CASE STUDY

SCN1A-related Seizure Disorder Diagnosed Using the Strand Clinical Exome Test

Introduction

Pediatric epileptic disorders include syndromes like Severe Infantile Multifocal Epilepsy, Benign Myoclonic Epilepsy, Lennox-Gastaut Syndrome, Myoclonic Astatic Epilepsy, Dravet Syndrome and Epileptiform Discharges, some of which fall under the umbrella of genetic epilepsy with febrile seizures plus (GEFS+). Differential diagnosis between these syndromes is based on symptoms, types of seizures and age of onset of seizures (Millichap et al. 2009).

Dravet Syndrome, found at the severe end of the spectrum of GEFS+ disorders, is characterised by frequent febrile seizures in infancy followed by afebrile seizures. A variety of generalised seizures (including myoclonic seizures) and partial seizures occur. Typically, these symptoms are evident in infants aged less than 1 year. Other symptoms like epileptiform discharges, partial seizures, generalized convulsions are common to Lennox-Gastaut syndrome, Myoclonic Astatic Epilepsy and Benign Myoclonic Epilepsy.

Given that symptoms alone cannot be sole diagnostic criteria for differential diagnosis, modern diagnostic techniques like the next-generation sequencing (NGS) - based Strand Clinical Exome Test can be used effectively to pinpoint the molecular variations present in a patient. According to a recent study, an underlying genetic cause can be identified in ~40% of individuals with early onset epilepsy (Berg et al. 2017). Identification of the actual genetic variant has been instrumental in enabling differential diagnoses in several other cases of congenital malformations, as well.

Gender : Female

Age : 6 years

Location: Ahmedabad, Gujarat

Diagnosis: Genetic epilepsy with febrile seizures plus (GEFS+)

Strand Test: Clinical Exome Test

Conclusion :

- Precise diagnosis of pediatric epilepsy
- Therapeutic options suitable for GEFS+ indicated

Patient Profile

Sonalika Deshmukh*, aged 6 years, had experienced frequent febrile seizures throughout childhood. In addition to these episodes, her overall development seemed also to be somewhat slow. Although she was a generally happy child, concerns about her future well-being had begun to weigh on her parents' mind.

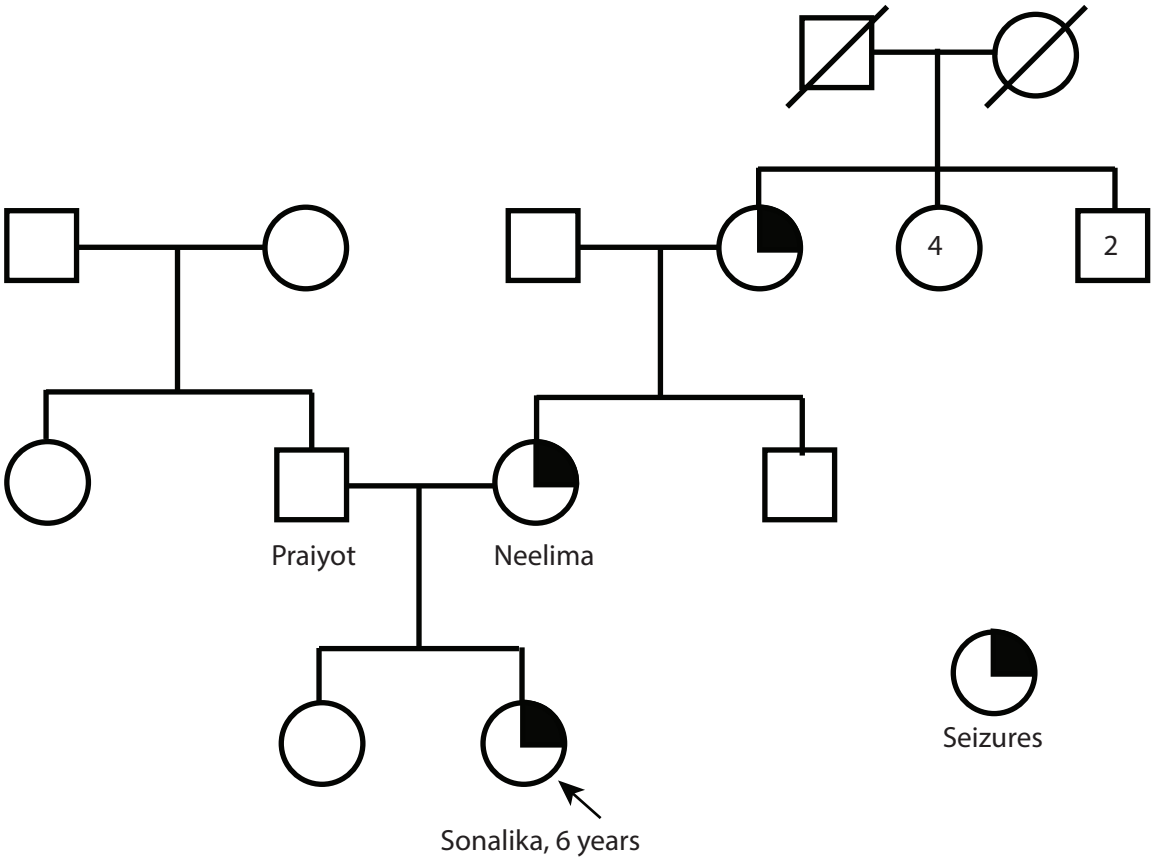
Her anxious parents, Neelima* and Prajyot Deshmukh* had consulted several doctors over the course of 6 years. Yet seizures had continued to occur even after treatment. They were then referred to Dr. Siddharth Shah at the Pediatric Neurology Clinic, Ahmedabad for a consultation. Dr. Shah suggested that Sonalika should do the Strand Clinical Exome Test to understand the genetic etiology of her seizures.

