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Population-specific Frequencies for *LRRK2* Susceptibility Variants in the Genetic Epidemiology of Parkinson's Disease (GEO-PD) Consortium

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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 International Parkinson and 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

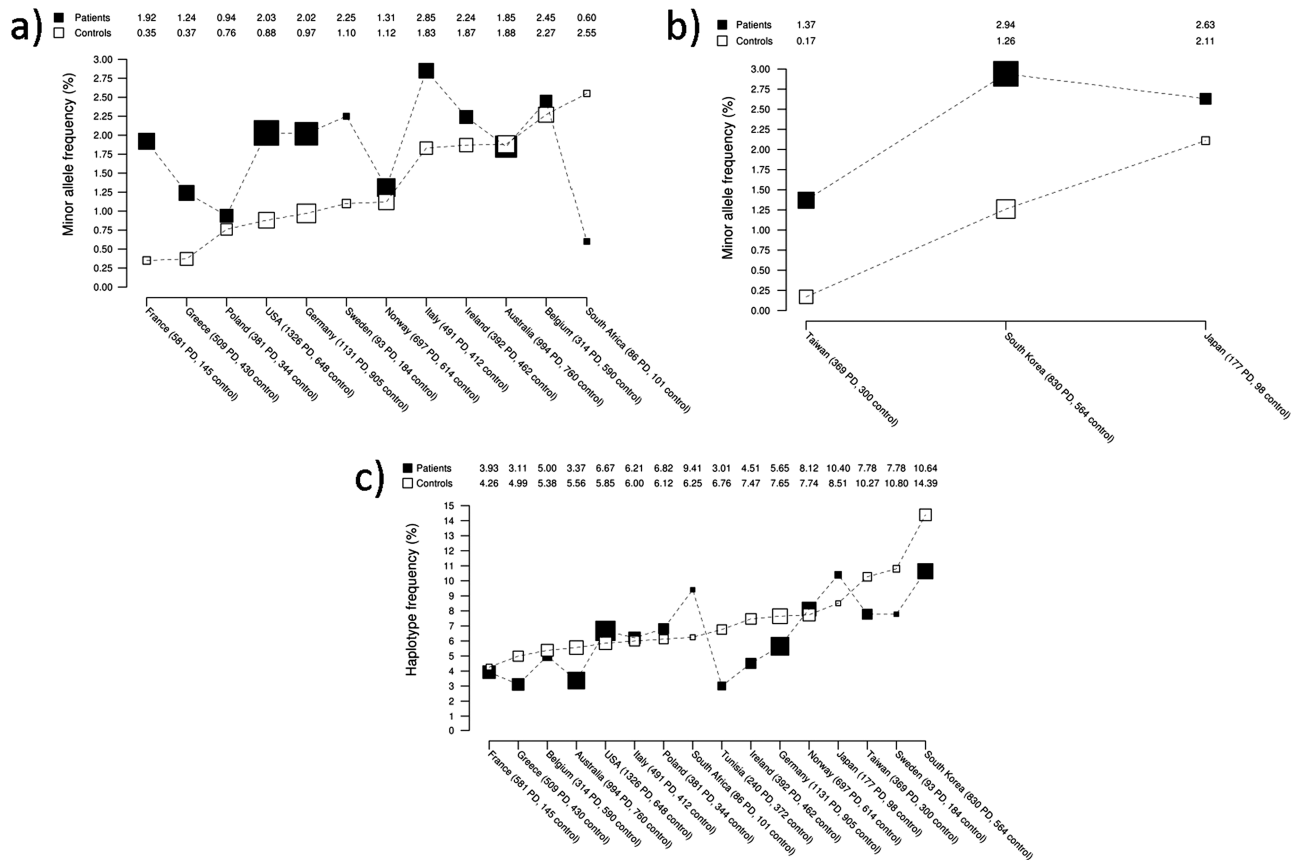


FIG. 1. Population-specific allele frequencies. **a:** Minor allele (C) frequency of p.M1646T is illustrated in patients with Parkinson’s disease (PD) and controls according to country. Larger boxes indicate larger sample sizes. Countries are ordered according to minor allele frequency (lowest to highest) 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.

(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 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.



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Usefulness of the Montreal Cognitive Assessment (MoCA) in Huntington's Disease

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ABSTRACT

Background: The Montreal Cognitive Assessment (MoCA) is a brief screening instrument for dementia that is sensitive to executive dysfunction. This study examined its usefulness for assessing cognitive performance in mild, moderate, and severe Huntington's disease (HD), compared with the use of the Mini-Mental State Examination (MMSE).

Methods: We compared MoCA and MMSE total scores and the number of correct answers in 5 cognitive-specific domains in 104 manifest HD patients and 100 matched controls.

Results: For the total HD sample, and for the moderate and severe patients, significant differences between both MoCA and MMSE total scores and almost all cognitive-specific domains emerged. Even mild HD subjects showed significant differences with regard to total score and several cognitive domains on both instruments.

Conclusions: We conclude that the MoCA, although not necessarily superior to the MMSE, is a useful instrument for assessing cognitive performance over a broad level of functioning in HD. © 2013 International Parkinson and Movement Disorder Society

Key Words: Huntington's disease, Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE), cognitive decline

Cognitive assessments are used clinically to diagnose and track individuals affected by disorders that impair cognition. However, comprehensive neuropsychological testing is unsuitable for most medical visits, when clinicians require rapid assessment of global cognitive functioning. Therefore, brief screening measures are useful tools to summarize information regarding the overall level of cognitive performance.

Although the Mini-Mental State Examination (MMSE) is the most frequently used brief cognitive instrument,^{1–3} the extent of its usefulness has been questioned with regard to milder forms of cognitive impairment^{1–3} and in dementing disorders characterized

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