FULL-LENGTH ORIGINAL RESEARCH

Heterozygous truncation mutations of the *SMC1A* gene cause a severe early onset epilepsy with cluster seizures in females: Detailed phenotyping of 10 new cases

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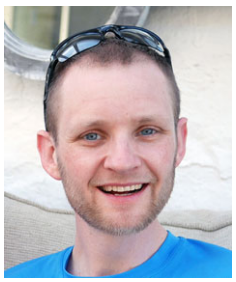

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Summary

Objective: The phenotype of seizure clustering with febrile illnesses in infancy/early childhood is well recognized. To date the only genetic epilepsy consistently associated with this phenotype is *PCDH19*, an X-linked disorder restricted to females, and males with mosaicism. The *SMC1A* gene, which encodes a structural component of the cohesin complex is also located on the X chromosome. Missense variants and small in-frame deletions of *SMC1A* cause approximately 5% of Cornelia de Lange Syndrome (CdLS). Recently, protein truncating mutations in *SMC1A* have been reported in five females, all of whom have been affected by a drug-resistant epilepsy, and severe developmental impairment. Our objective was to further delineate the phenotype of *SMC1A* truncation.

Method: Female cases with *de novo* truncation mutations in *SMC1A* were identified from the Deciphering Developmental Disorders (DDD) study (n = 8), from post-mortem testing of an affected twin (n = 1), and from clinical testing with an epilepsy gene panel (n = 1). Detailed information on the phenotype in each case was obtained.

Results: Ten cases with heterozygous *de novo* mutations in the *SMC1A* gene are presented. All 10 mutations identified are predicted to result in premature truncation of the *SMC1A* protein. All cases are female, and none had a clinical diagnosis of CdLS. They presented with onset of epileptic seizures between <4 weeks and 28 months of age. In the majority of cases, a marked preponderance for seizures to occur in clusters

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was noted. Seizure clusters were associated with developmental regression. Moderate or severe developmental impairment was apparent in all cases.

Significance: Truncation mutations in *SMC1A* cause a severe epilepsy phenotype with cluster seizures in females. These mutations are likely to be nonviable in males.

KEY WORDS: *SMC1A*, Epilepsy, Cluster, X-linked, Females, Intellectual disability.

Key Points

- Truncation mutations in *SMC1A* have been reported only in females
- This series takes the total number of published cases to 15
- Early childhood onset epilepsy and moderate-severe intellectual disability is seen in all cases
- Focal and generalized seizures are seen
- Seizures frequently occur in clusters, without a clear precipitant to the clusters
- Cases often lack the typical features of Cornelia de Lange Syndrome, which is caused by missense mutations in *SMC1A*

A number of X-linked epilepsies have been described in which females are exclusively, or disproportionately, affected. The most well-delineated is *PCDH19*-related epilepsy, a condition that typically presents with fever-sensitive focal seizures, often occurring in clusters, and in which developmental problems often become apparent after epilepsy onset.[1] Other examples include *CDKL5,*[2] *KIAA2022,*[3] *HNRNPH2,*[4] and *CASK*.[5] In contrast to *PCDH19*, in which (non-mosaic) male mutation carriers are usually asymptomatic, in *CDKL5*, *HNRNPH2, KIAA2022*, and *CASK*, males are presumed to be nonviable, although rare cases of more severely affected males have been described in *CDKL5*, *KIAA2022*, and *CASK*.[2,3,5]

The *SMC1A* gene, located at Xp11.22, encodes one of four core subunits that make up the cohesin ring. The cohesin ring plays important roles in cell division, transcription regulation, and DNA repair.[6] Derangements of the cohesin ring are known to cause Cornelia de Lange syndrome (CdLS), a multisystem developmental disorder first described in 1849.[7] Affected individuals are typically microcephalic with striking prenatal and postnatal growth restriction, often associated with feeding difficulties and gastroesophageal reflux.[8] They have a characteristic facial appearance with fine arched eyebrows, synophrys, long philtrum, thin upper vermilion, and low set posteriorly rotated ears. There is variable presence of malformation (limb, cardiac, diaphragmatic, gastrointestinal, and genitourinary). The reported prevalence of epilepsy ranges from 4% to 23%, with no particular seizure pattern described.[9]

