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# Phenotypic Spectrum of Seizure Disorders in MBD5-Associated Neurodevelopmental Disorder

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## Abstract

### Objective

To describe the phenotypic spectrum in patients with MBD5-associated neurodevelopmental disorder (MAND) and seizures; features of MAND include intellectual disability, epilepsy, psychiatric features of aggression and hyperactivity, and dysmorphic features including short stature and microcephaly, sleep disturbance, and ataxia.

### Methods

We performed phenotyping on patients with *MBD5* deletions, duplications, or point mutations and a history of seizures.

### Results

Twenty-three patients with MAND and seizures were included. Median seizure onset age was 2.9 years (range 3 days–13 years). The most common seizure type was generalized tonic-clonic; focal, atypical absence, tonic, drop attacks, and myoclonic seizures occurred frequently. Seven children had convulsive status epilepticus and 3 nonconvulsive status epilepticus. Fever, viral illnesses, and hot weather provoked seizures. EEG studies in 17/21 patients were abnormal, typically showing slow generalized spike-wave and background slowing. Nine had drug-resistant epilepsy, although 3 eventually became seizure-free. All but one had moderate-to-severe developmental impairment. Epilepsy syndromes included Lennox-Gastaut syndrome, myoclonic-atonic epilepsy, and infantile spasms syndrome. Behavioral problems in 20/23 included aggression, self-injurious behavior, and sleep disturbance.

### Conclusions

*MBD5* disruption may be associated with severe early childhood-onset developmental and epileptic encephalopathy. Because neuropsychiatric dysfunction is common and severe, it should be an important focus of clinical management.

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## Glossary

**DS** = Dravet syndrome; **FS+** = febrile seizures plus; **LGS** = Lennox-Gastaut syndrome; **MAE** = myoclonic-atonic epilepsy; **MAND** = *MBD5*-associated neurodevelopmental disorder.

*MBD5* (methyl-CpG-binding domain protein 5; OMIM #611472), located on chromosome 2q23.1, belongs to a family of genes involved in DNA methylation and chromatin remodeling.[1] Disruption of this gene through heterozygous deletion or point mutation leads to *MBD5*-associated neurodevelopmental disorder (MAND), with some patients described as having a Kleefstra syndrome phenotypic spectrum.[2] Intellectual disability occurs in all patients, with seizures, dysmorphic features including short stature and microcephaly, sleep disturbance, ataxia, aggressive behavior, and hyperactivity frequently observed.[3–5] *MBD5* deletions are not especially rare, found in 0.05% (1 in 2,000) of 17,477 samples that underwent clinical microarray testing.[3] Deletions or mutations are almost always de novo although inheritance from mildly affected or mosaic parents has been reported.[6]

Seizures occur in over 80% of patients with MAND; however, the epileptology has not yet been delineated.[3–5,7] Here, we analyzed the phenotypic spectrum in 23 patients with heterozygous deletion, duplication, or point mutation of *MBD5* and a history of seizures.

## Methods

We searched our epilepsy genetics research databases for patients with pathogenic variants involving *MBD5* and identified 9 individuals. Two patients were identified through the Epi4K research testing program.[8] Fourteen additional families volunteered to participate after social media patient groups brought attention to our research. Patients were ascertained from Australia, Italy, New Zealand, Finland, Canada, Germany, the United Kingdom, and the United States. We conducted personal interviews with all patients' families and reviewed medical records, EEG, neuroimaging, and genetic testing results. For medication response, we classified drugs as effective if caregivers reported a clear reduction in seizure frequency, even if seizures were not completely controlled. Wherever possible, epilepsy syndromes were classified according to the International League Against Epilepsy classification.[9,10] Genetic variants were classified per American College of Medical Genetics and Genomics guidelines.[11,12]

### Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent was provided for all patients by a parent or legal guardian. This study was approved by the Human Research Ethics Committee, Austin Health, or the local ethics committee.

### Data Availability

Anonymized data will be shared by request from any qualified investigator.

## Results

Twenty-three patients from 22 families were identified with a history of seizures in the context of a *MBD5* molecular lesion.

