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

L. Wang, MS<sup>1</sup>, M.G. Heckman, MS<sup>2</sup>, J. O. Aasly, MD<sup>3</sup>, G. Annesi, PhD<sup>4</sup>, M. Bozi, MD<sup>5,6</sup>, S. J. Chung, MD<sup>7</sup>, C. Clarke, MD<sup>8</sup>, D. Crosiers, MD<sup>9,10,11</sup>, G. Eckstein, PhD<sup>12</sup>, G. Garraux, MD<sup>13</sup>, G. M. Hadjigeorgiou, MD<sup>14</sup>, N. Hattori, MD, PhD<sup>15</sup>, B. Jeon, MD<sup>16</sup>, Y. J. Kim, MD PhD<sup>17</sup>, M. Kubo<sup>18</sup>, S. Lesage, PhD<sup>19</sup>, J. J. Lin, MD<sup>20</sup>, T. Lynch, MD<sup>21</sup>, P. Lichtner, PhD<sup>12</sup>, G. D. Mellick, PhD<sup>22</sup>, V. Mok, MD<sup>23</sup>, K. E. Morrison, MD<sup>24</sup>, A. Quattrone, MD<sup>25</sup>, W. Satake, MD PhD<sup>26</sup>, P. A. Silburn, MD<sup>27</sup>, L. Stefanis, MD<sup>6,28</sup>, J. D. Stockton, MD<sup>29</sup>, E. K. Tan, MD<sup>30,31</sup>, T. Toda, MD PhD<sup>26</sup>, A. Brice, MD<sup>19</sup>, C. Van Broeckhoven, PhD<sup>9,10</sup>, R. J. Uitti, MD<sup>32</sup>, K. Wirdefeldt, MD PhD<sup>33</sup>, Z. Wszolek, MD<sup>32</sup>, G. Xiromerisiou, MD<sup>14</sup>, D. M. Maraganore, MD<sup>34</sup>, T. Gasser, MD<sup>35</sup>, R. Kruger, MD<sup>35,36</sup>, M. J. Farrer, PhD<sup>37</sup>, O. A. Ross, PhD<sup>38</sup>, and M. Sharma, PhD<sup>1,35</sup> on behalf of the GEOPD consortium

<sup>1</sup>Centre for Genetic Epidemiology, Institute for Clinical Epidemiology and Applied Biometry, University of Tübingen, Germany <sup>2</sup>Division of Biomedical Statistics and Informatics, Mayo Clinic, Jacksonville, Florida <sup>3</sup>Department of Neurology, St Olavs hospital and NTNU Trondheim, Norway <sup>4</sup>Institute of Molecular Bioimaging and Physiology, National Research Council, Section of Catanzaro Italy <sup>5</sup>Psychiatry Athens Hospital, Neurology Department, Athens <sup>6</sup>2nd Neurology Clinic, University of Athens, Attikon Hospital, Athens <sup>7</sup>Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea <sup>8</sup>School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, UK and City Hospital, Birmingham <sup>9</sup>Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, VIB, Antwerp, Belgium <sup>10</sup>Institute Born-Bunge, University of Antwerp, Antwerp, Belgium <sup>11</sup>Department of Neurology, University Hospital Antwerp, Antwerp, Belgium <sup>12</sup>Helmholtz Zentrum München, German Research Centre for Environmental Health (GmbH), Ingolstaedter Landstr. 1, 85764 Neuherberg, Germany <sup>13</sup>Cyclotron Research Centre, Department of Neurology, University of Liège, Sart Tilman B30, 4000 Liège- Belgium <sup>14</sup>Department of Neurology, Faculty of Medicine, University of Thessaly and Institute of Biomedical Research and Technology, CERETETH, Larissa <sup>15</sup>Department of Neurology, Juntendo University School of Medicine, Tokyo, Japan <sup>16</sup>Institute Department of Neurology, Seoul National University Hospital <sup>17</sup>ILSONG Institute of Life Science, Hallym University, Hallym Institute of Translational Genomics & Bioinformatics, Department of Neurology, Hallym University Sacred Heart Hospital, Korea <sup>18</sup>Laboratory for Genotyping Development, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan <sup>19</sup>INSERM U 1127, CNRS UMR 7225, Sorbonne Universités, UPMC Univ Paris

