

CHD2 myoclonic encephalopathy is frequently associated with self-induced seizures



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Supplemental data at Neurology.org

ABSTRACT

Objective: To delineate the phenotype of early childhood epileptic encephalopathy due to de novo mutations of *CHD2*, which encodes the chromodomain helicase DNA binding protein 2.

Methods: We analyzed the medical history, MRI, and video-EEG recordings of 9 individuals with de novo *CHD2* mutations and one with a de novo 15q26 deletion encompassing *CHD2*.

Results: Seizures began at a mean of 26 months (12–42) with myoclonic seizures in all 10 cases. Seven exhibited exquisite clinical photosensitivity; 6 self-induced with the television. Absence seizures occurred in 9 patients including typical (4), atypical (2), and absence seizures with eyelid myoclonias (4). Generalized tonic-clonic seizures occurred in 9 of 10 cases with a mean onset of 5.8 years. Convulsive and nonconvulsive status epilepticus were later features (6/10, mean onset 9 years). Tonic (40%) and atonic (30%) seizures also occurred. In 3 cases, an unusual seizure type, the atonic-myoclonic-absence was captured on video. A phenotypic spectrum was identified with 7 cases having moderate to severe intellectual disability and refractory seizures including tonic attacks. Their mean age at onset was 23 months. Three cases had a later age at onset (34 months) with relative preservation of intellect and an initial response to antiepileptic medication.

Conclusion: The phenotypic spectrum of *CHD2* encephalopathy has distinctive features of myoclonic epilepsy, marked clinical photosensitivity, atonic-myoclonic-absence, and intellectual disability ranging from mild to severe. Recognition of this genetic entity will permit earlier diagnosis and enable the development of targeted therapies. *Neurology*® 2015;84:951–958

GLOSSARY

ASD = autism spectrum disorder; **CHD2** = chromodomain helicase DNA binding protein 2; **GSW** = generalized spike wave; **MAE** = epilepsy with myoclonic-atonic seizures.

The epileptic encephalopathies are severe epilepsy syndromes characterized by multiple seizure types and developmental slowing, often associated with regression; many begin in infancy or childhood. The etiology of these disorders is increasingly being recognized as due to de novo genetic mutations with a recent explosion in the number of causative genes identified.^{1,2}

In a cohort of 500 patients, targeted massively parallel sequencing identified de novo *CHD2* mutations as the cause of 6 (1.2%) cases of epileptic encephalopathy and was the fourth most frequently mutated gene after *SCN1A*, *CDKL5*, and *STXBPI*.¹ Two of the 6 patients had been diagnosed with epilepsy with myoclonic-atonic seizures (MAE) but their detailed phenotype was not reported; one had Lennox-Gastaut syndrome with prominent photosensitivity and 3 had nonspecific epileptic encephalopathies. In a later report,³ 3 patients with de novo *CHD2* mutations had an epileptic encephalopathy with fever sensitivity. *CHD2* encodes the

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chromodomain helicase DNA binding protein 2, which likely alters gene expression via chromatin modification. We present the phenotype of *CHD2* encephalopathy in 10 patients including 3 novel cases, further analysis of our 6 published cases, and a case with a 15q26 deletion encompassing several genes including *CHD2*.⁴

METHODS Nine cases were recruited to the Epilepsy Genetics Research Program at the University of Melbourne. They formed part of a large study of patients with epileptic encephalopathies and were identified through genetic testing.¹ Eight had *CHD2* mutations identified via targeted next-generation sequencing of candidate genes for epileptic encephalopathies.¹ Our ninth case harbored a de novo 15q26 deletion including *CHD2* (chr15: 91,027,533–93,477,874 [hg19]; 2.4 Mb).⁴ This case was included because the phenotype closely matched our other cases with *CHD2* encephalopathy. The tenth case was ascertained via whole-exome sequencing of the proband and his parents by the EuroEPINOMICS-RES Consortium. De novo status was confirmed through parental sequencing of *CHD2* in all cases. We reviewed the medical history, video, and EEG recordings of 10 individuals with *CHD2* encephalopathy. Where possible, we reviewed their inpatient video-EEG monitoring records.

Estimates of intellectual disability were made from psychometric testing and educational assessments when available. Autism spectrum disorder (ASD) was diagnosed by a developmental pediatrician. EEG with photic stimulation was performed using the Grass PS33 plus stroboscope. Studies typically included a superimposed pattern protocol together with a protocol in which photic stimulation frequencies were repeated.