### Genetic Findings

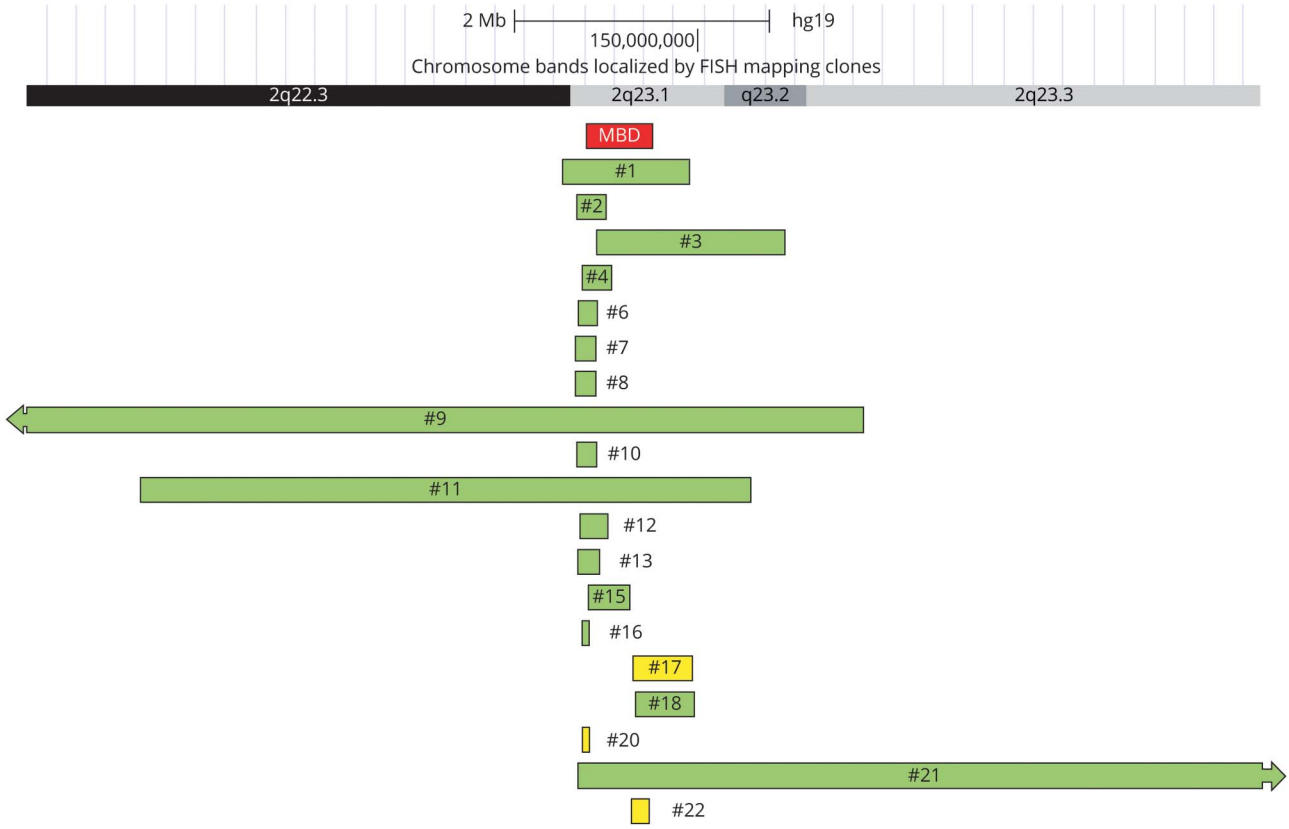
Nineteen of the 23 patients had heterozygous 2q23.1 deletions: 15 resulted in partial deletion of *MBD5* (11 proximal, 3 distal, and 1 data not available) and 4 had complete loss of *MBD5* (figure 1, table 1). Two patients had 2q23 microduplications with partial *MBD5* duplication (1 distal and 1 intragenic). The remaining 2 patients had point mutations resulting in truncation: p.Arg200* and p.Thr157Glnfs*4 (previously published[13]).

Pathogenic variants were de novo in 9 patients, with results from both parents not available in 10. Mutations were inherited from a mosaic parent in 4 patients from 3 families (figure 2). Patients 7 and 8 were brothers whose mosaic mother (20%–30% mosaicism in blood) had mild-moderate intellectual disability, but no history of seizures. Patient 13 had a mosaic carrier father (36% mosaicism in blood) of normal intellect and no history of seizures. Her older brother also inherited the deletion and had autism spectrum disorder and intellectual disability, without seizures. Patient 19 had parents who both tested negative for his mutation on blood-derived DNA; however, chorionic villus sampling of their next pregnancy showed that the fetus carried the mutation and the pregnancy was terminated. This suggested that 1 parent must be mosaic, with the mutation possibly limited to gonadal tissue. Patient 12 was mosaic for his deletion, affecting ~65% of cells in saliva. The results of other genetic testing performed are given in table e-1, links.lww.com/NXG/A402.

