



# Clinical analysis of *CHD2* gene mutations in pediatric patients with epilepsy

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## ABSTRACT

**Importance:** *CHD2* is a member of the chromodomain helicase DNA-binding (CHD) family of proteins, which have important roles in the regulation of gene expression. Dysregulation of this protein may lead to various disorders.

**Objective:** To delineate the genotypes and phenotypes of *CHD2*-related epilepsy.

**Methods:** We analyzed the medical history, magnetic resonance imaging findings, and video-electroencephalogram recordings of 17 patients with *CHD2* mutations in the Neurology Department of Beijing Children's Hospital from June 2016 to June 2021.

**Results:** Age at seizure onset ranged from 6 months to 10 years; the median age at onset was 4 years. Generalized tonic-clonic, myoclonic, eyelid myoclonic, atonic, atypical absence, myoclonic-atonic, and spasm seizures were observed. Ten of the 17 patients had multiple types of seizures. One patient exhibited photosensitivity epilepsy and one patient exhibited grid image-induced visual reflex epilepsy. Developmental disability was present in 14 patients, while autism features were present in five patients. Sixteen patients had *de novo* mutations of *CHD2*; one patient had an inherited variant. Eleven mutations were novel. One patient had two mutations; that patient exhibited development delay and refractory epilepsy. Seizures were controlled in eight patients, improved in seven patients, and resistant to treatment in two patients.

**Interpretation:** Phenotype severity in patients with *CHD2* variants ranged from drug-responsive seizures to severe epileptic encephalopathy. Most patients exhibited developmental disorders.

## KEYWORDS

*CHD2*, Epilepsy, Developmental disability, Phenotype, Seizure

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## INTRODUCTION

The chromodomain helicase DNA-binding (CHD) family of proteins comprises ATP-dependent chromatin remodelers that contribute to the reorganization of chromatin structure and deposition of histone variants necessary for regulating gene expression. CHD proteins are presumed to modify gene transcription by affecting chromatin structure through helicase function.<sup>1,2</sup>

Heterozygous pathogenic variants in *CHD2* (MIM: 602119) were identified in a group of neurodevelopmental disorders characterized by early-onset refractory epileptic encephalopathy, developmental delay, intellectual disability, and an autism spectrum disorder.<sup>1,3</sup> The classic atonic-myoclonic and absence types of seizures have been observed in many patients.<sup>4</sup> Some individuals have exquisite photosensitivity. Photosensitivity is a heritable abnormal cortical response to flickering light, which often manifests as electroencephalogram (EEG) changes that constitute a photoparoxysmal response.<sup>5</sup> Notably, there have been reports of several individuals with generalized epilepsy who carried a multigenic chromosomal deletion in the 15q26 region, which included *CHD2*.<sup>6,7</sup>

Recently, variants in the *CHD2* gene were identified as a cause of developmental epileptic encephalopathy. Several prominent features of the *CHD2*-developmental epileptic encephalopathy phenotype overlap with other developmental epileptic encephalopathies including myoclonic-atonic epilepsy, Lennox–Gastaut syndrome, West syndrome, and Jeavons syndrome.<sup>8</sup> A deletion that affected *CHD2* was also identified in genomic microarray analysis of patients with autism spectrum disorders (ASD).<sup>9</sup> The present study was performed to elucidate the phenotypic presentations and molecular genetic characteristics of *CHD2*-related epilepsy in a Chinese cohort.

## METHODS

### Ethical approval

This study was reviewed and approved by the Ethics Committee of Beijing Children's Hospital (No. 2020-Z-077). Written informed consent to participate in this study was provided by the participant's legal guardian.

### Participants

Pediatric epilepsy patients with *CHD2* mutations were recruited from June 2016 to June 2021. Clinical data were collected regarding seizure type, family history, examinations (e.g., EEG and brain magnetic resonance imaging), treatment, and follow-up findings. Clinical seizure types were defined in accordance with the ILAE 2017 operational classification of seizure types.<sup>10</sup>

### Genetic analysis

The detection of *CHD2* (RefSeq NM\_001271) mutation was performed using a next-generation sequencing-based gene panel for evaluation of epilepsy or whole-exome sequencing. The potential pathogenic variations were validated by Sanger sequencing. The mutation was examined for segregation in other family members. The pathogenicity of the variation was evaluated according to the guidelines of the American College of medical genetics and genomics.<sup>11</sup> Variants affected splicing were predicted using SIFT, PolyPhen, REVEL, and Mutation Taster software programs. All the mutations finished the conserved analysis by the GERP++ software program.

