CASE STUDY

Diagnosis of Joubert Syndrome Confirmed by Genetic Analysis

Quick Summary

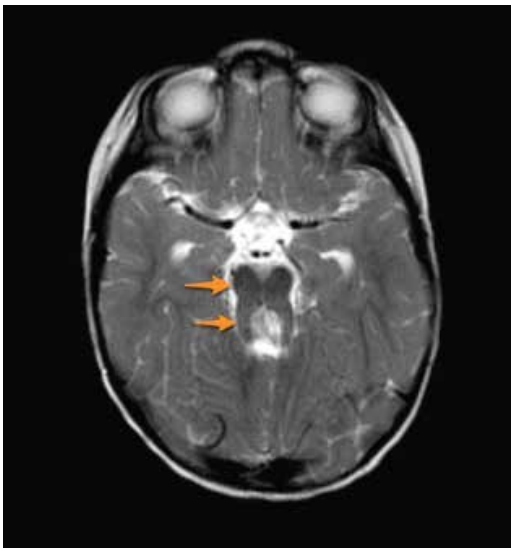
- Baby Snigdha*, aged 5 months, showed abnormal developmental features like persistent nodding and poor eye contact.
- Radiological investigations showed the presence of the 'Molar Tooth Sign' on her brain MRI, a characteristic feature of Joubert Syndrome.
- Genetic testing revealed that the child was homozygous for a chromosomal deletion covering the entire *NPHP1* gene.
- Parents were advised about options for management of developmental challenges in this baby as well as risks for bearing another child with the same mutation.

Introduction

Delays in the development of a baby can cause significant anxiety to parents. Milestones such as baby turning over on her stomach, stabilization of gaze and motor control over neck and limb muscles are usually evident in most babies in the first five-six months. The absence of such developmental milestones can suggest that the baby is suffering from a disorder of neuromuscular development. One such case of delayed development was recently referred to Strand for genetic analysis.

Patient Profile

Snigdha showed signs of slow development at the age of 5 months. She had poor eye contact with people around her and her head nodded persistently, displaying lack of control over neck muscles. A brain MRI was obtained to understand the reasons for delayed developmental milestones. The MRI showed the presence of a classic molar tooth sign in the cerebellar region, a clear indication of Joubert Syndrome (see representative Figure 1).



Snigdha was referred to a prominent pediatric geneticist in Hyderabad. Family history revealed that Snigdha was born to parents in a consanguineous marriage. In order to confirm the diagnosis of Joubert syndrome, a germline test- Strand's Neurodevelopmental Disorders Test – was prescribed.

Figure 1. Joubert Syndrome: Brain MRI shows presence of Molar Tooth Sign (orange arrows, representative image)

*Name changed to protect patient privacy

Joubert Syndrome

Joubert Syndrome is a developmental anomaly wherein the cerebellar vermis (the tissue that connects the right and left lobes of the cerebellum) and the brain stem are poorly developed. Uncoordinated muscle movements, irregular breathing patterns, uncoordinated eye movements, and the presence of the radiological molar tooth sign are some of the diagnostic features of this anomaly. Joubert Syndrome is a rare disorder with a frequency of incidence of 1/80,000 to 1/110,000 live births (Brancati et al. 2010). However, the incidence of this syndrome can be as high as 1/5000 live births in societies with a high degree of consanguinity and intermarriage, like Arab societies (Al-Gazali & Hamamy 2014; Ben-Salem et al. 2014).

Results of Genetic Testing

The Strand Neurodevelopmental Disorders Test was prescribed for baby Snigdha. This test is designed to ascertain mutations in 19 genes associated with Joubert syndrome.

RESULT ⊕ Positive for a heterozygous **'Pathogenic'** Variant which causes deletion of the *NPHP1* gene

Key Findings

Gene	Variation	Zygosity	Clinical significance
NPHP1	chr2:110881368-?_110962545+?del c.(?_-1)_(*1_?)del (Exons 1-20 deletion)	Heterozygous	Pathogenic

The identified NPHP1 deletion (homozygous state) has been confirmed by polymerase chain reaction (PCR).

Under normal circumstances, deletions of genomic regions are not detected in NGS analyses. However, Strand's proprietary bioinformatics software – Strand NGS and StrandOmics – have been designed to identify anomalous readouts, as well as copy number variations (See Figure 2, readouts between yellow arrowheads) that can potentially flag insertions and deletions. The software flagged a complete absence of the copies of the *NPHP1* gene. The neighbouring genes have been read accurately with a copy number of 2. This feature of Strand NGS- Strand's custom-designed software for analysis of NGS readouts- has been instrumental in identifying insertions and deletions in several other cases as well.

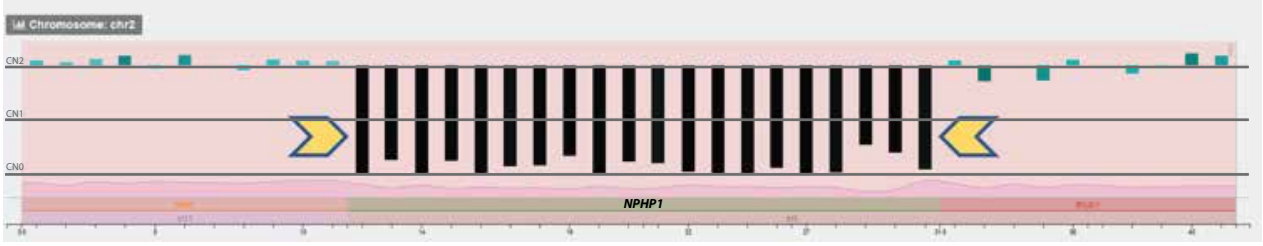


Figure 2. Identification of total absence of copies of the NPHP1 gene (area between yellow arrowheads)

Conclusions

- Baby Snigdha was found to be homozygous for a genomic deletion that contained the *NPHP1* gene. Deletions of this gene as well as pathogenic mutations in *NPHP1* are known to be associated with Joubert Syndrome (Koyama et al. 2017).
- The condition is inherited in an autosomal recessive manner. Snigdha's parents were advised that their risk of having another child that is homozygous for the same deletion is 25%, should they plan to have another child.
- Specific treatment options for Joubert Syndrome are not available.
- Counseling to manage Snigdha's developmental challenges was suggested to her parents.

Strand Neurodevelopmental Disorders Test

The genes assayed in this test are:
AHI1, ARL13B, B9D1, CC2D2A, CEP290, CEP41, INPP5E, KIF7, MKS1, NPHP1, OFD1, RPGRIP1L, TCTN1, TCTN2,TMEM138, TMEM216, TMEM237, TMEM67, TTC21B.

References

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