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Clinical Spectrum and Treatment Outcomes in Korean Pediatric Patients with *CHD2*-Related Disorders: Limited Genotype–Phenotype Correlation

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Purpose: The chromodomain helicase DNA-binding (CHD) protein family comprises adenosine triphosphate-dependent chromatin remodelers that regulate chromatin structure and gene expression. Pathogenic *CHD2* variants are associated with neurodevelopmental phenotypes, but these genotype–phenotype correlations remain unclear. This study aimed to delineate the clinical and genetic features of patients with *CHD2*-related disorders and to explore the associated genotype–phenotype relationships.

Methods: Among 22 patients with pathogenic or likely pathogenic *CHD2* variants identified using a customized 172-gene neurodevelopmental and epilepsy panel, 19 with sufficient clinical data were included. Demographic, clinical, neuroimaging, electroencephalographic, and genetic data were retrospectively reviewed.

Results: Eighteen pathogenic or likely pathogenic variants were identified, including eight novel variants: nine nonsense (50.0%), five splice-site (27.8%), two missense (11.1%), and two exon deletions (11.1%). All patients had epilepsy, with a median age of seizure onset of 2.33 years. Comorbidities included global developmental delay (89.5%), intellectual disability (82.0%), and neuropsychiatric symptoms (47.4%). Seizure types were heterogeneous, with a predominance of generalized-onset seizures, and 13 patients (68.4%) achieved seizure freedom. Marked phenotypic variability was observed: two unrelated patients with the same truncating variant had different developmental and seizure-related profiles, a symptomatic child with an inherited exon 5 deletion contrasted with her asymptomatic father, and a patient with an exon 17–29 deletion exhibited relatively mild features.

Conclusion: Epilepsy was a consistent manifestation in this study and was accompanied by diverse developmental and neurobehavioral features, with substantial genotype–phenotype discordance. Further research on genotype–phenotype correlation is warranted.

Keywords: CHD2; Genotype; Phenotype; Korea; Pediatrics

Introduction

Chromatin remodeling is a functional process that regulates gene expression by altering chromatin structure and, consequently, RNA transcription [1]. Chromatin remodeling protein complexes use ATPase activity to modify histone–DNA interactions; by influ-

encing the accessibility of RNA polymerase and transcription factors, they ultimately regulate gene expression [2]. The chromodomain helicase DNA-binding (CHD) family is one such group of chromatin remodelers and comprises nine members. Each member differs slightly in the type and arrangement of domains and subunits [2,3]. The *CHD2* gene (Online Mendelian Inheritance in Man [OMIM]: 602119), which encodes a member of the CHD protein family, is located on chromosome 15q26.1, contains 39 exons, and comprises four functional domains [4].

In 2008, a case report described a patient with short stature, developmental delay, and mild dysmorphic features who carried a balanced translocation, t(15;22)(q26.1;q11.2) [5]. Subsequent case reports and studies of genomic alterations involving 15q26.1 identified *CHD2* within this region, suggesting a potential association between *CHD2* and the observed clinical features; these conditions were later collectively referred to as *CHD2*-related disorders [6,7].

CHD2-related disorders have been associated with neurologic phenotypes in humans, including seizures, developmental delay, intellectual disability, and neuropsychiatric features such as autism spectrum disorder (ASD) [8-10]. More recent studies suggest that pathogenic variants in *CHD2* may contribute to developmental epileptic encephalopathy (DEE) [11-15]. Despite increasing recognition of *CHD2* as a causative gene for DEE, its clinical and genetic characteristics remain insufficiently understood [16,17] and have not been systematically investigated in Korean patients.

In this study, we aimed to delineate the clinical and genetic spectrum of *CHD2*-related disorders in Korean pediatric patients and to explore potential genotype–phenotype relationships and population-specific characteristics that may contribute to the understanding and diagnosis of these rare neurodevelopmental disorders.

Materials and Methods

We screened patients who visited the pediatric neurology center of Severance Hospital, a tertiary medical institution in South Korea, and performed a customized gene panel study containing 172 genes related to epilepsy and DEE from March 2015 to December 2022. Twenty-two patients with pathogenic/likely pathogenic variants in the *CHD2* gene were identified. Three patients with insufficient clinical data were excluded; thus, 19 participants were ultimately enrolled in this study.

Demographic, clinical, and radiologic characteristics were collected through a retrospective review of medical records. Seizure and epilepsy classifications were determined according to the 2024 guidelines of the International League Against Epilepsy. Seizure freedom was defined as the absence of clinical seizures for more than 1 year at the most recent follow-up. Given the retrospective design and heterogeneous follow-up durations, outcome assessment was descriptive and not adjusted for follow-up length. Psychiatric comorbidities (e.g., ASD and other behavioral disorders) were determined based on documented clinical diagnoses by pediatric neurologists/psychiatrists in the medical records; when available, diagnoses were supported by standardized assessments and Diagnostic and Statistical Manual of Mental Disorders-based clinical criteria.

