SEQUENCING-BASED DIAGNOSTICS FOR NEUROPSYCHIATRIC ILLNESS: LESSONS LEARNT

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Detailed genetic analysis of vital genes might help to understand not only the functioning of the gene involved but also different aspects of disease biology. In the current work we describe variations in the Phospholipase A2 Group 6 (PLA2G6) gene in exomes of patients with neuropsychiatric disease.

Mutations in the PLA2G6 gene cause neurodegenerative disorders, possibly due to their effects on membrane homeostasis. The 806 amino acid PLA2G6 protein has ankyrin repeat regions, a GXSXG lipase catalytic site, a nucleotide-binding domain, and a calmodulin-binding region. With a dN/dS ratio of 2.464 and missense variant Z-Score of 1.21 (gnomAD), the gene is highly conserved and is syntenic across many vertebrates. The disease-linked variants might influence the function and structure of the enzyme, and contribute to clinical presentation.

In-silico prediction methods and molecular docking analyses were performed to investigate the pathogenicity of PLA2G6 mutations. We employed PolyPhen 2, MUpro etc and did molecular docking analysis of antipsychotic drugs on the predicted AlphaFold structure of the protein using Schrodinger Maestro software package.

We detected a homozygous p.Arg741Gln variant in two individuals with Autosomal Recessive Early-Onset Parkinsonism (AREP), a p.Arg741Trp variant in an individual with Infantile neuroaxonal dystrophy (INAD), a heterozygous deleterious variant p. Asp377Tyr in three siblings diagnosed with schizophrenia with Parkinsonian features, a p.His117Arg variant in another person diagnosed to have schizophrenia and a p.Ile256Val in a healthy individual. All five mutations were predicted to be damaging and affected conserved amino acid positions and protein stability. The in-silico analysis of the pathogenic/deleterious variants of the human PLA2G6 gene shows that these mutations may impact the protein structure and function. The two individuals with AREP developed severe Parkinsonian side effects when treated with antipsychotics for their psychological symptoms. In the patients who had a diagnosis of schizophrenia, the PLA2G6 mutations were predicted to affect protein structure and possibly drug binding. Prolonged treatment with antipsychotics in these patients might have precipitated symptoms of PD and extrapyramidal symptoms in later life. Modeling the links between genetic variation, protein structure, and the impact on cell biology can thus help understand the risk of disease and its progression, as well as drug response and side effects. In addition, the occurrence of different variants in different world populations provide useful insights into the genetic epidemiology of these brain disorders. Endogamous and consanguineous mating due to prevalent social practices might provide increased opportunity for occurrence of homozygous variants that lead to recessive disorders.