Standard protocol approvals, registrations, and patient consents. The participants' parents provided informed consent for participation in the research study. The Austin Health Human Research Ethics Committee approved the study.

RESULTS Seizures. The 10 patients had a mean age of 17.9 years (range 6–36 years) with a mean age at seizure onset of 26 months (10–42 months); 6 were boys (table e-1 on the *Neurology*[®] Web site at Neurology.org). Seven cases presented with daily myoclonic seizures, 4 of whom also had absence seizures at onset. Seizure onset was explosive in 6 individuals with multiple daily myoclonic and absence seizures.

All patients developed multiple seizure types. Myoclonic seizures occurred in all and were symmetric, involving the upper limbs. Myoclonus was both spontaneous and triggered by environmental photic stimuli in 6. A seventh case self-induced generalized tonic-clonic seizures with the television; other reflex seizures were not seen. Absence seizures occurred in 9 cases, including typical (4), atypical absence (2), and eyelid myoclonia with absence (4). Prolonged absence seizures and focal dyscognitive seizures were not observed.

The pattern evolved with the development of tonic seizures in 4 patients at a mean of 3.6 years,

typically nocturnal, and atonic seizures in 3 at a mean of 4.5 years. Generalized tonic-clonic seizures were a later feature, present in 9 patients with a mean onset of 5.8 years. The pattern of generalized tonic-clonic seizures and tonic seizures changed from seizures at any time to predominantly from sleep after 8 years.

Convulsive status epilepticus began at a mean of 9.7 years in 3, and nonconvulsive status in 5 at mean 9.2 years. Nonconvulsive status epilepticus often included prominent myoclonic components. Fever was not a prominent trigger; only one boy had febrile seizures at 2 years.

The waking interictal EEG showed mild diffuse background slowing at seizure onset in 7 patients. The degree of slowing did not correlate with the degree of intellectual disability.

Bursts of generalized spike wave (GSW) and generalized polyspike wave were frequently seen awake and often markedly increased in sleep. GSW was often slow at a frequency of 2 to 2.5 Hz (range 1–5 Hz) with a frontal predominance. The GSW was brought out by eye closure in 3 patients.

Cases 1, 3, and 4 (at 20, 13, and 6 years, respectively) progressed to abundant, almost continuous slow spike wave that activated in sleep. Cases 1, 2, and 8 exhibited interictal multifocal epileptiform activity (table e-1).

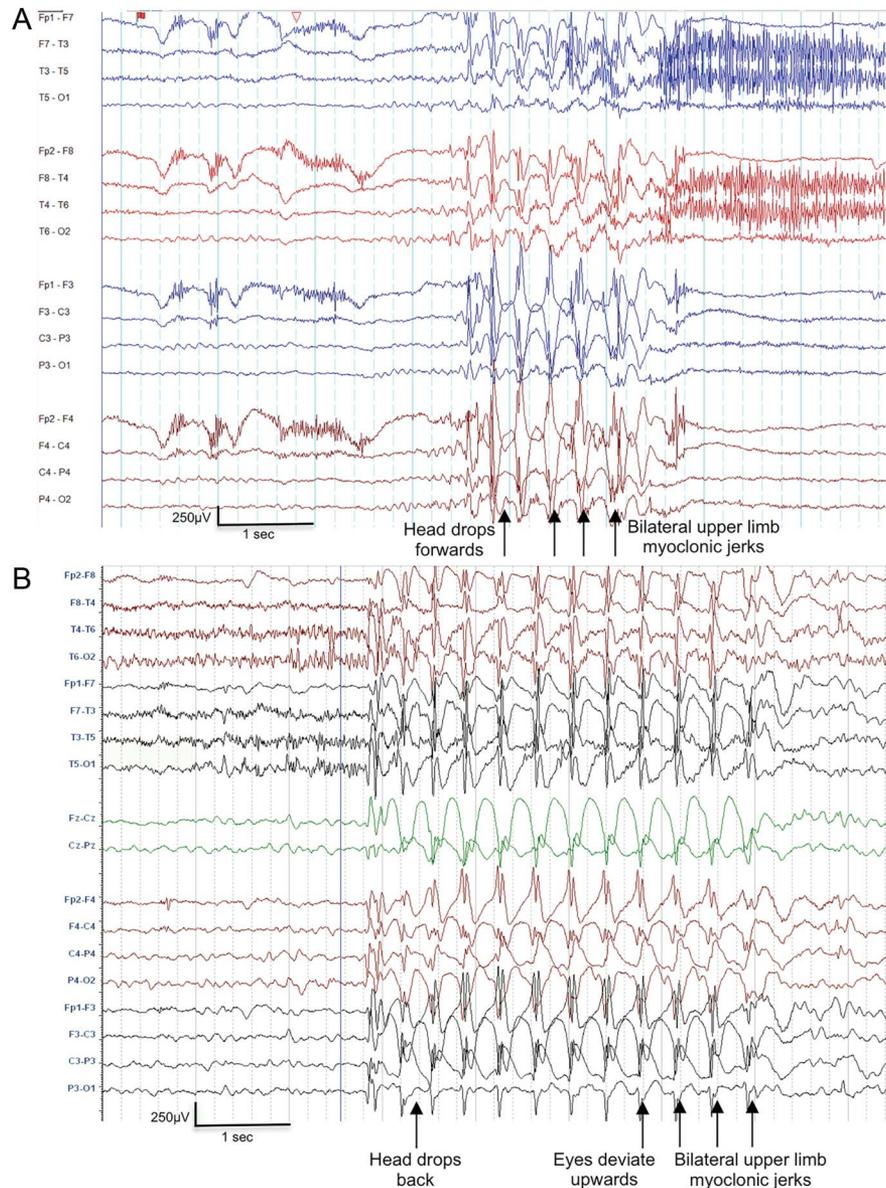
Atonic-myoclonic-absence seizure. An unusual seizure type was observed in 3 patients (cases 3, 4, 5) on home videos and had a mean onset of 22 months (table e-1, figure 1, videos 1–5). These seizures commenced with an atonic component causing an abrupt head nod or atonic fall with simultaneous eye elevation. The patients sometimes sustained injuries with the sudden loss of tone. The seizure progressed to a myoclonic absence phase characterized by ratchet-like tonic abduction of the upper limbs; myoclonic activity began while truncal atonia was still present. Seizures were brief, lasting 2 to 8 seconds, with rapid return of awareness. We termed this distinctive seizure type as an “atonic-myoclonic-absence seizure.”

