Ambry Genetics®
A TEMPUS COMPANY

GenomeReveal™

GenomeReveal™
CASE STUDY
HGSNAT

From Negative Exome to Clinical Trial: Genome Sequencing and RNA Analysis Enabled a Diagnosis of Sanfilippo Syndrome

CASE STUDY

Clinical Scenario

- 14 yo female presents with a history of autism
- Previous trio exome testing was negative

Clinical Features

- Nonverbal
- Autism
- Developmental regression
- Cerebral volume loss
- Seizures
- Sensorineural hearing loss
- Swallowing difficulties

Genetic Testing

Provider ordered **GenomeReveal**

Whole Genome Sequencing (WGS) was performed given previous negative exome results and a presentation highly suggestive of a genetic etiology.

RESULT DETAILS

- WGS detected two variants in the *HGSNAT* gene, confirming a diagnosis of Mucopolysaccharidosis (MPS) Type IIIC (Sanfilippo syndrome).
  - A truncating variant in *HGSNAT* (c.1700G>A p.Trp567Ter) was detected and determined to be in trans.
  - A second deep intronic variant in *HGSNAT* (c.1464+182A>G) was also detected and determined to be in trans.
  - RNA analysis was able to confirm the pathogenicity of both *HGSNAT* variants, allowing for a diagnosis of Sanfilippo Syndrome Type C.

Using WGS and RNA Analysis to End the Diagnostic Journey

WGS and RNA analysis can resolve diagnostic odysseys for patients with rare genetic disorders. In autosomal recessive conditions, diagnoses are frequently missed when standard exome sequencing identifies only a single pathogenic variant.

In this case, WGS and RNA analysis established a definitive Sanfilippo Syndrome Type C diagnosis by identifying a second deep intronic variant in trans, confirmed as pathogenic through RNA analysis.

This result provided long-sought answers for the family and enabled enrollment in a clinical trial for emerging therapies.

Points For Your Practice

Consider genome sequencing to detect intronic variants and improve diagnostic capability in recessive disorders.

RNA analysis can provide evidence supporting pathogenicity and clarify the impact of deep intronic variants.

Based on information from an actual patient case; individual identifiers have been modified to protect patient privacy

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