



Negative results

Evaluation of the interaction between *LRRK2* and *PARK16* loci in determining risk of Parkinson's disease: analysis of a large multicenter study



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ABSTRACT

A recent study MacLeod et al. has shown that an interaction between variants at the *LRRK2* and *PARK16* loci influences risk of development of Parkinson's disease (PD). Our study examines the proposed interaction between *LRRK2* and *PARK16* variants in modifying PD risk using a large multicenter series of PD patients (7715) and controls (8261) from sites participating in the Genetic Epidemiology of Parkinson's Disease Consortium. Our data does not support a strong direct interaction between *LRRK2* and *PARK16* variants; however, given the role of retromer and lysosomal pathways in PD, further studies are warranted.

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1. Introduction

Genetic discoveries made over the years either by using linkage, array, and/or exome-based approaches have helped in advancing our knowledge of the genetic underpinnings of Parkinson's disease (PD) (International Parkinson Disease Genomics Consortium et al., 2011; Lesage and Brice, 2009; Trinh and Farrer, 2013). As we discover new loci relevant to idiopathic PD pathogenesis, it has become imperative to also understand the gene–gene interaction effect in modulating PD risk in population (see [Supplementary Information](#)) (Elbaz et al., 2011). Although the results of most gene–gene interactions studies in PD to date have pointed toward independent effects for PD susceptibility variants, an exception to this has been an assessment of functional-genetic interaction between the *LRRK2* and *PARK16* loci in which overexpression of *RAB7L1*, a candidate gene for *PARK16* locus, reversed the effects of the *LRRK2* mutation and rescued the phenotypes (MacLeod et al., 2013). Therefore, this study aims to evaluate the interaction between several different *LRRK2* and *PARK16* variants in determining PD risk using a Caucasian series with more than 10,000 subjects from 14 different centers, and an Asian series with more than 5000 subjects from 5 different centers.

2. Methods

The Genetic Epidemiology of Parkinson's Disease (GEOPD) consortium includes investigators from 59 sites, across 30 countries and 6 continents, as of 2016. A total of 19 sites representing 17 countries and 4 continents agreed to contribute DNA samples and clinical data for the present study. In total, 15,976 subjects were included in this study, divided into a Caucasian series (5769 PD patients, 4988 controls) and an Asian series (1946 PD patients, 3273 controls). We selected 5 SNPs for the *PARK16* locus (rs823139 [*RAB7L1*], rs708725 [*RAB7L1*], rs823156 [*SLC41A1*], rs11240572 [*PM20D1*], and rs708723 [*RAB7L1*]) because previously published studies suggested associations with PD risk and the respective sites also provided coverage of the *PARK16* locus. We selected 2 SNPs from the *LRRK2* gene (rs1491942, rs7133914) due to previously demonstrated associations with PD and minor allele frequencies high enough to allow for reasonable interaction analysis. Analysis was performed separately for the Caucasian series, the Asian series,

and the combined series. We evaluated single variant associations using fixed effects logistic regression models adjusted for GEOPD site. Pairwise multiplicative interactions between *LRRK2* and *PARK16* variants were also examined using fixed effects logistic regression models. In addition to including terms for the given 2 individual variants and their interaction, these models were adjusted for the individual GEOPD site. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. Subjects were coded as either 0 (absence of the minor allele) or 1 (presence of the minor allele) for each variant. Variants with a MAF of 10% or greater in both the Asian and Caucasian series were examined under an additive model, with the subject coded as (0,1,2), depending on the number of copies of the minor allele. To account for the 10 tests of *LRRK2*-*PARK16* interaction that were performed in each series (Caucasian, Asian, or combined), we utilized a Bonferroni correction for multiple testing separately in each series, after which 2-sided *p*-values of 0.005 or lower were considered as statistically significant. All statistical analyses were performed using R Statistical Software. The local Ethics Committee at each GEOPD site approved the study. All participants signed an informed consent.

3. Results

Of the 10 interactions that were examined between the *PARK16* and *LRRK2* variants, nonsignificant evidence of gene–gene interaction was observed between *LRRK2* rs1491942 and *PARK16* rs11240572 in the combined series (interaction OR: 0.97, 95% CI: 0.74–1.01, *p* = 0.07, [Supplementary Table 1](#)). *PARK16* rs11240572 appeared to have no effect on PD risk for individuals with the common GG genotype for *LRRK2* rs1491942, but a slight protective effect for those with GC and CC *LRRK2* rs1491942 genotypes (see [Supplementary Information](#)). Investigating this further in the stratified data ([Supplementary Table 6](#)), we observed for noncarriers of *PARK16* rs11240572, *LRRK2* rs1491942 a statistically significant higher risk of PD development in the Caucasian and combined series (OR 1.17 and 1.15, *p*-value <0.001). However, after correcting for multiple testing, it no longer approached statistical significance under the interaction model. There were no other noteworthy interactions between *LRRK2* rs1491942 and *PARK16* variants in any series (all interaction *p* ≥ 0.25, [Supplementary Tables 3–5](#)), or between *LRRK2* rs7133914 and *PARK16* variants in the Caucasian series (all interaction *p* ≥ 0.096,

Supplementary Table 7). Interaction ORs ranged between 0.85 and 1.20, which supports the lack of a biologically meaningful interaction by lack of a notable deviation from an OR of 1. Between-site heterogeneity in interaction effects was generally relatively low (ranges between 0% and 35% with most around 0%), lending consistency to the lack of interaction. Models adjusted for age and gender using the subset of subjects with complete information and random effects models also produced similar results in gene–gene interaction analyses.

4. Discussion

The identification of genetic mutations in genes linked to familial forms of PD (e.g., *LRRK2*, *VPS35*, and *DNAJC13*), and genetic variability within the *PARK16* locus in genome wide association studies strongly implicates the role of retromer and lysosomal pathway in PD pathogenesis (Heckman et al., 2014; Soto-Ortolaza et al., 2013). Therefore, to understand the impact of interaction in world-wide populations, we performed a large multicenter study to assess the genetic evidence of interaction between *LRRK2* and *PARK16* locus. The results of our study do not provide evidence of a genetic interaction between *PARK16* and *LRRK2* variants with regard to risk of PD. Of note, the directionality of effect estimates, albeit with a much weaker effect size observed in the present study, involving the specific *LRRK2* rs1491942/*PARK16* rs11240572 interaction, are in agreement with previously published findings. Genetic interaction studies are limited by sample size and power because the variable of focus in an interaction study is the presence of the genotype of interest for both variants, and this occurs much less frequently than in the individual variant genotypes.

Therefore, even with our large sample size, power is still limited to detect moderate to small gene–gene interaction effects. Although there was some degree of concordance between our interaction findings and those that were previously reported, our results were much weaker than the strong *LRRK2*–*PARK16* interaction that was previously reported (Beilina et al., 2014; MacLeod et al., 2013). Even with the large GEPD sample size, which we have accrued to perform the present study, we are likely underpowered to detect weaker interaction effects. In addition, lack of genetic interaction does not exclude the presence of cellular or functional interaction. However, such genetic studies will be critical if we are to understand the role of gene–gene interaction in disease susceptibility.

Disclosure statement

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Company, by attending these advisory meetings he received personal compensation and has been consulting with Ohtsuka Pharmaceutical Company, Kyowa Hakko Kirin Pharmaceutical Company, GlaxoSmithKline, Novartis, and Schering-Plough, and when he attended these advisory board meetings where he received personal compensation. Dr Gasser holds a patent concerning the *LRRK2* gene and neurodegenerative disorders.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.neurobiolaging.2016.09.022>.

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