Imputation of sequence variants for identification of genetic risks for Parkinson’s disease: a meta-analysis of genome-wide association studies

International Parkinson Disease Genomics Consortium

Summary

**Background** Genome-wide association studies (GWAS) for Parkinson’s disease have linked two loci (MAPT and SNCA) to risk of Parkinson’s disease. We aimed to identify novel risk loci for Parkinson’s disease.

**Methods** We did a meta-analysis of datasets from five Parkinson’s disease GWAS from the USA and Europe to identify loci associated with Parkinson’s disease (discovery phase). We then did replication analyses of significantly associated loci in an independent sample series. Estimates of population-attributable risk were calculated from estimates from the discovery and replication phases combined, and risk-profile estimates for loci identified in the discovery phase were calculated.

**Findings** The discovery phase consisted of 5333 case and 12019 control samples, with genotyped and imputed data at 7689524 SNPs. The replication phase consisted of 7053 case and 9007 control samples. We identified 11 loci that surpassed the threshold for genome-wide significance (p<5×10⁻⁸). Six were previously identified loci (MAPT, SNCA, HLA-DRB5, BST1, GAK and LRRK2) and five were newly identified loci (ACMSD, STK39, MCCC1/LAMP3, SYT11, and CCDC62/HIP1R). The combined population-attributable risk was 60·3% (95% CI 43·7–69·3). In the risk-profile analysis, the odds ratio in the highest quintile of disease risk was 2·51 (95% CI 2·23–2·83) compared with 1·00 in the lowest quintile of disease risk.

**Interpretation** These data provide an insight into the genetics of Parkinson’s disease and the molecular cause of the disease and could provide future targets for therapies.

**Funding** Wellcome Trust, National Institute on Aging, and US Department of Defense.

Introduction

Parkinson’s disease was long thought to be a non-genetic disease. Recent advances in genotyping have enabled large-scale assessment of genetic risk factors associated with Parkinson’s disease. MAPT and SNCA have consistently shown associations in genome-wide association studies (GWAS). BST1, LRRK2, GAK, and HLA-DRB5 have been implicated in some studies but these associations have not been definitively confirmed.

Although an exciting next step in the genetic study of human disease will be the use of exome or genome sequencing in adequately powered large-scale population-based studies, this method is cost prohibitive at present. A compromise between array-based and sequence-based methods is the use of freely available sequence-based resources from the 1000 Genomes Project, which allows imputation of a large number of variants into existing genotyping studies.

We did a meta-analysis of Parkinson’s disease GWAS to investigate the associations of previously identified loci and identify novel risk loci for Parkinson’s disease.

Methods

**Study design** Investigators representing four published GWAS formed a consortium with the predetermined goal to discover new loci associated with Parkinson’s disease by a prospective meta-analysis of imputed sequence variants (discovery stage). We identified one additional dataset from the database of genotypes and phenotypes. A secondary requirement for inclusion of a dataset in this study was the ability to use custom-built ImmunoChip arrays to do replication analyses in independent sample series (replication stage). The five included datasets were from the USA National Institute on Aging, UK, Germany, France, and the USA database of genotypes and phenotypes.

We aimed to assess the biological consequences of risk variants identified in our study by examining the association between these alleles and both gene expression and DNA methylation. Our primary interest in these single nucleotide polymorphism (SNP)-based analyses was to investigate every locus associated with Parkinson’s disease and to test whether the disease-related SNPs were associated with DNA methylation or gene expression levels. Further, we wanted to test whether the most strongly disease-associated SNPs were also the most strongly associated quantitative trait locus SNPs.

**Data imputation and statistical analysis** After individual sample collection and study-specific quality control (webappendix pp 1–7), we used a Markov
**Dataset characteristics**

<table>
<thead>
<tr>
<th>Cases</th>
<th>Controls</th>
<th>Genome-wide association study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>Women (%)</td>
<td>Mean age at onset (years [SD])</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>USA–NIA</td>
<td>971</td>
<td>40.5%</td>
</tr>
<tr>
<td>UK</td>
<td>1205</td>
<td>43.3%</td>
</tr>
<tr>
<td>Germany</td>
<td>742</td>
<td>39.8%</td>
</tr>
<tr>
<td>France</td>
<td>1039</td>
<td>41.2%</td>
</tr>
<tr>
<td>USA–dbGAP</td>
<td>876</td>
<td>40.4%</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>523</td>
<td>-</td>
</tr>
</tbody>
</table>

NI = National Institute on Aging. NA = not available. dbGAP = database of genotypes and phenotypes. * Adjusted for component vectors 1 and 2 from multidimensional scaling analyses of the study population.
†Passed quality control in at least two of the included datasets. ‡Summary statistics scaled by study-specific genomic inflation factor estimates before meta-analysis.

