Case Report
J Genet Med 2023;20(2):70-74
https://doi.org/10.5734/JGM.2023.20.2.70
ISSN 1226-1769 (Print) 2383-8442 (Online)

JGM Journal of Genetic Medicine

A Korean case of *CTCF* related neurodevelopmental disorders

Seong Ryeong Kang[1], Soo Hyun Seo[2], Kyunghoon Kim[3,4], Hee Bum Yang[5], Hye Ran Yang[3,4], and Anna Cho[3,4]*
[1]Department of Pediatrics, Seoul National University Children's Hospital, Seoul, Korea
[2]Department of Laboratory Medicine, Seoul National University Bundang Hospital, Seongnam, Korea
[3]Department of Pediatrics, Seoul National University Bundang Hospital, Seongnam, Korea
[4]Department of Pediatrics, Seoul National University College of Medicine, Seoul, Korea
[5]Department of Surgery, Seoul National University Bundang Hospital, Seongnam, Korea

CCCTC-binding factor (CTCF) is a transcriptional regulator that binds to a complex DNA motif in various orientations and plays a crucial role in regulating gene expression, chromatin restructuring, and developmental processes. Mutations in the *CTCF* are associated with neurodevelopmental disorders. Here we report the first Korean case with a de novo heterozygous variant in the *CTCF* (c.1025G>A; p.Arg342His). She showed global developmental delay, failure to thrive, and dysmorphic face, which are phenotypes consistent with previous reports in the autosomal dominant intellectual developmental disorder 21 (MIM 615502). She also showed clinical features not previously reported, such as antral web and tracheobronchomalacia. Our case follows suit and expands understanding of this rare disorder by reporting common features and, on the other hand, unreported concomitant congenital anomalies.

Key words: CCCTC-binding factor, Chromosomal proteins, non-histone, Neurodevelopmental disorders, Intellectual disability.

Introduction

Advances in genetic sequencing technology have led to the discovery of numerous newly identified monogenic neurodevelopmental disorders. Among these recent discoveries are variations in the epigenetic machinery, which includes readers, writers, erasers, and chromatin remodelers [1]. CCCTC-binding factor (CTCF), a highly conserved transcriptional regulator, plays a wide range of roles in regulating gene expression through epigenomic mechanisms [2].

Specific features observed in humans with germline *CTCF* mutations include syndromic intellectual disability (ID) accompanied by microcephaly and growth retardation [3]. Konrad et al. [4] noted that certain symptoms, such as feeding abnormalities and failure to thrive, are commonly observed along with various birth defects and anomalies. These common phenotypes are referred to as mental retardation autosomal dominant 21 (MRD 21), which is caused by a heterozygous mutation in the *CTCF* on chromosome 16q22 and is registered as MIM 615502.

Here, we report the first Korean case with a de novo missense variant of the *CTCF*. This variant has not been reported previously. In this case, we describe the clinical features of the patient and the subsequent treatment at our center.

Received: 5 July 2023, Revised: 20 November 2023, Accepted: 1 December 2023, Published: 31 December 2023
*Corresponding author: Anna Cho, M.D., Ph.D. https://orcid.org/0000-0001-7500-5955
Department of Pediatrics, Rare Disease Center, Seoul National University Bundang Hospital, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea.
Tel: +82-31-787-7301, Fax: +82-31-787-4987, E-mail: annacho77@snu.ac.kr
Conflict of interest: The authors declare that they do not have any conflicts of interest.