Approximately 65% of CdLS cases are caused by mutations in genes (*NIPBL*, *SMC1A, SMC3*, *RAD21*, and *HDAC8*) that encode structural components or regulators of the cohesin ring.[10] To date, 60 cases of CdLS due to *SMC1A* mutation have been described, with a male-to-female ratio of 1:2.[11] All reported variants have been missense mutations or small in-frame deletions. This led to the previous hypothesis that mutations causing truncation of the *SMC1A* protein would be either asymptomatic or nonviable.[11] The absence of *SMC1A* protein truncating mutations in large databases comprised largely of asymptomatic individuals favored the hypothesis that they would be nonviable.[12] However, recently, *SMC1A* truncation mutations have been described in five cases, all female, none of whom had a clinical diagnosis of CdLS.[13–15] All five cases developed drug-resistant epilepsy and had severe developmental impairment. Age at presentation with first epileptic seizure ranged from <1 month to 17 months; 4 of 5 cases were reported to have a clustering pattern to the seizures.

Herein we report the phenotypes of 10 new cases of *SMC1A* truncation-related epilepsy, further delineating the phenotype. Our data help further define *SMC1A* truncation as a genetic epilepsy with distinct electroclinical features that can occur in cases without typical features of CdLS. We propose that, along with *PCDH19*, testing of the *SMC1A* gene should be considered in females with early childhood–onset drug-resistant epilepsy, particularly where there is a clustering pattern to the seizures.

Methods

Ethical compliance

The Deciphering Developmental Disorders (DDD) study has United Kingdom Research Ethics Committee approval (10/H0305/83, granted by the Cambridge South REC, and GEN/284/12 granted by the Republic of Ireland REC).

Case ascertainment

Eight of the 10 affected cases (cases 1–8) were recruited via United Kingdom NHS Regional Genetics Services to the Deciphering Developmental Disorders (DDD) project

(http://www.ddduk.org/). Case 9 was tested postmortem following the genetic result found in her twin sister through DDD. Case 10 was followed in pediatric neurology and genetics due to a severe developmental and epileptic encephalopathy.

A structured proforma, including detailed phenotypic data, was completed by both the clinical geneticist and the pediatric neurologist involved in each case; this was used in conjunction with information in the DDD database.

Sequencing and analysis

For cases 1–8, trio-based exome sequencing was performed as part of the DDD study as described previously.[16,17] Target capture using Agilent SureSelect 55 MB Exome Plus was performed on saliva- or blood-derived genomic DNA from each affected case and their parents, and was sequenced on Illumina HiSeq. DeNovoGear21 was used to identify *de novo* sequence variants and Ensembl Variant Effect Predictor (VEP version 2.6, http://www.ensembl.org/info/docs/tools/vep/index.html) was used to predict the effect of each genomic variant. PolyPhen-2 analysis was carried out at http://genetics.bwh.harvard.edu/pph2/. SIFT analysis was carried out at http://sift.bii.a-star.edu.sg/www/SIFT_seq_submit2.html (parameters used: Database UniProt-SwissProt2010_09; Median conservation of sequences 3.00; remove sequences >90% identical). Genbank accession for *SMC1A* is NM_006306.

Case 9 was postmortem sequenced locally for the variant found in her sister following her sister's result through DDD. Case 10 was tested using a custom gene panel of >100 candidate genes or genes associated with the epileptic encephalopathy, microcephaly, and genetic syndromes with seizures.

Results

Clinical findings

We obtained detailed phenotypic information on nine cases with *SMC1A* truncation. A further case who was more severely affected than all of the others (case 9), was the older sister of case 8; case 9 died at aged 11 months. We were unable to obtain details of her epilepsy other than that she began having seizures in the neonatal period. She had semilobar holoprosencephaly, partial anomalous pulmonary venous drainage, and dysmorphic facial features. Her sister, with the same mutation, had no structural organ anomalies, no dysmorphic features, and a normal magnetic resonance imaging (MRI) brain scan. All 10 cases identified were female, and they all presented with a drug-resistant epilepsy, although two cases eventually became seizure-free (case 2 from age 5 years, and case 4 from age 7 years). Prior to, and after, their genetic diagnosis, none were considered as having CdLS (see Supporting Information:Case histories for further clinical details of each case).

Development

Apart from the two cases who began having seizures in the neonatal period, concerns about developmental delay had clearly arisen prior to the onset of epileptic seizures. All 10 cases have moderate, severe, or profound developmental impairment, with all domains of development affected. None of the cases have any expressive language. One case (case 6) did develop babbling between 1 and 2 years of age before losing this ability following a 45 minute episode of tonic–clonic status epilepticus at the age of 3 years. None of the other cases were felt to have had any regression in their development associated with either epilepsy onset, or any period of poor seizure control. Four of the 10 cases have achieved independent mobility, albeit with significant delay. Three of the 10 cases have cerebral visual impairment.

