

Novel bandlike signal abnormality suggestive of heterotopia in patient with a *KCNQ1* frameshift mutation

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SUMMARY

Malformations of cortical development are associated with epilepsy and cognitive dysfunction, and can occur in patients with *SCN1A* ion channel mutations. We report a novel and subtle bandlike subcortical heterotopia on integrated positron emission tomography–magnetic resonance imaging (PET-MRI) in a patient with treatment-resistant epilepsy due to a de novo *KCNQ1* frameshift mutation. Our case highlights the potential for other channel mutations to cause both epilepsy and cortical malformations. Further scrutiny of high contrast resolution MRI studies is warranted for patients with *KCNQ1* and other epilepsy genes to further define their extended phenotype.

KEY WORDS: Band heterotopia, 7-T MRI, *KCNQ1* mutation.

CASE PRESENTATION

A 17-year-old right-handed woman with treatment-resistant focal epilepsy developed seizures at age 6 years, characterized by staring, head drop, and abnormal movements of the right arm, usually lasting about a minute. She was amnesic for her seizures. She was started on divalproex, with a good initial response. She was weaned off divalproex and was seizure free for 2 years before seizures recurred. She failed a retreatment of divalproex and developed a rash from oxcarbazepine therapy. Her current medications included clobazam, lamotrigine, levetiracetam, and topiramate. Average seizure frequency is two to three seizures per week, comprising episodes of staring, subtle behavioral arrest, and

bilateral hand automatisms, occasionally with a slow head drop. Her sister had one isolated febrile seizure at age 1 year. Her mother's pregnancy, labor, and delivery were unremarkable. Developmental milestones were normal. She currently has academic challenges in school that are considered secondary to seizures and antiepileptic drug side effects. Neurological examination was normal.

Video-electroencephalographic (EEG) findings revealed multifocal and generalized cortical hyperexcitability, as well as five electroclinical seizures with generalized EEG onsets. One electroclinical seizure had a broad left hemispheric onset, and one subclinical seizure had a right hemispheric onset.

A 3-T integrated positron emission tomography–magnetic resonance imaging (PET-MRI) study appeared normal except for a subtle ribbonlike T1 hypointense signal abnormality in the posterior cerebral hemisphere white matter, consistently ~1 cm deep to the cortical undersurface. The finding was bilateral (affecting the right hemisphere more than the left) and involved the bilateral occipital, parietal, temporal, and posterior frontal lobes, while sparing the mesial surfaces (Fig. 1). There was no corresponding abnormality appreciated on the susceptibility, diffusion, fluid-attenuated inversion recovery, or T2-weighted image sequences. It should be noted that visual detection of this T1

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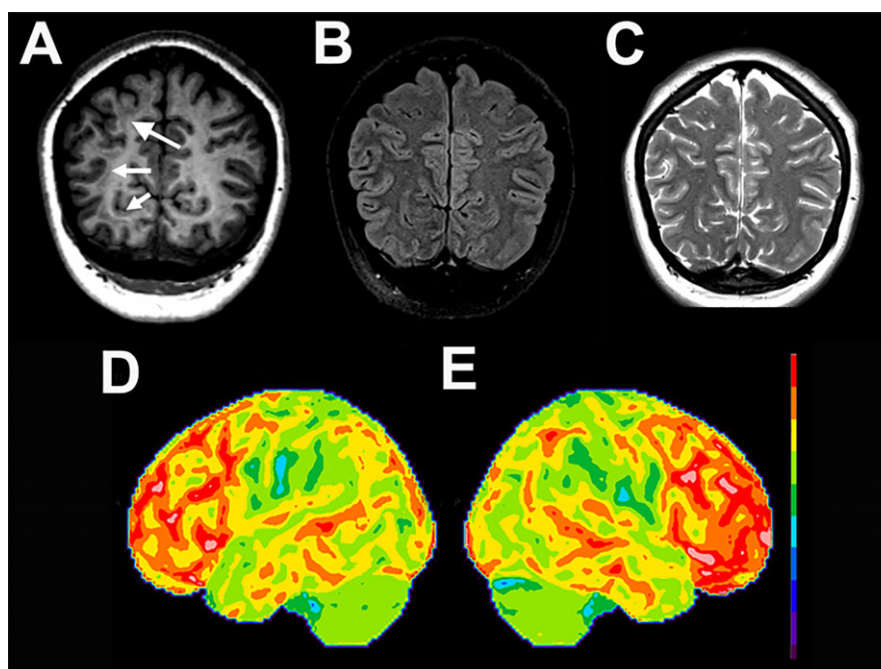


Figure 1.