### Seizures

Seizures began at median age 2.9 years (range 3 days to 13 years; table 2). Bilateral tonic-clonic seizures occurred in 19/23 (83%) patients, with focal impaired awareness seizures (FIAS; 9/23; 39%), tonic (8/23; 35%), unclassified drop attacks (7/23; 30%), myoclonic (7/23; 30%), atypical absences (7/23; 30%), myoclonic-atonic (1/23; 4%), atonic (1/23; 4%), hemiclonic (1/23; 4%), unclassified staring spells (absences vs FIAS; 1/23; 4%), and epileptic spasms (1/23; 4%) also observed. Convulsive status epilepticus occurred in 7/23 (30%) patients and nonconvulsive status epilepticus in 3/23 (13%). Fever and viral illnesses provoked seizures in 11

**Figure 1** Copy Number Variants of Patients With MBD5-Associated Neurodevelopmental Disorder




Green denotes deletion; yellow denotes duplication. This figure includes a screenshot from UCSC genome browser (genome.ucsc.edu).

patients; 1 patient's seizures were triggered by painful stimuli (e.g., mild accidental falls to the ground).

The most common interictal EEG findings were diffuse background slowing (11/23; 48%) and generalized spike-wave or polyspike-wave activity (10/23; 43%). Focal slowing and/or multifocal epileptiform discharges occurred in 9/23 (39%) patients. Epilepsy syndromes were defined in 7 patients: 3 had Lennox-Gastaut syndrome (LGS), 2 had myoclonic-atonic epilepsy (MAE), 1 had infantile spasms syndrome, and 1 had febrile seizures plus (FS+).

Ten patients had drug-resistant epilepsy. Although no drug was clearly superior, valproate showed the most consistent beneficial effect (12/14 cases), while carbamazepine exacerbated seizures in patient 2. Patient 2 became seizure-free during periods of illness and had dramatic reduction in seizure frequency on the ketogenic diet. Ketogenic diet therapy was also trialled in patient 5 with no benefit.

Twenty-one patients had available brain MRI results, with normal findings in 17/21 (85%). Of the patients with abnormal MRI, none had epileptogenic lesions (table 3). Patient 12 had a normal MRI, but fluorodeoxyglucose PET showed severe hypometabolism in the temporoparietal and occipital regions bilaterally.

## Development and Behavior

Developmental impairment was present in all patients: severe in 14, moderate in 8, and mild in 1 (table 3). Regression with seizures occurred in 5 patients. The most dramatic regression occurred in patient 2 whose early developmental milestones were normal to mildly delayed (sat at 8 months, walked at 17 months, and first word at 12 months). When seizures began at age 2 years, there was marked developmental regression, particularly involving language. By age 4 years, he had only single words that were mostly unintelligible.

Marked behavioral difficulties were reported in 16 patients, with hyperactivity and aggression most common. Self-injurious behaviors occurred frequently, including finger and nail biting, scratching and picking lips until they bled. Behavioral difficulties were not controlled by stimulants, antipsychotics, and sedatives although methylphenidate elicited some benefit. Sleep disturbance during childhood was reported in 17 patients and involved frequent nocturnal awakenings. Nine patients had microcephaly.

Three patients had signs of metabolic dysfunction, which were considered coincidental. Patient 2 had decreased biotinidase activity suggesting a partial biotinidase deficiency; his parents reported some improvement in seizure control with biotin therapy. Patient 5 had borderline hypoglycorrhachia on