Case

A late preterm female infant was delivered by emergency cesarean section for preterm labor at 34 weeks and 1 day of gestational age. The patient had an apgar scores of 5 and 6 at 1 minute and 5 minutes, respectively. Her birth weight was 2.5 kg (78th percentile). She was admitted to the neonatal intensive care unit for 4 months for respiratory distress syndrome, pneumothorax, pulmonary hemorrhage, severe bronchopulmonary dysplasia, periventricular leukomalacia, and grade 1 intraventricular hemorrhage. She was discharged with home O_2 inhalation via nasal prong (2-3 L/min). She was admitted to our center at the age of 5 months (corrected age of 4 months) with recurrent cyanosis. At the time of admission, she had fever and respiratory distress and was accompanied by ileus. Bronchoscopy showed tracheobronchomalacia, and upper gastrointestinal series and small bowel series showed an antral web. Therefore, gastroesophageal reflux-induced aspiration pneumonia was diagnosed and a Heineke-Mikulicz pyloroplasty was performed at 6 months of age (corrected age 5 months). Oral feeding was attempted after surgery, but feeding intolerance persisted. Videofluoroscopic swallowing study was performed and aspiration tendency was confirmed with penetration-aspiration scale 4 to 5 and nasogastric tube feeding only was started. She had global developmental delay (GDD). So the multiple anomaly and GDD refer her to the genetic department.

The detailed systemic review of the multiple anomaly is as follows. Perinatally, there were no other abnormalities except for polyhydramnios. Facial features include hypertelorism and a small lip are observed (Fig. 1). Congenital sensorineural hearing loss with hearing aids, both cochlear implants were performed at the age of 10 months (corrected age of 9 months). Ophthalmologic hyperopia, both abducens nerve palsy are present. In the cardiovascular system, she has patent ductus arteriosus, patent foramen ovale, pulmonary artery hypertension. The patient had an antral web in the gastrointestinal system. In the genitourinary system, she has medullary nephrocalcinosis with increased parenchymal echogenicity of both kidneys and hypercalciuria. In the muscular system, she has musculoskeletal rigidity. On the Baley Scale, a very delayed global development was observed at 26 months. Brain magnetic resonance imaging shows no specific structural abnormalities (Fig. 2). In the family history, the patient was born to non-consanguineous healthy parents in a Korean family. Her older brother has a borderline motor developmental delay. He walked on his own at the age of 3 years, but his motor development has caught up since then. Currently, the brother has not visited a healthcare provider, so we have not been able to perform the genetic test.

Chromosomal microarray performed at the outside hospital showed a normal karyotype, reported as arr (1-22, X)×2. For further genetic testing, she and her parents are enrolled in whole genome sequencing, which is National Project of Bio Big Data, and performed trio test. A de novo heterozygous mutation on

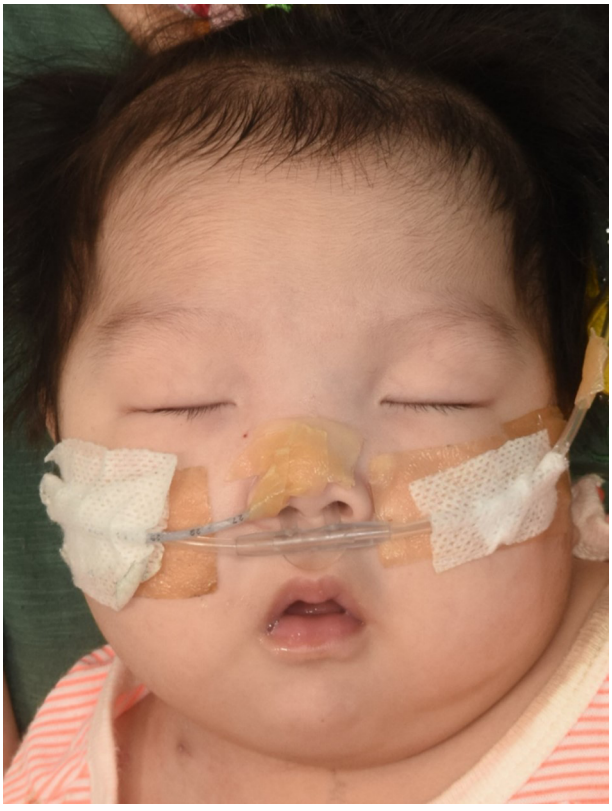

Fig. 1. The facial features of the patient. Note the presence of mild facial dysmorphism, including a hypertelorism and small lip, as is shared previous reported CCCTC-binding factor mutation cases.

