CASE STUDY

Precise Identification of An Inborn Error of Metabolism

Quick Summary

- Baby Sanaa* presented with lactic acidosis, high levels of pyruvate, acetoacetate, 2-hydroxy butyrate and 2-oxoglutataric acid in urine.
- Elevated levels of methionine and alanine in plasma and urine were detected as well in this case.
- Genetic counselling revealed a high degree of consanguinity in the family.
- Genetic testing showed that Baby Sanaa was homozygous for a VUS in the pyruvate carboxylase gene.
- Mutation-specific testing of both parents established that they were carriers of the same mutation.
- Dietary management strategies were suggested to manage Sanaa's health issues caused by the deficiency of pyruvate carboxylase enzyme.

Introduction

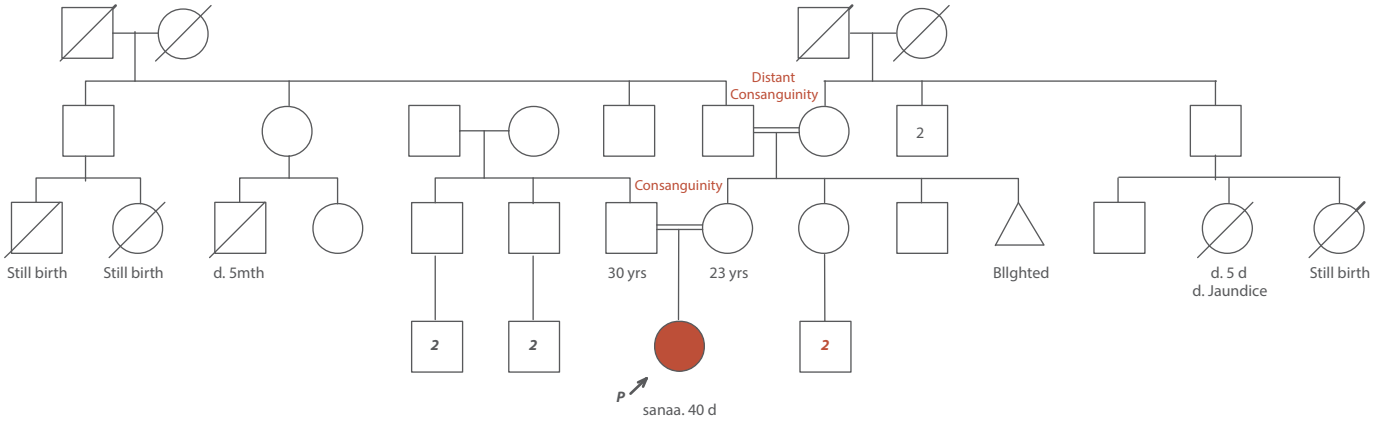
In India, 20,800 infants are born with inborn errors of metabolism (IEM), annually (Kumta 2005). Typically, infants with such disorders are born post uneventful pregnancies and deliveries, and are likely to present symptoms of deficient metabolism a few days post birth. Ketosis, acidosis, jaundice, refusal to feed a few days after birth, parental consanguinity and positive identification of other family members with a similar physiological problem are some of the indicators of an IEM disorder. One such case was referred to Strand Life Sciences for genetic diagnosis of an IEM.

Patient Profile

Baby Sanaa showed signs of lactic acidosis, high levels of pyruvate, acetoacetate, 2-hydroxy butyrate and 2-oxoglutataric acid in urine. Signs of hyperalaninemia or hypermethioninemia were also evident in her blood and urine. Her parents consulted a leading geneticist at a prominent clinic in Coimbatore. Her physician referred her to a genetic counsellor from Strand Life Sciences in order to find out her family history.

Name changed to protect patient privacy

Family Tree- Pre-Genetic Testing



The family tree revealed a high degree of consanguinity in baby Sanaa's family.

Given the high degree of consanguinity in the family tree, Sanaa's doctor advised her parents to get her DNA tested for inherited genes that might cause inborn errors of metabolism.

Results of Genetic Analysis

The Strand Inborn Errors of Metabolism test was used to analyze a blood sample provided by baby Sanaa. This test is designed to analyse 633 genes associated with Inborn Errors of Metabolism.