We did genome-wide dataset analyses at every site with MACH2DAT. We used non-integer allele numbers as a primary predictor of Parkinson’s disease in logistic regression models to account for imputation uncertainty. Webappendix pp 1–7 shows specific details of analyses of the datasets. Summary statistics from genome-wide association analyses of every dataset were included in the meta-analyses. For every dataset, we used basic covariates of component vectors 1 and 2 from either principal components or multidimensional scaling analyses of the case-control cohorts to identify random genomic differences between genotyped data from cases and controls in the discovery phase, which were used to adjust statistical models for covariates accounting for possible population substructure. This adjustment was not done in analyses of the UK dataset in the discovery phase of analyses.

For the replication step, we included the SNPs that passed genome-wide significance (fixed effects p<1×10^-5) and quality control on a custom ImmunoChip array (Illumina, San Diego, CA, USA) in collaboration with the Sanger Institute (Hinxton, UK). Additionally, we analysed two GWAS (from the Netherlands and Iceland) after the meta-analysis and included these in the replication stage by the same imputation procedure. These data were provided by consortium members who provided the GWAS data after the initial discovery phase. We included a quality control step in the replication analyses that removed SNPs with inconsistent results across the datasets (I²>75%). Webappendix pp 4–8 shows detailed descriptions of the replication analyses that were done in the five ImmunoChip replication cohorts (USA, UK, Netherlands, Germany, and France) and two in-silico GWAS datasets (Iceland and Netherlands).

We did fixed-effects inverse variance-weighted meta-analyses with meta-analysis helper (METAL), with the standard errors of the β coefficients scaled by the square root of study-specific genomic inflation factor estimates before combining the summary statistics across datasets. We calculated genomic control for both individual datasets and the entire meta-analysis for quality control. Genomic control is often estimated as the deviance of the median test statistic distribution from the expected null; genomic inflation factors less than 1.05 are the general standard in GWAS. We used fixed-effects meta-analyses as the primary method of discovery and R (version 2.11) to do a secondary random-effects meta-analysis for every SNP. This second analysis is useful to estimate the possible effect of study heterogeneity on results and to qualitatively infer the effect of study heterogeneity on replication success and generalisability for similar sample series. We calculated χ² tests for heterogeneity (Cochran’s Q) with METAL and we generated I² estimates with R. Meta-analyses and estimates of study heterogeneity were re-run with PLINK as a quality control measure.

We calculated risk-profile estimates on the basis of cumulative load of risk alleles for loci identified in the discovery phase, weighted by the discovery phase effect estimates (log_{ODD_discovery}). This profile model was applied to the ImmunoChip genotyped replication cohorts, and the effects were combined across cohorts by inverse variance weighting.

Population-attributable risk was estimated for the specific genetic contribution to disease of the risk loci.
Joint estimates were also used because of their slight overestimation of effect sizes in the discovery GWAS wherein natural genetic variation contributes to a form of ascertainment bias that often occurs in two-stage effects p values less than 1×10⁻⁵ the SNPs with the smallest p values per fixed-methylation site or transcript. All SNPs within 1 mb from any typed polymorphism and any assayed DNA samples of every brain. We tested the association between frozen tissue from both frontal cortex and cerebellum methylation and transcript expression were assessed in up to 350 people who had donated brain tissue and were neurologically healthy at the time of death. DNA in the UK cohort was not included because p values were not less than 0·1 in any other cohort and I² was greater than 75%. For simplicity, we have focussed only on the most significant SNP per locus that met these criteria, and its nearest gene or genes. However, we do recognise that the most proximal gene is not necessarily the gene functionally affected by risk alleles and that GWAS identify loci rather than specific genes. We confirmed the Parkinson's disease associations at the SNCA and MAPT loci and at BST1, LRRK2, GAK, and HLA-DRB5 (table 2). Additionally, we detected evidence of associations at five new loci (the closest gene to the top SNP at every loci is ACMSD, STK39, MCCC1/LAMP3, SYT11, and CCDC62/HIP1R). However, two of these loci (ACMSD and CCDC62/HIP1R) showed moderate evidence of heterogeneity across populations. We confirmed the Parkinson’s disease risk factor gene GBA and its pseudogene, in a region of the genome with low recombination. To test whether this proximity might contribute to the possible co-segregation of risk alleles at the SYT11 locus and GBA risk mutations we analysed data from a subset of patients with Parkinson’s disease.