**Table 1** Heterozygous Pathogenic Variants and Affecting *MBD5*

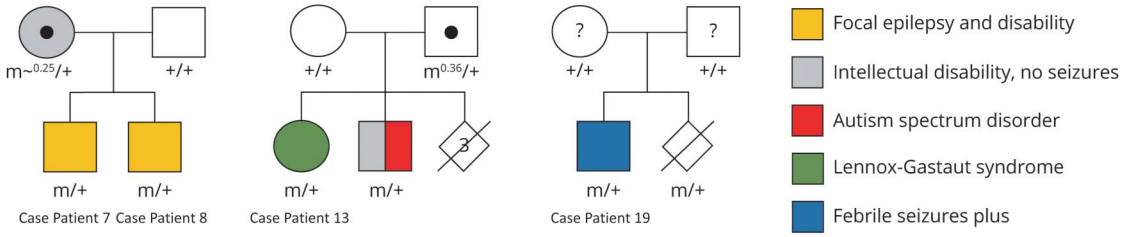
| No. | *MBD5* effect; inheritance | Del/Dup size | Breakpoints (build) | Genes affected |
|---|---|---|---|---|
| **1** | Complete deletion; de novo | 2.2 Mb | SNP-A-189490 to SNP-A-226411 | *ACVR2A*, *ORC4*, *MBD5*, *EPC2* |
| **2** | Proximal deletion (exons 1–2); N/A | 0.2 Mb | 148734048-148932576 (Hg19) | *ORC4*, *MBD5* |
| **3** | Distal deletion (exons 3–15); N/A | 1.5 Mb | 148839546-150345992 (Hg19) | *MBD5*, *EPC2*, *KIF5C*, *LYPD6B*, *LYPD6* |
| **4** | Proximal deletion (exons 1–3); de novo | 0.2 Mb | 148489085-148678668 (Hg18) | *ORC4*, *MBD5* |
| **5** | p.Thr157Glnfs*4 truncation; de novo | N/A | N/A | *MBD5* |
| **6** | Proximal deletion (exons 1–2); de novo | 0.1 Mb | 148715661-148842706 (Hg19) | *ORC4*, *MBD5* |
| **7** | Proximal deletion (exons 1–2); inherited (mosaic mother) | 0.1 Mb | 148669363-148788392 (Hg19) | *ACVR2A*, *ORC4*, *MBD5* |
| **8** | Proximal deletion (exons 1–2); inherited (mosaic mother) | 0.1 Mb | 148669363-148788392 (Hg19) | *ACVR2A*, *ORC4*, *MBD5* |
| **9** | Complete del; N/A | 10.1 Mb | 141060000-151150000 (Hg18) | *LRP1B*, *KYNU*, *ARHGAP15*, *GTDC1*, *ZEB2*, *ACVR2A*, *ORC4*, *MBD5*, *EPC2*, *KIF5C*, *LYPD6B*, *LYPD6*, *MMADHC*, *RND3* |
| **10** | Proximal deletion (exons 1–2); de novo | 0.1 Mb | 148703861-148829749 (Hg19) | *ORC4*, *MBD5* |
| **11** | Complete deletion; N/A | 3.7 Mb | 146855669-150602070 (Hg19) | *ACVR2A*, *ORC4*, *MBD5*, *EPC2*, *KIF5C*, *LYPD6B*, *LYPD6*, *MMADHC* |
| **12** | Proximal deletion (exons 1–3); de novo (mosaic; 65% cells) | 0.2 Mb | 148758479-148954077 (Hg19) | *ORC4*, *MBD5* |
| **13** | Proximal deletion (exons 1–2); inherited mosaic father) | 0.2 Mb | 148734046-148897348 (Hg19) | *ORC4*, *MBD5* |
| **14** | Partial deletion; N/A | 0.2 Mb | Not available | Not available |
| **15** | Proximal deletion (exons 1–4); N/A | 0.3 Mb | 148462331-148741534 (Hg18) | *ORC4*, *MBD5* |
| **16** | Proximal deletion (exons 1–2); N/A | 0.05 Mb | 148755020-148802565 (Hg19) | *ORC4*, *MBD5* |
| **17** | Distal duplication (exons 7–15); N/A | 0.4 Mb | 149218851-149655290 (Hg19) | *MBD5*, *EPC2*, *KIF5C* |
| **18** | Distal deletion (exons 7–15); de novo | 0.6 Mb | 149219863-149796844 (Hg19) | *MBD5*, *EPC2*, *KIF5C* |
| **19** | c.598C > T; p.Arg200* (truncation); inherited (parent mosaic) | N/A | N/A | *MBD5* |
| **20** | Proximal deletion (exons 1–2); N/A | 0.02 Mb | 148764203-148786336 (Hg19) | *ORC4*, *MBD5* |
| **21** | Complete deletion; de novo | 6.5 Mb | 148438001-154962504 (Hg19) | *ACVR2A*, *ORC4*, *MBD5*, *EPC2*, *KIF5C*, *LYPD6B*, *LYPD6*, *MMADHC*, *RND3*, *RBM43*, *NMI*, *TNFAIP6*, *RIF1*, *NEB*, *ARL5A*, *CACNB4*, *STAM2*, *FMNL2*, *PRPF40A*, *ARL6IP6*, *RPRM*, *GALNT13* |
| **22** | Intragenic duplication (exon 5); de novo | 0.085 Mb | 149052433-149137634 (Hg19) | *MBD5* |
| **23** | Distal deletion (exons 6–15); de novo | 0.789 Mb | 148914820-149703672 (Hg18) | *MBD5*, *EPC2*, *KIF5C*, *LYPD6B* |

Abbreviations: N/A = inheritance unknown; MLPA = multiplex ligation-dependent probe amplification, WES = whole exome sequencing, WGS = whole genome sequencing.

lumbar punctures at 8 and 10 years (CSF glucose 2.9 and 2.2 mM with CSF:serum ratios of 0.41 and 0.43, respectively). Patient 20 was diagnosed with galactosemia on newborn screening.

