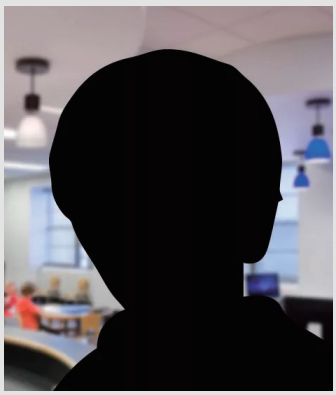
CASE STUDY

Genetic Analysis Helps Parents Understand Their Child's Health's Problems

Quick Summary

- Sagar Kothanur*, an 11-year-old, child presented with muscle weakness and mild enlargement of the liver.
- Diagnosis of his metabolic problem had eluded doctors for several years.
- Genetic counselling and testing was advised to the proband and his parents.
- Presence of a pathogenic mutation in the *AGL* gene was identified in proband and his parents.
- Identification of the mutation resulted in the diagnosis of the patient's condition as glycogen storage disorder type III.
- Diet management strategies were advised to the proband and his parents to overcome nutrition problems caused by the disorder.
- Parents were relieved to have achieved a resolution and management strategy for their child's health issues.



Introduction

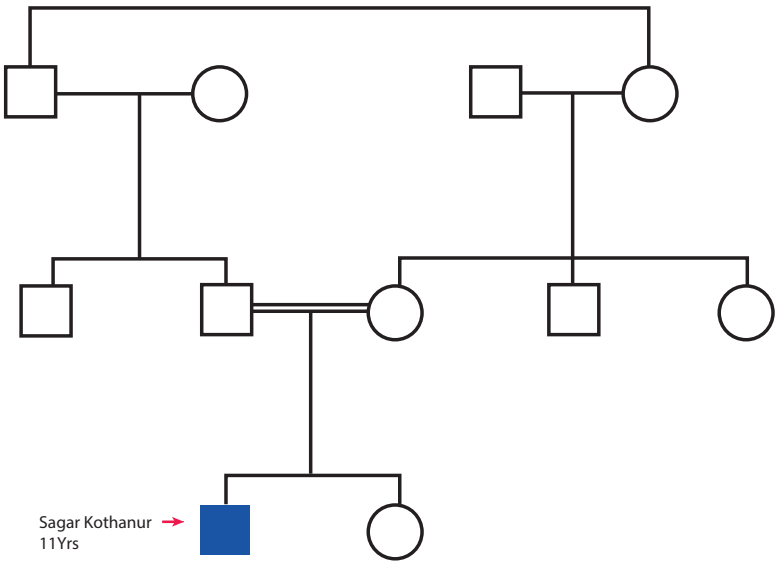
A child's health is the focal point of the lives of parents. Naturally, problems with a child's development and overall health, throughout the early years, create significant anxiety for parents. This is exactly the scenario that Mr. and Mrs. Kothanur faced for eleven years.

Patient Profile

Sagar Kothanur, an 11-year-old child had experienced muscle weakness from the age of 5 years. His other symptoms included distension of the abdomen and mild hepatomegaly. His health issues remained undiagnosed despite several consultations with various doctors. Their latest consultation was with a prominent geneticist in Pune. He advised a counselling session with Strand's genetic counsellor to draw up the family history.

Family Tree of Proband

The family history revealed that Sagar was the child of parents in a consanguineous marriage. His mother and father were cousins. His father's father and mother's mother were siblings. The family tree indicated the likelihood of inheritance of an autosomal recessive mutation.



Sagar's clinical symptoms indicated the possibility of the occurrence of a glycogen storage disease. Glycogen storage diseases (types GSD 0, GSD I, II, III, IV, V, VI, VII, VII, IX, X, XI, XII) are syndromes wherein conversion of glucose to glycogen and its storage in the liver and muscles are compromised (Hicks et al. 2011). Several genes are involved in the development of these diseases. Scientists have also understood the role

Name changed to protect patient privacy

of these genes in each specific subtype of glycogen storage disease. Sagar was advised to undergo genetic testing to pinpoint specific gene mutations in order to delineate the glycogen storage disorder that he was suffering from.

Genetic Test

Strand Life Sciences offers a spectrum of tests that can help to identify genetic mutations involved in inborn errors of metabolism. In Sagar's case the clinical exome test was used to identify the mutations that could cause his malnourished condition. A mutation in the *AGL* gene was found in his genome, indicating that he suffered from GSD-III disease (also known as Cori Disease or Forbes Disease)(Hicks et al. 2011).

RESULT 

Positive for a homozygous **'likely pathogenic'** variant in the *AGL* gene

Key Findings

Gene	Variation	Zygosity	Clinical significance
AGL	chr1:100357208delC c.2996delC p.Pro999HisfsTer13	Homozygous	Likely Pathogenic

Principal Findings

- Sagar has two copies of a 'likely pathogenic' variant in the *AGL* gene in his genome.
- Variations in the *AGL* gene cause glycogen storage disease type III (GSD-III also called Cori disease or Forbes disease). GSD-III is characterized by a reduction of *AGL* enzyme activity leading to the accumulation of structurally abnormal glycogen in the liver and muscle (GSD-IIIa and GSD-IIIc) or liver only (GSD-IIIb and GSD-IIId) thereby impairing the function of these organs. GSD-IIIa is the most common form of GSD-III, while types IIIc and IIId are extremely rare (Dagli et al. 1993).
- *AGL* deficiency presents during infancy and early childhood with marked clinical and enzymatic heterogeneity. Patients display a short stature as a consequence of liver disorder, which includes hepatomegaly, hyperlipidemia, ketotic hypoglycemia and elevated hepatic transaminases.
- The features as described in GSD-III due to *AGL* gene defects are similar to the presentation in the affected child.

