An estimation of global genetic prevalence of PLA2G6-associated neurodegeneration

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Introduction

PLA2G6-associated neurodegeneration (PLAN) comprises three diseases with overlapping features: infantile neuroaxonal dystrophy (INAD), atypical neuroaxonal dystrophy (atypical NAD), and PLA2G6-related dystonia-parkinsonism. INAD is an early-onset disease characterized by progressive loss of vision, muscular control, and mental skills. The prevalence of PLA2G6-associated diseases has not been previously calculated.

Methods

To provide the most accurate prevalence estimate, we utilized two independent approaches: literature-based approach which gathered variants through Mastermind Genomic Search Engine (Genomenon, Inc) and database-based approach which included collecting variants from ClinVar, Human Gene Mutation Database (HGMD) and high confidence predicted loss-of-function (pLoF) from gnomAD (Rare Genomes Project Genetic Prevalence Estimator; GeniE) (1). Genetic prevalence of PLAN was calculated based on allele frequencies from gnomAD, assuming Hardy–Weinberg equilibrium. As shown in Figure 1, the curation process involved manually curating selected variants according to the standards set by the American College of Medical Genetics and Association of Molecular Pathologists (ACMG/AMP) (2). Genetic and disease prevalences were calculated separately for pathogenic, VUS, and conflicting variants. The overall (or population-specific) allele frequency was summed across all selected variants and then used within the Hardy–Weinberg equation to calculate the carrier frequency (2pq) and the frequency of a disease-causing genotype (q2) (3).

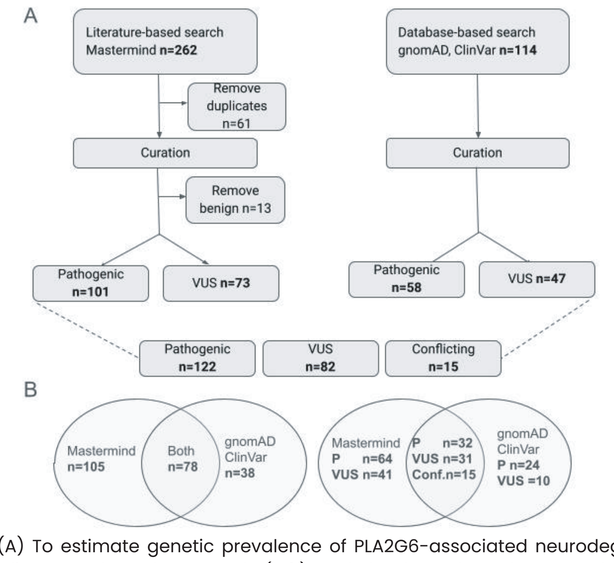

Figure 1. (A) To estimate genetic prevalence of PLA2G6-associated neurodegeneration, we have utilized a literature-based approach (left) and database-based approach (right). In total, 122 pathogenic, 82 VUS, and 15 conflicting variants were curated and classified. (B) Pathogenic and VUS variants recorded by two independent approaches.

Results

Using database-based and literature-based approaches, our analysis found 122 pathogenic, 82 VUS, and 15 variants with conflicting interpretations (pathogenic vs VUS) between two approaches. The most common PLA2G6 pathogenic variant, p.Tyr790*, accounted for 11.4% of all non-zero allele frequency pathogenic variants; it is a truncating variant that has been identified by both ClinVar and Mastermind databases. The second most common variant, p.Val421AlafsTer26, with 8% allelic frequency, is a frameshift mutation leading to a truncated protein, which was an unpublished variant found in ClinVar only. The third most common variant, p.Arg635*, with 6% allele frequency, is also a truncated variant found in both literature and ClinVar. The fourth and fifth most common variants, R635Q and R600Q, are both found at 4.9% allele frequency and are missense variants located in Patatin-like phospholipase domain.

Our analysis also showed a positive association of the number of articles published with the allele frequency of the PLA2G6 pathogenic variant. Allele frequency was available for 60 pathogenic variants in the gnomAD database. The carrier frequency for PLA2G6 variants was estimated to be 1 in 700 to 1 in 256 in the general population which corresponds to a genetic prevalence of 1 in 1,323,137 to 1 in 221,753 pregnancies. The highest estimated genetic prevalence is found in the African population and East Asian populations.

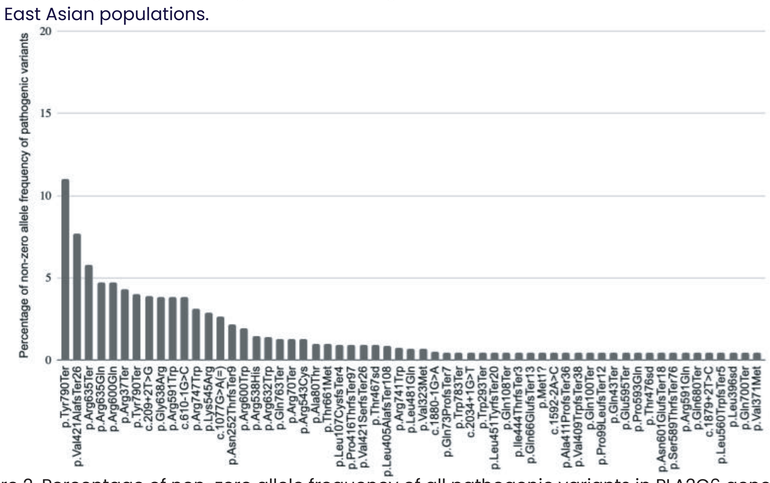

Figure 2. Percentage of non-zero allele frequency of all pathogenic variants in PLA2G6 gene.

