Updating the spectrum of *TPP1* mutations suspected of causing CLN2 disease (Batten disease) to enable earlier genetic testing and inform prevalence

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Background

Neuronal ceroid lipofuscinosis type 2 (CLN2 disease) is caused by mutations in *TPP1*[1]

CLN2 disease	▪ Rare, autosomal recessive, rapidly progressing lysosomal storage disorder ▪ OMIM 204500
Typical onset at 2–4 years	▪ Early presenting symptoms often include new-onset unprovoked seizures and/or language delay ▪ With disease progression, additional symptoms may appear, including loss of vision, motor function and/or cognitive function
Life expectancy from 6 years to early teens	▪ **Early identification, ideally presymptomatic, is crucial for effective management and treatment** ▪ **Diagnosis is based on enzyme activity and/or *TPP1* testing after symptom onset**

Prevalence of CLN2 varies between countries[1]

- Reported cases indicate a prevalence of 1 in 100,000 individuals
- Prevalence estimates vary greatly and are regionally limited
- The large number of variants of uncertain significance (VUSs) hinders genetic testing and genetic prevalence estimates
- **Our aim was to improve understanding of regional prevalence and pathogenic *TPP1* variants to support timely diagnosis**

Methods

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

Figure 1. Variant curation, model prevalence and reclassification workflow. MAF, minor allele frequency; P/LP, pathogenic / likely pathogenic.

1. Curate *TPP1* variants

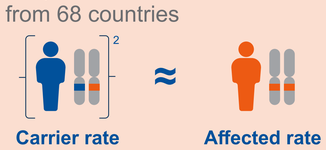
Data source (all public domain)
PubMed
ClinVar
Leiden Open Variation Database (LOVD)
The UCL CLN2 database

Extract P/LP variants

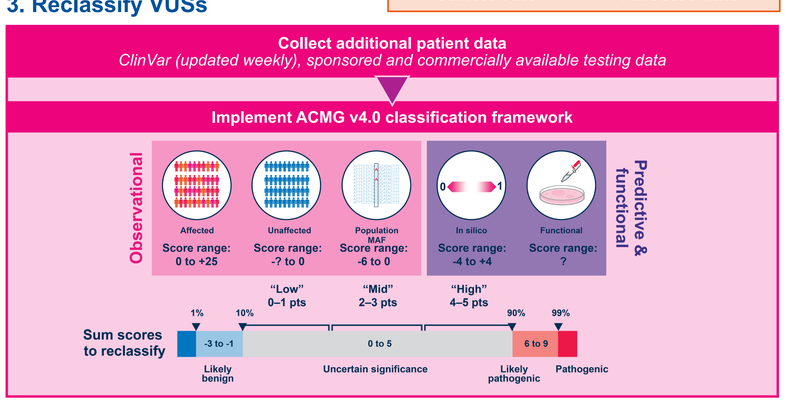
Extract VUSs

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 629,107 unaffected individuals from 68 countries



3. Reclassify VUSs

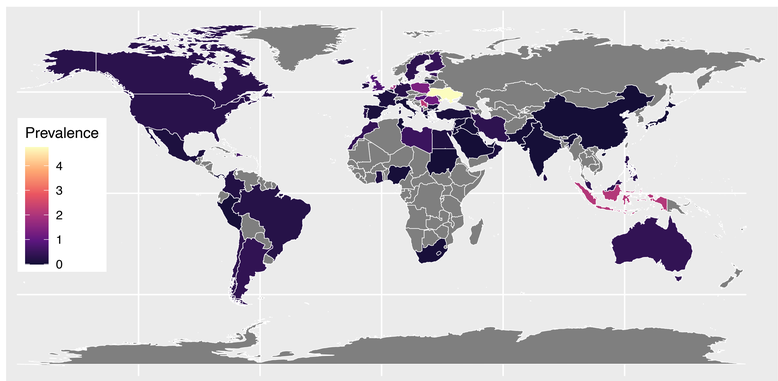


Results

Mean genetic prevalence of CLN2 across 68 countries was estimated at 0.23 per 100,000

