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# A De Novo Frameshift Variant in *SMC1A* Causes Non-Classic Cornelia de Lange Syndrome With Epilepsy: A Case Report and Literature Review

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## ABSTRACT

**Background:** Cornelia de Lange syndrome (CdLS) is a multisystem genetic disorder. Although individuals with variants in the *SMC1A* gene are less commonly seen in CdLS, they exhibit a high incidence of epilepsy and atypical phenotypic variability.

**Methods:** The clinical data of a patient with non-classic CdLS and epilepsy caused by an *SMC1A* variant were summarized. A literature review was conducted to analyze the genotype–phenotype correlations and epilepsy characteristics in related cases.

**Results:** A 5-year-6-month-old female patient presented with facial features, double outlet right ventricle (DORV), and recurrent epilepsy. Whole exome sequencing (WES) identified a de novo heterozygous frameshift mutation, c.2890_2893del (p.Ser964Valfs*26), in the *SMC1A* gene. A review of the literature identified several characteristics of non-classic CdLS with epilepsy caused by *SMC1A* variants: the majority of cases were non-classic (81.5%), predominantly female (68.2%), with a median onset age of 11.5 months. Common features included severe/profound developmental delay (52.6%), hypotonia (18.2%), cardiovascular anomalies (36.4%), and intrauterine growth retardation (IUGR) (22.7%). Among the non-classic cases, seizure clusters occurred in 22.7%, status epilepticus in 18.2%, and drug-resistant epilepsy in 33.3%. Genotypes in non-classic cases included missense mutations (40.9%), frameshift mutations (31.8%), splice site variants (9.1%), nonsense mutations (9.1%), deletions (4.5%), and truncations (4.5%).

**Conclusion:** Our study expanded the phenotypic data and mutational spectrum of non-classic CdLS with epilepsy caused by *SMC1A* variants. Compared to individuals with the classic form of CdLS, the non-classic cases appeared more frequently in females and were associated with a higher prevalence of severe/profound developmental delay and cardiovascular anomalies. In contrast, IUGR was significantly less common in non-classic individuals. Regarding epilepsy characteristics, some individuals including seizure clusters, status epilepticus, drug resistance, and hypotonia, no significant differences were observed between classic and non-classic cases. The predominant genotypes in non-classic cases were missense and frameshift mutations.

## 1 | Introduction

Cornelia de Lange syndrome (CdLS, OMIM 122470, 300590, 300882, 610759, and 614701) is a multisystem disorder characterized by distinctive facial features, limb anomalies, intellectual disability, and multiple organ malformations. Heterozygous mutations in seven genes (*NIPBL*, *SMC1A*, *SMC3*, *RAD21*, *BRD4*, *HDAC8*, and *ANKRD11*) have been identified as contributors to CdLS, with mutations in the *SMC1A* gene accounting for approximately 5% of cases (Kline et al. 2018). Although epilepsy is not considered a diagnostic criterion for CdLS, it is observed in approximately 45% of cases involving *SMC1A* variants (Kline et al. 2018; Barañano et al. 2022). Since 2006, various research groups have explored the genotype–phenotype correlation (Musio et al. 2006; Symonds et al. 2017; Huisman et al. 2017; Elwan et al. 2022; Barañano et al. 2022), yet the early identification and management of non-classic cases remain a significant challenge.

## 2 | Materials and Methods

### 2.1 | Ethical Compliance

This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. Written informed consent was obtained from the patient's parents.