Getting To the Root of the Problem

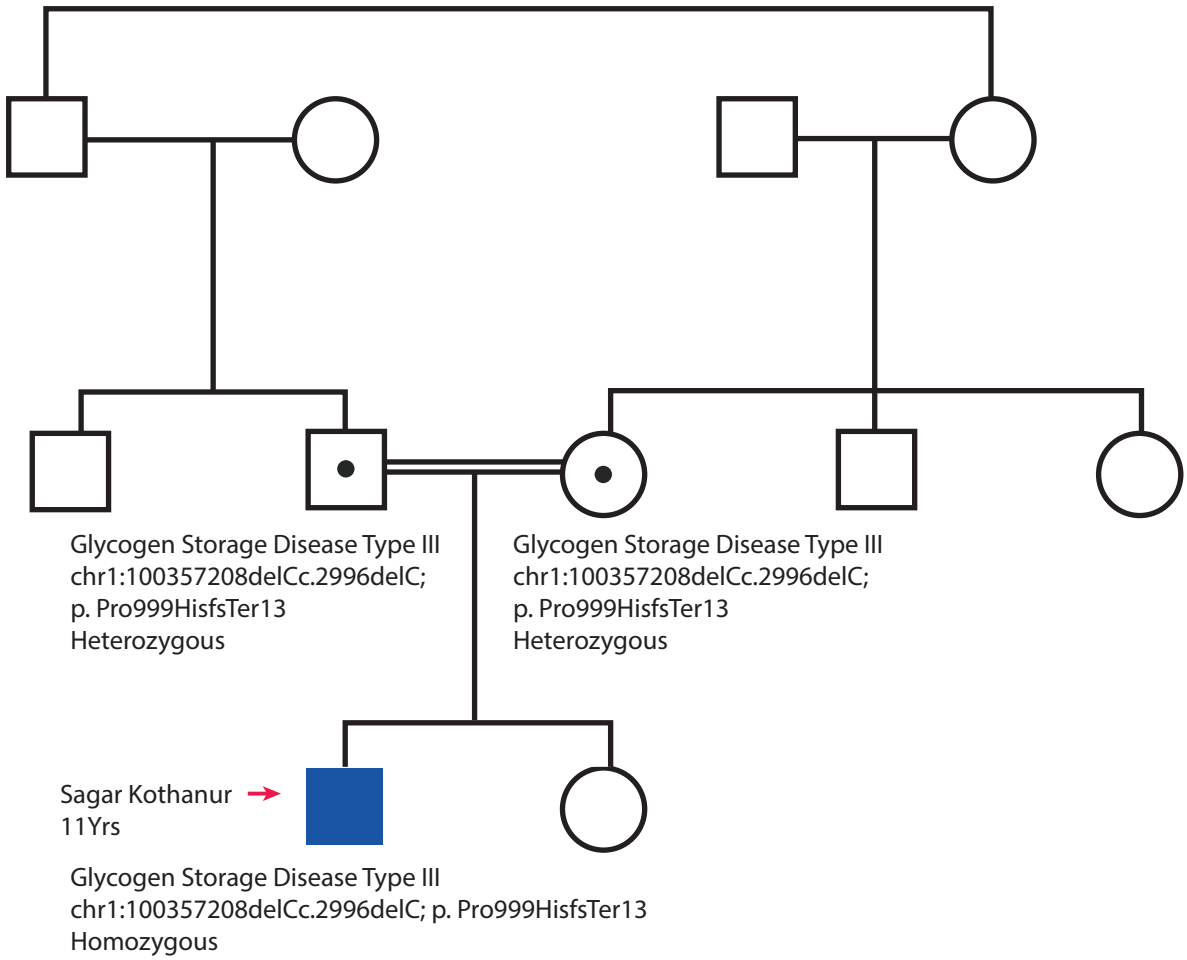
Given that Sagar had been diagnosed with a rare metabolic disorder, genetic testing was advised to his parents as well to confirm whether both parents also bear one copy of the mutated *AGL* gene, each. This disorder can occur only if each parent passes on one copy of the defective gene to the child. Essentially, this means that Sagar has received two copies of this defective *AGL* gene, one from each parent.

Parents are advised to undergo genetic testing to understand their risks of passing on mutant genes to other children, via future pregnancies.

Mr. and Mrs. Kothanur were advised to undergo mutation-specific testing* to understand their status. They were found to be heterozygous for the same gene mutation c.2996delC (p.Pro999HisfsTer13) in the *AGL* gene. Given that, both parents carried a copy of the mutant gene, the chances of one child inheriting both defective copies are 25%. This is exactly the scenario in this particular case of an inherited metabolic disorder.

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

Family Tree Post Genetic Testing



Patient Support Post Genetic Testing

- GSD-III diseases cannot be resolved by using specific therapeutic agents. However, the quality of life of the patient can be improved by making dietary changes (Kishnani et al. 2010).
- Patients suffering from GSD-III are advised to consume frequent high- protein meals. This helps to maintain gluconeogenesis and prevent hypoglycaemia.
- Periodic monitoring of calcium and vitamin D levels is advised. Periodic surveillance for symptoms of cardiomyopathy is also recommended. Supplementation with other vitamins and minerals is advised on a patient-specific evaluation.
- Sagar and his parents were counselled about such diet management strategies.
- The results of genetic tests performed for the proband and his parents cleared their doubts and confusion and helped outline a lifestyle management strategy.

Strand Clinical Exome Test

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

References

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Strand Life Sciences Pvt. Ltd.
5th Floor, Kirloskar Business Park, Bellary Road, Hebbal, Bangalore - 560 024
Phone: 1800-1022-695, support.strandx@strandls.com, www.strandls.com

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