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Lack of evidence for association of *UQCRC1* with Parkinson's disease in Europeans

Konstantin Senkevich[a,b,*], **Sara Bandres-Ciga**[c], **Ziv Gan-Or**[a,b,d], **Lynne Krohn**[a,d] **on behalf of the International Parkinson's Disease Genomics Consortium (IPDGC)**

[a]Montreal Neurological Institute, McGill University, Montréal, Quebec, Canada

[b]Department of Neurology and neurosurgery, McGill University, Montréal, Quebec, Canada

[c]Molecular Genetics Section, Laboratory of Neurogenetics, NIA, NIH, Bethesda, MD, USA

[d]Department of Human Genetics, McGill University, Montréal, Quebec, Canada

Abstract

Recently, a novel variant p.Y314S in *UQCRC1* has been implicated as pathogenic in Parkinson's disease (PD). In the present study, we aimed to examine the association of *UQCRC1* with PD in large cohorts of European origin. We examined common and rare genetic variation in *UQCRC1* using genome-wide association study data from the International Parkinson Disease Genomics Consortium, including 14,671 cases and 17,667 controls, and whole-genome sequencing data from the Accelerating Medicines Partnership–Parkinson's disease initiative, including 1647 patients with PD and 1050 controls. No common variants were consistently associated with PD, and a variety of burden analyses did not reveal an association between rare variants in *UQCRC1* and PD. Therefore, our results do not support a major role for *UQCRC1* in PD in the European population, and additional studies in other populations are warranted.

Keywords

Parkinson disease; Genetics; *UQCRC1*

[*]Corresponding author at: Montreal Neurological Institute, McGill University 1033 Pine Avenue, West, Ludmer Pavilion, room 308-309 Montreal, Quebec, H3A 1A1, Canada. Tel.: +1-438-979-5052; fax: +1-514-398-8248. Konstantin.senkevich@mcgill.ca (K. Senkevich).

Disclosure statement

Z.G-O. has received consulting fees from Lysosomal Therapeutics Inc., Idorsia, Prevail Therapeutics, Denali, Ono Therapeutics, Neuron23, Handl Therapeutics, Deerfield and Inception Sciences (now Ventus). None of these companies were involved in any parts of preparing, drafting, and publishing this study. Other authors have no additional disclosures to report.

CRediT authorship contribution statement

Konstantin Senkevich: Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing - original draft. **Sara Bandres-Ciga:** Data curation, Resources, Formal analysis, Software, Writing - review & editing. **Ziv Gan-Or:** Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Visualization, Writing - review & editing. **Lynne Krohn:** Conceptualization, Methodology, Project administration, Resources, Supervision, Visualization, Writing - review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2020.10.030.

1. Introduction

The genetics of Parkinson's disease (PD) has been extensively studied over the last 20 years (Bandres-Ciga et al., 2020). A recent genome-wide association study (GWAS) identified 90 independent risk variants (Nalls et al., 2019); however, these variants explain less than 50% of the heritability of PD (Nalls et al., 2019), suggesting that other, unknown common and rare genetic variants affect the risk of PD. A novel variant p.Y314S in *UQCRC1* encoding the ubiquinol-cytochrome c reductase core protein (UQCRC1) has been recently identified in 5 Taiwanese family members with parkinsonism by whole-exome sequencing (Lin et al., 2019). UQCRC1 is a mitochondrial protein and part of the respiratory chain III complex (Hoffman et al., 1993), which may play a role in mitochondrial respiration (Lin et al., 2019; Shan et al., 2019).

The purpose of this work is to examine the role of *UQCRC1* in a large-scale European PD population using GWAS and whole-genome sequencing (WGS) data from the International Parkinson Disease Genomics Consortium (IPDGC) and Accelerating Medicines Partnership–Parkinson's disease (AMP-PD) initiative.