Figure 1: Manhattan plot of Parkinson’s disease associations for all SNPs in the discovery phase
p values from fixed-effects meta-analysis for 7689524 SNPs successfully imputed or genotyped in at least two individual datasets. Genomic inflation factor=1·035. Red points=SNPs with p<5×10⁻⁸. Orange points=SNPs with p values ranging from less than 1×10⁻⁵ to 5×10⁻⁸. Regions containing red points were followed up in replication analyses. SNP=single nucleotide polymorphism.

Identified. In broad terms, it estimates the decrease in cases of a particular disease within a population that would occur if the risk factor were removed from that population. Effect sizes and minor allele frequencies were calculated from joint estimates from the discovery and replication phases combined, to lessen the overestimation caused by the so-called winner’s curse—a form of ascertainment bias that often occurs in two-stage GWAS wherein natural genetic variation contributes to a slight overestimation of effect sizes in the discovery phase. Joint estimates were also used because of their large sample size, which should generate more accurate effect estimates.

DNA methylation values at sites close to the risk variants and the expression of genes within the risk loci were treated as quantitative traits, and we assessed whether the alleles of SNPs across the risk loci were associated with either, denoting a quantitative trait locus. We provided more detail about the methods used to map quantitative trait loci. Brieﬂy, we used dense genotype data generated in up to 350 people who had donated brain tissue and were neurologically healthy at the time of death. DNA methylation and transcript expression were assessed in frozen tissue from both frontal cortex and cerebellum samples of every brain. We tested the association between any typed polymorphism and any assayed DNA methylation site or transcript. All SNPs within 1 mb from the SNPs with the smallest p values per locus with fixed-effects p values less than 1x10⁻⁵ were investigated as candidate loci that affect the expression and methylation values of proximal mRNA transcript probes and CpG methylation sites. With the minor allele as a reference for directionality, we used linear models to quantify the relation between quantitative trait loci and risk effect for all the loci that contained significant quantitative trait locus associations. We used linkage-adjusted Bonferroni correction for significance (webappendix pp 11–13).

Role of the funding source
The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All members of the writing group had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
The discovery phase included 5333 case and 12 019 control samples, with genotyped and imputed data at 7689524 SNPs (table 1; figure 1). 7053 case and 9007 control samples were included in analyses in the replication stage. Results of tests across the software packages METAL, R, and PLINK differed only slightly (data not shown).

We identified 11 loci that surpassed the threshold for genome-wide significance (p<5x10⁻⁸; table 2). One locus on chromosome 17 from 18601523 to 18602998 bp that contained six SNPs associated with Parkinson’s disease in the UK cohort was not included because p values were not less than 0·1 in any other cohort and I² was greater than 75%. For simplicity, we have focussed only on the most significant SNP per locus that met these criteria, and its nearest gene or genes. However, we do recognise that the most proximal gene is not necessarily the gene functionally affected by risk alleles and that GWAS identify loci rather than specific genes. We provided more detailed results for every region.

We confirmed the Parkinson’s disease associations at the SNCA and MAPT loci and at BST1, LRRK2, GAK, and HLA-DRB5 (table 2). Additionally, we detected evidence of associations at five new loci (the closest gene to the top SNP at every loci is ACMSD, STK39, MCCC1/LAMP3, SYT11, and CCDC62/HIP1R). However, two of these loci (ACMSD and CCDC62/HIP1R) showed moderate evidence of heterogeneity across populations. We provided further details about the replication phase of analysis. All five novel loci passed a Bonferroni threshold of p<0·0045 (correcting for the 11 SNPs tested in the replication phase) for association in the replication phase.

The SNP at the SYT11 locus is about 650 kb from the known Parkinson’s disease risk factor gene GBA and its pseudogene, in a region of the genome with low recombination. To test whether this proximity might contribute to the possible co-segregation of risk alleles at the SYT11 locus and GBA risk mutations we analysed data from a subset of patients with Parkinson’s disease.
who were included in the discovery phase analysis and who were from the USA, France, and Germany, in whom carriers of the GBA mutation have been identified. The results of this analysis suggested that the signal at the MAPT locus was 60.3% (95% CI 43.7–69.3). For risk estimates. The combined estimate across all studies was 2.5 times higher in the highest dose quintile of disease risk than in the lowest dose quintile of disease risk (table 3). The c index from receiver operator curves in the pooled cohorts was 0.63.