### 2.2 | WES and Bioinformatics Analysis

Informed consent for genetic analysis was obtained from the proband's parents, and peripheral blood samples were collected from the proband and her parents. Clinical exome sequencing was performed by Cipher Gene Technology Co., Beijing, China. Genomic DNA was extracted from the whole blood samples, and library preparation was conducted using the IDT XGen Exome Research Panel. Sequencing was carried out on the NovaSeq 6000 platform, generating raw data $>10$G with Q30 $\geq 80\%$. The clean paired-end reads were then aligned to the human reference genome (GRCh38/hg38) using Burrows–Wheeler Aligner (BWA), with subsequent processing using Samtools and Picard tools. Variants were annotated using Annovar, and pathogenicity was further evaluated through databases such as 1000 Genomes, dbSNP, OMIM, HGMD, and ClinVar. Protein structure and functional domains were predicted and analyzed using software packages including SIFT, PolyPhen-2, LRT, MutationTaster, and FATHMM. Variant pathogenicity was assessed in accordance with ACMG guidelines. Candidate gene variants were confirmed through Sanger sequencing. Copy number variations (CNVs) were detected using CNVkit and CNVnator tools, and annotated through an in-house annotation pipeline. The identified CNVs were analyzed and interpreted using databases such as OMIM, DECIPHER, DGV, and Orphanet.

### 2.3 | Clinical Diagnostic Criteria and Literature Review

The diagnostic criteria for CdLS were published by the Medical Director of the CdLS Foundation (Kline et al. 2018), categorizing the CdLS phenotype into cardinal and suggestive features. Cardinal features, each assigned a score of 2 if present, include synophrys/thick eyebrows, short nose/concave nasal ridge/upturned nasal tip, long/smooth philtrum, thin upper lip vermilion/downturned corners of mouth, hand oligodactyly/adactyly, and ongenital diaphragmatic hernia. Suggestive features are assigned a score of 1 each if present and include global developmental delay/intellectual disability, prenatal growth retardation $<2$SD, postnatal growth retardation $<2$SD, prenatally/postnatally microcephaly, small hands/ft, short fifth finger, and hirsutism. Individuals with a score of $\geq 11$ and at least 3 cardinal features are classified as having classic CdLS. Those with a score of 9–10 and at least 2 cardinal features are classified as having non-classic CdLS. A score of 4–8 with at least 1 cardinal feature warrants molecular testing for CdLS, whereas a score of $<4$ is insufficient to indicate the need for such testing.

We systematically searched the Wanfang, CNKI, and PubMed databases for articles published before March 1, 2023. The selection criteria for the articles were as follows: (1) all subjects met the diagnostic criteria and were diagnosed with CdLS, (2) case reports of epilepsy caused by *SMC1A* variants, and (3) the articles were written in English or Chinese.

## 3 | Results

### 3.1 | Case Presentation

A 5-year-6-month-old female patient was referred to Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology for evaluation of epilepsy. The proband was born at full term to a G2P2 mother with no history of asphyxia and without regular prenatal examinations. At birth, her measurements were as follows: body weight = 3300 g (0 to +1 SD), body length = 50 cm (0 to +1 SD), and head circumference = 32.5 cm (−1 to −2 SD). She has a healthy 8-year-old older brother. The parents denied consanguinity, family history of genetic disorders, or any other relevant medical history. Neonatal cardiac ultrasound revealed DORV, ventricular septal defect (VSD), patent foramen ovale (PFO), and pulmonary hypertension (PH). She underwent successful Blalock-Taussig, Bidirectional Glenn, and Rastelli surgeries at the ages of 10 months, 3 years, and 5 years, respectively, at another hospital. Other clinical data related to the complex congenital heart disease (CHD) were unavailable. She achieved developmental milestones with delays, sitting alone at 13 months, standing alone at 18 months, and walking independently at 2 years. The Gesell Developmental Schedules (GDS) at 4 years and 1 month indicated severe developmental delay, with development quotients (DQ) for gross motor skills, fine motor skills, adaptability, language, and personal-social skills of 38, 30, 23, 14, and 20, respectively (DQ $>85$ is considered normal). She was diagnosed with epilepsy at 4 years and 10 months after experiencing generalized tonic–clonic seizures 5 to 6 times per day without an apparent cause. Over the following 8 months, she was treated with up to 6 different combinations of antiepileptic drugs (AEDs), including valproic acid, levetiracetam, carbamazepine, phenobarbital, lamotrigine, and clonazepam, but the epilepsy remained drug-resistant. On physical examination at 5 years and 6 months, the patient had a height of 103.5 cm (−2 to −3

