

Population-specific Frequencies for *LRK2* Susceptibility Variants in the Genetic Epidemiology of Parkinson's Disease (GEO-PD) Consortium

Michael G. Heckman, MS,¹
 Alexandra I. Soto-Ortolaza, BSc,² Jan O. Aasly, MD,³
 Nadine Abahuni, MD,⁴ Grazia Annesi, PhD,⁵
 Justin A. Bacon, BSc,² Soraya Bardien, PhD,⁶
 Maria Bozi, MD,⁷ Alexis Brice, MD,^{8,9,10,11}
 Laura Brighina, MD, PhD,¹² Jonathan Carr, MD,¹³
 Marie-Christine Chartier-Harlin, PhD,^{14,15}
 Efthimios Dardiotis, MD,^{16,17} Dennis W. Dickson, MD,²
 Nancy N. Diehl, BS,¹ Alexis Elbaz, MD, PhD,^{18,19}
 Carlo Ferrarese, MD, PhD,¹² Brian Fiske, PhD,²⁰
 J. Mark Gibson, MD,²¹ Rachel Gibson, PhD,²²
 Georgios M. Hadjigeorgiou, MD,^{16,17}
 Nobutaka Hattori, MD, PhD,²³
 John P.A. Ioannidis, MD, DSc,^{24,25}
 Magdalena Boczarska-Jedynak, MD, PhD,²⁶
 Barbara Jasinska-Myga, MD, PhD,²⁶ Beom S. Jeon, MD,
 PhD,²⁷ Yun Joong Kim, MD, PhD,²⁸ Christine Klein, MD,²⁹
 Rejko Kruger, MD,³⁰ Elli Kyrtzi, MD,³¹
 Suzanne Lesage, PhD,^{8,9,10} Chin-Hsien Lin, MD,³²
 Timothy Lynch, FRCPI,³³ Demetrius M. Maraganore, MD,³⁴
 George D. Mellick, PhD,³⁵ Eugénie Mutez, MD,^{14,15,36}
 Christer Nilsson, MD, PhD,³⁷ Grzegorz Opala, MD, PhD,²⁶
 Sung Sup Park, MD,³⁸ Simona Petrucci, MD,³⁹
 Andreas Puschmann, MD, PhD,^{40,41} Aldo Quattrone, MD,⁴²
 Manu Sharma, PhD,³⁰ Peter A. Silburn, PhD,⁴³
 Young Ho Sohn, MD, PhD,⁴⁴ Leonidas Stefanis, MD,³¹
 Vera Tadic, MD,²⁹ Jessie Theuns, PhD,^{45,46}
 Hiroyuki Tomiyama, MD, PhD,²³ Ryan J. Uitti, MD,⁴⁷
 Enza Maria Valente, MD, PhD,³⁹
 Christine Van Broeckhoven, PhD,^{45,46}
 Simone van de Loo, PhD,⁴ Demetrios K. Vassilatis, PhD,³¹
 Carles Vilariño-Güell, PhD,⁴⁸ Linda R. White, PhD,⁴⁹
 Karin Wirdefeldt, MD, PhD,⁵⁰ Zbigniew K. Wszolek, MD,⁴⁷

Ruey-Meei Wu, MD,⁵¹ Faycal Hentati, MD,⁵²
 Matthew J. Farrer, PhD,⁴⁸ Owen A. Ross, PhD^{2*} on behalf of
 the Genetic Epidemiology of Parkinson's Disease (GEO-PD)
 Consortium