We identified quantitative trait associations at 18,969 SNPs spread across five of the identified Parkinson’s disease risk loci (summarised in figure 2, with complete results available from the authors upon request). The MAPT locus had many such associations, with 95.9% of all associations detected across all tissues (webappendix pp 32–33). Table 2 shows the combined population-attributable risk estimates. The combined estimate across all 11 identified loci was 60.3% (95% CI 43.7–69.3). For the MAPT and SNCA loci alone it was 25.6% (18.7–28.9), which was higher than the previous estimate of about 20%. The additional loci identified in this study (ACMSD, STK39, MCCC1/LAMP3, and CCDC62/HIP1R) had a combined estimate of 46.7% (30.7–56.8).

The odds ratio was 2.5 times higher in the highest quintile of disease risk than in the lowest quintile of disease risk (table 3). The c index from receiver operator curves in the pooled cohorts was 0.63.

**Table 2: Summary of significant loci**

<table>
<thead>
<tr>
<th>Candidate gene</th>
<th>Discovery phase</th>
<th>Replication phase</th>
<th>Combined PAR estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p value</td>
<td>AUC</td>
<td>Risk quintile OR (95% CI)</td>
</tr>
<tr>
<td>Chr 10:15405678</td>
<td>1.00</td>
<td>0.584</td>
<td>1.49 (1.25–1.78)</td>
</tr>
<tr>
<td>Chr 11:20838205</td>
<td>1.00</td>
<td>0.631</td>
<td>1.63 (1.27–2.08)</td>
</tr>
<tr>
<td>Chr 14:191944</td>
<td>1.00</td>
<td>0.706</td>
<td>1.16 (0.86–1.57)</td>
</tr>
<tr>
<td>Chr 18:2941668</td>
<td>1.00</td>
<td>0.631</td>
<td>1.21 (0.74–2.00)</td>
</tr>
</tbody>
</table>

Combined analyses showed low heterogeneity of effect (Cochran’s Q p=0.04). AUC=area under curve, indicated by the c index from receiver operator curves. OR=odds ratio. PAR=population-attributable risk. c index=p index of heterogeneity. p value=heterogeneity p value.

Table 3: Summary of risk-profile analyses

<table>
<thead>
<tr>
<th>p value</th>
<th>AUC</th>
<th>Risk quintile OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>&lt;2×10⁻⁶</td>
<td>0.584</td>
</tr>
<tr>
<td>UK</td>
<td>&lt;2×10⁻⁶</td>
<td>0.631</td>
</tr>
<tr>
<td>Germany</td>
<td>1.44×10⁻⁶</td>
<td>0.69</td>
</tr>
<tr>
<td>France</td>
<td>6.15×10⁻⁷</td>
<td>0.644</td>
</tr>
<tr>
<td>Netherlands</td>
<td>8.34×10⁻⁷</td>
<td>0.576</td>
</tr>
<tr>
<td>Combined</td>
<td>&lt;2×10⁻⁶</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Cases (%) | 886 (39.00%) | 1069 (47.13%) | 1185 (52.16%) | 1268 (55.93%) | 1394 (61.17%) |

Combined analyses showed low heterogeneity of effect (Cochran’s Q p=0.04). AUC=area under curve, indicated by the c index from receiver operator curves. OR=odds ratio.
alleles associated with increased risk and with decreased methylation (cerebellum \( r^2 = 0.9268, \ p < 2 \times 10^{-14} \); frontal cortex \( r^2 = 0.4667, \ p = 3.68 \times 10^{-9} \)). The MAPT locus showed associations for multiple probes within MAPT and probes within proximal genes, including ARL17A and PLEKH1. Methylation quantitative trait loci in the MAPT region included probes within KIAA1267, LRRC37A, and NSF.

Two SNPs in the ACMSD locus showed substantial associations, with expression levels in cerebellar tissues denoted by a proximal expression probe against the transcript MCM6, whose transcription start site is more than 750 kb from either associated SNP; the minor alleles at this pair of SNPs are associated with increased risk of Parkinson’s disease and decreased gene expression. In samples from the frontal cortex, DNA methylation values at one Cpg site within FGFR1 were associated with 27 proximal SNPs in the GAK region (>20 kb from the nearest SNP associated with Parkinson’s disease), and all effect estimates suggested risk of Parkinson’s disease and increased methylation (\( r^2 = 0.9897, \ p = 2 \times 10^{-16} \)).

