Supplementary material

Epileptic spasms are a feature of *DEPDC5* mTORopathy

Gemma L. Carvill[1], Douglas E. Crompton[2,3], Brigid M. Regan[2], Jacinta M. McMahon[2], Julia Saykally[1], Matthew Zemel[1], Amy L. Schneider[2], Leanne Dibbens[4,5], Katherine B. Howell [6,7,8], Simone Mandelstam[7,9,10], Richard J. Leventer[6,7,8,9], A. Simon Harvey[6,7,8,9], Saul A Mullen[2, 7], Samuel F. Berkovic[2], Joseph Sullivan[11], Ingrid E. Scheffer*[2,6,7] , Heather C. Mefford*[1]

Affiliations

1. Division of Genetic Medicine, Department of Pediatrics, University of Washington, Seattle, Washington, 98195, USA
2. Epilepsy Research Centre, Department of Medicine, The University of Melbourne, Austin Health, Melbourne, Australia
3. Neurology Department, Northern Health, Melbourne, Australia
4. Epilepsy Research Program, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, South Australia, Australia.
5. Sansom Institute for Health Research, University of South Australia, Adelaide, South Australia 5000, Australia.
6. Department of Neurology, Royal Children's Hospital, Melbourne, Australia
7. Florey Institute of Neuroscience and Mental Health, Melbourne, Australia
8. Murdoch Childrens Research Institute, Melbourne, Australia
9. Department of Paediatrics, The University of Melbourne, Melbourne, Australia
10. Department of Radiology, The University of Melbourne, Melbourne, Australia
11. Epilepsy Division, Department of Neurology & Pediatrics, University of California, San Francisco, 94143, USA

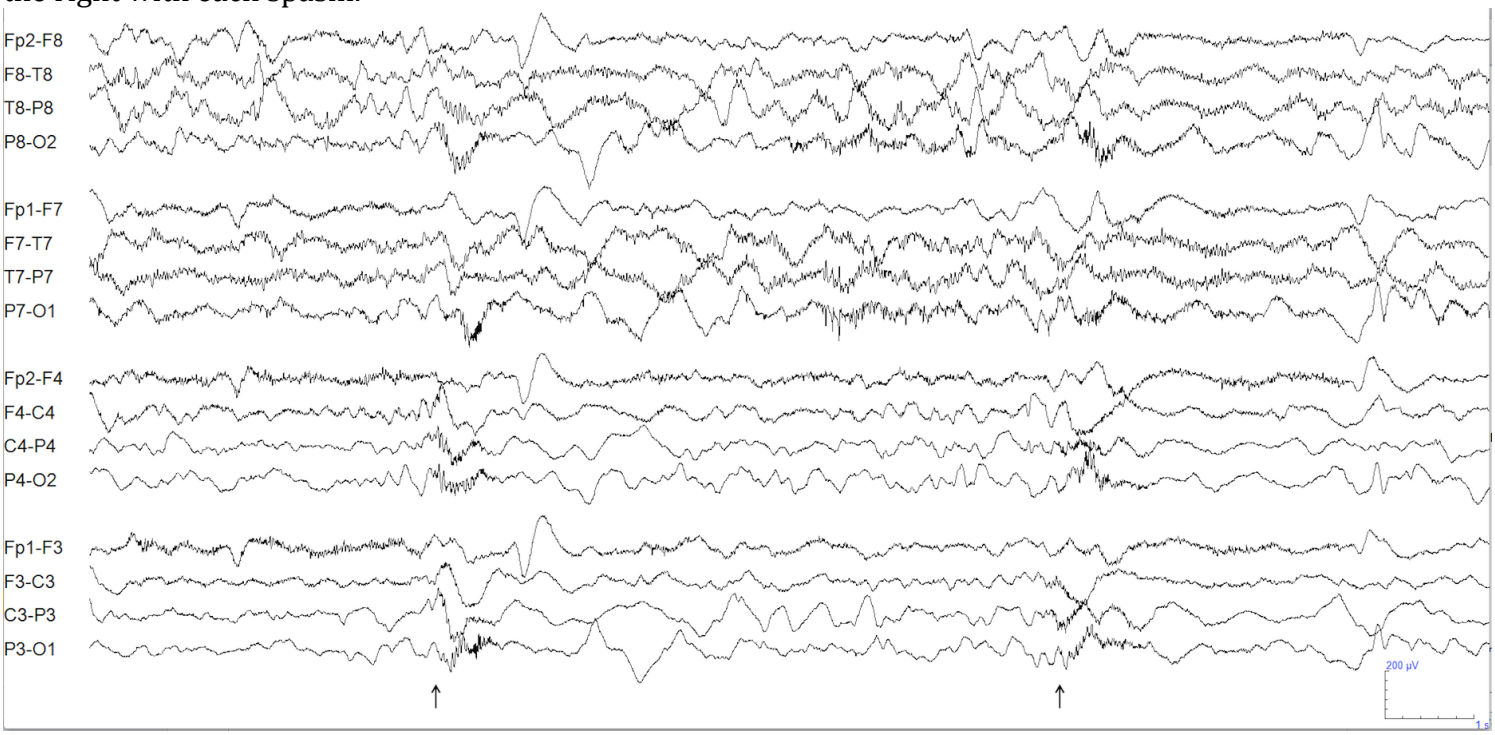
*To whom correspondence should be addressed: hmefford@uw.edu or scheffer@unimelb.edu.au

Table e-1 Disease-causing mutations identified in patients with infantile spasms in targeted and whole-exome sequencing studies.

