Analysis of Genome-Wide Association Studies of Alzheimer Disease and of Parkinson Disease to Determine If These 2 Diseases Share a Common Genetic Risk

Valentina Moskvina, PhD; Denise Harold, PhD; GianCarlo Russo, PhD; Alexey Vedernikov, MSc; Manu Sharma, PhD; Mohamad Saad, Peter Holmans, PhD; Jose M. Bras, PhD; Francesco Bettella, PhD; Margaux F. Keller, BS; Nayia Nicolaou, MSc; Javier Simón-Sánchez, PhD; J. Raphael Gibbs, MS; Claudia Schulte, PhD; Alexandra Durr, MD, PhD; Rita Guerreiro, PhD; Dena Hernandez, MS; Alexis Brice, MD, PhD; Hreinn Stefánsson, PhD; Kari Majamaa, MD, PhD; Thomas Gasser, MD, PhD; Peter Heutink, PhD; Nick Wood, PhD, FRCP, FMedSci; Maria Martinez, PhD; Andrew B. Singleton, PhD; Michael A. Nalls, PhD; John Hardy, PhD; Michael J. Owen, PhD, FRCPsych, FMedSci; Michael C. O’Donovan, FRCPsych, PhD; Julie Williams, PhD; Huw R. Morris, PhD, FRCP; Nigel M. Williams, PhD; for the IPDGC and GERAD Investigators

**IMPORTANCE** Despite Alzheimer disease (AD) and Parkinson disease (PD) being clinically distinct entities, there is a possibility of a pathological overlap, with some genome-wide association (GWA) studies suggesting that the 2 diseases represent a biological continuum. The application of GWA studies to idiopathic forms of AD and PD have identified a number of loci that contain genetic variants that increase the risk of these disorders.

**OBJECTIVE** To assess the genetic overlap between PD and AD by testing for the presence of potentially pleiotropic loci in 2 recent GWA studies of PD and AD.

**DESIGN** Combined GWA analysis.

**SETTING** Data sets from the United Kingdom, Germany, France, and the United States.

**PARTICIPANTS** Thousands of patients with AD or PD and their controls.

**MAIN OUTCOMES AND MEASURES** Meta-analysis of GWA studies of AD and PD.

**METHODS** To identify evidence for potentially pleiotropic alleles that increased the risk for both PD and AD, we performed a combined PD-AD meta-analysis and compared the results with those obtained in the primary GWA studies. We also tested for a net effect of potentially polygenic alleles that were shared by both disorders by performing a polygenic score analysis. Finally, we also performed a gene-based association analysis that was aimed at detecting genes that harbor multiple disease-causing single-nucleotide polymorphisms, some of which confer a risk of PD and some a risk of AD.

**RESULTS** Detailed interrogation of the single-nucleotide polymorphism, polygenic, and gene-based analyses resulted in no significant evidence that supported the presence of loci that increase the risk of both PD and AD.

**CONCLUSIONS AND RELEVANCE** Our findings therefore imply that loci that increase the risk of both PD and AD are not widespread and that the pathological overlap could instead be “downstream” of the primary susceptibility genes that increase the risk of each disease.
Alzheimer disease (AD) and Parkinson disease (PD) are the 2 common age-related neurodegenerative diseases. Clinically, AD occurs in both familial and sporadic forms and is characterized by progressive impairment in memory, judgment, decision making, orientation to physical surroundings, and language. Pathologically, the hallmarks of AD involve neuronal loss, the deposition of extracellular plaques containing β-amyloid, and neurofibrillary tangles containing tau. Parkinson disease involves the deposition of α-synuclein in intracellular Lewy bodies in multiple brain regions and manifests as both a movement disorder and a distinct form of cognitive impairment, characterized by visuospatial impairment and fluctuations in mental state. Changes in α-synuclein production, autophagy, or abnormalities in mitochondrial and lysosomal functions have been shown to be pathologically important in some familial forms of PD. Although advancing age is a common risk factor for both AD and PD, studies that have investigated the extent to which these 2 diseases co-occur in families have produced varying results. Generally, these have reported either no increased risk of AD in the relatives of patients with PD or an increased risk of AD in younger patients with PD or those with cognitive impairment. However, it is possible that the misdiagnosis of dementia with Lewy bodies or PD dementia may have confounded some of the older studies that reported a clinical overlap between AD and PD. It remains unclear if there is familial clustering of the co-occurrence of these 2 diseases.

