Case report

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Septo-optic dysplasia associated with chromosome 15q13.3 duplication: a case report

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Septo-optic dysplasia (SOD) is a rare congenital anomaly that is clinically defined by developmental delay and characteristic brain magnetic resonance imaging findings, including optic nerve hypoplasia, pituitary hormone abnormalities, and midline brain defects. The occurrence of SOD is generally sporadic; however, it can be inherited rarely. Although an association with *HESX1*, *SOX2*, and *SOX3* mutations has been identified, the detailed etiology is multifactorial and unclear. Here, we present the case of a 7-year-old girl who was clinically diagnosed with SOD and 15q13.3 duplication. Patients with duplication at chromosome 15q13.3 were reported to be diagnosed with autism spectrum disorder, epilepsy, and schizophrenia in previous studies. The relationship between SOD and the microduplication of 15q13.3 has not yet been explored. In this study, we suggest that there may be an association between chromosome 15q13.3 microduplication and SOD.

Keywords: Chromosome duplication; Microarray analysis; Septo-optic dysplasia

Introduction

Septo-optic dysplasia (SOD) is a rare congenital developmental anomaly with a reported incidence of 1 in 10,000 live births. A diagnosis of SOD, also known as de Morsier syndrome, is mainly made clinically on the basis of the presence of two or more combinations of the following triad: (1) optic nerve hypoplasia, (2) midline brain defects such as the absence or hypoplasia of the septum pellucidum and corpus callosum, and (3) hypopituitarism [1].

The main clinical signs or symptoms of SOD include developmental delay, seizures, hearing or olfactory abnormalities, visual impairment, and pituitary dysfunction [2]. SOD generally occurs sporadically, but it can also be inherited, albeit rarely. *HESX1* mutations are known to be related to familial cases, and recently, a link between *SOX2* and *SOX3* genes has also been identified [3]. However, the exact etiology is unclear and is thought to be multifactorial, including environmental and genetic factors.

Chromosome microarray analysis is a routine evaluation for many children with developmental delays; however, its utility in assessing SOD is unknown. We present the case of a 7-year-old girl with a clinical diagnosis of SOD and 15q13.3 duplication, and suggest possible associations between the two.

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Case

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Ulsan University Hospital (IRB No: 2022-09-045). Written informed consent was obtained for publication of this case report and accompanying images.

A 7-year-old girl with congenital nystagmus and infantile esotropia presented to the ophthalmology outpatient department and was referred to us because of developmental delays. She was born at 37 weeks and 4 days of gestation via spontaneous vaginal delivery, and her birth weight was 2.77 kg. Her family and perinatal histories were unremarkable. The patient had no history of seizures. Her muscle tone was normal with brisk deep tendon reflexes, and overall muscle power was above good grade.

She fell frequently and exhibited an ataxic gait pattern. She had difficulty performing tandem gait and keeping up with her studies. Dysmorphic features, including a flat nasal bridge, an inverted upper lip, and slender epicanthal folds, were observed. At that time, she obtained a full scale intelligence quotient score of 53 on the Korean Wechsler Intelligence Scale for Children, 4th edition and social quotient score of 73.5 on the Social Maturity Scale.

Brain magnetic resonance imaging (MRI) showed absence of the septum pellucidum, hypoplasia of the optic tract and pituitary gland, partial thinning of the corpus callosum, and closed-lip schizencephaly in the left frontoparietal lobe (Fig. 1). SOD was clinically suspected and other differential tests were performed. There