The HLA-DRB5 region contained 729 significant quantitative trait loci associations in the frontal and cerebellar tissue samples. For HLA-DRB5, we recorded an overall result similar to that identified at MAPT, with minor alleles associated with risk effects and with decreased DNA methylation (cerebellum \( r^2 = 0.4037, \ p = 9.67 \times 10^{-5} \); frontal cortex \( r^2 = 0.4977, \ p = 2 \times 10^{-16} \)).

In addition to probes within HLA-DRB5, methylation quantitative trait locus associations were detected within probes tagging CpG sites in BTN1L2, HLA-DQB2, and SLCA44A1. One CpG probe in the cerebellum samples was associated with 18 SNPs in the CCDC62/HIP1R region. We noted a relation between risk alleles and DNA methylation at a CpG site within GPR109B, for which increased risk estimates were closely associated with more negative methylation effects (cerebellum \( r^2 = 0.9777, \ p = 2 \times 10^{-16} \)).

Both the LRRK2 and SNCA genes play a part in Parkinson’s disease; thus, we examined these loci further for potential quantitative trait loci. Detection of LRRK2 with the array-based method showed expression that was too low to do an accurate analysis. However, we identified quantitative trait loci at the SNCA locus, where risk alleles were associated with increased SNCA expression. Although evidence suggests a link between SNCA expression and disease risk, the level of significance for this locus was not significant (\( p = 1 \times 10^{-4} \)) with the threshold for significance that we set (\( p = 3.55 \times 10^{-5} \)).

Discussion

SNCA, MAPT, and HLA-DRB5 have been confirmed as risk loci for Parkinson’s disease by previous GWAS and by our meta-analysis. We have also shown that, although previous GWAS were individually underpowered to prove the associations between the BST1, LRRK2, and GAK loci and Parkinson’s disease, our meta-analysis and replication analysis identified an association at these loci (panel). 1,3,5,6,9

GWAS investigate loci that often contain several genes and we should be mindful not to ascribe disease risk to any one gene within this locus in the absence of further biological evidence. However, the novel loci detected include biologically plausible candidate for Parkinson’s
disease risk. **ACMSD** is associated with picolinic and quinolinic acid homoeostasis and is a possible therapeutic target for several disorders that affect the CNS.24 The locus identified near **STK39** has been associated with autism, hypertension, and inflammatory status,25–27 although there have been no reports of this locus contributing to neurodegenerative phenotypes. The **LAMP3** locus might partly cause modulation of neuronal and neurosecretory function in PC12 cell lines.28 **HLA-DRB5** is associated with multiple sclerosis, immunocompetence, and histocompatibility.29–31 The association with Parkinson’s disease at **HLA-DRB5** supports the theory that inflammatory factors are associated with the pathogenesis of Parkinson’s disease.32 The protein product of **HIP1R** is associated with multiple sclerosis, immunocompetence, and histocompatibility.29–31 The association detected at the **SYT11** locus might partly cause modulation of neuronal inflammation.32 The association between genetic variability at the **LRRK2** locus and Parkinson’s disease is mechanistically interesting because data suggest that this association is a result of variability outside the common G2019S mutation, which raises the possibility that splicing or expression of wild-type **LRRK2** might be pathologically important. If this suggestion is correct, the role of **LRRK2** in Parkinson’s disease might relate to an exaggeration of its normal function rather than some gain of abnormal function.

Understanding of the pathobiologically relevant effect of the identified risk variants in Parkinson’s disease is challenging. However, we associated changes in expression and DNA methylation with risk alleles at five of the identified loci. This work has many caveats, not least of which is that it is associative and does not imply causality. However, these data do serve as a launching point for further investigation into the biological basis of Parkinson’s disease.

The absence of predictive capacity in the risk-profile estimates suggests that common genetic variability at these loci, the small risk estimates per locus in this meta-analysis (and GWAS-based studies in general), and the inability to include putative functional variants per locus, do not allow clinically relevant predictive power to be quantified. Additionally, no environmental factors were included in risk profiling or population-attributable risk estimates, which might have led to some overestimation of the genetic risk of Parkinson’s disease, because its cause is probably not entirely genetic.

Assumptions are unavoidable when modelling population-attributable risk with data from GWAS. Thus, we have probably overestimated the genetic component of Parkinson’s disease risk on the basis of these loci alone because bias inherent in using a case-control study will slightly skew the frequency of risk alleles higher. However, this calculation did allow us to rank the contribution of every locus to the genetic cause of Parkinson’s disease, and to estimate the possible decrease in the future incidence of Parkinson’s disease achieved by preventative treatments targeted at genetic causes. Risk-profile modelling provides a conservative estimate of genetic risk and has moderate predictive power. The identification of additional common and rare risk variants for Parkinson’s disease will probably revise our estimate of the genetic component of disease upward.