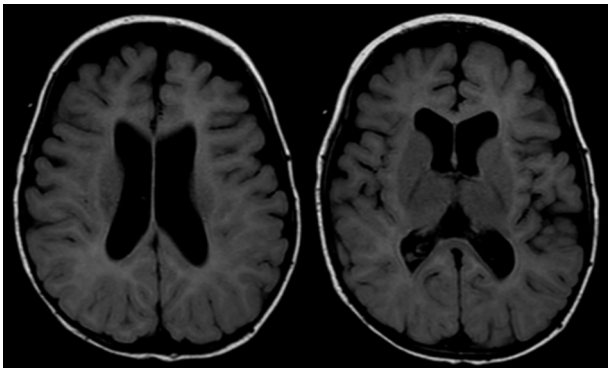

Fig. 2. The patient's brain magnetic resonance image. There is no specific brain anomaly on brain magnetic resonance T2-weighted and fluid attenuated inversion recovery axial image at 7 months old.

Table 1. Clinical features of our patient and previous reported individuals with *CTCF* variant

	Our study	Gregor et al. [3]				Bastaki et al. [6]		Chen et al. [7]	Hori et al. [5]			Konrad et al. [4]
		Individual 1	Individual 2	Individual 3	Individual 4	Individual 5	Individual 6	Individual 7	Individual 8	Individual 9	Individual 10	Individual 11-48 (n)
Defect in *CTCF*	c.1025G>A	c.375dupT	c.1186dupA	c.1699C>T	280 kb deletion	Deletion 67.1-68.2 Mb	Deletion 67.3-68.9 Mb	c.612delAAAG	c.615_618delGAAA	c.1699C>T	c.329dupT	LGD variants (8) Missense/in-frame variants (26) Large deletion (2)
Sex	Female	Male	Male	Male	Female	Female	Female	Female	Female	Female	Female	ND
Birth	34 wk	34 wk	40 wk	39 wk	40 wk	39 wk	39 wk	26 wk	ND	ND	ND	ND
Birth weight	2,500 g	SGA	2,620 g	2,990 g	2,900 g	2,515 g	2,490 g	560 g	2,800 g	2,650 g	1,900 g	IUGR/SGA (10/35)
Birth length	ND	< –2 SD	50 cm	54 cm	49 cm	47 cm	45 cm	ND	48 cm	50 cm	45 cm	ND
Birth OFC	ND	< –2 SD	33 cm	34 cm	ND	31 cm	31 cm	< –1.25 SD	ND	ND	ND	ND
Last weight	–0.6 SD	–2.35 SD	–0.96 SD	–1.15 SD	–1.74 SD	–2.3 SD	–0.9 SD	< –2 SD	< –2 SD	< –2 SD	< –2 SD	ND
Last length	–0.6 SD	–3.15 SD	–0.71 SD	–1.90 SD	–1.94 SD	–3.2 SD	–1.4 SD	< –2 SD	< –2 SD	< –3 SD	< –3 SD	Short stature (6/35)
Last OFC	+1.0 SD	–3.51 SD	–2.61 SD	–2.91 SD	–0.84 SD	–2.8 SD	–1.3 SD	< –2 SD	< –2 SD	< –2 SD	< –3 SD	ND
Developmental delay	+	+	+	+	+	+	+	+	+	+	+	Mild (16) Moderate (9) Severe (3)
Brain anomaly	-	+	ND	-	+	-	-	-	ND	-	-	ND
Facial anomaly	+	+	+	+	+	+	+	+	+	+	+	+ (12-14/31)
Vision anomaly	+	+	-	+	+	-	-	+	+	+	+	+ (23/29)
Hearing loss	+	-	-	-	-	-	-	ND	-	-	-	+ (11/33)
Palatal anomaly	-	+	-	-	-	-	-	-	+	-	-	+ (12/33)
Dental anomaly	-	-	+	-	-	-	-	-	-	+	+	ND
Cardiac defects	+	+	-	-	-	-	-	+	-	-	+	+ (1/31)
Gastrointestinal system anomaly	+	-	-	-	-	-	-	+	ND	ND	ND	ND
Feeding difficulty	+	+	+	+	+	+	+	ND	+	+	ND	+ (23/33)
Genitourinary system anomaly	+	+	+	+	-	-	-	+	-	-	-	ND
Hands/feet anomaly	-	+	+	-	+	+	+	+	+	-	-	ND
Other anomaly	Tracheobronchomalacia	Sacral dimple	-	-	Hypertrichosis	-	GH deficiency	-	GH deficiency	Bone age delay	-	ND
Recurrent infection	+	ND	ND	ND	ND	ND	ND	+	-	+	-	+ (15/32)

