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SPECIAL REPORT

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A novel possible familial cause of epilepsy of infancy with migrating focal seizures related to SZT2 gene variant

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Abstract

Seizure threshold-2 (SZT2) gene variants have been associated with a decrease in seizure threshold resulting in variable phenotypic expressions ranging from mild-moderate intellectual disabilities without seizures, to an early-onset epileptic encephalopathy with severe cognitive impairment. In addition, hypotonia and distinctive facial dysmorphism, including a high forehead and to a lesser extent ptosis and down-slanting palpebral fissures, were present in the majority. We herein report a novel SZT2 variant in one of two siblings both diagnosed with epilepsy of infancy with migrating focal seizures (EIMFS). This report is the fourth to document a possible familial case in EIMFS, a condition that was not previously associated with SZT2 variant. This report expands the phenotypic expression of SZT2, corroborates the importance of genetic counseling in some cases of EIMFS, and highlights the efficacy of potassium bromide in controlling the seizures associated with this condition.

KEYWORDS

familial epilepsy of infancy with migrating focal seizures, infantile epileptic encephalopathy, potassium bromide, SZT2

1 | INTRODUCTION

Seizure threshold-2 (SZT2) gene, located on chromosome 1p34.2, is highly expressed in the central nervous system (CNS) and has been associated with a decrease in seizure threshold.[1] This gene that acts by regulating the mechanistic target of rapamycin (mTOR) activation was first identified in 2013 by Basel-Vanagaite et al in two children diagnosed with an early-onset refractory epileptic encephalopathy.[2] Subsequently, a few additional cases with variable phenotypic expressions were reported, although the majority manifested with an early-onset pharmacoresistant epileptic encephalopathy associated with distinctive dysmorphic facial features.

We report a novel SZT2 gene variant in one of two siblings both diagnosed with the syndrome of epilepsy of infancy with migrating focal seizures (EIMFS). This is the first association between SZT2 variant and EIMFS and the possible fourth reported familial case of EIMFS.

These authors Tarek El Halabi and Maya Dirani contributed equally to the manuscript.

2 | CASES

Our two patients are sisters, born at 36 weeks of gestation to first degree cousins. They have an older brother, who is developmentally normal and with no history of seizures. Both had distinct dysmorphic facial features characterized by a high forehead, down-slanting palpebral fissures and ptosis (Table 1). The siblings had remarkably similar neurological findings, seizure semiologies, EEG features and clinical courses (Table 1).

The eldest sister (patient 1) started experiencing focal seizures characterized by behavioral arrest associated with blinking and flushing at 4 weeks of age. At the age of 4 months, the seizures recurred in clusters of 15-30 episodes daily with each seizure lasting from 30 seconds to 2.5 minutes despite treatment with multiple combinations of antiseizure medications (Table 1). On her examination at 5 months of age, she was severely delayed (Table 1). A long-term video/EEG recording revealed rare multifocal independent spikes with innumerable multifocal-onset seizures originating independently from various cortical areas and sometimes migrating from one hemisphere to the other during the same seizure event (Table 1). Semiologically, the seizures were characterized by staring, blinking, flushing, increased tone, apnea, and cyanosis with the oxygen saturation sometimes dropping down to 75%. An epilepsy protocol brain MRI revealed a persistent cavum septum pellucidum and a short corpus callosum of normal thickness (Figure S1A).[3] MR spectroscopy (MRS) and metabolic investigations were normal. Her immune workup showed a decrease in all lymphocyte subsets and a decrease in all immunoglobulin levels (Table 1). At that time, potassium bromide was added to her regimen and titrated to a dose of 80 mg/kg/day, which resulted in mild somnolence relative to her baseline state. This drug, according to her parents, resulted in a dramatic and sustained reduction in the frequency of her seizures with only rare and isolated recurrences until her death at the age of 11 months from cardiorespiratory arrest secondary to an infection.

