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# The spectrum of epilepsy and electroencephalographic abnormalities due to *SHANK3* loss of function mutations

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## Summary

**Objective—**The coincidence of autism with epilepsy is 27% in those individuals with intellectual disability[1]. Individuals with loss of function mutations in *SHANK3* have intellectual disability, autism and variably, epilepsy[2–5]. The spectrum of seizure semiologies and electroencephalographic (EEG) abnormalities has never been investigated in detail. With the recent report that *SHANK3* mutations are present in approximately two percent of individuals with moderate to severe intellectual disabilities and one percent of individuals with autism, determining the spectrum of seizure semiologies and electrographic abnormalities will be critical for medical practitioners to appropriately counsel the families of patients with *SHANK3* mutations.

**Methods—**A retrospective chart review was performed of all individuals treated at the Blue Bird Circle Clinic for Child Neurology who have been identified as having either a chromosome 22q13 microdeletion encompassing *SHANK3* or a loss of function mutation in *SHANK3* identified through whole exome sequencing.

For each subject, the presence or absence of seizures, seizure semiology, frequency, age of onset and efficacy of therapy were determined. Electroencephalograms were reviewed by a board certified neurophysiologist. Neuroimaging was reviewed by both a board certified pediatric neuroradiologist and child neurologist.

**Results—**There is a wide spectrum of seizure semiologies, frequencies and severity in individuals with *SHANK3* mutations. There are no specific electroencephalographic abnormalities found in our cohort, and EEG abnormalities were present in individuals diagnosed with epilepsy and those without history of a clinical seizure.

**Significance—**All individuals with a mutation in *SHANK3* should be evaluated for epilepsy due to the high prevalence of seizures in this population. The most common semiology is atypical absence seizure which can be challenging to identify due to comorbid intellectual disability in individuals with *SHANK3* mutations; however, no consistent seizure semiology, neuroimaging

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Dr. Holder has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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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.

findings or electroencephalogram findings were present in the majority of individuals with *SHANK3* mutations.

### Keywords

*SHANK3*; Phelan-McDermid Syndrome; epilepsy; electroencephalography; autism

## Introduction

Loss of function mutations in the *SHANK3* gene, either through chromosomal microdeletion in Phelan-McDermid Syndrome (PMS) or through missense/nonsense mutations, are a growing area of importance for neurologists and epileptologists[3]. Approximately two percent of individuals with moderate to severe intellectual disability and one percent of individuals with autism are estimated to harbor such mutations[6].

The protein product of the *SHANK3* gene is a scaffolding protein that localizes primarily to the post-synaptic density of excitatory synapses[7]. At the post-synaptic density, it bridges transmembrane proteins critical for synapse formation such as Neuroligins and neurotransmitter receptors such as NMDA glutamate receptors with the underling cytoskeleton, in particular F-actin elements[8; 9]. Loss of *SHANK3* in multiple model systems, cultured neurons to mice, has demonstrated synaptic dysfunction[10–13]. As such, SHANK3 is a critical protein for biogenesis and maintenance of synapses as well as synapse function.

Epilepsy has been reported in individuals found to have 22q13 deletions including *SHANK3* with a prevalence ranging from 17–70% in multiple case series (Table I). Most of these studies, however, have provided limited information about the semiology, frequency or severity of seizures in this population. Nor have they provided information about the spectrum or frequency of electroencephalographic abnormalities of these patients. Here we present a detailed report of the spectrum of seizures and electroencephalographic findings in individuals with *SHANK3* loss of function mutations. We find significant heterogeneity in seizure types and frequency in our cohort. Furthermore, we identify a wide spectrum of electroencephalographic abnormalities in our subjects which are present in both individuals diagnosed with epilepsy and those without.

## Patients and Methods

### Ethics

This study was approved by the Institutional Review Board of Baylor College of Medicine. All participants or their guardians provided informed written consent to participate in this study.

### Patient Selection and Evaluation

We retrospectively collected data from a single center (Texas Children's Hospital) through the electronic medical record. Information about the seizure characteristics of 24 individuals (10 males and 14 females) with either a chromosomal deletion encompassing chromosome 22q13 including *SHANK3*, point mutation, indel or microduplication of *SHANK3* predicted

to result in a loss of function mutation were analyzed. Data regarding the onset of first clinical seizure, seizure frequency, duration, semiology, response to pharmaceutical and non-pharmaceutical therapies and neuroimaging abnormalities were collected and analyzed.