Genomic data were extracted from leukocytes in venous blood samples using the QIAamp Blood DNA Mini Kit (Qiagen, Hilden, Germany). Sequencing data were analyzed using Sequencher version 5.3 software (Gene Codes Corp., Ann Arbor, MI, USA), and large-scale deletions and duplications were detected using the Multiplex Ligation-dependent Probe Amplification (MLPA) kit (MRC Holland, Amsterdam, The Netherlands). Targeted gene panel sequencing, alignment, variant calling, and interpretation pipeline were performed as previously described [13]. Genetic testing for patients' family members was also performed in the same manner, if needed. Pathogenic or likely pathogenic variants were determined according to the American College of Medical Genetics and Genomics guidelines [18].

This study was approved by the Institutional Review Board of Yonsei University Health System Severance Hospital (4-2020-0331), and written informed consent for genetic testing was obtained from the parents or guardians of all participants.

Results

1. Demographics and clinical manifestations

An overview of the patients' demographic and clinical features is provided in Table 1. Of the 19 patients, 11 (57.9%) were male. Four patients (21.1%) had documented perinatal events, including three premature births and one case of congenital hypothyroidism. All patients manifested seizures, with a median age at onset of 2.33 years (range, 0.25 to 8.00). Six patients (31.6%) had a family history of epilepsy or seizures based on medical record review, and 10 (52.6%) had a history of fever-provoked seizures before the diagnosis of epilepsy. Developmental delay involving at least one domain was observed in 17 of 19 patients (89.5%). Language delay was the most frequent feature (17/19, 89.5%), followed by intellectual disability (15/19, 82.0%) and motor delay (11/19, 57.9%). A diagnosis of global developmental delay (GDD) was established in 17 patients (17/19, 89.5%). Comorbid psychiatric disorders were present in nine patients (47.4%); attention-deficit/hyperactivity disorder (ADHD) was the most common (7/19, 36.8%), followed by ASD (1/19, 5.3%) and behavioral disorder with im-

Table 1. Patient characteristics

Demographic	No. (%)
Male sex	11 (57.9)
Perinatal history	
Preterm birth	3 (15.8)
Congenital hypothyroidism	1 (5.3)
Clinical manifestation	
Epilepsy	19 (100)
Global developmental delay	17 (89.5)
Delayed language development	17 (89.5)
Intellectual disability	15 (82.0)
Delayed motor development	11 (57.9)
Comorbid psychiatric disorders	9 (47.4)
ADHD	7 (36.8)
ASD	1 (5.3)
Behavior disorder	1 (5.3)
MRI findings	
Normal	12 (63.2)
Abnormal	7 (36.8)
Small pituitary gland	2 (10.5)
Diffuse cerebellar atrophy	2 (10.5)
Asymmetric ventricle, arachnoid cyst at left mid-cranial fossa	1 (5.3)
Thin corpus callosum (splenium and posterior body)	1 (5.3)
Incomplete rotation with suspicious mild T2 hyperintensity, left hippocampus	1 (5.3)

ADHD, attention-deficit/hyperactivity disorder; ASD; autism spectrum disorder; MRI, magnetic resonance imaging.

paired impulse control (1/19, 5.3%).

2. Magnetic resonance imaging findings

Brain magnetic resonance imaging (MRI) was performed in all patients. Abnormal MRI was defined as any structural finding documented in the official neuroradiology report and considered non-incidental by clinicians. Abnormal findings were identified in seven patients (36.8%), including a small pituitary gland in two patients (10.5%), cerebellar atrophy in two (10.5%), thin corpus callosum in one (5.3%), left hippocampal malrotation (incomplete inversion) in one (5.3%), and asymmetric ventricles in one (5.3%).

3. Characteristics of epilepsy and electroencephalogram findings

As shown in Table 2, seizure types were diverse. Generalized-onset seizures were the most common, occurring in eight of 19 patients (42.1%), followed by focal-onset seizures (6/19, 31.6%) and both focal- and generalized-onset seizures (5/19, 26.3%).