The identification of rare, highly penetrant mutations in genes causing familial PD and AD has had a considerable effect on our understanding of the pathogenesis of these complex and common disorders. The genes that cause familial AD have been related to the production of β-amyloid, whereas those identified in familial PD have implicated α-synuclein production and abnormalities of mitophagy in the disease process. We know from work on mendelian neurodegenerative disease genetics that single mutations can have pleiotropic effects. For example, the C9orf72 expansion can cause frontotemporal lobar degeneration or amyotrophic lateral sclerosis, but the basis for this phenotypic variation is unknown. More recently, our understanding of the idiopathic forms of AD and PD has been greatly enhanced by a number of large genome-wide association (GWA) studies. These GWA studies have replicated the already established association between sporadic AD and variants at the APOE locus on chromosome 19 and have identified several novel susceptibility loci that implicate endocytosis, innate immunity, and lipid processing as important pathogenetic mechanisms. In PD, as well as providing evidence that variants at the genes encoding α-synuclein (SNCA) and the microtubule-associated protein tau (MAPT) are also risk factors for the idiopathic form of the illness, these studies have collectively identified variants at 18 loci that significantly modify risk for PD.

Despite AD and PD being clinically distinct entities, there is pathological evidence of Lewy body deposition in AD (which is central to dementia with Lewy bodies) that has been reported to be more extensive in familial AD cases and in AD cases with a variant pathology. Similarly, an AD pathology has been reported in some PD cases, with there being a correlation between a cortical amyloid pathology, a neurofibrillary tangle pathology, and dementia in PD. Moreover, although a tau neuropathology is considered to be a hallmark feature of AD, it is intriguing that GWA studies of PD have identified strong evidence for an association at the area containing the MAPT gene, including studies looking at pathologically defined disease. Taken as a whole, these studies suggest the possibility of a pathological overlap between AD and PD, with some suggesting that the 2 diseases represent a biological continuum. As a result, it has been suggested that our understanding of any biological overlap could be greatly improved by the combined analysis of AD and PD genetic risk factors.

Although GWA studies offer a powerful approach for identifying loci that increase the risk of disease, the identification of loci that confer an increased genetic risk for apparently separate diseases can suggest an overlap in disease etiology and pathogenesis. In the present study, we have assessed the genetic overlap between PD and AD by testing for the presence of potentially pleiotropic loci in 2 recent GWA studies of AD and PD. Comparisons of pleiotropic loci with those that increase the risk of either PD or AD could potentially lead to a greater understanding of the biological pathways that are common to or distinctive of both disorders and could thus help us identify plausible pharmacological targets.

**Methods**

**AD GWA Study Data Set**

The GWA study of AD included 3177 AD cases and 7277 controls from the United Kingdom, the United States, and Germany that had been typed with the Illumina Chips 610K and 550K. The mean (SD) age of the individuals was 74.1 (8.8) years for AD cases and 54.5 (14.3) years for controls, and about 27% of the controls were elderly screened controls. Full details of the samples and analysis methods used are provided in the primary study. Imputation was performed on this data set using IMPUTE2 and the 1000 genomes (www.1000genomes.org/) Dec2010 reference panel (National Center for Biotechnology Information genome build 37.1). As recommended by Howie and colleagues, we used an imputation quality “INFO” score of 0.4 or higher as the quality-control filter, and this resulted in 7 401 079 markers remaining in our analysis. This imputed GWA study was then analyzed using logistic regression accounting for 7 covariates: chip, country of data collection, sex, age, and 3 principal components obtained with EIGENSTRAT software based on individual genotypes for the GERAD study participants. The genome-wide inflation factor (genomic control) for this study was λ = 1.09, while the genomic control λ1000 which is a recommended measure of genomic control for the analysis of large data sets, was λ = 1.02.