## RESULTS

### Clinical features

In total, 17 children with *CHD2*-related epilepsy were collected, including 7 boys and 10 girls. The age at epilepsy onset ranged from 6 months to 10 years and 5 months; the median age at onset was 4 years (Table 1). All patients' families denied a history of hypoxia asphyxia at birth. Four patients had a history of febrile convulsion (patients 1, 8, 12, and 14); one patient had a family history of febrile convulsion (patient 2). One patient had a family history of epilepsy (patient 17); the patient's sister had been diagnosed with epilepsy, and her convulsive seizures were currently controlled. The father of patient 12 had a history of dystonia.

Seizure types varied among the 17 patients: 14 (82.3%) patients had generalized tonic-clonic seizures (GTCS), eight (47.1%) patients had myoclonic seizures, three (17.6%) patients had eyelid myoclonic seizures, two (11.8%) patients had tonic seizures, two (11.8%) patients had atypical absence seizures, one (5.9%) patient had atonic seizures, one (5.9%) patient had spastic seizures, and one (5.9%) patient had myoclonic dystonic seizures. Among the 17 patients, 10 (58.8%) had multiple types of seizures. One patient exhibited photosensitivity and one patient exhibited grid image-induced visual reflex epilepsy (patients 14 and 12). Epilepsy syndromes were present in patient 3 (West syndrome) and patient 9 (Lennox–Gastaut syndrome). Fourteen (82.4%) patients had a developmental delay before seizure onset. Five patients had autistic features including lack of eye contact, stereotypical behavior, and speech delay, in addition to intellectual disability.

### Video EEG and magnetic resonance imaging

Video EEG was performed on 10 patients. Abnormal discharges were observed in 10 (100%) patients during the interictal period. Generalized spikes, multiple spikes, and spikes plus slow waves were detected in 9 (90.0%) patients;

**TABLE 1** The clinical features and genotypes of 17 patients with *CHD2*-related epilepsy

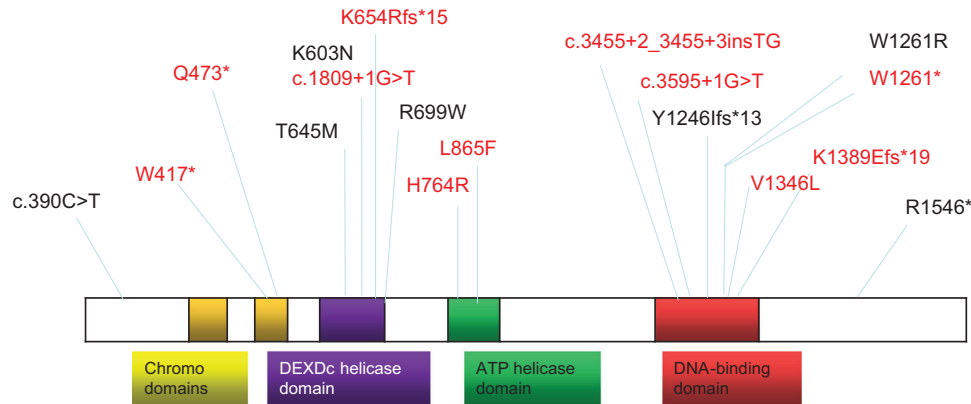
Patient number/ Sex	Age at seizure onset/ Age at last follow-up (year)	Seizure types/ Onset age (year)	Epileptic syndrome	AEDs	Whether seizure has been controlled	Developmental delay and autistic features	Mutations and protein effect	Sequencing methods	Transmission and ACMG criteria	Reported/ Novel	Function prediction and conserved analysis
1/F	1.5/2.7	MS/1.5	–	VPA	Yes	–/–	c.390C>T (p.S130S), synonymous, affect splicing	Trio-WES	<i>De novo</i> /PS2 + PM2 (LP)	Reported <sup>12</sup>	Uncertain/ Nonconserved
2/F	4.5/8.3	GTCS/4.5; MS/4.5	–	VPA	Yes	+/–	c.3455+2_3455+3insTG, splicing	Trio-WES	<i>De novo</i> /PS2 + PM2 + PP3 (LP)	Novel	Uncertain/ Nonconserved
3/M	1.5/5.5	GTCS/2; ES/1.5	West syndrome	VPA, NZP, TPM	ES cured; GTCS reduced more than 50%	+/–	c.3595+1G>T, splicing	Trio-WES	<i>De novo</i> /PVS1 + PM2 + PS2 (P)	Novel	Damaged/ Conserved
4/M	1.5/3	GTCS/1.5	–	VPA, LTG	Yes	+/–	c.1934C>T (p.T645M), missense	Panel	<i>De novo</i> /PS1 + PS2 + PM2 + PP3 (P)	Reported <sup>13</sup>	Damaged/ Conserved
5/M	7/10	GTCS/7; MS/7	–	LEV	Yes	+/–	c.3782G>A (p.W1261*), nonsense	WES	<i>De novo</i> /PVS1 + PS2 + PM2 (P)	Reported <sup>14</sup>	Damaged/ Conserved
6/M	3/8	GTCS/4; MS/3	–	VPA, PB, OXC, LEV	All reduced more than 50%	+/+	c.1960_1961del (p.K654Rfs*15), frameshift	WES	<i>De novo</i> /PVS1 + PS2 + PM2 (P)	Novel	Uncertain/ Nonconserved
7/F	10/12.9	GTCS/10	–	VPA	Yes	+/–	c.1250G>A (p.W417*), nonsense	WES	<i>De novo</i> /PVS1 + PS2 + PM2 (P)	Novel	Damaged/ Conserved
8/F	2.5/6.9	GTCS/2; eMS/5	–	LEV	Yes	–/–	c.1417C>T (p.Q473*), nonsense	Panel	<i>De novo</i> /PVS1 + PS2 + PM2 (P)	Novel	Damaged/ Conserved
9/F	3/5	TS/3; GTCS/3; eMS/3; MS/3; aAS/3; MAS/3	Lennox–Gastaut syndrome	VPA, TPM, LTG, CZP, VNS	All reduced more than 50%	+/+	c.3781T>C (p.W1261R), missense	Panel	<i>De novo</i> /PS2 + PM2 + PP3 (LP)	Novel	Damaged/ Conserved