Although our cohort is relatively small, we looked for genotype-phenotype correlations. Surprisingly, phenotypic severity was not more severe in patients with deletions affecting multiple genes. For example, patient 5 with a simple *MBD5* truncation point mutation had one of the most severe phenotypes with a refractory developmental and epileptic encephalopathy and severe behavioral disturbance. The lack of strong genotype-phenotype correlation was further emphasized by the 2 families in which sibling pairs inherited the same deletion from a mosaic parent but had marked phenotypic differences, with 1 not having epilepsy at all. We did, however, observe greater phenotypic severity in patients with complete deletion of *MBD5* compared with those with only partial gene deletion. Of those with partial deletions, the mildest phenotypes (patients 10, 16, and 20) were seen in individuals with loss of the proximal end of *MBD5*.

**Figure 2** Pedigrees of Families With Inheritance From Mosaic Parent




The parents of patient 19 (right) both tested negative for the mutation on blood sequencing; however, chorionic villus sampling of their second pregnancy showed that the fetus carried the same mutation, so one of the parents is assumed to have low-level (likely gonadal) mosaicism. "m" = deletion/truncation mutation affecting *MBD5*; "$m^{0.x}$" = mosaic with x% of cells having deletion; "+" = wild type. Central black circle indicates mosaic carrier; central question mark indicates possible mosaic carrier.

## Discussion

With increasing access to molecular testing including high-resolution chromosomal microarray, more patients with disruption of *MBD5* resulting in MAND will be identified. Understanding the epileptology of this genetic disease is critical for prompt diagnosis and optimal management. We analyzed the phenotypes of a global cohort of patients with *MBD5* deletion, duplication, or point mutation and a history of seizures. We found a spectrum of phenotypes associated with *MBD5* pathogenic variants, which often resulted in a severe early childhood-onset developmental and epileptic encephalopathy.

A broad spectrum of phenotypes was observed, and no genotype-phenotype correlation could be identified. The size of the cohort limits this analysis, and as the epileptology of further cases is described, correlations may become apparent. Phenotypes were more severe in patients with complete *MBD5* gene deletion and milder in those with deletion of only the proximal end of the gene. This phenomenon could be explained by the deletion of fewer and different contiguous genes in the patients with proximal deletions. However, substantial phenotypic differences were noted in siblings carrying the same deletion, suggesting that variable expressivity in MAND reflects the involvement of modifier genes, epigenetic, or environmental influences.

Our molecular data highlight the importance of mosaicism, both in patient 12 and, even more critically, in 3/22 (14%) families who had 2 affected pregnancies. In 1 family, antenatal testing identified a second affected child despite negative testing of parental blood, strongly implicating gonadal mosaicism or low-level mosaicism in 1 parent that was missed on conventional sequencing. This suggests that inheritance from parents with low-level mosaicism may be more frequent than previously thought with key implications for reproductive counseling.[14]

Multiple seizure types were usual, including both generalized and focal, with tonic-clonic, focal, absence, atonic, myoclonic, and tonic seizures. EEG studies showed generalized and multifocal epileptiform activity. Seizures were often initially medically refractory but sometimes spontaneously resolved in childhood (age 4–7 years). Neuropsychiatric and developmental features were prominent including moderate-to-severe developmental impairment, language deficits, sleep disturbance, hyperactivity, and aggression.

Fever provoked seizures in 10 patients in our cohort, a pattern reported in 4 published cases.[4,5,15,16] An additional study described hemiclonic seizures with alternating sides beginning at 10 months of age, a feature classically associated with Dravet syndrome (DS), a well-recognized developmental and epileptic encephalopathy associated with *SCN1A* mutations.[17,18] Our cases, together with those reported, suggest that epilepsy in MAND sometimes has phenotypes on the genetic epilepsy with febrile seizures plus spectrum, including DS, MAE, FS+, and febrile seizures.[19]

MAND is typically associated with normal neuroimaging or thin corpus callosum with mild hypomyelination in rare cases. There are rare reports of focal cerebral malformations with *MBD5* pathogenic variants, but these were associated with relatively large heterozygous deletions involving loss of many genes other than *MBD5*.[4,20,21]

The neuropsychiatric and behavioral abnormalities commonly observed in *MBD5* pathogenic variants included sleep disturbance, developmental disability, language impairment, aggressive, and hyperactive behavior.[4] When these occur, families should be counseled that these features are likely intrinsic to the genetic syndrome rather than secondary to medications or uncontrolled seizures. This is an important observation because some patients may undergo unnecessary investigations or medication changes, potentially jeopardizing seizure control, when the etiology of these behaviors is poorly understood.