Her sister (patient 2) started to experience seizures at two weeks of age, characterized by behavioral arrest, increased tone, grimacing, and flushing. An EEG performed at day 21 of life was normal, although her typical spell was not captured (Table 1). At week 6 of life, the patient experienced a cluster of similar episodes along with apnea and cyanosis and associated on the surface EEG with ictal onsets originating independently from multiple brain regions with migration of the ictal discharge from one hemisphere to the other during the same seizure event (Figure 1A). A brain MRI showed a persistent cavum septum pellucidum with a corpus callosum of normal length and thickness (Figure S1B).[3] MRS and metabolic investigations were normal (Table 1). An immune profile revealed a reduction of lymphocytes and a low IgM level (Table 1). On examination, the patient had severe developmental delay and her seizures remained poorly controlled despite treatment with various combinations of antiseizure medications (Table 1). At the age of 6 months, she experienced flexor and tonic spasms in clusters associated with hypsarrhythmia (Figure 1B) that responded to ACTH. Subsequent serial video/EEG recordings documented slowing of the background, multifocal independent spikes, and focal seizures originating from multiple independent brain regions. An EEG performed at 15 months while maintained on phenobarbital, levetiracetam, clonazepam, lacosamide, and valproate depicts one of her innumerable recorded focal-onset seizures (Figure 1C). Her seizures persisted and recurred in cluster multiple times daily until potassium bromide was introduced at 18 months of age, after which, according to her parents' report, she remained seizure free till her death from sepsis one month later. While on potassium bromide, the child was more somnolent and sedated relative to her baseline state.

Key Points

- Seizure threshold-2 gene is highly expressed in the central nervous system and acts by regulating the mechanistic target of rapamycin (mTOR).
- We are reporting a new possible familial case affecting two sisters harboring a SZT2 gene variant.
- Both siblings were diagnosed with the syndrome of epilepsy of infancy with migrating focal seizures.
- Both sisters were highly pharmacoresistant and experienced a dramatic reduction in seizure frequency following the introduction of potassium bromide.

Whole exome sequencing revealed a SZT2 homozygous variant Chr1(GRCh37):g.43868902C > T; NM_015284.3:c.82C > T; p.(Arg28*), with homozygosity confirmed by parental testing who were both heterozygous for that variant. The SZT2 homozygous variant c.82C > T p.(Arg28*) creates a premature stop codon and is classified as likely pathogenic (Class 4) according to the ACMG guidelines. No other variants were found.

3 | DISCUSSION

We present two siblings, one of whom had a documented novel homozygous nonsense variant in the SZT2 gene, c.82C > T p. (Arg28*), resulting in an early stop of protein translation. This variant was never reported hitherto and was

