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Title: Population-Based Incidence Estimates of Classical Homocystinuria Using the Genome Aggregation Database (gnomAD)

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ABSTRACT (298 words, excluding spaces/600 max)

Introduction: Classical homocystinuria (HCU) is a rare inborn error of sulfur amino acid metabolism. Literature suggests that its prevalence (~0.5:100,000 to 0.3:100,000 worldwide) may be underestimated. We used the Genome Aggregation Database (gnomAD) (v2.1.1) to estimate the incidence of HCU based on population allele frequencies (AFs) across 6 ancestries.

Methods: gnomAD was accessed on Jan 4, 2022 to retrieve variants' AFs. ClinVar and other databases were queried to obtain pathogenicity information. HCU incidence estimates were calculated based on the Hardy-Weinberg principle, assuming full penetrance. REVEL was used to infer additional pathogenic variants. Manual curation was performed to reduce possible false positives/negatives from the final model. Incidence was calculated as the squared sum of the pathogenic alleles (q), and q was calculated from the carrier frequency (2pq) with p=1.

Results: We identified 1,294 total variants (358 were missense). One hundred sixteen variants were used to calculate incidence estimates: 55 designated pathogenic in ClinVar; twenty-three considered pathogenic based on sequence consequence after filtering and manual curation; and 38 missense variants predicted to be pathogenic based on REVEL and ClinVar, literature, or functional evidence. Highest HCU estimate was in Non-Finnish European with 1.54 per 100,000 and pooled AF 0.00392. Incidence in Latino/Admixed American was 0.60 per 100,000 with pooled AF 0.00245, African/African American was 0.54 per 100,000 with pooled AF 0.00233, and Finnish European was 0.19 per 100,000 with pooled AF 0.0014. Lowest estimates were in South Asian with 0.15 per 100,000 and pooled AF 0.00124 and in East Asian with 0.02 per 100,000 and pooled AF 0.0005.

Conclusions: This genomic population-based approach suggests that the incidence of HCU may be higher than historical estimates in some populations. Estimated risk of pathogenic variants differed

based on ancestry, however, the analysis was limited by availability of ClinVar submissions for all ancestry types and characterization of variants.

DISCLOSURES:

TP: Employee and stockholder, Travere Therapeutics, Inc.

HJB: None

FPR: Shareholder, Ranomics, Inc. Scientific advisory board member and shareholder, SeqWell, Constantiam Biosciences, Inc and BioSymetrics, Inc.

IVDS: None

SR: Employee, Travere Therapeutics, Inc.