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BRAT1 encephalopathy: a recessive cause of epilepsy of infancy with migrating focal seizures

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ABBREVIATIONS

EIMFS	Epilepsy of infancy with migrating focal seizures
RMFSL	Rigidity and multifocal seizure syndrome, lethal neonatal

Epilepsy of infancy with migrating focal seizures (EIMFS), one of the most severe developmental and epileptic encephalopathy syndromes, is characterized by seizures that migrate from one hemisphere to the other. EIMFS is genetically heterogeneous with 33 genes. We report five patients with EIMFS caused by recessive *BRAT1* variants, identified via next generation sequencing. Recessive pathogenic variants in *BRAT1* cause the rigidity and multifocal seizure syndrome, lethal neonatal (RMFSL) with hypertonia, microcephaly, and intractable multifocal seizures. The epileptology of *BRAT1* encephalopathy has not been well described. All five patients were profoundly impaired with seizure onset in the first week of life and focal seizure migration between hemispheres. We show that *BRAT1* is an important recessive cause of EIMFS with onset in the first week of life, profound impairment, and early death. Early recognition of this genetic aetiology will inform management and reproductive counselling.

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What this paper adds

- Recessive *BRAT1* pathogenic variants cause epilepsy of infancy with migrating focal seizures (EIMFS).
- *BRAT1* EIMFS has seizure onset in the first week of life and profound impairment.

[main text]
Epilepsy of infancy with migrating focal seizures (EIMFS) is one of the most severe epilepsy syndromes within the large group of developmental and epileptic encephalopathies.[1,2] EIMFS is highly genetically heterogeneous, with 33 genes reported in one or more cases.[3–8] Most frequently EIMFS is associated with de novo variants that follow dominant inheritance (e.g. *KCNT1, SCN2A*) and, rarely, with homozygous or compound heterozygous variants in recessive diseases (e.g. *SLC25A22*).[8] Onset of EIMFS occurs within the first 6 months of life, at a mean age of 3 months.[1] The hallmark of this severe epilepsy syndrome is seizures that migrate from one hemisphere to the other, which is ideally captured both clinically and on electroencephalography (EEG). Seizures typically escalate in frequency to become virtually continuous, culminating in status epilepticus. EIMFS is associated with developmental regression or stagnation, typically resulting in profound developmental impairment.

Recessive pathogenic variants in *BRAT1*, encoding breast-cancer-1(*BRCA1*)-associated ataxia telangiectasia mutated activator-1 protein, cause a rare syndrome called rigidity and multifocal seizure syndrome, lethal neonatal (RMFSL) (OMIM #614498). Neonates present with microcephaly and hypertonia with multifocal seizures beginning in utero or during the first week of life. RMFSL is often associated with death in infancy or childhood.[9–12] The epileptology has not been well described. Interestingly, less severe recessive *BRAT1* phenotypes have been more recently reported. Online Mendelian Inheritance in Man (OMIM) has adopted a collective term for patients with milder features, neurodevelopmental disorder with cerebellar atrophy with or without seizures (OMIM #618056). These patients present with a wider spectrum of features including later onset of seizures (3mo–3y), intrafamilial variation,

ambulation in some patients, and intellectual disability alone without neurological decline and longer survival.[10,11]

CASE SERIES

We identified five patients from four families with EIMFS (Table S1, online supporting information) who had recessive *BRAT1* pathogenic variants from Australia, Canada, Hong Kong, and the USA. All patients underwent detailed electroclinical phenotyping. The study was approved by the Human Research Ethics Committee of Austin Health and the local institutional research board of collaborating groups. Parents or legal guardians provided written informed consent for research participation.

BRAT1 mutations were identified by reanalysis of a commercial gene panel (patients 1 and 2 [sisters], and patient 5) or research whole exome sequencing (patients 3 and 4). Two patients had homozygous pathogenic variants in the setting of parental consanguinity (patients 3 and 4), and three, born to non-consanguineous parents, had compound heterozygous pathogenic variants (patients 1, 2, and 5). Two variants were recurrent (p.Gln322* in patients 1 and 2, p.Thr465Thr in patient 5), two were novel (p.Gln762*, p.Glu374*), and two were present in population databases in the heterozygous state (ExAC, gnomAD), but have not been previously reported in affected individuals (c.1498+1G>A, p.Leu454del).

Seizures started on day 1 of life in four cases and day 4 in patient 3. All had the pattern of focal seizures migrating between hemispheres (Table S1, Fig. S1, and Videos S1, S2, and S3, online supporting information). One patient had possible in utero seizures based on maternal report. At the age of 9 months, patient 3 developed epileptic spasms with hypsarrhythmia. All had microcephaly, which was congenital in patients 1, 2, 3 and 5, and acquired in patient 4. All five patients had generalized hypertonia consistent with the rigidity described in RMFSL.