The ictal EEG showed paroxysms of 3- to 4-Hz GSW and generalized polyspike wave activity (figure 1). The atonic component of the atonic-myoclonic-absence seizure correlated with the aftergoing slow wave of the initial GSW discharge, and each myoclonic jerk corresponded with the spike of the spike wave complex (figure 1).

This seizure type was noted only in children aged 2 to 7 years and captured on home video. Patient 5 also had seizures recorded at 14 and 18 years that resembled typical myoclonic absence seizures without the preceding atonic component (videos 6 and 7).

Photosensitivity. Seven of 10 patients exhibited extreme clinical photosensitivity with atonic myoclonic absence

Figure 1 EEG of atonic-myoclonic-absence seizure



(A) Case 4, aged 14 years. Bipolar montage; (B) Case 5, aged 5.5 years. Bipolar montage. Ictal recordings show a paroxysm of 3 Hz generalized polyspike wave activity. The seizure begins with the head dropping forward or backward followed by bilateral myoclonic ratcheting abduction of the upper limbs. The jerks correlate with the spike of the spike wave complex.

or absence seizures with eyelid myoclonia (table e-1). Six patients were compelled to self-induce these seizures by placing their face adjacent to the television screen and had to be restrained from this activity (video 5). In addition, case 1 had seizures induced by the repetitive flash of a digital camera as an infant. In contrast to the striking clinical history of photosensitivity, only one case (8) had a recorded photoparoxysmal response on EEG. This comprised a grade 4 response showing GSW across all frequencies. No cases demonstrated head turning toward a light stimulus or “hand-flapping” in sunlight to induce seizures.

Developmental course and behavioral features. Development was normal in the first year of life in all 10 patients. All patients walked by 18 months. Speech delay became evident between 1 and 2 years and preceded seizure onset (table 1). Seven had moderate to severe intellectual disability and 3 had mild impairment (table e-1, figure 2). Six of the 7 more-severe cases had a history of regression that correlated temporally with the explosive onset of seizures. In general, regression tended to occur during periods of seizure exacerbation. At the milder end, case 8 was succeeding in mainstream schooling until he first regressed at age 9 years with seizure recurrence;

Table 1 Comparison of electroclinical features of CHD2 encephalopathy with Dravet syndrome, epilepsy with myoclonic-atonic seizures, and Lennox-Gastaut syndrome

