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LETTER TO THE EDITOR

Heterozygous PINK1 p.G411S in rapid eye movement sleep behaviour disorder

Ziv Gan-Or,[1,2] Jennifer A. Ruskey,[1,2] Dan Spiegelman,[1,2] Isabelle Arnulf,[3] Yves Dauvilliers,[4] Birgit Högl,[5] Christelle Monaca-Charley,[6] Ronald B. Postuma,[2,7] Jacques Y. Montplaisir[8,9] and Guy A. Rouleau[1,2,10]

1 Montreal Neurological Institute, McGill University, Montréal, QC, H3A 0G4, Canada
2 Department of Neurology and Neurosurgery, McGill University, Montréal, QC, H3A 0G4, Canada
3 Sleep Disorders Unit, Pitié Salpêtrière Hospital, Centre de Recherche de l'Institut du Cerveau et de la Moelle Epinière and Sorbonne Universities, UPMC Paris 6 univ, Paris, 75013, France
4 Sleep Unit, National Reference Network for Narcolepsy, Department of Neurology Hôpital-Gui-de Chauliac, CHU Montpellier, INSERM U1061, Montpellier, 34000, France
5 Sleep Disorders Clinic, Department of Neurology, Medical University of Innsbruck, Innsbruck, 6020, Austria
6 University Lille North of France, Department of Clinical Neurophysiology and Sleep Center, CHU Lille, Lille, 59000, France
7 Department of Neurology, Montreal General Hospital, Montréal, QC, H3G 1A4, Canada
8 Centre d'Études Avancées en Médecine du Sommeil, Hôpital du Sacré-Cœur de Montréal, Montréal, QC, H4J 1C5, Canada
9 Department of Psychiatry, Université de Montréal, Montréal, QC, H3T 1J4, Canada
10 Department of Human Genetics, McGill University, H3A 0G4, Montréal, QC, Canada

Correspondence to: Ziv Gan-Or,
Montreal Neurological Institute and Hospital,
Department of Neurology and Neurosurgery,
McGill University, 1033 Pine Avenue West,
Ludmer Pavilion, room 324,
Montreal, QC, H3A 1A1,
Canada
E-mail: ziv.gan-or@mcgill.ca

Sir,

In a recent study published in *Brain*, Puschmann *et al.* (2016) strengthened the suggested association between the heterozygous *PINK1* mutation p.G411S and Parkinson's disease. They performed a meta-analysis showing that patients with Parkinson's disease had a pooled odds ratio (OR) of 2.89 for carrying the p.G411S mutation. Furthermore, the authors demonstrated that the p.G411S mutation led to reduced kinase activity and interfered with ubiquitin phosphorylation by PINK1 (Puschmann *et al.*, 2016). Biallelic mutations in *PINK1* are well-established causes of autosomal-recessive early onset Parkinson's disease, and account for 3.7% of patients with early onset Parkinson's disease (Kilarski *et al.*, 2012). However, the role of heterozygous *PINK1* mutations in Parkinson's disease is still not clear. In a study of rare *PINK1* variants, the carrier frequencies in Parkinson's disease patients and controls were 1.8% and 1.5%, respectively, and a meta-analysis with previous studies resulted in non-significant OR of 1.62 (Marongiu *et al.*, 2008). Other studies, however, suggested that heterozygous *PINK1* variants may indeed increase the risk of developing Parkinson's disease (Abou-Sleiman *et al.*, 2006; Toft *et al.*, 2007).

To further examine the role of the *PINK1* p.G411S mutation in synucleinopathies, we analysed next generation sequencing data from targeted capture of *PINK1*, generated by molecular inversion probes as was previously described (Ross *et al.*, 2016). The frequency of the mutation was examined in a cohort of 350 patients with REM sleep behaviour disorder (RBD), a prodromal synucleinopathy that can progress to either Parkinson's disease, dementia with Lewy bodies (DLB) or multiple system atrophy

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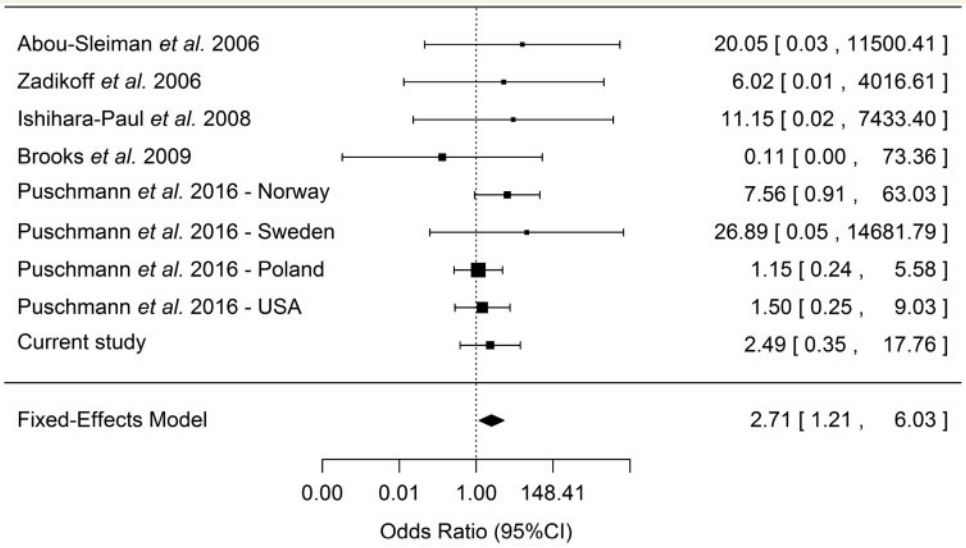