(Continues)

TABLE 1 (Continued)

Patient number/ Sex	Age at seizure onset/Age at last follow-up (year)	Seizure types/Onset age (year)	Epileptic syndrome	AEDs	Whether seizure has been controlled	Developmental delay and autistic features	Mutations and protein effect	Sequencing methods	Transmission and ACMG criteria	Reported/ Novel	Function prediction and conserved analysis
10/F	2.3/8	MS/2.3; TS/4.5	–	VPA, TPM, LTG, CZP	All reduced more than 50%	+/-	c.2291A>G (p.H764R), missense	WES	<i>De novo</i> /PS2 + PM2 + PP2 + PP3 (LP)	Novel	Damaged/ Conserved
11/F	0.5/6	MS/0.5	–	LEV, NZZP, VPA	Reduced more than 50%	+/-	c.3734dupA (p.Y1246Ifs*13), frameshift	Panel	<i>De novo</i> /PVS1 + PS2 + PM2 (P)	Reported <sup>3</sup>	Uncertain/ Nonconserved
12/M	2.3/10.5	GTCS/2.3; eMS/7	–	TPM, VPA, LTG, NZZP, KD, VNS	No	+/+	c.1809G>T (p.K603N), missense; c.1809+1G>T, splicing	Trio-WES	<i>De novo</i> /PS2 + PM2 (LP); PVS1 + PS2 + PM2 (P);	Reported <sup>15</sup> Novel	Damaged/ Conserved
13/F	5/10	GTCS/5	–	LEV	Yes	-/-	c.4164dupG (p.K1389Efs*19), frameshift	Panel	<i>De novo</i> /PVS1 + PS2 + PM2 (P)	Novel	Uncertain/ Nonconserved
14/F	1.5/7.5	GTCS/1.5	–	VPA	Yes	+/-	c.4636C>T (p.R1546*), nonsense	Panel	<i>De novo</i> /PVS1 + PS2 + PM2 (P)	Reported <sup>3</sup>	Damaged/ Conserved
15/M	4/7.8	GTCS/4	–	OXC, LEV, TPM, CZP, PER	Reduced more than 50%	+/+	c.2095C>T (p.R699W), missense	Trio-WES	<i>De novo</i> /PS2 + PM1 + PM2 + PP3 (LP)	Reported <sup>16,17</sup>	Damaged/ Conserved
16/F	5.8/7.6	GTCS/5.8; MS/6	–	VPA, OXC, LEV, CLB, NZZP, KD	No	+/+	c.2593C>T (p.L865F), missense	Panel	<i>De novo</i> /PS2 + PM1 + PM2 + PP3 (LP)	Novel	Damaged/ Conserved
17/M	3/5.6	GTCS/3; aAS/4; AtS/4	–	VPA, CZP, LEV, TPM	All reduced more than 50%	+/-	c.4036G>C (p.V1346L), missense	Panel	Unaffected father/PM2 (VUS)	Novel <sup>†</sup>	Damaged/ Conserved

