



Heterozygous *TREM2* Mutation in Semantic Variant of Primary Progressive Aphasia

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Dear Editor,

Triggering receptor expressed on myeloid cells 2 (*TREM2*) protein, which is expressed on the membranes of a subset of myeloid cells, regulates immune responses in the brain.¹ Genetic variants of *TREM2* are associated with increased risks of developing Alzheimer's disease (AD) and frontotemporal dementia (FTD).^{2,3} In this study we identified a semantic variant in a primary progressive aphasia (svPPA) patient with one heterozygous *TREM2* mutation.

The 50-year-old right-handed male presented with a 10-year history of progressive anomia and comprehension difficulty. He also exhibited irritable and aggressive behaviors as well as alcohol and gambling addictions. Neuropsychological testing revealed poor performance in most tasks, but his visuospatial function was relatively spared (84.37th percentile). His language function assessed using the Western Aphasia Battery was indicative of Wernicke's aphasia. As shown in Fig. 1A, which was adapted from our previous report,⁴ MRI revealed atrophy in the bilateral anterior temporal lobes (left>right), while [¹⁸F]THK5351 positron emission tomography (PET) revealed greater [¹⁸F]THK5351 retention in the anteroinferior temporal regions. [¹⁸F]FDG PET showed hypometabolism in the bilateral anterior temporal areas (left>right) (Supplementary Material, Supplementary Fig. 1 in the online-only Data Supplement). He was diagnosed with svPPA based on the results of the neuropsychological testing and neuroimaging findings.⁵ The family history (Fig. 1B) showed that the proband's father (I-2) and half-brother (II-1) also reportedly exhibited aggressive and violent behaviors as well as alcohol addiction that required interventions from hospitalization to institutionalization in an asylum, while the proband's mother (I-3) and sisters (II-2 and II-3) had no history of neurological or psychiatric diseases.

Whole-exome sequencing identified one heterozygous *TREM2* variant in the proband: c.574G>A, p.Ala192Thr (NM_018965). Sanger sequencing for the proband (II-4) and additional unaffected family members (I-3, II-2, and II-3) (Fig. 1C) confirmed that the variant segregated with the phenotype in the family. Moreover, there was neither any gene mutation associated with FTD (e.g., *TARDP*, *MAPT*, *GRN*, *C9orf72*, *VCP*, *CHMP2B*, *FUS*, *ITM2B*, *TBK1*, and *TBP*) nor any gene mutation that is not commonly linked to FTD (e.g., *PSEN1*).

The heterozygous rare variants of *TREM2* including R47H, D87N, and Q33X reportedly increase the risk of AD.² Additionally, *TREM2* variants such as R47H, R62H, and T66M have been associated with a predisposition to FTD.³ Meanwhile, recent studies have identified the A192T variant in a Chinese individual with late-onset AD⁶ and a Korean patient with early-onset AD.⁷

This study was subject to some limitations. First, since the patient did not undergo amyloid PET, and so we could not exclude the possibility of amyloid pathology being present. However, the [¹⁸F]FDG PET findings indicated that the possibility of AD would be low, even if it were. Second, we presumed that the proband had a family history of this neurological disease because his father and half-brother had similar clinical phenotypes. However, we could

