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CASE REPORT

# SYNGAP1 mutation in a pediatric patient with autism spectrum disorder and intellectual disability

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**ABSTRACT**

Autism spectrum disorder (ASD) is a disease characterized by interaction and communication deficiencies. Patients diagnosed with intellectual disability (ID) exhibit deficiencies in at least two behaviors associated with adaptation skills. The high level of association between neurodevelopmental diseases, especially ID, and ASD clearly reveals the presence of etiopathogenesis with an underlying multi-factorial and possibly a common genetic background. The SYNGAP1 gene has been associated with both ASD and non-syndromic ID. We report the case of a 13-year-old adolescent with SYNGAP1 gene mutation diagnosed with ASD, moderate ID, and epilepsy. The motor development of the patient, who had started walking at the age of 4, was delayed, and his language development was evidently inadequate since he still had no word. Stereotypical behaviors were observed with insufficient social interaction. As a result of the genetic analysis, the patient was determined to be heterozygous for a single nucleotide change (C>T) resulting in a false sense of mutation at position c.3134 in exon 15 of the SYNGAP1 gene. Thus, the present study aimed to contribute to the knowledge base on patients with rare SYNGAP1 mutation that plays a role in the etiological background of ASD, ID, and epilepsy comorbidity. To the best of our knowledge, this variant has not been reported in the scientific literature to date.

**Keywords:** Autism spectrum disorder, intellectual disability, SYNGAP1 mutation

## INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social interaction and communication skills, and restrictive and repetitive behavior (1). Intellectual disability (ID) is a common neurodevelopmental disorder characterized by an intelligence quotient score of 70 or less, and deficiencies in at least two behaviors associated with adaptation skills (1,2). Although the etiology of these diseases is not clear, genetic factors were claimed to be significant. The high level of association between neurodevelopmental diseases, especially ID, and ASD clearly reveals the presence of etiopathogenesis with an underlying multi-factorial and possibly a common genetic background (2,3).

Since maternal 15q11-q13 duplication affecting synaptic plasticity is the most common cytogenetic anomaly in individuals with ASD, SYNGAP1 gene mutation, the ASD and ID association, which was first identified in a case diagnosed with ID and ASD in 2009, is rare; however, it is considered an important factor (4). The SYNGAP1 gene encodes a brain-specific synaptic Ras GTP-ase activating protein required for synaptic plasticity and synapse function, a

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brain-specific Ras/Rap guanosine triphosphatase activating proteinrequired for synaptic plasticity and cognition which is part of the N-methyl-D-aspartate (NMDA) receptor complex (5). SYNAGP1 is also known to be associated with encephalopathy (4). The SYNGAP1 gene positively and negativelyregulates the density of NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors at glutamatergic synapses. In studies on mice, heterozygous SYNGAP1 gene (SYNGAP1$^{-/+}$ mice) mutations exhibited behavioral and cognitive impairments. However, SYNGAP1-induced disorders disrupt the excitatory/inhibitory balance in the hippocampus and cortex, leading to accelerated glutamatergic synapse maturation. This alters the synaptic plasticity required in cognitive and behavioral development (6). In the present case report, a 13-year-old adolescent patient with ASD, moderate ID, and epilepsy and diagnosed with SYNGAP1 gene mutation was reported.

## CASE

A 13-year-old boy was admitted to our clinic through his parents for his inability to speak, inadequate social-emotional reciprocity and repetitive behavior. The patient had been born normal and weighed 3.5 kg. The parents of the patient were close relatives. The patient was the only child. The patient, who had started walking when he was 4 years old, did not use any words. The patient had no toilet training.

The patient did not say any words or express any phrases. He was unable to communicate verbally. He avoided eye contact. He did not follow any instructions. He just screamed when he was in distress or needed attention. He showed no imitation behavior. He had no role-playing skills. Stereotypes were observed. He did not interact with his peers. He displayed peripheral gaze, stereotypical behaviors such as shaking his head and body, and self-harming behaviors such as hitting on his head and biting his fingers. No extensive auditory or visual impairments were observed in the central nervous system. On physical examination gait abnormality and mild dysmorphic facial features (short philtrum, hypertelorism, small pointed chin and broad mouth with diastema of the upper teeth) were observed. The patient had no previous syndromic diagnosis. The patient's weight was 42 kg, and was 150 in height. Due to the epilepsy diagnosis, the patient was treated twice a day for 500 mg valproic acid. The last epileptic seizure had occurred 3 years ago.