### Electroencephalogram interpretation

Electroencephalograms were obtained at a single site with review by a board certified neurophysiologist. The video-EEG recordings were obtained using the Nicolet video-EEG system (Natus Medical, Inc.) while patients were awake, drowsy and, when possible, asleep with a 21-channel EEG acquisition system using silver-chloride surface electrodes. The EEG data was reviewed in both bipolar and referential montages.

## Results

### Clinical findings

We retrospectively evaluated twenty-four subjects with *SHANK3* mutations including twenty individuals with chromosomal deletions of 22q13.33 including *SHANK3* and four individuals with point mutations identified by whole exome sequencing resulting in either frameshift or mis-splicing of the *SHANK3* coding frame (Table II). We found eleven out of 24 subjects had a history of at least one lifetime seizure (46%), including two of the four individuals with point mutations. The spectrum of seizure semiologies varied significantly from atypical absence seizures (90%) being the most common seizure type to tonic (54%), atonic (18%), tonic-clonic (9%) and myoclonic (9%) in those individuals with a history of clinical seizure. Six of the eleven subjects with a history of seizure had more than one seizure type (54%), and two patients from this cohort (8%) were diagnosed with Lennox-Gastaut Syndrome based upon the combination of multiple seizure types (including tonic seizures), intractability of their seizures and characteristic EEG finding of generalized bursts of 1.5–2 Hz spike and slow wave activity. Five of our 24 subjects (20%) had a history of status epilepticus requiring emergency intravenous medication for cessation of seizure activity. The onset of first seizure ranged from 14 months to 14 years with a mean age of onset of 5.2 years ± 3.9 (SD). The frequency of seizures similarly varied from a single lifetime seizure to hundreds of seizures per day (Table II).

### Electrographic findings

Electroencephalographic abnormalities were identified in fourteen out of twenty-one subjects (67%) for which EEG data was available. The spectrum of EEG abnormalities was wide from slowing or absence of the occipital dominant rhythm (42%) to focal spike and slow wave discharges (38%) to generalized spike and slow wave discharges (19%) (Figure 1). Several patients had combinations of the above abnormalities. Of the twenty-one patients with EEG data available, five had an abnormal EEG (either slow occipital dominant rhythm or focal spike and slow wave activity or both) but no history of clinical seizure (23%).

Most individuals with multiple seizure types had an abnormally slow occipital dominant rhythm (83%) while the majority of individuals with a single seizure type were found to have an age-appropriate occipital dominant rhythm (60%). Similarly, both individuals with high seizure burden of hundreds of seizure per day prior to anti-convulsant medication were

found to have a significantly slowed occipital dominant rhythm. However, it should be noted that three of the ten individuals (30%) for whom we have EEG data and without a history of seizure had abnormally slow occipital dominant rhythm.

## Neuroimaging

Of our 24 subjects, 21 had an anatomic brain magnetic resonance imaging (MRI) available for review (88%). The abnormalities identified varied greatly between individuals (Figure 2). The most common abnormalities were dysmorphisms of the corpus callosum (29%) and T2 hyperintensities of the deep white matter (24%). Anatomic brain abnormalities were detected in both individuals with history of seizures (33%) and without (38%).

## Treatments

The type and number of anti-convulsant medications prescribed varied greatly among subjects. The most commonly prescribed anti-convulsant was lamotrigine (17%) followed by levetiracetam and topiramate (12% each) and then several others in less than 10% of this population (rufinamide, zonisamide, perampanel, felbamate, valproate, carbamazepine, oxcarbazepine, lacosamide, phenytoin, methsuximide, chlorazepate, lorazepam, phenobarbital). While underpowered to evaluate for efficacy in this study, no medication was clearly superior for seizure prophylaxis. There was a trend for those with one seizure type to respond to fewer medications than those with multiple seizure semiologies. All individuals with only one semiology (six) were maintained on less than two anti-convulsant medications while three of five individuals with multiple seizure types required two or more maintenance anti-convulsant medications ($p=0.06$, Fisher's exact test). Two individuals were found to have pharmaco-resistant epilepsy and had implantation of vagus nerve stimulators with mild improvement in seizure frequency (<50% reduction in seizures).

