TMEM230 variants in Parkinson's disease

To the Editor — Deng and colleagues published an article in *Nature Genetics* reporting that mutations in *TMEM230* cause Parkinson's disease[1]. The authors studied 65 members of a kindred, including 13 affected individuals, in which Parkinson's disease appears to segregate as an autosomal-dominant trait. A linkage study was performed, and a two-point logarithm-of-odds score of 3.3 was reported for markers on chromosome 20p13–12.3. Through exome sequencing of four affected individuals and one unaffected family member and subsequent variant filtering, the authors identified a single missense variant in *TMEM230* (NM_001009923.1), encoding p.Arg141Leu.

The authors stated that this *TMEM230* variant fully cosegregated with disease in the kindred, thus indicating that it is disease causing. However, in segregation analysis of Mendelian disorders, all individuals carrying a mutation are assumed to be affected by disease, and individuals without the mutation are assumed to be unaffected. We are therefore concerned by the pedigree information presented in Supplementary Fig. 1 of ref. [1], in which 11 unaffected individuals in the family seem to carry the disease haplotype and presumably also the *TMEM230* variant. Unaffected individuals may carry a disease-related variant, owing to reduced penetrance, but such a high number of unaffected mutation carriers seems unlikely and therefore warrants further evidence. This presence of the variant in many unaffected individuals was not further discussed in the article.

The results of a linkage study followed by exome sequencing could potentially be influenced by the inclusion of phenocopies in the analyses. As noted by Deng et al., one member (II-1) of the studied family has a pathological diagnosis of progressive supranuclear palsy. This rare neurodegenerative disorder often cannot be clinically distinguished with certainty from Parkinson's disease. However, progressive supranuclear palsy is pathologically a tauopathy and is generally considered to have disease mechanisms different from those of Parkinson's disease[2]. Thus, we would be very cautious in including individuals with known progressive supranuclear palsy in a study of familial Parkinson's disease, because the inclusion of a potential phenocopy in the analyses might lead to false-positive findings. In fact, exome sequencing was performed for four affected individuals, including the son (III-1) of the individual diagnosed with progressive supranuclear palsy. Filtering out all genetic variants not present in all four individuals would lead to the removal of a truly pathogenic mutation, if one of the sequenced individuals were a phenocopy. Of note, a *DNAJC13* alteration encoding p.Asn855Ser, was previously reported in the same family and was not present in the subject with progressive supranuclear palsy and his offspring[3].

By screening additional patients with Parkinson's disease, the authors identified further rare variants in *TMEM230*. The most frequent variant was identified in seven Chinese familial cases. This was a complex mutation with a combined deletion and insertion located at the end of the gene and encoding p.*184ProGlyext*5. In most patients with this mutation, the mutation occurred in the homozygous state, and several obligate mutation carriers were not affected by disease. The variant was not found in the exome data analyzed by the authors, and it is not present in public databases, including data from the Exome Aggregation Consortium (ExAC; http://exac.broadinstitute.org/).

However, interpretation of exome sequencing data, including those from ExAC, is not always straightforward. We inspected data from the ExAC database and found that there are no listed variants in the last 37 nucleotides of *TMEM230* exon 5 and the adjacent part of the 3′ untranslated region. By comparing the genomic sequences of this to region to sequence databases through BLAST (http://blast.ncbi.nlm.nih.gov/Blast.cgi/), we found high sequence identity (98%) to a genomic region on chromosome 11. Owing to this sequence similarity, we suspect that complex mutations within this region might be removed in the bioinformatic analyses of exome sequencing data. In our opinion, further studies are needed until a pathogenic role can be assigned to the variant.

A number of genes causing monogenic forms of Parkinson's disease have been identified in recent years[4]. Genetic discoveries have had immense importance for the scientific community and underlie most of the current thinking and progress in research on neurodegenerative diseases[5]. However, given the provided genetic evidence, we are concerned that the identified *TMEM230* variants may not be involved in the development of Parkinson's disease. ❐

Editorial note: the journal apologizes to the authors for the unusual delay in the peer review and publication of this exchange of Correspondence and Reply.

Zafar Iqbal and Mathias Toft*
Department of Neurology, Oslo University Hospital, Oslo, Norway.
**e-mail: mathias.toft@gmail.com*

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References

1. Deng, H. X. et al. *Nat. Genet.* **48**, 733–739 (2016).
2. Golbe, L. I. *Semin. Neurol.* **34**, 151–159 (2014).
3. Vilariño-Güell, C. et al. *Hum. Mol. Genet.* **23**, 1794–1801 (2014).
4. Hernandez, D. G., Reed, X. & Singleton, A. B. *J. Neurochem.* **139**, 59–74 (2016).
5. Singleton, A. & Hardy, J. *Neuron* **90**, 1154–1163 (2016).

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Competing interests

The authors declare no competing interests.