Supplementary Information

Patient #1 Additional Details

Past medical history: The patient was ambidextrous. She had a history of hypertension, hyperlipidemia, migraines, and remote history of an ANA-positive connective tissue disease treated over 30 years prior with steroids. Medications at the time of presentation included losartan, hydrochlorothiazide, simvastatin, aspirin, ranitidine, escitalopram, flonase and astepro nasal sprays, and a number of vitamin supplements (folic acid, C, D3, CoQ10, biotin, omega 3, calcium).

Neuropsychological test results: At initial presentation, neuropsychological testing demonstrated multi-domain amnestic mild cognitive impairment (aMCI) with disruption of frontotemporal systems (left greater than right). The patient's Blessed Information-Memory-Concentration (BIMC) score was 6 (range 0-37), with questions missed on short-term memory and the current date. She scored 23/30 on the Montreal Cognitive Assessment (MoCA), missing 1 point each on attention and abstraction, and missing 5/5 points on delayed recall. Her global clinical dementia rating (CDR) scale (range 0-3) and CDR sum of boxes (range 0-18) scores were both 0.5. At 12 months after her initial presentation (while on levetiracetam therapy), her BIMC score was 2, slightly improved from prior. She scored 22/30 on the MoCA, missing 1 point for clock draw, 2 points for attention, and missing 5/5 on delayed recall. Her global CDR was 0.5, and CDR sum of boxes was 2.0.

Family history and genetic analysis: The patient was an *APOE3/APOE4* heterozygote. Her father and paternal aunt had developed dementia in their 50s, and her brother had recently been diagnosed with AD at age 70. Five younger siblings (ages 54-61) were clinically unaffected.

We concentrated on variants in genes with known association to dementia and epilepsy. Whole exome sequencing of the patient and four siblings identified an *APOE4* variant rs429358 [c.388T>C; p.C130R; http://www.ncbi.nlm.nih.gov/clinvar/variation/17864/] in all five siblings, but no pathogenic variants in genes known to cause early onset, autosomal dominant AD (*PSEN1, PSEN2, APP*) (Supp. Figure 2).
While we identified the presence of the known pathogenic nonsynonymous *APOE* ε4 variant rs429358 [c.388T>C; p.C130R; http://www.ncbi.nlm.nih.gov/clinvar/variation/17864/] in all five siblings, we found no definite pathogenic variants in the principal genes for familial/early onset AD *(APP, PSEN1 or PSEN2)* that would have been exclusively shared by the two oldest affected individuals III-1 and III-2 but absent from their younger presently asymptomatic siblings. We therefore expanded our molecular screen to genes associated with other dementia types and found a known rare nonsynonymous variant c.509A>G, p.H170R, rs147373451 in the *NOTCH3* gene known to be linked to cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)[1]. Though the variant is predicted to be pathogenic[1], it was not only seen in both affected siblings but also in their presently unaffected 54 year old sister (Supp. Figure 2b). Thus the functional contribution of this snv to dementia and epilepsy risk remains unclear. In the absence of plausible cause due to genic variation in *PSEN1*, *PSEN2*, or *APP*, we reviewed exomes of all siblings for variants in over 470 genes linked to human epilepsy and identified a known rare nonsynonymous variant rs200138205, c.3457G>A, p.E1153K, in the *SCN2A* gene (Supp. Figure 2b). While detrimental variants in the *SCN2A* gene have been identified in connection with intellectual disability, autism, and early onset epilepsy[2,3], the role of this gene in late onset epilepsy in the context of AD is unclear. Moreover the *SCN2A* variant was present not only in the proband