RESULT **VUSD** A homozygous **'variant of unknown significance with probable damaging effect'** (VUSD) was detected in exon 17 of the *PC* gene.

Key Findings

Gene	Variation	Zygosity	Clinical significance
PC	chr11:66618234T>C c.2384A>G p.Asp795Gly	Homozygous	Variant of Unknown Significance

Baby Sanaa was found to be homozygous for a mutation in the *PC* gene, which codes for the pyruvate carboxylase enzyme. This gene variant has been labeled as a variant of unknown significance with probable damaging effect (VUSD). The mutation alters a conserved residue, resulting in the production of an inactive enzyme product.

Pyruvate carboxylase is involved in the conversion of pyruvate to oxaloacetate. Oxaloacetate is an important substrate for other biochemical reactions and hence maintenance of adequate cellular concentrations of oxaloacetate, by pyruvate carboxylase, is essential.

Pyruvate carboxylase is also involved in processes like gluconeogenesis, lipogenesis and the biosynthesis of neurotransmitters. Failure to thrive and developmental delay along with recurrent seizures are the principal effects of pyruvate carboxylase deficiency (Wang & De Vivo 1993).

Key Findings

- Baby Sanaa has two copies of a mutant *PC* gene. The clinical significance of this particular mutation (gene variant) is unknown. However, given the fact that she showed signs of metabolic acidosis, and predicted production of an inactive enzyme protein (using multiple *in silico* analysis tools), the variant has been classified as a 'Variant of Unknown Significance with probable damaging effect (VUSD)'.

- Sanaa's parents were advised to undergo mutation-specific testing, to ascertain their genetic status as heterozygous carriers of this gene variant. This was advised in view of the fact that if found to be heterozygous, the chances of their other children being homozygous for this variant are 25%.

- Sanaa's parents were advised about dietary strategies to manage her condition. A high-carbohydrate and high-protein diet could help prevent the onset of gluconeogenesis. They were advised against letting the child undergo fasting or go on ketogenic diets, in the future.

Mutation Specific Testing

Sanaa's parents were advised to undergo mutation-specific testing (MST) to understand their genetic status vis-à-vis this *PC* gene variant. Strand offers MST tests to relatives of probands to identify if they are carriers of genes that cause rare diseases, as well as genes involved in hereditary cancers. These MSTs provide an economical avenue for understanding the genetic predisposition of a family towards IEM disorders as well as familial cancers.

Results of MST- Sanaa's Mother

- **Heterozygous** for the tested variant, c.2384A>G (p.Asp795Gly), in the *PC* gene.

Gene name: *PC* **Genetic Alteration** : chr11:66618234T>C; c.2384A>G; p.Asp795Gly

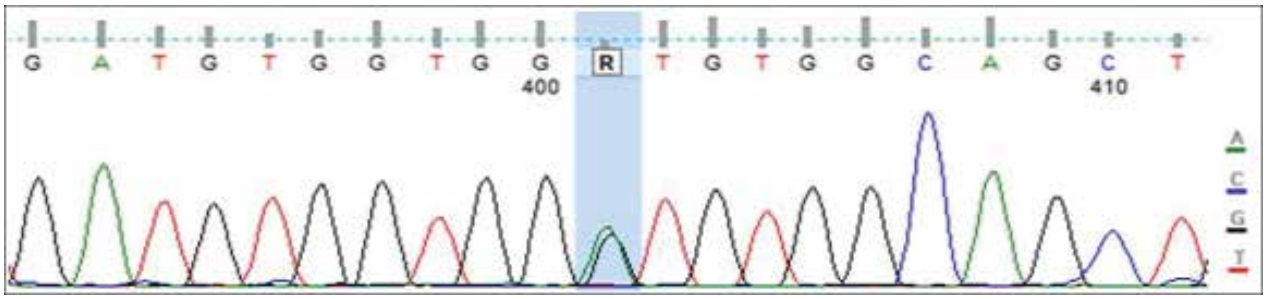


Figure 1: Sanger sequencing data (electrophoregram) from the individual showing a **heterozgous** nucleotide change **'A>G'** at position c.2384 in the *PC* gene (RefSeq id:NM_000920). This variation was confirmed by sequencing with both forward and reverse primers.