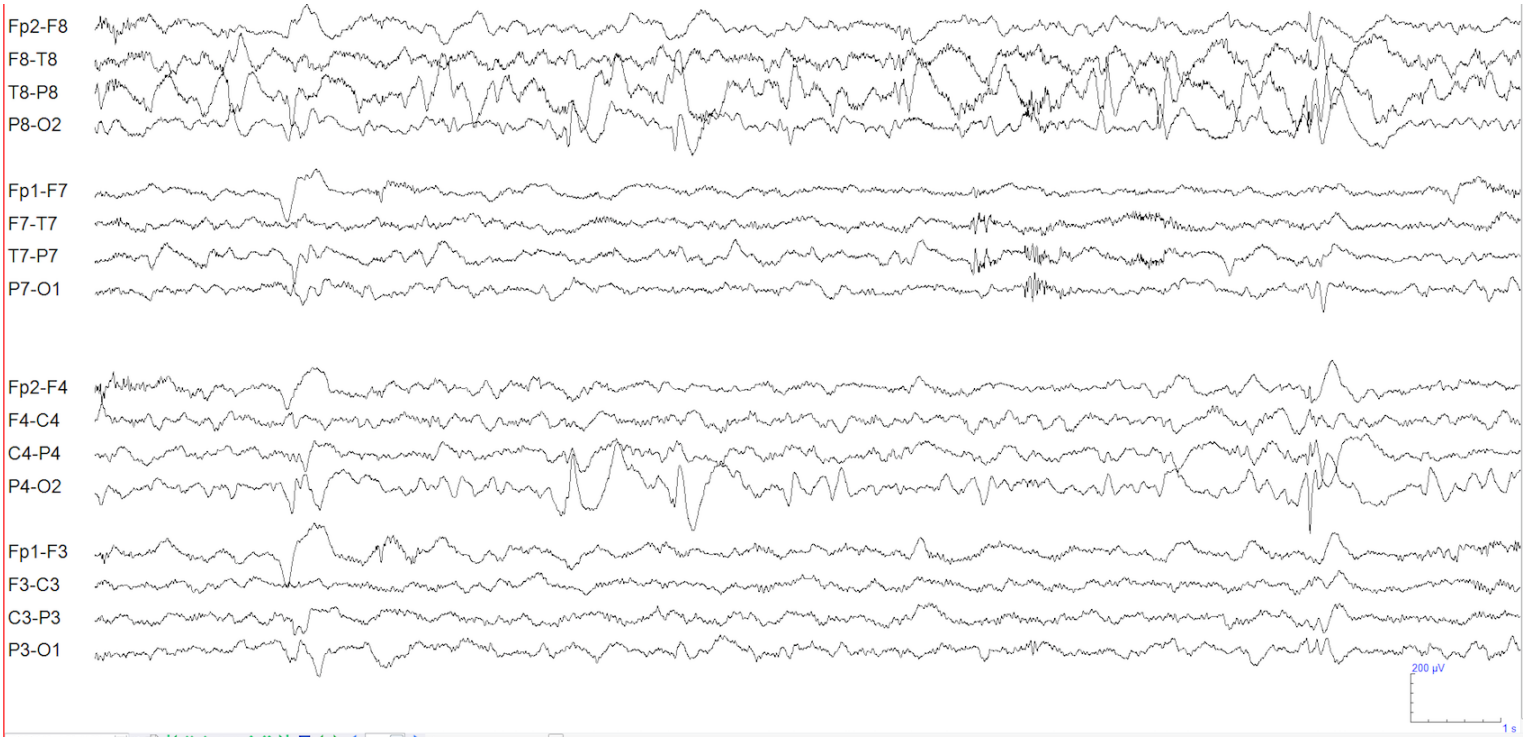
Gene	Carvill *et al*[1]	Epi4k consortium[2]	Michaud *et al*[3]	*TOTAL*
STXBP1	0	4	2	***6***
CDKL5	2	2	0	***4***
KCNQ2	1	1	0	***2***
ALG13	0	1	1	***2***
SCN1A	1	0	0	***1***
PNPO	0	0	1	***1***
ASDL	0	0	1	***1***
ARX	0	0	1	***1***
DCX	0	1	0	***1***
GABRA1	0	1	0	***1***
GABRB3	0	1	0	***1***
GRIN1	0	1	0	***1***
KCNT1	0	1	0	***1***
NEDDL4	0	1	0	***1***
PTEN	0	1	0	***1***
SCN2A	0	1	0	***1***
SCN8A	0	1	0	***1***
CASK	0	0	0	***0***
TOTAL	***4***	***17***	***6***	***27***
TOTAL** # infantile spasms **in cohort	***81***	***149***	***38***	***268***
% Solved	**5%**	**11%**	**16%**	

Figure e-1: EEG examples from individuals (A)A:III:2, (B)C:III:3 and (C)D:II:1.

