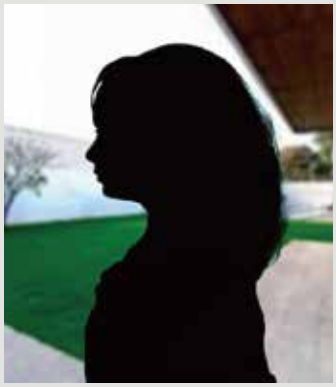
CASE STUDY

Glycogen Storage Disease Identified By Strand's Clinical Exome Test

Quick Summary



- Parineeta* presented with hepatomegaly, hypoglycaemia, and muscle weakness.
- Genetic counselling revealed a high degree of consanguinity in the family.
- Parineeta was found to be homozygous for a VUSD in the *AGL* gene through genetic testing.
- Analysis enabled by Strand's Clincal Exome Test supported the diagnosis of glycogen storage disease type III.
- Dietary management strategies were suggested to manage Parineeta's health issues.

Introduction

India is facing an increase in the cases of infants born with congenital physiological defects, owing to a high birth rate and greater control over infectious diseases. Estimates suggest that 12.1% of all the cases recommended for genetic counselling were cases of identifiable syndromes. Data from hospitals in Delhi and Mumbai shows a high prevalence of glycogen storage diseases, galactosemia and Wilson disease (Verma 2000). Strand Life Sciences offers tests for genetic diagnosis of several such inherited syndromes.

Patient Profile

Parineeta is a happy-go-lucky 5-year old child with a keen interest in drawing and Lego blocks. She enjoys all her kindergarten activities except for sports. For some reason her stomach hurts when asked to participate in vigorous activities. She also feels tired very quickly, and her arms and legs hurt quite a bit. While other kids can do cartwheels easily, she loses her balance whenever she tries. Her pediatrician has noted hepatomegaly, hypoglycaemia (low levels of sugar in the blood), and weakness in her limb muscles.

Parineeta's parents were asked to consult a leading geneticist in Coimbatore to delve deeper into her health issues and understand the reasons for her symptoms.

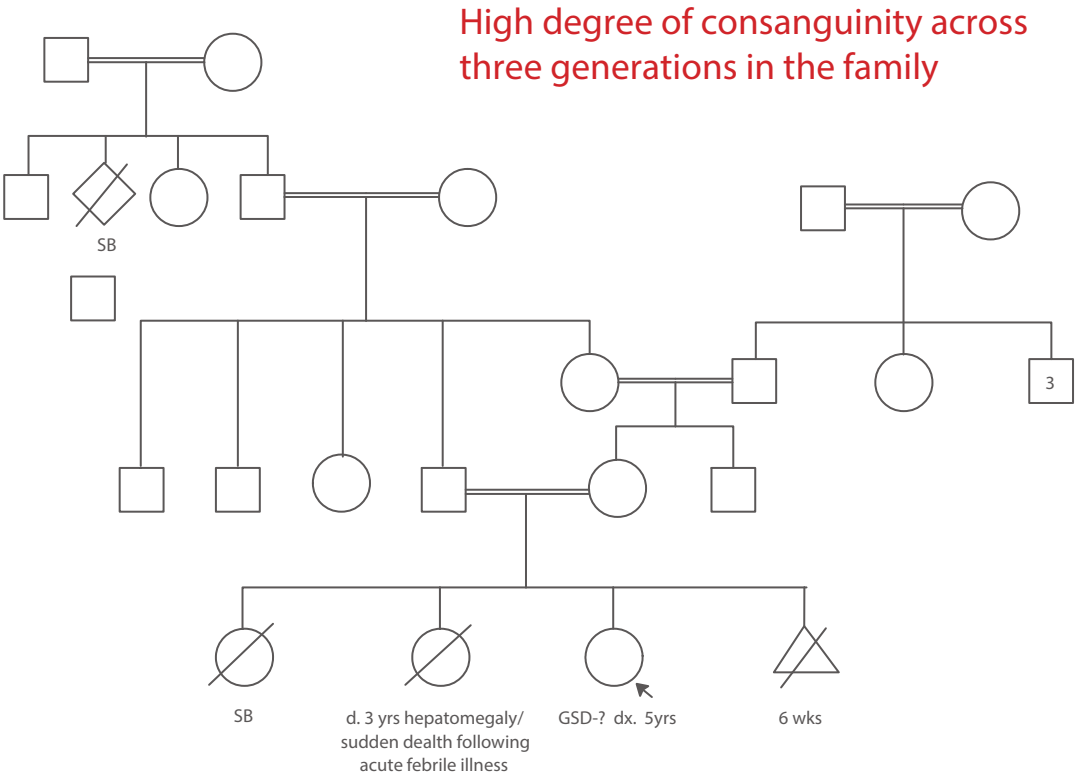
The expert geneticist lent a patient ear to the family's story and also recommended a session with a genetic counsellor from Strand Life Sciences. The doctor suggested genetic testing in order to understand why a chirpy 5-year-old should present with hepatomegaly, hypoglycaemia, and muscle weakness. The symptoms indicated a deficit in glucose metabolism but a definite diagnosis had to be arrived at.