Seizures

Age at onset of first seizure ranged from the neonatal period to 28 months of age (median 4.5 months). The first epileptic seizure was an afebrile generalized motor seizure (generalized tonic–clonic, or generalized clonic) in five cases, a focal seizure in two cases, a generalized tonic seizure in one case, and generalized tonic–clonic febrile convulsion in one case. Seven cases demonstrated both focal and generalized seizure types, whereas two cases had generalized seizures only. Seven cases demonstrated a clear predisposition for seizures to occur in clusters. For example, case 6 currently has clusters of between 3 and 10 focal-onset seizures, occurring over a period of 24 hours, every 10–21 days, with complete seizure freedom between clusters. Case 8 has clusters of six to seven generalized tonic–clonic seizures occurring two to three times per month. Two cases have had episodes of convulsive status epilepticus, and one case has had episodes of nonconvulsive status epilepticus.

Electroencephalography (EEG)

All nine cases for whom we have seen EEG studies or EEG reports have demonstrated focal or multifocal abnormalities. Typically, the interictal EEGs show independent multifocal spike and sharp-wave complexes seen in both awake and sleep recordings (see Fig. 1B and Fig. 1D), as well as subclinical runs of generalized spike-wave abnormalities, lasting several seconds (Fig. 1A). Ictal EEG studies show generalized slowing of background (Fig. 1C), followed by focal spike discharge widely distributed over one hemisphere (Fig. 1E). In other EEG studies in the same case, the spike discharge may be over the other hemisphere.

Epilepsy treatment

From this small case series, no single antiepileptic drug has emerged as clearly more efficacious than others. In fact, although six of the referrers reported one or more antiepileptic drug to be particularly efficacious in their case, in all six cases this was a different drug. One case became seizure

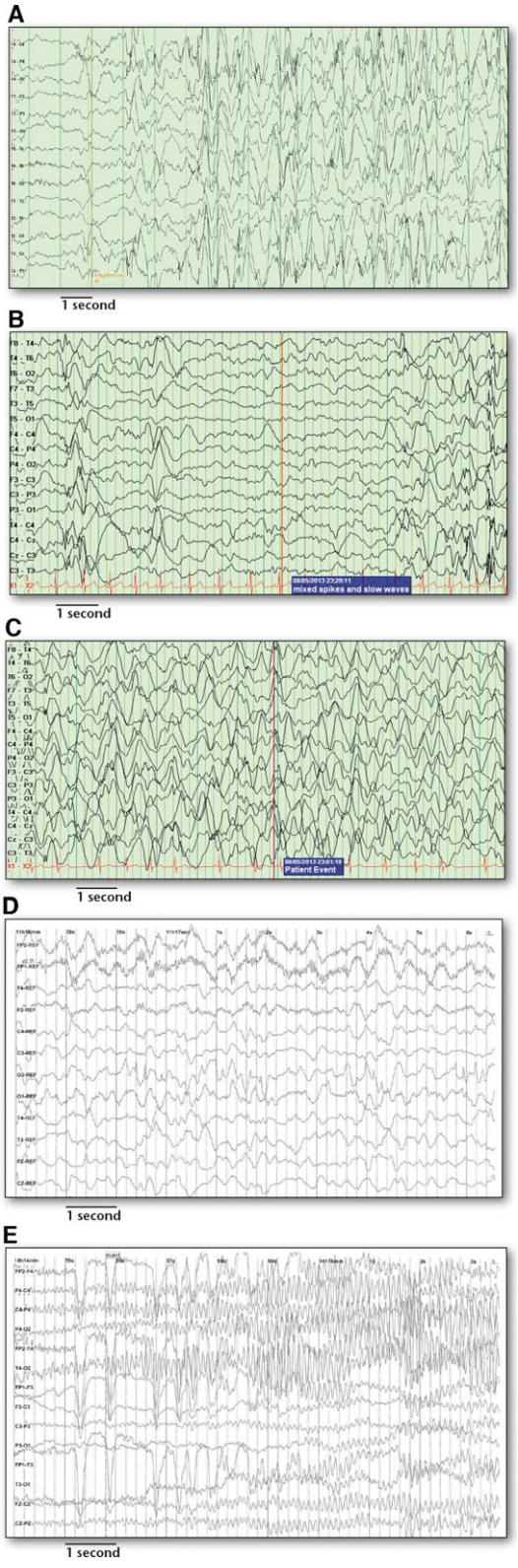

Figure 1.
EEG studies from three cases. (**A**) Interictal sleep EEG from case 1 showing generalized irregular spike/sharp and slow activity in sleep without any clinical accompaniment. (**B**) Interictal EEG study from case 6 showing short bursts of mixed spike and slow waves with a bilateral but asymmetric distribution. (**C**) Ictal EEG study from case 6 during a focal-onset seizure showing generalized spike and slow wave activity. (**D**) Interictal EEG study from case 10 showing irregular spike/sharp and slow wave activity, more prominent in the left temporal and occipital regions. (**E**) Ictal EEG from case 10 showing right-sided sharp waves and left-sided slow waves.