SD), weight of 15 kg (−1 to −2 SD), and head circumference of 48 cm (−1 to −2 SD). Additionally, she presented with characteristic facial features (Figure 1a), including widely spaced eyes, a concave nasal bridge, smooth philtrum, downturned corners of the mouth, microtia, and small hands (Figure 1b). However, muscle strength and tone in the limbs were normal. Genetic and metabolic evaluations, including thyroid screening, ammonia, lactate, plasma amino acids, urine amino acids, organic acids, and acylcarnitines, were all within normal limits. A video-EEG revealed a slow baseline rhythm, with high-amplitude slow delta waves observed bilaterally in the frontotemporal regions during sleep (Figure 2). After admission, treatment with perampanel was initiated, resulting in a positive response. As seizure frequency significantly decreased, other AEDs were gradually reduced or discontinued. By the age of 5 years and 9 months, seizures were effectively controlled with a regimen of perampanel, valproic acid, and lamotrigine. However, cranial MRI revealed gliosis in the left occipital lobe, atrophy of the left hippocampus (Figure 3a), and cerebromalacia in the right cerebellum (Figure 3b). At the same time, the GDS indicated profound

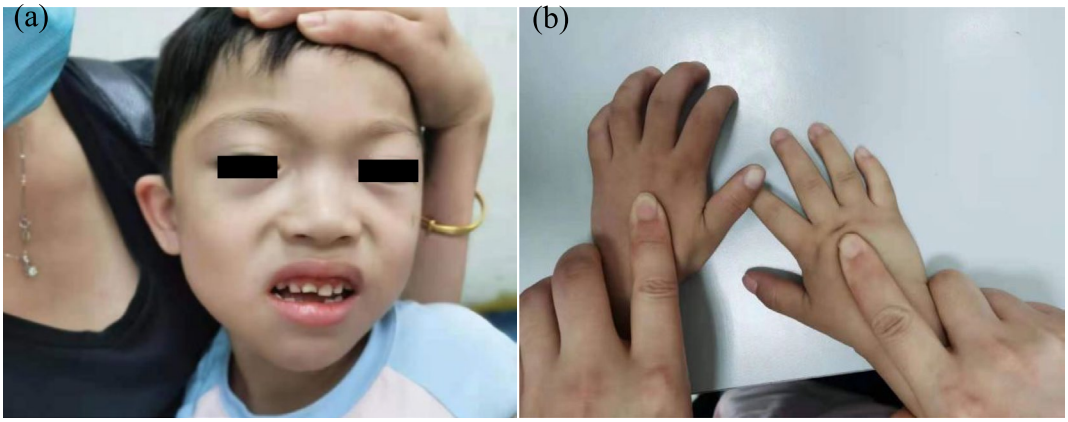


**FIGURE 1** | Characteristic facial features (a) and small hands (b) of the proband.


**FIGURE 2** | Video-EEG of the proband.

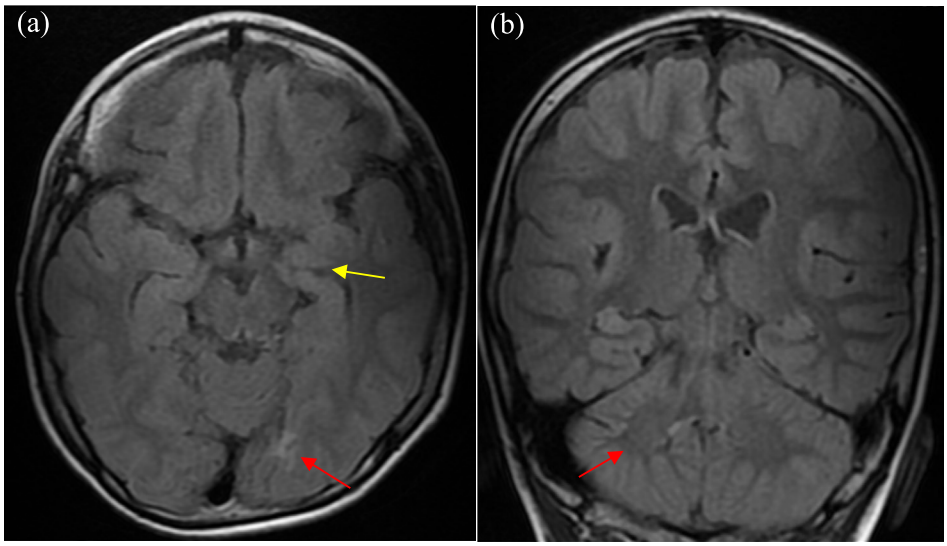


**FIGURE 3** | (a) gliosis in the left occipital lobe (red arrow), atrophy of the left hippocampus(yellow arrow). (b) cerebromalacia in right cerebellum (red arrow).

developmental delays, with DQs for gross motor skills, fine motor skills, adaptability, language, and personal-social skills at 24, 17, 14, 12, and 19, respectively.

### 3.2 | Scoring System of Phenotype of CdLS

Based on the diagnostic criteria, the proband exhibited 3 cardinal features (concave nasal bridge, smooth philtrum, and downturned corners of the mouth) and 2 suggestive features (small hands and developmental delay with intellectual disability), resulting in a comprehensive score of 8, classifying her as having non-classic CdLS.

