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Abstract Topic:- Pharmacogenetics

Abstract Title:- Advancing epilepsy treatment through personalized medicine: Insights from pharmacogenomic studies of valproic acid in two cases.

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Aims:-This study aims to investigate the impact of pharmacogenomics on the response to antiepileptic drugs, particularly valproic acid, in the context of pediatric epilepsy cases. It seeks to shed light on the role of genetic variations in influencing individual responses to medications, with a focus on valproic acid, which is approved for the treatment of complex partial seizures as both monotherapy and adjuvant therapy.

Methods:- With informed parental consent, we extracted DNA from EDTA blood samples. Subsequently, we prepared the NGS Library using the Roche Kappa Hyper Plus kit, followed by hybrid capture-based technology and paired-end sequencing on the Illumina Novaseq 6000 platform. Gene variants were annotated and filtered using the in-house and commercial analysis workflow to predict their effects.

Results:- In the first case study, a 7-year-old patient was presented with recurrent myoclonic epileptic seizures and was recommended valproic acid as part of the treatment regimen. However, PGx evidence showed a clear avoidance of the drug. Genetic screening identified 2 potent variants which can impact kidney function and can result in adverse events. A pathogenic variant NC_000001.11:g.976215A>G in the PERM1 gene, associated with renal tubular epithelial cell apoptosis was found. Scientific evidence also suggested Valproic acid and carbamazepine to stimulate renal tubular dysfunction. PGx analysis revealed a high side effect and poor response to valproic acid with Hepatotoxicity and Weight gain being the possible side effects. Hence, an alternate drug was suggested.

The second case study of a 6year old male revealed a moderate impact homozygous variant in the CHD2 gene (NC_000015.10:g.92978374A>G) and GABRD gene (NC_000001.11:g.2029235C>T), associated with developmental and epileptic encephalopathy, idiopathic generalized epilepsy. Sodium valproate, one of the key antiepileptic drugs for myoclonic and generalized epilepsies, is known to inhibit histone deacetylase activity, alter chromatin structure9 and was generally a favorable drug for patients with CHD2 encephalopathy. Notably, valproate emerged as a good treatment option in this case based on the PGx analysis.

Conclusions:- These case studies underscore the significance of personalized medicine in epilepsy treatment, where genetic insights can guide the selection of antiepileptic drugs and mitigate adverse effects. They highlight the potential of pharmacogenomics to enhance the precision and effectiveness of epilepsy management, ultimately leading to improved patient outcomes. Furthermore, the findings from these studies may have implications for drug labeling and the development of clinical guidelines in the field of epilepsy therapeutics.

Keywords:- Pharmacogenomics, Personalized medicine, Antiepileptic drugs, valproic acid