Brain magnetic resonance imaging (MRI) within the first 3 months of life revealed white matter volume loss (patients 2 and 3), thinning of the corpus callosum (patient 2), and underopercularization of the Sylvian fissure (patient 1). Neonatal subdural or intraventricular haemorrhages were seen in patients 1 (Fig. 1), 3, 4, and 5.

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All five patients are deceased. Four died by 14 months of age, including two by 2 months, reflecting the poor survival often seen in EIMFS and RMFSL. Patient 3 had a similarly severe disease course, but survived until 4 years 3 months.

DISCUSSION

We report a cohort of five patients with EIMFS associated with homozygous or compound heterozygous pathogenic variants in *BRAT1*. While *BRAT1* is known as the cause of RMFSL, it was found in two patients in a developmental and epileptic encephalopathy cohort paper who were noted to have EIMFS with no clinical data provided,[13] and the epileptology of RMFSL has not been characterized.

Three of the *BRAT1* variants seen in our patients are present in population control databases (gnomAD, ExAC), but none has been reported in the homozygous state which we found in patient 3. This reflects previously reported patients with RMFSL who have *BRAT1* variants found in the heterozygous state in control population databases.[11] Patients 1, 2, and 4 had truncating variants, similar to reported patients with RMFSL.

Patient 3 had a homozygous variant at a 5' splice site, which is predicted to alter the mRNA sequence. This finding is similar to a different homozygous splice site pathogenic variant described in a Chinese female.[12] Patient 5 had a single amino acid deletion and a synonymous variant predicted to affect splicing. A less severe outcome may be associated with a splice site variant in the homozygous state. If residual correct splicing exists,[10] it could potentially explain the longevity of patient 3 who lived until 4 years 3 months. Improved longevity was also reported for the siblings with the mildest phenotype of *BRAT1* encephalopathy who were alive at 10 and 6 years respectively; they had a splice site variant, albeit in the compound heterozygous state with a truncating variant.[11] Similarly, another patient with different splice site and truncating variants lived to 5 years 9 months whilst their affected sibling with the same variants died at 2 months of age.[14] Thus, it is likely that modifying genetic factors ameliorate the phenotype. Patients with compound heterozygous pathogenic variants have been previously recognized to have milder phenotypes,[12] although *BRAT1* encephalopathy could never be termed a mild disorder.

BRAT1 encephalopathy has been associated with Ohtahara syndrome with a suppression-burst EEG in one Japanese sister with compound heterozygous *BRAT1* pathogenic variants; the epilepsy syndrome in her affected sister was not reported.[15] In a recent Korean series, patients with *BRAT1* mutations had later onset at 3 months; one patient presented with West syndrome and two patients presented with EIMFS, although further details are not provided.[13] A Chinese patient was recently reported with myoclonic seizures from shortly after birth and frequent ictal activity from multiple cortical areas; EIMFS was not described.[12] The neuropathology of *BRAT1* encephalopathy shows microcephaly, diffuse neuronal loss, gliosis of the cerebral and cerebellar white matter, thinning of the corpus callosum, and abnormal myelination,[12] reflecting the imaging findings in our patients and reported cases. Four of our

five cases had haemorrhages in different locations on brain MRI, despite a non-traumatic birth in three of four. We speculate that their rigidity may place them at increased risk of intracranial haemorrhage.

Pathogenic variants in *BRAT1* have also been associated with a milder group of phenotypes, termed neurodevelopmental disorder with cerebellar atrophy with or without seizures by OMIM, where children may walk and have limited speech, and live as long as 10 years of age. This contrasts starkly with our cohort of patients who did not achieve any major developmental milestones and were deceased by the age of 5 years.

BRAT1 was originally identified as a binding partner of BRCA1 and is now recognized to play a role in sensing damaged DNA and apoptosis, and also in mitochondrial homeostasis. In vitro studies in BRAT1 knockdown models show increased apoptosis, decreased cell proliferation and migration, decreased phosphorylation of ATM required for DNA damage response, and a role in the regulation of mitochondrial function.[9,12,14] Interactions between BRAT1 and the mTOR signalling pathway underlie cell growth and proliferation. Whether disruption of one or all of these pathways underlies the neurodegeneration seen in patients with *BRAT1* encephalopathy remains to be elucidated.[9,12]

Patients with EIMFS associated with *BRAT1* encephalopathy have an even more severe course than the typically severe picture of EIMFS, characterized by earlier seizure onset and death in early childhood. Key pointers to *BRAT1* EIMFS are: onset of seizures on day 1 of life or in utero, congenital microcephaly, hypertonia, and profound developmental delay. Onset of EIMFS in utero or on day 1 of life has also been reported for *SCN2A* and *KCNT1*; however, their median onsets are 3.5 days and 24 days respectively.[7] Four of our cases had onset in utero or on day 1 of life, and one had onset at 4 days of age.

