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LETTER TO THE EDITOR

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

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Sir,

We read with great interest that Gan-Or *et al.* (2017) have observed an association (albeit not reaching statistical significance) of the heterozygous PINK1 p.G411S mutation and rapid eye movement sleep behaviour disorder [RBD; effect size odds ratio (OR) of 2.49] in their multicentre cohort of 350 RBD patients and 869 controls subjects (Gan-Or *et al.*, 2017). Given the strong correlation of RBD with Parkinson's disease, we interpret this as further support for our observation on 9142 individuals showing that heterozygous PINK1 p.G411S mutation confers a marked increase in Parkinson's disease risk odds ratio = 2.89, $P = 0.027$ (Puschmann *et al.*, 2017).

We have not systematically enquired about RBD symptoms in all case-control series that were included in our multicentre study. RBD has previously been shown to correlate well with synucleinopathies (Schenck *et al.*, 2013; Iranzo *et al.*, 2014). We thus compiled information on RBD and other signs and symptoms that might particularly suggest synucleinopathy in a patient with Parkinson's disease. Such data were available on 20 of 21 probands with PINK1 p.G411S mutation from our case series and the Ukrainian and Australian families we reported. Five of 20 probands had RBD, 10 had hallucinations, seven had signs of dysautonomia (marked orthostatism, excessive sweating, constipation), seven had cognitive dysfunction, and one patient had α-synuclein pathology at neuropathological examination (Hoffman-Zacharska *et al.*, 2013). In total, 16 of the 20 patients showed at least one of these features, possibly indicating that heterozygous carriers of PINK1 p.G411S are more likely to develop symptoms suggesting synucleinopathy.

As Gan-Or *et al.* rightly note, for a background lifetime disease risk of Parkinson's disease in the range of 1–3%, and an association with an OR < 5, the majority of heterozygous mutation carriers will not develop Parkinson's disease during their lives. This is in line with the lack of cosegregation of the mutation with Parkinson's disease in several of our families reported and can make replication difficult for this type of rare variant. Reduced penetrance has also been shown for the *GBA* (Ran *et al.*, 2016) and *LRRK2* gene mutations, including LRRK2 p.G2019S (Marder *et al.*, 2015), although this mutation is clearly considered 'pathogenic'. Indeed, this scenario may be even more true for PINK1 and parkin mutants whose enzymatic functions are activated by mitochondrial damage, which is dependent on stress levels that may not only vary from individual to individual, but also from cell to cell.

We agree that the contribution of PINK1 p.G411S on overall heritability of Parkinson's disease will be quite modest, as this particular mutation is rare. What we do not know at present is whether there are additional mutations in *PINK1* and/or other recessive Parkinson's disease genes that similarly increase Parkinson's disease risk in heterozygous form. It is conceivable that a large number of such variants taken together may contribute more significantly to the missing heritability for Parkinson's disease. We expect that the widespread use of next-generation sequencing will create possibilities to explore such questions in the near future. In agreement with Gan-Or *et al.*, it is also clear from our work that specific variants in these recessive Parkinson's disease genes likely have different mechanistic effects on pathway function and disease risk, and elucidating these (as we have for p.G411S) will likely guide therapeutic intervention strategies. For instance, in the case of parkin, various missense mutations are known to cause distinct molecular and cellular phenotypes, depending on the type and location of the amino acid exchange (Fiesel *et al.*, 2015). Thus, in addition to genetic studies, structural and functional assessment will be crucial to experimentally determine pathogenicity, especially for rare variants.

The influence of mutations in early-onset recessive genes, such as *PRKN*/parkin and *PINK1*, on more typical late-onset Lewy body Parkinson's disease remains equivocal. Carriers of homozygous *PINK1* mutations typically develop Parkinson's disease with an onset very early in life and with features that are clinically quite distinct from late-onset Parkinson's disease. Not much is known about the neuropathology of these patients. To our knowledge, only three patients with homozygous or compound heterozygous *PINK1* mutations have been examined post-mortem, and these had markedly variable clinical picture and pathology, including cell loss in the substantia nigra with or without α-synuclein deposition (Takanashi *et al.*, 2016). The association of PINK1 p.G411S with RBD indeed adds another interesting aspect. While some patients with clinical Parkinson's disease diagnosis may not have α-synuclein pathology, 81–91% of individuals with RBD have been shown to develop a neurodegenerative disease, with the vast majority a synucleinopathy (Schenck *et al.*, 2013; Iranzo *et al.*, 2014); these results may link PINK1-related disease with synuclein pathology. Furthermore, our study showed how p.G411S-mutated PINK1 interferes with the PINK1/parkin-mediated mitochondrial quality control pathway. Thus, the association of p.G411S with both Parkinson's disease and RBD may provide additional

evidence for the role of the mitochondria in the pathogenesis of synucleinopathies (Truban *et al.*, 2016).

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