**Longitudinal outcomes—**Of the eleven patients described here with *SHANK3* loss of function mutation and a history of seizure, five (subjects 1, 2, 4, 11 and 13) were evaluated at least twice in clinic.

Patient 2 developed epilepsy at eight years of age with the first seizure being generalized tonic-clonic and lasting more than five minutes thus requiring intravenous medication. Seizures evolved to include atonic and myoclonic seizures at 9 years of age and tonic seizures by 10 years of age at which time he was diagnosed with Lennox-Gastaut syndrome. Medication history included initiation of 14 different anti-convulsants in multiple combinations. Ketogenic diet was also attempted, initially with reduction of seizure burden by 90% but then return of multiple daily seizures leading to its discontinuation. A vagus nerve stimulator was also implanted at 10 years of age with initially >50% reduction in seizure burden following escalation of therapy, but subsequent increasing seizure burden. Following multiple injuries from atonic seizures despite use of a protective helmet, corpus callosotomy was performed at 15 years of age with significant reduction in frequency and severity of atonic seizures for more than two years. Initial neuroimaging was normal but developed into T2 hyperintensity of the left hippocampus suggestive of mesial temporal sclerosis.

Patient 4 developed epilepsy at two years of age. The initial seizure type was atypical absence seizure and this remains her only semiology. Initial treatment with lamotrigine was not efficacious, and she was transitioned to zonisamide therapy with less than one seizure per month.

Patient 1 had her first seizure at 14 months of age which was an episode of febrile status epilepticus. This initial event was characterized by a tonic seizure with decreased responsiveness. This was followed by multiple daily atypical absence seizures at which point she was initiated on levetiracetam therapy which reduced her seizure burden from daily to less than one per month.

Patient 11 had a history of two lifetime seizures both occurring with fever. The first was at one year of age. Both lasted less than one minute in duration. This patient was never placed on anti-convulsant medication.

Patient 13's only seizure occurred at 6 years of age and was associated with illness. The seizure lasted for approximately 30 minutes requiring intravenous medication. She has never required daily anti-convulsant medication.

## Discussion

Here we present extensive data of seizure characterization and electroencephalogram abnormalities in individuals with *SHANK3* mutations. *SHANK3* haploinsufficiency is believed to be the etiology of the cognitive abnormalities in individuals with Phelan-McDermid Syndrome due to a similar phenotype in an individual with a balanced translocation disrupting *SHANK3* and multiple studies which have identified individuals with point mutations, indels or small duplications involving the *SHANK3* gene who have similar autistic traits and intellectual disability as individuals with chromosomal deletions encompassing *SHANK3*[11; 14; 15]. Epilepsy is present in a substantial number of individuals with Phelan-McDermid Syndrome with a pooled prevalence of 32% in unique studies available from the literature including this one. Whether or not mutations in *SHANK3* underlie the increased propensity for epilepsy in Phelan-McDermid Syndrome is unclear. In our cohort, we identified four individuals by exome sequencing with variants in *SHANK3* predicted to be deleterious. Of these, two developed epilepsy. Furthermore, the largest study to date of 22q13 deletions found no significant differences in deletion size in those with epilepsy and those without[2]. These data provide preliminary evidence that loss of function mutations in *SHANK3* can increase the likelihood to develop epilepsy; however, confirmation will require larger cohorts of individuals with indels and nonsense mutations in *SHANK3*.

One previous study investigating the seizure types associated with Phelan-McDermid Syndrome suggested that epilepsy associated with this disorder is mild and easily pharmacologically controlled[16]. We find in our cohort some individuals with *SHANK3* deletions do have infrequent and easily managed epilepsy, but we also identified individuals with intractable seizures including Lennox-Gastaut Syndrome. Lennox-Gastaut Syndrome

has been previously reported in one adult with a chromosome 22q13 deletion including the *SHANK3* gene[17].