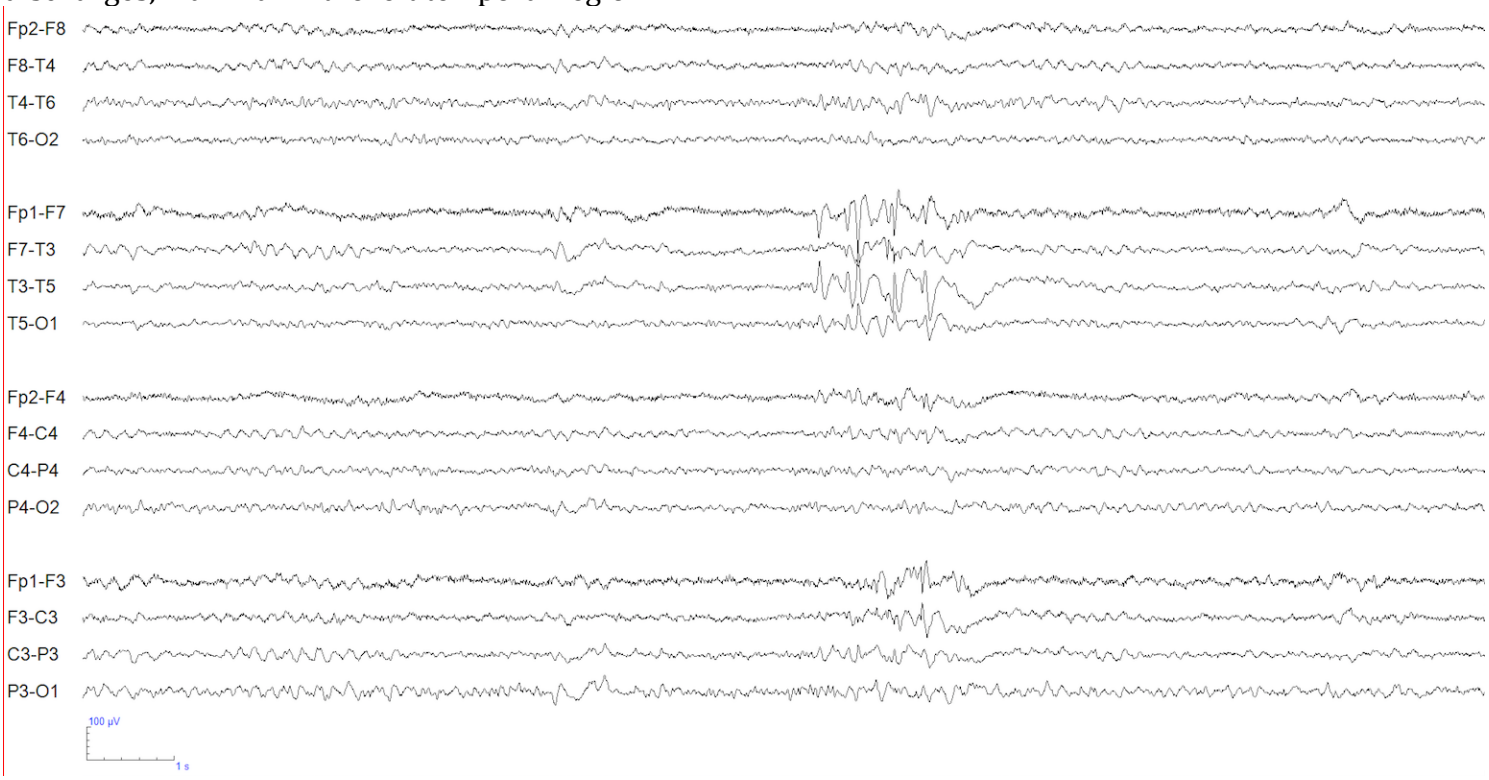
(A) A:III:2: EEG during a cluster of spasms at 4 months old showing spasm complexes (marked with an arrow), consisting of a slow wave paroxysm with after-going fast activity seen bilaterally. Some clinical asymmetries were seen (not shown), with greater movement of the right arm than left, and eye deviation to the right with each spasm.