### 3.3 | Genetic Variant Detection Analysis

At the age of 5 years and 10 months, a de novo heterozygous frameshift variant, NM_006306.4: exon19: c.2890_2893del (p.Ser964Valfs*26), in *SMC1A* was detected in the proband (Figure 4). This variant was not identified in her parents and was absent from the ExAC, gnomAD, and HGMD databases. The same variant was submitted to ClinVar on February 14, 2024, with no related cases reported. No pathogenic CNVs were detected. Pathogenicity analysis of the variant was conducted following ACMG guidelines, classifying it as a pathogenic variant (PVS1 + PM6 + PM2_Supporting), due to its frameshift nature.

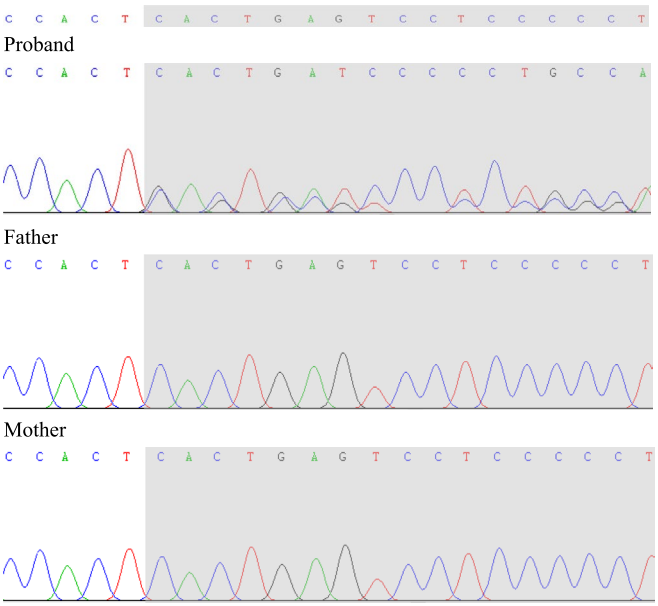


**FIGURE 4** | A de novo heterozygous frameshift variant in *SMC1A* was detected in the proband, and this variant was not identified in her parents.

### 3.4 | A Literature Review of CdLS With Epilepsy Caused by *SMC1A* Variants

A review of the literature identified 27 individuals with CdLS and epilepsy caused by *SMC1A* variants (Table 1). Based on the CdLS phenotype scoring system, the cases were classified as either classic (18.5%, 5/27) or non-classic (81.5%, 22/27). The male-to-female ratio was 1:2 (9:18). IUGR was observed in 29.6% (8/27) of the individuals. All exhibited varying degrees of developmental delay, categorized as unavailable (11.1%, 3/27), mild (14.8%, 4/27), moderate (29.6%, 8/27), severe (22.2%, 6/27), or profound (22.2%, 6/27). Hypotonia was noted in 18.5% (5/27) of cases. Cardiovascular anomalies were present in 33.3% (9/27), including PFO ($n = 4$), VSD ($n = 2$), pulmonary stenosis (PS), pulmonary atresia (PA), coarctation of the aorta (CoA), left ventricular non-compaction (LVNC), left ventricular fibroelastosis (LVFCT), and double outlet right ventricle (DORV), each seen in one case.