TABLE 1 Characteristics of the two siblings

	Patient 1	Patient 2
Dysmorphic facial features	High forehead, down-slanting palpebral fissures and ptosis	High forehead, down-slanting palpebral fissures and ptosis
Psychomotor development	*At 5 months*: complete head lag, axial and appendicular hypotonia, could not sit, did not reach for objects with absent visual tracking and no reactivity to auditory or visual stimuli. Never acquired any milestone.	At *6 months*: complete head lag, axial and appendicular hypotonia, could not sit, did not reach for objects with absent visual tracking and no reactivity to auditory or visual stimuli. Never acquired any milestone.
Age at first seizure	1 mo	2 wk
Initial semiology	Behavioral arrest, blinking and flushing	Behavioral arrest, increased tone, grimacing and flushing
Stormy phase	At 4 months: staring, blinking, flushing, increased tone, apnea and cyanosis with desaturation ± unilateral increased tone or clonic jerking	At 6 weeks: behavioral arrest, facial cyanosis, increased tone, apnea and desaturation At 6 months: epileptic spasms
Seizure frequency	Multiple times daily in clusters	Multiple times daily in clusters
Seizure Duration	1-2 min	1-2 min
Initial EEG	Multifocal independent spikes with innumerable multifocal-onset seizures originating independently from the right parasagittal, right posterior temporal, and left frontotemporal regions and sometimes migrating from one hemisphere to the other (at 5 months)	Normal (at 2 wk)
Subsequent Worse EEG	Same as initial EEG	Generalized slowing, multifocal independent spikes with ictal activity originating independently from the right frontotemporal, left temporal or bilateral temporal areas, and on occasions, the ictal discharge propagated from one hemisphere to the other (at 6 wk) Hypsarrhythmia (at 6 mo)
Brain MRI	Persistent cavum septum pellucidum and a short corpus callosum of normal thickness	Persistent cavum septum pellucidum with a corpus callosum of normal length and thickness
Brain MRS	Normal	Normal
Metabolic workup	Normal	Normal
Immune workup	Decrease in all lymphocyte subsets and a decrease in all immunoglobulin levels	Decrease in cytotoxic T lymphocytes, T helper lymphocytes and natural killer cells. Normal B lymphocyte levels. Low IgM with adequate levels of IgG and IgA
AEDs tried in multiple combinations	Phenytoin, carbamazepine, oxcarbazepine, levetiracetam, clonazepam, valproate, potassium bromide	Levetiracetam, valproate, phenobarbital, clonazepam, lacosamide, ACTH, potassium bromide
Other treatment	Biotin, pyridoxine, folinic acid	Biotin, pyridoxine, folinic acid
Outcome	Death at 11 mo	Death at 19 mo

not identified on the NHLBI Exome Sequencing Project (ESP) Exome Variant server (http://evs.gs.washington.edu/EVS). The population allele frequency of this variant was found to be 3.54e-6 (using gnomAD database; https://gnomad.broadinstitute.org), which reflects the rarity and pathogenic likelihood of this nonsense variant.

SZT2 gene variant was first reported by Vanagaite et al in two unrelated children who shared common dysmorphic facial features, a distinctive early-onset refractory epilepsy with encephalopathy and absent developmental milestones.[2] Since its original description, 19 additional cases were reported. Most were sporadic with only four families affected accounting for 9 of the 21 cases.[4-6] We are reporting a new possible familial case, the second of an Arabic descent,[5] harboring a SZT2 gene variant.

SZT2 loss-of-function variants alter the mechanistic target of rapamycin (mTOR) signalling.[7] This may explain the role of its variants in epileptogenesis.[1] It was recently shown that SZT2 dysfunction leads to a hyperactivation of the mTORC1 signaling pathway resulting in increased cell proliferation, disturbed connectivity of the brain and epileptogenesis.[1,8,9] SZT2 gene variants are associated with differing phenotypic expressions ranging from mild-moderate intellectual disabilities without seizures,[10] to an early-onset epileptic