Figure 1 Forest plot of the effect of the *PINK1* p.G411S mutation in Parkinson's disease and RBD. A forest plot including data from eight previously published populations, which included data on carriers of *PINK* p.G411S in other patients and controls. As this mutation was shown to have a functional effect, which is not random and should be similar across all carriers, a fixed-effect model was used. When usinga random-effect model, a marginal *P*-value of 0.06 was achieved. The heterogeneity was not significant across the different populations (Tarone's test for heterogeneity $P = 0.62$), further suggesting the fit of a fixed-effect model.

(Postuma *et al.*, 2015), and compared to 869 control subjects. All patients and controls were of European ancestry (validated using genome-wide association study data), and the majority were French or French-Canadian. Patients with RBD were collected through the international RBD study group (Postuma *et al.*, 2015) and were diagnosed according to the ICSD-2 criteria (International Classification of Sleep Disorders, version 2) (Thorpy, 2012). All patients and control subjects signed informed consent at enrolment, and the study protocols were approved by the respective institutional review boards. We performed a meta-analysis combining the current data with data collected by Puschmann *et al.* (2016) from previous studies (Fig. 1). Studies that had no carriers of the mutation in both patients and controls were not included. 'Metafor' R package was used, applying the Cochran-Mantel-Haenszel test, with a fixed-effect model and continuity correction of 0.1. Tarone's test was used to examine heterogeneity (Gan-Or *et al.*, 2015*b*).

The average coverage of the probe covering the *PINK1* p.G411S across all samples was $>300\times$. Four carriers were identified: two RBD patients (0.6%) and two controls (0.2%, $P > 0.05$, Fisher's exact test). Although not statistically significant, these frequencies have similar effect size and directionality as those reported by Puschmann *et al.* (2016). The age at diagnosis of RBD of the two patients was 65 and 69 years, and while the first patient had not yet converted to an overt synucleinopathy, the second patient was diagnosed with Parkinson's disease at the age of 70. As RBD can be considered as a synucleinopathy in progress (Postuma *et al.*, 2015), the current data could be added to the meta-analysis from Puschmann *et al.*, which used studies that identified carriers of the *PINK1* p.G411S mutation in patients or controls (Abou-Sleiman *et al.*, 2006; Zadikoff *et al.*, 2006; Ishihara-Paul *et al.*, 2008; Brooks *et al.*, 2009; Puschmann *et al.*, 2016). Adding our data, the OR for having the *PINK1* p.G411S mutation was 2.71 (95% confidence interval 1.21–6.03, $P = 0.016$, Tarone's test for heterogeneity $P = 0.62$, Fig. 1).

Our results provide some additional support for the association between the *PINK1* p.G411S mutation and Parkinson's disease. There are conflicting reports on synucleinopathy and Lewy bodies in *PINK1*-associated Parkinson's disease, as some post-mortem studies identified Lewy bodies in *PINK1*-associated Parkinson's disease while others did not (Samaranch *et al.*, 2010; Takanashi *et al.*, 2016). The identification of two carriers of the *PINK1* p.G411S mutation among the RBD cohort, who have *de facto* early-stage synucleinopathy, may suggest that *PINK1*, at least in some cases, may be associated with α-synuclein pathology. Of note, although the ORs calculated here and in previous studies are higher than those typically seen in genome-wide association studies of Parkinson's disease (Nalls *et al.*, 2014), the overall effect of the p.G411S mutation is still very small. If the life-time risk for Parkinson's disease is 1–3%, and if the OR represents the risk for Parkinson's disease, carriers of the *PINK1* p.G411S mutation have more than a 90% chance of never developing Parkinson's disease. Considering this reduced penetrance with the low frequency of this variant (allele frequency of 0.002 in the ExAC database, http://exac.broadinstitute.org/), it seems that the role of this variant in Parkinson's disease is minor. However, it is important to

note that other *PINK1* mutations may also contribute to Parkinson's disease in the heterozygous form. A previous meta-analysis of various rare *PINK1* mutations suggested that they do not confer increased risk for Parkinson's disease (Marongiu *et al.*, 2008); however, collapsing all rare *PINK1* variants together into a single meta-analysis is based on the hidden assumption that different rare *PINK1* variants carry the same effect on risk for Parkinson's disease. It is more likely that different variants have different effects on Parkinson's disease risk, as occur in other Parkinson's disease-related genes, such as *GBA* (Gan-Or *et al.*, 2015*a*) and *LRRK2* (Gan-Or *et al.*, 2015*a*). While a mutation such as p.G411S may indeed be a risk variant, other *PINK1* mutations may have no effect on Parkinson's disease risk, or the opposite effect (i.e. they may be protective), and pooling them together may hide the effects of specific variants. Studies of individual mutations and more advanced analysis methods that take into account different effect directions of individual variants should be performed to better study the role of heterozygous *PINK1* mutations in Parkinson's disease.

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