SSIEM 2022 Annual Symposium, 30 August – 2 September, Freiburg, Germany
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gnomAD Abstract

Population-based incidence estimates of classical homocystinuria using the Genome Aggregation Database (gnomAD)

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ABSTRACT (1,999 characters including spaces/2,000 max)

Background: 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) as an orthogonal approach to estimate the incidence of HCU based on population allele frequencies (AFs) across 6 ancestries.

Methods: gnomAD was accessed on 04JAN2022 to retrieve variants' AFs. Additional databases were queried to cross-reference variants' pathogenicity information. HCU incidence estimates were calculated based on the Hardy-Weinberg principle assuming full penetrance. REVEL was used to predict missense pathogenicity. Manual curation was performed to reduce possible false positives/negatives from the final model. Incidence was calculated as the squared sum of the carrier AF of the mutant alleles (q) with p=1.

Results: We identified 1294 total variants (358 were missense). 116 variants were used to calculate incidence estimates: 55 designated pathogenic in ClinVar; 23 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 1.54/100,000 and pooled AF 0.00392. Incidence in Latino Admixed American was 0.60/100,000 with pooled AF 0.00245, in African/African American was 0.54/100,000 with pooled AF 0.00233, and in Finnish European was 0.19/100,000 with pooled AF 0.0014. Lowest estimates were in South Asian with 0.15/100,000 and pooled AF 0.00124 and in East Asian with 0.02/100,000 and pooled AF 0.0005.

Discussion: 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.

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TP: Employee, Travere Therapeutics.
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IVDS: none
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Proposed key words: Homocystinuria, incidence, allele frequencies, gnomAD

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