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Abstract Topic: - Clinical Genetics

Abstract Title: - KMT2D Gene Mutation Unveils Kabuki Syndrome: A Genotype-Driven Discovery

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Aims: - To evaluate a 1.9-year-old male child with ventricular and atrial septal defects was referred to the Paediatric Cardiology unit of our hospital. He presented with global developmental delay, spinal dimple on abnormal brain MRI and was referred to the Molecular Genetics department for genetic evaluation in August 2023.

Methods: - Whole exome sequencing (WES) was carried out followed by analysis using a targeted panel for congenital and structural heart defects (1498 genes).

Results: - No clinically significant variations among the 1498 genes screened were observed. Further, analysis of other pathogenic variants in the whole exome (>20,000 genes) revealed a protein truncating novel loss of function variation p.L4089fs*17 in exon 40 of the KMT2D gene in heterozygous form, reported as likely pathogenic as per ACMG variant classification guidelines. Genetic counselling disclosed features such as blue sclera, broad nose with a flattened tip, arched eyebrows, long eyelashes, large dysplastic ears, high arched palate, clinodactyly and mild hypotonia. This genotype-driven analysis lead to a correlation with a rare, congenital, multisystem syndrome called Kabuki Syndrome (KS).

KS is mainly characterized by distinct facial features, short stature, varying degrees of intellectual disability, skeletal abnormalities and atypical dermatoglyphics. The incidence of KS has been reported to be 1 in 32,000 births, the prevalence of the syndrome in India is unknown but Indian cases with variable manifestations of the syndrome have been reported. About 50-80% of KS cases have mutations or large deletions in the KMT2D gene, encodes a histone H3 lysine 4 (H3K4)-specific methyltransferase, most of which are dominant de novo protein truncating. This de novo nature emphasizes the importance of genetic testing to assess recurrence risk of the disease in the family. Another gene, carrying mostly point mutations, associated with this syndrome is KDM6A (no mutation identified in the present case).

Conclusions: - This case underscores the significance of comprehensive clinical evaluation, genetic counselling and family investigations as management of KS requires a multidisciplinary approach. The importance of genetic assessment is emphasized, as this case showcases the value of genotype-driven analysis, using WES instead of a targeted approach. This approach becomes crucial in diagnosing rare

multisystemic disorders like KS with diverse manifestations and aids in the identification and interpretation of pertinent variants, especially when phenotype-driven analysis proves inconclusive.

Keywords: - No clinically significant variations among the 1498 genes screened were observed. Further, analysis of other pathogenic variants in the whole exome (>20,000 genes) revealed a protein truncating novel loss of function variation p.L4089fs*17 in exon 40 of the KMT2D gene in heterozygous form, reported as likely pathogenic as per ACMG variant classification guidelines. Genetic counselling disclosed features such as blue sclera, broad nose with a flattened tip, arched eyebrows, long eyelashes, large dysplastic ears, high arched palate, clinodactyly and mild hypotonia. This genotype-driven analysis lead to a correlation with a rare, congenital, multisystem syndrome called Kabuki Syndrome (KS).

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