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Abstract Topic:- Clinical Genetics

Abstract Title:- Whole-exome sequencing revealed a digenic variant in a patient with leigh syndrome

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Aims:-To investigate digenic variants which is pivotal for deciphering the intricate genetic interactions underlying complex diseases, offering insights into disease etiology and genetic mechanisms beyond clinical applications.

Methods:- Whole exome sequencing (WES) was performed for patient and familial segregation by Sanger sequencing. In-silico analysis was done using damage prediction tools like SIFT, PolyPhen, CADD and SpliceAI. Enzyme assay was carried out for the four mitochondrial respiratory chain complexes (I, II, III and IV) using spectrophotometry.

Results:- A 5-month-old baby, born to consanguineous parents presented with microcephaly, motor delay, bronchiolitis, failure to thrive and metabolic acidosis. The levels of serum ammonia and lactate were elevated. TMS findings were abnormal and was suspected to be affected with Leigh disease or organic acidemia. Histopathological analysis was normal and mitochondrial respiratory complex assay showed reduced activity of both complex I and IV in muscle.

Analysis of WES identified the presence of digenic variants, a missense variant in NDUFA11 (c.586G>A [p. Gly196Arg]) gene and a 3'splice-site variant in PET100 (c.115-3C>G) gene. The segregation analysis for these variants confirmed the autosomal recessive inheritance pattern in the family.

Conclusions:- In summary, digenic variants NDUFA11 (c.586G>A [p. Gly196Arg]) and PET100 (c.115-3C>G) gene were observed and co-segregated with the disease phenotype, which may be responsible for the Leigh phenotype. Further, the functional characterization will demonstrate the role of these variants in disease pathogenesis.

Keywords:- Leigh Syndrome, Mitochondrial disorder.