† A different nucleotide change (c.4036G>T), resulting in the same amino acid substitution (p.V1346L) has been reported.<sup>18</sup> Abbreviations: aAS, atypical absence seizure; ACMG, the American College of Medical Genetics and Genomics; AEDs, antiepileptic drugs; AtS, atonic seizure; M, male; F, female; VUS, variants of unknown significance; WES, whole-exome sequencing; GTCS, generalized tonic-clonic seizure; TS, tonic seizure; MS, myoclonic seizure; MAS, myoclonic-atonic seizure; ES, epileptic spasms; eMS, eyelid myoclonus; CLB, clobazam; CZP, clonazepam; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; NZZP, nitrazepam; TPM, topiramate; VPA, sodium valproate; KD, ketogenic diet; VNS, vagus nerve stimulation; P, pathogenic; LP, likely pathogenic.



**FIGURE 1** Schematic illustration of *CHD2* variants identified in this study. Red entries are novel variants found in this study.

a slow background rhythm was detected in one patient, and electrical status epilepticus in sleep was detected in one patient. Clinical seizures were recorded in eight patients. Six types of convulsions (myoclonic, eyelid myoclonic, atypical absence, and myoclonic dystonia in awake periods; tonic and tonic-clonic seizures in sleep periods) were detected in patient 9. Two patients (patients 1 and 11) exhibited myoclonic seizures; two patients (patients 8 and 12) exhibited eyelid myoclonic seizures. Patient 12 exhibited grid image-induced eyelid myoclonic seizures (170 times). Patient 10 exhibited myoclonic seizures and tonic seizures. Atypical absence seizures were detected in patient 17. GTCS was detected in patient 16. Ten patients received intermittent photostimulation during EEG monitoring. Patient 14 had a photoparoxysmal response induced by intermittent photostimulation.

Brain magnetic resonance imaging was performed in 17 patients; no abnormalities were found in 14 patients. The T2-weighted-fluid-attenuated inversion recovery signal in the bilateral hippocampus was slightly hyperintense in patient 9. Patient 17 exhibited subtle structural lesions such as deepened bilateral frontal-parietal sulcus and slightly widened bilateral ventricles; patient 11 had an arachnoid cyst in the occipital cistern.

### Treatment and follow-up

The follow-up interval ranged from 13 months to 7 years. In this study, valproic acid (VPA), levetiracetam (LEV), nitrazepam, and clonazepam were the anti-seizure medications (ASMs) frequently used for the treatment of *CHD2*-related seizures. Seizures in eight patients were controlled by VPA (four patients), LEV (three patients), and VPA combined with lamotrigine (one patient). Seizures were improved (seizure frequency decreased by more than 50%) in seven patients. Two patients (patients 12 and 16) were resistant to treatment. Thirteen patients were treated with VPA (nine patients received VPA combined with

other ASMs); this treatment was effective in five (38.5%) patients. Eight patients were treated with LEV (five patients received LEV combined with other ASMs); this treatment was effective in three (37.5%) patients. Four patients were treated with nitrazepam; seizures decreased by more than 50% in two patients and were resistant to treatment in two patients. Three patients were treated with clonazepam and all showed improvement. Seven patients were treated with only one ASM; 10 patients were treated with two or more ASMs. Patient 9 received ASMs and vagus nerve stimulation; this approach led to seizure reduction by more than 50%. Patient 12 was treated with four ASMs, a ketogenic diet, and vagus nerve stimulation; however, this approach did not lead to seizure control (Table 1).

