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TMEM230 IN PARKINSON'S DISEASE

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Abstract

A study on familial Parkinson disease (PD) described four variants in the gene *TMEM230* (Chr. 20p13) as cause of PD (1). The aim of this study was to test if variants in the *TEMEM230* gene are associated with PD in two independent American European datasets. No variants in the *TMEM230* region were found associated with PD, age at onset or cerebrospinal fluid α-synuclein levels.

Parkinson Disease (PD) is the second most common neurodegenerative disorder after Alzheimer Disease (2), yet the cause of the majority of PD cases remains unknown. Several studies have described genetic variants associated with the disease [reviewed by (3)]. Although the monogenic forms of PD are rare (5–10%), their study has led to the finding of important genes and genetic variants that in some cases have also been found to be involved in the sporadic cases (3). Recently, a study with familial PD described several mutations in the gene *TMEM230* (Chr. 20p13) (1). However, at least one independent study in Caucasian population thus far failed to find an association of *TMEM230* variants and unrelated PD cases (4). The *DNAJC13* gene, p.N855S mutation was suggested to cause autosomal dominant late-onset PD and to co-segregate with PD within five families of Dutch–German–Russian Mennonite origin from Saskatchewan and British Columbia, albeit with incomplete penetrance and with phenocopies (5). The same group reported that rare variants in

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DNAJC13 were associated with increased or decreased risk for developing PD in Caucasian Canadian and Norwegian populations (6). However, subsequent studies in Chinese, Caucasian or French-Canadian/French populations found no mutations or variants in *DNAJC13* associated with PD (7–11). These findings have deeply questioned the genetic role of *DNAJC13* gene in PD. In addition, the pathogenic mutations in the *TMEM230* gene were reported in the same original Saskatchewan family (1). However, a close look at the initial report of *TMEM230* in PD revealed an unusual large number of unaffected mutation carriers, the lack of mutations that co-segregate with PD in independent families and a high occurrence of homozygous mutations among Chinese patients in a dominantly inherited disorder (1) (Farrer et al., 2017 – unpublished data). In addition, an increasing number of negative reports in both Chinese and Caucasian populations have also questioned the role of *TMEM230* mutations both in the general population and in families with autosomal dominant PD (12–15). The aim of this study was to test the association of *TMEM230* with PD in two independent cohorts. We also tested the potential association of these variants with cerebrospinal fluid (CSF) α-synuclein levels or age at onset using survival analysis.

We used two large European Ancestry PD datasets: GWAs data and DNA from the Washington University in Saint Louis (WUSTL) Movement Disorder Clinic (MO, USA) (16) and GWAs and Whole Exome Sequencing (WES) data from the Parkinson's Progression Markers Initiative (PPMI) consortium (www.ppmi-info.org). This study was approved by the Washington University in Saint Louis Institutional Review Board and the Human Research Protection Office (approval number: 201107095). PD clinical diagnoses were based on UK Brain Bank criteria (17). Population baseline characteristics have been previously described (18, 19). In summary, the WUSTL dataset contains 499 PD cases and 294 healthy controls, with 41.61% females. The PPMI dataset is smaller, 340 PD cases and 140 healthy controls with 34.38% females. We genotyped the variants described by Deng et al. (1) in the WUSTL dataset. WES data were downloaded from the PPMI web page, then standard quality control filters were applied (18, 20).

PPMI Dataset

The variants corresponding to the *TMEM230* region were annotated using SNPEff (21). Then, we used plink1.9 (22) to test the possible association between each of the TMEM230 variants and PD status (diagnosis), CSF α-synuclein levels, and age at onset correcting for age, sex, and the first two principal components. Bonferroni correction for multiple comparisons was also applied. To assess the possible association of the *TMEM230* region with PD status we performed a gene-based analysis including only non-synonymous variants with a MAF < 1% and using SKAT (23). To run the survival analysis for age at onset we only included non-synonymous variants with MAF < 1% and applied a CMC burden test modification. Briefly, we added the allele counts for each individual and used that count to perform the survival analysis correcting for sex and the first two principal components. We also have compared the variance burden of the gene region between the WES data and the ExAC non-Finnish database (24).

Seventeen variants were found in the PPMI WES dataset. One variant (rs45610034; p=0.02) located on the 3′ UTR was nominally associated with PD risk and another one

(chr20:5081276:G:A; p=0.05) also in the same region was associated with age at onset, although none of them passed the multiple test correction threshold. No variants were associated with CSF α-synuclein level. The gene based analysis with the three variants annotated as loss-of-function using SKAT Binary revealed that the region was not associated with PD status, α-synuclein levels or age at onset in our dataset. When comparing the cMAF (cumulative minor allele frequency) *TMEM230* region with the cMFAf ound in the ExAC database for the same region, the PPMI dataset does not seem to be enriched in *TMEM230* variants compared with the non-Finnish population of ExAC (data not shown). We also genotyped using KASPar methodology the four *TMEM230* variants described by Deng et al. We did not find any carriers in the WUSTL cohort composed of 499 PD cases and 294 healthy controls.

Due to the controversial results on the *DNAJC13* gene, p.N855S mutation findings (5), we also compared the cMAF in the PPMI dataset with the cMAF in ExAC for *DNAJC13*. The PPMI dataset is not enriched in variants in the *DNAJC13* region compared with the non-Finnish European ExAC population (data not shown). Moreover, the mutation p.N855S was not present in the ExAC or the PPMI databases.

In conclusion, our results do not support a role of genetic variants in either *TMEM230* or *DNAJC13* in PD risk. However, the investigated cohorts are mainly composed by sporadic unrelated PD cases (10% had family history) whereas the cohorts from Deng et al are mainly family based. Thus the described variants could be genotyping errors as suggested by Farrer et al (http://www.biorxiv.org/content/early/2017/01/01/097030) or very rare and relate only to familial forms of PD. The later is supported by two variants reaching significant p-values in their association with PD status or age at onset in the *TMEM230* region in the studied cohort. In summary, *TMEM230* may represent a new candidate gene for PD that should be further investigated in larger sporadic and familial cohorts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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