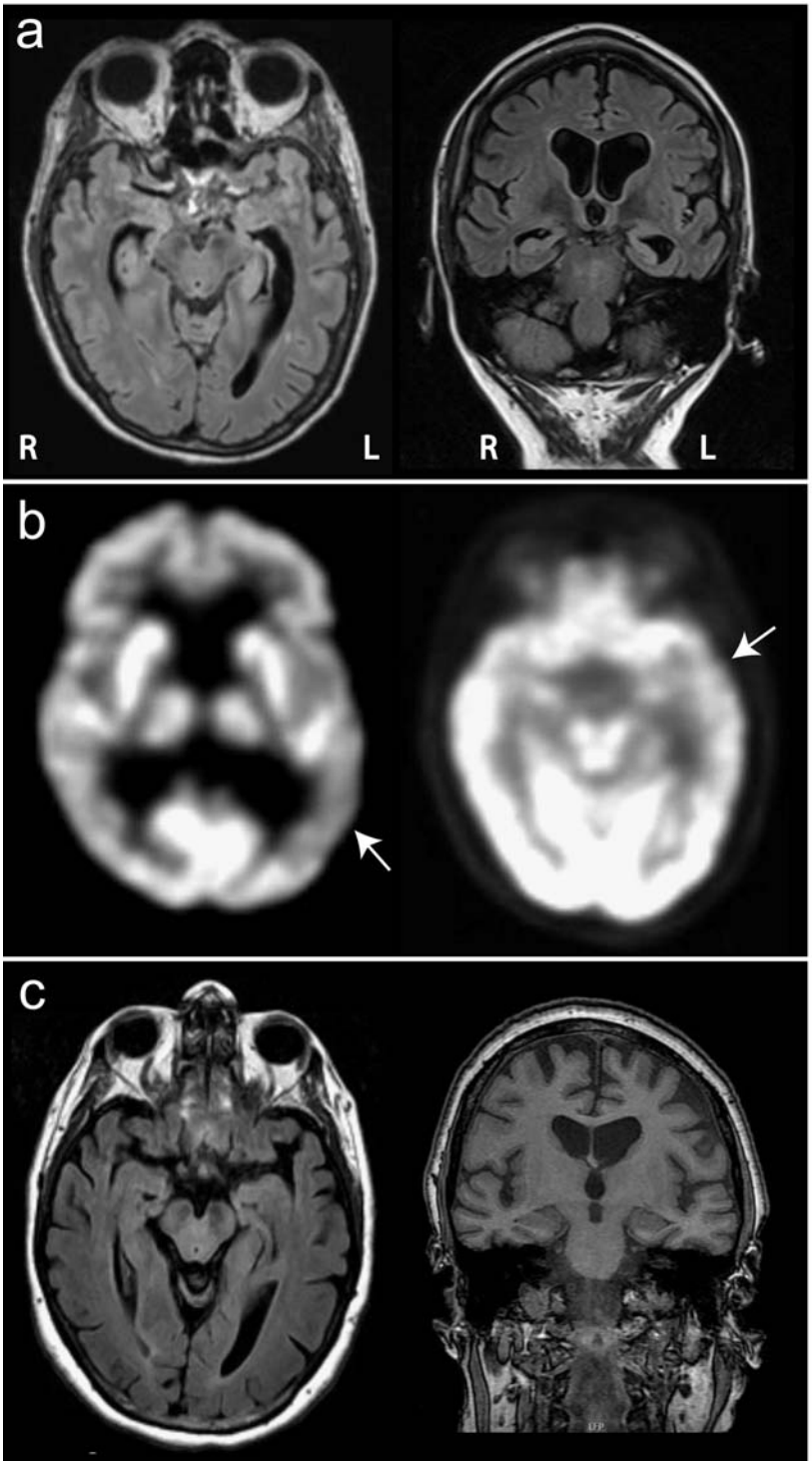
affected with AD and epilepsy but also in two presently asymptomatic younger siblings (Supp. Figure 2b). Thus, while variants of possible pathogenic significance in *NOTCH3* (CADASIL) and *SCN2A* (EIEE, Dravet syndrome) were identified in the proband and her unaffected siblings, none of the individuals fit either of these phenotypes[1,2].

Genetic classification of this case as either autosomal dominant or sporadic AD is therefore unclear. The pedigree is consistent with autosomal dominant inheritance, however the lack of pathogenic variants in three known FAD genes, presence of the *APOE4* allele, and later age of onset are typical of the sporadic form. Semi-dominant inheritance of the *APOE4* allele and an association with mesial temporal seizures have been reported[4–6]. Whether *APOE4* is a risk factor for epilepsy in AD, and whether there are oligogenic, proepileptic genetic factors that contribute to the dual phenotype of AD and epilepsy remain unknown.