### Genetic analysis

Eighteen *CHD2* mutations were detected from 17 patients (Table 1), including four nonsense mutations, seven missense mutations, three frameshift mutations, and four splicing-site mutations. Sixteen patients had *de novo* mutations, while one patient (patient 17) had an inherited pathogenic variant (c.4036G>C, p.V1346L) from his unaffected father. Patient 17 was a 5-year-old boy with a developmental disorder and epileptic encephalopathy; his older sister carrying the same variants was also diagnosed with ASM-responsive epilepsy and GTCS seizures. His sister had a normal intelligence quotient and her seizure was controlled by LEV. Patient 12 had two *de novo* mutations, including one pathogenic variant and one likely pathogenic variant; the corresponding clinical phenotype was serious and involved refractory epilepsy. Of the 18 mutations, 11 were novel (Figure 1).

## DISCUSSION

The *CHD2* gene encodes a member of the CHD family of proteins, which are characterized by a chromatin-remodeling domain (i.e., the chromodomain) and an

SNF2-related helicase/ATPase domain.<sup>1,19</sup> The CHD2 protein has important roles in chromatin structure modulation, DNA recombination and repair, cell cycle regulation, and cell differentiation. Dysregulation of this protein may have adverse effects on human development.<sup>4,20</sup>

A recent study suggested that CHD2 might contribute to a broad spectrum of neurodevelopmental disorders, such as epilepsy, developmental delay, congenital anomalies, and/or autism spectrum disorder.<sup>21</sup> CHD2 knockdown zebrafish exhibited clinical and electrographic seizures that paralleled the human phenotype.<sup>22</sup> Veredice et al.<sup>6</sup> reported CHD2 mutation-related epilepsy in a 30-month-old girl with refractory myoclonic epilepsy, developmental retardation, and photosensitivity. In addition to the small structural variations associated with CHD2-related epilepsy, microdeletions or duplications have been found in the 15q26.1–q26.2 region, which contains multiple genes (e.g., CHD2 and RGMA), in patients with epilepsy. The CHD2 gene is the main pathogenic gene associated with epilepsy in these patients.<sup>23–25</sup>

CHD2-related epilepsy includes many types of seizures, such as absence, myoclonic, myoclonic dystonia, and GTCS. In the present study, various types of seizures were observed. The most common types of seizures were GTCS and myoclonic seizures. Ten patients had two or more types of seizures. All patients exhibited generalized seizures, while none exhibited focal seizures; these findings were consistent with the results of other studies.<sup>1,22</sup> Phenotype severity in patients with CHD2 variants ranged from drug-responsive seizures to severe epileptic encephalopathy. The CHD2 gene is also reportedly associated with photosensitive epilepsy.<sup>4</sup> Studies from China reported three patients with light sensitivity (3/18, 16.7%).<sup>3</sup> In our study, only one patient exhibited light sensitivity characteristics. Martins da Silva et al.<sup>26</sup> reported that the incidence of photosensitive epilepsy in patients with epilepsy was 5%. However light sensitivity is indeed a characteristic of CHD2-related epilepsy.<sup>20</sup> Study from Suls et al.<sup>22</sup> showed that three individuals with CHD2 mutations had fever-sensitive generalized seizures. In our study, four patients experienced fever-sensitive generalized seizures, indicating that CHD2 may also be associated with fever-sensitive epilepsy. The CHD2 gene also was reported as ASD and developmental delay candidate gene.<sup>20</sup> De Maria et al.<sup>27</sup> reported CHD2-related phenotypes to encompass a wide spectrum of conditions with developmental delay, including prominent language impairment, attention deficit hyperactivity disorder, and ASD. In our study, 14 patients (82.4%) exhibited developmental disability and five patients exhibited autistic features. These findings indicated that CHD2 mutations may lead to epilepsy, developmental delay, intellectual disability, and behavioral problems.

CHD2 mutations are mainly *de novo*.<sup>3,21</sup> Only a few familial cases have been reported.<sup>28</sup> In this study, one patient and his sister had an inherited pathogenic CHD2 variant from their unaffected father. The clinical characteristics of the patient with inherited mutations were similar to the characteristics of the patient with *de novo* mutations. We also identified a patient with two CHD2 mutations; that patient had drug resistance epilepsy and the seizures were not controlled despite multiple treatment methods.

In conclusion, our patients with CHD2 mutations exhibited epilepsy, developmental delay, and behavioral problems; phenotypic variability was present. Most CHD2 mutations were *de novo*. VPA and LEV were useful as a treatment for epilepsy caused by CHD2 gene mutations.

## CONFLICT OF INTEREST

None.

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