Our findings should, however, be considered with some caution, given that this study had several limitations. Given the small size of the cohort, it was not possible to conduct statistical analyses or to make meaningful comments

**Table 2** Epilepsy Features

| No./ Sex/ Age | Sz onset | Seizure types (initial seizure type in bold) | Seizure triggers | SE? | EEG | Electroclinical syndrome | Epilepsy course | Effective meds | Ineffective meds |
|---|---|---|---|---|---|---|---|---|---|
| **1/ M/ 10 y** | 2 y | GTC, atonic, myoclonic, myoclonic-atonic | Hot weather, febrile illnesses | Yes[a] | Diffuse slowing; generalized SW/PSW | MAE | Refractory initially, Sz-free since age 4 y | PHT, CLN, TPM, LEV, VPA | — |
| **2/ M/4 y** | 2 y | Atypical absence, DA, GTC, myoclonic, tonic | None | Yes[a] | Diffuse slowing; generalized ShW, GSW, increase in sleep | — | Refractory | VPA, LTG, KD, biotin | CBZ (worsened) |
| **3/ M/5 y** | 4 m | GTC, myoclonic, tonic | Viral illnesses | Yes | Diffuse slowing; focal slowing (L temporal), generalized and multifocal ShW, SW at 4 m (not present at 4 y) | — | Only 3 sz clusters but 2 involved SE | LEV, CLN, TPM | — |
| **4/F/ 6 y** | 3 y | Atypical absence, GTC | Pain | No | Diffuse slowing; generalized SW | — | Controlled with LTG | LTG | — |
| **5/F/ 26 y** | 6 m | Atypical absence, DA, FIAS, GTC, myoclonic, tonic | Hot weather, febrile illnesses | Yes | Diffuse slowing; parieto-occipital spikes independent bilaterally; generalized SW/PSW | — | Refractory | LTG, PHT, VPA, CLB, LEV | GAB, TPM, KD |
| **6/F/ 10 y** | 3 y | FS, GTC | Fever, sleep | No | Normal background; centrotemporal or diffuse SW | — | 2 sz total; sz-free for >3 y | VPA | — |
| **7/ M/ 10 y** | 4 y | FS, FBTC, FIAS | Febrile illnesses | No | Normal background; diffuse epileptiform discharges with TPO predominance | Focal epilepsy | Refractory initially; now sz-free | VPA, LEV, TPM | — |
| **8/ M/ 11 y** | 7 y | FBTC, FIAS | No | No | Normal background; diffuse epileptiform discharges with TPO predominance | Focal epilepsy | Sz-free | LEV | — |
| **9/ M/ 13 y** | 10 m | Hemiclonic, F | Sleep | Yes | Diffuse and multifocal epileptiform discharges | Focal epilepsy | Refractory initially; Sz-free since 4 y | VPA, TPM, CLB, PHT | VIG, LTG, LEV |
| **10/ F/ 3.5 y** | 2.5 y | FS | Febrile illness | No | Normal | FS | Only one event; not treated | — | — |
| **11/ F/11 y** | 0.3 y | ES, GTC, FIAS | Hot weather | No | Hypsarrhythmia with ES; normal when other sz types emerged | West | Responded well to medication | ACTH, VPA, OXC | TPM, VGB, CLN |
| **12/ M/ 13 y** | 2.5 y | GTC, FIAS, myoclonic, tonic, DA, atypical absence | Sleep | Yes | Diffuse slowing; multifocal epileptiform discharges; generalized slow SW and PSW; PFA | LGS | Refractory | VPA, ETX, LTG, LEV, TPM | CLB |
| **13/ F/28 y** | 2.5 y | GTC, tonic, atypical absence, myoclonic, DA, FIAS | Sleep, illness | Yes | Generalized 1.5 Hz SW, PSW, ShW; diffuse slowing | LGS | Refractory | LTG, VPA,CLB, CLN, LEV | TPM, ETX |
| **14/ M/5 y** | 1.5 y | FS, GTC, DA, myoclonic | Febrile illness, sleep | Yes | Diffuse slowing; generalized slow SW, PSW | MAE | Refractory | VPA, CLB, LTG | TPM, LEV |