When classified by semiology, generalized tonic or generalized tonic-clonic seizures were observed in 14 patients (73.6%). Other seizure types included myoclonic seizures in seven patients (36.8%), myoclonic-atonic seizures in five (26.3%), eyelid myoclonia with absences in three (15.8%), focal impaired-awareness seizures in two patients (10.5%), and absence seizures and focal mo-

Table 2. Epilepsy characteristics

Characteristic	Value
Age of seizure onset (yr)	2.33 (0.25–8.00)
History of fever-provoked seizures	10 (52.6)
Family history of epilepsy or seizure	6 (31.6)
Seizure type	
Generalized-onset	8 (42.1)
Focal-onset	6 (31.6)
Both focal-onset and generalized-onset	5 (26.3)
Seizure semiology	
GT or GTC	14 (73.6)
Myoclonic	7 (36.8)
Myoclonic-atonic	5 (26.3)
Eyelid myoclonia with absences	3 (15.8)
Focal impaired consciousness seizure	2 (10.5)
Absence	1 (5.3)
Focal motor seizure	1 (5.3)
Epilepsy syndrome	
EMAtS	4 (21.1)
IESS	1 (5.3)
LGS	1 (5.3)
Epilepsy course	
Well controlled (seizure free for >1 year)	13 (68.4)
Recurrence after ASM discontinuation	4 (21.1)

Values are presented as median (interquartile range) or number (%).
GT, generalized tonic seizure; GTC, generalized tonic-clonic seizure; EMAtS, epilepsy with myoclonic-atonic seizure; IESS, infantile epileptic spasm syndrome; LGS, Lennox–Gastaut syndrome; ASM, anti-seizure medication.

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tor seizures in one patient each (5.3%).

Based on semiology, clinical features, electroencephalogram (EEG) patterns, and MRI findings, six patients were diagnosed with specific epilepsy syndromes: four with epilepsy with myoclonic-atonic seizures (EMAtS) and one each with infantile epileptic spasm syndrome (IESS) and Lennox–Gastaut syndrome (LGS). The patient initially diagnosed with IESS and one patient with EMAtS eventually progressed to LGS.

EEG was performed in all patients. At the initial EEG evaluation, abnormal findings were present in all but three patients. Generalized spike-wave or polyspike-wave discharges were the most frequent findings, observed in nine patients (47.4%), followed by multifocal sharp waves (7/19, 36.8%). At the most recent follow-up, six patients demonstrated normal EEG findings. One of these (patient 14) had normal findings at the initial evaluation, while among the remaining five patients (patients 3, 5, 9, 13, and 16) whose EEGs normalized over time, three were among the four individuals diagnosed with EMAtS.

4. Treatment responses

The follow-up period ranged from 1 to 12 years. With anti-seizure medication (ASM) treatment, 13 patients (68.4%) achieved seizure freedom, generally with one or two ASMs (range, 1 to 3). Among these, four patients attempted ASM withdrawal but experienced seizure recurrence within 6 months; all regained seizure freedom after resuming treatment. Time-to-event analyses were not performed due to the limited sample size and non-uniform follow-up intervals.

Five of the six patients had intractable seizures despite trials of at least four ASMs. The remaining patient received only two ASMs, and his seizures had not remained well controlled for more than 1 year at the last follow-up; however, the limited follow-up duration precludes assessment of long-term outcomes.

The most frequently used ASMs were valproic acid (VPA) (13/19, 68.4%), levetiracetam (LEV) (7/19, 36.8%), and clobazam (CLB) and lamotrigine (each 5/19, 26.3%). Among the 13 patients with well-controlled seizures, seven received monotherapy (five with VPA and two with LEV). Five patients were managed with dual therapy: four received regimens combining VPA with CLB, LEV, and lacosamide, respectively, and one received LEV plus oxcarbazepine. One patient achieved seizure freedom with a three-drug regimen (VPA, zonisamide, and ethosuximide).

5. Genetic analysis

Eighteen pathogenic/likely pathogenic variants were identified in 19 individuals, including eight novel variants. These comprised nine nonsense variants (50.0%), five splice-site variants (27.8%), and two missense variants (11.1%). Two individuals carried large deletions involving one or more exons. Notably, one recurrent truncating variant was identified in two unrelated patients. Despite harboring the same variant, these two patients (patients 1 and 11) exhibited distinctly different clinical features, including differences in age at seizure onset, seizure semiology, and EEG and MRI findings. Inheritance analysis revealed that six patients had *de novo* variants, while one patient (patient 7) inherited an exon 5 deletion from her asymptomatic father. Detailed clinical, electroencephalographic, neuroimaging, and genetic information for each patient, as outlined above, is provided in Table 3.

Discussion

In this study, seizures were the most common clinical manifestation, observed in all patients. Seizures were accompanied by heterogeneous seizure types and multiple epilepsy syndromes, followed by GDD (17/19, 89.5%). Overall, the clinical spectrum observed in this study aligns closely with previously reported *CHD2*-related disorders, particularly with respect to developmental delay and phenotypic heterogeneity. The largely comparable distribution of seizure types and epilepsy syndromes across studies supports the consistency of *CHD2*-associated epilepsy phenotypes despite differences in cohort size and study design [10,17,19].

