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Wiedemann-Steiner Syndrome with a 2-Year Follow-Up

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Abstract

Wiedemann-Steiner syndrome (WDSTS) is an exceptionally rare genetic syndrome characterized by postnatal growth retardation, facial dysmorphism, hairy elbow, and short stature. It is known that the occurrence of WDSTS is due to mutations in KMT2A gene. It is noteworthy that not a great number of WDSTS have been identified yet; thereby, new phenotypes and features continue to be added. In this report, we describe a 5-year-old male patient presented with developmental delay, hypothyroidism, facial dysmorphism, and behavioral signs such as autistic spectrum features. By Whole Exome Sequencing (WES), a new mutation in KMT2A was found and WDSTS was diagnosed genetically. According to a genetic test, a variant in exon 27 of the KMT2A gene c.6647delT (p.Pro2215fs) was found. This mutation was not reported previously, also this case was the first WDSTS diagnosed in Iran. This syndrome is a rare genetic disorder representing a broad range of phenotypes. The mentioned low frequency emphasizes the importance of a phenotype-genotype correlation to be established. The phenotype comparison between our case and previously reported patient did not reveal any difference related to age or sex in patients with WDSTS.

Key Words: Exome sequencing, Facial dysmorphism, Growth retardation, Wiedemann-Steiner syndrome.

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1- INTRODUCTION

Wiedemann-Steiner syndrome (WDSTS, OMIM 605130) is an infrequent dominant autosomal genetic syndrome that is described as a clinical entity with notable phenotypical variations (1). Clinical characteristics include hypertrichosis cubiti, developmental delay, and skeletal and facial dysmorphism. Its considerable facial features comprise a short nose, round face, hypertelorism, short palpebral fissures, arched or thick eyebrows, high arched palate, long eyelashes, and strabismus (2, 3). Also, hypertrichosis on the back, variable levels of intellectual disability, and behavioral difficulties have been reported (4). Generally, failure in normal development, such as neuropsychiatry and a broad range of facial dysmorphic indications, are thought the main prominent, but nonspecific features of WDSTS. Considerably, a wide spectrum of phenotypes is associated with WDSTS. This syndrome was described initially in 1989 by Wiedemann et al. (5), and later in 2000 by Steiner et al (6).

In 2012, whole-exome sequencing identified heterogeneous de novo mutations in the KMT2A (lysine methyltransferase) gene, as the etiology of WDSTS (1). KMT2A gene encodes a histone methyltransferase, as a transcription factor, that is crucial to regulating the gene expression within the early development. Regarding its role in chromatic-mediated transcription, WDSTS is considered a chromatin remodeling defect (3). To date, 142 pathogenic and likely pathogenic variants have been identified for the KMT2A gene, according to LOVD 3.0 (https:/databases.lovd.nl/shared/variants/KMT2A).

Herein, we describe the case of a five-year-old boy with confirmed WDSTS, using whole-exome sequencing. Prior to diagnosis, he presented with major features of growth deficiency, and also it should be noted that the child was conceived by a donated egg.

2- CASE PRESENTATION

We describe the case of a 5-year-old male patient, who was the only child of his family. The parents did not show any considerable feature or indication, phenotypically. The mother's pregnancy had been achieved using egg donation process. He was born at term, following an uncomplicated pregnancy and a normal delivery. He exhibited a low birth weight of 1.85 Kg, and also hypotonia and growth deficiency were experienced from birth. As hypothyroidism was diagnosed after birth, he underwent levothyroxine treatment. He showed favorable responses to the treatments. The global growth delay was observed (noted in the growth chart, **Fig. 1**). Therefore, we started the growth hormone (GH) therapy, since age three years. The GH therapy with a dose of 0.05 (milligram per kilogram of body weight) has been carried out. Therefore, he had a 22 cm height gain, during 2 years of GH therapy. As our patient exhibited a language and speech development delay, he received regular speech and occupational therapies every week.

In physical examination, we observed a flat and round face, hypertelorism, short nose, long philtrum, low-set ears, and high-arched palate (**Fig. 2**). Also, the patient's parents were concerned about educational difficulties. Mental conditions such as autistic spectrum features were present that lead to notable intellectual disability; moreover, we found psychomotor delay on physical examination.

A combination of clinical manifestations and features implied that a genetic test was necessary. To understand the genetic basis of the features described above, we perform a Whole Exome Sequencing (WES).