Continued

**Table 2** Epilepsy Features *(continued)*

| No./ Sex/ Age | Sz onset | Seizure types (initial seizure type in bold) | Seizure triggers | SE? | EEG | Electroclinical syndrome | Epilepsy course | Effective meds | Ineffective meds |
|---|---|---|---|---|---|---|---|---|---|
| **15/ M/9 y** | 1.5 y | Tonic, DA GTC, atypical absence, gelastic | Febrile illness, sleep | Yes | Diffuse slowing; generalized and multifocal (R and L frontocentral) slow 1.5–2 Hz SW, PSW | LGS | Refractory | OXC, LEV, CLB, NIT | — |
| **16/ M/ 15 y** | 13 y | GTC, atypical absence | — | No | Normal background; 3–3.5 Hz generalized SW | — | Only 3 GTC | VPA | LTG |
| **17/ F/7 y** | 3 y | FS, hemiclonic, DA | Febrile illness | Yes | Official reports not available; parents reported ESES diagnosis at age 3 y | — | Refractory | LEV, CLN, IVIG | — |
| **18/ M/ 11 y** | 2 y | FS | Febrile illness | No | Not performed | FS | Only one febrile seizure; not medicated | — | — |
| **19/ M/ 3.3 y** | 9 m | FS, GTC | Febrile illness | No | Normal | FS+ | Seizure-free on LEV | LEV | VPA |
| **20/ M/ 3.3 y** | 2.9 y | Staring spells (absences vs FIAS) | — | No | Normal (at 6 m) | — | 3 events; not medicated | — | — |
| **21/ M/ 2.3 y** | 3 d | FIAS, tonic | — | No | Normal | — | Cluster of events in first week of life, then 2 likely FIA seizures at 26 m; not medicated | — | — |
| **22/ F/ 12.5 y** | 8 y | FIAS, GTC, tonic | — | No | Focal SW and PSW right frontocentral region | — | Sz controlled on OXC | OXC | — |
| **23/ M/ 11 y** | 18 m | GTC | — | No | Diffuse slowing | — | Sz controlled on VPA and LEV | VPA, LEV | — |

Abbreviations: ACTH = adrenocorticotropic hormone; CBZ = carbamazepine; CLB = clobazam; CLN = clonazepam; DA = drop attacks; ES = epileptic spasms; F = focal; FBTC = focal to bilateral tonic-clonic; FIAS = focal with impaired awareness seizures; FS = febrile seizures; FS+ = febrile seizures plus; G = gelastic; GAB = gabapentin; GTC = generalized tonic-clonic; IVIG = intravenous immunoglobulin; KD = ketogenic diet; LEV = levetiracetam; LGS = Lennox-Gastaut syndrome; LTG = lamotrigine; MAE = myoclonic-atonic epilepsy; NCSE = nonconvulsive status epilepticus; NIT = nitrazepam; OXC = oxcarbazepine; PB = phenobarbital; PFA = paroxysmal fast activity; PHT = phenytoin; PSW = polyspike-wave; RUF = rufinamide; ShW = sharp-slow wave; SW = spike-wave; Sz = seizure; TPM = topiramate; TPO = temporoparieto-occipital; VGB = vigabatrin; VPA = valproic acid.
Medications were classified as "effective" if there was reported to be at least partial improvement in seizure control, and "ineffective" if there was no apparent improvement.
[a] Status epilepticus was the initial presentation of seizures.

regarding genotype-phenotype correlation. As a retrospective study in which many patients self-referred, there are potential biases, most notably selection and recall biases. There was a preponderance of patients with copy number variants in our cohort because only 2 individuals had truncating *MBD5* variants. This may relate to the accessibility of different investigations because CGH microarrays are far more readily available than gene panels around the world so that point mutations may be being missed in patients who lack access to next-generation sequencing.

In summary, patients with *MBD5* pathogenic variants and seizures may have a range of phenotypes, including early childhood-onset developmental and epileptic encephalopathy. Epilepsy syndromes include infantile spasms syndrome, LGS, and MAE. Convulsive status epilepticus and nonconvulsive status epilepticus are fairly frequent, and seizures are often provoked by fever or environmental hyperthermia. Parental genetic testing should be offered because inheritance from mosaic parents may be more common than currently appreciated with important implications for genetic counseling.

## Disclosure

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**Table 3** Developmental Impairment, Behavioral Issues, and Other Clinical Features

