Congenica

Enabling genomic medicine

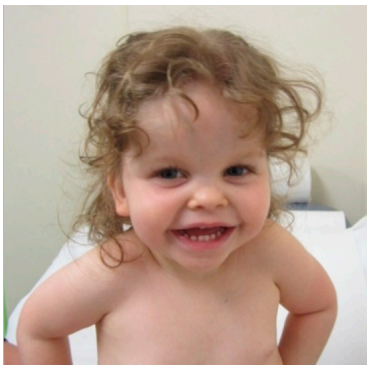
Congenica's Sensitive Secondary Pipelines Assist in Diagnosis of Complex Case

Congenica's accurate and sensitive secondary pipelines, and comprehensive visualization tools enable a diagnosis of a low-level mosaic variant

Patient Profile

A couple attended the Genetics Clinic with their adopted daughter, aged two-and-a-half years. A review revealed she has developmental delay, mild facial dysmorphism (widened distance between the eyes), short stature and small fifth toenails. A soft heart murmur was identified, and an echocardiogram was scheduled.

> **"Congenica has demonstrated its diagnostic utility for this case, where the low levels of the variant could have led to a missed diagnosis. It provides reassurance to our clinical team that such patients will not be missed in the future, thanks to Congenica's accurate and sensitive pipelines."**
>
> Dr. Meriel McEntagart, the lead Clinical Geneticist for this case, from St George's NHS Hospital Trust.



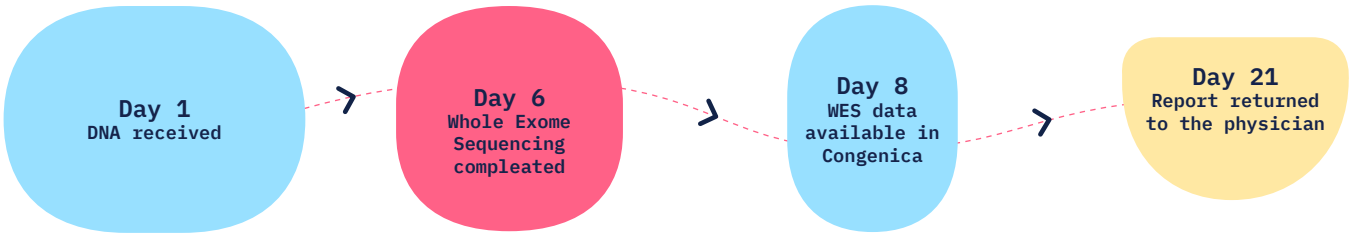
Diagnosis Through a Dynamic Workflow

Congenica contains multiple interpretation workflows, allowing clinicians to work across different clinical scenarios and family structures. In this case, the biological parents were unavailable. So, DNA extracted from the white blood cells of this little girl was sequenced by singleton, whole exome sequencing.

The dynamic workflow used in this analysis utilized phenotype-based variant prioritization and virtual gene panels to identify the causal variant. Using these filters, a clinical review quickly identified a novel heterozygous, likely pathogenic variant in the *ARID1A* gene.

Variants in *ARID1A* are associated with Coffin-Siris syndrome, which has many variable signs and symptoms. It is a rare condition, which is diagnosed in females more frequently than in males, with approximately 140 cases reported in the medical literature.

There is an overlap in the clinical features identified in this child and the Coffin-Siris syndrome phenotype. These include: the abnormality of the fifth toenails, developmental delay and facial dysmorphism. In addition, cardiac abnormalities and short stature are less commonly identified features. However, this little girl has a milder presentation than is classically observed in individuals with Coffin-Siris syndrome.



The causal variant was identified in only ~17% of reads, suggesting it could be a case of mosaicism. Individuals with mosaicism usually have similar phenotypes to those with a non-mosaic form of the same condition, but this is not always the case. This may explain why the symptoms present in this little girl are milder than those usually seen in individuals with Cofin-Siris syndrome.

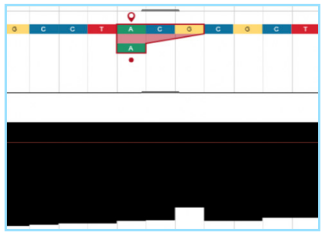


Fig 1: The coverage track.

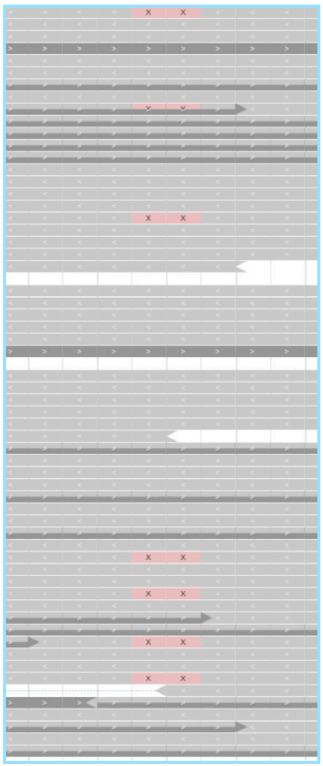


Fig 2: The sequence alignments track.

How Congenica Aided The Diagnosis

Raw sequencing data was processed using Congenica's integrated secondary pipelines and uploaded into the Congenica platform for review.

Congenica's integrated secondary pipelines are accurate and sensitive, enabling the identification of a low-level mosaic variant in this case.

Within Congenica, the variant can be viewed in more detail in the Genome Browser via the coverage track (Figure 1) and the sequence alignments track (Figure 2).

The Genome Browser's coverage track shows a slight drop in the number of reads at the deletion site and the sequence alignments track identifies the variant in a reduced number of reads than expected for a heterozygous call.

The ability to view sequence alignments and coverage in the Genome Browser corroborates the variant call, providing further confidence in the diagnosis in this case. The variant was further confirmed by Sanger sequencing (Figure 3).

The accuracy of the pipelines has been further validated via the UK's Genomics Quality Assessment Body, GenQA, where an external assessment of the secondary pipelines achieved full marks under the body's pilot QA scheme.

The Outcome for the Family and Medical Community

A clear diagnosis gives this couple the opportunity to support their daughter and her additional needs, providing peace of mind for the family.

This case clearly demonstrates the powerful diagnostic capabilities of Congenica's pipelines to call these low-level variants. Its secondary pipelines were fundamental in enabling identification of a mosaic variant, with the ability to view sequence alignments and coverage in the Genome Browser supporting the variant call and providing further confidence in this case.

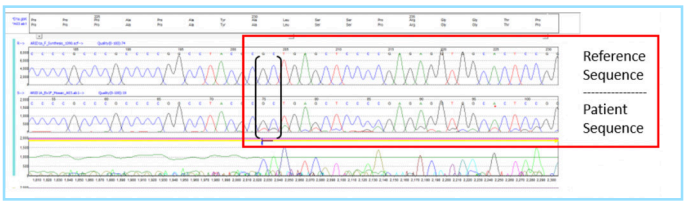


Fig 3: The start of the mosaic heterozygous 2bp deletion is indicated by brackets. The variant introduces a shift in the reading frame, as evidenced by the low level background peaks in the electroperogram following the mutation start point.

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