Estimating the global burden of Inborn Errors of Metabolism

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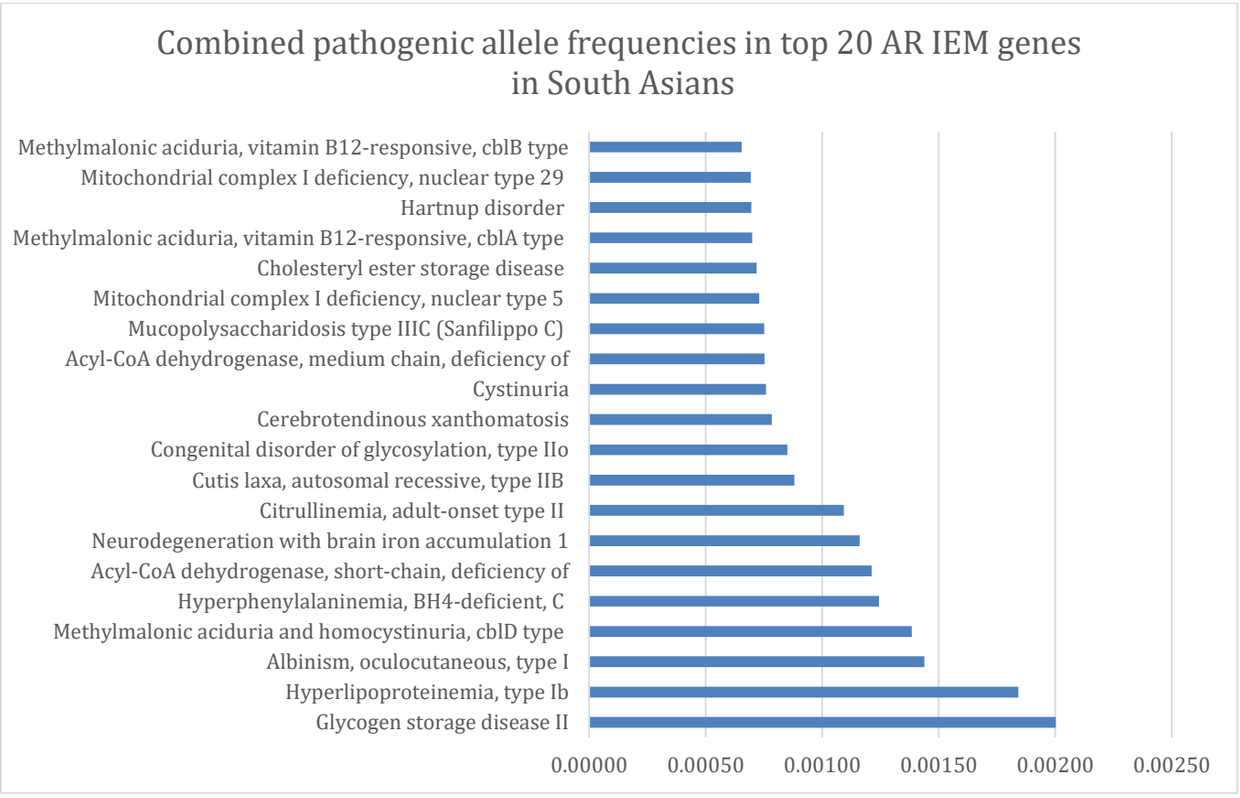
Background & Objectives: For the developing nations it is always a challenge to allocate resources for rare diseases due to high prevalence of infectious and emerging lifestyle diseases. Estimation of the rare disease burden therefore would provide critical data for deciding allocation of scarce resources. Here we wanted to estimate gene specific combined minor allele frequency of pathogenic variants for different ethnicities from the gnomAD dataset for 235 genes associated with Inborn Errors of Metabolism (IEM) phenotypes in OMIM.

Method (s) and Results: We retrieved population specific carrier frequencies for 1,72,829 variants in 235 AR IEM genes from gnomAD v2.1 dataset. Out of these 7200 variants were probable loss of function (plof) and 60345 variants were missense / inframe deletion. We classified these variants based on plof status, ClinVar annotation, allele frequency of <0.005 and InterVar annotation. We therefore narrowed down to 7,256 pathogenic variants in 217 AR IEM genes.



Conclusions (Significance and Impact of the Study): We estimated Hyperlipoproteinemia, type Ib to be the second commonest IEM (carrier frequency 4/1000) in South Asians and Citrullinemia, adult-onset type II to be the commonest IEM (carrier frequency 31/1000) in East Asians. Overall for South Asians we estimated 84 out of 1000 are carriers for at least one AR IEM disease and at least 30 out of a million conceptions have an AR IEM. These are much lower than the estimates for East Asians (275/434) and African Americans (260/228). Whether these observations have some biological reasons or due to inadequate capture of rare alleles needs to be elucidated. We now have a starting point for designing a newborn screening study to validate our findings.

Conflict of interest disclosure: The authors declare no potential conflicts of interest, whether scientific, financial and personal.

Keywords: Inborn Error of Metabolism, gnomAD, ClinVar, Birth prevalence, Carrier frequency