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06 UMR S 1127, Institut du Cerveau et de la Moelle épinière, ICM, Paris, France <sup>20</sup>Department of Neurology, Chushang Show-Chwan Hospital, Nantou and Chung-Shan Medical University Hospital, Taichung, Taiwan <sup>21</sup>The Dublin Neurological Institute at the Mater Misericordiae University Hospital, and Conway Institute, University College Dublin, Ireland <sup>22</sup>Eskitis Institute for Cell and Molecular Therapies, Griffith University, Australia <sup>23</sup>Clinical Neurology Research Centre, Department of Medicine & Therapeutics, The Chinese University of Hong Kong, 10/F, Clinical Sciences Building, Prince of Wales Hospital, Shatin, New Territories, Hong Kong <sup>24</sup>Faculty of Medicine, University of Southampton, Southampton, UK <sup>25</sup>Institute of Neurology, Department of Medical Sciences, University Magna Graecia, Catanzaro, Italy and Institute of Molecular Bioimaging and Physiology, National Research Council, Section of Catanzaro Italy <sup>26</sup>Division of Neurology/Molecular Brain Science, Kobe University Graduate School of Medicine <sup>27</sup>University of Queensland Centre for Clinical Research, Herston, Australia <sup>28</sup>Divisions of Basic Neurosciences & Cell Biology, Biomedical Research Foundation of Academy of Athens, Athens 11527, Greece <sup>29</sup>Neurosciences Department, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust <sup>30</sup>Department of Neurology, Singapore General Hospital, National Neuroscience Institute, Singapore <sup>31</sup>Duke-NUS Graduate Medical School <sup>32</sup>Department of Neuroscience, Mayo Clinic Jacksonville, USA <sup>33</sup>Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden <sup>34</sup>Department of Neurology, NorthShore University HealthSystem, Evanston, IL, USA <sup>35</sup>Department of Neurodegenerative Diseases, Hertie Institute for Clinical Brain Science Research, University of Tübingen, Germany <sup>36</sup>Clinical and Experimental Neuroscience, Luxembourg Centre for Systems Biomedicine, University of Luxembourg, and Centre Hospitalier de Luxembourg (CHL), Luxembourg <sup>37</sup>Djavad Mowafaghian Centre for Brain, University of British Columbia, Vancouver, British Columbia, Canada V6T 2B5 <sup>38</sup>Department of Neurology, Mayo Clinic Jacksonville, USA

## Abstract

A recent study has shown that an interaction between variants at the *LRRK2* and *PARK16* loci influences risk of development of PD (MacLeod D. et al, 2013). Our study examines the proposed interaction between *LRRK2* and *PARK16* variants in modifying PD risk using a large multi-center series of PD patients (5769) and controls (4988) from sites participating in the Genetic Epidemiology of Parkinson's Disease (GEoPD) 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.

## 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 PD (Trinh J., Farrer M., 2013; Lesage S., Brice. A., 2009; International Parkinson Disease Genomics Consortium et al., 2011). 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 A., 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 D., 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 5,000 subjects from five different centers.

## 2. Methods

The GEPD consortium includes investigators from 59 sites, across 30 countries and 6 continents, as of 2016. A total of 19 sites representing 17 countries and four continents agreed to contribute DNA samples and clinical data for the current 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 five 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 two 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 GEPD 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 two individual variants and their interaction, these models were adjusted for the individual GEPD 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. In order 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 GEPD site approved the study. All participants signed an informed consent.

## 3. Results

Of the ten interactions that were examined between the *PARK16* and *LRRK2* variants, non-significant 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, 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 non-carriers 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% to 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*, *DNAJC13*) and genetic variability within the *PARK16* locus in GWAS strongly implicates the role of retromer and lysosomal pathway in PD pathogenesis (Heckman M.G., et al., 2014; Soto-Ortolaza A.I., et al., 2013). Therefore, to understand the impact of interaction in world-wide populations, we performed a large multi-center 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 the individual variant genotypes.

Therefore even with our large sample size, power is still limited to detect moderate to small gene-gene interaction effects. While 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 A., et al., 2014; MacLeod D., et al., 2013). Even with the large GEPD sample size, which we have accrued to perform the current study, we are likely underpowered to detect weaker interaction effects. Additionally, 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.

#### Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## References

- Beilina A, Rudenko IN, Kaganovich A, et al. Unbiased screen for interactors of leucine-rich repeat kinase 2 supports a common pathway for sporadic and familial Parkinson disease. *PNAS*. 2014; 7:2626–2631.
- Elbaz A, Ross OA, Ioannidis JP, et al. Independent and joint effects of the *MAPT* and *SNCA* genes in Parkinson disease. *Annals of neurology*. 2011; 69:778–792. [PubMed: 21391235]
- Heckman MG, Elbaz A, Soto-Ortolaza AI, et al. Protective effect of *LRRK2* p.R1398H on risk of Parkinson's disease is independent of *MAPT* and *SNCA* variants. *Neurobiology of aging*. 2014; 35:266. e265-214.
- Nalls MA, Plagnol V, et al. International Parkinson Disease Genomics C. Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet*. 2011; 377:641–649. [PubMed: 21292315]
- Lesage S, Brice A. Parkinson's disease: from monogenic forms to genetic susceptibility factors. *Human molecular genetics*. 2009; 18:R48–R59. [PubMed: 19297401]
- MacLeod DA, Rhinn H, Kuwahara T, et al. *RAB7L1* interacts with *LRRK2* to modify intraneuronal protein sorting and Parkinson's disease risk. *Neuron*. 2013; 77:425–439. [PubMed: 23395371]
- Soto-Ortolaza AI, Heckman MG, Labbe C, et al. GWAS risk factors in Parkinson's disease: *LRRK2* coding variation and genetic interaction with *PARK16*. *American journal of neurodegenerative disease*. 2013; 2:287–299. [PubMed: 24319646]
- Trinh J, Farrer M. Advances in the genetics of Parkinson disease. *Nature reviews Neurology*. 2013; 9:445–454. [PubMed: 23857047]