**PD GWA Study Data Set**

The GWA data on PD were obtained from the meta-analysis of 5 PD studies (2 from the United States [from the National Institute on Aging and from the database of Genotypes and Phenotypes], 1 from the United Kingdom, 1 from Germany, and 1 from France) that included 5333 cases and 12 298 controls.
A total of 5571 controls (434 from the German study and 5137 from the UK study) were also in the AD GWA study. Imputation was performed on this data set using identical methods and quality-control parameters as were applied to the AD data set. This resulted in a total of 781566 single-nucleotide polymorphisms (SNPs) remaining in our analysis and a genomic control $\lambda = 1.083$ ($\lambda_{1000} = 1.01$). The summary statistics for each marker in the PD data set were obtained using fixed-effects inverse-variance-weighted meta-analyses with METAL software (www.sph.umich.edu/csg/abecasis/metal/).

**Statistical Analysis**

In our study, all analyses were based on the summary statistics (allele frequencies, effect sizes, and corresponding standard deviations) available for 2 GWA studies, one of AD and the other of PD. We had available data for 7303091 SNPs that had passed the quality-control filter in both studies. We removed SNPs with large differences in minor allele frequencies between controls from the AD GWA study and controls from the PD GWA study by excluding imputed SNPs whose maximum ratio of allele frequencies for either allele ($\text{max(freq}(a)_{\text{AD}},\text{freq}(a)_{\text{PD}}))$, where $a$ is the allele and $i = 1,2$) was greater than 5. This procedure excluded 1503235 SNPs of which more than 95% had a minor allele frequency of less than 0.05, leaving a total of 779856 SNPs for further analyses.

**SNP-Based Analysis**

We performed a meta-analysis that combined the AD and PD GWA studies. However, because 5571 controls were used in both studies, we adjusted for the lack of independence by using inverse-variance meta-analysis, in which variance estimators accounted for the correlations of the overlapping controls. To avoid overcorrection, the test statistic for each SNP was corrected by the number of shared controls determined for each particular SNP. There was no overall inflation of the AD-PD meta-analysis statistics ($\lambda_{1000} = 1.00$).

**Polygenic Score Analysis**

The polygenic score analysis is designed to test whether the polygenes (ie, alleles of small effect that the GWA study is underpowered to detect) confer an aggregate risk and whether some number and the location of the chromosome were obtained from the dbSNP132 database, genome build 37.1.

To calculate gene-wide $P$ values, we first corrected all SNP $P$ values in the AD and PD imputed data sets for genomic control $\lambda$ and used the corrected $P$ values to generate gene-wide $P$ values. The LD correlation structure for each gene was derived from the data in the 1000 genomes Dec2010 reference panel because this was the reference panel used for imputation. Because the 1000 genomes data set contains only 283 European subjects, for the gene-based analysis, we used only SNPs with a minor allele frequency of 0.01. The GWA analysis was performed using approximation statistics adjusted for set-based analysis of genetic data on the summary $P$ values while controlling for LD and the different number of markers per gene. A total of 27174 and 28054 genes were analyzed in the AD and PD GWA studies, respectively, of which 27167 were common to both studies. Evidence in favor of pleiotropy was then assessed by testing whether the number of significant genes that overlapped between the 2 studies was greater than expected by chance using a $\chi^2$ test with 1 df for a $2 \times 2$ contingency table quantifying the numbers of significant vs not significant genes in AD vs PD studies, assuming that the genes were independent and the 2 studies were independent. Note that the gene-wide $P$ values were calculated for each study separately, and therefore the $\chi^2$ analysis is not adjusted for shared controls. This, as well as the nonindependence of genes due to LD, may cause an inflation of the significance of re-
sults when testing for gene overlap. Because the overlap was not significant (see the Results section), we did not run any further analyses to adjust for this inflation.