Bandlike signal heterotopia identified on 3-T magnetic resonance imaging (MRI) and fluorodeoxyglucose (FDG)-positron emission tomography (PET) studies. **(A)** Coronal T1-weighted MRI demonstrates a hypointense band of signal abnormality in the subcortical white matter (arrows) that is more pronounced in the right hemisphere. **(B, C)** The lesion is not isointense to gray matter, and there is no corresponding signal abnormality on the companion coronal fluid-attenuated inversion recovery **(B)** or T2-weighted images **(C)**, as would be expected for a classic gray matter band heterotopia. **(D, E)** FDG-PET surface reconstructed images of the left **(D)** and right **(E)** hemispheres demonstrate relatively symmetric mild decreased FDG uptake in the posterior cerebral hemispheres, particularly in the parietal opercular regions (FDG uptake scaled relative to primary motor cortex).

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hypointense signal band required careful windowing of the contrast on the volumetric T1 images; a cursory review with typical window settings (or use of postcontrast volumetric T1 only) would make this very challenging to recognize. It is important to note that the subcortical white matter T1 hypointense signal band was not isointense to the overlying cortex, as would be expected for a typical gray matter band heterotopia.^{1–3} Although the MRI findings in our case were quite distinct from band heterotopia, the ribbonlike pattern parallel to the undersurface of the cortex suggested a migrational abnormality, potentially due to a genetic, metabolic, or early developmental problem leading to premature arrest of neuronal migration. However, we doubt this was due to a prenatal or perinatal injury in light of the subsequently diagnosed genetic disorder. Furthermore, in contrast to a typical band heterotopia, simultaneous fluorodeoxyglucose (FDG)-PET revealed highly concordant mild glucose hypometabolism throughout the bilateral posterior hemispheres (Fig. 1D,E).^{1,2} A high-resolution volumetric T1 sequence using 7-T MRI confirmed the MRI abnormality observed on conventional 3-T MRI (Fig. 2A–C).

Neuropsychological testing found general intellectual functioning in the borderline range, with impairments in processing speed, left hand dexterity, aspects of

visuoconstruction, naming, verbal fluency, verbal list-learning, figural fluency, and set-shifting; overall, the findings suggested diffuse bilateral cerebral dysfunction. The consensus at interdisciplinary epilepsy surgery conference was to recommend vagus nerve stimulation (VNS), because seizure onsets were generalized or multifocal, and neither resection nor responsive neural stimulation appeared likely to help given widespread EEG seizure onsets and diffuse bilateral abnormalities on both MRI and FDG-PET. Whole exome sequencing was then obtained because of the novel imaging findings and identified a heterozygous de novo *KCNQ1* variant. The Agilent Clinical Research Exome Kit (Gene Diagnostics) based on human genome build GRCh37/UCSC hg19 was used and analyzed for sequence variants using a custom-developed analysis tool (Xome Analyzer, mean depth of coverage = 197×, quality threshold = 97.4%). The mutation is a frameshift in exon 1 (c.191delC p.Pro64LeufsX22) and is considered pathogenic. She was referred for cardiac evaluation and had a normal routine electrocardiogram (ECG) and 24-hour Holter study. After cardiology clearance, she underwent VNS placement with preoperative prophylactic beta-blockade. Three months after VNS placement, she had a 40% reduction in seizure frequency.