The clinical characteristics of epilepsy revealed that the mean age at first seizure was 8 months (range: 2 months to 4 years and 10 months). The types of initial seizures were unavailable in 40.7% (11/27) of cases, whereas 22.2% (6/27) presented with generalized seizures, 22.2% (6/27) with both generalized and focal seizures, and 14.8% (4/27) with febrile seizures. Among these

**TABLE 1** | Summary of clinical features and mutations type observed among 27 individuals with CdLS and epilepsy caused by *SMC1A* variants.

| No. | References | Nationality | Gender | IUGR | CdLS type | Severity of developmental delay | Age at first seizure | Hypotonia |
|---|---|---|---|---|---|---|---|---|
| 1 | Musio et al. (2006) | Italy | Male | − | Classic | Severe | NA | − |
| 2 | Musio et al. (2006) | Italy | Male | + | Non-classic | Moderate | NA | − |
| 3 | Musio et al. (2006) | Italy | Male | + | Non-classic | Moderate | NA | − |
| 4 | Musio et al. (2006) | Italy | Male | − | Non-classic | Moderate | NA | − |
| 5 | Borck et al. (2007) | France | Male | + | Non-classic | Severe | NA | − |
| 6 | Deardorff et al. (2007) | United States | Male | + | Non-classic | NA | NA | − |
| 7 | Deardorff et al. (2007) | United States | Female | + | Classic | Moderate | NA | − |
| 8 | Deardorff et al. (2007) | United States | Female | + | Classic | Moderate | NA | − |
| 9 | Deardorff et al. (2007) | United States | Female | − | Non-classic | Mild | NA | − |
| 10 | Gervasini et al. (2013) | Italy | Male | + | Classic | Moderate | NA | − |
| 11 | Hansen et al. (2013) | Switzerland | Female | + | Non-classic | Mild | 3 months | − |
| 12 | Pavlidis et al. (2014) | Italy | Female | − | Non-classic | NA | 2 years 1 month | − |
| 13 | Wenger et al. (2017) | United States | Female | − | Non-classic | Profound | 2 months | − |
| 14 | Fang et al. (2020) | China | Female | − | Non-classic | Severe | 3 months | − |
| 15 | Lian et al. (2020) | China | Female | − | Non-classic | Moderate | 4 months | − |
| 16 | Lee et al. (2021) | South Korea | Male | − | Non-classic | Profound | 4 years 1 month | − |
| 17 | Lee et al. (2021) | South Korea | Male | − | Non-classic | Profound | 1 year 5 months | − |
| 18 | Liu and Dong (2021) | China | Female | − | Non-classic | NA | 8 months | − |
| 19 | Yang et al. (2021) | China | Female | − | Non-classic | Severe | 3 months | + |
| 20 | Yang et al. (2021) | China | Female | − | Non-classic | Moderate | 8 months | + |
| 21 | Barañano et al. (2022) | United States | Female | − | Classic | Profound | 2.5 months | + |

(Continues)

**TABLE 1** | (Continued)

| No. | References | Nationality | Gender | IUGR | CdLS type | Severity of developmental delay | Age at first seizure | Hypotonia |
|---|---|---|---|---|---|---|---|---|
| 22 | Barañano et al. (2022) | United States | Female | – | Non-classic | Profound | 15 months | + |
| 23 | Barañano et al. (2022) | United States | Female | – | Non-classic | Profound | 18 months | + |
| 24 | Zhang et al. (2022) | China | Female | – | Non-classic | Mild | 21 months | – |
| 25 | Odanaka et al. (2022) | Japan | Female | – | Non-classic | Mild | 2 years | – |
| 26 | Zhao et al. (2023) | China | Female | – | Non-classic | Severe | 5 months | – |
| 27 | This study | China | Female | – | Non-classic | Severe | 4 years 10 months | – |