Fourteen patients experienced more than one seizure type, and seizures were well controlled in approximately two-thirds of the cohort. Among the six patients with intractable seizures, four (66.7%) had abnormal brain MRI findings. Both patients with cerebellar atrophy on MRI (patients 10 and 14) belonged to the intractable epilepsy group; cerebellar atrophy has been previously described in *CHD2*-related disorders [17], although its relationship to seizure severity has not been established. In contrast, other structural abnormalities did not show a consistent association with treatment response. Two patients exhibited pituitary hypoplasia (patients 4 and 7), yet only one progressed to LGS while the other achieved good seizure control. Additionally, one patient (patient 15) demonstrated focal seizures in the context of left hippocampal signal abnormality and incomplete rotation, but her seizures remained well controlled. Although cerebellar or posterior-predominant atrophy has been reported in a subset of patients with *CHD2*-related disorders, including cases with longitudinal progression, prior studies likewise have not demonstrated a consistent or predictive association between MRI abnormalities and epilepsy severity or treatment response [15,20]. Taken together, while cerebellar atrophy was observed only in intractable cases in our cohort, there is currently no evidence supporting a causal or predictive relationship between MRI abnormalities and seizure refractoriness

Table 3. Clinical and genetic characteristics of patients with CHD2 variants

Patient	Age of seizure onset (yr)	Sex	History of FC	Seizure semiology	Epilepsy classification	Comorbidities	Initial EEG findings	Controlled seizure	ASMs (used at last)	MRI findings	Gene variant	AA change	Protein effect	Previous report	ACMG classification
1	6.75	M	Yes	GT	Focal epilepsy	ID (mild), language delay, motor delay, ADHD	Occasional independent sharp wave from both frontal areas	Yes	VPA, LCS	Asymmetric lateral ventricle (Lt>Rt) Arachnoid cyst at left mid-cranial fossa	c.1897_1898delCT	p.Leu633AspfsTer2	Nonsense	Reported	P
2	2.33	M	No	GTC, Ms	Both focal-onset and generalized-onset seizures	ID (severe), language delay, motor delay, ASD	Normal	Yes	VPA, CLB	Normal	c.4279-1G>A		Splicing	Unreported	LP
3	0.92	M	Yes	GTC, M-At	EMAtS	ID (moderate), language delay, motor delay	Frequent GSW	Yes	VPA	Normal	c.3885dupA	p.Ile1296Asnfs*Ter8	Nonsense	Reported	LP
4	3.83	M	Yes	Eyelid myoclonia with Ab, GT, Ms	LGS	ID (severe), language delay, motor delay, ADHD	Frequent GSW, occasional multifocal sharp waves	No	VPA, ZNS, LCS, CLB, PER	Slightly small size of the pituitary gland r/o pituitary hypoplasia	c.2698C>T	p.Arg900Ter	Nonsense	Reported	P
5	1.83	F	No	Eyelid myoclonia with Ab, Ms, M-At	EMAtS	ID (moderate), language delay, motor delay	Frequent GSW	Yes	VPA	Normal	c.3172G>T	p.Glu1058Ter	Nonsense	Reported	LP
6	4.83	M	Yes	FIC, GT	Focal epilepsy	ID (moderate), language delay, motor delay	Very frequent rhythmic slow spike-and-wave from both frontal areas	No	VPA, LEV, RUF, LMT, TPM	Thinning of corpus callosum splenium and posterior body	c.4137+3A>G		Splicing	Reported	LP
7	1.83	F	Yes	Eyelid myoclonia with Ab, Ms	Generalized epilepsy	ID (moderate), language delay, motor delay	Frequent 3–4 Hz GSW, frequent multifocal sharp waves	Yes	VPA, ZNS, ETX	Slightly decreased pituitary volume	Exon 5 deletion		Single-exon deletion	Reported	LP

