Congenica

Enabling genomic medicine

Expediting an Accurate Diagnosis through Streamlined Clinical Workflows

Congenica's intuitive inheritance filtering workflow facilitates fast and accurate identification of causal variants.

Patient Profile

A couple had two first trimester miscarriages before the birth of their son. A subsequent male pregnancy was also lost due to hypoplastic left heart syndrome, a severe abnormality of heart development.

Due to their reproductive history the parents were referred to the genetics clinic where their living son was examined and found to have microcephaly, global developmental delay, hypotonia and a ventricular septal defect (VSD). Additional distinctive features were identified including characteristic features of the face and hands. Further examination by MRI revealed a complex mass in the pineal region consistent with a tumour.

The clinical suspicion that an underlying inherited disorder was involved was supported by post mortem examination of the lost male pregnancy, which revealed some shared phenotypic features. The physicians caring for the family hypothesized that both male siblings could be affected with the same condition with variable cardiac presentation.

William's parents said,

> **"We are not only lucky, but also very grateful to be able to find out about William's genetic disorder. Not only does it help with understanding William's developmental delays, it has also helped us understand the risks with future pregnancies. It has brought us more opportunities to support William and his additional needs, as well as getting support for future pregnancies. As a family, we would like to thank you."**

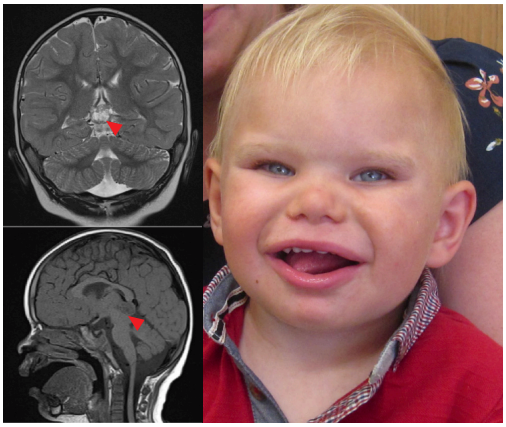


Figure 1: *Brain MRI showing complex mass in the pineal region.*
Figure 2: *Distinctive features include: upslanting and narrow palpebral fissures, synophrys, depressed nasal bridge, a wide mouth, brachycephaly and microcephaly with a head circumference <0.4 centile.*

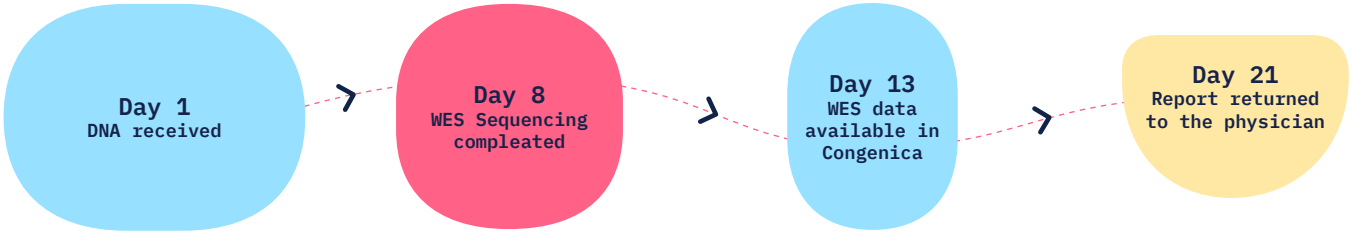
The Diagnosis

To determine whether an inherited condition may explain the family's clinical history, DNA samples from the sibling pair were sent to Congenica for "duo" whole exome sequencing (WES).

Using the "Sequencer-to-Congenica" pipeline, Congenica rapidly processed the whole exome sequencing data and the software's powerful inheritance tools were used to filter the variants based on the family structure.

DNA variants shared between the two siblings were identified and ranked to facilitate timely variant interpretation by Congenica's in-house team of clinical experts.

A single variant in the *UBE2A* gene was identified as the likely cause of the physical and developmental issues affecting the family. After multiple pregnancy losses, the likely cause of the disorder observed in this family was found and reported within 3 weeks using Congenica.



The Diagnostic Outcome

Disease causing variants in the *UBE2A* gene are inherited in an X-linked recessive manner. A literature review of 22 case reports of males with pathogenic variants in *UBE2A* revealed that the signs and symptoms observed in this case are shared across many of the published cases, including his characteristic facial features and developmental delay. Significantly, cardiac defects are also present in six individuals and pineal gland abnormalities in three.

The impact on the family of having received an accurate and rapid diagnosis is significant. They have a diagnosis for their son and have an accurate recurrence risk for future pregnancies. The family are now pursuing the option of preimplantation genetic diagnosis for future pregnancies.

Streamlined Diagnostic Analysis

Congenica's flexible interpretation workflows allow clinicians and scientists to review and assess different clinical scenarios and family structures in a single interface, expediting a speedy diagnosis. Congenica's clinical team used the software's Family Comparison filters to quickly reduce the number of candidate variants to review from 70 to 3 and accurately identified a likely pathogenic novel hemizygous variant in the *UBE2A* gene, located on the X chromosome. The variant was shared by both affected males in the family.

The variant is novel and has not been previously reported. Congenica's splice prediction algorithms predict that the variant will destroy a known splice acceptor site and disrupt normal splicing of the *UBE2A* gene.

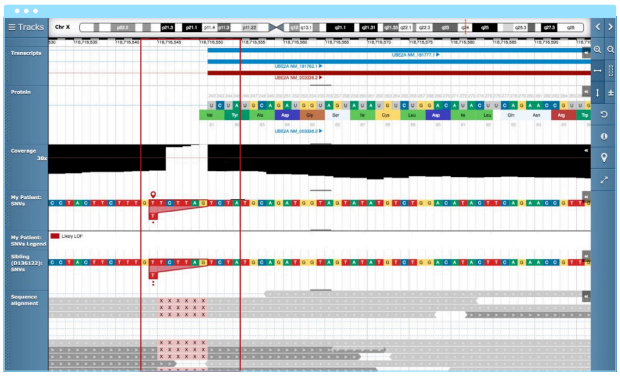


Figure 3: Congenica's integrated genome browser. The red box highlights that the c.242-3_244delTAGTCT variant spans the start of the 5th exon of the UBE2A gene and is present in both siblings. The hemizygous deletion can be clearly seen in the Coverage track.

Are you interpreting genomic data in the most efficient way possible?

The Congenica clinical decision support platform is empowering healthcare professionals to provide life-changing answers. Congenica unlocks the opportunity for diagnosis and characterization of genetic diseases, providing confidence for clinicians and clarity for their patients.