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Case Report

A novel mutation in the *GATAD2B* gene associated with severe intellectual disability

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Abstract

Background: The human GATA zinc finger domain containing 2B (GATAD2B) encodes a subunit of the MeCP1-Mi-2/nucleosome remodeling and deacetylase complex, which is involved in chromatin modification and transcription. Recently, patients with severe intellectual disabilities and characteristic features associated with *GATAD2B* mutations have been identified.

Case report: The patient was a 4-year-old male with dysmorphic features, including frontal bossing, hypertelorism, epicanthal folds, down-slanting palpebral fissures, a flat nasal bridge, a high arched palate, and micrognathia. He spoke no meaningful words and exhibited severe intellectual disability. Hypermetropic astigmatism and mild spasticity of the lower extremities were noted. Whole-exome sequencing revealed a *de novo* missense mutation in *GATAD2B* (NM_020699:exon4:c.502C>T; p.(Glu168*)).

Conclusion: We report a novel *GATAD2B* mutation in a boy exhibiting bilateral leg spasticity and white matter abnormalities on brain magnetic resonance imaging.

Keywords: *GATAD2B*; Intellectual disability; Haploinsufficiency; Hypotonia; Neuroradiological findings

1. Introduction

Intellectual disability (ID) is a group of disorders involving neurological dysfunction with an extremely heterogeneous clinical presentation. It has an estimated prevalence rate of 1–3% [1]. Recently, with the emergence of next-generation sequencing, the genetic factors associated with ID have become clearer, and more than 800 ID-related genes have identified [2–4].

The human GATA zinc finger domain containing 2B (GATAD2B) encodes a subunit of the MeCP1-Mi-2/nucleosome remodeling and deacetylase complex, which is involved in chromatin modification and transcription. *De novo* loss-of-function mutations in *GATAD2B* in two individuals with severe ID using whole-exome sequencing (WES) were detected [4]. By searching for microdeletions encompassing *GATAD2B* in databases, a third individual with such a microdeletion and a fourth individual with a loss-of-function mutation in *GATAD2B* were identified [5]. In the report of the exomes of 41 probands and their parents, a *de novo* splicing mutation in *GATAD2B* was found in a patient with ID though no precise description of the patient was provided [6]. Another WES on a cohort of 71 patients with unresolved white matter abnormalities reported that one individual with severe ID had a *de novo* loss-of-function mutation in *GATAD2B* [7]. Recently two novel

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heterozygous frameshift mutations in *GATAD2B* in two unrelated Chinese patients with ID were reported [8]. The common features of these cases included severe ID and dysmorphic features, such as thin and light hair, a broad forehead, deeply set eyes, hypertelorism, telecanthus, down-slanting palpebral fissures, a wide nasal base, a short philtrum, and a broad mouth. Patients with 1q21.3 microdeletions involving *GATAD2B* also exhibited characteristic facial features and ID [9].

Here, we report a novel *GATAD2B* mutation in a boy who exhibited bilateral leg spasticity and white matter abnormalities on brain magnetic resonance imaging (MRI).

2. Case report

The patient was a 4-year-old male, the second child of healthy and non-consanguineous Japanese parents. He had a healthy older brother and a healthy younger sister. At birth (at 38 weeks of gestation), he weighed 3258 g, measured 52.0 cm in length, and had a head circumference of 32.7 cm.

He was hypotonic, and his developmental milestones were delayed. He was able to sit independently at 18 months of age and was able to walk unaided at 3 years of age. He spoke no meaningful words, but could understand some simple words. His interest in objects was limited. He exhibited severe ID. He did not show any behavioral abnormalities and did not fit the criteria for autism spectral disorders.

At 4 years of age, a physical examination revealed that his height was 93.3 cm (−1.6 standard deviations [SD]), his weight was 15.3 kg (−0.2 SD), and his head circumference was 52.0 cm (+0.1 SD). In addition, dysmorphic features, including frontal bossing, hypertelorism, epicanthal folds, down-slanting palpebral fissures, a flat nasal bridge, a high arched palate, and micrognathia, were seen (Fig. 1). Fetal pads were found in his fingers. Hypermetropic astigmatism, increased bilateral patellar reflexes and Achilles tendon reflexes, and contracture of the ankle joint were also confirmed. Furthermore, mild spasticity of the lower extremities was noted.

T2-weighted brain MRI performed at 4 years of age revealed high signal intensity in the cerebral white matter. Small cystic lesions were observed in the periventricular white matter of the left occipital horn (Fig. 2). These abnormal findings could explain the mild spasticity of the lower extremities. Conventional cytogenetic studies and tests for metabolic abnormalities produced normal results. WES was carried out.