It is unclear exactly what distinguishes those individuals who will have a single seizure semiology and infrequent seizures from those that have multiple seizure types. There was no significant difference in deletion size, neuroimaging finding or other clinical characteristic (Table II). The only parameter that trended with multiple seizure types was slow or absent occipital dominant rhythm (five of six) in individuals with multiple seizure types versus those with a single seizure type (two of five). Together, these data demonstrate that medical practitioners must educate families caring for individuals with *SHANK3* loss of function mutations that epilepsy can become pharmacoresistent and intractable.

Why haploinsufficency of *SHANK3* would predispose to epilepsy is unclear. Multiple lines of mice with loss of function mutations in *SHANK3* have been reported to date[10; 12; 13]. Only one (*Shank3* alpha/beta isoform knockout) has been reported to have spontaneous seizures although these seizures were not characterized in detail[10]. Excitatory neurons differentiated from patient iPSCs with *SHANK3* deletions have been reported[18]. These neurons display multiple molecular and neurophysiologic abnormalities. Importantly, they have increased input resistance compared to control neurons. This indicates a tendency to increased excitability potentially underlying the elevated prevalence of epilepsy in individuals with *SHANK3* mutations compared with the general population.

Recently, a mechanism for the increased input resistance of stem cell derived neurons has been proposed[19]. Utilizing neurons derived from human embryonic stem cells with a targeted mutation of *SHANK3*, impairment of $I_h$ currents was identified due to reduced expression of subunits of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. Moreover mutations in HCN channels have been clinically associated with epilepsy[20]. Intriguingly while the seizures were polymorphic in individuals with *HCN1* mutations, all patients reported in this study were diagnosed with atypical absence seizures. Together, these data suggest a mechanism by which hapolinsufficiency of *SHANK3* might predispose to epilepsy and why there is a wide spectrum of seizure semiologies with atypical absence being the most common type of seizure in patients with *SHANK3* haploinsufficiency.

There are no consistent neuroimaging abnormalities that are likely to predispose to seizures. In particular, there is no evidence in our population or from previous reports of migrational abnormalities that are likely causative of their seizures. In our cohort, we found neuroimaging abnormalities as frequently in subjects with a history of seizures as those without. What is less clear is whether individuals with *SHANK3* mutations have microscopic neuroanatomic abnormalities or abnormalities in connectivity that might be responsible for both the cognitive dysfunction and propensity for epilepsy. This will require more advanced neuroimaging techniques such as diffusion tenor imaging or functional magnetic resonance imaging to determine.

## Summary

Loss of function mutations in *SHANK3* either through chromosomal deletion or point mutation predispose to seizures and electroencephalographic abnormalities. Atypical absence seizures are the most common seizures in individuals with *SHANK3* mutations; however, there is a wide spectrum of seizure types. No specific electroencephalographic abnormality is present in our cohort, and abnormalities were seen in both individuals with a history of seizures and those without. Neuroimaging in our cohort did not identify a specific abnormality associated with seizures. No pharmacologic therapies were clearly superior for treating patients in our cohort. Individuals with loss of function mutations in *SHANK3* should be monitored for seizure activity.

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**Key Point Box**

- Seizures occur in greater than 30% of children with *SHANK3* mutations
- The most common seizure type is atypical absence
- A subset of patients with *SHANK3* mutations have medically intractable epilepsy
- There are no pathognomonic abnormalities on EEG in children with *SHANK3* mutations
- EEG abnormalities are seen in children harboring *SHANK3* mutations with and without history of seizures