¹Biostatistics Unit, Mayo Clinic, Jacksonville, Florida, USA; ²Department of Neuroscience, Mayo Clinic, Jacksonville, Florida, USA; ³Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway; ⁴Department of Neurology, Goethe University, Frankfurt am Main, Germany; ⁵Institute of Neurological Sciences, National Research Council, Cosenza, Italy; ⁶Division of Molecular Biology and Human Genetics, University of Stellenbosch, Cape Town, South Africa; ⁷General Hospital of Syros, Syros, Greece; ⁸Université Pierre et Marie Curie-Paris 6, Centre de Recherche de l'Institut du Cerveau et de la Moelle Épineuse, Medical Research Unit S975, Paris, France; ⁹Institut National de la Santé et de la Recherche Médicale, Unit 975, Paris, France; ¹⁰Centre National de la Recherche Scientifique, Medical Research Unit 7225, Paris, France; ¹¹Department of Genetics and Cytogenetics, Hôpital de la Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France; ¹²Department of Neuroscience-Section of Neurology, University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy; ¹³Division of Neurology, University of Stellenbosch, Cape Town, South Africa; ¹⁴University Lille Nord de France, Centre de Recherche Jean-Pierre Auber, Lille, France; ¹⁵Institut National de la Santé et de la Recherche Médicale, Unit 837, Lille, France; ¹⁶Department of Neurology, Laboratory of Neurogenetics, Faculty of Medicine, University of Thessaly, Larissa, Greece; ¹⁷Institute of Biomedical Research and Technology, Center for Research and Technology-Thessaly, Larissa, Greece; ¹⁸Institut National de la Santé et de la Recherche Médicale, Unit 1018, Centre for Research in Epidemiology and Population Health, Villejuif, France; ¹⁹Université de Versailles Saint-Quentin, Medical Research Unit 1018, Versailles, France; ²⁰The Michael J. Fox Foundation for Parkinson's Research, New York, New York, USA; ²¹Department of Neurology, Royal Victoria Hospital, Belfast, Ireland; ²²Research and Development, GlaxoSmithKline Pharmaceuticals Ltd., Stevenage, United Kingdom; ²³Department of Neurology, Juntendo University School of Medicine, Tokyo, Japan; ²⁴Clinical and Molecular Epidemiology Unit, Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, Greece; ²⁵Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, California, USA; ²⁶Department of Neurology, Medical University of Silesia, Katowice, Poland; ²⁷Department of Neurology, Seoul National University Hospital, Seoul, South Korea; ²⁸ILSONG Institute of Life Science and Department of Neurology, Hallym University, Anyang, South Korea; ²⁹Section of Clinical and Molecular Neurogenetics at the Department of Neurology, University of Luebeck, Luebeck, Germany; ³⁰Department for Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research and German Center for Neurodegenerative Diseases (DZNE), University of Tübingen, Tübingen, Germany; ³¹Divisions of Basic Neurosciences and Cell Biology, Biomedical Research Foundation of the Academy of Athens, Athens, Greece; ³²Department of Neurology, National Taiwan University Hospital Yun-Lin Branch, Yun-Lin, Taiwan; ³³Dublin Neurological Institute at the Mater Misericordiae University Hospital and Conway Institute of Biomolecular and Biomedical Research, University College, Dublin, Ireland; ³⁴Department of Neurology, North Shore University Health System, Evanston, Illinois, USA; ³⁵Eskitis Institute for Cell and Molecular Therapies, Griffith University, Brisbane, Queensland, Australia; ³⁶Centre Hospitalier Régional Universitaire de Lille, Lille, France; ³⁷Clinical Memory Research Unit,

*Correspondence to: Dr. Owen A. Ross, Department of Neuroscience, Mayo Clinic Jacksonville, 4500 San Pablo Road, Jacksonville, FL 32224; ross.owen@mayo.edu

Funding agencies: The present study and original funding for the GEO-PD Consortium was supported by grants from the Michael J. Fox Foundation. The Mayo Clinic is a Morris K. Udall Center of Excellence in PD Research (P50 NS072137).

Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the Acknowledgments section online.

Received: 20 August 2012; **Revised:** 7 November 2012; **Accepted:** 27 January 2013

DOI: 10.1002/mds.25600

Department of Clinical Sciences, Lund University, Lund, Sweden; ³⁸Department of Laboratory Medicine, Seoul National University Hospital, Seoul, South Korea; ³⁹Mendel Laboratory, Istituto di Ricovero e Cura a Carattere Scientifico Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Italy; ⁴⁰Department of Neurology, Skåne University Hospital, Lund, Sweden; ⁴¹Department of Neurology, Clinical Sciences, Lund University, Lund, Sweden; ⁴²Department of Medical Sciences, Institute of Neurology, University Magna Graecia and Neuroimaging Research Unit, National Research Council, Catanzaro, Italy; ⁴³University of Queensland Centre for Clinical Research, Royal Brisbane Hospital, Brisbane, Queensland, Australia; ⁴⁴Department of Neurology, Yonsei University College of Medicine, Seoul, South Korea; ⁴⁵Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, VIB, Antwerp, Belgium; ⁴⁶Laboratory of Neurogenetics, Institute Born-Bunge, University of Antwerp, Antwerp, Belgium; ⁴⁷Department of Neurology, Mayo Clinic, Jacksonville, Florida, USA; ⁴⁸Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada; ⁴⁹University Hospital and Norwegian University of Science and Technology, Trondheim, Norway; ⁵⁰Department of Clinical Neuroscience and Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden; ⁵¹Department of Neurology, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan; ⁵²Institut de Neurologie, Laboratoire de Neurobiologie Moleculaire, La Rabta, Tunis, Tunisia

ABSTRACT

Background: Variants within the leucine-rich repeat kinase 2 gene are recognized as the most frequent genetic cause of Parkinson's disease. Leucine-rich repeat kinase 2 variation related to disease susceptibility displays many features that reflect the nature of complex, late-onset sporadic disorders like Parkinson's disease.