The general development details of the patient whose chronological age was determined to be 13 years old in psychometric examination (Ankara Developmental Screening Inventory), were as follows: 10-11 months, cognitive-linguistics : 7-8 months, fine motor: 8-9 months, gross motor: 15-16 months, social skill-self-care: 10-11 months. The patient's Childhood Autism Rating Scale score was 51. The patient was diagnosed with moderate ID and ASD based on DSM-5 (1). Considering these clinical diagnoses, SYNGAP1 mutation was detected in the patient who was consulted to the genetics department. The patient was evaluated in the medical genetics department. Written informed consent was obtained from the patient's parents (Since the genetic tests are for clinical diagnostic purposes only, an ethical committee's approval is not required for this purpose and only informed written consent forms were obtained). G-band karyotyping and chromosomal microarray analysis were performed on the patient with unexplained developmental delay/ID, ASD, epilepsy and dysmorphic findings. The result was 46, XY and no translocation, deletion or duplication was detected. In order to determine the underlying genetic cause, it was decided to perform an whole exome sequencing analysis. The patient's genomic DNA was extracted from whole blood samples using the QIAamp® DNA Blood Mini Kit (Qiagen). Exome sequencing of the patient's genomic DNA was perfomed using the Illumina NextSeq system. Exome data alignment, variant invocation and variant interpretation were done. As a result of the analysis, it was determined that the patient was heterozygous for a single nucleotide change (C>T) resulting with missense mutation at position c.3134 in exon 15 of the SYNGAP1 gene. The c.3134C>T variant was classified as possible pathogenic according to American College of Medical Genetics and Genomics (ACMG) guidelines. To our knowledge, this variant has not been reported in the scientific literature to date.

## DISCUSSION

In the present case report, we described a 13-years-old male patient with moderate ID, ASD, and epilepsy with SYNGAP1 mutation. It was observed that copy number variations (CNVs) or structural variation within the genome contributed significantly to the etiology of both ID and ASD. Although ASD and ID were classified as two separate diagnoses, the clinical overlap is often detected in most cases. ID accompanies ASD in 67% of individuals (2). Although it is difficult to determine which genes are involved after this clinical conflict,

SYNGAP1 is one of the clear and strong candidates identified so far (2). SYNGAP1 is one of the most common postsynaptic proteins associated with NMDA receptors allowing synaptic GTP to be converted GDP. (7,8). Increased effect of the AMPA receptor in postsynaptic glutamatergic neurons with SYNGAP1 disruption in mice triggers seizures (9).

SYNGAP1 de novo mutations have been identified in some patients with ASD (10,11). It was suggested that the social and communicative problems and stereotypically limited behavior patterns observed in ASD were likely caused by an imbalance in the synaptic stimulant/inhibitor rate. SYNGAP1 gene mutations increase AMPA receptor-mediated synaptic currents in neural circuit formation. These mismatches between the neural circuits lead to disruption of synaptic plasticity, causing some irregularities in behavioral and cognitive processes. (9,12). CNVs such as SHANK2, SYNGAP1 and ILRAPL1 were identified in associated non-syndromic ID and ASD, and genetic similarity and overlap between these two diseases were identified (2). Furthermore, patients with SYNGAP1 mutation were demonstrated to suffer from moderate to severe ID as well (5). The basic clinical features (ID, epilepsy, autistic features) of our patient were consistent with previously reported cases about patients with SYNGAP1 mutation. Moreover, the SYNGAP1 mutation not only causes autistic symptoms but also encephalopathy. Generally, in non-syndromic ID, genes are either located on the X chromosome or are autosomal recessive. However, the SYNGAP1 mutation is a common cause of autosomal dominant non-syndromic ID (2). In addition, SYNGAP1 heterozygosity leads to several circuit-specific pathologies that may contribute to phenotypes observed in patients, including low activity in cortical neurons necessary for tensile skills (3). In a neuropathological study of the brains of people with SYNGAP1 mutations, a significant loss of Purkinje cells and astrocytes in the cerebellum was found. However, it was observed that the unsteady and ataxic gait of the patients indicated cerebellar pathology and this was a part of this phenotype, and the SYNGAP1 mutation played an important role in the development of encephalopathy (4). SYNGAP1 heterozygosity impairs sensory processing by reducing touch-related activity in the somatosensory cortex (13). Distinctive dysmorphism is observed in the SYNGAP1 mutation (14). The possible mechanism in epilepsy due to SYNGAP1 mutation is the increase in neuronal excitability caused by AMPAR activity (15).

In conclusion, the accumulation of knowledge on patients with rare SYNGAP1 mutation that plays a role in the etiological background of ASD, ID and epilepsy comorbidity has continued with the present case report. Thus, the SYNGAP1 mutation could help understand the underlying mechanisms of ASD, ID, and encephalopathy. Further research is needed to clarify the contribution of this mutation to neurodevelopmental disorders. One of the important reasons for this case to be brought to our clinic late was the low socioeconomic status of the family. The delay in determining the diagnosis of the neurodevelopmental disorder in this case, together with his access to special education opportunities later, caused his clinical condition to deteriorate. Considering the comorbidities in the case, delayed pharmacotherapy of epilepsy and ASD and a marked decrease in functionality are observed.

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| Category 1 | Concept/Design | M.E.T., F.H.C., F.D., T.C., S.T. |
| | Literature review | M.E.T., F.H.C., F.D., T.C., S.T. |
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