CASE STUDY

Childhood Onset Slowly Progressive Leukoencephalopathy Diagnosed Using the Strand Clinical Exome Test

Introduction

Leukodystrohies are progressively debilitating disorders wherein degradation of the white matter (myelin sheath) of nerves is a hallmark characteristic. There are 20-25 known leukodystrophy syndromes including Fabry disease, Krabbe disease, Sjogren-Larsson syndrome and Zellweger syndrome (Köhler et al. 2018; Steinberg et al. 1993).

Demyelination of nerves in the brain, spinal cord, and peripheral nerves results in cognitive problems, physical imbalance, and sensory deficits in these disorders.

Patient Profile

Debasis Upadhyay*, aged 18 years, had always been considered as a person with cognitive dificulties. He had other behavioural problems like regressive and self-harming behavior, generalized seizures and spasticity since childhood.

He was referred to Dr. Neeta Naik, a renowned pediatrician who specializes in neurodevelopmental disorders.

Along with the behavioral and developmental problems since infancy, his physical examination at present revealed normal head size, coarse facies, and generalized hyperpigmentation, but no organomegaly. Neurologic examination revealed visual impairment, lack of ambulation, and spasticity in all 4 limbs. Sensory evaluation was not possible. His ophthalmic evaluation showed severe retinitis pigmentosa. MRI revealed difiuse, extensive cerebral white matter abnormalities along with thinning of the cortex.

Gender : Male

Age : 18 years

Location: Mumbai, Maharashtra

Diagnosis: Leukoencephalopathy and Neuropathy

Strand Test: Clinical Exome

Conclusion :

- Precise diagnosis of RPIA deficiency
- Parents' questions about origin of son's condition finally answered

Family History

Debasis was born from a nonconsanguineous marriage, normal birth and no other family history.

Results of Genetic Testing

RESULT + **Variant of Unknown Significance 'VUS' identified in the *RPIA* gene**

The Strand Clinical Exome Test was prescribed for Debasis with the intention of arriving at a differential diagnosis between known leukodystrophy disorders. Instead, a mutation was found in the *RPIA* gene in his genome.

* Name changed to protect patient privacy

Key Findings

Gene	Variation	Zygosity	Clinical significance
RPIA	chr2:89035250T>C c.592T>C p.Phe198Leu	Homozygous	Variant of Unknown Significance

Debasis is homozygous for a variant of unknown significance or a 'VUS' mutation in the *RPIA* gene.

RPIA codes for an enzyme – ribose-5- phosphate isomerase - that is involved in the isomerization of ribose into ribulose in the pentose phosphate pathway (Genetics Home Reference). Deficiencies of this enzyme can result in accumulations of polyols. Instances of this deficiency are rare, with only a handful of cases reported (Naik et al. 2017; Wamelink et al. 2010; Huck et al. 2004). The variant identified in this case is a novel variant.

The exact role of this genetic variant in the manifestation of ribose-5- phosphate isomerase deficiency is not known. Given the manifestation of neurological deficits in Debasis, this variant is likely to be pathogenic. However, there is insufficient evidence to support its classification into the 'pathogenic' category, given that this enzymopathy is rare.

Conclusion

- Debasis, an 18-year-old boy with severe cognitive disabilities and behavioral problems was diagnosed with ribose-5-phosphate isomerase deficiency.
- Analysis using the Strand Clinical Exome Test showed that Debasis is homozygous for a VUS mutation in the *RPIA* gene.
- This is a very rare case of ribose-5- phosphate isomerase deficiency presenting with leukoencephalopathy and loss of frontal brain tissue.
- Incidence of leukdystrophic abnormalities was suspected upon clinical examination of the patient. However, the genetic profile, obtained using the Strand Clinical Exome test, provided clear evidence for the incidence of ribose-5- phosphate isomerase deficiency.
- Genetic testing helped reach a diagnosis and provide an answer to Debasis' parents who worked really hard for his care. A metabolic test and Magnetic Resonance Spectroscopy (MRS) was performed for confirming the diagnosis.
- The genetic diagnosis of this very rare condition helped justify poor prognosis of the condition.

Strand Clinical Exome Test

The Strand® Clinical Exome test is a Laboratory Developed Test (LDT) that was developed and its performance characteristics determined by Strand Center for Genomics and Personalized Medicine at Strand Life Sciences. The test covers ~4500 genes and is a comprehensive test for IEM disorders as well as neuromuscular and neurocognitive developmental disorders.

References

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