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Table 3. Continued

Patient	Age of seizure onset (yr)	Sex	History of FC	Seizure semiology	Epilepsy classification	Comorbidities	Initial EEG findings	Controlled seizure	ASMs (used at last)	MRI findings	Gene variant	AA change	Protein effect	Previous report	ACMG classification
8	2.58	M	Yes	M-At, Ms	EMAtS, LGS	ID (severe), language delay, motor delay, ADHD	Frequent GSW	No	TPM, LEV. LMT, ETX, CLB	Normal	c.1269dupA	p.Glu424ArgfsTer3	Nonsense	Reported	LP
9	2.58	F	No	GT, Ms-At	EMAtS	Normal	Frequent GSW, frequent multifocal sharp waves	Yes	LEV	Normal	c.4507C>T	p.Arg1503Trp	Missense	Reported	LP
10	0.25	M	No	GT, Ms	IESS, LGS	ID (severe), language delay, motor delay, ADHD	Frequent GSSW, GPFA	No	VPA, CLB, LMT, ZNS, CBD	Cerebellar atrophy	c.1349C>A	p.Ser450Ter	Nonsense	Unreported	LP
11	1.17	M	Yes	GTC	Focal epilepsy	ID (moderate), language delay, motor delay	Rare focal slowing in Rt. occipital area	Yes	VPA, CLB	Normal	c.1897_1898delCT	p.Leu633AspfsTer2	Nonsense	Reported	P
12	1.00	M	Yes	GTC, M-At, Ms	Both focal-onset and generalized-onset seizures	ID (severe), language delay, motor delay	Frequent multifocal sharp waves, frequent GSSW	Yes	VPA	Normal	c.2692C>T	p.Gln898Ter	Nonsense	Unreported	LP
13	2.00	F	Yes	GT	Generalized epilepsy	ID (mild), language delay, attention-deficit	Less well-organized GSW	Yes	VPA	Normal	c.693-1G>C		Splicing	Unreported	LP
14	5.00	F	Yes	GT	Focal epilepsy	ID (mild)	Normal	No	LEV, LMT, LCS, TPM	Diffuse cerebellar atrophy, small Rathke cleft cyst in pituitary gland	c.3748dup	p.Cys1250LeufsTer9	Nonsense	Unreported	LP
15	8.00	F	No	FIC, Fc motor	Focal epilepsy	ID (mild), language delay, motor delay, ADHD	Frequent multifocal sharp waves, Occasional GSW	Yes	VPA	Incomplete rotation with suspicious mild T2 hyperintensity, left hippocampus	c.2605_2606delinsTT	p.Ala869Phe	Missense	Reported	LP
16	6.58	F	No	GTC	Focal epilepsy	ID (borderline), language delay, ADHD	Occasional 3–4 Hz GSW	Yes	LEV	Normal	c.3323_3324del	p.Ser1108Ter	Nonsense	Reported	P

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Table 3. Continued

Patient	Age of seizure onset (yr)	Sex	History of FC	Seizure semiology	Epilepsy classification	Comorbidities	Initial EEG findings	Controlled seizure	ASMs (used at last)	MRI findings	Gene variant	AA change	Protein effect	Previous report	ACMG classification
17	3.17	M	No	GT	Generalized epilepsy	ID (moderate), motor delay, ADHD	No interictal epileptiform discharge	Yes	LEV, OXC	Normal	Exon 17–29 deletion		Multi-exon deletion	Unreported	LP
18	0.92	F	No	Ab	Generalized epilepsy	ID (borderline), language delay, motor delay	Normal	Yes	VPA, LEV	Normal	c.2727+5G>C		Splicing	Unreported	LP
19	2.00	M	No	GTC	Both focal-onset and generalized-onset seizures	ID (moderate), language delay, motor delay	Frequent GSW, GSSW, multifocal sharp waves	No	LEV, LMT	Normal	c.1377+2T>C		Splicing	Unreported	LP

FC, febrile convulsion; EEG, electroencephalography; ASM, anti-seizure medication; MRI, magnetic resonance imaging; AA, amino acid; ACMG, American College of Medical Genetics and Genomics; GT, generalized tonic seizure; ID, intellectual disability; ADHD, attention-deficit/hyperactivity disorder; VPA, valproic acid; LCS, lacosamide; Lt, left; Rt, right; P, pathogenic; GTC, generalized tonic-clonic seizure; Ms, myoclonic seizure; ASD, autism spectrum disorder; CLB, clobazam; LP, likely pathogenic; M-At, myoclonic-atonic seizure; EMAtS, epilepsy with myoclonic-atonic seizures; GSW, generalized spike-and-wave; Ab, absence seizure; LGS, Lennox–Gastaut syndrome; ZNS, zonisamide; PER, perampanel; r/o, rule out; FIC, focal impaired consciousness seizure; LEV, levetiracetam; RUF, rufinamide; LMT, lamotrigine; TPM, topiramate; ETX, ethosuximide; IESS, infantile epileptic spasm syndrome; GSSW, generalized slow spike-and-wave; GPFA, generalized paroxysmal fast activities; CBD; cannabidiol; Fc, focal; OXC, oxcarbazepine.

in *CHD2*-related DEE, underscoring the need for further investigation in larger cohorts.

