Congenica

Enabling genomic medicine

Accelerated Diagnosis Enables Appropriate Patient Care

Whole Exome Analysis using Congenica reveals diagnosis, allowing clinicians to cease costly and invasive testing months earlier.

Accelerating the Diagnosis

The pediatric neurologists and clinical genetics team at St. George's University Hospital were facing a challenging case – a 4-month old infant had been experiencing severe uncontrolled seizures of unknown etiology and her parents were desperate for answers.

After an initial battery of tests failed to provide a definitive diagnosis, the team knew they would have to wait weeks for international experts to review the child's scans and up to 6 months for confirmatory genetic testing.

Looking to get answers sooner, they collaborated with Congenica to see if their clinical decision support platform could deliver a diagnosis faster.

Using whole exome trio analysis of the child and her parents, Congenica's clinical services team provided the accurate diagnosis of vanishing white matter (VWM) disease within three weeks, eliminating the need for further invasive and costly testing and informing the proper course of care much faster than the traditional diagnostic route.

The St. George's team said,

> **"The child's parents were extremely grateful for the efforts we went to in order to make the diagnosis. They now know what they are facing and their options for future pregnancies."**

Patient Profile

The child's birth was uncomplicated. Her head circumference and weight at birth were both normal (50th to 75th percentile), as was her early social and visual development. Newborn screening at day 5 detected moderate sensorineural hearing loss, which was soon followed by an observation of poor head control.

At three months, the child began to experience seizures and she was referred to a pediatric neurologist for further examination. Her seizures failed to respond to medication and began to worsen in terms of frequency, length, and intensity, which lead to prolonged hospital stays.

Clinical Investigation

To explore whether a neurometabolic disorder was the underlying cause of the seizures, the child was given a host of tests, including blood, urine and cerebrospinal fluid tests, nerve conduction studies, and ophthalmology examinations.

When results were inconclusive, an MRI brain scan was conducted and showed the child had an absence of white matter within the cerebral hemispheres (Figure 1). With this knowledge, the diagnostic team hypothesized that the child had a hereditary hypomyelinating or leukoencephalopathic disorder.

With over 140 potential causative genes for such disorders, pinpointing the exact cause of the child's seizures would not be easy.

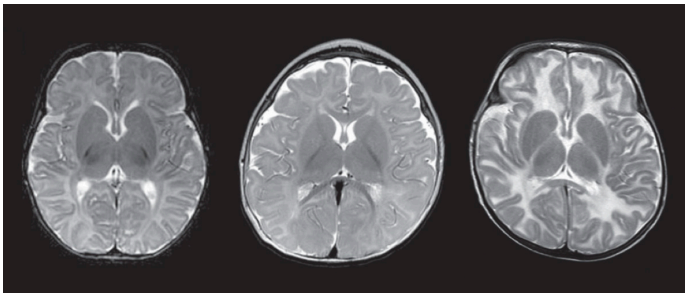

Figure 1: *Brain MRI images of* ***(A)*** *normal 2-month old female,* ***(B)*** *normal 6.5-month old male, and* ***(C)*** *patient at 4 months with the absence of white matter within the cerebral hemispheres suggestive of a hereditary hypomyelinating or leukoencephalopathic disorder.*
(T2 fast spin echo imaging)

A New Approach

With a suspected hereditary hypomyelinating or leukoencephalopathic disorder at hand, the St. George's University Hospital team took an unconventional approach – they set out on a traditional diagnostic journey involving expert clinical consultation and single-gene testing, while simultaneously enlisting Congenica to perform whole exome trio analysis in the hope of getting answers for the family as quickly as possible.

By taking this bilateral approach, the team received a confirmed genetic diagnosis of Vanishing White Matter (VWM) disease from Congenica within just three weeks. This diagnosis was later supported through the traditional diagnostic route, which included a review of the primary MRI brain images, and clinical diagnosis by an international expert, taking over four weeks, alongside in-house confirmatory genetic testing of Congenica's findings.

Had Congenica not been used to reach an early diagnosis, the traditional route could have taken an additional 6 months and would have likely also involved a battery of additional invasive and costly tests, something that both the parents and the St. George's team wanted to avoid.

The family was counselled about their daughter's prognosis and was advised that future pregnancies would carry a 25% risk of this condition, and therefore options such as prenatal diagnosis or preimplantation genetic diagnosis could be explored in the future. Additionally, genetic testing was made available to the wider family.

Diagnostic Method

Congenica's clinical services team performed whole exome trio analysis using the Congenica platform, to explore and compare variants within the child's and parents' exomes to uncover the causal gene mutation.

Congenica's clinical decision support software helps speed up the genetic-diagnostic process by providing an integrated, web-based application. In this case, it took about fifteen minutes for Congenica to pinpoint a potential causal mutation on the *EIF2B5* gene. As shown in Figure 2, biparentally inherited mutations in the *EIF2B5* gene were identified with Congenica.

