Mutations in *TMEM230* are rare in autosomal dominant Parkinson's disease

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Keywords

Parkinson's disease, genetics, *TMEM230*, familial parkinsonism

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A recent linkage analysis in a large autosomaldominant Parkinson's disease (ADPD) kindred identified a new locus for ADPD on chr.20p13. A missense Arg141Leu mutation within the *TMEM230* gene has been suggested as causative of the disease [1]. Additional variants in the same gene have been found in two young onset US PD cases and seven Chinese PD patients, of which five were homozygous for the new identified mutation.

Here we reported the results of a sequencing analysis of the *TMEM230* gene in 86 Italian familial PD Caucasian patients compatible with an AD inheritance (two or more PD cases in at least two consecutive generations) collected between 2012 and 2016. Other patients with PD but without a history of AD inheritance were not included in this study. Demographic data of the patients are reported in Supplementary Table 1. All patients were collected at our Hospital, IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, and the clinical diagnosis of PD was based on the presence of at least two of the following signs: bradykinesia, resting tremor and rigidity, along with a positive response to levodopa treatment and absence of other causes of parkinsonism. All subjects were screened for SNCA, GBA, and common LRRK2 mutations, but we did not remove those carrying pathogenic variants from the analysis. The ethics committee of IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico approved the study and all patients provided written informed consent. To detect mutations, we performed a polymerase chain reaction of all exons and intron-exon boundaries of the *TMEM230* gene (isoforms NM_001009923.1 and NM_014145) using primers reported in Supplementary Table 2. Sanger sequencing of all exons was performed. The identified variants were annotated according to the longer cDNA sequence deposited in Genbank (accession number NM_001009923.1) and their frequencies were checked in dbSNP.

No pathogenic variants were identified. Two intronic (c.174+5G>C, c.412-44G>A) and four exonic known polymorphisms were detected (p.Met64Thr, p.Pro102Pro, p.Lys103Lys, p.Ala110Ala) (Supplementary Table 3).

These results suggest that *TMEM230* mutations are not a frequent cause of PD with AD inheritance in the Italian population. In the original cloning paper a single mutation was found to be present in several PD patients of Chinese ancestry, some in homozygous state, suggesting a high frequency of this variant in familial cases from that specific population. Further genetic analyses in other populations are warranted to detect other possible population-specific *TMEM230* mutations. Furthermore, the additional variants reported in US patients lacking a clear co-segregation need to be confirmed in other studies. In this regard, additional

screening in familial cases would beAimCpoCrtEanPtTinEoDrdeMr tAoNassUesSsCthReIcPo-Tsegregation of TMEM230 variants with PD.

Disclosure statement

The authors declare no competing financial or personal interests that can influence the presented work. All authors have approved the final article.

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