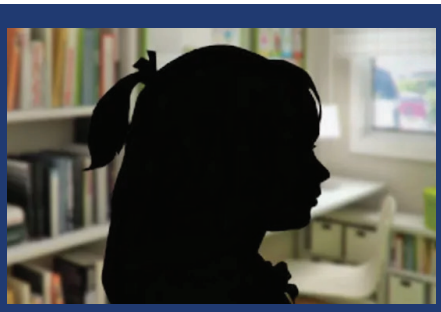
Solving the Metabolic Riddle: Genetic Analyses Reveal the Cause Behind Hypoglycaemia and Seizures Evident in a Child



Gender: Female

Age: 9 years

Diagnosis: Hypoglycaemia and generalized seizures. Genetic testing advised.

Key Findings:

- Mutation in Fructose 1,6-bispho phatase gene *(FBP1)* identified
- Proband homozygous
- Parents advised to test themselves as well as proband's sibling
- Detailed analysis of mutant gene was enabled by Strand NGS and Sanger sequencing offered as

Patient Profile

A 9-year-old girl, Arpita*, was brought to a prominent hospital in Bangalore for a consultation with a renowned endocrine specialist. Generalized seizures and hypoglycaemia were her principal health issues. In addition to these symptoms, she also suffered from vomiting, hepatomegaly and increased sensorium. Blood tests showed that she had high serum lactate levels as well. Episodes of hypoglycaemia and seizures had started when Arpita was 1.5 years old.

The doctors handling the case advised a liver biopsy as well as genetic tests to understand whether inherited genetic mutations were the cause of Arpita's health issues.

Family Tree- Pre-Test Genetic Counselling

Arpita's father's mother and mother's father were siblings. Essentially, her parents were cousins and therefore were in a consanguineous marriage. Given this family history, her physician prescribed the Strand Clinical Exome Test to ascertain whether an inborn error of metabolism was present in the child.

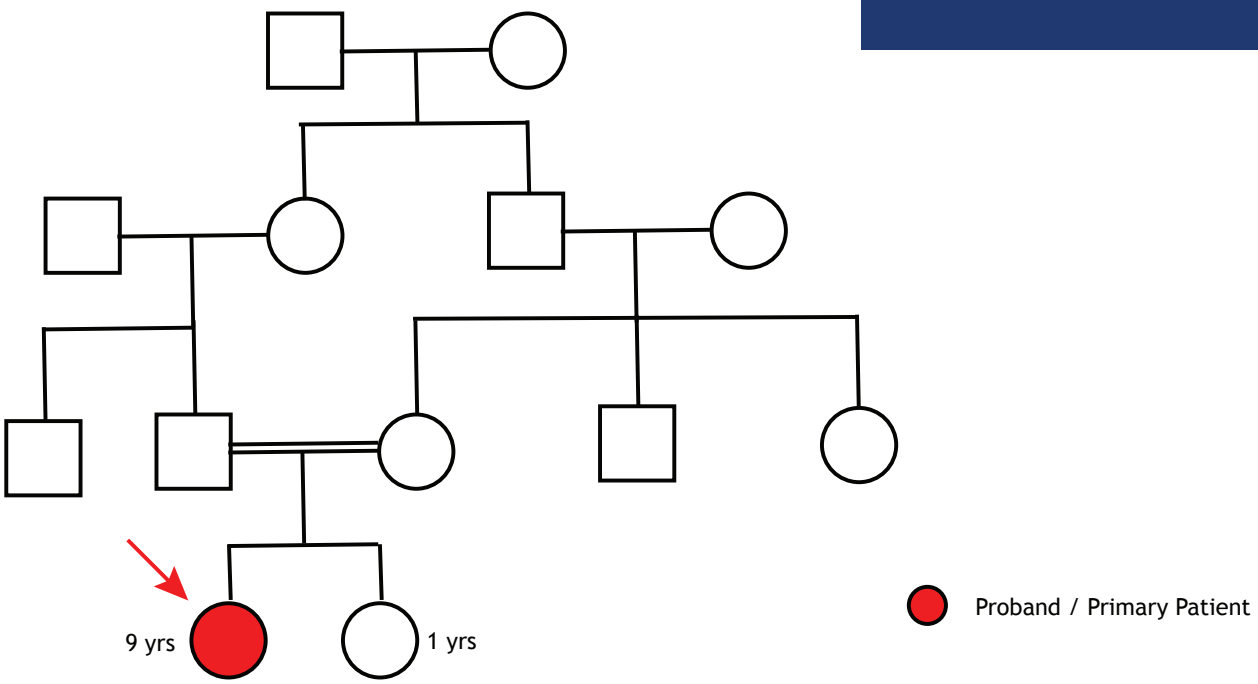


Figure 1. Arpita's Family Tree

*Name changed to protect patient privacy

Results of Genetic Testing

Arpita was found to be homozygous for a mutation in the *FBP1* gene. This gene codes for an enzyme, fructose 1,6-bisphophatase, that is involved in the synthesis of glucose from substances like lactic acid, amino acids, and glycerol. Deficiency of this enzyme has been linked with metabolic acidosis, ketosis, elevated levels of serum lactic acid, and even coma (Li et al. 2017).

