Letter to the Editor

KMT2D-related disorder with a restricted spectrum distinct from Kabuki syndrome: A rare case report describing male twins in Taiwan and a literature review

Dear Editor,

Kabuki syndrome is a rare congenital disorder typically characterized by facial dysmorphism, intellectual disability, developmental delay, and various congenital anomalies. Gene mutations that affect KMT2D are the main causes. Here, we report a pair of full-term monozygotic twins harboring a novel mutation in the KMT2D gene, but without the typical Kabuki face or developmental delay.

1. Case report

Monozygotic male twins presented hypoplastic nipples and external ear malformations at birth. Congenital hypothyroidism and bilateral sensorineural hearing loss were also observed. Both twins had a broad nasal root, a flat midface, bilateral cupped ears, and hypoplastic nipples (Online Fig. S1). Developmental milestones of the twins were normal and intellectual disability and/or speech delay were absent. Hypocalcemia and short stature were observed at 1 year-6 months of age.

Whole exome sequencing was performed and revealed a single novel heterozygous missense variant, c.10595T > C (p.Ile3532Thr) located in exon 38 of the KMT2D gene; this was present in both twins. This variant is not found in the literature and neither has it been described in the 1000 Genomes Project, ExAC, gnomAD or an in-house Taiwanese database. The variant was confirmed by Sanger sequencing and has occurred de novo. In silico analysis revealed that amino acid position 3532 of the protein is conserved in all vertebrates and that a change in this amino acid is likely to damage protein structure and function; this was predicted using PolyPhen2, SIFT, PROVEAN, CADD, and Mutation Taster. According to the ACMG guidelines, this variant should be classified as “Likely Pathogenic”.

2. Discussion

Individuals with Kabuki syndrome linked to KMT2D pathogenic variants are more likely to have distinctive Kabuki facial phenotypes and developmental delay. However, both of our patients do not have typical Kabuki features or suffer from developmental delay.

Similarly to our findings, three studies of individuals with KMT2D-related disorder without typical characteristics of the Kabuki syndrome have recently been reported in the literature. Mutated sites of all variants in these reports were found to be located in highly conserved areas of exons 38 (amino acids 3503–3580) and 39 (amino acids 3581–4510) of the KMT2D gene. The cases mentioned above do not have typical Kabuki features, but do have some common phenotypes.

We compared our twins with the previous reports mentioned above (two individuals in our study and sixteen cases from previous reports, eighteen cases in total.) (Online Table S1). Several phenotypes were found to be presented in more than half of the affected individuals and these included hearing loss (94%), congenital choanal atresia (78%), nipple athelia (67%), hypothyroidism (67%), short stature/growth failure (67%), external ear abnormalities (61%), dental anomalies (56%), neck pit or branchial sinus anomalies (50%) and lacrimal duct anomalies (50%). Athelia or hypoplastic nipples is a special clinical feature associated with this restricted spectrum of

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individuals and is distinct from Kabuki syndrome. It has never been reported for any variant of KMT2D, except in the studies carried out by Baldridge et al.,² and Cuvertino et al.,³ which emphasized hypoplastic nipples as a rare symptom associated with this restricted spectrum.

Our twins show a strong similarity in the phenotype of patients described in the above three studies. Furthermore, our novel variant in ΚΜΤ2Δ is located within the highly conserved area of exon 38. This strongly suggests that our variant belongs to this group, namely a restricted spectrum of missense KMT2D variants that is distinct from classic Kabuki syndrome.

Informed consent

The parents of our two subjects provided their informed consent for all published information, including partial facial photographs.

Declaration of competing interest

The contributing authors all declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2022.06.005.

References


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