Results

First, we focused on the 29 regions already known to show a GWA with either AD9-13 or PD15,16,19 separately, and it was revealed that only 3 loci (rs356165, rs9897399, and rs6857) yielded genome-wide significant evidence for association in the combined AD-PD analysis ($P = 5.4 \times 10^{-18}, 8.3 \times 10^{-16},$ and $1.7 \times 10^{-11}$, respectively), although at a higher level than in the PD GWA study or the AD GWA study on their own, respectively. Moreover, although 2 of these SNPs (at the SNCA [rs356165] and MAPT locus [rs9897399]) were genome-wide significant loci in the primary PD GWA study ($P = 1.2 \times 10^{-28}$ and $8.3 \times 10^{-16}$, respectively), they failed to provide nominal evidence for association in the AD GWA study ($P = .38$ and $0.11$, respectively). Conversely, the high levels of association obtained for the SNP at the APOE locus (rs6857) in the AD GWA study ($P = 4.4 \times 10^{-99}$) was not replicated in the PD GWA study ($P = .154$).

We set out to identify pleiotropic alleles, which we define herein as an allele that significantly increases the risk of both PD and AD. We considered all SNPs that had already reached the threshold of genome-wide significance in either the primary AD or PD GWA study (n = 341), irrespective of the direction of effect in the other study. For these SNPs, we compared the $P$ values obtained in the PD-AD combined meta-analysis with the lowest $P$ values in either of the primary GWA studies. This revealed that, although 105 SNPs remained genome-wide significant loci in the combined PD-AD analysis, only 1 SNP (rs2732653) had a greater level of significance ($P = 3.5 \times 10^{-18}$) than in either of the primary GWA studies ($P = 5 \times 10^{-16}$ in the PD GWA study) (Figure). Table 1 gives details of the best AD-PD-associated SNPs per region, which were earlier reported as associated with AD or PD. Table 1 is split into 2 parts (the top part corresponds to AD, and the bottom part corresponds to PD) and presents the odds ratios and $P$ values in AD, PD, and AD-PD studies. To assess the significance of this observation, we randomly sampled 341 independent SNPs from the appropriate primary GWA study (ie, if an SNP was originally implicated in the AD GWA study, then the random SNPs were taken from the PD GWA study, and vice versa) and performed a meta-analysis (allowing for shared controls) with the 341 genome-wide significant SNPs. At each of the 10 000 simulations, we counted the number of SNPs that had meta-analysis $P$ values less than the original genome-wide significant $P$ values. This revealed that, on average, we should expect a mean (SD) of 30.5 (3.8) SNPs with smaller $P$ values in the combined PD-AD meta-analysis. Our observation of only 1 SNP with a smaller $P$ value in the combined PD-AD meta analysis is significantly less than expected by chance ($P = 7.5 \times 10^{-15}$) and was calculated by comparing the original number of SNPs (ie, 1) with a normally distributed random variable whose mean (SD) value obtained from the simulations was 30.5 (3.8). This indicates that there is no evidence that the SNPs reported to be genome-wide significant SNPs in either AD or PD show a significant overlap.

