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Successful diagnosis of Gitelman syndrome after detecting the c.1670-191CYT variant in the SLC12A3 gene – using CentoGenome®

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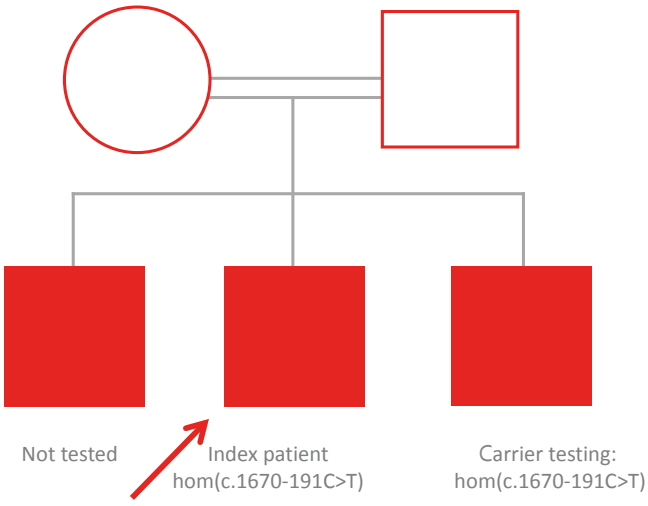
Geographic region

United Arab Emirates, Middle East

Clinical information

The index patient is a 2 year old male presenting failure to thrive, hypokalemia, hypomagnesemia and alkalosis. Bartter syndrome was suspected.

The unaffected parents are consanguineous and have two other sons who are affected in a similar way. Whole exome sequencing has not shown any variants relevant to the phenotype described (no intronic coverage).



Diagnostic procedure

The symptoms of the patient were higly heterogeneous and a large number of candidate genes could be associated with each symptom. The family history, with unaffected consanguineous parents, and two more sons with similar symptoms, additionally increased number of candidate genes.

Using whole genome sequencing (CentoGenome®), a homozygous variant in the SLC12A3 gene, c.1670-191C>T was detected. The variant was also detected in both parents of the index patient in a heterozygous state which confirmed the homozygous state of the variant in the index patient. It was previously described as disease-causing for Gitelman syndrome by Nozu et al., 2009 (HGMD Professional 2015.4 - PMID: 19668106). Carrier testing for one affected brother was performed and a known familial variant in the SLC12A3 gene, c.1670-191C>T, in a homozygous state was detected.

Homozygous pathogenic variants in SLC12A3 are associated with Gitelman syndrome (GS), a renal tubular salt-wasting disorder characterized by hypokalemic metabolic alkalosis with hypomagnesemia and hypocalciuria. Transient periods of muscle weakness and tetany, sometimes accompanied by abdominal pain, vomiting and fever are often seen in GS patients. Some patients are completely asymptomatic except for the appearance at adult age of chondrocalcinosis that causes swelling, local heat, and tenderness in the affected joints.

Due to the lack of complete coverage, this variant could not be identified with WES analysis. CentoGenome® enabled us to identify the genetic cause. In addition genetic counseling for the actual diagnosis was available for the family for an early and effective symptomatic treatment.

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