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Rare variants in *MC1R/TUBB3* exon 1 are not associated with Parkinson's disease

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Tell-Marti and colleagues recently published a variant (rs1805008; p.R160W) in the melanocortin 1 receptor (*MC1R*) gene associated with an increased risk of Parkinson's disease (PD) in a Spanish series¹. According to ExAC Browser (<http://exac.broadinstitute.org/>) this variant is a common variant in non-Finnish Europeans (Minor allele frequency; MAF = 0.08) and it may help explain the previous associations establishing that PD patients have an increased risk of developing melanoma². Interestingly, the single exon of *MC1R* gene overlaps the first exon of the tubulin, beta 3 class III (*TUBB3*) gene. The *TUBB3* protein is the main component of microtubules³ and therefore may be a more plausible candidate to be involved in PD than *MC1R*.

We sequenced the *MC1R* gene (*TUBB3* exon 1) to identify variants in our PD patient-control series of 889 PD cases (age = 68.30±11.11 years, age at onset = 62.39±13.08 years, 36.56% females) and 940 healthy controls (age = 65.03±12.74 years, 57.67% females). All subjects included in the study are unrelated, non-Hispanic Caucasians recruited at Mayo Clinic, Jacksonville. We found 37 nonsynonymous variants in *MC1R/TUBB3* exon 1 that were split into 29 missense, 4 frameshift, 3 stop mutations and 1 inframe insertion; thirty variants had a MAF<0.01 (Supplementary Table 1).

None of the variants, including the reported p.R160W substitution, showed a statistically significant association with PD after Bonferroni correction (Supplementary Table 1). Gene burden test analysis taking into account only rare variants (MAF<1%) did not show an increase frequency of rare variants in cases in comparison with controls either (data not shown). These findings support a meta-analysis⁴ and a genotyping study⁵ which also failed to replicate the association between PD and variants in *MC1R*.

From our data, the replication studies and polymorphic nature of the *MC1R* gene it is unlikely that variation alters the individual susceptibility to PD. However, the genomic overlap with *TUBB3* could indicate biological relevance to the region. In addition, 100kb upstream from *MC1R* gene is located Transcription factor 25 (*TCF25*), which has been

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Potential Conflicts of Interest

There are no conflicts of interest.

reported to be a leucine-rich repeat kinase 2 (*LRRK2*) interactor⁶. A reanalysis of *TUBB3* exons 2 to 5 and the *TCF25* gene, which are highly conserved, may be warranted in the original Spanish series to exclude linked variants in these genes. As the number of PD exomes that are available to study increases genomic regions of interest including candidate genes such as this may well be worth a second look.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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