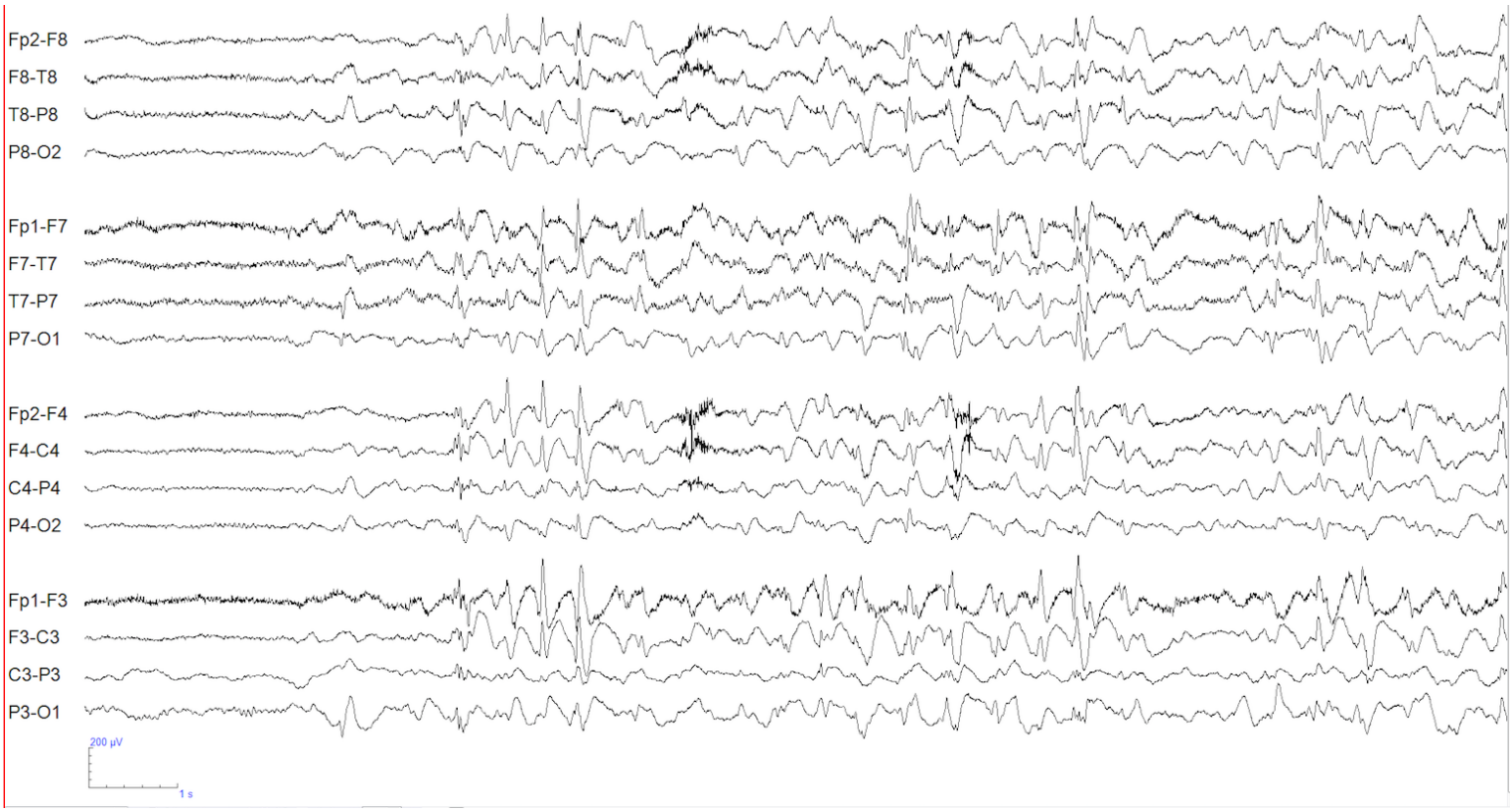
A:III:2: Interictal EEG recording at 7 months old showing an excess of focal slowing in the left mid-posterior temporal region, and focal epileptiform discharges maximal over the left temporal region.