Since Arpita is homozygous for this mutation, bearing two mutant copies of the gene, she suffers from a complete deficiency of the fructose-1,6-bisphophatase enzyme, manifested as hypoglycaemia and periodic seizures.

RESULT A homozygous **'pathogenic'** variant that results in a 331bp ALU sequence element insertion was detected in exon 2 of the *FBP1* gene

Key Findings

Gene	Variation	Zygosity	Clinical significance
FBP1	chr9:g.97382716_97382717insKT305716.1:g.87_417 c.227_228insKT305716.1:g.87_417 p.Leu77GlyfsTer39	Homozygous	Pathogenic

Strand's Bioinformatics Software Enabled Deep Genetic Analysis

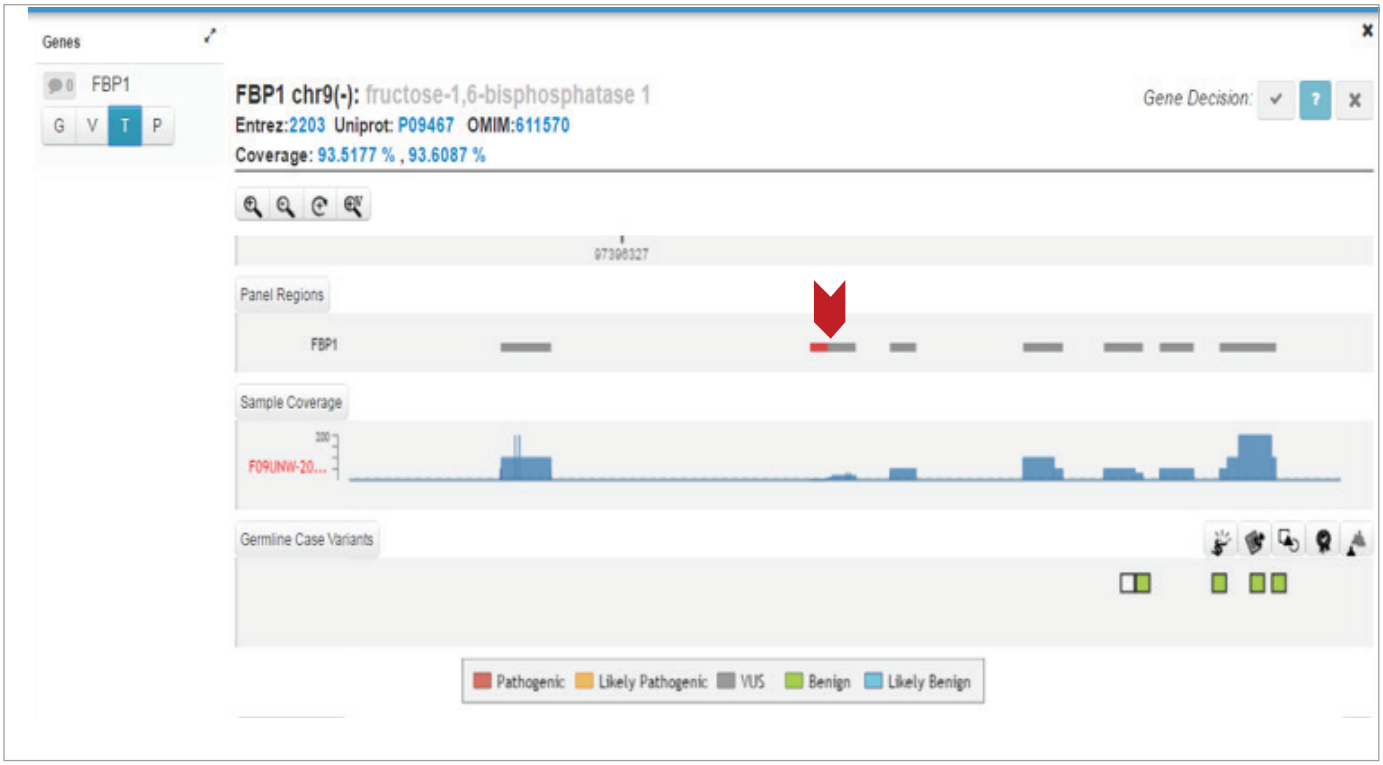


Figure 2. NGS analysis of Arpita's DNA with low readouts of the FBP1 gene (arrowhead)