Results of MST- Sanaa's Father

- **Heterozygous** for the tested variant, c.2384A>G (p.Asp795Gly), in the *PC* gene.

Gene name: *PC* **Genetic Alteration** : chr11:66618234T>C; c.2384A>G; p.Asp795Gly

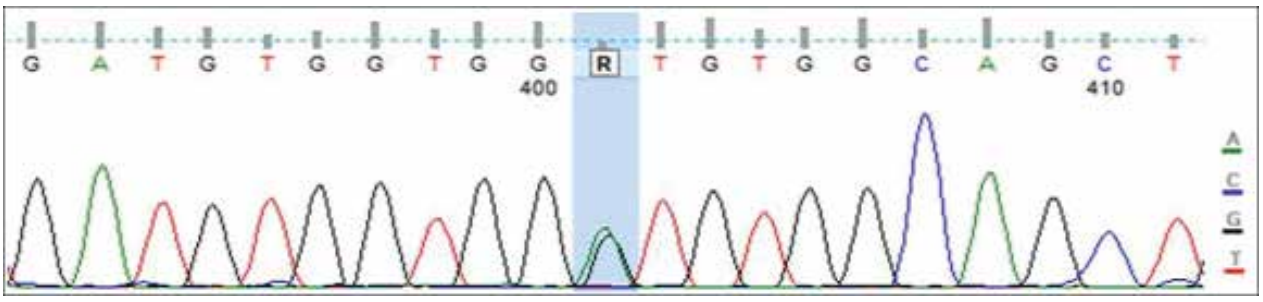


Figure 2: Sanger sequencing data (electrophoregram) from the individual showing a **heterozgous** nucleotide change **'A>G'** at position c.2384 in the *PC* gene (RefSeq id:NM_000920). This variation was confirmed by sequencing with both forward and reverse primers.

Sanaa's parents were found to be heterozygous for the *PC* gene VUSD identified in her genomic DNA. Their chances of transmitting two variant copies of this gene to another child are 25%, since *PC* is inherited in an autosomal recessive fashion (Breen et al. 2014).

Conclusion

- Metabolic acidosis observed in 40-day old baby Sanaa was suspected to be caused by an inherited disorder.
- Genetic counselling, followed by analysis using the Strand Inborn Errors of Metabolism test, revealed that baby Sanaa was homozygous for a variant of the pyruvate carboxylase *(PC)* gene.
- Mutation specific testing of DNA from her parents confirmed their status as heterozygous carriers of the same mutation in the *PC* gene.
- Counselling for planning children in the future was provided to the parents, based on the results of these tests.
- Baby Sanaa's health can be managed using specific dietary strategies advised for individuals suffering from pyruvate carboxylase deficiency.

Strand Inborn Errors of Metabolism Test

The Strand Inborn Errors of Metabolism test covers 633 genes. Genes involved in IEM disorders are typically inherited in Mendelian inheritance patterns.

References

Breen, C. et al., 2014. Unsuccessful treatment of severe pyruvate carboxylase deficiency with triheptanoin. European Journal of Pediatrics, 173(3), pp.361–366. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24114256 [Accessed May 30, 2017].

Kumta, N.B., 2005. Inborn errors of metabolism (IEM) — an Indian perspective. The Indian Journal of Pediatrics, 72(4), pp.325–332. Available at: http://link.springer.com/10.1007/BF02724016 [Accessed May 29, 2017].

Wang, D. & De Vivo, D., 1993. Pyruvate Carboxylase Deficiency, Available at: http://www.ncbi.nlm.nih.gov/pubmed/20301764 [Accessed May 30, 2017].

Strand Center for Genomics & Personalized Medicine
(A unit of Strand Life Sciences Pvt. Ltd.)
UAS Alumni Association Building, Veterinary College Campus,
Bellary Road, Hebbal, Bangalore – 560 024
Phone: 1800-1022-695, support.strandx@strandls.com, www.strandls.com

Strand Center for Genomics & Personalized Medicine is accredited by

CAP ACCREDITED # 8750941

Certificate No. M-0849

#StayAheadOfCancer

Strand ID: RD-597103072017