free shortly after introduction of phenobarbitone, one case became seizure free shortly after introduction of gabapentin, and one case achieved seizure freedom for 1 year after levetiracetam was initiated. In all cases multiple medications were tried (range 4–8). Three cases tried the ketogenic diet; two of them were felt to benefit significantly in terms of seizure control, and one of them remains on it at present (after 4.5 years). Two have tried vagus nerve stimulation, both without perceived benefit.

Growth

Short stature and progressive microcephaly were seen in the majority of cases. Overall, height and head circumference are proportionally small. Most recent height measurement was >2 Z-scores below the mean in seven of nine cases on most recent height measurement, and mean most recent height was −3.0 Z-scores (standard deviation [SD] 1.5). None of the cases had microcephaly at birth, although mean birth occipitofrontal circumference (OFC) was −1.5 Z-scores below the mean. Most recent OFC was >2 Z scores below the mean in eight of nine cases, with a mean most recent OFC of −3.0 Z-scores (SD 1.6). The cases also demonstrated a deceleration in weight gain. Only one of 10 cases had a low birth weight (>2 Z-scores below the mean), although mean birth weight for the 10 cases was −1.29 Z-scores (SD 0.67). However, in five of nine cases the most recent weight was >2 Z-scores below then mean, and the mean most recent weight for the group was −2.2 Z-scores (SD 1.4).

Dysmorphism and associated anomalies

Two cases have no dysmorphic features and no congenital anomalies, and another one has dysmorphic features but no congenital anomalies. Four cases have congenital cardiac anomalies: two atrial septal defect *plus* ventricular septal defect, one atrial septal defect only, and one partial anomalous pulmonary venous drainage. Two cases have had cleft palate, and two have bifid thoracic vertebrae. From photographs the primary authors have seen, there appears to be a characteristic facial appearance, consisting of a flattened mid-face, a short, upturned nose, and a shallow philtrum (Fig. 2).

Genetic findings

The phenotypic findings of the 10 cases from our study, along with those of the previously reported five cases are

Figure 2.
Facial appearances, from left to right: case 6, case 4, case 8, and case 10.
Epilepsia © ILAE

summarized in Table 1. The genetic findings of the 10 new cases are summarized in Table 2. In all 10 cases the mutation had arisen *de novo* and was predicted to lead to premature truncation of the SMC1A protein.

Discussion

Analysis of the 10 cases reported herein, and the previously published 5 cases, allows delineation of a distinct epilepsy phenotype associated with *SMC1A* truncation mutations. Eight of our 10 cases were recruited from a large cohort of patients who had been referred for genetic investigation of a developmental disorder (the DDD study), not specifically for epilepsy.[17] Despite the broad entry criteria for the DDD study, all the *SMC1A* truncation cases identified from this cohort have been found to have a severe drug-resistant epilepsy, suggesting that the correlation between *SMC1A* truncation and the epilepsy phenotype is strong. All five previously reported cases in the literature also had drug-resistant epilepsy.[13–15] In addition, Hansen et al. reported a female with a *de novo* splice-site mutation in *SMC1A* who had infantile-onset epilepsy characterized by convulsive seizures "occurring in impressive clusters lasting 24–48 h.[18]" In their discussion, Hansen et al. commented that although the diagnosis of Cornelia de Lange syndrome was not considered initially, "retrospectively the girl's symptoms and facial gestalt [were] compatible with mild Cornelia de Lange syndrome (CdLS)." We argue that *SMC1A* truncation does not represent a mild form for CdLS, since these female patients are affected by a more severe developmental disorder than is typical for CdLS caused by *SMC1A* variants.