The protocol for the present study was approved by the institutional review board. Written informed consent was obtained from the patient's parents. DNA was extracted from a peripheral blood sample according to the standard protocol. Exome analyses were performed

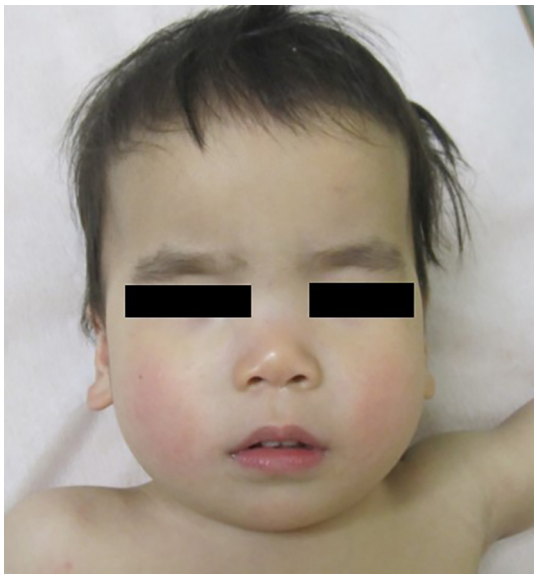

Fig. 1. Facial features of our patient at 4 years of age. Note the frontal bossing, hypertelorism, epicanthal folds, down-slanting palpebral fissures, flat nasal bridge, high arched palate, and micrognathia. We took the written permission to use the patient's photograph from the guardian.

using the HiSeq 2500 platform (Illumina, CA) and SureSelect XT Human All Exon V6 (Agilent Technologies, Santa Clara, CA), as described previously [10]. Reads were aligned to GRC37 using Burrows-Wheeler Aligner (http://bio-bwa.sourceforge.net/). Variants were called using the GATK Unified Genotyper and using ANNOVA (http://annover.openbioinfomatics.org/en/latest/). Candidate variants were validated by Sanger sequencing.

A *de novo* missense mutation in GATAD2B (NM_020699:exon4:c.502C>T; p.(Glu168*)) was revealed. This variant is not listed in the Exome Aggregation Consortium (ExAC) database, exome variant server (EVS) database, 1000 Genome database, Human Genetic Variation Database, or our in-house exome database. No other candidate genes were identified in autosomal recessive or X-linked inheritance models.

3. Discussion

We identified a novel *GATAD2B* mutation in a boy with severe ID. The mild spasticity of the lower extremities and abnormal brain MRI findings exhibited by this patient were not seen in the six previously reported patients with *GATAD2B* mutations. Willemsen et al. reported that severe ID; limited speech; childhood hypotonia; thin hair; and particular facial features, including a typical, tubular nose with a broad tip, deeply set eyes, a broad forehead, a short philtrum, a broad mouth, a grimacing facial expression, strabismus, and long fingers, are characteristic features of patients with

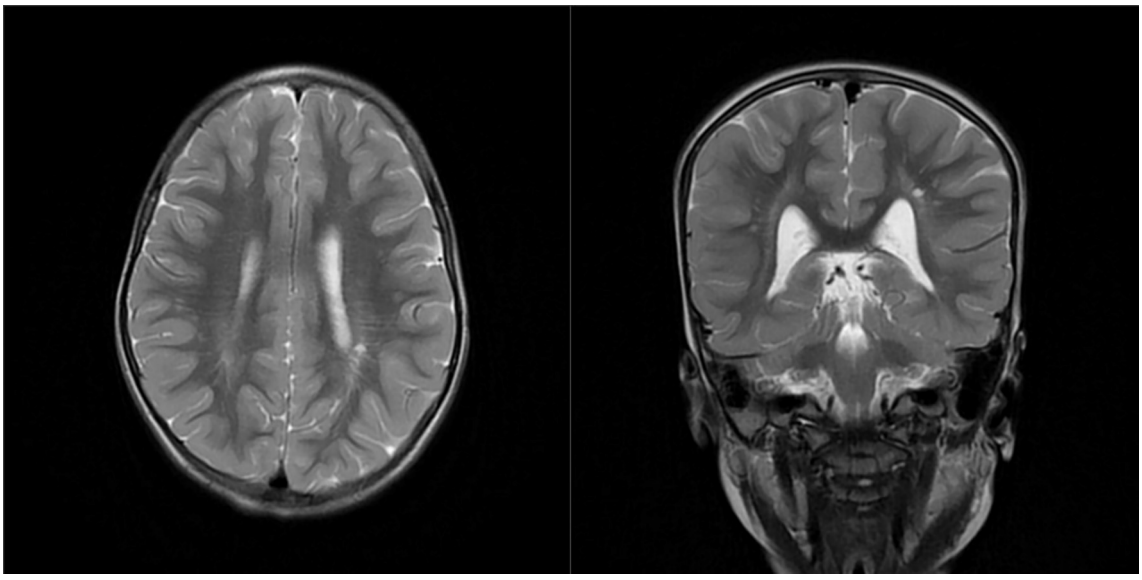

Fig. 2. MRI findings. Axial and coronal T2-weighted brain MRI demonstrated high signal intensity in the cerebral white matter and small cystic lesions in the periventricular white matter of the left occipital horn.