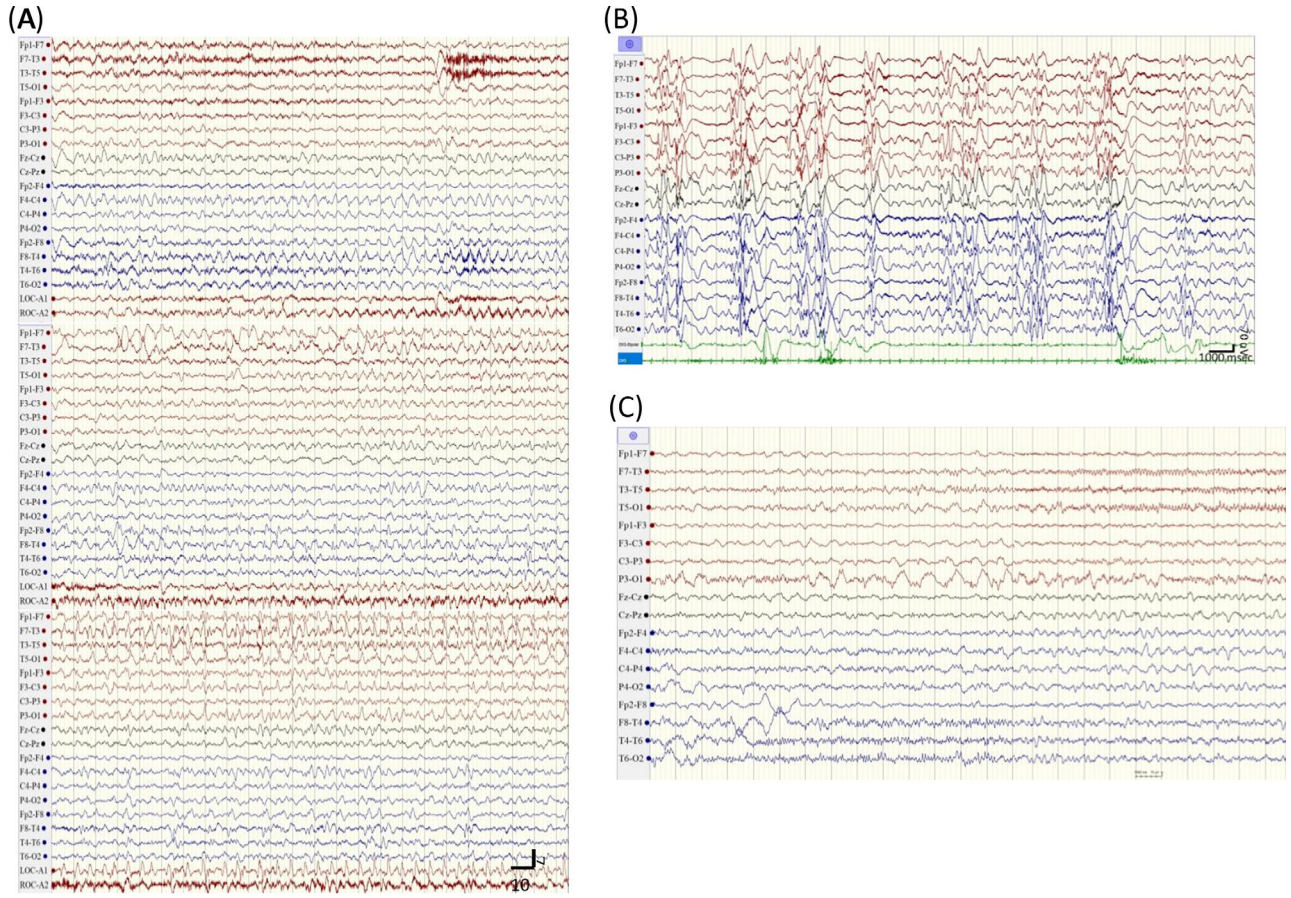

FIGURE 1 A, Consecutive EEG pages showing an ictal activity originating from the right hemisphere and migrating to the left hemisphere. B, Hypsarrhythmia with epileptic spasms in clusters seen on the EMG channel. C, Focal seizure that originated from the right temporal area and propagated 25 s later to the left temporal area

encephalopathy with severe cognitive impairment.[6] The severity of clinical manifestations varies according to the extent of residual protein function. As such, a biallelic truncating variant, as described in our patient, will result in a complete loss of SZT2 function and lead to a severe phenotype while the milder form is associated with homozygous in-frame deletions of a single amino acid.[11] Characteristically, hypotonia and facial dysmorphism, including a high forehead and to a lesser extent ptosis and down-slanting palpebral fissures, were present in the majority of reported patients including ours.[4,11,12] Although no genetic testing was done on the first child, as the WES was not available in our institution at the time, she was almost certainly affected by the same condition in view of her indistinguishable dysmorphic features, and essentially identical clinical course, EEG findings, and seizure semiology.

