The First Turkish case with HIVEP2-related intellectual disability

İlknur Erol[1], Şeyda Beşen[1], Elif Perihan Öncel[1], Leman Tekin Orgun[1], Özge Sönmezler[2], Atıl Bişgin[2]

[1]Baskent University Faculty of Medicine, Adana Dr. Turgut Noyan Application and Research Center, Departmant of Pediatric Neurology, Adana, Turkey

Cukurova University AGENTEM (Adana Genetic Diseases Diagnosis and Treatment Center) and Medical Genetics Department of Medical Faculty, Adana, Turkey

ICNC 2022 17th INTERNATIONAL CHILD NEUROLOGY CONGRESS

INTRODUCTION

The genetic basis of mental motor retardation is still unknown. The human immunodeficiency virus type-1 regulatory binding protein 2 (HIVEP2) gene is a new, closely associated with non-syndromic intellectual disability and plays a role in the regulation of many genes involved in the neurodevelopmental pathway. HIVEP2-related intellectual disability is a rare disorder. At least 12 individuals with the condition have been described in the medical literature.

OBJECTIVES

Herein, we report first Turkish patient who is associated with HIVEP2 related Intellectual Disability (ID).

CASE

A male patient, who is currently 6.5 years old was admitted with hypotonia and recurrent ear infections at the age of 7 months old. He was born at term after an uncomplicated pregnancy to healthy consanguineous parents. At birth, his weight was 3300g, his length was 50 cm, and his head circumference was 35 cm. His family history was not remarkable. At the time of the first admission, his head circumference was 42,4 cm (<3rd percentile), length 69 cm (25-50th percentile); and weight 7,9 kg (25-50th percentile). Physical examination at that time revealed dysmorphic features such as hypertelorism, broad nasal root, low set ears, down slanting eyes, long filtrum and microcephaly (Figure1 and 2).

CASE

He was social and affectionate and also had hypotonia with brisk deep tendon reflexes. When he reapplied one and half years later, his motor delay became more prominent and his cognitive functions and speech were retarded. He walked at the age of 2.5 years and continued to have imbalance and fine motor skills incompetence at 6 years old. His language development was markedly retarded and he started to form two-word sentences at the age of 6 years. FISH was sent for Angelman syndrome because he was friendly, lovable, and sympathetic. The genetic evaluation including karyotype analysis, microarray and test for Angelman syndrome were all normal. The brain MRI and EEG were also normal. A new *heterozygous HIVEP2 gene c.3G>A mutation* was detected by WES. The same mutation in HIVEP2 was also detected in the mother as heterozygous.

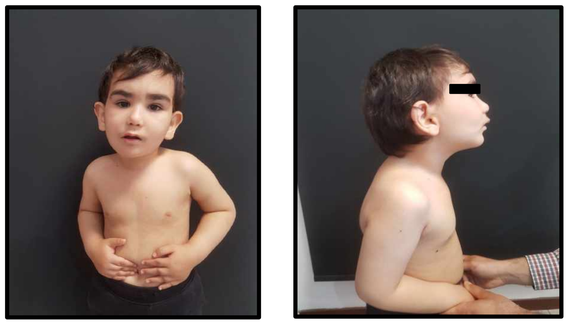

Figure 1 and 2. Hypertelorism, broad nasal root, low set ears, down slanting eyes, long philtrum and microcephaly

DISCUSSION

Over the last years, broad sequencing approaches such as WES substantially contributed to the definition of the molecular causes underlying syndromic ID. Recently, pathogenic variants in HIVEP2 have been reported as a cause of ID, developmental delay, behavioral disorders, and dysmorphic features. In HIVEP2 knock-out mice decreased maturation of neurons and expression of dopamine receptors in the dentate gyrus region of the hippocampus were detected. Behavior abnormalities including anxiety and hyperactivity were also observed in HIVEP2 knock-out mice. To date, only 12 patients with pathogenic de novo nonsense or frameshift variants and one patient with a pathogenic missense variant in HIVEP2 have been reported. Mo et al. evaluated all 12 patients with HIVEP2 mutation and reported that the most common clinical findings were neonatal complications, hypotonia, developmental delay, intellectual disability, language impairment, gastroesophageal reflux, and strabismus. Microcephaly, epilepsy and movement disorder as reported as rarer findings. They demonstrated that HIVEP2-related disease causes difficulties in emotional and behavioral symptoms as well as impairments in adaptive and socially related behaviors. **Our case is the first Turkish patient in the literature who had HIVEP2 mutation.** He had moderate ID, developmental delay, minimal dysmorphic features and also Angelman-like phenotype. Goldsmith and et al. also presented two patients who had Angelman-like phenotype with HIVEP2 mutation.

To our knowledge, this case is the third case presented with an Angelman-like phenotype. There are currently 12 cases reported in the literature with the pathogenic HIVEP2 variants. We consider that the clinical spectrum will be expanded with the documentation of new cases and also the identification of new genes and elucidation of their functions have revealed their role in the pathogenesis of non-syndromic ID. Therefore it is possible to provide genetic counseling to the families and it is also considered to use it if there is a targeted treatment option.

CONCULUSION

The HIVEP2 gene is a rare autosomal dominant cause of mental motor retardation and has been shown to cause global developmental delay, mild dysmorphic findings, hypotonia, behavioral problems, minimal structural brain abnormalities, and Angelman-like phenotypes. Through this case, it is aimed to discuss intellectual disability without a clear genetic background by associating it with HIVEP2 mutation based on clinical findings.

To date, only 12 patients with pathogenic de novo variant in HIVEP2 have been reported.. Since the mutation of our case was inherited from the mother, there has been still an unclarified genetic situations such as incomplete penetrance or variable expression patterns.

Diseases associated with HIVEP2 are newly defined, and as more cases and mutations are defined, the relationship between inheritance pattern and genotype phenotype will be understood more clearly.

REFERENCES

1. Rauch A, Wieczorek D, Graf E, Wieland T, Endele S, et al: Range of genetic mutations associatedwith severe non-syndromic sporadic intellectual disability: an exome sequencing study. Lancet 2012; 380: 1674–1682

2. Srivastava S, Engels H, Schanze I, et al. Loss-of-function variants in HIVEP2 are a cause of intellectual disability. Eur J Hum Genet. 2016;24:556-61

3. Mo A, Snyder LG, Babington O, Chung WK, Sahin M, Srivastava S. Neurodevelopmental profile of HIVEP2-related disorder. Dev Med Child Neurol. 2022;64:654-661.

CONTACT

Prof. Dr. İlknur EROL;

e-mail: ilknur_erol@yahoo.com;

Phone:+905053837661