Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

De Novo Mutation in *TMEM151A* and Paroxysmal Kinesigenic Dyskinesia

We read with great interest the article by Tian and colleagues.[1] Heterozygous mutations in *TMEM151A*, encoding transmembrane protein 151 A, a protein of undetermined function, have been very recently associated with paroxysmal kinesigenic dyskinesia (PKD) in the Chinese population.[1-4] *TMEM151A* is highly expressed in the brain, including the cerebral cortex and the thalamus and is highly conserved among species. To definitively confirm the association between *TMEM151A* and PKD, other mutations in the same gene should be identified in independent cohorts from different populations.

We applied whole exome sequencing (WES) on 23 French patients with sporadic PKD who tested negative for *PRRT2* (proline-rich transmembrane protein 2) mutations as well as their asymptomatic parents. PKD diagnosis was made by movement disorders specialists according to the consensus clinical criteria.[5] WES, bioinformatic analysis, and variant prioritization were performed as previously described.[6] Variants were classified according to the American College of Human Genetics and Genomics (ACMG) criteria.[7] All patients gave written informed consent before genetic testing, and a local ethics committee approved the study. We identified a de novo missense variant (c.166G > C [p.Gly56Arg]) in *TMEM151A* in a single patient (Fig. 1) through trio-based exome sequencing. This variant, absent from public databases including Exac, 1000G, and GnomAD, led to a substitution in the second transmembrane domain of the protein near previously reported pathogenic variants, such as c.140 T > C [p.Leu47Pro] or c.133 T > G [p.Cys45Arg]. It was predicted to be damaging by Polyphen, with a Combined Annotation Dependent Depletion (CADD) score above 20. The phenotype was consistent with previous reports of *TMEM151A*-related PKD. The patient had no history of infantile seizures and presented with brief attacks of dystonia triggered by voluntary movements, surprise, or stressful events beginning after age 16. Before medication initiation, the patient experienced between 10 and 20 attacks a day, usually lasting a few dozens of seconds. Attacks could be focal or generalized, affecting speech or involving the face or upper and lower limbs subsequently or simultaneously. The attacks totally ceased after the initiation of low doses of lamotrigine (50 mg/d). This variant was subsequently classified as likely pathogenic (class IV) according to the ACMG criteria (PS2 + PM1 + PM2 + PP2 + PP4).[7] No other de novo class IV or V variant was identified in this cohort. The *TMEM151A* mutation was identified in one of 23 patients of our *PRRT2*-negative PKD cohort, which is in accordance with the frequency of 4.8% found by Tian et al.[1]

We report on a de novo mutation in *TMEM151A* in a patient with PKD. Our findings confirm *TMEM151A* variants as a genetic cause of PKD and suggest that de novo mutations in this gene are infrequently responsible for

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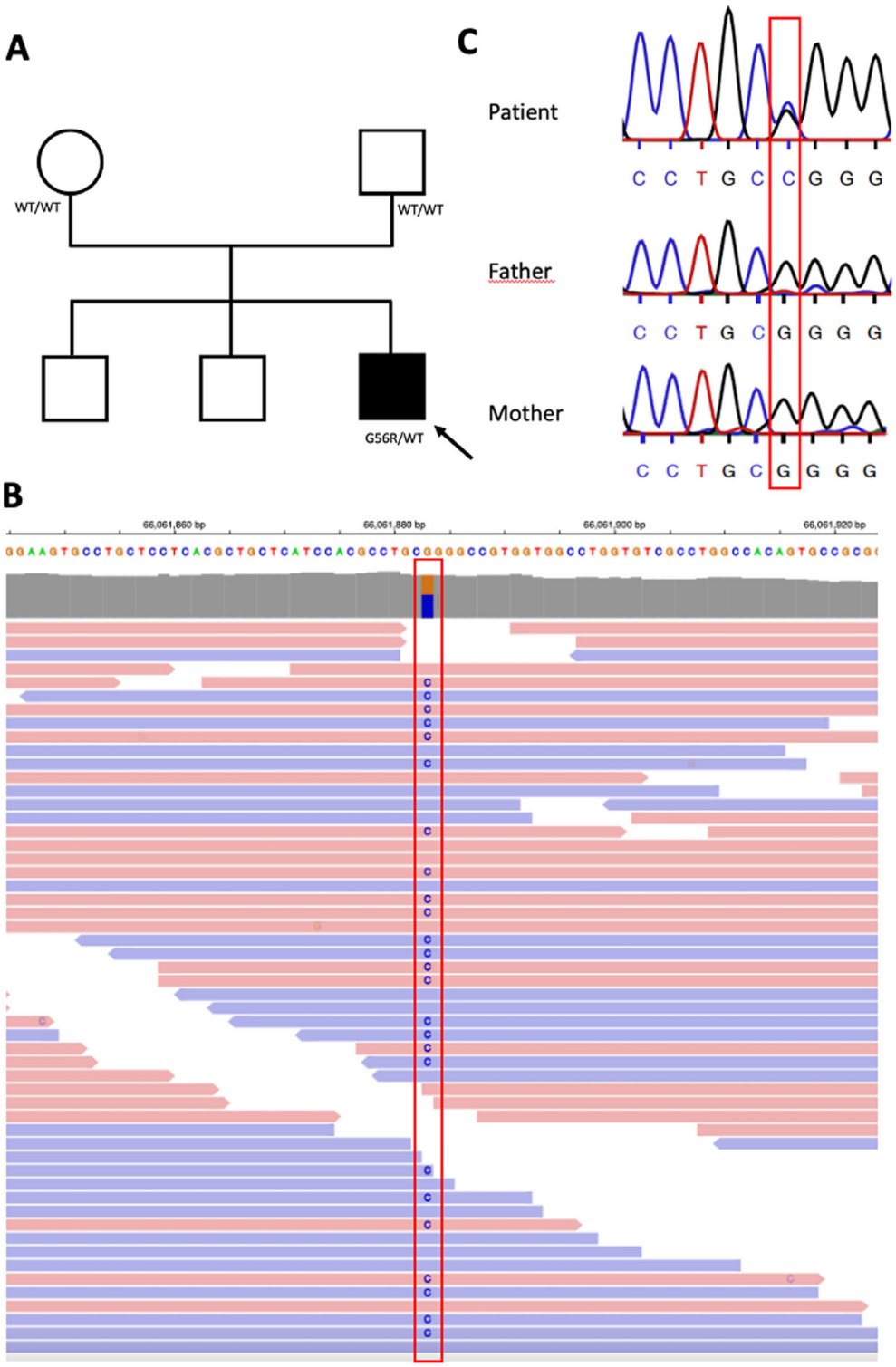