	CHD2 encephalopathy (n = 10) ¹	CHD2 encephalopathy (other groups) ^{3,7,21} (n = 5)	Dravet syndrome ^{9,10}	Epilepsy with myoclonic-atonic seizures ^{5,10}	Lennox-Gastaut syndrome ²²
Age at onset	1-4 y	6 mo to 3.5 y	5-8 mo	7 mo to 6 y	Peak 3-8 y
Family history of epilepsy	3/10	Not reported	~50%, often GEFS+ ^{9,23}	32%, often GEFS+ ²⁴	Unusual
Febrile seizures	1/10	3/5	Usual	33%	Unusual
Tonic seizures	4/10; mean onset 3 y, 7 mo	2/5	Unusual, late	Rare, late	Always
Developmental delay before seizure onset	9/10	2/5	No	Rare	Often
Seizure remission	Controlled in 3/10 for 2-5 y	No	No	Common, seizures abate at 3 y in 50%	No
EEG	GSW, GPSW	GSW, GPSW	GSW, GPSW; multifocal epileptiform discharges	Biparietal theta, GSW, GPSW	Diffuse slow spike wave, low-voltage fast activity in sleep
Photosensitivity clinical	7/10, 6/10 self-induce	Not reported, not reported in 4	16% self-induce, 2% with TV	Not documented	Very rare
Photosensitivity electrical	1/10 EEG	Present in one ¹⁹	45% EEG ¹⁰	28% EEG ^{6,8}	
MRI brain	Progressive atrophy in 3/10, corpus callosum atrophy in 3/10	Mild atrophy 1/5	Normal	Normal	Often abnormal
Intellectual disability	3/10 mild, 7/10 severe	1/5 severe, 3/5 mild, 1/5 not reported	25% mild, 25% moderate, 50% severe	Variable, often normal	Most

Abbreviations: GEFS+ = genetic epilepsy with febrile seizures plus; GPSW = generalized polyspike wave; GSW = generalized spike wave.

multiple seizures occurred and proved refractory to treatment. Case 9 had speech regression at 24 months.

Four patients had a formal diagnosis of ASD in addition to their intellectual disability. One also had attention deficit hyperactivity disorder as did 2 without ASD. Challenging behavior was reported in 8 patients and was independent of the degree of intellectual disability. It primarily involved aggressive behavior, and required risperidone in 3 cases. In addition, patient 10 developed a prominent psychotic illness at 19 years requiring hospitalization and quetiapine.

Five individuals have reached adulthood. They showed a broad spectrum of disability, with case 1 (31 years) at the severe end of the spectrum being fully dependent on others for support, whereas case 9 (35 years) had the second mildest outcome in our series. She lived at home with her family and never worked but sang in a choir for “disadvantaged” people.

