CASE STUDY

Novel Presentation of Cornelia de Lange Syndrome: Holoprosencephaly with Colpocephaly

Introduction

Delayed developmental milestones and abnormal development are significant causes of concern for parents of newborns. Genetic syndromes with developmental abnormalities are usually characterized by strong physical manifestations such as microcephaly (small head), cleft lip and palate and slanted eyes. However, genetic syndromes can also show a variety of other manifestations with defects ranging from mild to severe. Holoprosencephaly or incomplete separation of brain hemispheres is one such sign.

Typically, in the first month of development, fetal brain tissue starts developing into the right and left hemispheres with appropriate connections between the two. Cavities within the brain, known as ventricles are also formed at this stage. Anomalous development of these features can result in severe cognitive disabilities. Holoprosencephaly is usually a clinical symptom of syndromes such as Pallister-Hall, Rubinstein-Taybi, Pseudotrisomy 13, Kallmann syndrome and others (Solomon et al. 1993). Non-syndromic holoprosencephaly results from mutations in genes like *SHH, ZIC2, SIX3, TGIF1, GLI2, PTCH1, FGF8, NODAL, FOXH1* and others. Genetic tests based on clinical exome panels can be effectively used to distinguish between all these possibilities.

Gender: Female

Age: 11 months

Location: Mumbai, Maharashtra

Diagnosis: Cornelia de Lange Syndrome

Strand Test: Clinical Exome

Conclusion:

- Unusual presentation of Cornelia de Lange Syndrome
- Diagnosis confirmed by genetic analysis

Patient Profile

Sireesha*, a 11-month-old baby, born to Chaitra* and Rajeev Sondhi*, showed signs of developmental delay. She was of small stature and had been a reluctant feeder right from birth. Of late, her mother had begun to suspect diminished hearing capabilities as well as problems with her vision. Sireesha's responses to somewhat distant visual cues were not strong. Sireesha also had a long philtrum (the gap between the base of the nose and the bow of the lips) as well as thin downturned lips.

Chaitra and Rajeev consulted Dr. Omkar Hajirnis, a Pediatric Neurologist in Thane for a medical evaluation of Sireesha's signs and symptoms. Dr. Omkar Hajirnis suggested getting a brain MRI to understand the causes of these developmental delays.

The MRI scan showed that Sireesha has a condition known as Semilobar Holoprosencephaly. Her brain hemispheres had not separated and formed fully. Additionally, she also had a condition known as colpocephaly.

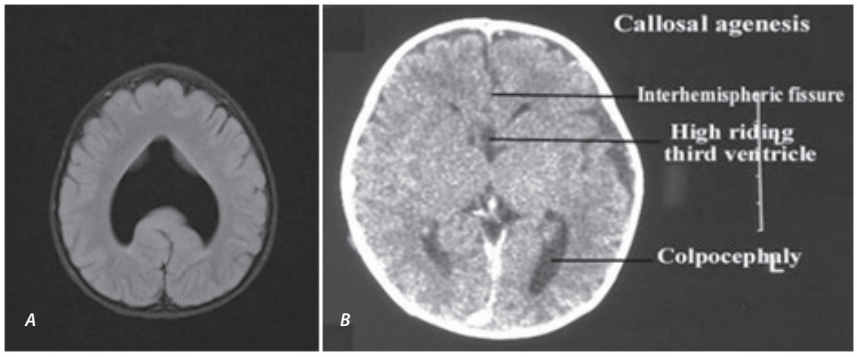

Figure 1. A) Representative Image of Semilobar Holoprosencephaly. B) Representative Image of Colposcopy

Holoprosencephaly is usually a strong sign of several developmental syndromes (Solomon et al. 1993).

In order to arrive at a differential diagnosis, Dr. Omkar Hajirnis prescribed the Strand Clinical Exome Test for analysis of Sireesha's DNA.

* *Name changed to protect patient privacy*

Family History

Chaitra and Rajeev are a non-consanguineous couple. There has been no incidence of congenital developmental anomalies in the family on either side.