Methods: The Genetic Epidemiology of Parkinson's Disease Consortium recently performed the largest genetic association study for variants in the leucine-rich repeat kinase 2 gene across 23 different sites in 15 countries.

Results: Herein, we detail the allele frequencies for the novel risk factors (p.A419V and p.M1646T) and the protective haplotype (p.N551K-R1398H-K1423K) nominated in the original publication. Simple population allele frequencies not only can provide insight into the clinical relevance of specific variants but also can help genetically define patient groups.

Conclusions: Establishing individual patient-based genomic susceptibility profiles that incorporate both risk factors and protective factors will determine future diagnostic and treatment strategies. © 2013 Movement Disorder Society

Key Words: Parkinson's disease; LRRK2; genetics; association study

As we enter an era of personalized medicine defined by the individual genomic profile, it will be critical that we understand the independent and joint influences of disease-associated genetic variation.^{1,2}

Determining appropriate genetic testing and understanding the ramifications of results will decide the utility of such approaches from a diagnostic and prognostic viewpoint. The interpretation of clinical genetic testing may be most difficult with regard to late-onset sporadic disorders, such as Parkinson's disease (PD), in which a number of genetic loci have been nominated to alter disease risk, including highly penetrant mutations co-segregating with disease in families and common, less penetrant risk factors.³

Recently, the Genetic Epidemiology of Parkinson's Disease (GEO-PD) Consortium performed a large case-control study evaluating the associations of 121 different rare and common coding variants in the leucine-rich repeat kinase 2 (*LRRK2*) gene with susceptibility to PD.⁴ Our study was comprised of a total of 8611 PD cases and 6929 controls, representing three ethnicities (Caucasian, Asian, and Arab-Berber). The results of the study nominated new risk factors—p.M1646T in the Caucasian series and p.A419V in the Asian series—as well as a protective haplotype (p.N551K-R1398H-K1423K) across all 3 series.^{4,5} In our analyses, we provided odds ratio estimates of association using a number of different statistical models involving combined data from 23 GEO-PD sites. Herein, we provide population-specific frequencies, which were not previously presented for p.M1646T, p.A419V, or the protective haplotype. These simple allele and haplotype frequencies can be equally helpful in the interpretation of results and in determining the clinical relevance of each variant.

As displayed in Figure 1a, the minor allele (C) for p.M1646T had a maximum frequency of 2.85% in patients with PD and 2.55% in controls for any individual country, and it was more common among patients than among controls for 11 of the 13 countries in which it was observed (Fig. 1a). The p.A419V substitution was more common in patients with PD compared with controls for each Asian country, with minor allele frequencies ranging from 0.17% to 2.94% (Fig. 1b). The frequency of the protective p.N551K-R1398H-K1423K haplotype varied between countries within patients (from 3.01% to 10.64%) and controls (from 4.26% to 14.39%) (Fig. 1c). The lower haplotype frequency in patients was observed for the majority of countries, with the most discrepant results occurring for the two smallest populations. Individual population frequencies and their 95% confidence intervals are provided in Supporting Tables 1 through 3 along with the originally presented population-specific odds ratios¹ and previously unreported, population-specific *P* values for association.

Of the PD genes that have been identified thus far, *LRRK2* is particularly important owing to the relatively high frequency of its mutations, its involvement in both familial and sporadic disease, and its potential