BRAT1 is an important cause of EIMFS with phenotypic characteristics distinguishing it from other recessive causes such as *ALG1, ALG3, QARS, RFT1, SLC12A5, SLC25A22,* and *TBC1D24*.[3–8] We report five patients in whom the typical syndrome associated with *BRAT1* mutations, RMFSL, was not suspected. Earlier recognition of a genetic aetiology in patients with EIMFS ends the diagnostic odyssey and is critical for accurate reproductive counselling. Looking to the future, early genetic diagnosis will be essential for implementation of precision therapies.

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SUPPORTING INFORMATION

The following additional material may be found online:

Table S1: Clinical features of patients with EIMFS associated with *BRAT1* pathogenic variants

Figure S1: EEG tracings from patient 2 demonstrating one seizure with migration between hemispheres and three focal seizures with videos (see Video S1, S2 and S3)

Video S1: Video of patient 2 at age 23 days: focal seizure characterized by right lower limb clonic and tonic activity

Video S2: Video of patient 2 at age 35 days: focal seizure characterized by right upper limb clonic activity

Video S3: Video of patient 2 at age 4 months: focal seizure characterized by left upper limb clonic activity

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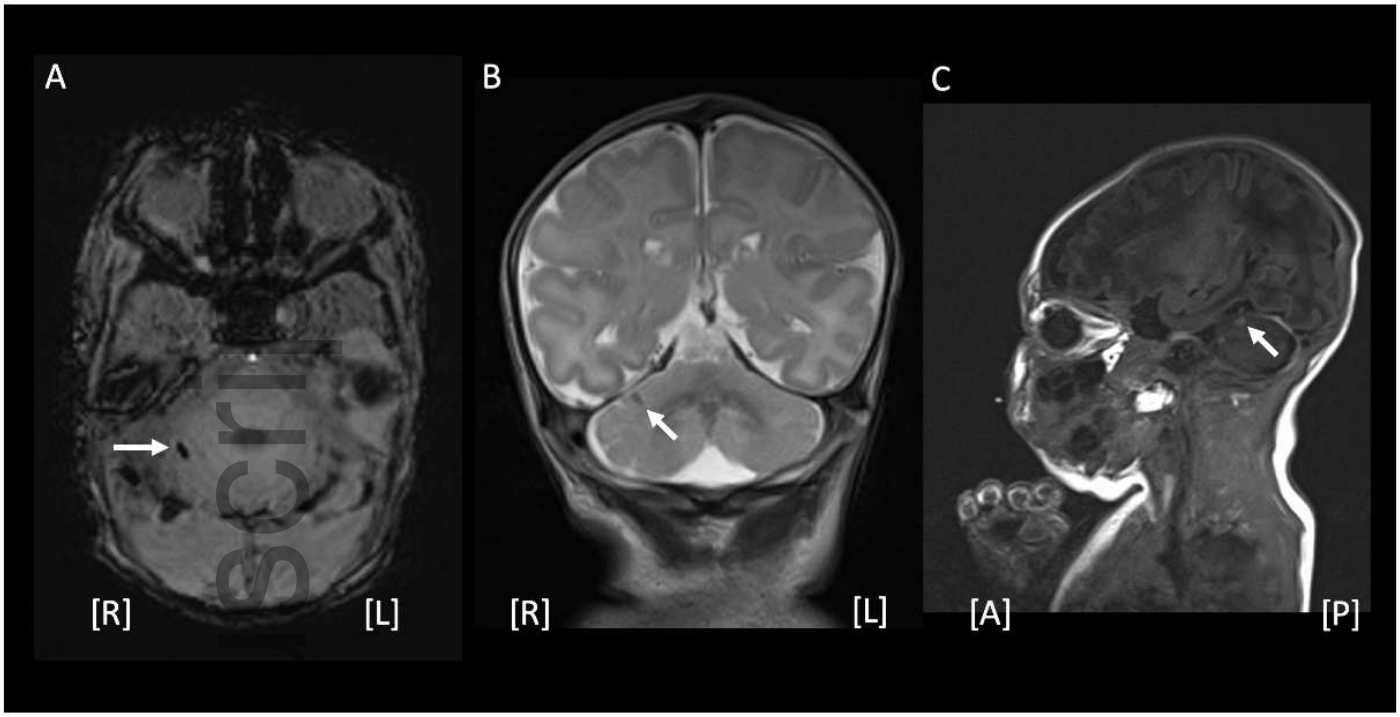
[Figure legend]

Figure 1: Brain magnetic resonance imaging for patient 1 on day 3 of life. Right cerebellar haemorrhage seen as (a) hypointense on axial susceptibility-weighted imaging, (b) hypointense on coronal T2-weighted imaging, and (c) hyperintense on sagittal T1-weighted imaging.



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