FIG 1. (**A**) Pedigree of the family. WT: Wild Type (**B**) Visualization of the (c.166G > C [p.Gly56Arg]) variant (between red lines) in the patient in the *TMEM151A* (Transmembrane protein 151 A) sequence through the Integrated Genome Viewer. The replacement of the reference G by a C (blue) is present on half of the patient's read, meaning heterozygosity. (**C**) Sanger sequencing of the (c.166G > C [p.Gly56Arg]) variant (between red lines). The variant is present in a heterozygous state in the patient but absent in the two asymptomatic parents, compatible with a de novo occurrence. [Color figure can be viewed at wileyonlinelibrary.com]

sporadic PKD cases.[4] Further works are warranted to refine the phenotype/genotype correlations among *TMEM151A*-related disorders. Whether *TMEM151A* is a transmembrane protein involved in synaptic function and whether *TMEM151A*-related PKD is underpinned by its loss of function also remain to be elucidated.

Data Availability Statement

Anonymized data pertaining to the research presented will be made available upon reasonable request from external investigators.

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Increased Stroke Risk in Patients with Parkinson's Disease with LRRK2 Mutations

We appreciate the opportunity to comment on the letter by Macías-García and colleagues who reported an interesting increased stroke risk in Parkinson's disease (PD) patients with LRRK2 mutation.[1] In this context we would like to share our experience with our cohort of PD patients. All patients were previously screened for the presence of mutations in the *LRRK2*, *GBA*, *SNCA*, and *PARKIN* genes.[2] In addition we collected the following information: sex; age; age at disease onset; disease duration; Hoehn & Yahr scale; LEDD (Levodopa Equivalent Daily Dose); Charlson Comorbidity Index (CCI); presence of diabetes, arterial hypertension, hyperlipidemia, atrial fibrillation; smoking habit, and history of cerebrovascular (ie, ischemic or haemorrhagic stroke and transient ischemic attack [TIA]) and coronary artery disease (CAD). Ischemic strokes were classified through the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification. In addition, all available brain-MRI and computed tomography (CT) reports were reviewed. One hundred and twenty PD patients, including 46 *GBA*-related (*GBA*-PD), 14 *LRRK2*-related (*LRKK2*-PD), and 60 sporadic PD (sPD) patients, were assessed. sPD patients were paired one by one for age, sex, age at PD onset, and CCI with *GBA*-PD and *LRRK2*-PD patients obtaining three homogeneous and comparable groups. ANOVA, paired t test and χ^2 square tests were applied as appropriate using Matlab® software, among *GBA*-PD, *LRKK2*-PD, and sPD patients. The main results are summarized in Table 1. We did not find significant differences among any of the three-group comparisons, including cerebrovascular disease occurrence. As discussed in the supplementary material, the only statistically significant comparison was found between genetic PD patients (*GBA*-PD together with *LRKK2*-PD) and sPD patients in terms of CAD prevalence ($P = 0.05$). Our results confirm the findings by Macías-García et colleagues[1] who did not find an increased stroke risk among *GBA*-PD compared to sPD. Differently from their analysis, we did not find a different stroke risk in *LRKK2*-PD compared to sPD. Globally we tracked only one ischemic stroke event in *GBA*-PD group (TOAST classification: cardioembolic), and therefore, further analyses in this respect were not performed. We can instead confirm that our groups were homogeneous and therefore

Key Words: GBA; ischemic; LRRK2; Parkinson's disease; stroke

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