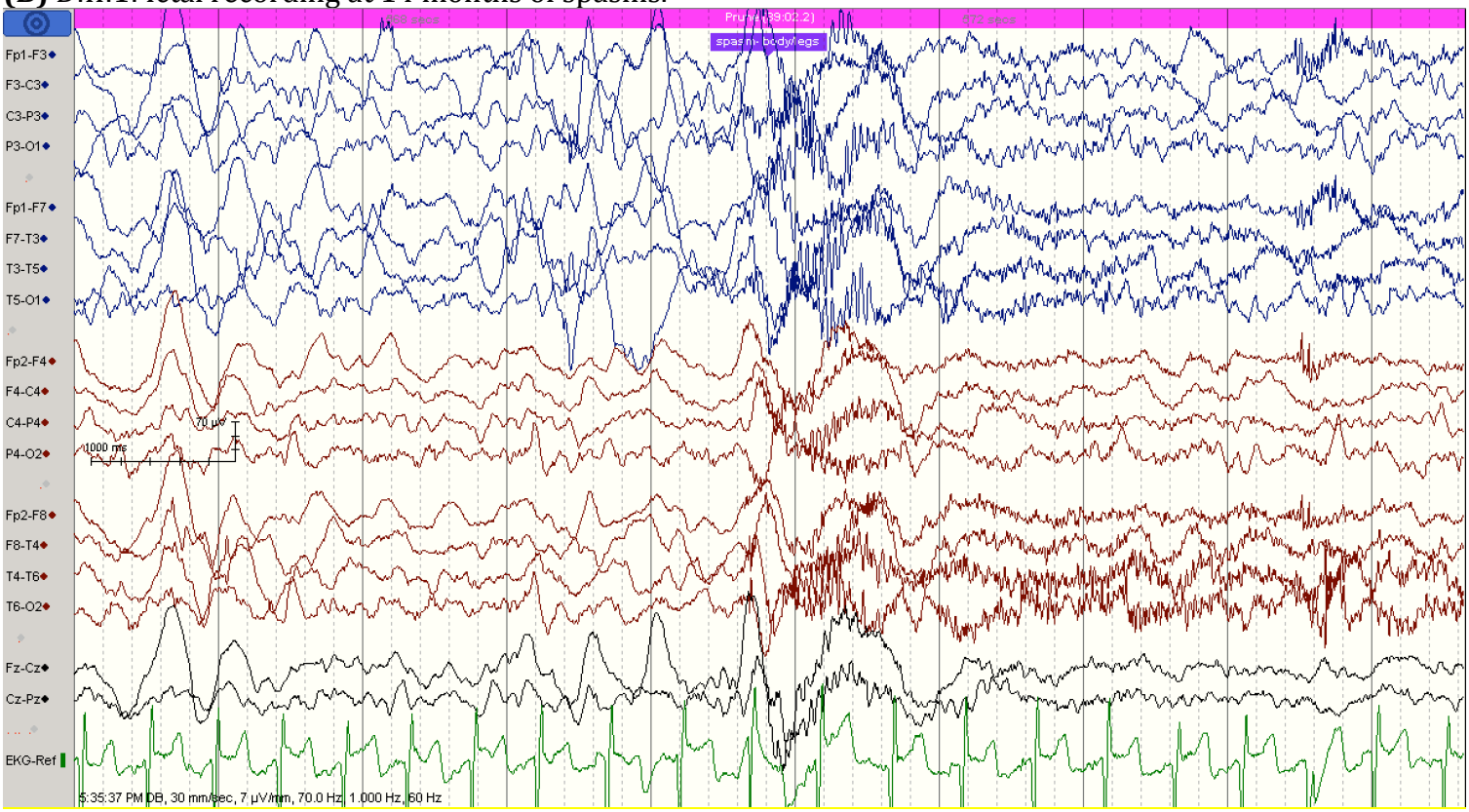
(B) C:III:3: Interictal EEG recording at 12 years old showing an excess of focal slowing and focal epileptiform discharges, maximal in the left temporal region



C:III:3: Ictal EEG recording at 15 years old during an atypical absence seizure showing bisynchronous 2.5Hz spike-wave activity



(B) D:II:1: Ictal recording at 14 months of spasms.



D:II:1: Interictal recording at 14 months showing focal fast activity in left frontocentral region on a background of hypsarrhythmia.

