The power of NGS-based CNV analysis within an exome

Patient information

A young adult presented as an infant with feeding difficulties, growth retardation, recurrent infections, dysmorphic features and multiple congenital anomalies including bilateral coloboma and bilateral choanal atresia.

The patient has severe intellectual disability and developmental delay, endocrine abnormalities, seizures and hepatic adenomas and had been given a clinical diagnosis of CHARGE syndrome despite some atypical features.

Previous genetic testing

Previous testing performed at another laboratory, including sequencing and MLPA of *CDH7* and a chromosomal microarray, was negative.

Clinical question

The patient has two adult siblings who are concerned about the risk to have a similarly affected child. In addition, confirming a diagnosis may have implications for the patient's medical management.

Testing at Blueprint Genetics

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.

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Diagnostic summary

The patient was found to have a heterozygous *de novo*, likely pathogenic 3.4kb deletion in the *SMC1A* gene; c.(2973+1_3286-1)del, encompassing exons 20-21.

The deletion was confirmed by qPCR. The *SMC1A* gene is located at Xp11.2. The deletion is expected to maintain the translational reading frame, but results in a protein lacking 103 amino acids. There are no individuals with overlapping deletions in the Exome Aggregation Consortium (ExAc) data set. Intragenic *SMC1A* deletions have been reported in at least 2 other females with severe developmental phenotypes. *SMC1A* variants are known to cause a phenotype resembling Cornelia de Lange syndrome (CdLS). Sequence analysis did not detect any known disease-causing sequence variants that would explain the patient's phenotype.

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 *SMC1A* deletion was not identified in either parent, the risk for the patient's siblings to have a similarly affected child is low.

With a confirmed diagnosis, this patient can have appropriate surveillance for health issues and prevention of secondary complications known to occur more frequently in individuals with CdLS.

Blueprint Genetics' Take Home

Blueprint Genetics' analytic validation has demonstrated a 92.3% sensitivity to detect single exon deletions, and 100% sensitivity for 2 exon deletions and duplications.

To date, no publications have compared the performance of NGS-based CNV analysis to chromosomal microarray. However, WES with high quality CNV analysis was able to detect a 2-exon deletion in this patient despite the fact that the patient had a previous normal CMA. A normal CMA does not rule out the possibility of deletions or duplications in your patient.

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

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

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