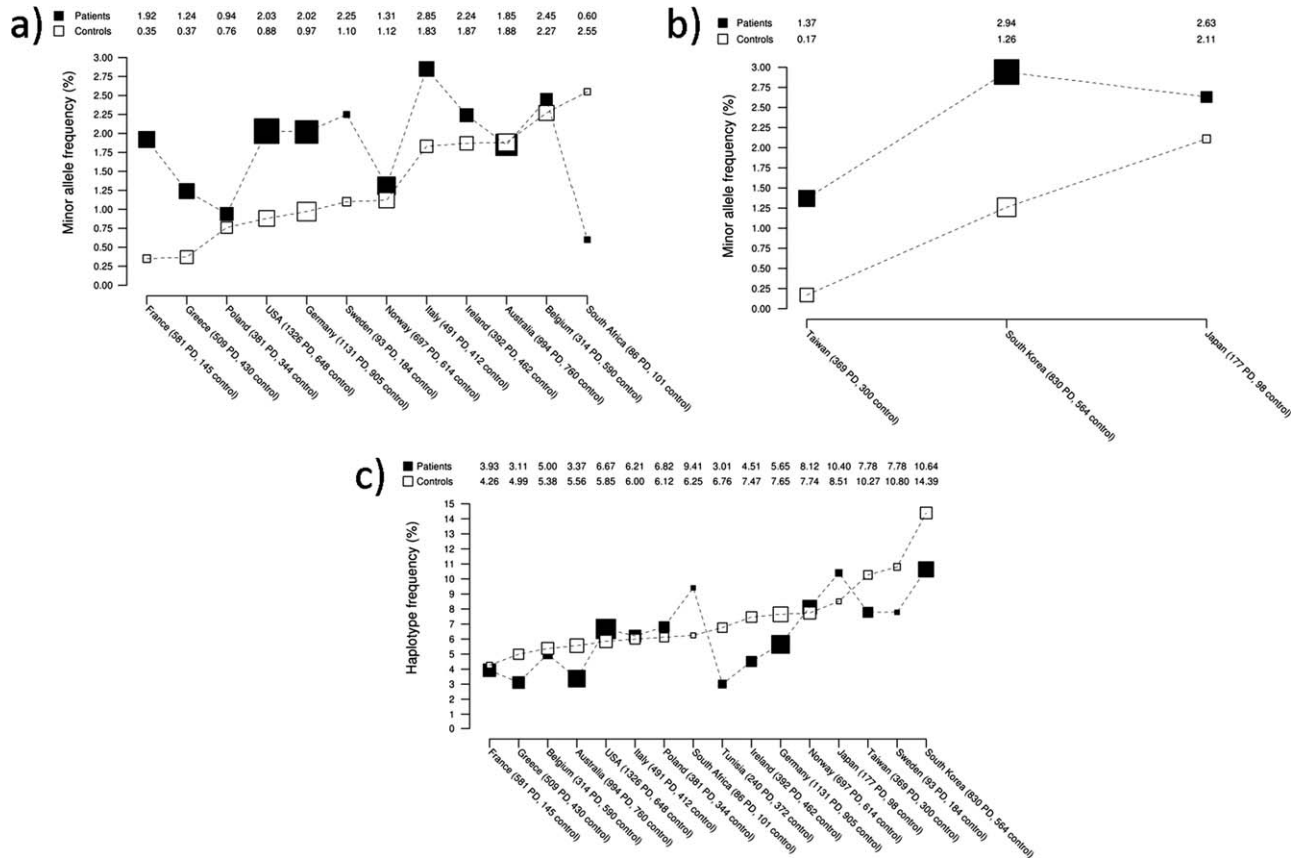


FIG. 1. Population-specific allele frequencies. **a:** Minor allele (C) frequency of p.M1646T is illustrated in patients with Parkinson’s disease (PD) and controls according to country. Larger boxes indicate larger sample sizes. Countries are ordered according to minor allele frequency (lowest to highest) in controls. Minor allele frequencies are connected by dashed lines within patients with PD and controls to enhance visual display. **b:** Minor allele (T) frequency of p.A419V is illustrated in patients with PD and controls according to country in the Asian series. Larger boxes indicate larger sample sizes. Countries are ordered according to minor allele frequency (lowest to highest) in controls. Minor allele frequencies are connected by dashed lines within patients with PD and controls to enhance visual display. **c:** Frequency of the protective p.N551K-R1398H-K1423K (G-A-A) haplotype is illustrated in patients with PD and controls according to country. Larger boxes indicate larger sample sizes. Countries are ordered according to haplotype frequency (lowest to highest) in controls. Haplotype frequencies are connected by dashed lines within patients with PD and controls to enhance visual display.

as a therapeutic target. As we have presented here, the newly identified, risk-modifying susceptibility variants p.A419V and p.M1646T and the p.N551K-R1398H-K1423K haplotype are apparent across a range of population-specific frequencies. Key next steps will involve determining the frequency of these variants in other populations and ethnicities as well as evaluating interactions with other PD susceptibility variants.

