A Case of *OTUD6B*-Related Disorder

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ICNC 2022
17th INTERNATIONAL CHILD NEUROLOGY CONGRESS
ANTALYA, TURKEY | OCTOBER 3-7, 2022

INTRODUCTION

Biallelic pathogenic variants of *OTUD6B (ovarian tumor domain-containing 6B)* have newly been defined to cause intellectual disability with seizures. Very few cases have been reported so far. This gene is expressed in the brain, lungs, liver, cardiovascular system, skin, gastrointestinal tract, endocrine glands, and lymphocytes. The *OTUD6B*-related disorder was first described in 2017 by Santiago-Sim et al. It mainly affects the central nervous, skeletal and gastrointestinal systems and causes dysmorphic craniofacial and distal extremity features.

CASE

Twenty-month-old boy was referred due to multiple congenital anomalies and seizures. He was the third child of healthy parents who were first-degree cousins. He was born at term with a birth weight of 2.2 kg. At birth, flattened nasal bridge, short neck, long philtrum, thin upper lip, prominent ear, hypertelorism, high palate, abnormal toes and syndromic appearance was noticed.

His seizures started at six months old. He also had congenital hypothyroidism. On physical examination, dysmorphic facial appearance, bilateral congenital hip dislocation, hyperelasticity, sacral dimple, scoliosis, right undescended testis, and distal extremity anomalies were found (Figure1). Whole exome analysis was performed, and a novel homozygous pathogenic mutation (c.725 T>G) in *the OTUD6B* gene was detected. His parents were heterozygous for the same mutation.

DISCUSSION

OTUD6B gene codes a member of a subfamily of deubiquitinating enzymes (DUBs), located on chromosome 8q21.3 and contains even exons that encode a 323-amino acid protein. The phenotypic manifestations of *OTUD6B*-related disorder are variable (summarized in table 1). The most severe *OTUD6B* phenotype includes the inability to walk, microcephaly, speech deficiency, and feeding problems. Although our case has similar phenotypic and clinical features to other cases,

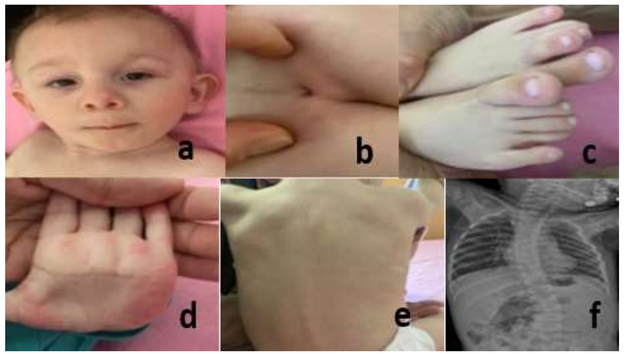

Figure 1. a- Dysmorphic facial appearance b- Sacral dimple c- Distal extremity features d- Simian line e- Scoliosis f- Chest X-RAY and scoliosis

he did not carry any of the previously described homozygous genetic variants. In this regard, it was the first case defined with c.725 T>G P.1242R homozygous pathogenic variant.

CONCLUSION

Given the homozygous pathogenic variant identified in our case, the clinical manifestations were consistent with those of other patients. This syndrome with clinically variable multisystemic involvement is rare and the available literature is limited. Our case is a new *OTUD6B*-related mutation, which is not found in the literature, and we think that it will contribute to the literature.

Table 1. Comparison of current case with previously reported cases

Feature	Present case	Santiago-Sim et al. (2017) (n:12 patient)	Straniero L et al. (2018)	Romero-Ibarguengoitia ME et al. (2020)	Alkuraya FS et al. (2020)	Börklü E et al. (2022)
OTUD6B variants (NM_016023)	c.725 T>G (novel mutation)	c.433C>T (n:6) c.469_473delTTAAC (n:1) c.173-2A>G (n:1) c.647A>G (n:1) c.324 + 1G>C/c.405+1G>A (n:1) c.631G>T (n:1)	c.324+1G>C and c.405+1G>A	c.433C>T	c.631G > T	c.815T>G
Mental retardation	+	12/12	+	+	N/A	+
Motor growth retardation	+	12/12	+	+		+
Intrauterine growth retardation	-	7/12	+	-	+	-
Growth retardation	+	9/12	-	+	-	+
Microcephaly	+	9/12	+	+	+	+
Feeding difficulties	-	9/12	+	+	+	-
Epilepsy	+	9/12	-	+	-	-
Congenital heart disease	+	4/12	+	-	+	+
Facial dysmorphism	+	12/12	+	+	+	+
Distal limb abnormalities	-	10/12	+	-	+	+
Polydactyly	-	-	-	+	+	+
Butterfly vertebra	-	-	-	-	+	N/A
Pyloric stenosis	-	-	-	-	+	N/A
Hypothyroidism	+	-	-	+	-	N/A
Hypogonadism	-	-	-	+	-	N/A

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