A Diagnostic Odyssey Solved

Patient information

A 5-month-old male presented with hypotonia, neonatal hypoglycemia, a sacral vestigial tail, and reflux. He required a G-tube as he was unable to consume sufficient nutrients orally. He also had hyperreflexia with clonus, tongue fasciculations, peripheral pulmonary stenosis, and developmental delay.

The family history was non-contributory.

Previous genetic testing

Previous testing with normal results included: chromosomal microarray, plasma amino acids, urine organic acids, plasma acylcarnitines, Prader-Willi methylation testing, Spinal muscular atrophy genetic testing, Myotonic dystrophy genetic testing, Congenital myasthenic syndromes genetic testing, very long chain fatty acids, ammonia, creatine kinase, and pyruvate.

Previous testing with abnormal results included: elevated lactate, and a brain and MRI with parturitional hemorrhages.

Clinical question

What is the diagnosis for this child? Confirming a diagnosis will provide information regarding prognosis and allow for appropriate management, surveillance and possible prevention of secondary complications. In addition, it will end the need for additional, and at times costly and invasive, testing in search of a diagnosis in a young child. Lastly, it will provide information regarding recurrence risk for the parents of this patient.

Genetic testing

A Whole Exome Family Plus Test, including sequencing and CNV analysis for the proband and unaffected parents, was requested.

The test focuses primarily on well-established disease genes. If negative, or if only part of the phenotype is explained, variants in candidate genes are also assessed.

Blueprint Genetics

Diagnostic summary

Given that there was no reported family history of the same disease, the exome data of the patient and parents were analyzed for *de novo* variants and variants following a recessive inheritance pattern. To account for incomplete penetrance of pathogenic variants, rare inherited heterozygous variants were analyzed.

The patient was identified to have a heterozygous nonsense variant, c.5543T>G, p.(Leu1848*) in *NSD1*. This variant occurred de novo. The variant introduces a premature termination codon at protein position 1848. It is predicted to cause loss of normal protein function either through protein truncation (1847 out of 2696 aa) or nonsense mediated mRNA decay. This variant has been identified in a cohort of individuals with a clinical diagnosis of Sotos syndrome. It has not been observed in the large reference population cohorts of the Genome Aggregation Database (gnomAD). Heterozygous loss of function variants in *NSD1* are a well-established mechanism of disease in Sotos syndrome.

Blueprint Genetics' Whole Exome Sequencing

We offer two types of whole exome sequencing tests (seq & CNV analysis included):

Whole Exome Plus (index patient)

Whole Exome Family Plus (index patient + parents)

Diagnostic implications

As the *NSD1* variant was not identified in either parent, the risk for the patient's parents to have another affected child is expected to be low, but not zero, due to the possibility of germline mosaicism in one of the parents.

Blueprint Genetics' Take Home

After a diagnostic odyssey involving over a dozen different investigations (genetic, biochemical, and imaging testing), none of which were informative, the WES Family Plus analysis at Blueprint Genetics was able to make a diagnosis of Sotos syndrome and provide an answer for the family.

The diagnostic odyssey for this patient has now ended. The focus can now be on management and surveillance for known features and complications of Sotos syndrome.

Read more about us, our services, and customer support at **blueprintgenetics.com**

Contact us with any questions, we're here to help!

We are continuously developing our services and offering. We may amend service descriptions from time to time by posting new versions on our website. For up-to-date information, please visit blueprintgenetics.com.

Join the conversation #GeneticKnowledge

www.blueprintgenetics.com

CSNSD1A41-02

Blueprint Genetics