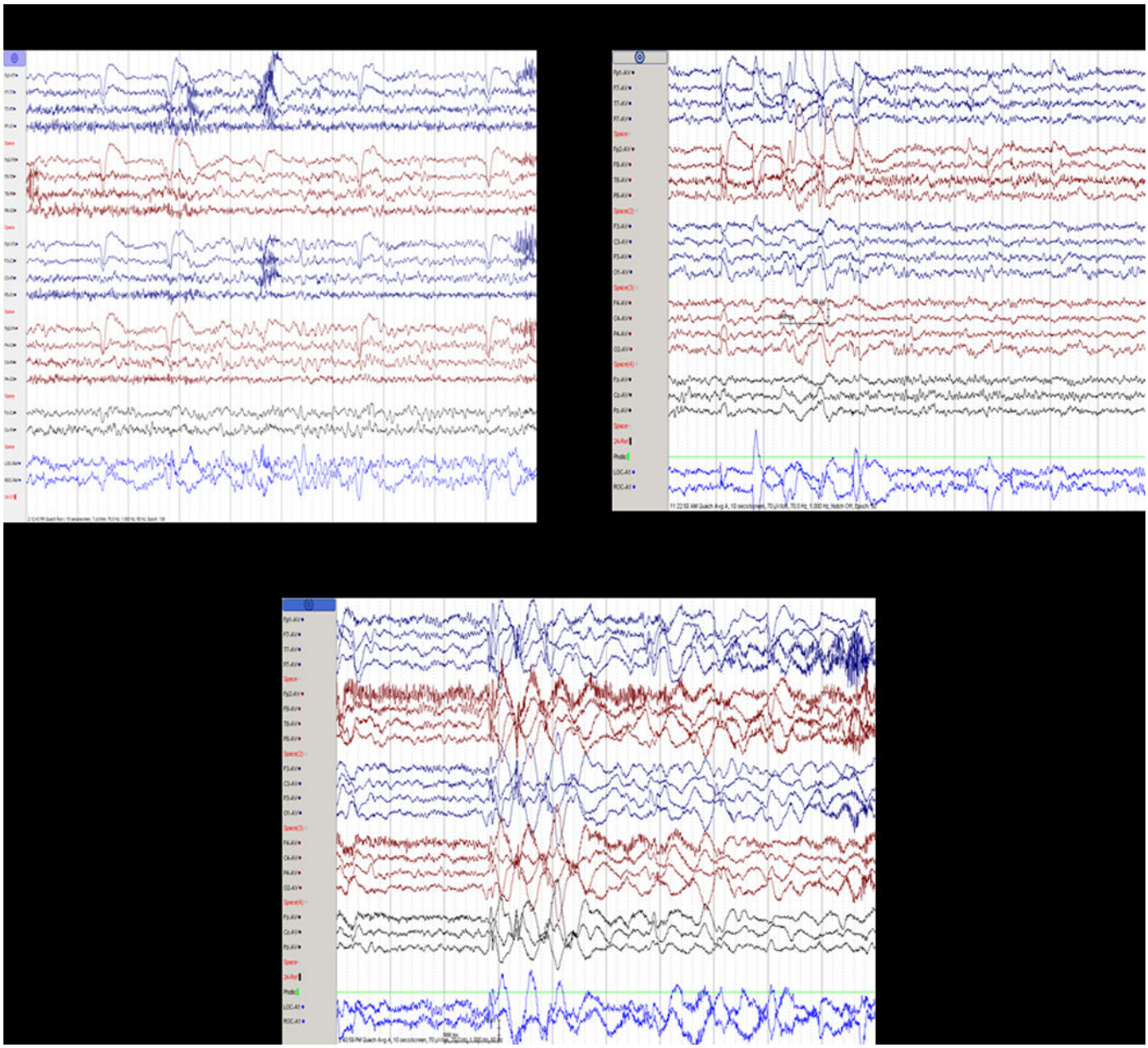

**Figure 1.**

Electroencephalograms in individuals with loss of function mutations in *SHANK3* (A) Subject 22 with generalized slowing of the occipital dominant rhythm (B) Subject 4 with frontal dominant generalized burst of 1.5 Hz spike and slow wave activity (C) Subject 2 with generalized burst of 1.5–2.5 Hz spike and slow wave activity.