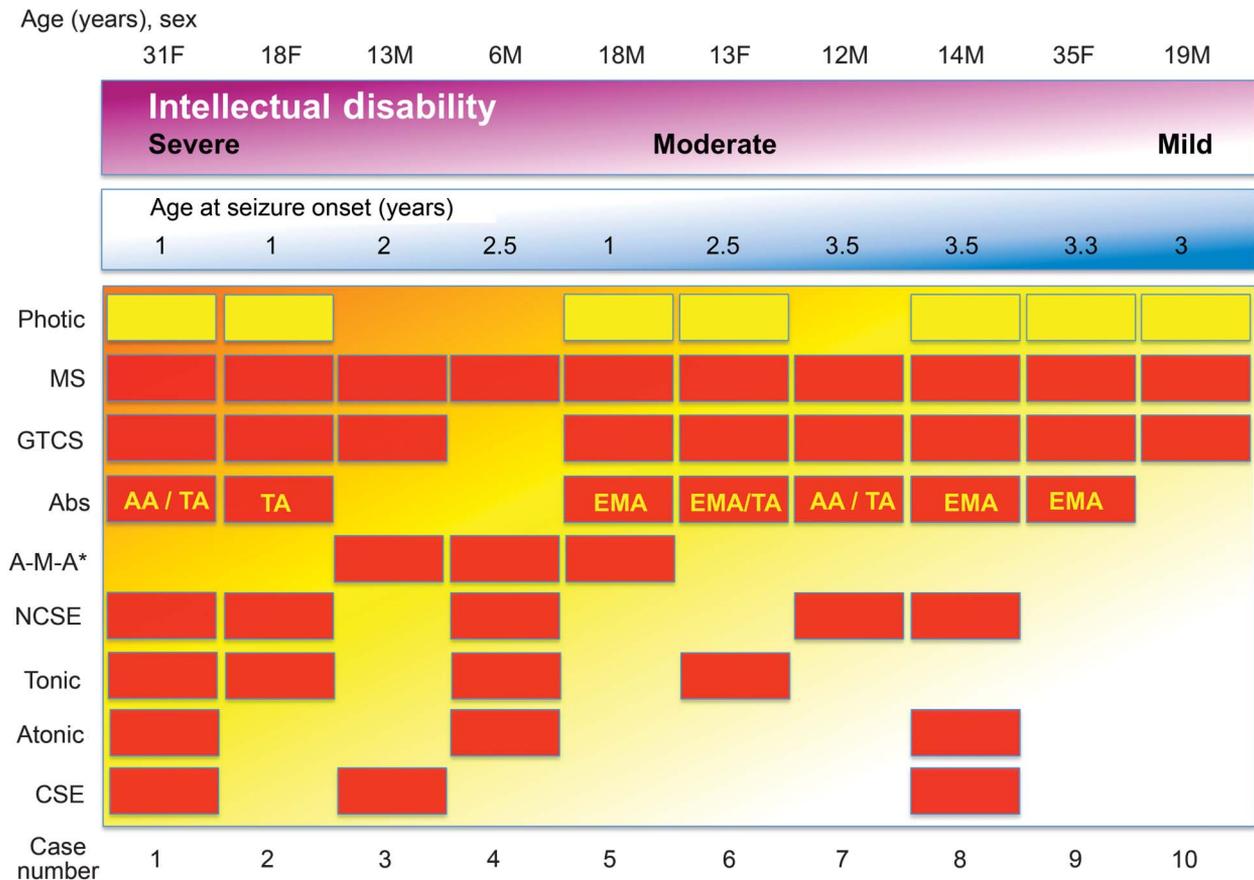
Four individuals had short stature (less than third centile) and the 2 most severe cases had head circumferences less than third centile (table e-1) but there were no consistent dysmorphic features. Neurologic examination was normal. Five patients had a crouch gait and 4 had ataxia. At 5 years, case 3 exhibited chorea with facial dyskinesia and ataxia that improved after the withdrawal of sodium valproate. While case 5 at 9 years had ataxia and vomiting associated with valproate, ataxia in case 8 from age 13 years was independent of the withdrawal and reintroduction of sodium valproate.

Seizures remained refractory to treatment in 7 of 10 cases; 3 cases, before the age of 10 years, had a period of seizure control of more than a year’s duration. Three individuals trialed the ketogenic diet, which did not produce significant benefit.

Neuroimaging. MRI brain studies were reviewed in 7 cases and showed progressive atrophy in 3 of 4 individuals with sequential studies (figure 3, table e-1). Parenchymal atrophy was most marked posteriorly and associated with atrophy of the splenium of the corpus callosum and mild diffuse cerebellar atrophy in 3 cases (figure 3). Case 8 had a combination of callosal truncation (presumably developmental) and progressive atrophy. Two of the 4 cases with ataxia had cerebellar atrophy on MRI. Generalized atrophy correlated to some extent with the degree of intellectual disability as the 2 mildest cases (9 and 10) had normal MRI scans in adult life. White matter maturation was age-appropriate and hippocampal sclerosis was not seen.

Molecular results. Our cohort included 3 new cases with novel mutations, 6 from our previous

Figure 2 *CHD2* encephalopathy spectrum



CHD2 encephalopathy presents with a spectrum of severity including age of seizure onset, intellectual outcome, and seizure types. Cases are ranked by their level of intellectual disability and age at onset. All cases had myoclonic seizures and 7 had photic-induced seizures. Cases with a milder intellectual disability had fewer seizure types and were less likely to have atonic seizures, tonic seizures, and convulsive status epilepticus. Photic seizures were equally likely across the spectrum. *A-M-A is likely to be underrecognized. AA = atypical absence; Abs = all absence seizure types; A-M-A = atonic-myoclonic-absence seizure; CSE = convulsive status epilepticus; EMA = absence with eyelid myoclonia; GTCS = generalized tonic-clonic seizures; MS = myoclonic seizures; NCSE = nonconvulsive status epilepticus; TA = typical absence.

publication identifying the role of *CHD2* in epileptic encephalopathies,¹ and one from our study of copy number variants.⁴ All cases have de novo mutations. Seven had mutations resulting in premature truncation, 2 had missense mutations, and case 9 had a 2.4-Mb deletion that included the 5' end of *CHD2* resulting in a partial gene deletion.³ The phenotype of this patient was consistent with *CHD2* encephalopathy. The location of the mutations is shown in figure 4.