- Broad variation across countries, with highest prevalence in Ukraine (4.75 per 100,000 [95% CI: 1.86–15.76]) **(Figure 2)**
  - Elevated prevalence was also seen across eastern Europe (Serbia, Poland, Romania, and Hungary)
  - Two main mutations drive this elevated prevalence:
    - Splice mutation NM_000391.4(TPP1):c.5091G>C
    - Stop gain mutation NM_000391.4(TPP1):c.622C>T (p.Arg208*)
- Additional high-prevalence countries include:
  - Indonesia (2.09 per 100,000)
  - Netherlands (1.78 per 100,000)
  - United Kingdom (0.81 per 100,000)

Figure 2. Genetic prevalence estimates of CLN2 disease



Overall, our model was concordant with published data

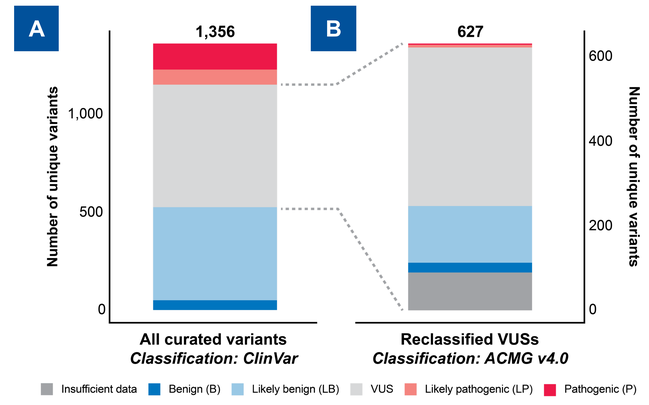
- Initial estimates were not concordant with published prevalences across eight countries (Lin's r^2 = 0.05)
- High prevalence in Newfoundland, Canada (approximately 9 per 100,000) is the likely cause of low concordance[2]
- **With the removal of Canada, concordance improved (Lin's r^2 = 0.65)**

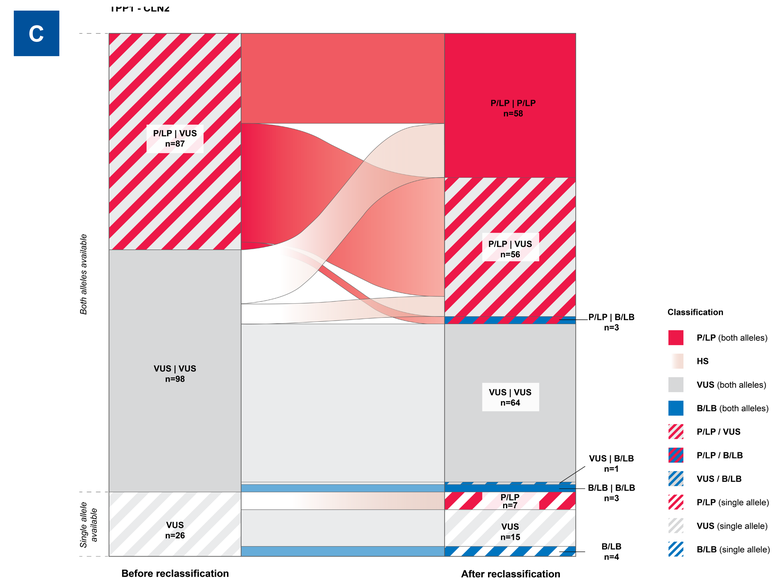
- Our model underestimated prevalence in six of eight countries
  - The model was conservative, therefore lower prevalence estimates compared with the literature were expected

Reclassification of VUSs increased the number of patients with two P/LP alleles by 14.4%

- After curation of all data, 1,356 variants were identified in *TPP1* and 627 VUSs were identified
- Nine (1.4%) of 627 VUSs were reclassified as P/LP using the ACMG framework **(Figure 3)**
- The number of patients with at least one VUS was reduced by 35.5%
- Genetic prevalence was increased by ~3–4 additional patients worldwide (0.00004 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

- **Estimated genetic birth prevalence of CLN2 across 68 countries is low (0.23 per 100,000), but varies widely between countries**
- **Early and broad genetic testing, for example with epilepsy gene panels, is the fastest route to timely CLN2 diagnosis, and resolving VUSs is essential to enable this**
- **Translational *TPP1* assays are being explored to classify further VUSs and mutations not yet observed in patients**

References

1. Mole SE, et al. *Orphanet J Rare Dis* 2021;16(1):185. **2.** Moore SJ, et al. *Clin Genet 2008*;74(3): 213–222.

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