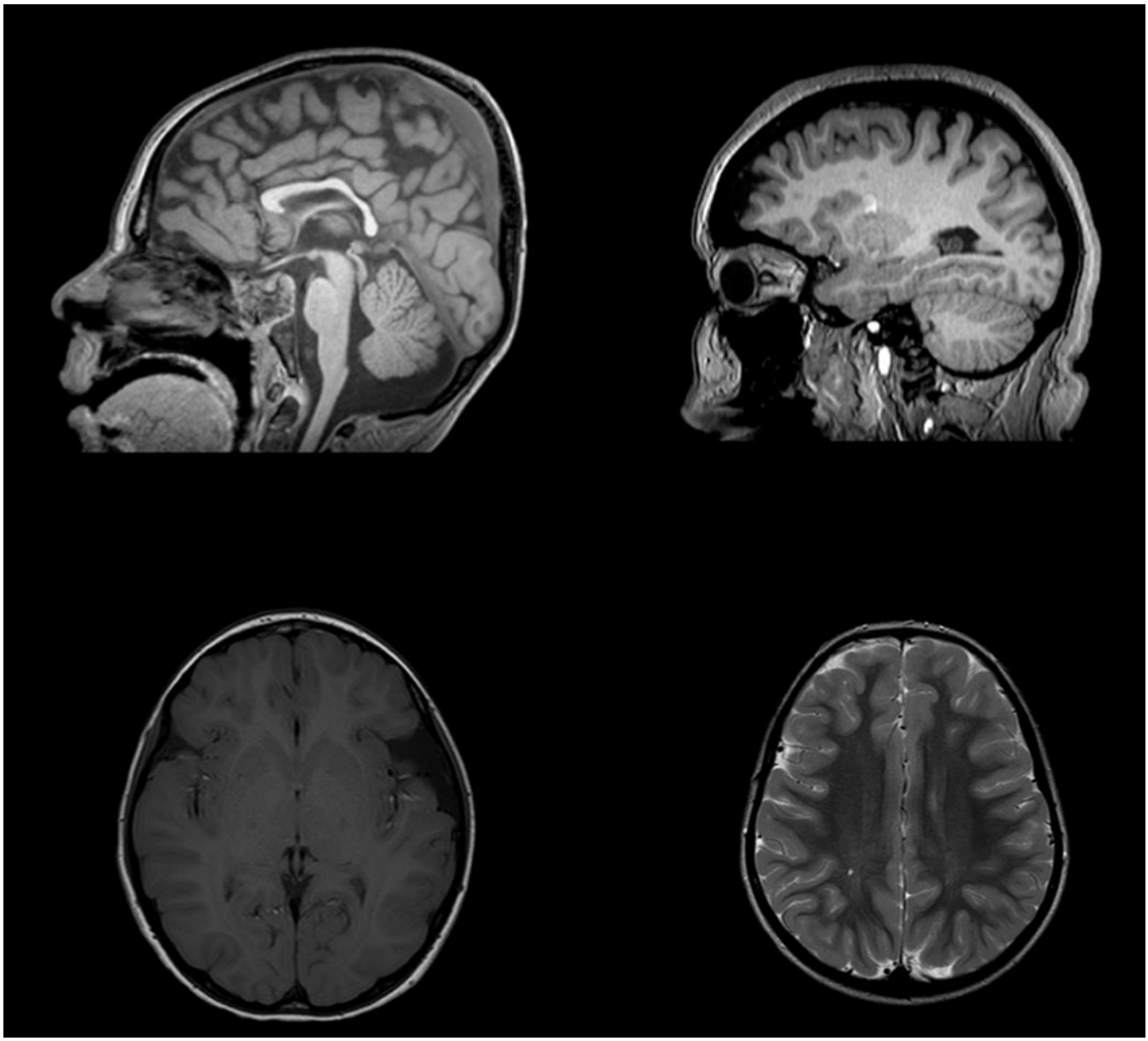

**Figure 2.**

Brain Magnetic Resonance Imaging (MRI) in individuals with loss of function mutations in *SHANK3* (A) Sagittal T1 weighted image of subject 9 demonstrating thinning of the corpus callosum (B) Sagittal T1 weighted image of subject 17 with mild cerebral volume loss (C) Axial T1 weighted image of subject 21 with left sylvian fissure arachnoid cyst (D) Axial T2 weighted image of subject 4 with mild T2 hyperintensity of the posterior centrum semiovale.

