Congenica

Enabling genomic medicine

Congenica Enables Five Minute Diagnosis of Previously Unsolved Case

The Platform's de-novo filtering and variant prioritization helps increase diagnostic yield and accelerates case throughput

Patient Profile

A couple had their first child, a son. The pregnancy and birth were uncomplicated but at four-to-five-months-old he started to have infantile spasms. By nine-months-old, he was having up to eight per day. His parents expressed concerns that the infantile spasms were not being taken seriously by healthcare professionals and instead were being attributed to gastro-oesophageal reflux.

EEG analysis confirmed the presence of a modified hypsarrhythmia pattern of seizure. Treatment using medication was started and the seizures stopped almost immediately. After three months, his medication was stopped altogether without any recurrence of the seizures.

A subsequent MRI examination revealed an abnormal signal in several areas of his brain and (now at three years old) he has a profound intellectual disability, global developmental delay and some dysmorphic features.

The couple wanted more children but decided to wait until they had a diagnosis for their son's condition in order to understand the risk of having another similarly affected child. To enable this, DNA from the family was sent to another provider for whole genome sequencing analysis, but when their physician received the results no likely causal variants were identified.

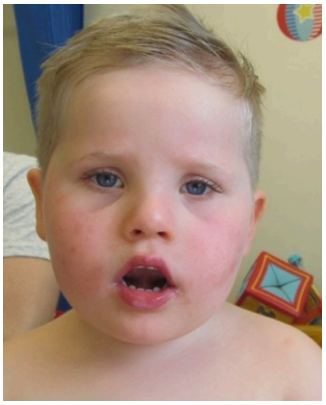

Figure 1: *Photograph of the boy showing some dysmorphic features, including epicanthic folds and an open-mouthed appearance.*

Expediting the Diagnosis

The physician was still suspicious that the boy's condition had an underlying genetic cause. A few months later, Congenica performed whole exome trio sequencing, data processing and analysis. A likely pathogenic variant in the *NEXMIF* gene on the X chromosome was revealed as the cause of this boy's condition.

Within just five minutes, the causal variant was identified thanks to Congenica's accurate variant annotation, advanced filtering and variant ranking processes.

In this case, Congenica's high quality de-novo annotation, filtering and Exomiser variant ranking were key tools in resolving this previously unsolved case.

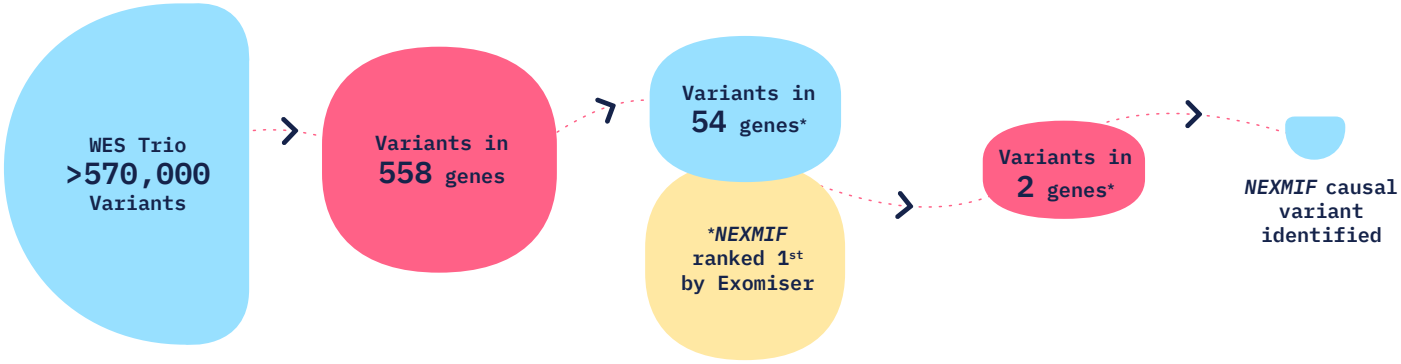

Figure 2: *Filtering reduced the number of variants from 570,331 to hundreds of variants in 558 genes. NEXMIF was ranked first by Exomiser at this stage, the Gene Panel (>1500 genes) then reduced the candidate variants from 558 to 54 genes. Again, NEXMIF was ranked first by Exomiser and the De-novo Inheritance filter reduced variants from 54 to 2 genes. The NEXMIF causal variant was subsequently identified.*

Solving the Unsolvable

Congenica's variant annotation and filtering features provided the advanced and accurate diagnostic capability and efficiencies for this developmental disorder case. The software's de-novo functionality quickly highlighted the causal variant, which was missed by other tools.

The integrated Genome Browser provided added confidence in this case by allowing scientists and physicians to visually examine parental sequencing alignments. As expected in this case, the results seen in the Genome Browser support the de-novo annotation.

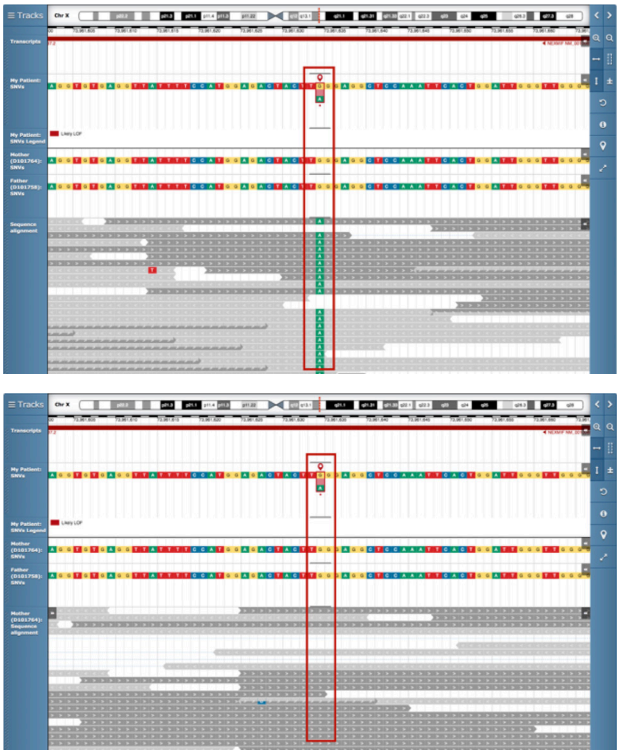

Figure 4: *The top Genome Browser image shows the variant is present in the child and is clearly visible in his sequence alignments (red box). The bottom Genome Browser image clearly shows the variant (highlighted in red box) is not present in the parental sequence alignments.*

Diagnostic Outcome for the Family and Medical Community

The family were reassured to know that the causal variant arose de-novo. So, the recurrence risk for future pregnancies is very low, and the couple are expecting their second child.

The case subsequently formed part of an internationally collated *NEXMIF* case series, which was presented at the American Epilepsy Society in 2018. Congenica also submitted this variant to the GeneMatcher online repository. This diagnosis has further contributed to the knowledge of this rare genetic disorder.

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