Our next approach was to evaluate whether a shared set of common variants has an important role to play in both PD...
Table I. Data on SNPs in Regions Known to Be Associated With Alzheimer Disease or Parkinson Disease Based on a Combined Genome-Wide Association Analysis

<table>
<thead>
<tr>
<th>Chr</th>
<th>SNPs, No.</th>
<th>Region</th>
<th>Meta-analysis of Parkinson Disease and Alzheimer Disease</th>
<th>Parkinson Disease</th>
<th>Alzheimer Disease</th>
<th>Candidate Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>SNP</td>
<td>Base Pairs</td>
<td>OR (SE)</td>
<td>P Value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>768</td>
<td>207 627 693-207 925 361</td>
<td>1-207819492</td>
<td>207 819 492</td>
<td>0.57</td>
<td>(0.11)</td>
</tr>
<tr>
<td>2</td>
<td>468</td>
<td>127 770 555-127 899 932</td>
<td>rs6733839</td>
<td>127 892 810</td>
<td>1.10</td>
<td>(0.02)</td>
</tr>
<tr>
<td>6</td>
<td>1214</td>
<td>47 310 009-47 679 836</td>
<td>rs9367271</td>
<td>47 327 031</td>
<td>1.10</td>
<td>(0.03)</td>
</tr>
<tr>
<td>7</td>
<td>169</td>
<td>143 068 887-143 143 397</td>
<td>rs7806047</td>
<td>143 106 884</td>
<td>0.88</td>
<td>(0.04)</td>
</tr>
<tr>
<td>8</td>
<td>194</td>
<td>27 434 831-27 504 956</td>
<td>rs1532277</td>
<td>27 466 181</td>
<td>0.94</td>
<td>(0.02)</td>
</tr>
<tr>
<td>11</td>
<td>830</td>
<td>59 820 327-60 129 305</td>
<td>rs7949816</td>
<td>60 045 900</td>
<td>0.92</td>
<td>(0.03)</td>
</tr>
<tr>
<td>11</td>
<td>858</td>
<td>85 615 264-85 904 657</td>
<td>1-85677094</td>
<td>85 677 094</td>
<td>1.21</td>
<td>(0.06)</td>
</tr>
<tr>
<td>19</td>
<td>280</td>
<td>1 010 022-1 093 668</td>
<td>rs56059558</td>
<td>1 032 228</td>
<td>0.86</td>
<td>(0.05)</td>
</tr>
<tr>
<td>19</td>
<td>2147</td>
<td>44 912 202-45 910 672</td>
<td>rs6857</td>
<td>45 392 254</td>
<td>1.29</td>
<td>(0.04)</td>
</tr>
<tr>
<td>15</td>
<td>152</td>
<td>51 701 749-51 714 806</td>
<td>rs200656</td>
<td>51 724 326</td>
<td>1.06</td>
<td>(0.03)</td>
</tr>
</tbody>
</table>

Abbreviations: Chr, chromosome; OR, odds ratio; SNP, single-nucleotide polymorphism.

and AD as a whole. To achieve this, we adopted the approach previously described by the International Schizophrenia Consortium and summarized the variation across all nominally (P ≤ .05) associated loci into quantitative polygenic scores. We initially limited our analysis to the 18 186 SNPs that, following LD pruning (assuming a uniform distribution of LD between PD and AD cohorts), were nominally associated with PD. We did not identify a significant inflation in the polygenic scores of the AD cases compared with controls (P = .243; Table 2). Both increasing and decreasing the strin-
Analysis of GWA Studies of AD and of PD

Table 2. Results of Polygenic Score Analysis of PD “Score” Alleles in the AD GWA Study