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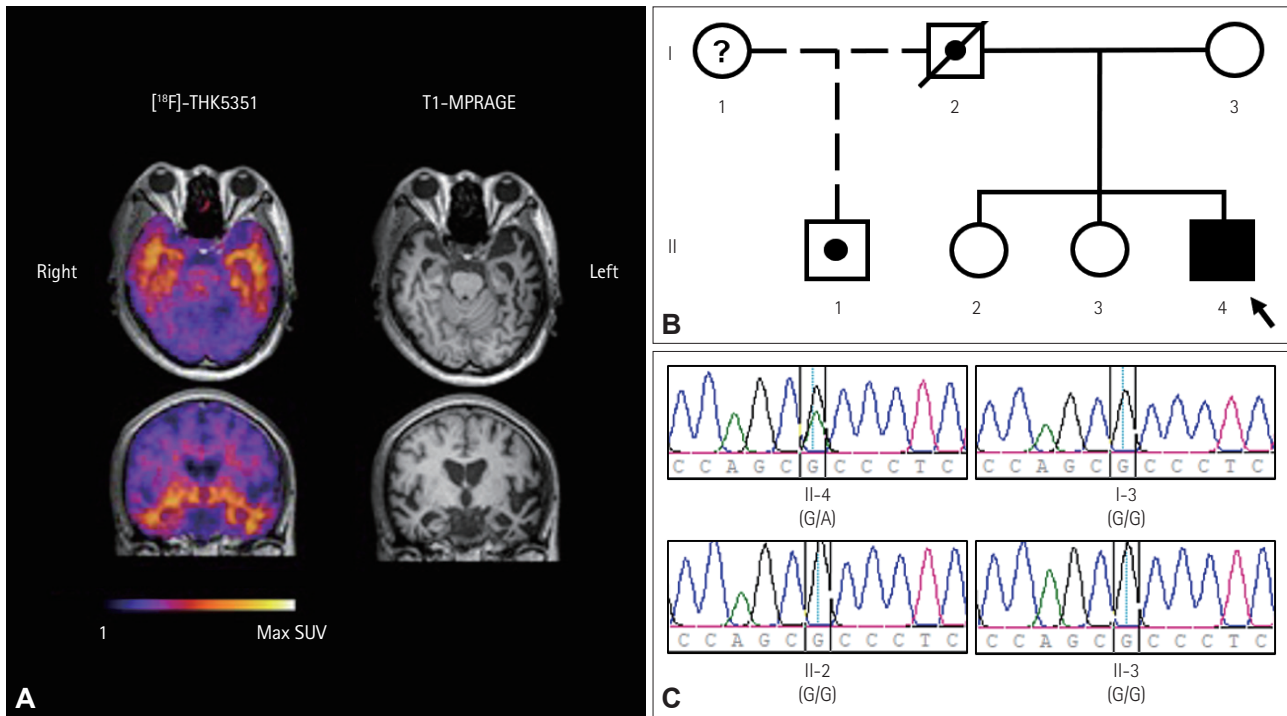


Fig. 1. Brain images, family pedigree, and sanger sequencing. A: Axial and coronal $[^{18}\text{F}]\text{-THK5351}$ positron emission tomography and T1-weighted magnetization-prepared rapid gradient-echo brain MRI images of an semantic variant in a primary progressive aphasia patient. $[^{18}\text{F}]\text{-THK5351}$ retention was increased in the bilateral anteroinferior temporal areas (left>right). B: Family pedigree. Arrow indicates the proband with the A192T variant (black filled square). A slash through a symbol indicates a deceased family member. White symbols represent unaffected family members, and white symbols with a center black dot represent presumed affected individuals carrying the *TREM2* variant. A question mark indicates an unknown family history. The dashed line indicates an unmarried relationship. C: Sanger sequencing of *TREM2* in the proband (II-4) and unaffected family members (I-3, II-2, and II-3). SUV: standardized uptake value.

not confirm that the mutation in *TREM2* was inherited, since it was not possible to obtain any clinical diagnosis, neuroimaging, or genetic test results from any of them.

To our knowledge, this is the first report of an svPPA patient with the rare *TREM2* heterozygous A192T variant. Although rare cases of the genetic transmission of svPPA have been reported,⁸ our findings suggest that the A192T variant is associated with an increased risk of svPPA. Associations of *TREM2* variants with the risk of early- or late-onset AD as well as FTD may be due to immunological and inflammatory dysregulation in the central nervous system.⁹

Supplementary Materials

The online-only Data Supplement is available with this article at <https://doi.org/10.3988/jcn.2020.16.2.352>.

Author Contributions

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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