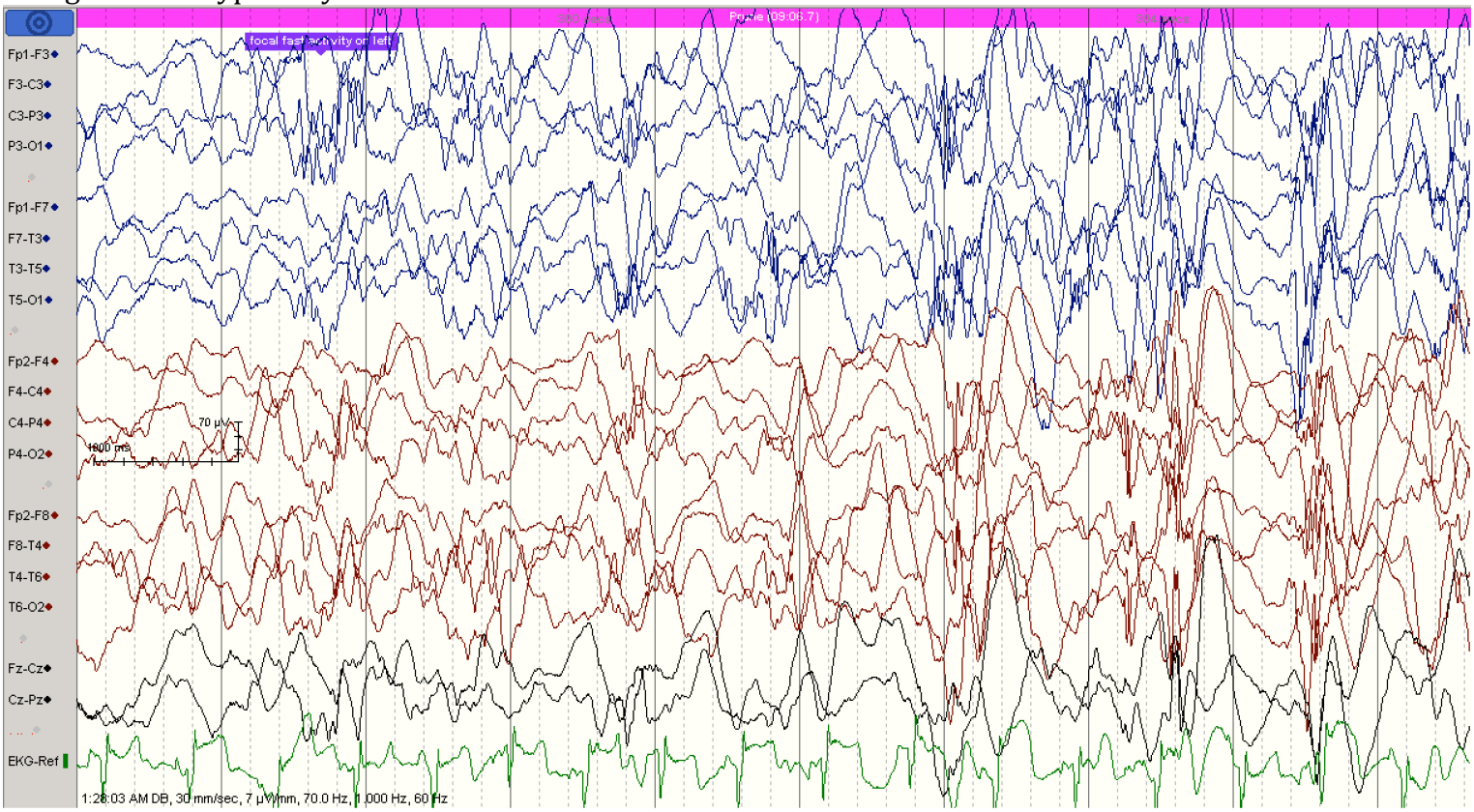
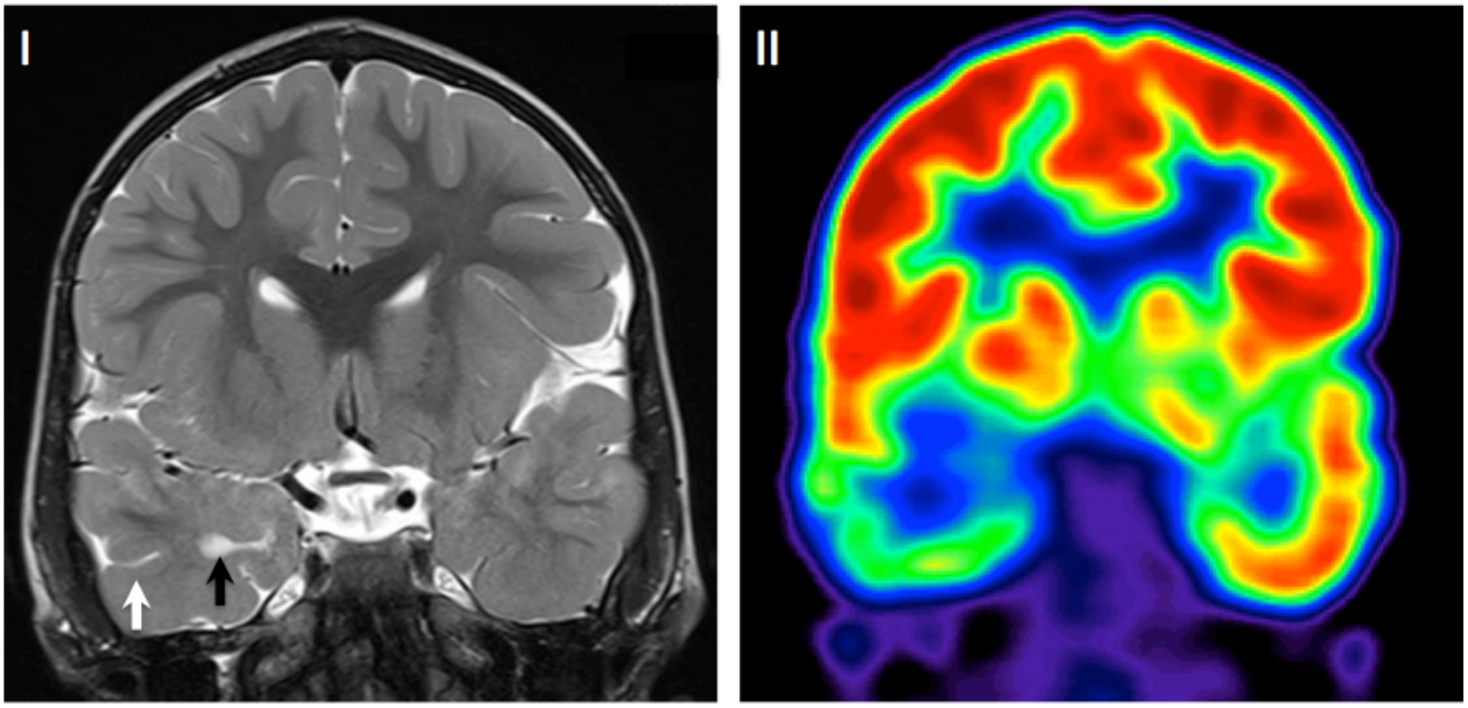