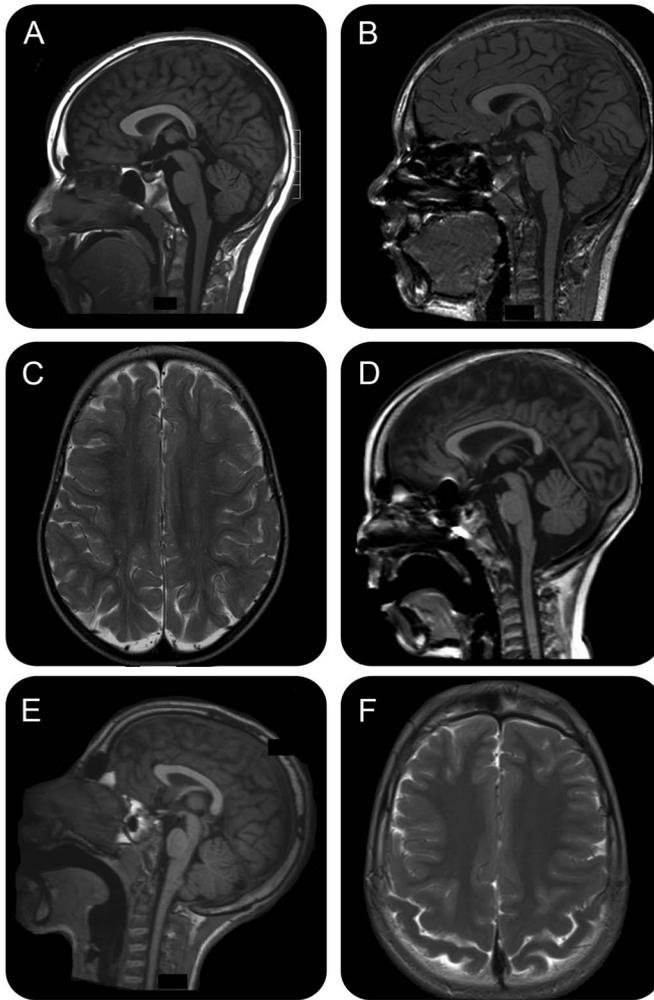
DISCUSSION With the recent explosion in gene discovery, an increasing number of novel genetic epileptic encephalopathies are being recognized. In contrast to Dravet syndrome in which the electroclinical phenotype was described well before the genetic finding of *SCN1A* mutations, we are now in a position to delineate the electroclinical phenotype of patients who share the same genetic cause. The power of massively parallel sequencing to rapidly and inexpensively screen panels of known genes¹ makes possible the recognition of

novel electroclinical syndromes through deep phenotypic analysis following gene identification.

CHD2 encephalopathy begins in the second year of life and is characterized by myoclonic, absence, and generalized tonic-clonic seizures and clinical photosensitivity. We distinguished a spectrum of severity in terms of age at onset, epilepsy severity, and cognitive outcome (figure 2). Microcephaly occurred in only the 2 most severe cases. Mean seizure onset in our 10 cases was 26 months with the more severe end of the spectrum (7 cases) having a mean onset of 23 months vs 34 months at the milder end (3 cases) (figure 2). *CHD2* encephalopathy is associated with refractory epilepsy but, in the milder cases, a period of seizure freedom of more than a year may occur. The hallmark of *CHD2* encephalopathy, self-induced photic seizures with the television, was common across the spectrum.

The severe phenotype was characterized by moderate to severe intellectual disability and tonic seizures. A similar pattern is described in other epileptic

Figure 3 MRI of *CHD2* encephalopathy



MRIs demonstrating progressive posterior atrophy. (A, B) Case 8 sagittal T1 MRIs at 10 years (A) and sagittal T1 at 11 years (B) demonstrate a truncated, hypoplastic corpus callosum with progressive atrophy and an atrophic cerebellar vermis. (C, D) Case 3 axial T2 at 2 years (C) and T1 sagittal at 7 years (D) demonstrate generalized atrophy more marked posteriorly and atrophic cerebellar vermis. The callosal atrophy is also more pronounced posteriorly. (E, F) Case 6 sagittal T1 (E) and axial T2 (F) at 12 years demonstrate generalized atrophy more prominent posteriorly.

encephalopathies such as MAE in which the severe cases develop tonic seizures.⁵

We identified an unusual seizure type beginning with atonia and followed by myoclonic absence (videos 1–5, figure 1), which we coined an atonic-myoclonic-absence seizure. It is unclear whether this seizure type occurs in all cases as we first recognized it through home videotapes in a few cases. It may be an age-dependent seizure type and therefore only recordable for a limited time. It is of interest that these appear to have the inverse sequence of classic myoclonic-atic seizures whereby a single myoclonic jerk heralds the onset of the seizure followed by atonia.⁶ Patient 8 had a history of seizures that was suspicious of the atonic-myoclonic-absence seizure type at age 2.5 years, but video was not captured.