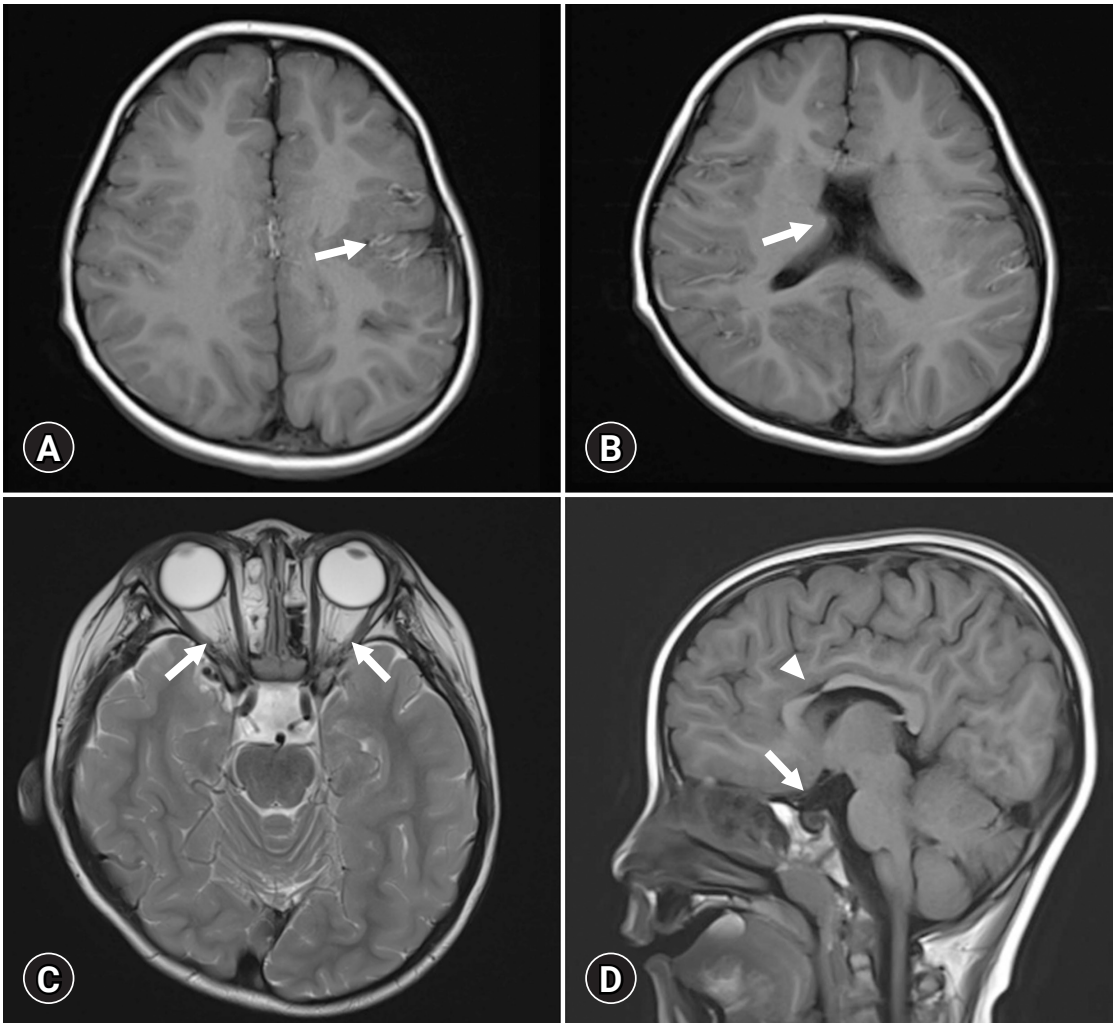

Fig. 1. (A) Axial T2-weighted fluid-attenuated inversion recovery (FLAIR) image shows closed-lip schizencephaly in left frontoparietal lobe (arrow). (B) Axial T2-weighted FLAIR image shows abscence of the septum pellucidum (arrow). (C) Axial T2-weighted turbo spin echo shows hypoplasia of both optic nerves (arrows). (D) Sagittal T1-weighted FLAIR image shows partial thinning of genu of corpus callosum (arrowhead) and hypoplasia of the pituitary stalk and pituitary gland (arrow).

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were no abnormal findings on an electroencephalogram. The absolute P100 latency was prolonged on the left side in the visual evoked potential test (P100 = 155 ms). Measurement of anterior pituitary hormones revealed low anti-thyroglobulin antibodies (< 20 IU/mL), high thyroid-stimulating hormone (8 μIU/mL), and low cortisol (< 1.0 μg/dL). Genetic testing was performed, and chromosome microarray analysis confirmed a 432-kb duplication on 15q13.3 (Fig. 2). The parents and other family members refused genetic testing for financial reasons.

Discussion

Several studies have shown features related to chromosome 15q13.3 duplication. Patients with duplication at chromosome 15q13.3 have behavioral problems, dysmorphism, autism, mental retardation, and language delays [4]. Until recently, the reported diseases related to this chromosomal region included developmental delay, multiple congenital anomalies, epilepsy, schizophrenia, autism spectrum disorder, attention deficit hyperactivity disorder, major depressive disorder, Alzheimer disease, Parkinson disease, and congenital heart disease [5]. Microduplication of 15q13.3 involving *CHRNA7* can disturb neuronal homeostasis by affecting nicotinic receptors in the brain. The alpha 7 nicotinic acetylcholine receptors are members of the ligand-gated ion channel family and are encoded by *CHRNA7*. These nicotinic receptors are found in the brain both pre- and postsynaptically, and are highly expressed in the hippocampus, cingulate gyrus, lateral geniculate nucleus, medial geniculate nucleus, and thalamus [6]. These receptors mediate synaptic signal transduction and regulate neurotransmitter release in the hippocampus and other brain regions [7]. The alpha 7 nicotinic receptors are also required for the development of normal local inhibitory neurocircuits and play an important role during the prenatal period [8]. However, it is still controversial whether microduplication in this chromosomal region is benign or pathological [9]. Because the 15q13.3 duplications have lower penetrance than other genomic diseases, the mutation is also observed in healthy controls and the phenotypes are variable; thus, disease association is difficult to determine [10].