The presence of seizure clustering is a strong theme that has emerged in our cases. Seven of 10 cases were noted to have seizure clustering. Seizure clustering was also noted in four of five of the previously reported cases. The only other genetic epilepsy for which seizure clustering has emerged as a prominent feature is *PCDH19*-related epilepsy. As with *SMC1A*, *PCDH19*-related epilepsy is an X-linked disorder, affecting mostly females. The *PCDH19* phenotype has now been well defined, and can be summarized as follows: normal development before onset of seizures; seizure onset between 3 months and 3 years (median 11 months);[19] clusters of convulsive seizures that are markedly fever sensitive;

Table 1. Summary of the phenotypic features from our 10 cases and the previously reported 5 cases

Feature	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Current age	6 years	6 years	3 years	8 years	10 years	5 years	4 years	14 years
Birth OFC Z-score/ most recent OFC Z-score	−0.8/−3.5	−1.5/−4.5	−1.6/−0.8	−2.0/−2.5	−1.2/−2.0	Unknown/−3.0	Unknown/−2.0	Unknown/−2.0
Most recent height Z-score	−2.3	−2.6	0.06	−2.6	−4.5	−3.2	−2.5	−3.7
Tone	Low	Low	Axial hypotonia, peripheral hypertonia	Low	Low	Low	Low, with increased dynamic tone at ankles	Unknown
Developmental impairment	Moderate–severe impairment	Severe impairment	Severe impairment	Severe impairment	Severe impairment	Moderate–severe impairment	Moderate–severe impairment	Moderate–severe impairment
Gross motor development	Can run with unsteady gait	Unable to sit without support	Unable to sit without support	No independent mobility	Unable to sit without support	Walking from 30 months	Can take a couple of steps with support	Walking from 2.5 years. Unsteady on feet with frequent falls, aged 7
Speech	None. Smiles and makes hand gestures	None	None	None	None	Lost speech aged 3 years following SE	None. Coos, laughs, cries appropriately	None
Autism	–	–	–	+	–	–	–	+
Age at first seizure	15 months	5–6 weeks	4 months	5 months	6 months	5 months	4 weeks	28 months
First seizure semiology	Cluster of GTCS	GTCS	Generalized tonic	Focal→bilateral clonic	Cluster of GTCS	Focal→bilateral tonic	Bilateral clonic	FS
Further seizure types	GTCS, hemiclonic, drop attacks, atypical absence	Focal	FS, CSE, focal, myoclonic, spasms, tonic, atypical absence	Focal, generalized tonic	GTCS, myoclonic, atypical absence, tonic, spasms, NCSE, reflex sensory	Focal→bilateral tonic focal→bilateral clonic	GTCS, hemiclonic	GTCS
Seizure clusters?	+	–	+	+	+	+	+	+
Seizure freedom?	No	Yes, aged 5 years	No	Yes, aged 7 years	No	For 1 year then recurred	No	No
AEDs tried	PHT, VPA, LEV, LMT, CLB, TPM, CBZ	CBZ, VPA, TPM, CLB, RUF, LEV, GBP KD, VNS	GBP, AZA, CZP, LZP, VPA, LEV, pyridoxine	VPA, LMT, CBZ, TPM, LEV, PHT, CLB, PB	PB, CBZ, CLB, VPA, LMT, TPM, LEV, pyridoxine, KD	CBZ, VPA, TPM, PB, LEV, KD	TPM, VPA, LEV, CBZ	PB, LEV, TPM, LMT, CBZ, CLB, VNS
Beneficial AEDs	VPA, PHT, CBZ	GBP (seizure free)	STP	PB (seizure free)	CLB, KD	LEV (seizure free for 1 year), KD	None	None
EEG	Independent left and right sided	Diffusely slow with sharp	High amplitude background	Multifocal epileptic activity	Continuous high-voltage waves	High voltage slow background	Frequent multi-spike and slow right	

Continued

Table 1. Continued.