Psychiatric symptoms were observed in nine patients in our study, with ADHD being the most frequent (7/19, 36.8%), followed by ASD (1/19, 5.3%). While *CHD2* has historically been implicated in ASD and was initially highlighted in genetic analyses of individuals with ASD [21], our findings demonstrate a higher prevalence of ADHD than ASD among patients with *CHD2*-related disorders. Previous studies have also reported ADHD or attentional and behavioral dysregulation in individuals with *CHD2* variants, suggesting that the neuropsychiatric impact of this gene extends beyond its original association with autism [9,17,22]. *CHD2* is an adenosine triphosphate-dependent chromatin remodeler critical for cortical circuit organization and gamma-aminobutyric acid (GABA)-ergic interneuron development, and it regulates activity-dependent transcriptional programs and neuronal differentiation [22,23]. Furthermore, epigenetic dysregulation has increasingly been implicated in cortical network dysfunction and ADHD-like behavioral phenotypes [24]. Consequently, it is biologically plausible that *CHD2* haploinsufficiency contributes to attentional deficits and ADHD-like behavioral manifestations. These findings suggest that the phenotypic spectrum of *CHD2*-related disorders is broader than previously recognized and includes attentional and behavioral domains, indicating the need to clarify the contribution of this gene to ADHD.

In terms of genetic variation, truncating variants accounted for the majority (84.2%), and mutations were distributed across a wide range of gene regions, without clustering in a specific domain or showing associations with particular phenotypes. This pattern supports *CHD2* haploinsufficiency as the principal pathogenic mechanism and suggests that no clear mutational hotspot has been identified, consistent with previous reports [8]. Given this lack of regional clustering and the predominance of loss-of-function variants, genotype–phenotype correlations in *CHD2*-related disorders are expected to be limited. Nevertheless, our cohort revealed three notable observations that further illustrate the extent and nature of phenotypic variability associated with *CHD2* haploinsufficiency.

First, two unrelated male patients carrying the same truncating *CHD2* variant exhibited markedly different clinical trajectories despite sharing an identical predicted loss-of-function mechanism. Both patients ultimately developed epilepsy with GDD and intellectual disability, but differed substantially in age at seizure onset, seizure semiology, developmental profiles, and EEG/MRI findings. One patient (patient 1) had later-onset seizures, pre-existing motor and speech delay with ADHD, focal interictal epileptiform discharges on EEG, and structural MRI abnormalities, including asymmetric lateral ventricles (left > right) and a left middle cranial

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fossa arachnoid cyst. In contrast, the other (patient 11) had earlier-onset seizures, isolated language delay before epilepsy onset, subsequent developmental regression, focal slowing on EEG, and normal MRI findings. The loss of *CHD2* function, although a well-established molecular mechanism, does not fully explain the considerable phenotypic divergence of these individuals. The variability in clinical presentation is therefore likely influenced by additional modifying factors, including interindividual genetic background, differences in epigenetic regulation, and environmental influences, each of which may contribute to differences in seizure susceptibility and neurodevelopmental outcomes [4,10,23-25].

A second example of variable expressivity was observed in a patient (patient 7) with an inherited exon 5 deletion. Although the daughter developed multiple generalized seizure types, GDD, and multifocal epileptiform discharges, her father—who carried the same variant—had only a few febrile seizures in childhood and no persistent neurologic or developmental abnormalities. This marked intrafamilial divergence highlights incomplete penetrance and variable expressivity in *CHD2*-related disorders. Exon-level deletions involving coding regions of *CHD2* are predicted to result in loss-of-function and are therefore consistent with a pathogenic interpretation, given the established haploinsufficiency mechanism of *CHD2*. Supporting this mechanism, Chenier et al. [9] reported *de novo* deletions affecting *CHD2* exonic sequences, with deletions confirmed and parental follow-up performed using orthogonal methods such as multiplex ligation-dependent probe amplification, array comparative genomic hybridization, and/or fluorescence *in situ* hybridization. In our study, interpretation of the inherited exon 5 deletion is limited by the retrospective nature of paternal phenotyping, as well as by the inability to definitively confirm or exclude somatic or germline mosaicism using routine clinical assays; accordingly, segregation-based inference regarding penetrance is constrained. Independent of these interpretive limitations, additional confirmatory analyses were performed to exclude the possibility that the identified *CHD2* exon 5 deletion represented a technical artifact. Validation using long-range polymerase chain reaction verified the presence of the exon-level deletion, and concordant exon 5 copy number loss was consistently observed in both the proband and the father (Supplementary Figs. 1 and 2), supporting the authenticity of this structural variant. In parallel, a comprehensive review of all variants detected by the targeted epilepsy gene panel revealed no additional pathogenic or likely pathogenic variants that could plausibly account for the proband's clinical phenotype. Several variants of uncertain significance, including those in alanyl-tRNA synthetase (*AARS*), seizure threshold 2 (*SZT2*), and carnitine palmitoyltransferase 1B (*CPT1B*), were identified; however, these were considered unlikely contributors based on inheritance pattern, known disease mechanisms, population frequency, and lack of clinical correlation. Taken together, these additional evaluations support the *CHD2* exon 5 deletion as the most relevant genetic finding in this patient. The marked phenotypic discordance within this family may be compatible with a two-hit model, in which *CHD2* haploinsufficiency establishes a baseline vulnerability, while additional perinatal or developmental factors—such as the patient's preterm birth and prior germinal matrix hemorrhage—act as secondary hits that may amplify epileptogenesis and neurodevelopmental impairment [17,26,27].

