Updating the spectrum of *GALNS* mutations suspected of causing Morquio A syndrome (MPS IVA) to enable genetic prevalence estimation and improve diagnosis

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Background

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

MPS IVA
- MPS IVA, also known as Morquio A syndrome (OMIM 253000), is caused by mutations in the *GALNS* gene[2]

Heterogeneous onset[3,4]
- Symptom onset occurs within the first year of life for the classical phenotype, while symptoms may not occur until the teen years or adulthood for the non-classical phenotype[3,4]
- Common symptoms include skeletal abnormalities, pulmonary complications, and corneal clouding[4]

Need for timely diagnosis[2,4]
- Given the progressive nature of the disease, early diagnosis is needed to facilitate timely access to treatment and improve clinical outcomes[2,4]

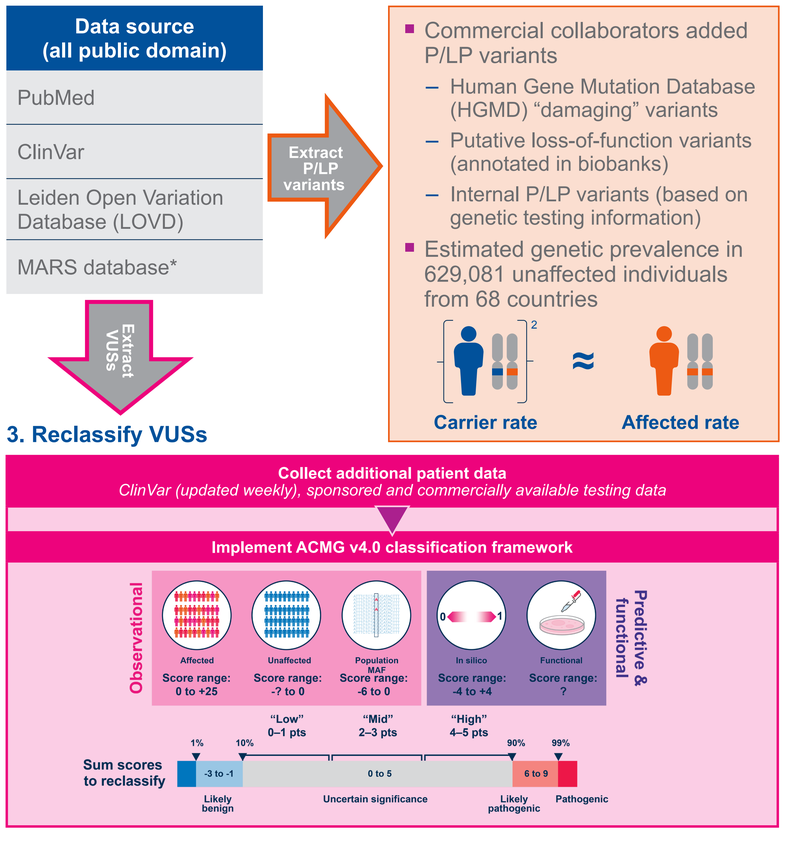
Prevalence varies widely between countries[5]

- Currently, understanding of MPS IVA prevalence is limited by several factors, including disease rarity, lack of newborn screening programs, and complex, heterogeneous presenting symptoms[5]
- **Our aim was to improve understanding of the global prevalence of MPS IVA and causative *GALNS* variants to support timely diagnosis and treatment**

Methods

- To model prevalence, we collated pathogenic and likely pathogenic (P/LP) variants reported in *GALNS* **(Figure 1)**

Figure 1. Variant curation, model prevalence and reclassification workflow. *Internal BioMarin Morquio A Registry Study database. MAF, minor allele frequency; VUS, variant of unknown significance.

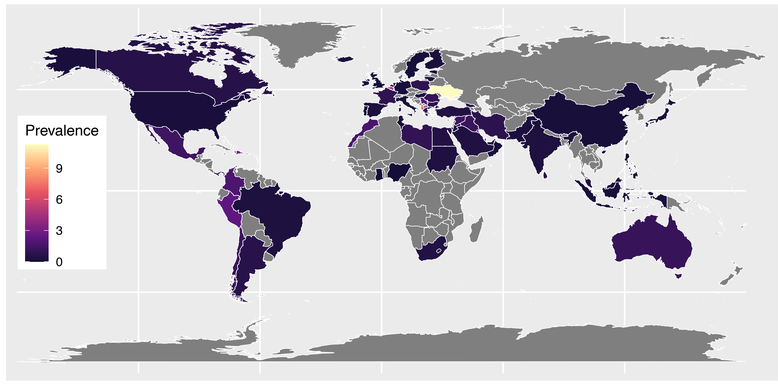


Results

Mean genetic birth prevalence of MPS IVA across 68 countries was estimated at 0.4 per 100,000