Feature	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
	epileptiform abnormalities	transients seen over both temporal regions	activity with epileptiform discharges over left and occasionally right hemisphere		without epileptiform discharges		centrotemporal region	Right-sided spike and slow wave abnormalities
MRI(s)	Normal	Cerebral volume loss	Small hemorrhage along the posterior falx and tentorium	Normal	Small cavum septum vergae	Normal	Normal	Normal
Dysmorphisms	Mild facial asymmetry with the right side of the face appearing fuller than the left; mild left ptosis; short, slightly up-turned nose; thin upper lip; shallow philtrum; small hands and feet	Bitemporal narrowing; upslanting palpebral fissures; thin, straight eyebrows; mildly posteriorly rotated ears; tapering of digits; short 5th fingers; short broad halluces; overlapping 2nd and 3rd toes	Hirsutism of the forehead, back, arms and upper lip; bitemporal narrowing with low anterior hairline; long eyelashes; downturned corner of mouth with midline groove of the lower lip	Small widely spaced teeth; deep-set eyes; downward sloping palpebral fissures; short, slightly up-turned nose; shallow philtrum; low-set posteriorly rotated ears; syndactyly of the 1st and 2nd toes	Deviation of both halluces at the metatarsophalangeal joint; left 3rd finger camptodactyly; left 5th finger clinodactyly	Puffy eyes; right nasal deviation; small over-folded right pinna; short, slightly upturned nose; thin upper lip; shallow philtrum; clinodactyly of the middle toes of both feet; central incisor	None	None
Malformations	None	Bilateral congenital hip dysplasia; bilateral talipes; bifid T8 vertebra	Cleft palate; multiple small cysts in kidneys	ASD; VSD	Bifid T6 vertebra; ASD; choanal atresia	Cleft palate	None	None

Feature	Case 9	Case 10	Lebrun	Goldstein 1	Goldstein 2	Jansen 1	Jansen 2
Current age (age at report)	Died aged 11 months	Died aged 9 years 2 months	7 years	4 years	3 years	46 years	14 years
Birth OFC Z-score/ most recent OFC Z-score	−1.7/Unknown	−1.3/−6.3	−3.9/−2.5	Unknown/−2.0	−1.0/0.0	Unknown/−2.5	Unknown/−1.7
Most recent height Z-score	Unknown	−5.0	−2.0	Unknown	−0.05	−2.5	−2.0
Tone	Not known	Low neonatally	Axial hypotonia, peripheral hypertonia	Axial hypotonia, peripheral hypertonia	Unknown	Axial hypotonia, peripheral hypertonia	Normal
	Profound impairment	Severe impairment	Severe impairment	Severe impairment	Severe impairment	Severe impairment	Severe impairment

Continued

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Table 1. Continued.

Feature	Case 9	Case 10	Lebrun	Goldstein 1	Goldstein 2	Jansen 1	Jansen 2
Developmental impairment							
Gross motor development	None	Unable to sit	Delayed	Non ambulant	Walked at 12 months	Never crawled or walked	Walked at 2 year; suddenly stopped walking at 5 years
Speech	None	None	None	None	None. Coos, interacts	None	None
Autism	–	–	–	–	–	–	–
Age at first seizure	<1 month	2 months	<1 month	4 months	17 months	9 months	2 years
First seizure semiology	Unknown	GTCS	Focal with eyelid myoclonia	Generalized tonic	Focal/atypical absence, GTCS	GTCS	GTCS
Further seizure types	Unknown	GTCS, myoclonic, CSE,	Focal, spasms	Tonic, focal→bilateral clonic, CSE	Focal/atypical absence, GTCS	GTCS	GTCS
Seizure clusters?	–	–	–	+	+	+	+
Seizure freedom?	No	No	No	No	Yes	No	No
AEDs tried	Unknown	TPM, VPA, LEV, RUF	Unknown	PB, LEV, CLB, TPM, CZP, VPA, KD	LEV, TPM, OXC, VPA, PB	PTY, PB, CBZ, VPA, VGB, CZP	LMT, TPM, CBZ, CLB, LEV, CZP, OXC, carnitine, pyridoxine, KD, Estrogen
Beneficial AEDs	Unknown	None	Unknown	PB, LEV, VPA	VPA, PB	None	Estrogen
EEG	Unknown	Multifocal epileptogenic activity, more often over the right hemisphere	Hypsarrhythmia (when presented with infantile spasms)	Multifocal epileptiform discharges	Generalized epileptiform activity or occipital abnormalities	"Centrencephalic" epilepsy	Unknown
MRI(s)	Semilobar holoprosencephaly	Thin abnormally shaped carpus callosum and minimal cerebral atrophy	Thin corpus callosum	Mild symmetric T2 hyperintensities in the periatrial white matter on FLAIR sequencing with possible thickening of the insular cortex	Mild enlargement of extra-axial spaces; slight thinning of the corpus callosum. Temporal lobes prominent sulci and hippocampi round and somewhat smaller	Slightly enlarged ventricles, hypotrophy cerebellar vermis	Mild periventricular white matter abnormalities
Dysmorphisms	Hypotelorism; small low-set posteriorly rotated ears; bilateral 5th finger clinodactyly; overlapping 4th and 5th fingers;	Expressionless face, straight eyebrows; short, upturned nose; flattened midface; short philtrum; downturned corners	Mild synophrys; small hands; small feet; thin nose and upper lip; retrognathia; triangular face	Long eyelashes; short nose; hirsutism on legs and back	None	Low anterior hairline; flat midface; straight eyebrows with deep set eyes; small and elongated ears with a prominent anti-helix; long nose; short philtrum; eversion of	Mild trigonocephaly; mildly up slanting palpebral fissures with blepharophimosis; posteriorly rotated Ears; full cheeks, full lips and short

Continued

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Table 1. Continued.

