A Novel Candidate Frameshift Mutation For Leigh Syndrome

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Introduction:

Leigh syndrome (LS) is progressive neurodegenerative mitochondrial disorder which is characterized by focal, symmetrical and necrotic lesions in the thalamus, the brain stem and the columns of the spinal cord.

SURF1 gene, one of the genes responsible for Leigh syndrome, is located at chromosome 9p34 which encodes a protein localized to the inner mitochondrial membrane. This protein is involved in the biogenesis of cytochrome c oxidase complex.

A couple who have consanguinity between them have been admitted to our department due to the fact that they have 3 children who died with the suspicion of mitochondrial disease. Children had similar findings such as difficulty swallowing, tremor, hypotonia, difficulty breathing. Mitochondrial genome analysis of one of them was normal. We planned the Whole-Exome Sequencing for the detection of common heterozygous variants.

Methodology:

DNA extraction

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Library Preparation with illumina Nextera Exom Kit

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Sequencing with illumina Nextseq 500 platform

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Analyze data and annotate variants

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Sanger Sequencing for Confirmation

Results:

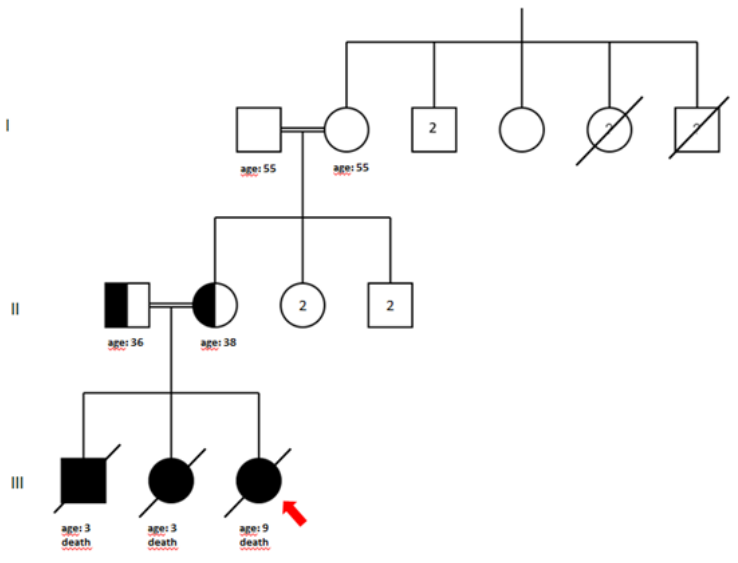

