CENTOGENE
THE RARE DISEASE COMPANY

CentoGenome®

CASE STUDY: DIAGNOSIS OF GITELMAN SYNDROME

CASE HISTORY

The patient was a 2-year-old male with a clinical suspicion of Bartter syndrome. He presented with failure to thrive, hypokalemia, hypomagnesemia and alkalosis. He was born to healthy, consanguineous parents and had two affected siblings. Previous whole exome testing was negative.

REASONS FOR TESTING

Multiple previous evaluations, including whole exome sequencing, failed to confirm a diagnosis for this patient. Additional testing was considered with the aim of confirming a diagnosis in order to potentially identify targeted management or treatment options for the patient, and enable prenatal testing in subsequent pregnancies.

TEST ORDERED

Whole genome sequencing, CentoGenome® Trio, was ordered on the patient to target all relevant genes related to the patient's phenotype in one test.

RESULTS

A deep intronic homozygous pathogenic variant was detected

GENE	VARIANT	ZYGOSITY	CLASSIFICATION	INHERITANCE
SLC12A3	c.1670-191 C>T	Hom.	Pathogenic	Maternal/ Paternal

- ***SLC12A3* (NM_000339.2) c.1670-191 C>T** has been described in the literature as pathogenic[1], and has been identified in four affected individuals tested at CENTOGENE. It is located in intron 13 and it creates a new donor splice site within the intron resulting in the inclusion of a novel cryptic exon in mRNA

- Parental testing confirmed that each parent is a carrier of this variant. Additionally, carrier testing in one affected sibling also detected the familial variant in a homozygous state

POST-TESTING

- Testing with CentoGenome® Trio enabled the identification of the variant; carrier testing for one affected brother also detected the familial variant in a homozygous state
- The patient and the affected siblings started symptomatic treatment oriented to alleviate common clinical manifestations that are associated with electrolyte abnormalities
- The family received genetic counselling focused on understanding the risk of recurrence in future pregnancies

DISEASE INFORMATION

Pathogenic variants in *SLC12A3* gene are associated with Gitelman syndrome (GS), an autosomal recessive disease. GS, also referred to as familial hypokalemia-hypomagnesemia, is characterized by hypokalemic metabolic alkalosis in combination with significant hypomagnesemia and low urinary calcium excretion. In the majority of cases, symptoms do not appear before the age of six years and the disease is usually diagnosed during adolescence or adulthood. Transient periods of muscle weakness and tetany, sometimes accompanied by abdominal pain, vomiting and fever are often seen in GS patients. Paresthesia, especially in the face, frequently occur. Remarkably, some patients are completely asymptomatic except for the appearance at adult age of chondrocalcinosis that causes swelling, local heat, and tenderness over the affected joints. Blood pressure is lower than that in the general population. Sudden cardiac arrest has been reported occasionally. In general, growth is normal but can be delayed in GS patients with severe hypokalemia and hypomagnesemia.[2]

CONCLUSION

CentoGenome® was able to diagnose the patient as having Gitelman syndrome due to a homozygous intronic pathogenic variant not previously detected by whole exome sequencing which is restricted to exon analysis. The results ended the diagnostic odyssey, and allowed appropriate treatment and management resulting in mitigation of the patient's symptoms. The confirmed diagnosis also provided risk information to help the family with pre-conceptional counseling for future pregnancies.

REFERENCES

[1] Nozu *et al.* 2009, PMID: 19668106

[2] Clinical features summary by Glaudemans *et al.* 2012, PMID: 2009145

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