As further loci and functional variation influencing disease susceptibility are identified, it will be important to assess the combined effects and determine individual genetic risk scores based on informed genetic evaluations and population ethnicity. For example, to date, it appears that the genetic risk associated with the *MAPT* locus is not present in Asian populations; *LRRK2* harbors both Asian and Caucasian ethnic-specific risk factors, whereas the *LRRK2* protective haplotype and variants at *SNCA* appear to be relevant across a number of diverse populations.^{4,6,7} In addition, given the late-onset sporadic nature of PD, it will also be crucial to determine the joint effects of the

different genetic loci identified to influence PD risk. Another recent study by the GEO-PD Consortium evaluated the independent and joint effects of disease-associated genetic variation at the *SNCA* and *MAPT* loci in Caucasian populations.¹ The results of that study showed that individuals who harbored the risk allele at both genes had an increased risk of PD under an additive model, with no gene-gene interaction observed.

Identifying those individuals at risk of PD will require a paradigm shift in the diagnostic setting, combining clinical genetic testing and premotor symptom evaluation. Akin to the story of statins within the setting of cholesterol and vascular disease, intervention strategies for PD may need to be implemented well in advance of symptomatic presentation. Recent studies in Alzheimer’s disease have highlighted that the disease pathology may start anywhere up to 25 years before the manifestation of cognitive issues.⁸ Unfortunately, however, no effective biomarker for disease progression has been identified for PD to date, and

this makes the identification of early disease presentation or the effectiveness of intervention therapies difficult to interpret.

Genetic discrimination of patients not only will be crucial for preclinical diagnostics but also will play a critical role in the development of therapeutics and disease intervention strategies. The design of clinical drug trials has largely been based on the clinical manifestation of the motor symptoms and is characterized by the use of patients with PD who are in the advanced disease state. If the pathology associated with PD has initiated decades preceding the clinical manifestation of the movement disorder, then these patients may not represent the group most suited to drug intervention. A two-pronged approach of symptomatic relief and neuroprotective strategies may need to be implemented well in advance of the clinical presentation, and those compounds tested to date may have been administered too late in the disease course. In addition, we also may find that the genetic discrimination of patients also may identify those at highest risk of developing therapeutic-related complications, eg dyskinesia and impulse control disorders, looking to pharmacogenomics to pave the way in drug administration.

Furthermore, to date, clinical drug trials have not been fully informed; ie, they have not used genetically homogenous populations for specific targeted therapies. For example, it is likely that not every patient with PD will benefit from LRRK2 inhibition. As highlighted in our study, the protective p.N551K-R1398H-K1423K haplotype is present in some PD patients. If, as presumed, the toxic mechanism underlying LRRK2 disease is an increase in kinase activity, then it would support evidence that the protective haplotype lowers kinase activity.⁵ Under these circumstances, use of an LRRK2 inhibitor may be prove ineffectual and perhaps even damaging given recent insights from LRRK2 knockout model studies.^{9,10} Therefore, the design of LRRK2 inhibitor clinical trials should use the fundamental understanding we have of individual genomics and develop inclusion/exclusion criteria based on genetic understanding of disease risk. This scenario also holds true for the development of potential α -synuclein knockdown studies based on the toxic over-expression hypothesis.^{11–13} Indeed, combinatorial drug approaches that combine targeted therapies may present the most effective action.

The use of next-generation sequencing technologies has exploded over the last few years. In 2011, we witnessed the first PD gene identified using these methods.^{14,15} As the approaches of whole-exome and whole-genome sequencing become both more affordable and commercially available, many more individuals will present at the clinic with these data. This will produce an increase in the number of potential PD

genes nominated and a vast quantity of rare variants in both novel and known PD loci that will need to be interpreted. Large multi-ethnic studies like those performed by the GEO-PD Consortium on variants in LRRK2, SNCA, and MAPT will be required to fully understand the role of each of these genes in PD and the clinical impact each will have. ■

Acknowledgements: The present study and original funding for the GEO-PD Consortium was supported by grants from Michael J. Fox Foundation. Original funding for the GEO-PD was supported by a grant from The Michael J. Fox Foundation for Parkinson's Research Edmond J. Safra Global Genetics Consortia program. The Mayo Clinic is a Morris K. Udall Center of Excellence in PD Research (P50 NS072187). We acknowledge all of the patients and control participants who kindly donated DNA to make collaborative studies like these possible. For additional acknowledgements and a list of GEO-PD Consortia member sites, please see the Appendix online.

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