| #/Sex/Age | Developmental milestones (sat/walked/first word) ID degree Regress with seizures? | Microcephaly? | Sleep issues | Behavioral issues | MRI brain | Musculoskeletal abnormalities |
|---|---|---|---|---|---|---|
| **1/M/10 y** | 8 m/20 m/2 y<br>Severe<br>No | Y | Frequent waking from age 4 y | Agitation, hyperactivity, anxiety, aggression; self-mutilation | Normal at age 2.2 y; mild thickening of corpus callosum noted at 14 y | Idiopathic torticollis |
| **2/M/4 y** | 8 m/17 m/12 m<br>Severe<br>Yes | N | Frequent waking with nocturnal tonic seizures | N | Normal (age 2.1 y) | N |
| **3/M/5 y** | 18 m/4 y/3 y<br>Severe<br>No | Y | No | Irritability, aggression, violent tantrums, obsessiveness, inflexibility | Normal (age 4.5 mths) | Abnormal increased left foot and ankle tone with fixed, plantar-flexed, hindfoot varus, inverted position |
| **4/F/6 y** | 6 m/18 m/3.5 y<br>Severe<br>No | N | Sleep initiation difficulty | ADHD, anxiety, tantrums, self-mutilation | Normal (age 3.2 y) | N |
| **5/F/26 y** | ?/3 y/NV<br>Severe<br>No | N | Frequent waking | Compulsive behavior, severe agitation, violence, self-mutilation | "Global reduction in white matter" (age 10 y) | N |
| **6/F/10 y** | ?/?/NV<br>Severe<br>No (behavior worsened at 6 y) | Y | Parasomnias, bruxism and sleep talking | Fluctuating aggressiveness, irritability | Chiari I malformation (age 6.5 y) | N |
| **7/M/10 y** | ?/2 y/2.5 y<br>Severe<br>No | N | N | Hyperactivity | Normal (age 5 y) | N |
| **8/M/11 y** | ?/2 y/4 y<br>Severe<br>No | Y | Pavor nocturnus | Hyperactivity | Normal (age 6 y) | N |
| **9/M/13 y** | 20 m/NA/NV<br>Severe<br>No | Y | N | N | Mild hypomyelination, thin CC (age 3 y) | N |
| **10/F/3.5 y** | 7 m/19 m/11 m<br>Mild<br>No | N | N | N | Not performed | N |
| **11/F/11 y** | 17 m/23 m/NV<br>Severe<br>No | N | Frequent waking; "tears apart bedroom" | Bangs head, scratches arms; self-stimulation | Normal (age 5 mths) | N |
| **12/M/13 y** | 8 m/15 m/13 m<br>Moderate-severe<br>Yes | N | Frequent waking and very active | N | Normal (age 3 y) | N |
| **13/F/28 y** | 8 m/15 m/?<br>Moderate<br>Yes | Y | Frequent waking | Obsessive behaviors and tantrums | Normal (age 8 y) | N |
| **14/M/5 y** | 10 m/19 m/NV<br>Moderate-severe<br>No | N | Frequent waking (average 10/night) | Bites self; bangs head against wall | Normal | N |
| **15/M/9 y** | 9 m/17 m/17 m<br>Moderate-severe<br>Yes | N | Frequent waking | Tantrums; bites hands | Normal (ages 2.5 y and 10 y) | N |

Continued

**Table 3** Developmental Impairment, Behavioral Issues, and Other Clinical Features *(continued)*

| #/Sex/Age | Developmental milestones (sat/walked/first word) ID degree Regress with seizures? | Microcephaly? | Sleep issues | Behavioral issues | MRI brain | Musculoskeletal abnormalities |
|---|---|---|---|---|---|---|
| **16/M/15 y** | 7 m/15 m/18 m<br>Moderate<br>Yes | N | Frequent waking | Misbehaves frequently | Normal | N |
| **17/F/7 y** | 3 y/NA/NV<br>severe<br>No | Y | Frequent waking with nocturnal seizures | N | Not available | Congenital bilateral talipes equinovarus |
| **18/M/11 y** | 1y/2y 3m/2y<br>Severe<br>No | N | Frequent waking from age 6 y | Poor attention and concentration, hyperactivity, repetitive hand mannerisms | Normal (age 2 y) | N |
| **19/M/3.3 y** | 8m/16m/2y 4m<br>Moderate<br>No | N | N | Hyperactivity | Normal | N |
| **20/M/3.3 y** | 12 m/21 m/2.5 y<br>Moderate<br>No | N | N | Pushing other children; pinching himself | Normal | N |
| **21/M/2.3 y** | 2 y/NA/10 m<br>Moderate<br>No | N | Frequent waking | N | Normal (age 2.3 y) | N |
| **22/F/12.5 y** | 10 m/2.5 y/4 y<br>Moderate<br>No | Y | Frequent waking | N | Normal (age 8.5 y) | N |
| **23/M/11 y** | 6 m/2.5 y/16 m<br>Severe<br>No | Y | Frequent waking | Food-hoarding behaviors and other obsessions; had self-injurious behaviors when younger; now, hits and scratches others | Focal T2 hyperintensities in occipital white matter; mild cerebral and cerebellar atrophy (age 1.9 y) | N |

Abbreviations: ADHD = attention deficit hyperactivity disorder; CC = corpus callosum; NA = non-ambulatory; NV = non-verbal.

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Continued

## Appendix *(continued)*

| Name | Location | Contribution |
|---|---|---|
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## Appendix *(continued)*

| Name | Location | Contribution |
|---|---|---|
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