Feature	Case 9	Case 10	Lebrun	Goldstein 1	Goldstein 2	Jansen 1	Jansen 2
	left rockerbottom foot; hypoplastic nails of the 4th and 5th toes	of the mouth; small hands with tapering fingers				the lower lip; disorganized dentition; small, narrow hands with tapering fingers; syndactyly of the 2nd and 3rd toes and a mildly broad first toe	philtrum; hands small with slender fingers
Malformations	Partial anomalous pulmonary venous drainage	ASD; VSD	None	None	None	Cleft palate	None

GTCS, generalized tonic–clonic seizure; FS, febrile seizure; CSE, convulsive status epilepticus; NCSE, nonconvulsive status epilepticus; PHT, phenytoin; VPA, sodium valproate; LEV, levetiracetam; LMT, lamotrigine; CLB, clobazam; TPM, topiramate; CBZ, carbamazepine; RUF, rufinamide; GBP, gabapentin; KD, ketogenic diet; VNS, vagus nerve stimulation; PB, phenobarbitone; OXC, oxcarbazepine; VGB, vigabatrin; CZP, clonazepam; ASD, atrial septal defect; VSD, ventricular septal defect.

and progression to multiple seizure types including focal seizures and absences.[1] Developmental stagnation or regression may be noted after epilepsy onset, although up to 40% of *PCDH19* cases continue to have normal development.[19,20] Dysmorphism and malformation are not commonly associated with *PCDH19*.[21]

Epilepsy onset and seizure clustering are remarkably similar in these *SMC1A* cases to those seen in *PCDH19*-related epilepsy. Seizure onset was from <4 weeks to 28 months (median five months). Although bilateral motor seizures predominated, nine of 15 had multiple seizure types. Despite certain similarities, a number of features distinguish *SMC1A* truncation–related epilepsy from *PCDH19*. From our 10 cases and the five previously reported cases, 12 of 15 were noted to have dysmorphic features and six of 15 had malformations (cardiac, vertebral, and palatal). These cases are also notable for short stature, a marked progressive microcephaly, and for the presence of a moderate to severe developmental impairment, which clearly preceded seizures in those cases with later-onset epilepsy. In terms of their epileptic seizures, these *SMC1A* truncation cases do not appear to demonstrate the same degree of fever sensitivity as is seen in *PCDH19*. Furthermore, myoclonic seizures, hemiclonic seizures, and tonic seizures were reported in multiple cases in this series, but these seizure types are not typically seen in *PCDH19*-related epilepsy.[20]

There are phenotypic similarities between the cases reported here and CdLS, including short stature, microcephaly and developmental delay, as well as dysmorphic features and congenital anomalies in some. Four of our cases had structural cardiac anomalies, including atrial septal defect (ASD) and ventricular septal defect (VSD). A wide variety of structural cardiac defects are seen in CdLS, including ASD and VSD. Pulmonary stenosis, not seen in any of our cases, is the most frequently reported cardiovascular anomaly in CdLS.[22,23] Bifid vertebrae, seen in two of our cases, are not a frequently reported feature of CdLS.[11]

What appears to distinguish *SMC1A* truncation carriers most from the typical CdLS phenotype is the absence of the characteristic facial features, and the severity of the epilepsy and developmental disorder. Although not a core feature of the syndrome, epilepsy is seen more frequently in CdLS than in the general population, with the estimated prevalence in various reports ranging from 4% to 23%.[9] Although epilepsy does not appear to be more frequently seen in *SMC1A*-related CdLS than in CdLS due to mutations in other cohesin complex genes,[10] it is notable that the majority of, although not all, male *SMC1A* cases reported have epilepsy as a feature.[24–27]

Whether *SMC1A* truncation should be considered separate from CdLS, or as a subtype of CdLS, is a matter for debate. It is notable that we have shown that *SMC1A* truncation can cause a severe developmental disorder and drug-resistant epilepsy in cases where CdLS was not otherwise