| No. | Cardiovascular anomalies | First seizure types | Seizure clusters | Status epilepticus | Effects of AEDs | Nucleotide change | Amino acid change | Mutation type |
|---|---|---|---|---|---|---|---|---|
| 1 | – | NA | – | – | NA | c.1478A>C | p.E493A | Deletion |
| 2 | – | FS | – | – | NA | c.2493-2495del | NA | Frameshift |
| 3 | – | FS | – | – | NA | c.2493-2495del | NA | Frameshift |
| 4 | – | FS | – | – | NA | c.2493-2495del | NA | Frameshift |
| 5 | – | FS | – | – | Good control | c.3254A>G | p.Tyr1085Cys | Missense |
| 6 | – | NA | – | – | Good control | c.1486C>T | p.R496C | Missense |
| 7 | PS | NA | – | – | Good control | c.1487G>A | p.R496H | Missense |
| 8 | – | NA | – | – | Good control | c.1487G>A | p.R496H | Missense |
| 9 | – | NA | – | – | NA | c.1487G>A | p.R496H | Missense |
| 10 | – | NA | – | – | NA | c.3497A>C | p.N1166T | Missense |
| 11 | – | GE | + | – | NA | c.1731G>A | p.E577 | Splice site |
| 12 | – | GE, FE | – | – | Good control | c.1487G>A | p.Arg496His | Missense |
| 13 | LVNC | GE | – | – | Partial control | c.1636_1638delATT | p.Ile546del | Deletion |
| 14 | PFO | GE | + | – | Uncontrolled | c.1489C>T | p.Q497* | Truncation |
| 15 | PFO | GE | – | – | Partial control | c.607A>G | p.K203E | Missense |
| 16 | – | NA | – | – | Good control | c.2368C>T | p.Arg790Trp | Missense |
| 17 | – | NA | – | – | Good control | c.2368C>T | p.Arg790Trp | Missense |
| 18 | CoA | NA | – | – | NA | c.1979-1980insTGAA | p.K660Nfs*9 | Frameshift |
| 19 | – | GE, FE | – | – | Uncontrolled | c.2561dupA | p.K854fs | Frameshift |
| 20 | PDA | GE, FE | – | – | Partial control | c.3441+1G>A | NA | Splice site |
| 21 | – | GE, FE | + | + | Uncontrolled | c.421G>A | p.E141K | Missense |
| 22 | – | GE | + | + | Uncontrolled | c.20_23del | p.17Rfs*42 | Frameshift |
| 23 | – | GE, FE | + | + | Uncontrolled | c.287G>C | p.R96P | Missense |

(Continues)

**TABLE 1** | (Continued)

| No. | Cardiovascular anomalies | First seizure types | Seizure clusters | Status epilepticus | Effects of AEDs | Nucleotide change | Amino acid change | Mutation type |
|---|---|---|---|---|---|---|---|---|
| 24 | – | GE, FE | – | + | Partial control | c.2923C>T | p.Arg975Ter | Nonsense |
| 25 | PA, VSD, DCM | NA | – | – | Uncontrolled | c.2860G>T | p.Glu954* | Nonsense |
| 26 | PFO, LVFCT | NA | – | – | NA | c.607A>G | p.K203E | Missense |
| 27 | DORV, VSD, PFO | GE | + | + | Good control | c.2890_2893del | p.Ser964Valfs*26 | Frameshift |

Abbreviations: –, absence; +, presence; ASD, atrial septal defect; CoA, coarctation of aorta; DORV, double outlet right ventricle; FE, focal epilepsy; FS, febrile seizures; GE, generalized epilepsy; LVFCT, left ventricular false chordae tendineae; LVNC, left ventricular non-compaction; NA, not available; PA, pulmonary atresia; patent ductus arteriosus; PFO, patent foramen ovale; PS, pulmonary stenosis; TGA, transposition of the great arteries; VSD, ventricular septal defect.

patients, 22.2% (6/27) experienced seizure clusters, and 18.5% (5/27) had status epilepticus. Regarding AEDs treatment, the outcomes were unavailable in 33.3% (9/27), whereas 29.6% (8/27) achieved good seizure control, 14.8% (4/27) had partial control, and 22.2% (6/27) remained uncontrolled.