Confirmation of this seizure type using video-EEG with EMG is required to determine whether it is sensitive and specific for *CHD2* encephalopathy.

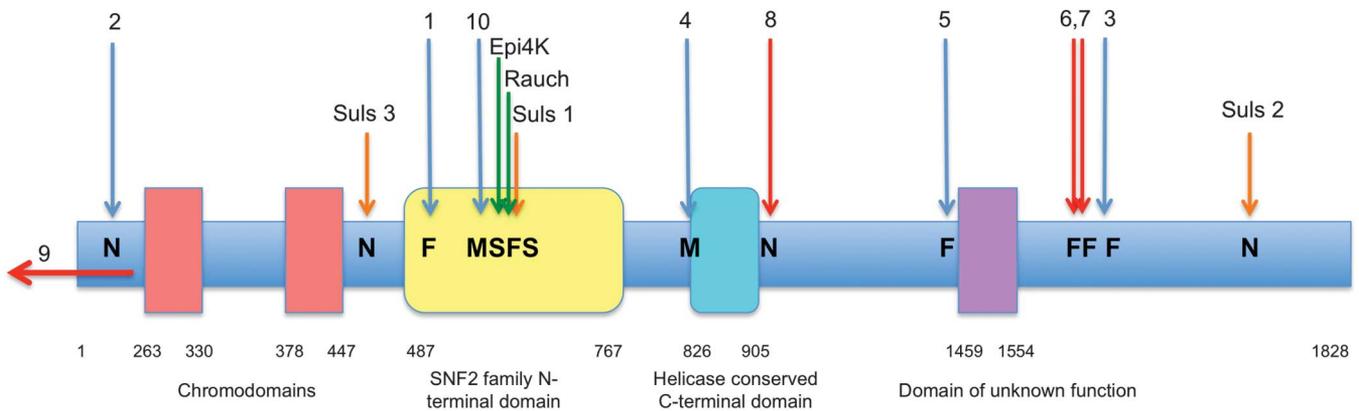
How were these patients previously conceptualized regarding their epilepsy syndrome? While 4 cases were thought to have severe genetic (formerly idiopathic) generalized epilepsies, 3 had been previously diagnosed with MAE,¹ described by Doose et al.⁷ This was partly because of their prominent drop attacks and the explosive onset of multiple seizure types associated with GSW. While these epilepsies share many features, there are elements that distinguish them (table 1). First and foremost, the *CHD2* encephalopathy cases do not have the archetypal seizure that defines the syndrome of MAE, the myoclonic-atic seizure. In contrast to MAE, *CHD2* encephalopathy has the following features: (1) development is usually delayed before seizure onset; (2) seizure remission may occur in milder cases; and (3) clinical photosensitivity is seen in the majority of cases compared with less than a third of patients with MAE.⁸ It was surprising that only one patient showed electrical photosensitivity despite the marked clinical photosensitivity in 7 cases and self-induction with television screens seen in 6 patients.

CHD2 encephalopathy can be readily distinguished from Dravet syndrome by its later mean seizure onset of 26 months compared with 6 months, its high frequency of clinical photosensitivity compared with <50%, and the archetypal feature of self-induced seizures, which is much rarer in Dravet syndrome (table 1).^{9,10} The paucity of febrile seizures and abnormal development before seizure onset are also key features that separate *CHD2* encephalopathy from Dravet syndrome.

Three patients have been recently described with *de novo* mutations who had mild intellectual disability, epileptic encephalopathy, and a predilection to seizures with fever (table 1, figure 4).³ Clinical photosensitivity was not noted. One case had ASD and 2 had ataxia, one of whom showed atrophy on MRI in keeping with our findings. We observed a more posterior pattern of atrophy involving the parenchyma and corpus callosum with additional cerebellar involvement in those cases with ataxia.

