Congenica

Enabling genomic medicine

Ending an 8 Year Odyssey: Delivering a Diagnosis in 20 Days

Congenica's clinical decision support platform used to facilitate quicker, cost-effective care.

Patient Profile

The routine ultrasound examination of a couple's first pregnancy identified that the male fetus was affected with a very severe abnormality of the skeleton, including extremely short and bent bones in the arms and legs and abnormal skull development. The abnormalities were so severe they were incompatible with survival, consistent with the clinical diagnosis of a lethal skeletal dysplasia.

The detected skeletal abnormalities were suspected of being the result of an inherited disorder, and initial diagnoses included thanatophoric dysplasia (TD), but analysis of the *FGFR3* gene (known to cause TD) failed to confirm this diagnosis, and despite extensive clinical evaluation by international experts the cause of the disorder in the family remained unknown.

When two subsequent pregnancies identified male fetuses with identical skeletal abnormalities, a DNA sample from the second affected fetus was also sent to a specialist international laboratory, but again no cause was identified.

> **"Congenica's combination of flexible workflows and data visualization tools have helped provide a diagnosis where other approaches have failed - all within a 20-day diagnostic window. This is a powerful tool that has helped this family bring 8 years of turmoil to a close."**
>
> Professor Sahar Mansour, Consultant Clinical Geneticist and Physician, St George's University Hospitals NHS Foundation Trust

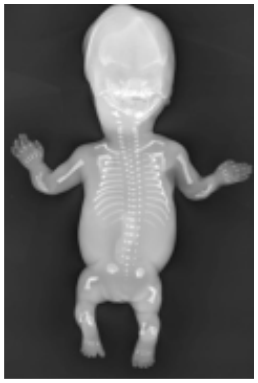


Figure 1: *An X-ray examination was consistent with a diagnosis of thanatophoric dysplasia but notably the fetus lacked the temporal lobe dysplasia, which is usually observed in this condition.*

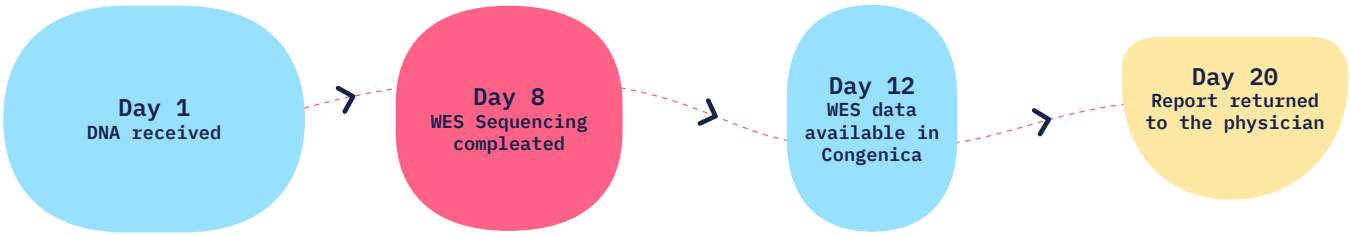
A Rapid & Accurate Clinical Diagnosis

Given that extensive clinical review and analysis of likely candidate genes had failed to provide a molecular diagnosis, a more gene agnostic approach was taken; a DNA sample from the third affected pregnancy (a singleton) was sent to Congenica for whole exome sequencing (WES) analysis.

Using the Sequencer-to-Congenica pipeline, Congenica rapidly processed the whole exome sequencing data and annotated variants to facilitate timely variant interpretation in the software by Congenica's in-house team of clinical experts*.

After eight years of waiting, the likely cause of the skeletal abnormalities observed in this family was found and reported within just 20 days from DNA receipt using Congenica software.

**Congenica's variant alignment and variant calling bioinformatic pipeline is accurate as well as rapid, as evidenced by successful participation in the EMQN / GenQA* (Pilot EQA scheme for Next Generation Sequencing (2018)) external quality assessment scheme.*



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 and enabling more cost-effective care.

In this case, Congenica's clinical team used an integrated clinical workflow within the software to capture multiple clinical scenarios and variant types. A review of the whole exome data was carried out using standard settings and no candidate variants were detected. Analysis of the case continued, utilizing Congenica's curated lists feature.

Congenica's curated variant lists ensure that known causal variants are returned irrespective of the type of variant or its frequency. This was a vital attribute in this case because, unlike most genes, the *RMRP* gene encodes a noncoding RNA molecule and not a protein. Using standard analysis settings, such variants are easy to miss. Curated lists are generated from known data sources, such as ClinVar or literature sources, or can be bespoke and uploaded by the User.

In this case, Congenica's flexible, accurate and effective clinical workflows allowed rapid identification the *RMRP* causal variants, providing a fast and accurate diagnosis.

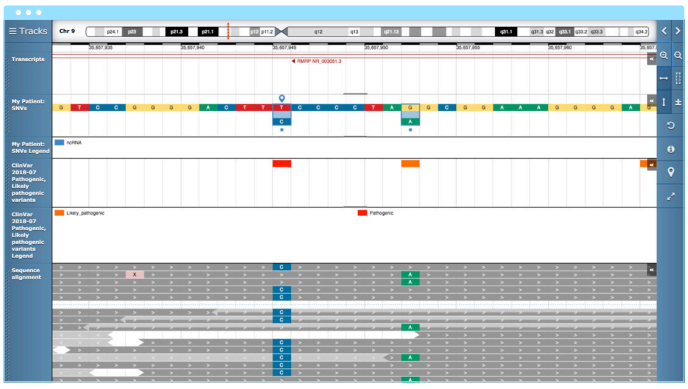


Figure 2: *Sequence alignments of the RMRP gene visualized in Congenica's integrated genome browser showing the (n.71A>G and n.64C>T) causal variants. As the variants are located on the same sequencing read the genome browser demonstrates clearly that the variants are present in a compound heterozygous state.*

Diagnostic Outcome

Disease causing variants of the *RMRP* gene are inherited in an autosomal recessive manner and to date have been associated with three clinical disorders: metaphyseal dysplasia without hypotrichosis, cartilage-hair hypoplasia and anauxetic dysplasia.

Whilst prenatal manifestations of these disorders have been described in the literature, to our knowledge this family is the first case in the world where variants in the *RMRP* gene have been implicated in a prenatal lethal skeletal dysplasia.

This not only widens the understanding of the clinical spectrum of the gene, but also enables accurate genetic counselling and improved prognostication and clinical decision-making, going forward.

For the family, an eight-year diagnostic odyssey has now come to an end, providing them with accurate information for future reproductive choices and allowing carrier screening for other family members.

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.