2. Methods

The study populations included 14,671 patients with PD and 17,667 controls from IPDGC and 1647 patients with PD and 1050 controls from AMP-PD (https://amp-pd.org/). Quality control of IPDGC GWAS data was performed on both individual and variant levels as previously described (Nalls et al., 2019). Similar quality control procedures were performed in the AMP-PD WGS data, as described by AMP-PD (https://amp-pd.org/whole-genome-data). We extracted *UQCRC1* genotyping data from both data sets using gene coordinates determined by UQCRC1 position (+/− 100kb): hg19: chr3:48,536,432–48,747,098; hg38: chr3:48,499,002–48,709,646. We used ANNOVAR (Wang et al., 2010) to annotate both data sets. PLINK 1.9 (Chang et al., 2015) was used for logistic regression (adjusted for age, sex, and first 10 principal components) to study the association between common *UQCRC1* variants (with minor allele frequency [MAF] > 0.01) and PD in the IPDGC cohort. In the AMP-PD cohort, to study the burden of rare variants (defined as variants with MAF <0.03 in the current data), a variety of methods were applied, including sequence kernel association test and its optimized version, combined multivariate and collapsing, Zeggini and Madsen-Browning tests, as a part of the Rvtest package (Zhan et al., 2016). Bonferroni correction was applied to correct for multiple comparisons. All codes used in the present study are available at our GitHub at https://github.com/ipdgc/IPDGC-Trainees/blob/master/UQCRC1_IPDGC_trainee.md.

3. Results

Using the IPDGC GWAS data, we identified 140 common variants in the selected region (Fig. 1). None of the common variants annotated to *UQCRC1* were associated with PD (Supplementary Table 1). In the AMP-PD WGS data, we identified 94 variants with MAF <0.03 within or close to *UQCRC1* (Supplementary Table 2), including 9 nonsynonymous variants (Supplementary Table 2). We performed burden tests for 3 categories of variants: 1)

all rare variants, 2) all rare coding variants, and 3) all rare nonsynonymous variants. None of the burden tests showed association between rare *UQCRC1* variants and PD (Table 1). In both cohorts, we did not find the *UQCRC1* p.Y314S variant described in the original study (Lin et al., 2019).

4. Discussion

In the present study, we performed a comprehensive analysis of common and rare variants in *UQCRC1* using GWAS and WGS data from large cohorts of patients with PD and controls.

In the original study in which *UQCRC1* variants were implicated, the authors described a family in which 5 carriers of *UQCRC1* p.Y314S had late-onset levodopa responsive parkinsonism and axonal type sensorimotor polyneuropathy (Lin et al., 2019). In addition, autosomal dominant inheritance was demonstrated and there were no asymptomatic carriers of this variant, based on a family tree authors present (Lin et al., 2019). Recent replication study in an eastern Chinese population did not reveal association between *UQCRC1* and PD (Lin et al., 2020).

It is possible that this variant is associated with a specific form of atypical parkinsonism, but not with typical PD. It has been shown that a number of genes previously reported as PD-associated (such as *DNAJC13*, *UCHL1*, *HTRA2*, *GIGYF2*, and *EIF4G1*) do not play a role in PD and thus should not be regarded as PD genes (Foo et al., 2014; Krüger et al., 2011; Lesage et al., 2010; Saini et al., 2020). Furthermore, other genes (e.g., *ATP13A2*, *FBXO7*) that are associated with atypical forms of parkinsonism are often cited as PD-associated genes (Dehay et al., 2012; Deng et al., 2015; Weissbach et al., 2019). It is important to properly define which genes are involved in typical PD and which genes are not, particularly in the era of targeted drug development.