Our findings are consistent with the previous case reports in the literature of copy number variants incorporating *CHD2* and intragenic *CHD2* mutations (figure 4). The most similar phenotype of photosensitive myoclonic encephalopathy was reported in a girl with a large 5-Mb deletion that included 56 genes.¹¹ Among her seizure types was “massive myoclonias with head drop associated with irregular spike and slow waves,”¹¹ reminiscent of the atonic-myoclonic-absence seizure. MRI demonstrated cerebellar hypoplasia with thinning of the posterior body

Figure 4 Location of mutations in *CHD2*



The location of all reported de novo *CHD2* mutations associated with epilepsy is shown. The red arrows denote the 3 novel mutations reported here, blue arrows our 6 cases in Carvill et al.,¹ orange arrows the 3 Suls et al.³ cases, and green arrows the single cases of Epi4k² and Rauch et al.¹² Suls 1 is an approximated position based on where the splice site mutation is predicted to truncate the protein.³ The arrow (case 9) represents the partial gene deletion. F = frameshift; M = missense mutation; N = nonsense mutation; S = splice site mutation.

of the corpus callosum. She had multiple dysmorphic features that were not evident in our cases and may relate to deletion of other genes. An earlier onset of seizures at 6 months was noted in the single case with a de novo splice site mutation from the EPI4K study.¹¹ A de novo *CHD2* mutation has also been reported in a child with intellectual disability and absence epilepsy (T604Lfs*19)¹² and another case with ASD alone (D856G).¹³

Case 9 had a chromosome 15q26 microdeletion that results in partial deletion of *CHD2*. Her phenotype was consistent with *CHD2* encephalopathy but, remarkably, given the number of contiguous genes deleted, was at the mild end of the *CHD2* phenotypic spectrum. Of the 5 published cases with deletions of varying size that encompass *CHD2*, all had seizures and 4 had delayed development before seizure onset at 6 to 48 months. Intellectual disability was mild to severe.^{11,14–17}

The missense, nonsense, frameshift, and splice site mutations in *CHD2* encephalopathy do not cluster in any definite pattern within the gene (figure 4), and the location or type of mutation does not correlate with disease severity. *CHD2* is among the genes that are most intolerant to functional variation (ranked in top 2.5%).¹⁸ In keeping with this, all functional variation in the exome variant server are missense changes, and only 2 missense changes in 6,500 individuals are in the SNF2 (sucrose non-fermentable 2) domain (figure 4). Notably, 8 of 10 mutations reported here cause premature truncation; only 2 cases carry missense mutations and both lie within highly conserved helicase domains. Therefore, the phenotype in patients with *CHD2* encephalopathy is likely due to haploinsufficiency of the CHD2 protein.

It is thought that *CHD2* belongs to the SNF2-like family of ATPase (adenosine triphosphatase) proteins

that have a role in chromatin remodeling and therefore may affect transcription of many genes. However, our knowledge of the function of *CHD2*, particularly in the brain, is incomplete and warrants further investigation to delineate its biological role. Sodium valproate, one of the key antiepileptic drugs for myoclonic and generalized epilepsies, inhibits histone deacetylase activity and alters chromatin structure.¹⁹ Valproate was generally a favorable drug for patients with *CHD2* encephalopathy.

Knocked down *chd2* zebrafish exhibit a seizure-like phenotype as well as structural abnormalities of microcephaly, body curvature, absent swim bladder, and stunted growth.³ A murine *Chd2* model confirmed that the CHD2 protein is widely expressed during development in many tissues, although no aberrations were noted in the brain.²⁰

CHD2 mutations produce a distinctive myoclonic epileptic encephalopathy with prominent clinical photosensitivity in the majority of cases. The atonic-myoclonic-absence seizures may prompt investigation for a *CHD2* mutation. Recognition of *CHD2* encephalopathy will lead to improved diagnosis for patients and families. Understanding the neurobiology of this disorder will form the basis for the development of genetically targeted therapies to improve outcome of this severe epileptic encephalopathy.

AUTHOR CONTRIBUTIONS

R.H. Thomas: draft/revise manuscript, data analysis, acquisition of data. L.M. Zhang: draft manuscript, data analysis, acquisition of data. G.L. Carvill: revise manuscript, data analysis, acquisition of data. J.S. Archer: revise manuscript, data analysis. S.B. Heavin: revise manuscript, acquisition of data. S.A. Mandelstam: revise manuscript, data analysis. D. Craiu: revise manuscript, acquisition of data. EuroEPINOMICS-RES Consortium: acquisition of data. S.F. Berkovic: revise manuscript, acquisition of data. D.S. Gill: revise manuscript, acquisition of data. H.C. Mefford: revise manuscript, study design, data analysis, acquisition of data, obtain

funding. I.E. Scheffer: draft/revise manuscript, study design, data analysis, acquisition of data, obtain funding.

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