SOD can be clinically suspected in children with developmental delay, seizures, strabismus or nystagmus, optic nerve hypoplasia, and insufficiency of cortisol, growth hormone, luteinizing hormone, follicle-stimulating hormone, and thyroid hormone. Typical brain MRI findings in SOD show absence of the septum pellucidum, optic nerve hypoplasia, schizencephaly, and structural abnormality of the pituitary gland. These findings imply an abnormality in the forebrain or anterior neural plate development [1,2].

HESX1, suggested to be a key gene in SOD, is a transcriptional repressor that plays an important role in early pituitary commitment and proliferation. In an animal model, a SOD phenotype was observed when *HESX1* was mutated. *SOX2* and *SOX3* belong to the same SOXB1 family and are associated with developmental dysfunctions involving loss of DNA binding and transcriptional activation. *SOX2* mutations can cause defects in the corpus callosum, eye disorders, hearing loss, short stature, and other congenital defects. Other genes have also been reported, including *OTX2*, *PROKR2*, *FGF1*, and *FGF8* [2,3,11,12]. However, in practice, the causative gene for SOD has been identified in less than 1% of cases [2]. Moreover, it is difficult to determine a clear correlation.

The patient reported here had clinical symptoms and laboratory and brain MRI findings indicative of SOD. Chromosome microarray analysis revealed 15q13.3 microduplication. The relationship between SOD and microduplication of 15q13.3 has not been pre-

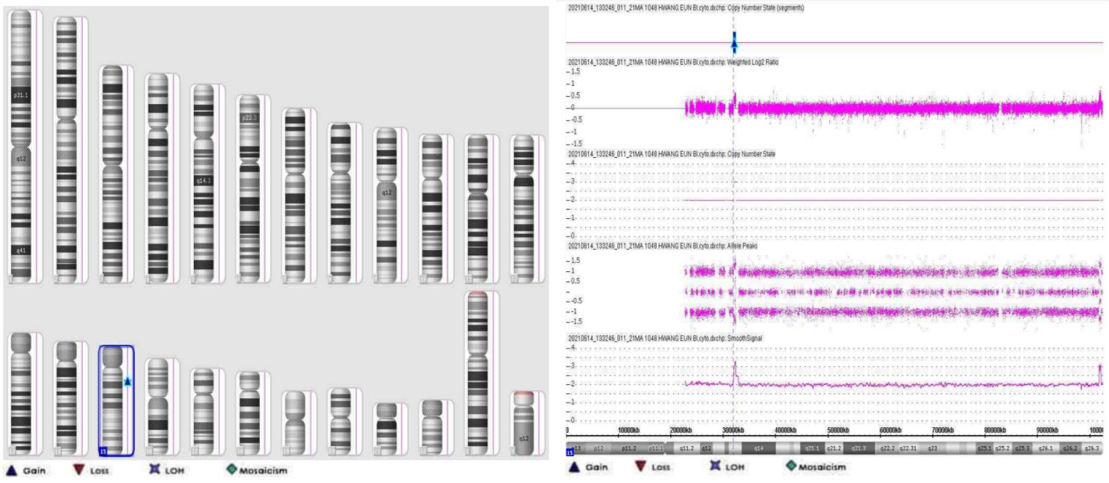

Fig. 2. Chromosome microarray analysis detects duplication of a 432 kb on the chromosome 15q13.3 region.

viously investigated, and there is no strong evidence for a causal relationship between them. However, although cases involving both SOD and duplication of 15q13.3 are rarely discovered, the two coexist in this case and have overlapping phenotypes.

In conclusion, we suggest a correlation between these two conditions. To the best of our knowledge, this is the first case report of SOD and chromosome 15q13.3 microduplication. Further studies on additional cases are needed to verify this association and determine how duplication contributes to SOD.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization, Data curation, Supervision: SHK, DP; Formal analysis: JAH, SHK; Methodology: JAH; Writing-original draft: JAH; Writing-review & editing: SHK, DP.

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