<table>
<thead>
<tr>
<th>$P_r$ Value</th>
<th>Discovery: Pruned PD Target: AD</th>
<th>Target $P$ Value</th>
<th>Target $R^2$</th>
<th>Discovery: Clumped PD Target: AD</th>
<th>Target $P$ Value</th>
<th>Target $R^2$</th>
<th>Discovery: Clumped AD Target: PD</th>
<th>Target $P$ Value</th>
<th>Target $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;.0001</td>
<td>.650</td>
<td>0.000047</td>
<td>.417</td>
<td>0.000152</td>
<td>.042</td>
<td>0.00044</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;.001</td>
<td>.499</td>
<td>0.000105</td>
<td>.925</td>
<td>2.0 × 10$^{-5}$</td>
<td>.187</td>
<td>0.00019</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;.01</td>
<td>.894</td>
<td>0.000004</td>
<td>.646</td>
<td>4.9 × 10$^{-5}$</td>
<td>.820</td>
<td>5.6 × 10$^{-6}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;.05</td>
<td>.243</td>
<td>0.000314</td>
<td>.476</td>
<td>0.00012</td>
<td>.931</td>
<td>8.0 × 10$^{-7}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;.10</td>
<td>.587</td>
<td>0.000068</td>
<td>.644</td>
<td>4.9 × 10$^{-5}$</td>
<td>.939</td>
<td>6.4 × 10$^{-7}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;.20</td>
<td>.663</td>
<td>0.000044</td>
<td>.861</td>
<td>7.0 × 10$^{-6}$</td>
<td>.809</td>
<td>6.5 × 10$^{-6}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;.30</td>
<td>.532</td>
<td>0.000090</td>
<td>.790</td>
<td>1.6 × 10$^{-3}$</td>
<td>.728</td>
<td>1.3 × 10$^{-3}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;.40</td>
<td>.244</td>
<td>0.000312</td>
<td>.973</td>
<td>2.7 × 10$^{-7}$</td>
<td>.764</td>
<td>9.7 × 10$^{-6}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;.50</td>
<td>.221</td>
<td>0.000345</td>
<td>.949</td>
<td>9.6 × 10$^{-7}$</td>
<td>.877</td>
<td>2.6 × 10$^{-6}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;.60</td>
<td>.237</td>
<td>0.000322</td>
<td>.926</td>
<td>2.0 × 10$^{-6}$</td>
<td>.904</td>
<td>1.6 × 10$^{-6}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;.70</td>
<td>.258</td>
<td>0.000294</td>
<td>.993</td>
<td>1.8 × 10$^{-8}$</td>
<td>.947</td>
<td>4.8 × 10$^{-7}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;.80</td>
<td>.314</td>
<td>0.000233</td>
<td>.988</td>
<td>5.4 × 10$^{-8}$</td>
<td>.930</td>
<td>8.4 × 10$^{-7}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;.90</td>
<td>.277</td>
<td>0.000272</td>
<td>.985</td>
<td>8.4 × 10$^{-8}$</td>
<td>.937</td>
<td>6.7 × 10$^{-7}$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; GWA, genome-wide association; PD, Parkinson disease.

*For the PD GWA study$^3$ and the AD GWA study$^5$, which were pruned or clumped by performing linkage disequilibrium, with $r^2 < 0.25$; $R^2$ is based on Nagelkerke’s pseudo-$R^2$ measure.

Discussion

In the present study, we have analyzed 2 large GWA studies for the presence of loci that confer an increased risk of both PD and AD. Because both primary GWA studies yielded significant evidence for a large number of susceptibility loci, we hypothesized that pleiotropic alleles that increased the risk of both PD and AD would yield a stronger association signal in a combined PD-AD meta-analysis compared with that obtained in the primary GWA studies. Our analysis of the combined PD and AD signals revealed no significant evidence for the presence of alleles that increase the risk of both diseases.

However, it is plausible that the risk of PD and AD could be influenced by large numbers of polygenic alleles, each with very small individual effects. In this case, although our analysis was probably underpowered to detect such variants, it is possible that their aggregate risk could be detected by the use of a polygenic approach. We therefore also analyzed the GWA data sets for a net effect of potentially polygenic alleles. While individual polygenic alleles may be weakly associated with disease, when they are combined, these same polygenic alleles can have a significant predictive ability, with subjects who have higher polygenic scores generally having a higher risk of some complex diseases.$^{33,36}$ We therefore hypothesized that when compared with unaffected controls, patients with AD should have a higher average polygenic score for PD risk alleles. Despite this, our analysis failed to identify any significant evidence to support a shared polygenic risk between PD and AD.