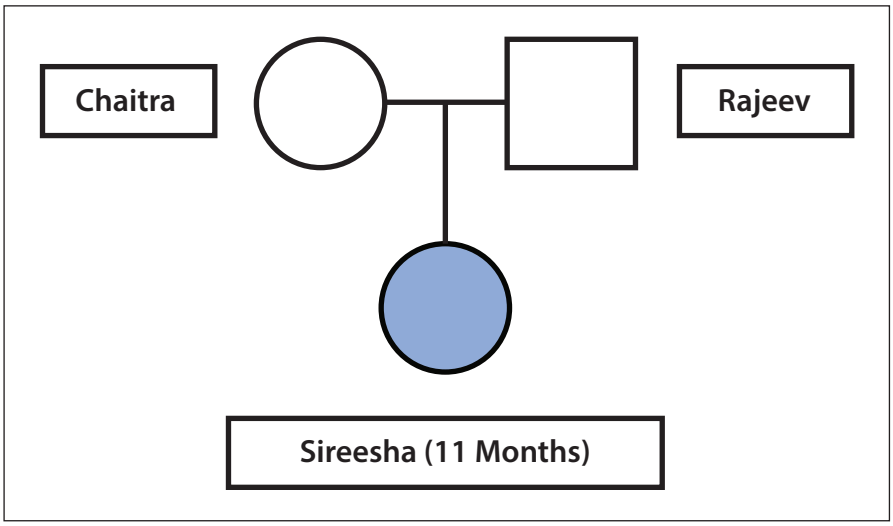

Figure 2. Family Tree - Pre-Test Genetic Counselling

Results of Genetic Testing

The Strand Clinical Exome Test is designed to assess more than 4500 genes that play a role in various inherited disorders.

In Sireesha's case, surprisingly, mutations in genes associated with syndromic as well as non-syndromic holoprosencephaly were not identified.

Instead, a heterozygous pathogenic mutation was detected in the *SMC1A* gene.

RESULT Positive for a heterozygous **'pathogenic'** mutation in the *SMC1A* gene

Gene	Variation	Zygosity	Clinical significance
SMC1A	chrX:53430524delT c.2394delA p.Lys798AsnfsTer31	Heterozygous	Pathogenic

The *SMC1A* gene produces a protein that participates in a protein complex known as Cohesin. The cohesin complex binds to sister chromatids in the cell division process and facilitates cell division. Additionally, this protein complex is also engaged in cell growth and expression of genes (Brooker & Berkowitz 2014).

Developmental anomalies resulting from mutations in the *SMC1A* gene were first described by Dutch pediatrician Cornelia Catharina de Lange. The set of anomalies that are characteristically found in this genetic background are known as **Cornelia de Lange Syndrome (CdLS).**

Mutation-Specific Testing* For Parents

The identification of this novel, pathogenic mutation in the *SMC1A* gene in Sireesha necessitates the investigation into her parents' status as carriers of the same mutation. If the parents are carriers of the same mutation, then the chances of another child inheriting the mutation in a heterozygous pattern are 50%.

The parents were advised to undergo Mutation-Specific Testing to understand whether they are also carriers of the same mutation.

Chaitra was found to be negative for the presence of this mutation.

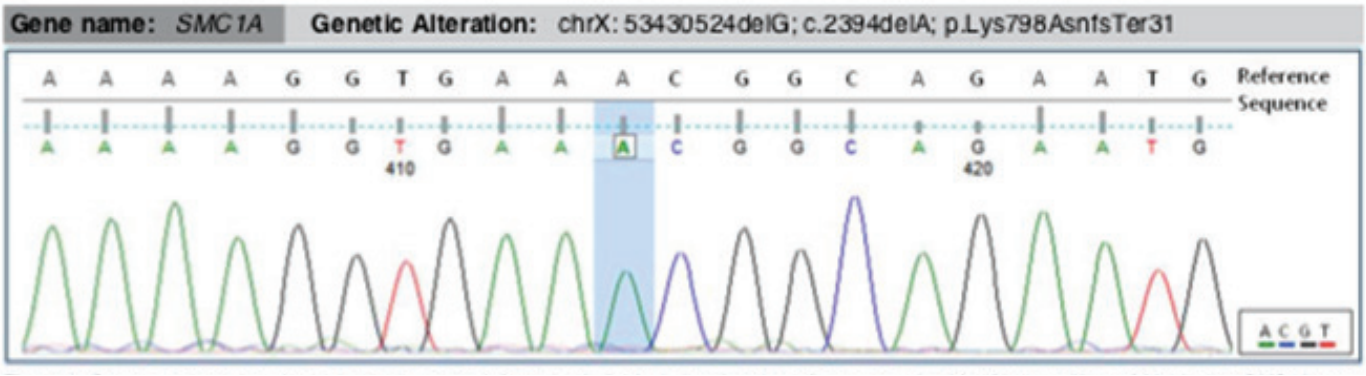

Figure 1. Sanger sequencing data (electropherogram) from the individual showing the reference nucleotide 'A' at position c.2394 in the SMC1A gene (RefSeqid : NM_006306). This finding was confirmed by sequencing with both forward and reverse primers.

Similarly, Rajeev's DNA was also analyzed to understand whether he was heterozygous for the same mutation. The deletion of the adenine nucleotide, evident in Sireesha, was not detected in Rajeev's genome.

