orphanet J Rare Dis* 2019;14(1):118. **2.** Giugliani R, et al. *Pediatrics 2007*; 120(2):405–418. **3.** Thümler A, et al. *J Inherit Metab Dis* 2012;35(6):1071–1079. **4.** Burton BK, et al. *Mol Genet* Metab 2025; 145(3):109135. **5.** Çelik B, et al. *Diagnostics (Basel)* 2021;11(2):273. **6.** Wahhab SBA, et al. *Ann Med Surg (Lond)* 2023;85(10): 4835–4843. **7.** Al-Jasmi FA, et al. *JIMD Rep* 2013;10:1–9.

Acknowledgements

Medical writing support was provided by Emma Conran, Porterhouse Medical, UK, and funded by BioMarin Pharmaceutical Inc. according to GPP Guidelines.

Financial disclosures

AP, SLP, EI, SK, and RP are employees of BioMarin. RM, MS, MC, and VP are employees of Genomics PLC. CB and MR are employees of CENTOGENE GmbH.

Presented at the ACMG Annual Clinical Genetics Meeting; March 10–14, 2026; Baltimore, MD, USA