**Table I**

Seizure and EEG characterization from previous studies of Phelan-McDermid Syndrome

| Study | Prevalence of seizures | Types of seizures described | EEG findings | Number of patients |
|---|---|---|---|---|
| **Phelan et al.**[21] | 27% | N/A | N/A | 37 |
| **Wilson et al.**[22] | 70% | N/A | N/A | 51 |
| **Luciani et al.**[23] | 24% | N/A | N/A | 33 |
| **Manning et al.**[24] | 27% | “Petit mal and focal” | N/A | 11 |
| **Lindquist et al.**[25] | 33% | N/A | N/A | 6 |
| **Jeffries et al.**[26] | 17% | N/A | N/A | 30 |
| **Cusmano et al.**[5] | 23% | N/A | N/A | 107 |
| **Dhar et al.**[4] | 30% | N/A | N/A | 11 |
| **Soorya et al.**[3] | 41% | “Generalized” (5/6), “partial-onset” (1/6) | 34% with abnormality | 32 |
| **Sarasua et al.**[2] | 27% | N/A | N/A | 151 |
| **Figura et al.**[16] | 50% | “Myoclonic, tonic, generalized tonic-clonic” | Multifocal spike and wave | 6 |
| **Denayer et al.**[27] | 14% | N/A | N/A | 7 |
| **Nesslinger et al.**[28] | 14% | N/A | N/A | 7 |

N/A = not available

**Table II**

Clinical Characteristics of Subjects

| Subject | Age | Genetic abnormality | Age first SZ | Frequency of SZ prior to medication | Frequency of SZ on medication | SZ semiology | Duration of SZ | SE | EEG findings | Neuroimaging findings |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 2 years | 22q deletion (44753814–51197838) hg19 | 14 month | daily | <1 per month | atypical absence, tonic | 10–15 seconds | yes | excess beta activity, foci of SW activity - left central and parietal regions, intermittent slowing (delta) - bilateral occipital regions | thinning of corpus callosum |
| **2** | 17 years | 22q13.33 (GS-99K24 X1) | 8 years | hundreds per day | daily | tonic, atypical absence, atonic, myoclonic, tonic-clonic | seconds to > 5 minute | yes | poorly organized ODR 6 Hz, frontocentral 8–10 Hz sharps evolving into 3–4 Hz spike and polyspike; bursts of generalized 1.5–2.5 Hz SW, intermittent generalized 3–5 Hz in 50% of recording | originally normal, evolved into left mesial temporal sclerosis |
| **3** | 9 years | 22q13.3 (49138472–49535360 X1) | 5 years | three times per week | 2 times per month | atypical absence, tonic | 15–20 seconds | no | ODR 7–8 Hz,, frontal 1.5–2 Hz generalized SW/polyspike | normal |
| **4** | 11 years | 22q13.33 (49177451–49525470), 2p12 (76910620–77354922 x1) hg18 | 9 years | <1X/week | <1X/week | atypical absence | 30 seconds | no | ODR 8 Hz with slower fused waveforms; multifocal SW/ polyspike most frequent in the right frontal region, rare generalized SW | increased T2 signal in centrum semiovale, small corpus callosum |
| **5** | 10 years | 22q13.33 (49484191–49525470 X1) hg18 | none | none | N/A | N/A | N/A | no | None | normal |
| **6** | 6 years | 22q13.33 (47061550–51304566 X1) hg19 | 2 years | 10–20 × per day | N/A | atypical absence | 20 sec - 1 min | no | ODR 8–8.5 Hz with some slower activity; active foci of SW in isolation and in runs in the left and right temporoparietocentral regions | brachycephalic, otherwise normal |
| **7** | 12 years | 22q13.33 (48771374–51178264 X1); 7q31.1 (111056675–111191737 X1) hg19 | none | none | N/A | N/A | N/A | no | ODR 6–7 Hz poorly developed and sustained; sharp waves and spikes over left and right temporal; anterior temporal and frontal regions independently | T2 prolongation of subcortical white matter bilateral temporal poles, slightly foreshortened corpus callosum |