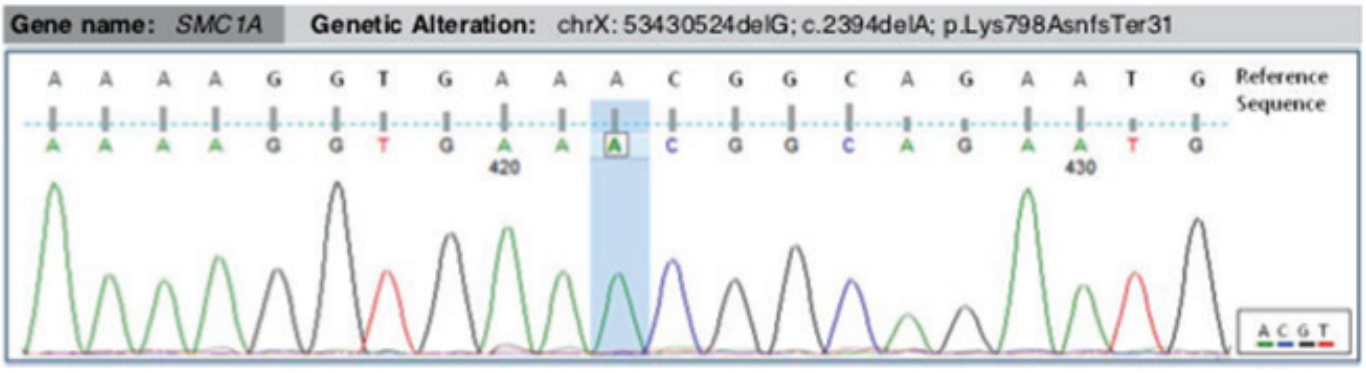

Figure 2. Sanger sequencing data (electropherogram) from the individual showing the reference nucleotide 'A' at position c.2394 in the SMC1A gene (RefSeqid : NM_006306). This finding was confirmed by sequencing with both forward and reverse primers.

The absence of this mutation in the genomes of both parents suggests that this deletion is a **de novo** variant of the *SMC1A* gene.

The parameter marked with an * are not accredited by NABL and CAP.

Conclusions

- Holoprosencephaly and colpocephaly, in Sireesha's case, indicated the incidence of syndromes like Kallmann syndrome, Rubinstein-Taybi syndrome and other anomalous developmental syndromes.
- The possibility of non-syndromic holoprosencephaly was also not negated on clinical examination of the child.
- Results of the Strand Clinical Exome Test negated the incidence of the classic syndromes associated with holoprosencephaly.
- Instead, a mutation in the *SMC1A* gene was identified.
- Mutations in the *SMC1A* gene as well as other genes like *NIPBL*, *RAD21* and *HDAC8* are usually found in CdLS.
- The identified mutation indicates that Sireesha is a case of CdLS, albeit with a rare presentation of semilobar holoprosencephaly and colpocephaly.
- Mutations in the *SMC1A* gene result in a less severe phenotype of CdLS, when compared with mutations in *NIPBL* and other genes. In some cases, the presentation of mild CdLS can resemble that of Rett syndrome (Huisman et al. 2017).
- Genomic analysis of both parents indicated that the identified *SMC1A* variant is not a hereditary variant but a ***de novo*** variant.
- This case is one of the rare reports of Cornelia de Lange Syndrome presenting as holoprosencephaly along with colpocephaly.

Counselling and Management Options

Sireesha's parents were advised about the diagnosis of CdLS. In the post-test counselling session, Chaitra and Rajeev were made aware of the extent of developmental delays that she might suffer from. There are no specific therapies available for the treatment of CdLS. Results from one study show that growth hormone therapy can help to overcome developmental deficits evident in CdLS (de Graaf et al. 2017).

Strand Clinical Exome Test

The Strand® Clinical Exome test is a Laboratory Developed Test (LDT) that was developed and its performance characteristics determined by the Strand Center for Genomics and Personalized Medicine at Strand Life Sciences.

References

Brooker, A.S. & Berkowitz, K.M., 2014. The Roles of Cohesins in Mitosis, Meiosis, and Human Health and Disease. In Methods in molecular biology (Clifton, N.J.). pp. 229–266. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24906316 [Accessed December 12, 2017].

de Graaf, M. et al., 2017. Successful Growth Hormone Therapy in Cornelia de Lange Syndrome. Journal of Clinical Research in Pediatric Endocrinology. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28588001 [Accessed December 11, 2017].

Huisman, S. et al., 2017. Phenotypes and genotypes in individuals with SMC1A variants. American Journal of Medical Genetics Part A, 173(8), pp.2108–2125. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28548707 [Accessed December 12, 2017].

Solomon, B.D., Gropman, A. & Muenke, M., 1993. Holoprosencephaly Overview, University of Washington, Seattle. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20301702 [Accessed December 11, 2017].

strand New Generation Healthcare

Strand Life Sciences Pvt. Ltd.
5th Floor, Kirloskar Business Park, Bellary Road, Hebbal, Bangalore - 560 024
Phone: 1800-1022-695, support.strandx@strandls.com, www.strandls.com

#StayAheadOfCancer

Strand is accredited by

CAP ACCREDITED COLLEGE of AMERICAN PATHOLOGISTS # 8750941

Certificate No. MC - 2434

Strand ID: RD503622012018