CASE STUDY

Differential Diagnosis Between Kabuki Syndrome and Noonan Syndrome Facilitated by Strand Clinical Exome Test

Patient Profile

Developmental defects in infants need early diagnoses in order to bring in corrective measures before long-term damage sets in. Diagnosis can be a challenge if symptoms presented by the individual show a considerable overlap with one or more developmental syndromes. In such situations, genetic tests can pinpoint the exact mutations responsible for the aberrant developmental features and provide an accurate diagnosis.

Patient Profile

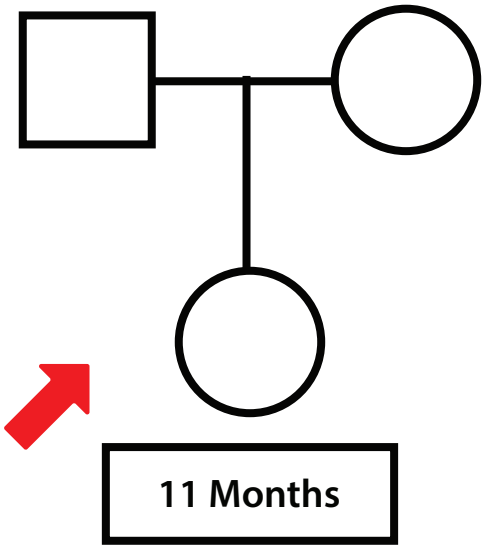
A 11-month-old girl, Sphoorti*, presented with features like a long face, flared pinnae, shallow orbits, nystagmus, cataract, cardiac abnormalities and global delayed development. Her parents consulted a leading geneticist in Kochi in order to get a proper diagnosis. The symptoms were suggestive of both Noonan syndrome (Roberts et al. 2013) and Kabuki syndrome (Cheon & Ko 2015). In order to understand the molecular causes of Sphoorti's health issues, the Strand Clinical Exome Test was prescribed.

Family History

Sphoorti's parents, Kalyanaraman* and Vasundhara* are a non-consanguineous couple. Sphoorti is their firstborn child. They do not have a prior history of abortions or stillbirth.

Family Tree - Pre-test Genetic Counselling

Kalyanaraman and Vasundhara are a non-consanguineous couple. Their family history did not indicate the presence of developmental issues in any individual. Considering this history, and the child's symptoms, the Strand Clinical Exome Test was prescribed for Sphoorti.



Gender: Female

Age: 11 months

Location: Kochi, Kerala

Diagnosis: Kabuki Syndrome

Strand Test: Clinical Exome Test

Conclusion:

- A pathogenic variant of the *KMT2D* gene identified in the child's genome
- Differential diagnosis between Kabuki syndrome and Noonan syndrome facilitated by the Strand Clinical Exome Test.
- Parents counselled about health management strategies to manage the developmental delays in the child

*Name changed to protect patient privacy

Results of Genetic Testing

The Strand Clinical Exome Test is designed to identify mutations in ~4500 genes that are associated with multiple developmental abnormalities and rare inherited disorders.

RESULT A heterozygous **'pathogenic'** variant was identified in exon 3 of the *KMT2D* gene

In Sphoorti's case, a pathogenic mutation in the *KMT2D* gene was identified in her genome.

Gene	Variation	Zygosity	Clinical Significance	Inheritance
KMT2D	chr12:49448413_49448414insC c.303dupG p.Ser102GlufsTer6	Heterozygous	Pathogenic	Dominant

Key Findings

- Germline pathogenic variations in the *KMT2D* gene have been shown to be associated with Kabuki syndrome, which manifests as typical facial features, minor skeletal anomalies, persistence of fetal fingertip pads, mild to moderate intellectual disability, and postnatal growth deficiency (Adam et al. 1993).
- Kabuki syndrome, caused due to variations in the *KMT2D* gene, is inherited in an autosomal dominant mode, which means one copy of the altered gene in an individual is sufficient for the disease to manifest. If the variant is not a new variant (de novo) in this individual, then each first degree relative (siblings and parents) has a 50% chance of having this variation. However, de novo variations have also been reported in this gene (Badalato et al. 2017).
- Syndromes such as Noonan Syndrome, Hardikar syndrome, CHARGE syndrome, van de Woud's syndrome and Kabuki syndrome share clinicopathological features. A clear differential diagnosis between these, especially between Kabuki and Noonan syndrome was provided by the clear identification of a pathogenic mutation in the *KMT2D* gene, in this case.

Treatment Plan

Kabuki syndrome affects multiple organ systems and hence corrective treatment for developmental anomalies is not available. There is some early evidence that treatment of children affected with Kabuki syndrome with recombinant growth hormone (rGH) can help to overcome some of the deficiencies in the development of the musculoskeletal system. However, significant gains are not evident if the children are treated later in childhood (Schott et al. 2017).

Conclusions

- 11-month-old Sphoorti was referred to a prominent geneticist in Kochi, owing to the presentation of features such as long face, nystagmus, cataract, cardiac abnormalities and global delayed development.
- The incidence of Kabuki syndrome or Noonan syndrome was suspected.
- A pathogenic mutation in the *KMT2D* gene was identified using the Strand Clinical Exome test.
- A clear differential diagnosis between Kabuki syndrome and Noonan syndrome was established by the genetic test.
- The child's parents were counselled about strategies to manage the developmental delays in their daughter.

Strand® Clinical Exome Test

The Strand® Clinical Exome Test is a laboratory-developed test designed for the identification of genetic variants that can cause several developmental disorders. The test covers more than 4500 genes and has been effective in diagnosing neuro-muscular, skeletal, nephrological, neurological and mitochondrial disorders as well as inborn errors of metabolism.

References

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