| Subject | Age | Genetic abnormality | Age first SZ | Frequency of SZ prior to medication | Frequency of SZ on medication | SZ semiology | Duration of SZ | SE | EEG findings | Neuroimaging findings |
|---|---|---|---|---|---|---|---|---|---|---|
| **8** | 15 years | 22q13 deletion (no data) | 5 years | hundreds per day | 1–2 per day | atonic, atypical absence | seconds to >5 minute | yes | ODR 4–5 Hz; low amplitude spike discharges - left central; polyspike at right frontoparietal | arachnoid cyst |
| **9** | 5 years | 22q13 (48533991–51178264 X1) 12p13.33 (189216–8185497 X3) hg19 | none | none | N/A | N/A | N/A | no | ODR 8–9 Hz; normal | mild increased FLAIR signal in periventricular white matter of frontal, parietal and temporal lobes, moderate reduction in cerebral white matter volume including corpus callosum thinning, mild decreased size of the left hippocampus |
| **10** | 12 years | 22q13.2 deletion by karyotype | 3 years | daily | 1/2–3 weeks | atypical absence, tonic | minute to hours | yes | no ODR, right centroparietooccipital sharps | mild thinning of the corpus callosum, generalized loss of white matter |
| **11** | 4 years | 22q13.2-3(43572964–51171678 X1) | 1 year | 2 lifetime with fever | N/A | tonic | 1 minute | no | ODR 6 Hz with slower waveforms; during sleep - bursts of generalized anterior dominant SW/polyspike | mild hypoplasia of the posterior body of the corpus callosum, large cystic cavum septum pellucidum |
| **12** | 17 years | 22q13.2-3 (43014031–51171678 X1) | none | none | N/A | N/A | N/A | no | ODR 5–6 Hz; SW in right parietal and frontal | curvilinear cortical T2 hyperintensity right extreme capsule, infratentorial/ supratentorial volume loss, persistent cavum septum pallucidum et vergae, giant cisterna magna |
| **13** | 13 years | 22q13.31-3 (45680160–51178264 X1) 2q37.3 (241994956–242938241 X3) hg19 | 6 years | one | N/A | atypical absence | 30 minute | yes | ODR 8 Hz, normal | none |
| **14** | 28 years | 22q13.31q13..33 deletion by FISH | none | none | N/A | N/A | N/A | no | normal per parental report | none |
| **15** | 19 years | 22q13.33 (49451411–49525130 X1) hg18 | none | none | N/A | N/A | N/A | no | 10–11 Hz, normal | cerebellar ectopia |
| **16** | 7 years | 22q13.33 (G248p86064C8–G248p86149G7 X1) BAC array | none | none | N/A | N/A | N/A | no | ODR 10–11 Hz, excessive beta activity | normal |
| **17** | 16 years | 22q13 deletion by FISH | none | none | N/A | N/A | N/A | no | ODR 9.5–10 Hz; occasional moderate voltage sharp waves right frontocentral regions near midline and right centrotemporal regions occasionally in serial | left sylvian fissure arachnoid cyst; mild cerebral volume loss, partial empty sella |

| Subject | Age | Genetic abnormality | Age first SZ | Frequency of SZ prior to medication | Frequency of SZ on medication | SZ semiology | Duration of SZ | SE | EEG findings | Neuroimaging findings |
|---|---|---|---|---|---|---|---|---|---|---|
| **18** | 12 years | 22q13.33 (49469317–49525130 X1) hg18 | none | none | N/A | N/A | N/A | no | none | normal |
| **19** | 9 years | 22q13.33 (50103257–51178264 x1) hg19 | none | none | N/A | N/A | N/A | no | none | none |
| **20** | 3 years | 22q13.33 (51137,176–51,197,838 X1) | none | none | N/A | N/A | N/A | no | poorly sustained ODR of 8 Hz | persistent cavum septum pellucidum et vergae |
| **21** | 13 years | 15q11.2 dup; *SHANK3* c.2313+1G>A | none | none | N/A | N/A | N/A | no | ODR 8–9 Hz, normal | left sylvian fissure arachnoid cyst |
| **22** | 14 years | *SHANK3* indel (q51160326–51160327) | 14 years | unknown | 1/week | atypical absence | 3 minute | no | no ODR | normal except mild cerebellar tonsillar ectopia |
| **23** | 14 years | *SHANK3* indel (q51160326–51160327) | 7 years | multiple times per week | 2–3 times per week | atypical absence, tonic | 3–5 minutes | no | ODR 9–10 Hz, normal | normal |
| **24** | 13 years | *SHANK3* c.3727dupG(p.A1212fs) | none | none | none | none | none | no | Normal | bilateral T2 hyperintensities of posterior centrum semiovale |

ODR = Occipital Dominant Rhythm; SW = spike and slow wave