Patient #2 Additional Details

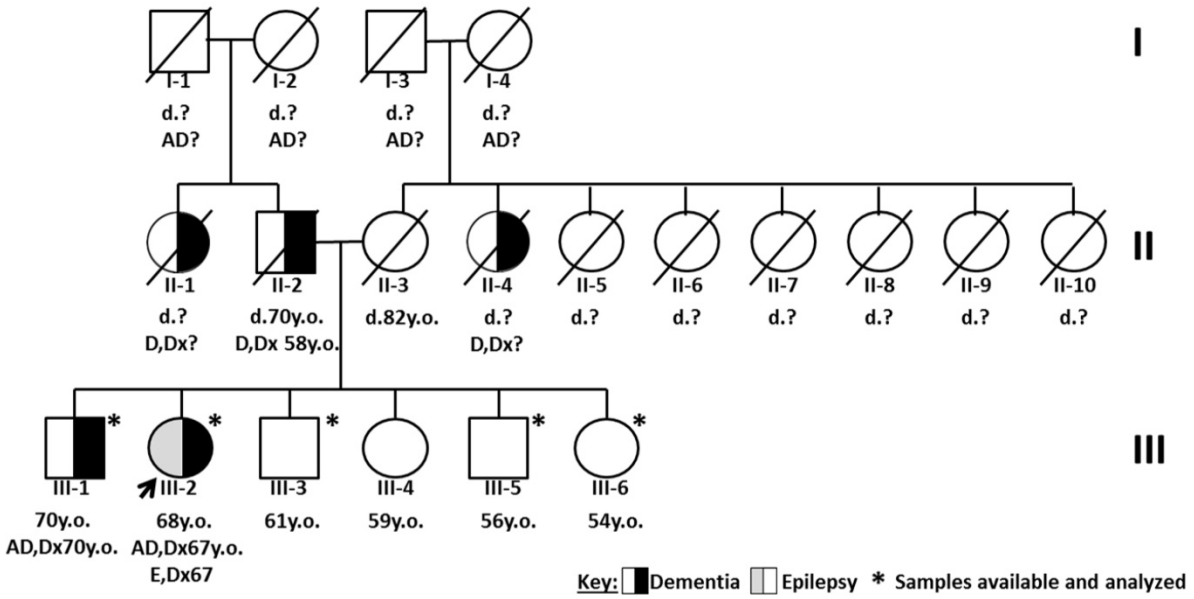
Past medical history: The patient was left-handed. She had a history of hypertension, hypothyroidism, celiac disease, mutation-negative essential thrombocythemia (treated with hydroxyurea), depression, and anxiety. Medications at the time of her FO electrode monitoring included: donepezil, memantine, duloxetine, fluoxetine, levothyroxine, hydrochlorothiazide, hydroxyurea, and several vitamin supplements (B12, C, D3).

Neuropsychological test results: At the time of referral, she made 19 errors on the BIMC.



Supplementary Figure 1. Neuroimaging findings. (A-B): Patient #1. A. T2-FLAIR weighted MRI, with axial (left) and coronal (right) images demonstrating diffuse atrophy. R = right, L = left. B. ^{18}FDG-PET images showing left parietal (left) and left temporal (right) hypometabolism. Arrows point to the areas of abnormality. (C): Patient #2. C. *Left*, T2-FLAIR weighted MRI, axial view. *Right,* T1 weighted MRI, coronal view. Both images demonstrate diffuse atrophy. The left-right orientation for B and C are the same as shown in (A).

a



b

Summary table of detrimental variants identified the *APOE4, NOTCH3*, and SCN2A genes.

Gene	Variant	Position	Variant type	AA change	Zygosity	Frequency 1000 Genome	Frequency EXAC	DB SNP	Predicted functional impact	III-1 (AD)	III-2 (AD+E)	III-3	III-4	III-5	III-6
APOE4	c.388T>C	19:454119	ns	p.C130R	Het	328/184 (15%) TGEUR	18.343% ± 0.444%	rs429358	pathogenic	yes	yes	yes	n/a	yes	yes
NOTCH3	c.509A>G	19:153029	ns	p.H170R	Het	2/758 (0.26%) TGEUR	0.191% ± 0.027%	rs147373451	pathogenic	yes	yes	–	n/a	–	yes
SCN2A	c.3457G>A	2:1662217	ns	p.E1153K	Het	3/21529 (0.014%)	0.009% ± 0.007%	rs200138205	pathogenic	–	yes	yes	n/a	yes	–

Supplementary Figure 2. Pedigree and extended genetic findings from Patient #1. A. Pedigree and analysis of proband and 4 siblings. B. Summary of variants in genes linked to dementia and epilepsy. The *APOE4* variant, but no known pathogenic variants in *PSEN1, PSEN2,* or *APP* were identified in the proband. Variants in *NOTCH3* and *SCN2A* genes with a potential impact on this patient's phenotype were also found in unaffected siblings, and the proband does not match the expected phenotype for these disorders.

Supplementary References

1. Schmidt, H. *et al.* Genetic variants of the NOTCH3 gene in the elderly and magnetic resonance imaging correlates of age-related cerebral small vessel disease. *Brain* **134,** 3384–97 (2011).
2. Shi, X. *et al.* Clinical spectrum of SCN2A mutations. *Brain Dev.* **34,** 541–545 (2012).
3. Jiang, Y. *et al.* Detection of Clinically Relevant Genetic Variants in Autism Spectrum Disorder by Whole-Genome Sequencing. *Am. J. Hum. Genet.* **93,** 249–263 (2013).
4. Li, Z., Ding, C., Gong, X., Wang, X. & Cui, T. Apolipoprotein E ε4 Allele was Associated With Nonlesional Mesial Temporal Lobe Epilepsy in Han Chinese Population. *Medicine (Baltimore).* **95,** e2894 (2016).
5. Genin, E. *et al.* APOE and Alzheimer disease: a major gene with semi-dominant inheritance. *Mol. Psychiatry* **16,** 903–7 (2011).
6. Briellmann, R. S. *et al.* APOE epsilon4 genotype is associated with an earlier onset of chronic temporal lobe epilepsy. *Neurology* **55,** 435–437 (2000).