Finally, we also performed a gene-based association analysis, which, given the potential of allelic heterogeneity, was aimed at detecting genes that harbor multiple disease-causing SNPs, some of which confer the risk of PD and some
of which confer the risk of AD. This analysis also failed to identify evidence for a significant excess of genes that confer the risk of both PD and AD.

Our findings therefore imply that loci that increase the risk of both PD and AD are not widespread and that the pathological overlap could instead be “downstream” of the primary susceptibility genes that increase the risk of each disease. Moreover, because the vast majority of the cases included in these GWA studies are clinically, rather than pathologically, diagnosed, our results suggest that clinically diagnosed cases of AD are unlikely to be inadvertently contaminated with substantial numbers of cases of pathological PD dementia, and vice versa. Nevertheless, the conclusion that AD and PD do not genetically overlap may be premature. It is possible that the power of our analyses may have been impaired by the exclusion of dementia with Lewy bodies, the phenotype that shares with both AD and PD certain pathological and clinical symptoms, from both primary GWA analyses. Alternatively, our study was limited to the analysis of alleles represented directly or indirectly by SNPs on the arrays. It is therefore possible that the future application of more refined analyses to larger AD and PD studies, which also better capture data from rare alleles, could identify genetic variants that confer an increased risk of both PD and AD.

ARTICLE INFORMATION

Accepted for Publication: February 20, 2013.
Published Online: August 5, 2013.

Author Affiliations: Medical Research Council Centre for Neuropsychiatric Genetics and Genomic Epidemiology of Psychological Medicine and Clinical Neurosciences, Cardiff University School of Medicine, Wales (Moskvina, Harold, Russo, Vedernikov, Holmans, Owen, O’Donovan, J. Williams, Morris, N.M. Williams); Department for Neurodegenerative Diseases, Herie Institute for Clinical Brain Research, and Institute for Clinical Epidemiology and Applied Biometry, University of Tübingen, Germany (Sharma, Schulte; Gasser); Institut National de la Sante et de la Recherche Médicale, UMR 1043, Centre for Physiopathologie de Toulouse-Purpan, Toulouse, France (Saad, Durr, Martinez); Paul Sabatier University, Toulouse, France (Saad, Martinez); Department of Molecular Neuroscience, Institute of Neurology, University College London, England (Bras, Gibbs, Guerreiro, Hernandez, Wood, Hardy); deCODE Genetics, Scientific Services, Reykjavík (Iceland (Bettella, Stefánsson)); Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland (Keller, Gibbs, Hernandez, Singleton, Nalls); Department of Clinical Genetics, Section of Medical Genomics, VU University Medical Center, Amsterdam, the Netherlands (Nicolaou, Simón-Sánchez, Heutink); German Center for Neurodegenerative Diseases, Tübingen, Germany (Schulte, Gasser); Université Pierre et Marie Curie-Paris, Centre de Recherche de l’Institut du Cerveau et de la Moelle Épinière, UMR 5975, Paris, France (Durr, Brice); Assistance Publique Hôpitaux de Paris, Hôpital de la Salpêtrière, Département de Génétique, France (Durr, Brice); Institut National de la Sante et de la Recherche Médicale, Paris, France (Brice); Centre National de la Recherche Scientifique, UMR 7225, Paris, France (Brice); Department of Neurology, Institute of Clinical Medicine, University of Oulu, Finland (Majamaa); University College London Genetics Institute, London, England (Wood).


Conflict of Interest Disclosures: None reported.

Funding/Support: This work was supported by Parkinson’s United Kingdom (formerly The PD society; reference KO906: grants 8047 and J-0804) and the Medical Research Council (grant G0700943). In addition, part of the study was undertaken at University College Hospital/University College London (UCL) using funding from the Department of Health National Institute for Health Research Biomedical Research Centre. The German work was also supported by the German Genome Network (plus grant OIGSO8134 from the German Ministry for Education and Research). This work was also supported in part by the Intramural Research Program of the National Institute on Aging, National Institutes of Health, Department of Health and Human Services (projects Z01 AG009549-06 and Z01 AG009950-10). The French GWA scan work was supported by the French National Agency of Research (www-agence-nationale-recherche.fr; grant ANR-08-MNP-012) and by the National Research Funding Agency (grant ANR-08-NEUR-004-01) in the ERA-NET NEURON framework (www.neuron-eranet.eu).

