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Lin et al.[1] recently reported that rare ubiquinol-cytochrome c reductase core protein I (UQCRC1) variants are associated with autosomal dominant (AD) forms of parkinsonism and polyneuropathy. They first identified an heterozygous substitution (c.941A>C, p.Tyr314Ser - RefSeq NM_003365.2) in the mitochondrial (UQCRC1) gene, which co-segregated with the disease within a large Taiwanese family with PD and polyneuropathy. Additional analysis of 699 unrelated PD probands with familial PD and 1934 sporadic PD patients revealed another two variants (c.931A>C, p.Ile311Leu and c.73_74insG, p.Ala25Glyfs*27) in UQCRC1 only in probands with familial PD but no overt polyneuropathy. All substitutions were absent in 1077 controls and in the Taiwan Biobank exome database of healthy participants (n=1517 exomes). Pathogenicity was reinforced by functional studies using CRISPR/Cas9-based knock-in human dopaminergic cell lines, Drosophila and mouse models. Altogether, their genetic data combined with in vitro and in vivo studies supported the functional pathogenicity of rare UQCRC1 variants in familial parkinsonism with polyneuropathy. Given the autosomal dominant inheritance of UQCRC1 variants in Taiwanese families, we selected specific cases with dominant transmission from our large collection of PD families to identify rare variants in UQCRC1. This represents the first attempt to replicate these findings in AD PD Caucasian families, consistent with the original article's discovery cohort.

Our cohort of 3540 PD index cases included 1131 probands with inheritance compatible with autosomal dominant transmission (at least 2 affected in two generations). Among them 994 underwent targeted or whole exome sequencing revealing the disease-causing gene in 220 cases. Exome data from 163 families in which no known causative gene was identified was analysed in this study. This cohort consisted in 241 sampled PD patients (143 males, 60% ; 98

females, 40%), with a mean age of onset at 42 years +/- 16 (SD). Most of the patients were European Caucasian (n = 219, 91%), six North Africans and 16 of unknown origin. They all were examined by trained neurologists using the same diagnostic form. They all fulfilled the UKBrain bank diagnostic criteria for "probable" PD[2].

Exome sequencing was performed at the ICM IGenSeq core facility or Integragen (Evry, France). Exons were captured using the Roche V.3 or Twist_Refseq 40Mb kit followed by a massively parallel sequencing on the NextSeq500 or NovaSeq system (Illumina). We excluded genetic variants that did not alter coding sequences and variants with a minor allele frequency >0.01 in control subjects in one or more reference databases (The Genome Aggregation Database, GnomAD[3]). Combined Annotation Dependent Depletion (CADD[4]) scores were used to summarize how deleterious amino acid substitutions are to protein function.

No variant fulfilling these criteria was identified, indicating the absence of disease-causing variants in *UQCRC1* in our population. Considering the total number of families with AD PD included in the study (383 in total), the *UQCRC1* gene seems very rarely implicated in familial European Caucasian cases. However, the precise frequency of *UQCRC1* variants in the Asian population cannot be precisely evaluated because the number of families with autosomal dominant inheritance among the 669 index cases screened by Lin *et al*[1] is not indicated. In addition, two recent studies including 1647 European and 452 Asian sporadic PD patients respectively did not find any evidence for association of *UQCRC1* with Parkinson's disease[5,6].

As mentioned by the authors, the low frequency of pathogenic variants in UQCRC1 in familial PD suggest that variants in this gene are a rare genetic cause of AD parkinsonism, found, until now, only in the asian population. Their absence in this first large cohort of selected families with AD inheritance (the more likely candidate families for identifying dominant variants) can be due to different factors. First, they could be absent or extremely rare in the Caucasian population. Second, exome analysis did not allow testing for other types of variants such as copy number variants or extragenic regulatory variants that have yet not been described for *UQCRC1*. Third, *UQCRC1* variants may cause a specific syndrome which combines parkinsonism and early onset polyneuropathy, an extremely rare phenotype already described in some specific syndromes[7] and which was not reported in our cohort. Indeed, Lin et al[1] provide a detailed description of the polyneuropathy which occurs long before PD symptoms in their large family. In contrast, no overt polyneuropathy was reported in the two remaining *UQCRC1* families but no electrophysiological studies were performed to exclude its presence.

Therefore, it would be interesting to screen for *UQCRC1* specifically in pedigrees with the very rare phenotype of AD parkinsonism and polyneuropathy in a follow up study.

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The data that support the findings of this study are available from the corresponding author, TC, upon reasonable request.

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