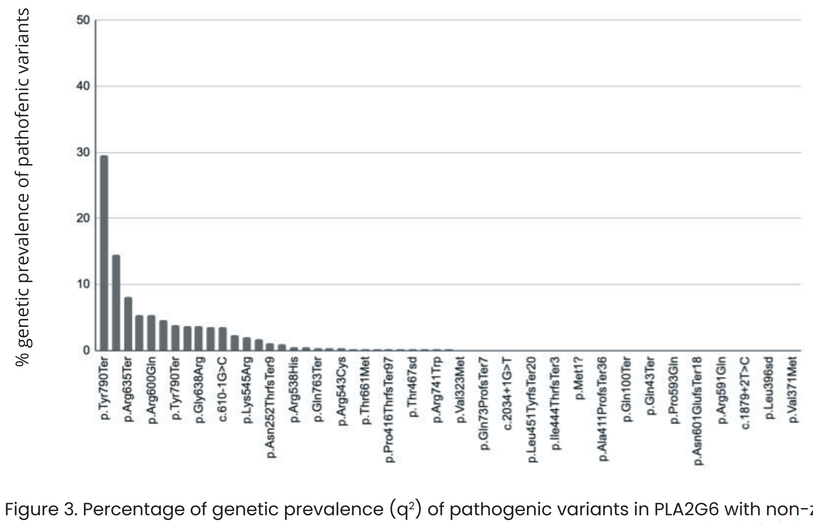

Figure 3. Percentage of genetic prevalence (q^2) of pathogenic variants in PLA2G6 with non-zero allele frequencies.

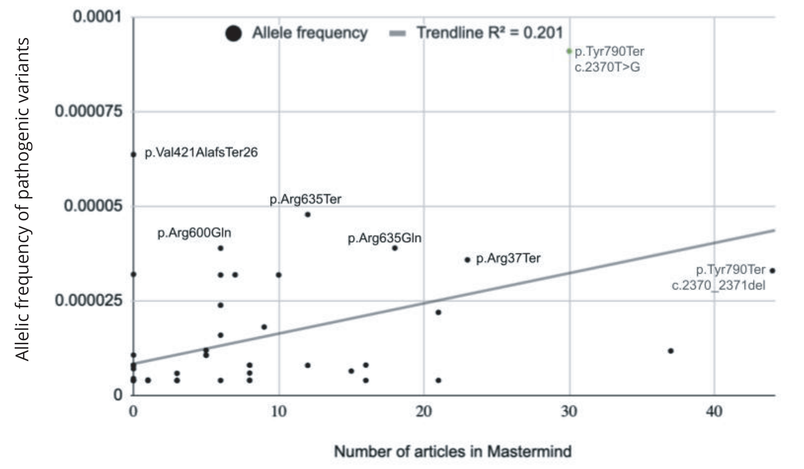

Figure 4. Relationship between allele frequency and the number of articles associated with the variant in Mastermind.

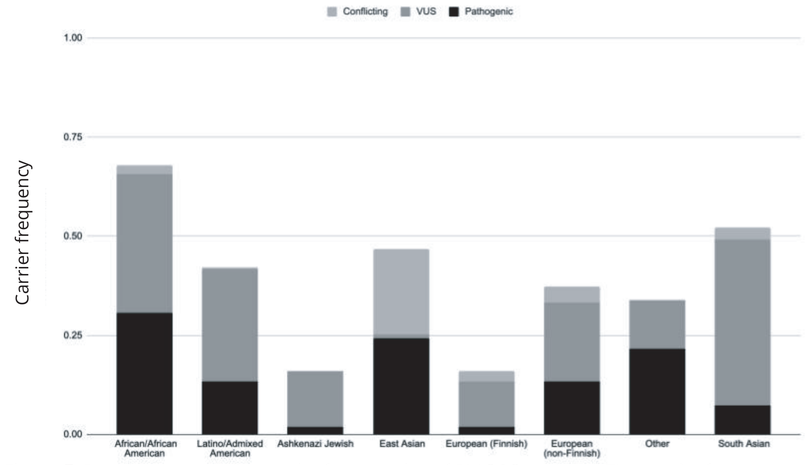

Figure 5. Population-specific carrier frequencies of PLA2G6 variants. The carrier frequency was calculated using the Hardy–Weinberg equilibrium equation and the sum of the allele frequencies of the specified variants. Variants that had conflicting interpretations of pathogenicity (P vs VUS) between database and literature approach are also included in the chart.

Conclusions

Our estimates highlight the significant underdiagnosis of PLA2G6-associated neurodegeneration and underscores the need for increased awareness and diagnostic efforts. Furthermore, our study revealed a higher carrier frequency of PLA2G6 variants in African and Asian populations, stressing the importance of expanded genetic sequencing in non-European populations to ensure accurate and comprehensive diagnosis. Future research should focus on confirming our findings and implementing expanded sequencing strategies to facilitate maximal and accurate diagnosis, particularly in non-European populations.

References

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3. Chunn LM, Bissonnette J, Heinrich S V, Mercurio SA, Kiel MJ, Rutsch F, et al. Estimation of ENPP1 deficiency genetic prevalence using a comprehensive literature review and population databases. Orphanet J Rare Dis. 2022;17(1):421.