Figure 1: Family History

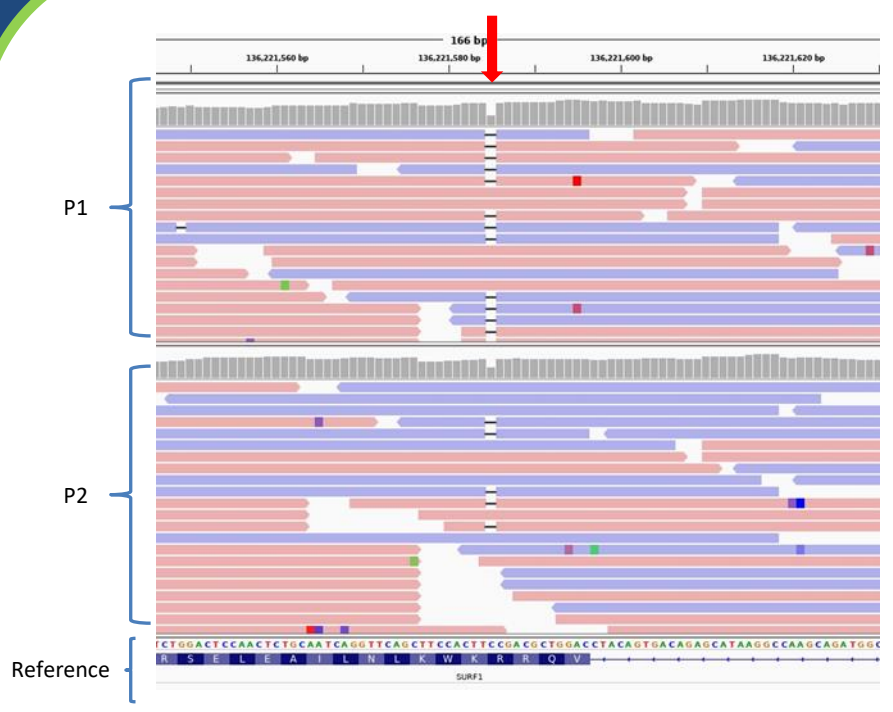

Figure 2: NGS results (Integrative Genomics Viewer-IGV)

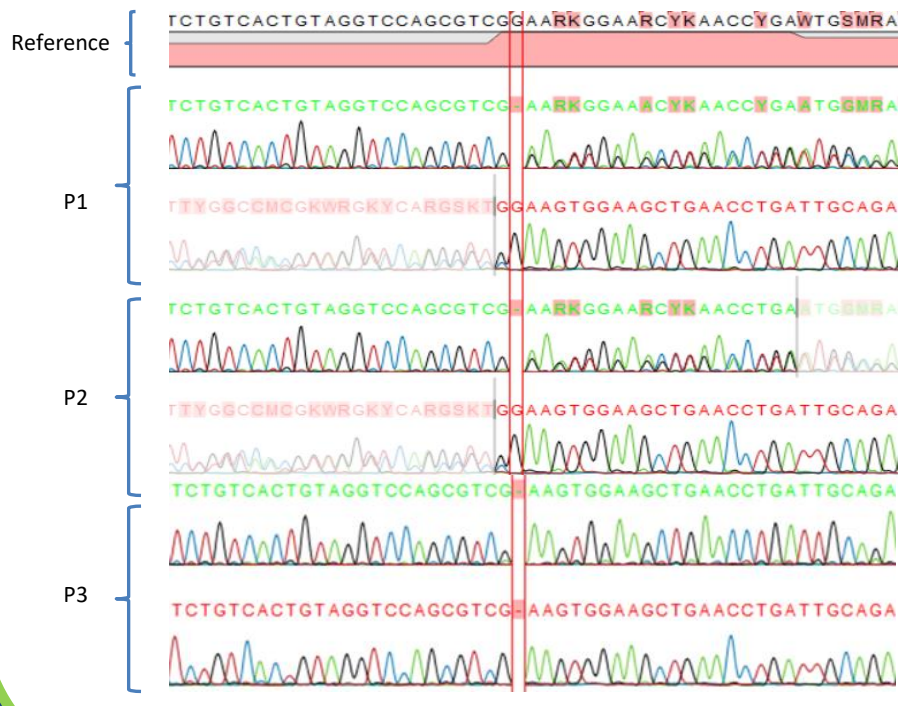

Figure 3: Sanger results

With the molecular analysis;

- In both father and mother, we identified a heterozygous deletion in *SURF1* (NM_003172.3) gene c.252delG with next generation sequnecing.
- We also determined the same variant as homozygous in their passed away child with Sanger sequencing.

Conclusion

- *SURF1:* c.252delG variant which is not found in clinical databases such as ClinVar or Human Genome Database (HGMD). According to American College of Medical Genetics (ACMG) criteria it is classified as 'pathogenic'.
- Identified heterozygous variant both in healty father and mother, also determined in former ex-child as homozygous and compatible with ressessive inheritence patern and famillial segregation. As a result we evaluated this novel variant as **likely pathogenic**.
- With this mutation, we added a new one to the variants detected in the *SURF1* gene

Reference:

Farina L., Chiapparini L., Uziel G. MR Findings in Leigh Syndrome with COX Deficiency and SURF-1 Mutations. American Society of Neuroradiology. 23, August 2002

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Tiranti V., Hoertnagel K.,Carrozzo R. Mutations of SURF-1 in Leigh Disease Associated with Cytochrome c Oxidase Deficiency. *Am. J. Hum. Genet. 63:1609–1621, 1998*