Family Tree – Pre Genetic Testing

A detailed record of Parineeta's family history of marriages and medical ailments was drawn up by Strand's genetic counsellor. Parineeta's parents are cousins and therefore are in a consanguineous marriage. They have had a tragic history of losing three other children. One girl child was stillborn, another girl child also presented with hepatomegaly and was lost to a febrile illness at the age of 3 years, and one pregnancy was medically terminated at 6 weeks.

**Name changed to protect patient privacy*

Parineeta's maternal grandparents, and both sets of great-grandparents were also in consanguineous marriages.



Given this family history, the incidence of an inborn error of metabolism in Parineeta was suspected. The Strand Clinical Exome Test was prescribed to her.

Results of Genetic Testing

Parineeta was found to be homozygous for a 'Variant of Unknown Significance with a probable damaging effect (VUSD)' in one of the tested genes, the *AGL* gene.

RESULT VUSD A homozygous **'variant of unknown significance with probable damaging effect'** (VUSD) was detected in exon 18 of the *AGL* gene.

Key Findings

Gene	Variation	Zygosity	Clinical significance
AGL	chr1:100349697T>C c.2330T>C p.Leu777Pro	Homozygous	Variant of Unknown Significance

Key Interpretations

- The *AGL* gene codes for a de-branching enzyme that is necessary for breakdown of glycogen into glucose.
- A deficiency of this enzyme activity, owing to the presence of the VUSD in both copies of the *AGL* gene, is responsible for the hypoglycaemia evident in Parineeta.
- Germline pathogenic variations in the *AGL* gene have been shown to be associated with glycogen storage disease type III (GSD III), which manifests as hypoglycemia, hyperlipidemia, hepatomegaly, and elevated blood levels of liver enzymes (Dagli *et al.* 1993; Sentner *et al.* 2016).
- The mutation present in Parineeta's genome results in a missense substitution (p.Leu777Pro) in a conserved residue in the protein. Analysis of predicted protein sequence using *in silico* prediction tools indicates that the mutation is probably damaging to protein function.

Conclusions

- Parineeta's health issues were caused by a VUSD mutation in the *AGL* gene.
- Mutation-specific testing was advised to her parents and other family members to understand the inheritance pattern of this gene variant.
- Diet management strategies were suggested to Parineeta's parents to cope with her low blood sugar levels.

References

Dagli, A., Sentner, C.P. & Weinstein, D.A., 1993. Glycogen Storage Disease Type III, Available at: http://www.ncbi.nlm.nih.gov/pubmed/20301788 [Accessed May 9, 2017].

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Verma, I.C., 2000. Burden of genetic disorders in India. Indian journal of pediatrics, 67(12), pp.893–8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11262988 [Accessed June 23, 2017].

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