Table 1
Comparison of the reported cases involving mutations in the *GATAD2B* gene and their characteristic clinical features.

Patients	Sex	Gene mutations	Psychoneurotic symptoms	Eye disorders	Brain MRI	Other features
Our patient	Male	c.502C>T (p.Gln168*)	–	Hypermetropic astigmatism	White matter	Spasticity of the lower extremities
de Ligt et al. (2012)	Female	c.1408C>T (p.Gln470*)	Tics, wandering at night	Strabismus, hypoplastic optic nerve	–	IUGR
Willemsen et al. (2013)	Female	c.584dup (p.Asn195Lysfs*30)	Hyperactivity	Hypermetropic astigmatism strabismus	No abnormality	–
Willemsen et al. (2013)	Female	A 240 kb de novo deletion of chromosome 1q21.3 encompassing 10 genes, including GATAD2B	Low frustration tolerance, absence of epilepsy	Astigmatism, strabismus	–	–
Willemsen et al. (2013)	Female	c.565_566delAG(p.Gln190ALafs*34)	Hyperactivity, inappropriate laughter, obsession with shiny objects, self-mutilation, absence of epilepsy	Strabismus hypermetropic astigmatism	–	Persistent constipation
Hamdan et al. (2014)	Female	c.1217_2A>G (splice site)	Absence of epilepsy autistic traits	–	Myelination delay	Mildly lax ligaments
Vanderver et al. (2016)	Male	c.820C>T (p.Gln274*)	–	–	White matter	Hypospadias
Luo et al. (2017)	Male	c.80_81insGATGT (p.Leu28Metfs*18)	–	–	–	–
Luo et al. (2017)	Female	c.552_555delGAAA (p.Lys184Asnfs*2)	Hyperactivity	–	–	–

All of the patients exhibited hypotonia in infancy, severe intellectual disability with language retardation, and dysmorphic features. MRI: magnetic resonance imaging; IUGR: intrauterine growth restriction.

GATAD2B mutations. However, our patient showed severe ID and dysmorphic features, and his features were different from those of the previously reported patients. He displayed midface hypoplasia without a tubular nose with a broad tip. In addition, fetal pads, like those found in Kabuki syndrome, were also noted.

Table 1 summarizes the previously reported cases of patients with *GATAD2B* mutations. Some overlapping characteristics were shared among the cases. Five of the nine patients, including our patient, had eye disorders, including strabismus, hyperopia, and a hypoplastic optic nerve. Behavioral abnormalities, including tics, wandering at night, low frustration tolerance, hyperactivity, and inappropriate laughter, were also seen [5,8]. Our patient needs to follow his behavior attentively though now he didn't have behavioral abnormalities. Vermeulen et al. reported that *GATAD2B*-related syndrome, which is caused by microdeletion of the *GATAD2B* gene, results in low levels of adaptive functioning, particularly in social functioning, and weaknesses in communication skills. Patients with this condition have difficulty with expressive language, but their non-verbal communication skills are relatively well conserved [11].

Brain MRI of our patient showed abnormalities in the cerebral white matter. As Table 1 shows, brain MRI findings were not described precisely in previous reports about patients with mutations in the *GATAD2B* gene. One patient also showed cerebral white matter abnormalities [7]. The patient showed global developmental delay and dysmorphic features. However, spasticity of lower extremities was not described in their report. The mutation was found by using WES among patients with unresolved white matter abnormalities. Our patient showed normal MRI finding at the age of 2. Subsequent MRI studies at the age of 4 revealed white matter abnormalities. Our patient was the second case, which could confirm the association between white matter abnormalities and *GATAD2B* mutations. Since neuronal knockdown of the Drosophila *GATAD2B* ortholog, simj, resulted in impaired learning and altered synaptic morphology [5], *GATAD2B* mutations might give rise to neurodevelopmental abnormalities. Therefore, neuroradiological studies might be important for diagnosing patients with the mutations.

In conclusion, we report the case of a patient with a novel mutation in the *GATAD2B* gene. Our report further indicates that haploinsufficiency of *GATAD2B* causes a syndrome involving hypotonia, ID, and dysmorphic features. We suggest careful follow up with brain MRI findings is necessary in the patients with *GATAD2B* mutations.

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