Figure e-2: (A) MRI and FDG-PET of focal cortical dysplasia in individual A:III:2 and (B) MRI of focal cortical dysplasia in individual D:II:1.

(A) Individual A:III:2: Coronal T2-weighted MRI (I) performed at age 32 months showing an abnormal right anterior temporal lobe with blurred grey white junction, dilated temporal horn (black arrow) and deep horizontal sulcus (white arrow) suggestive of cortical dysplasia. The corresponding coronal FDG PET image (II) shows marked hypometabolism of the right anterior temporal lobe.



(B) Individual D:II:1: Axial T1 weighted image (I) of the high frontal lobes demonstrate cortical thickening, irregularity and loss of grey-white differentiation (arrow)in the left frontal lobe. Axial T2 (II) at the same level demonstrates diffuse high signal intensity within the frontal white matter both medially and laterally (long arrows) compared to normal T2 hypointense white matter signal on the right (short arrows). There are also similar but more subtle findings in the left postcentral region.

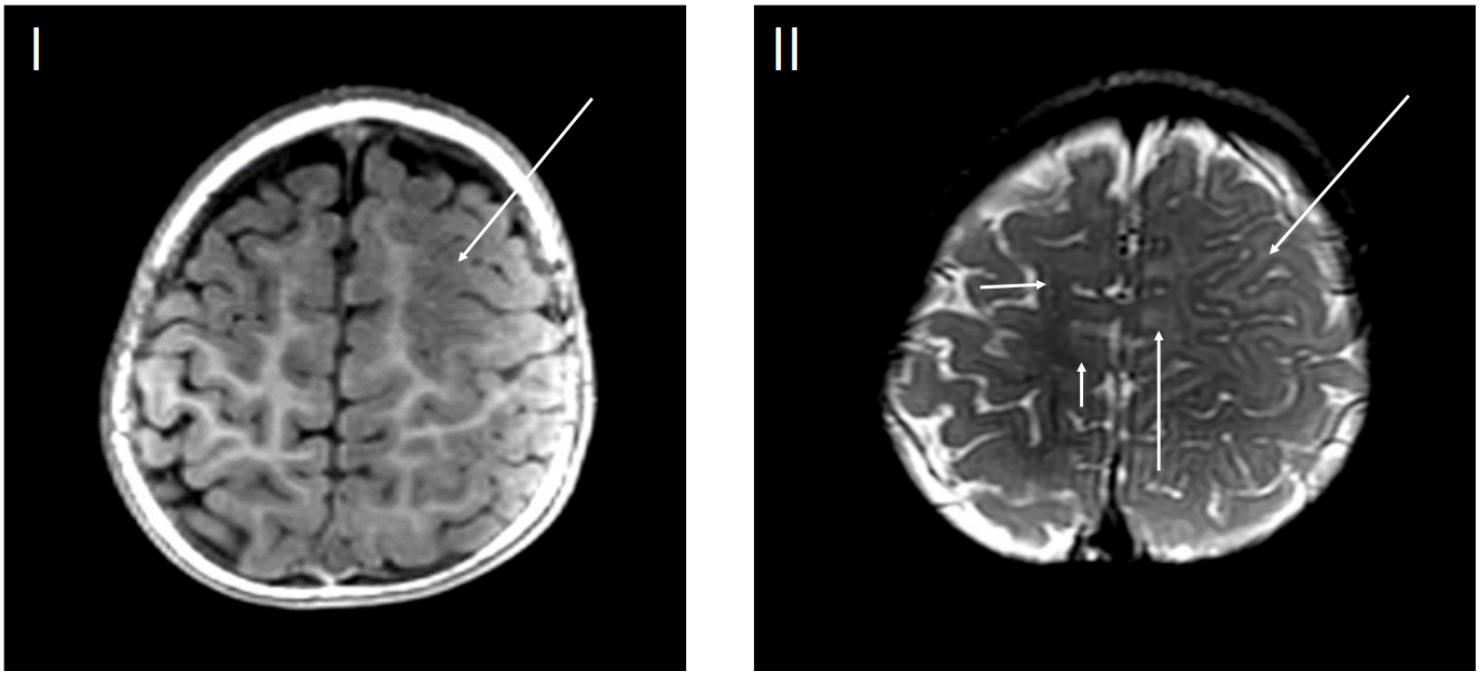
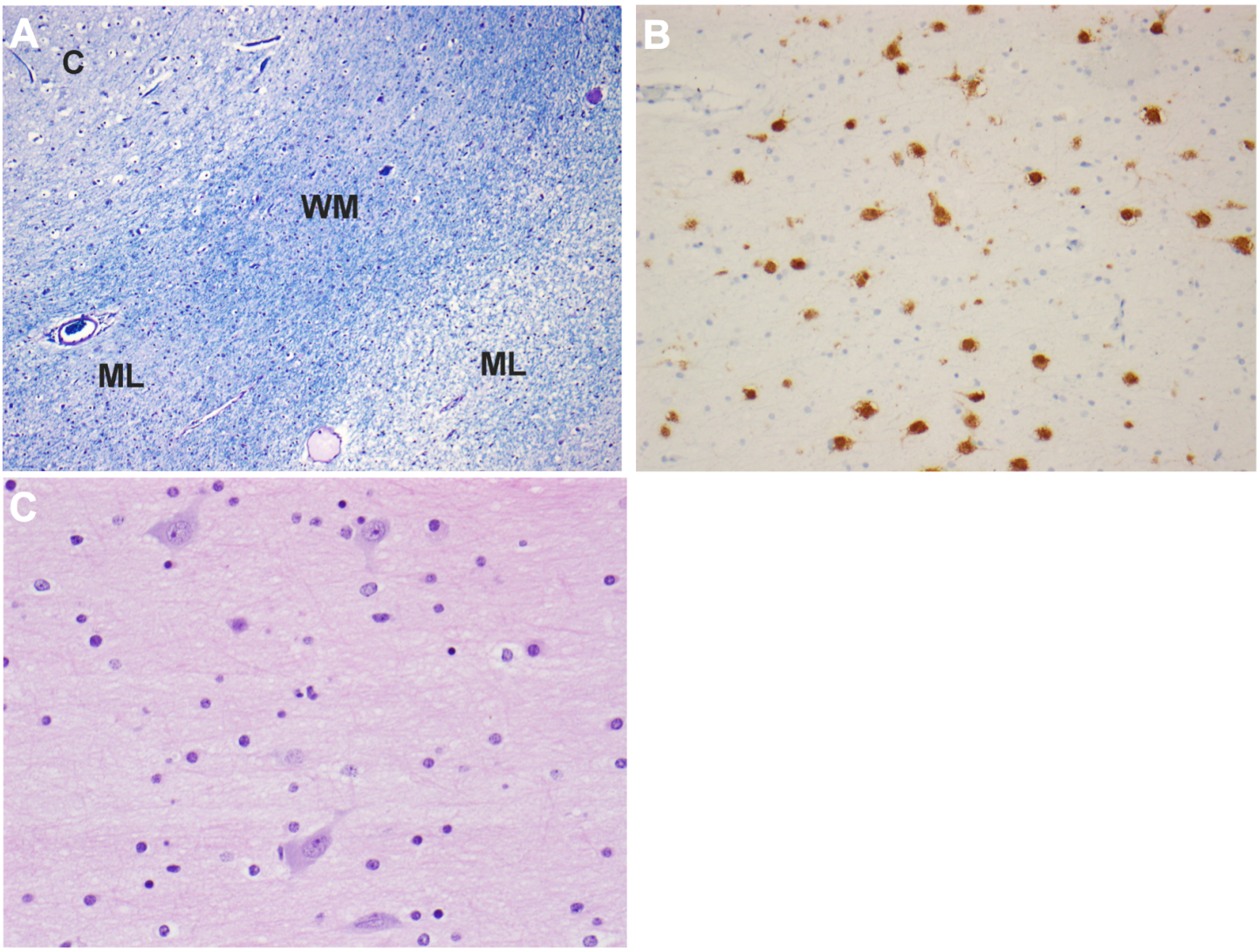


Figure e-3: Histology of left frontal tissue D:II:1 reveals FCD Type IIA with (A) Areas of dysmyelination; LFB-PAS Luxol-fast Blue and Periodic Acid-Schiff stain; C=cortex, WM= white matter, ML= myelin loss, 100X. **(B)** Neurons present in white matter; NeuN immunohistochemistry, 200X. **(C)** Dysmorphic neurons; Hematoxylin and eosin stain, 400X.



Supplementary references

1. Carvill GL, Heavin SB, Yendle SC, et al. Targeted resequencing in epileptic encephalopathies identifies de novo mutations in CHD2 and SYNGAP1. Nat Genet 2013;45:825-830.
2. Allen AS, Berkovic SF, Cossette P, et al. De novo mutations in epileptic encephalopathies. Nature 2013;501:217-221.
3. Michaud JL, Lachance M, Hamdan FF, et al. The genetic landscape of infantile spasms. Hum Mol Genet 2014.