In Arpita's case, an insertion of a 331 base pair ALU sequence (a sequence of repetitive DNA bases) in exon 2 of the *FBP1* gene was detected after careful analysis. The genomic region of the *FBP1* gene was underrepresented in the NGS readouts, compared to readouts from other samples, in the first round of analysis. Normally, this underrepresentation would have been missed out in the analytical workflow, owing to reduced number of readouts. However, Strand's proprietary bioinformatics platforms- Strand NGS and StrandOMICS- have been designed to identify such features of NGS readouts and flag them for further analysis. In Arpita's case, this genomic fragment was then analyzed again by Sanger sequencing. Insertion of the ALU sequence in the *FBP1* gene was revealed by Sanger sequencing. This insertion was predicted to cause a frameshift mutation, resulting in the formation of an incomplete protein product.

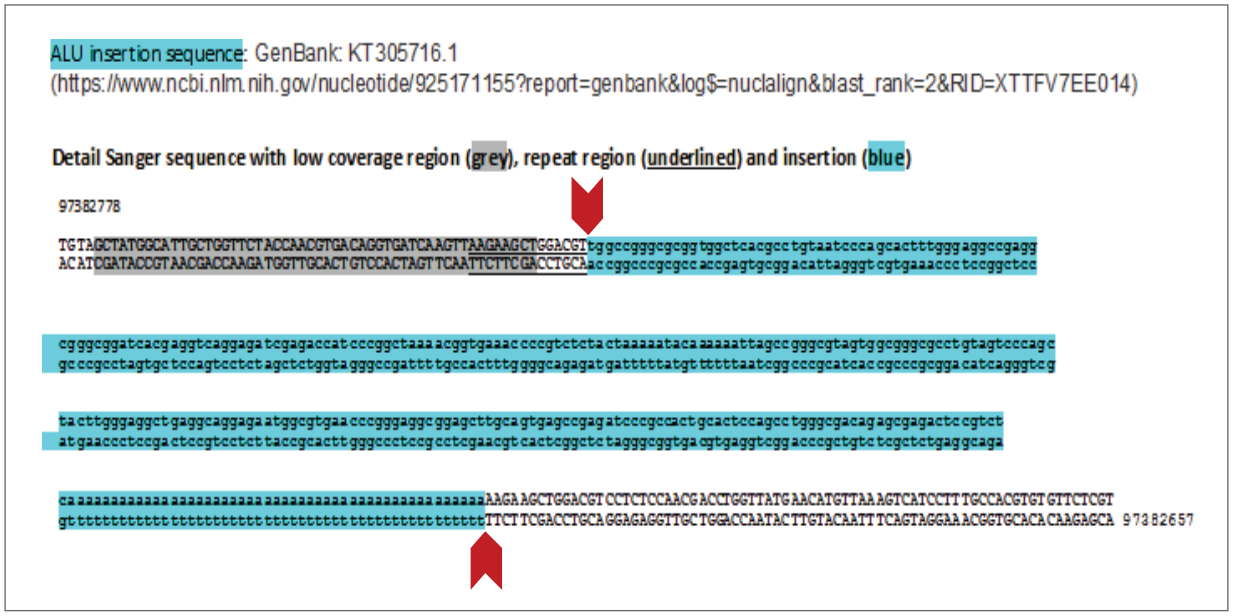


Figure 3. Sanger sequencing of the FBP1 gene led to the identification of an ALU insertion (region between arrowheads) resulting in a loss of function mutation

Conclusions

- The Strand Clinical Exome Test was prescribed to understand the genetic causes of symptoms such as hypoglycaemia and periodic seizures in a 9-year old child.
- Arpita was found to be homozygous for a mutation in the *FBP1* gene, caused by an insertion of an ALU sequence in exon 2.
- Identification of the ALU insertion was facilitated by critical analysis enabled by Strand NGS- Strand's proprietary bioinformatics software- followed by Sanger sequencing offered by Strand at no additional cost to the patient.
- Arpita's parents were counselled and advised about management strategies such as appropriate food choices for Arpita.
- Mutation-specific testing* was advised to the family, especially since Arpita has a sibling. Arpita's parents are expected to be heterozygous for the same mutation and hence their chances of transmitting two copies of the same mutation to another child, are 25%.

The parameter marked with an * are not accredited by NABL and CAP.

Strand Clinical Exome Test

The Stand Clinical Exome test includes genes involved in inherited metabolic disorders. The test is a comprehensive test that can assay for > 4500 genes

References

Li, N. et al., 2017. Clinical and Molecular Characterization of Patients with Fructose 1,6-Bisphosphatase Deficiency. International journal of molecular sciences, 18(4). Available at: http://www.ncbi.nlm.nih.gov/pubmed/28420223 [Accessed May 23, 2017].

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