Table 2. Summary of genetic findings from our 10 cases

Case	Base change	Amino acid change	Predicted effect on protein	Zygosity	Inheritance	X-inactivation studies
1	c.1591C>T	p.Gln531Ter	Truncation	Heterozygous	*De novo*	Moderately skewed
2	c.3145C>T	p.Arg1049Ter	Truncation	Heterozygous	*De novo*	Not done
3	c.549G>A	pGlu183Glu	Splice-site interference	Heterozygous	*De novo*	Not done
4	c.2197G>T	p.Glu733Ter	Truncation	Heterozygous	*De novo*	Normal
5	c.3326_3330delATGGC insC	p.Asp1109AlafsTer102	Truncation	Heterozygous	*De novo*	Not done
6	c.2923C>T	p.Arg975Ter	Truncation	Heterozygous	*De novo*	Not done
7	c.511C>T	p.Arg171Ter	Truncation	Heterozygous	*De novo*	Normal
8	c.2477delA	Frameshift	Truncation	Heterozygous	*De novo*	Not done
9	c.2477delA	Frameshift	Truncation	Heterozygous	*De novo*	Not done
10	c.3115C>T	p.Gln1039Ter	Truncation	Heterozygous	*De novo*	76:24 ratio in blood

considered. This may have implications for practice when clinicians are considering, and interpreting, genetic testing.

The underlying pathophysiology of CdLS caused by *SMC1A* mutations is not fully understood. *SMC1A* is a structural component of the cohesin ring, which binds to chromatin and plays an important role in the transcriptional regulation of a large number of other genes.[28] There are 60 published cases of *SMC1A*-related CdLS (35 female and 25 male), and all reported variants are either missense variants or deletions that preserve the reading frame of the protein.[11,24–27,29–33] In those cases in which there is familial inheritance of an *SMC1A* mutation, males demonstrate a more severe phenotype than females.[24] Functional studies using human lymphoblastoid cell lines of CdLS patients and healthy controls have demonstrated that in CdLS, mutant *SMC1A* is almost fully transcribed and incorporated into the cohesin complex.[29] Because mutant *SMC1A* would be present in all male cells, whereas in females it would be present only in those cells in which the mutated *SMC1A* allele is not inactivated, this could explain why male *SMC1A* CdLS patients appear to be more severely affected than females within the same family. However, *SMC1A* appears to escape inactivation in some, but not all, females,[34] leading to a hypothesis that mutant *SMC1A* may exert a dominant negative effect in female CdLS cases.[29]

The absence of any reported males with *SMC1A* truncation mutations implies that complete *SMC1A* deficiency is incompatible with viability. The mechanism of pathogenesis in females with *SMC1A* truncation can only be speculated. Lebrun et al.[15] demonstrated that in their female case of *SMC1A* loss-of-function there was a reduced level of *SMC1A* transcript. However, if *SMC1A* does escape X-inactivation, then haploinsufficiency is unlikely to be the causative mechanism because female haploinsufficient cells would have the equivalent of a normal male complement of *SMC1A*.[35] It is possible that truncated *SMC1A* is transcribed and translated, escapes nonsense-mediated decay, and exerts a dominant negative effect. To gain a greater understanding of the mechanism would require full investigation of human *SMC1A* inactivation (including specifically in relevant tissues) and the extent to which truncated transcripts undergo nonsense-mediated decay. Another valuable line of inquiry would be further definition of the role of *SMC1A* as a transcriptional regulator, whether such transcriptional regulation follows a cyclical pattern, and how this may relate to the clustering pattern of seizures seen.

Finally, it is interesting to note that despite a recent proliferation of large exome sequencing studies investigating children with early onset epilepsy, *SMC1A* has not emerged as an important gene until now. One reason for this may be that recruitment to previous studies has focused on defined electroclinical syndromes such as Ohtahara syndrome, infantile spasms, Dravet syndrome, Lennox-Gastaut syndrome, and epilepsy with myoclonic atonic seizures.[36–40] This series demonstrates that through the investigation of a broader group of children with developmental disorders, genetic syndromes with well-defined phenotypes can emerge.

Summary

SMC1A-truncation mutations are seen only in females, and cause a condition in which the typical features of CdLS are often absent. These patients are all affected by a moderate-to-severe developmental impairment and a drug-resistant epilepsy, which characteristically demonstrates a clustering pattern. Further investigation into how *SMC1A* truncation leads to this phenotype is required. It is likely that disrupted transcriptional regulation of other genes plays an important role.

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Disclosure

None of the authors have any disclosures to make in relation to this manuscript. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Case histories of 10 new *SMC1A* truncation cases.

Table S1. Phenotype details for *SMC1A* patients.