Further evidence of phenotypic variability was observed in a patient (patient 17) with a large deletion involving exons 17–29 who exhibited only mild clinical features, including well-controlled seizures, moderate intellectual disability, ADHD, normal MRI findings, and no interictal epileptiform discharges on EEG. The relatively mild phenotype despite extensive genomic loss suggests that deletion size alone does not determine clinical severity and that the pathogenic impact of *CHD2* variants may differ across functional domains. Together with the absence of a mutational hotspot in our study, these findings indicate that domain-specific contributions to *CHD2* function remain incompletely understood, highlighting the need for future studies examining regional functional effects and modifier interactions that shape phenotypic outcomes.

Collectively, our findings reinforce that *CHD2*-related disorders arise predominantly from haploinsufficiency, but that clinical expression is strongly modulated by additional factors, resulting in substantial variability in severity, seizure type, developmental impact, and neurobehavioral outcomes. Future studies delineating the structural and regulatory functions of each *CHD2* domain, as well as identifying genetic or environmental modifiers, will be essential to understanding the mechanisms underlying this heterogeneity.

This study has several limitations. First, as a single-center retrospective study with a relatively small sample size, the generalizability of our findings is limited. Second, the cohort was ascertained through a targeted epilepsy/DEE gene panel workflow at a tertiary pediatric neurology center, which may have introduced selection bias toward individuals with pediatric-onset and epilepsy-predominant phenotypes. Therefore, milder *CHD2*-related presentations (e.g., minimal epilepsy, preserved cognition) or adult-onset phenotypes are likely underrepresented, and our findings should be interpreted as reflecting the clinical spectrum of panel-tested pediatric patients rather than the full spectrum of *CHD2*-related disorders.

Epilepsy was the consistent and dominant clinical manifestation in our cohort of patients with *CHD2*-related disorders, accompanied by diverse developmental, cognitive, and neurobehavioral features. The discordance between genotype and phenotype ob-

served across identical variants, inherited variants with divergent presentations, and large deletions with a mild phenotype reflects the substantial heterogeneity characteristic of *CHD2*-related disorders.

Accordingly, although *CHD2*-related disorders appear to be primarily driven by haploinsufficiency, clinical manifestations—including seizure type and severity, developmental trajectories, and neurobehavioral profiles—show considerable variability and cannot be explained by genotype alone. Comprehensive studies examining genotype–phenotype correlations, along with investigations into developmental, genetic, and environmental modifiers, will be essential to elucidate the mechanisms underlying this heterogeneity and to increase diagnostic precision and clinical prognostic assessment.

Supplementary material

Supplementary materials related to this article can be found online at https://doi.org/10.26815/acn.2025.01249

Conflicts of interest

Se Hee Kim and Ara Ko are managing editors, Joon Soo Lee is an editorial board member, and Hoon-Chul Kang is an associate editor of the journal, but they were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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References