The genotypes of individuals with classic CdLS included missense (80.0%, 4/5) and deletions mutations (20.0%, 1/5). For non-classic CdLS cases, the genotypes included missense mutations (40.9%, 9/22), frameshift mutations (31.8%, 7/22), splice site variants (9.1%, 2/22), nonsense mutations (9.1%, 2/22), deletions (4.5%, 1/22), and truncations (4.5%, 1/22).

### 3.5 | A Comparison of Individuals With Classic and Non-Classic CdLS With Epilepsy Caused by *SMC1A* Variants

When comparing the clinical features of classic and non-classic CdLS with epilepsy caused by *SMC1A* variants (Table 2), several differences were identified: female individuals were slightly more common in non-classic cases. Additionally, severe/profound developmental delay and cardiovascular anomalies appeared to be more frequent in non-classic cases. In contrast, IUGR was significantly less common in non-classic individuals. Hypotonia, seizure clusters, status epilepticus, and drug-resistant epilepsy were similar between classic and non-classic individuals.

**TABLE 2** | A comparison of individuals with classic and non-classic CdLS with epilepsy caused by *SMC1A* variants.

| Category | Classic (%) | Non-classic (%) |
|---|---|---|
| No. of cases | 5/27 (18.5) | 22/27 (81.5) |
| Female | 3/5 (60.0) | 15/22 (68.2) |
| IUGR | 3/5 (60.0) | 5/22 (22.7) |
| Severe and profound developmental delay | 2/5 (40.0) | 10/19 (52.6) |
| Hypotonia | 1/5 (20.0) | 4/22 (18.2) |
| Cardiovascular anomalies | 1/5 (20.0) | 8/22 (36.4) |
| Seizure clusters | 1/5 (20.0) | 5/22 (22.7) |
| Status epilepticus | 1/5 (20.0) | 4/22 (18.2) |
| Epilepsy good/partial control | 2/3 (66.7) | 10/15 (66.7) |
| Epilepsy uncontrolled | 1/3 (33.3) | 5/15 (33.3) |

## 4 | Discussion

### 4.1 | CdLS Individuals Caused by *SMC1A* Variants

CdLS is a clinically and genetically heterogeneous disorder. Of the seven pathogenic genes identified, mutations in *NIPBL*, *SMC3*, *BRD4*, *ANKRD11*, and *RAD21* are associated with the autosomal dominant form of CdLS, whereas *SMC1A* and *HDAC8* mutations are responsible for the X-linked form. The *SMC1A* gene, located on chromosome Xp11.22, spans 9.7 kB, comprises 25 exons, and encodes one of the four core subunits of the cohesin complex (with 1233 amino acids). This gene plays critical roles in cell division, chromatin structure, gene expression, and transcriptional regulation (Kline et al. 2018). The first case report of three affected males from a family with epilepsy and *SMC1A* variants was published in 2006 (Musio et al. 2006). Since then, an increasing number of individuals with *SMC1A* variants have been identified, often presenting with milder craniofacial features or even lacking the recognizable CdLS facial pattern (Borck et al. 2007; Gervasini et al. 2013; Goldstein et al. 2015; Lebrun et al. 2015; Jansen et al. 2016). This study presents a larger series specifically exploring the phenotype of CdLS individuals with epilepsy caused by *SMC1A* variants, with a particular focus on non-classic cases.