Group Information for IPDGC Investigators: The investigator were Allissa Dillman, Dena G. Hernandez, Janet Brooks, Sean Chong, Mark R. Cookson, J. Raphael Gibbs, Matthew Moore, Margaux F. Keller, Michael A. Nalls, Andrew B. Singleton, Bryan J. Traynor, and Sampath Arepalli, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; Gavin Charlesworth and Vincent Plagnol, UCL Genetics Institute, London, England; Mina Ryten, Danial Trabzuni, Rita Guerreiro, Dena G. Hernandez, Jose M. Bras, J. Raphael Gibbs, and John Hardy, Department of Molecular Neuroscience and Reta Lila Weston Laboratories, Institute of Neurology, UCL, London, England; Claudia Schulte, Daniela Berg, Kathrin Brockmann, Thomas Gasser, Heiko Huber, and Manu Sharma, Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, and German Center for Neurodegenerative Diseases, Tübingen, Germany; Una-Marie Sheerin and Kailash Bhatia, UCL Institute of Neurology, London, England, Maria Martinez and Mohamad Saad, INSERM U563, Centre de Physiopathologie de Toulouse-Purpan, and Paul Sabatier University, Toulouse, France; Javier Simón-Sánchez, Zoltan Bochdanovits, Peter Heutink, and Patrizia Rizzu, Department of Clinical Genetics, Section of Medical Genomics, VU University Medical Centre, Amsterdam, the Netherlands; Suzanne Lesage, Marie Vidalhiet, Alexis Brice, and Jen-Christophe Corvol, INSERM, UMR 5975 (formerly UMR 5679), and Université Pierre et Marie Curie, Paris, France; Roger Barker, Department of Neurology, Addenbrooke’s Hospital, University of Cambridge, England; Sarah E. Hunt, Emma Gray, Sarah Edkins, Avazeh Tashakori-Ghanbaria, Jeffrey Barret, Panagiotis Deloukasim, and Simon Potter, Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, England; Yoav Ben-Shlomo, Department of Social Medicine, Bristol University, England; Karin D. van Dijk and Henk W. Berendse, Department of Neurology and Alzheimer Center, VU University Medical Center, Amsterdam, the Netherlands; Daan Velseboer and Rob M. A. de Bie, Department of Neurology, Academic Medical Center, University of Amsterdam, the Netherlands; Alessandro Biffi, Center for Human Genetic Research and Department of Neurology, Massachusetts General Hospital, Boston, and Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts; Bas Bloem, Bart van de Warrenburg, and Bart Post, Department of Neurology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands; Otfrid Riess and Michael Bonin, Department of Medical Genetics, Institute of Human Genetics, University of Tübingen, Germany; David J. Burn, Newcastle University Clinical Ageing Research Unit, Campus for Ageing and Vitality.
and Joanne Knight Alzheimer’s Research Initiative of the Washington University Alzheimer’s Disease Research Centre, the University College Hospital/UCL Biomedical Centre, Lundbeck SA, the German Federal Ministry of Education and Research (Kompetenzzentren Demenzen [grant 01GI0420]), Bundesministerium für Bildung und Forschung, and Competence Network Dementia Förderkennzeichen [grants 01GI0102 and 01GI0711]), and we thank the Eli Lilly company for their financial support (to Dr Williams). We also thank the Hersenstichting Nederland (www.hersenstichting.nl), the Neuroscience Campus Amsterdam, and the section of medical genomics, the Prinses Beatrix Fonds (https://prinsesbeatrixfonds.nl), for sponsoring this work.

REFERENCES