Most patients with an STZ2 variant (18/21; 86%) experienced seizures with a variable age at onset but mostly during the first 10 months of life.[6,11] The reported seizure types consisted of focal-onset seizures, tonic seizures, and atypical absences.[6,13] Focal or multifocal epileptiform discharges were seen on the interictal EEG[6,13] while the ictal findings, described in only two previous cases originated from the temporal area.[6] We are the first to report that EIMFS can be secondary to a STZ2 variant. This condition, first described in 1995,[14] is a severe form of pharmacoresistant epilepsy characterized by recurrent seizures with an onset in the first 6 months of life, EEG documentation of seizures with multifocal ictal origins, and migration from one cortical region to another, in addition to profound developmental regression.[15,16] Focal motor seizure is the most frequent and characteristic seizure type encountered in this syndrome.[15,16] Although our two siblings did not have this particular seizure type, they both experienced recurrent daily clusters of focal impaired awareness seizures characterized by generalized stiffening and eye blinking associated with prominent autonomic manifestations, a semiology frequently described in this syndrome.[15,16] In addition, the co-occurrence of infantile spasms in our second case associated with hypsarrhythmia has been described in infants with EIMFS.[16] Initially considered to be nonfamilial and of an unknown etiology, this condition was recently linked to several mutations most commonly affecting the KCNT1 and SCN2A genes.[17] All were de-novo mutations

except for three previous reports of familial EIMFS.[18–20] Our two patients were highly pharmacoresistant but both experienced a dramatic reduction in seizure frequency following the introduction of potassium bromide. Potassium bromide was reported to be effective in reducing seizure frequency in several cases diagnosed with EIMFS of various etiologies.[16,21–24]

It was initially suggested that SZT2 variants are associated with two distinctive MRI findings consisting of a thick and shortened corpus callosum (CC) along with a persistent cavum septum pellucidum (CSP).[2] Subsequent accounts however failed to consistently describe those findings and reported normal imaging studies or different types of abnormalities including delayed myelination, dilated ventricles, atrophy, heterotopia, or subependymal nodules.[6,12,13] Both our patients had evidence of a persistent CSP on brain MRI with an abnormally short but not thickened CC in one of them. Interestingly, the detected CSP might not represent an incidental finding since it was reported to be a developmental anomaly that may contribute to epileptogenesis.[25]

Basel-Vanagaite et al (2013) published a very similar variant (early homozygous truncation of SZT2 at position 25) in a 10-year-old girl, the sixth child of nonconsanguineous parents of Iraqi Jewish descent. One of her brothers, probably affected by the same condition, died at the age of three years from a pulmonary infection. Like our two siblings, this girl had the same facial dysmorphic features (high forehead, down-slanting palpebral fissures, and ptosis), severe developmental delay, hypotonia, and absence of developmental milestones.[2] Her seizures however started later at the age of 4 years (although the seizure onset in her affected brother was at the age of two months) and consisted of highly refractory focal impaired awareness seizures semiologically characterized by drooling and perioral cyanosis with occasional focal to bilateral tonic-clonic seizures. Her interictal EEG was characterized by a slow background with multifocal epileptiform discharges, and her ictal EEG revealed focal 6 Hz or 12-14 Hz discharges that secondarily generalized.[2] However, unlike our two siblings, there was no mention of ictal propagation from one hemisphere to the other.

Both siblings suffered from repeated infections and were found to have abnormalities in their immune workup. Whether SZT2 variants are associated with immunodeficiency will need to be confirmed in subsequent studies.

In summary, our findings expand the phenotypic spectrum of SZT2 variants and corroborate the importance of genetic counseling in some cases of EIMFS. In addition, they suggest that potassium bromide might be useful for the management of refractory seizures associated with SZT2 variants.

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CONFLICTS OF INTERESTS

None of the authors has any conflict of interest to disclose. 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 online in the Supporting Information section.

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