Family History

Prajyot and Neelima are a non-consanguineous couple. It was noted that Sonalika's mother and her maternal grandmother both had episodes of seizures in their childhood indicative of familial seizure disorder.

* Name changed to protect patient privacy

Family Tree - Pre-Test Genetic Counselling



Results of Genetic Testing

The Strand Clinical Exome test showed that Sonalika had a mutation in the *SCN1A* gene.

RESULT **A likely pathogenic variant in the *SCN1A* gene was identified**

Key Findings

Gene	Variation	Zygosity	Inheritance	Clinical significance
SCN1A	chr2:166894608G>T c.2624C>A p.Thr875Lys	Heterozygous	Dominant	Likely Pathogenic

- A mutation in the *SCN1A* gene was identified in 6-year-old Sonalika, using the Strand Clinical Exome test.
- The *SCN1A* gene codes for one subunit of a sodium channel protein that is expressed in nerve cells.
- The identified mutation results in change of a conserved and essential amino acid residue in the *SCN1A* protein and is predicted to have a damaging effect on protein function by 6 *in-silico* prediction tools.

- Other studies have reported the co-segregation of this mutation with manifestation of Dravet Syndrome (Depienne et al. 2008; Depienne et al. 2010).
- Considering these factors, the genetic variant identified in Sonalika has been classified as being 'likely pathogenic'.
- Mutations in *SCN1A* have been reported to cause epileptic seizures when inherited in autosomal dominant fashion.

Discussion

Considering Sonalika's mother's history of seizures in her childhood, mutation-specific testing for the mutation identified in the SCN1A gene was carried out for her. She was identified to be a carrier for the same mutation as her daughter. This is indicative of the familial type of seizure syndrome Generalized epilepsy with febrile seizures plus (GEFS+) (Genetics Home Reference).

In a family with GEFS+, epilepsy with variable expressivity and incomplete penetrance is inherited in an autosomal dominant manner. Although the complete range of associated phenotypes can be seen within any family, the seizure phenotypes tend toward the mild end of the spectrum (Scheffer & Berkovic, 1997) because the more severe seizure types have a reproductive disadvantage and, thus, are less likely to be familial (Claes et al. 2001). Information about her mother's type of epilepsy is not available but may indicate Sonalika's seizures to be towards the mild end of the spectrum.

Considering variable presentation seen in the family with the same mutation for seizures, it is important to have a detailed family history and to genetically evaluate other symptomatic individuals in the family. This may help in discussing the risk for a seizure disorder in the next pregnancy and variable expressivity seen in seizure disorders.

Treatment Plan

Sonalika's parents were counselled post diagnosis. They were advised about strategies to manage their daughter's developmental challenges.

GEFS+ can be treated using a combination of Stiripentol and other anti-epileptic drugs (Czuczwar et al. 2008). Similarly, a combination of valproate or topiramate and clobazam may also work to control seizures in GEFS+.

Conclusion

- A 6-year-old child, Sonalika was referred to Dr. Siddharth Shah, Ahmedabad, for diagnosis and management of pediatric epilepsy.
- The Strand Clinical Exome Test facilitated the identification of a *SCN1A* mutation in the child's genome.
- The genetic mutation identified in Sonalika's DNA was classified as 'likely pathogenic' based on analysis using *in-silico* prediction tools and evidence from other similar cases.
- Therapeutic options as well as strategies for management of Sonalika's developmental challenges were provided to her parents.

Strand Clinical Exome Test

The Strand® Clinical Exome test is a Laboratory Developed Test (LDT) that was developed at the 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.

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