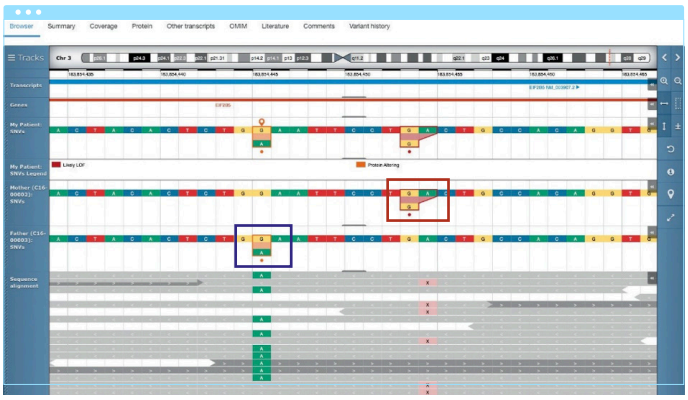

Figure 2: *Screenshot from Congenica clearly showing the patient had inherited mutations in the EIF2B5 gene coming from both the father (left, blue boxing) and mother (right, red boxing). Mutations in EIF2B5 are thought to be responsible for sixty-five percent of cases of leukoencephalopathy with vanishing white matter*

The timeline in Figure 3 compares at which point key diagnostic milestones were reached in this case using whole exome trio analysis with Congenica versus the traditional diagnostic approach of expert clinical consultation and subsequent gene testing.

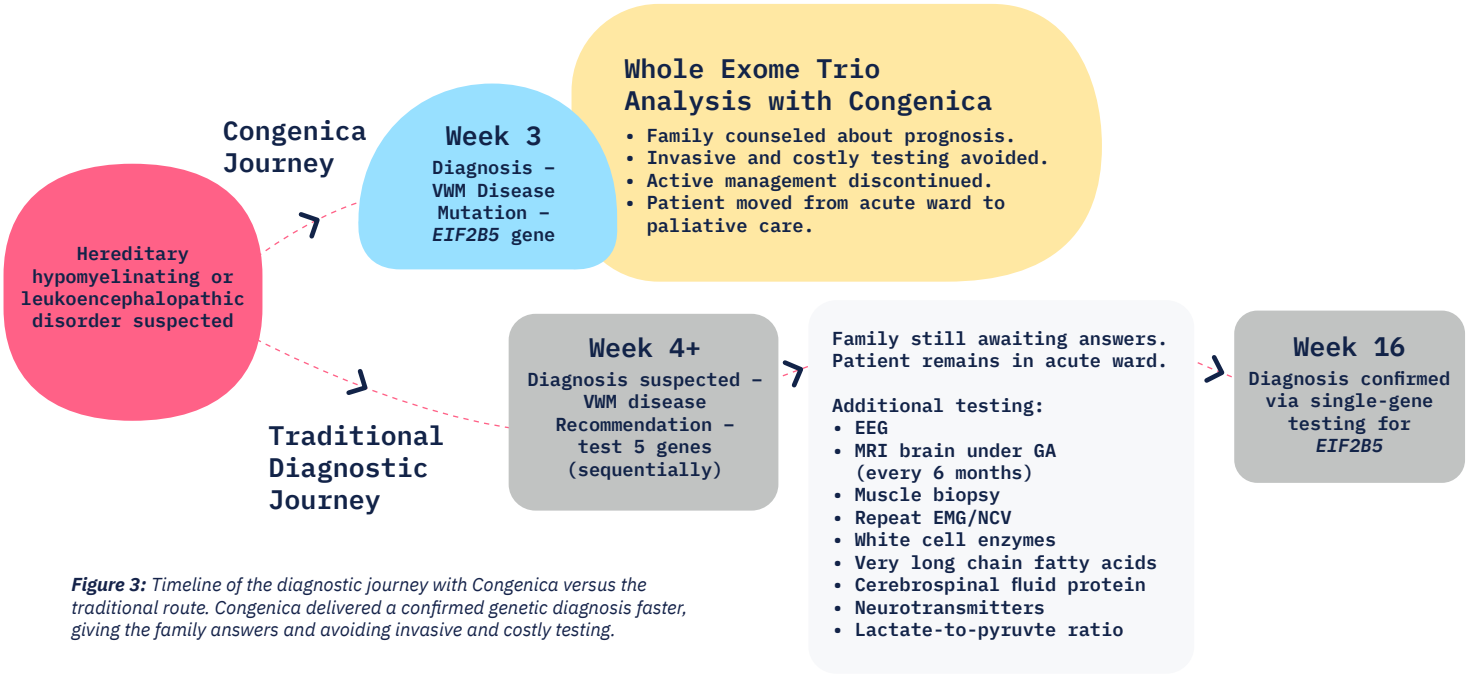

Figure 3: *Timeline of the diagnostic journey with Congenica versus the traditional route. Congenica delivered a confirmed genetic diagnosis faster, giving the family answers and avoiding invasive and costly testing.*

Optimizing care for patients

Leading hospitals such as St. George's University Hospital have chosen to partner with Congenica because its platform helps deliver diagnoses quickly and accurately.

Congenica seamlessly handles vast amounts of disparate data and is truly scalable in terms of what genetic data it analyzes. It can examine and identify mutations in a single gene, gene panel, exome, or entire genome. It can explore the genetic data of an individual patient or a child and parents (trio analysis).

Visual reports of results are accessible via Congenica's secure, intuitive interface, thereby empowering team members who are spread across specialties and locations to visualize results, add commentary, and collaborate remotely.

Moreover, it does all this alongside deep clinical phenotyping, providing a clinical diagnostic tool that is at once fast and accurate.

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.