### 4.2 | Phenotype of the Non-Classic CdLS Individuals With Epilepsy Caused by *SMC1A* Variants

In the study by Huisman and colleagues, the male-to-female ratio among CdLS individuals was 1:2.6 ($n = 51$). Similarly, the ratio in non-classic cases from our study was 1:2.1 ($n = 22$), indicating that the incidence in females was not significantly higher in non-classic cases compared to the overall CdLS population. In the reported case series (Huisman et al. 2017), the incidence rates of IUGR and developmental delay among suggestive features were 26.8% (11/41) and 60.8% (31/51), respectively. In our cohort of CdLS individuals with epilepsy, the incidence of IUGR was slightly higher at 29.6% (8/27), whereas 100% of

the individuals experienced developmental delay. Additionally, severe to profound developmental delay appeared to be more frequent in non-classic cases, whereas IUGR was significantly less common compared to classic CdLS cases. Furthermore, Chatfield and colleagues highlighted various types of cardiovascular anomalies, including CoA, ASD, and PS (Chatfield et al. 2012). Although PFO and VSD were relatively common in our review, several cases of CHD, such as tetralogy of Fallot, were also reported (Chatfield et al. 2012). Notably, DORV had not previously been reported in non-classic CdLS with epilepsy, and the proband in this study expands the known phenotypic spectrum. The incidence of cardiovascular anomalies in non-classic CdLS individuals was slightly higher than in classic cases.

### 4.3 | Clinical Characteristics of Epilepsy in Non-Classic CdLS Individuals Caused by *SMC1A* Variants

Epilepsy occurs in approximately 20% of CdLS cases, typically presenting as focal seizures that generally respond well to standard AEDs therapy (Kline et al. 2018; Elwan et al. 2022). In contrast, among the 22 non-classic CdLS individuals with epilepsy caused by *SMC1A* variants reviewed in this study, the initial seizure types were more commonly generalized or a combination of generalized and focal seizures, often with infant-onset characteristics. Despite this, the incidence of seizure clusters, status epilepticus, drug resistance, and hypotonia was not high, with no significant differences between classic and non-classic individuals. Epilepsy was well-controlled or partially controlled in 66.7% of non-classic cases. Developmental and epileptic encephalopathy (DEE), a form of early-onset intractable epilepsy associated with severe/profound developmental delay, was also observed, although it lacked the characteristic facial features of CdLS (Bozarth et al. 2023). The characteristics of seizure clusters, status epilepticus, and drug resistance are more pronounced in DEE, making it relatively easy to differentiate DEE from non-classic CdLS with epilepsy based on seizure features (Barañano et al. 2022; Bozarth et al. 2023). Certain combinations of AEDs can be particularly effective in some cases. In the case of this proband, seizures were gradually controlled following the introduction of perampanel. Perampanel has been approved by the US FDA for the treatment of focal–onset seizures, with or without bilateral tonic–clonic seizures, and generalized tonic–clonic seizures (Fernandes et al. 2021). It has shown good efficacy, safety, and tolerability in treating refractory epilepsy in children (Fernandes et al. 2021). However, in our review, only the proband was treated with a combination that included perampanel. Further studies involving larger cohorts are needed to evaluate the effectiveness of perampanel in epilepsy associated with *SMC1A* variants.

### 4.4 | Genotype of the Classic and Non-Classic CdLS Individuals Caused by *SMC1A* Variants

Previous literature reviews have shown that the primary mutation types in *SMC1A*-associated CdLS were deletions and missense mutations (Symonds et al. 2017; Huisman et al. 2017; Gervasini et al. 2013; Jansen et al. 2016). In comparison, our review found that missense and frameshift mutations were more common in non-classic CdLS cases. In contrast, *SMC1A*-associated DEE is predominantly caused by nonsense, frameshift, and splice site mutations (Bozarth et al. 2023).

## 5 | Conclusions

This study expanded the phenotypic and mutational spectrum of CdLS with epilepsy caused by *SMC1A* variants and provided further insights into the clinical features of non-classic individuals.

#### Author Contributions

Y.L. designed the study. Y.Y., L.C., Z.W., and Y.D. analyzed the data and reviewed the analyses. Y.Y. wrote the article. All authors approved the final article and agreed to be accountable for all aspects of this work.

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The authors are grateful to the proband and her parents in this study.

#### Conflicts of Interest

The authors declare no conflicts of interest.

#### Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

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