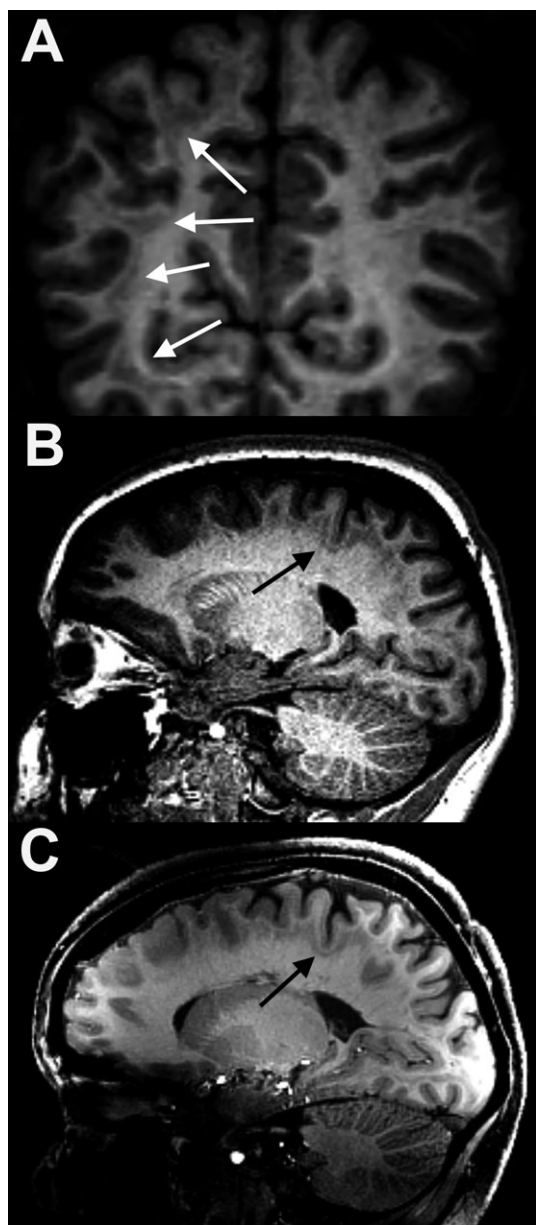


Figure 2. Findings on 3-T magnetic resonance imaging (MRI) demonstrating band heterotopia corroborated by 7-T MRI study. **(A)** Magnified coronal T1 image from Fig. 1A with scalp removed demonstrates the T1 hypointense band approximately 1 cm deep to the cortex in the posterior hemispheres. The abnormality was bilateral, but better visualized in the right hemisphere (arrows). **(B)** Companion right parasagittal image at 3-T also demonstrates the finding (arrow). **(C)** A follow-up high-resolution 7-T MRI also confirmed the finding (arrow).

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This unique case highlights a novel MRI finding associated with a diffuse bilateral seizure network and suggests an occult malformation of cortical development. The subtle bandlike T1 hypointensity was not detected on previous MRI for this patient and was only recognized with careful

scrutiny of the volumetric three-dimensional T1-weighted scan. The malformation does not have the same signal characteristics as the overlying gray matter on any MRI sequence, but is distributed similarly to a classic gray matter band heterotopia. Along with EEG findings, the simultaneously obtained FDG-PET and subsequent 7-T MRI helped to corroborate the MRI finding as meaningful. The imaging led to whole exome sequencing, which identified a novel de novo *KCNQ1* frameshift mutation. Previous work in the field has provided strong evidence that prenatal and perinatal insults, often in the setting of a genetic predisposition, are involved in the pathogenesis of malformations of cortical development.³ This has also been demonstrated in the case of the malformative spectrum with typical band heterotopias, which result from mutations of either the *LIS1* or the *DCX* (*XLIS*) gene.³ Here, we postulate that this novel MRI abnormality in our case is a migrational abnormality most likely due to haploinsufficiency of *KCNQ1* and the resultant deficiency of the potassium channel protein Kv7.1. Furthermore, there is precedent for the *KCNQ1* gene having an essential role in neuronal network synchronization and epileptogenesis. In postmortem studies assessing risk factors in sudden death in epilepsy (SUDEP), *KCNQ1* has been identified as a molecular risk factor for SUDEP and cardiac arrhythmias.⁴ This is further supported by data from animal models, where mutant knockin mice with mutations in human tetrameric voltage-gated potassium channel KvLQT1 (Kv7.1) demonstrate brief focal seizures, with a high incidence of concurrent EEG/ECG events. Other animal models with dominant point mutations in the *Kcqn1* gene have failed to demonstrate a clear epileptic phenotype, but have revealed auditory defects in these animals.⁴ Other ion channel mutations (e.g., *SCN1A*) also have been associated with malformations of cortical development.⁵ Additional cases are needed to corroborate the MRI findings, and animal models could further delineate the underlying pathophysiology.

DISCLOSURES OF CONFLICT OF INTEREST

T.S. is a speaker for Siemens Healthcare (unpaid). T.S. is cofounder and chief scientific officer for Velona Technologies, a start-up focused on medical devices for image-guided procedures (unpaid and unrelated to the work presented here). The other authors report no disclosures and no conflict of interest. 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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