- Prevalence per 100,000 was highest in Ukraine (11.25 [95% CI:5.39–30.38]) and lowest in Portugal (0.011 [95% CI: 0.00–0.18]) **(Figure 2)**
- This estimation was based on the identification of 437 P/LP variants

Figure 2. Global estimates of prevalence of MPS IVA



Our model's estimates were concordant with the literature, with some notable outliers

- In 15 countries, modeled prevalences were concordant with literature estimates (Lin's r^2 = 0.71)
- Some notable outliers were observed such as the UAE where published estimated prevalence is 1.41:6 but our model estimated a prevalence of 0.18 (95% CI: 0.11–0.35)
- **This discrepancy may be driven by consanguinity, which was not captured in our model, and sample ascertainment differences between published epidemiology and genetic biobanks**

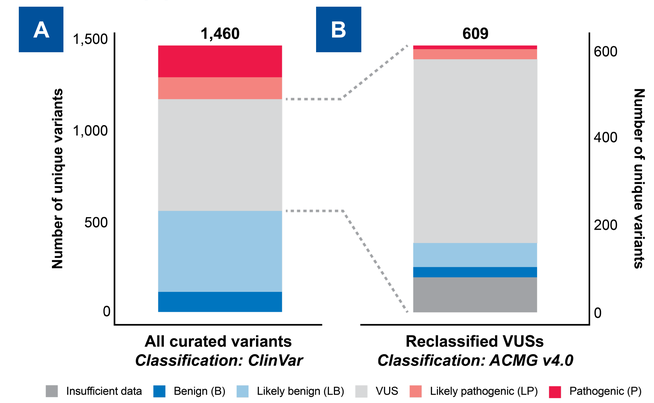
Prevalence can vary markedly even in specific geographic regions

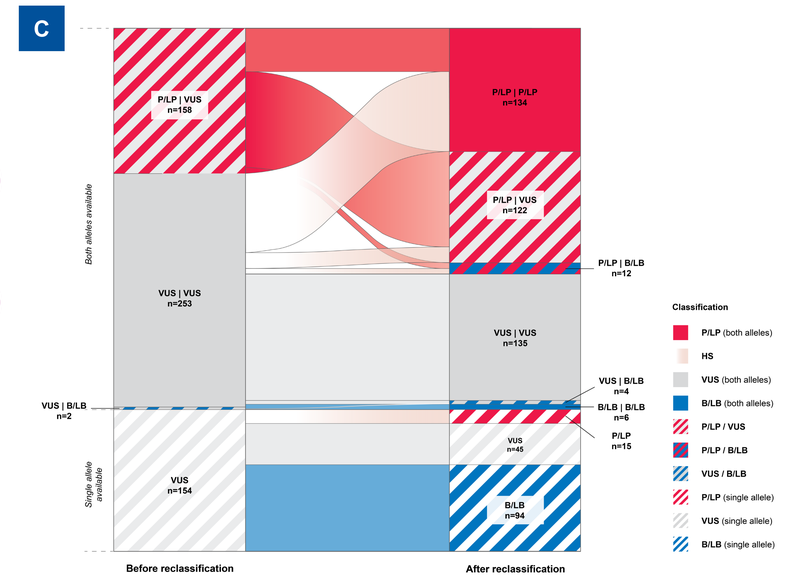
- In the Middle East, prevalence per 100,000 varied from 3.73 (95% CI: 1.53–9.06) in Bahrain to 0.06 (95% CI: 0.01–0.30) in Lebanon

Reclassification of VUSs increased the number of patients with two P/LP alleles by 25.0%

- 31 (5.1%) of 609 VUSs were reclassified as P/LP variants **(Figure 3)**
- Reclassification of VUSs increased the number of patients with two P/LP-classified variants by 25.0%
- The number of patients with at least one VUS was reduced by 46.0%
- This increased global prevalence by 11 additional patients (0.0001 per 100,000)

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

- **The estimated mean genetic birth prevalence of MPS IVA across 68 countries is 0.4 per 100,000**
- **Further functional screening, to generate additional data to help potentially reclassify more VUSs as P/LP variants, is crucial to further develop our understanding of disease prevalence and to improve disease diagnosis and timely access to treatment**

References

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