1. Li B, Carey M, Workman JL. The role of chromatin during transcription. Cell 2007;128:707-19.
2. Murawska M, Brehm A. CHD chromatin remodelers and the transcription cycle. Transcription 2011;2:244-53.
3. Micucci JA, Sperry ED, Martin DM. Chromodomain helicase DNA-binding proteins in stem cells and human developmental diseases. Stem Cells Dev 2015;24:917-26.
4. Wilson MM, Henshall DC, Byrne SM, Brennan GP. CHD2-related CNS pathologies. Int J Mol Sci 2021;22:588.
5. Li MM, Nimmakayalu MA, Mercer D, Andersson HC, Emanuel BS. Characterization of a cryptic 3.3 Mb deletion in a patient with a "balanced t(15;22) translocation" using high density oligo array CGH and gene expression arrays. Am J Med Genet A 2008;146A:368-75.
6. Veredice C, Bianco F, Contaldo I, Orteschi D, Stefanini MC, Battaglia D, et al. Early onset myoclonic epilepsy and 15q26 microdeletion: observation of the first case. Epilepsia 2009;50:1810-5.
7. Capelli LP, Krepischi AC, Gurgel-Giannetti J, Mendes MF, Rodrigues T, Varela MC, et al. Deletion of the RMGA and CHD2 genes in a child with epilepsy and mental deficiency. Eur J Med Genet 2012;55:132-4.
8. Lamar KJ, Carvill GL. Chromatin remodeling proteins in epilepsy: lessons from CHD2-Associated epilepsy. Front Mol Neurosci 2018;11:208.
9. Chenier S, Yoon G, Argiropoulos B, Lauzon J, Laframboise R, Ahn JW, et al. CHD2 haploinsufficiency is associated with developmental delay, intellectual disability, epilepsy and neurobehavioural problems. J Neurodev Disord 2014;6:9.
10. Carvill GL, Mefford HC. CHD2-related neurodevelopmental disorders. In: Adam MP, Bick S, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews. Seattle: University of Washington, Seattle; 2021 [cited 2026 Feb 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK333201
11. Carvill GL, Heavin SB, Yendle SC, McMahon JM, O'Roak BJ, Cook J, et al. Targeted resequencing in epileptic encephalopathies identifies de novo mutations in CHD2 and SYNGAP1. Nat Genet 2013;45:825-30.
12. Suls A, Jaehn JA, Kecskes A, Weber Y, Weckhuysen S, Craiu DC, et al. De novo loss-of-function mutations in CHD2 cause a fever-sensitive myoclonic epileptic encephalopathy sharing features with Dravet syndrome. Am J Hum Genet 2013;93:967-75.
13. Ko A, Youn SE, Kim SH, Lee JS, Kim S, Choi JR, et al. Targeted gene panel and genotype-phenotype correlation in children with developmental and epileptic encephalopathy. Epilepsy Res 2018;141:48-55.
14. Lund C, Brodtkorb E, Oye AM, Rosby O, Selmer KK. CHD2 mutations in Lennox-Gastaut syndrome. Epilepsy Behav 2014;33:18-21.

15. Thomas RH, Zhang LM, Carvill GL, Archer JS, Heavin SB, Mandelstam SA, et al. CHD2 myoclonic encephalopathy is frequently associated with self-induced seizures. Neurology 2015;84:951-8.
16. Chen J, Zhang J, Liu A, Zhang L, Li H, Zeng Q, et al. CHD2-related epilepsy: novel mutations and new phenotypes. Dev Med Child Neurol 2020;62:647-53.
17. De Maria B, Balestrini S, Mei D, Melani F, Pellacani S, Pisano T, et al. Expanding the genetic and phenotypic spectrum of CHD2-related disease: from early neurodevelopmental disorders to adult-onset epilepsy. Am J Med Genet A 2022;188:522-33.
18. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-24.
19. Zhu L, Peng F, Deng Z, Feng Z, Ma X. A novel variant of the CHD2 gene associated with developmental delay and myoclonic epilepsy. Front Genet 2022;13:761178.
20. Clara-Hwang A, Stefani S, Lau T, Scala M, Aynekin B, Bernardo P, et al. Expanding the mutational landscape and clinical phenotype of CHD2-related encephalopathy. Neurol Genet 2024;10:e200168.
21. Pinto D, Pagnamenta AT, Klei L, Anney R, Merico D, Regan R, et al. Functional impact of global rare copy number variation in autism spectrum disorders. Nature 2010;466:368-72.
22. Feng W, Fang F, Wang X, Chen C, Lu J, Deng J. Clinical analysis of CHD2 gene mutations in pediatric patients with epilepsy. Pediatr Investig 2022;6:93-9.
23. Bollati V, Baccarelli A. Environmental epigenetics. Heredity (Edinb) 2010;105:105-12.
24. Sarkisova K, van Luijtelaar G. The impact of early-life environment on absence epilepsy and neuropsychiatric comorbidities. IBRO Neurosci Rep 2022;13:436-68.
25. Lewis EM, Chapman G, Kaushik K, Determan J, Antony I, Meganathan K, et al. Regulation of human cortical interneuron development by the chromatin remodeling protein CHD2. Sci Rep 2022;12:15636.
26. Cristancho AG, Marsh ED. Epigenetics modifiers: potential hub for understanding and treating neurodevelopmental disorders from hypoxic injury. J Neurodev Disord 2020;12:37.
27. Parenti I, Rabaneda LG, Schoen H, Novarino G. Neurodevelopmental disorders: from genetics to functional pathways. Trends Neurosci 2020;43:608-21.