Overall, we did not find any evidence to support an important role for *UQCRC1* in patients with PD of European origin. However, additional studies in other populations are required to further study the potential role of *UQCRC1* in PD, and we cannot rule out the possibility that very rare, specific *UQCRC1* variants are associated with PD or with atypical forms of parkinsonism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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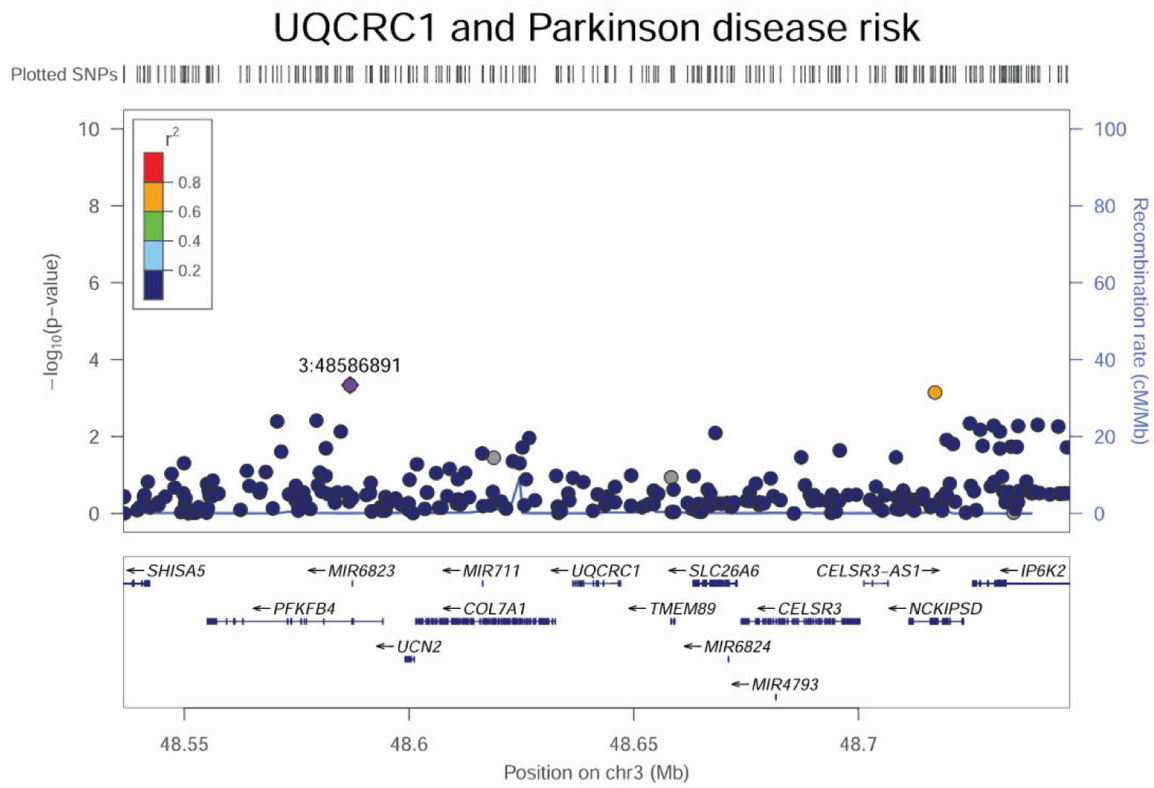

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hilite range: 0 – 0 [0 – 0]
reference SNP: chr3:48586891
number of SNPs plotted: 266
min P-value: 4.6E-4 [chr3:48586891]
max P-value: 9.88E-1 [chr3:48536675]

Fig. 1.

LocusZoom plot of IPDGC GWAS summary statistics showing variants with MAF more than 1% near the *UQCRC1* gene. Abbreviations: GWAS, genome-wide association study; IPDGC, International Parkinson Disease Genomics Consortium; MAF, minor allele frequency.

Table 1

Burden tests for *UQCRC1* in the AMP-PD cohort

Burden test	All variants			Coding variants			Nonsynonymous variants		
	NumVar	NumPolyVar	*p*-value	NumVar	NumPolyVar	*p*-value	NumVar	NumPolyVar	*p*-value
Zeggini	73	54	0.562	18	13	0.619	12	9	0.721
SKAT-O	73	54	0.77	18	13	0.586	12	9	0.712
SKAT	73	54	0.865	18	13	0.476	12	9	0.594
Madson-Browning	73	54	0.487	18	13	0.046	12	9	0.109
Fp	73	54	0.712	18	13	0.489	12	9	0.898
CMC	73	54	0.596	18	13	0.629	12	9	0.731

Key: AMP-PD, Accelerating Medicines Partnership–Parkinson's disease; CMC, combined multivariate and collapsing; NumPolyVar, number of polymorphic genotypes; NumVar, number of variants; SKAT, sequence kernel association test; SKAT-O, sequence kernel association test optimized version.