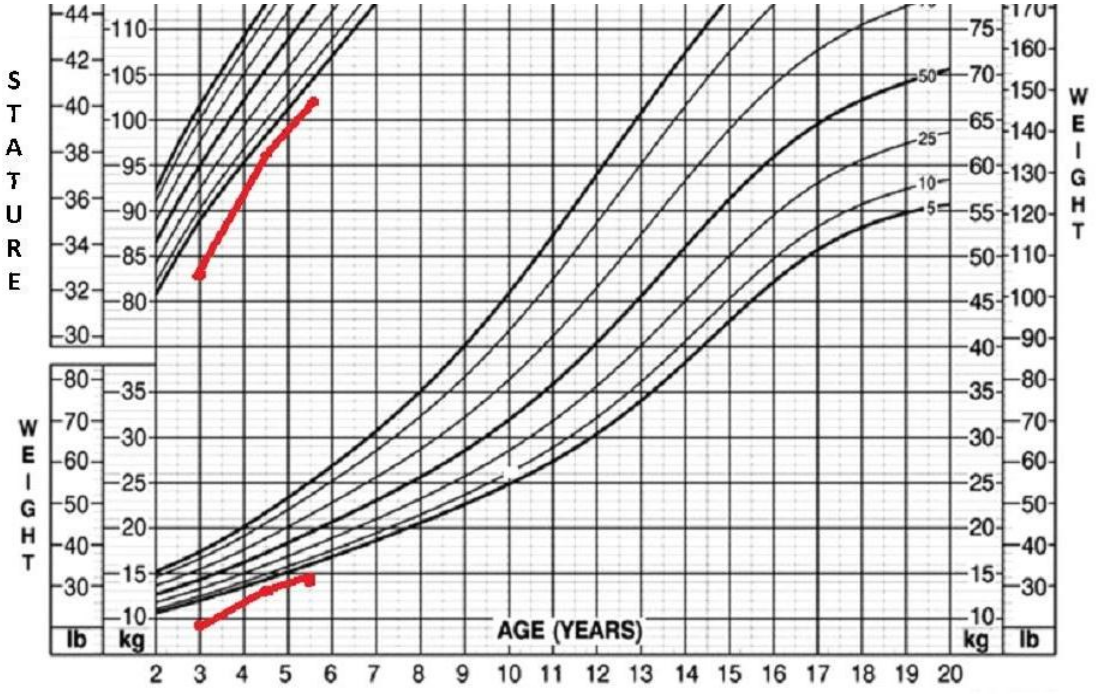

Fig. 1: Reference growth chart for weight and height. As shown, short stature and underweight were reported at ages 3-5 years.

Fig. 2: Long philtrum, short nose, low-set ears, and flat round face can be seen in these photos. It should be noted that some facial features, such as hypertelorism and short palpebral fissures cannot be seen in the pictures due to protecting the identity of described case.

The genetic test identified a heterozygous variant in exon 27 of KMT2A gene c.6647delT (p.Pro2215fs). Based on the genetic test, the detected variant confirmed the presence of WDSTS. In addition to clinical features mentioned above, small palpebral fissures were present as typical craniofacial features.

Considerably, this mutation has not been found in the control databases. This variant is absent from control (or at exceptionally low frequency if recessive) in Exome Sequencing Project, Exome Aggregation Based Consortium, or 1000 Genomes project. Multiple computational analysis estimated the deleterious effect on the gene and gene product. Because of its high evolutionary conservation, the detected variant was potentially considered disease-causing. This variant generates a frameshift change which leads to the premature truncation of the protein. Based on the American College of Medical Genetics and Genomics (ACMG), this was classified as class 2-likely pathogenic variants. Informed written and verbal consent was achieved from the patient's parents for the publication of the case report and using images.

3- DISCUSSION

Exome sequencing has changed the face of monogenic disease studies in the last decades. Using this diagnostic tool, dysmorphological syndromes with genetic and clinical heterogeneity could be identified time and cost-effectively. This has boosted diagnostic performance by more than 25% which resulted in a clear understanding of molecular pathways recruited in pathologies with Mendelian inheritance (7). This method allows the detection of new genes responsible for unclear genetic cases without any previous diagnosis. As reported, the found variant was related to WDSTS.

The responsible gene for our case syndrome was KMT2A that is a member of KMT2A family. The KMT2 family, comprising KMT2A-E, encodes histone methyltransferases which are known as a major player in the regulation of chromatin-mediated transcription of different developmental genes within (8, 9). Furthermore, KMT2 gene family mutations have been found in association with human diseases such as Kabuki syndrome, a congenital malformation syndrome with multiple malignancies. Mutation in germline KMT2D results in Kabuki syndrome. The pathogenic mechanisms underlying the link between KMT2 family mutations and clinical phenotypes such as congenital anomalies are still unclear, however some overlapping clinical phenotypes are reported between WDSTS and Kabuki syndrome (10).

Diagnosis of WDSTS was reported challenging, due to extensive variation in phenotypes, and also the fact that these phenotypes have not been described clearly, yet (11). Our patient showed common facial features reported in other studies, including small palpebral fissures, high-arched palate, and hypertelorism (2, 11, 12). Some of them appeared from birth, but some others have developed during the years. One of the major common features of WDSTS is hypertrichosis, which is considered a prominent phenotype in 80% of WDSTS patients (11, 13, 14). However, our case of WDSTS did not exhibit generalized hypertrichosis nor hypertrichosis cubiti. Also, prenatal growth retardation reported by other studies was present in our patient, as described.

Neurological manifestations have been found in WDSTS, such as psychomotor development delay and intellectual disability which are reported in almost 100% of patients (11). Both of them were reported in our patient. In addition, he presented speech and language difficulties, as reported. Within WDSTS, irritability

combined with hetero-aggression, hyperactivity, and autistic features are prominent behavioral features that were reported in about 20% of cases (15). Among these conditions, only autistic spectrum features were present.

4- CONCLUSION

In summary, we described a 5-year-old patient who had features relevant to a genetic disorder. By WES, a pathogenic variant was found in KMT2A gene and WDSTS diagnosis was confirmed. Distinct facial features, growth delay, behavioral and psychomotor disorders were observed. In the literature, Hypertrichosis was found to be the common feature among WDSTS cases, but this feature was not observed in our case. The genetic findings and clinical manifestations of our case and other reported cases implicate that mutation in KMT2A gene can cause a broad spectrum of features in WDSTS.

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