CTCF, CCCTC-binding factor;+, present; -, not present; GH, growth hormone; IUGR, intrauterine growth restriction; LGD, likely gene-disruptive; ND, no data; SGA, small for gestational age; SD, standard deviation; OFC, occipito-frontal circumstance.

CTCF (c.1025G>A; p.Arg342His) was found. This was found for the first time in the Genome Aggregation Database version 3.1.2 dataset. The variant was classified as 'likely pathogenic' according to the American College of Medical Genetics and Genomics classification and confirmed by Sanger sequencing.

Discussion

CTCF-associated neurodevelopmental syndrome is an extremely rare disorder with only dozens of cases reported worldwide to date (Table 1). Gregor et al. [3] first reported a total of four de novo cases with a common phenotype of syndromic ID, microcephaly, and growth retardation. Since then, several sporadic cases have been described [5-7]. There have also been reports of *CTCF* variants found in different several large cohorts [8-10]. Recently, an international collaboration has expanded the mutational and clinical spectrum of *CTCF*-associated neurodevelopmental disorders [4].

As with previous *CTCF* variants, our patient shares the phenotype of intellectual developmental disorder. She also has common features such as hypertelorism and small lips, feeding difficulties, and recurrent infections. The diversity of *CTCF* phenotypes makes it difficult to detect *CTCF* mutations clinically [4]. In our patient, tracheomalacia, antral web is a new phenotype that has not been reported before. CTCF is an epigenetic machinery, which explains why patients have a wide range of symptoms and varying degrees of ID [1]. CTCF is a chromatin looping insulator [11] and is involved in chromatin organization to regulate gene expression. Because the sites at which the insulator acts are located throughout the genome, *CTCF* variants can affect a wide variety of sites, resulting in a wide variety of phenotypes [12].

Her older brother had a borderline developmental delay without growth disorders or anomalies. We initially considered the possibility of familial developmental delay syndrome, but an isolated *CTCF* syndrome was diagnosed in this case. This suggests that the causes of developmental delay can be very complex and diverse. It also suggests that the interpretation of family history in the process of genetic diagnosis can sometimes be complicated. Our limitation is that her brother was not genetically tested. Although he had a borderline motor developmental delay, he has since caught up and does not have the common *CTCF* phenotypes, so we suspect that he is not a *CTCF* variant. Therefore, accurate genetic diagnosis can be of great help in broadening the clinical understanding of the complex syndrome. Additional research is necessary to uncover the specific pathogenic mechanisms involved, and it is important to identify more patients with detailed phenotypical information to gain a clearer understanding of this rare disease from a clinical perspective.

The Institutional Review Board of Seoul National University Bundang Hospital approved this study (B-2307-838-701), and this study was conducted in accordance with the Declaration of Helsinki. Written informed consent for molecular study and publication was obtained from the patient's parents.

Acknowledgements

We extend our gratitude to the patient and her parents for their valuable contribution to this study.

Funding

Whole genome sequencing was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Ministry of Health and Welfare, Ministry of Science and ICT, Ministry of Trade Industry and Energy, Korea Disease Control and Prevention Agency (No. 2020M3E5D7086780, The National Project of Bio Big Data).

Authors' Contributions

Conception and design: SRK, AC. Acquisition of data: SHS, KK, HBY, HRY, AC. Analysis and interpretation of data: SRK, AC. Drafing the article: SRK. Critical revision of the article: AC. Final approval of the version to be pulished: AC.

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