**Interpretation**

Up to now, to our knowledge this study is the largest genetic analysis of Parkinson’s disease undertaken and has confirmed the associations at six previously implicated loci and also identified five new loci. This study provides evidence that common genetic variation plays an important part in the cause of Parkinson’s disease. We have confirmed a strong genetic component to Parkinson’s disease, which, until recently, was thought to be completely caused by environmental factors. The genomic loci described show the rapid pace of growth in the specialty of genome-wide association studies of complex disease, and the future predictive use of genes identified in such studies.

**Contributors**

MAN, VP, JS-S, MM, JH, PH, AB, TG, ABS, and NWW designed the study. MAN, MM, JH, PH, AB, TG, ABS, and NWW obtained funding. DGH, MSh, U-MS, JS-S, CS, SL, SS, KS, MM, JH, PH, AB, TG, ABS, and NWW collected samples. KS, MM, JH, PH, AB, TG, ABS, and NWW supervised the study. MAN, VP, MSh, U-MS, Msa, JS-S, CS, SL, MM, AB, and ABS did the data analysis and data management. Vincent Plagnol (UCL Genetics Institute, London, UK), Dena G Hernandez (Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA), Michael A Nalls (Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA), and NWW supervised the study. MAN, MM, AB, and ABS did the data analysis and data management.

**International Parkinson Disease Genomics Consortium members**

Michael A Nalls (Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA), Vincent Plagnol (UCL Genetics Institute, London, UK), Dena G Hernandez (Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA), and NWW supervised the study. MAN, MM, AB, and ABS did the data analysis and data management.
This work was supported by the Intramural Research Programs of the National Institutes of Health, a Parkinson’s Institute Foundation; Greater St Louis Chapter of the APDA; Hersenstichting Nederland; Neurosciences Campus Amsterdam; and the section of medical genomics, the Prinses Beatrix Fonds. The KORA (Cooperative Research in the Region of Augsburg) research platform was started and financed by the Forschungszentrum für Umwelt und Gesundheit, which is funded by the German Federal Ministry of Education, Science, Research, and Technology and by the State of Bavaria. This study was also funded by the German National Genome Network (NGFNplus number 01GS08134, German Ministry for Education and Research); by the German Federal Ministry of Education and Research (NGFN 01GR0686, PopGen); and 01EW0908 in the frame of ERA-NET NEURON and Helmholtz Alliance Mental Health in an Ageing Society (HA-215), which was funded by the Initiative and Networking Fund of the Helmholtz Association. The French GWAS work was supported by the French National Agency of Research (ANR-08-MNP-012). This study was also sponsored by the Landspitali University Hospital Research Fund (grant to SSv); Icelandic Research Council (grant to SSv); and European Community Framework Programme 7, People Programme, and IAPP on novel genetic and phenotypic markers of Parkinson’s disease and Essential Tremor (MarkMD), contract number PIAP-CA-2008-150536 (to HA). We used the Biowulf Linux cluster at the National Institutes of Health, Bethesda, MD, USA, and DNA panels, samples, and clinical data from the National Institute of Neurological Disorders and Stroke Human Genomics Resource Center DNA and Cell Line Repository. People who contributed samples are acknowledged in descriptions of every panel on the repository website. We thank The French Parkinson’s Disease Genetics Study Group: Y Agid, M Anheim, A-M Bonnet, M Borg, A Brice, E Broussolle, J-C Corvol, P Damier, A Destée, A Durr, F Durif, S Klebe, E Lohmann, M Martinez, P Pollok, O Rascol, F Tison, C Tranchant, M Vein, F Vialet, and M VidaliSet. We also thank the members of the French JC Consortium: Annick Alpérovitch, Claudine Berr, Christophe Tourour, and Philippe Amouyel for allowing us to use part of the JC cohort; and D Zelenika for support in generating the genome-wide molecular data. We used genome-wide association data generated by the Wellcome Trust Case-Control Consortium 2 (WTCCC2) from UK patients with Parkinson’s disease and UK control individuals from the 1958 Birth Cohort and National Blood Service. Genotyping of UK replication cases on ImmunoChip was part of the WTCCC2 project, which was funded by the Wellcome Trust (083948/Z/07/Z). UK population control data was made available through WTCCC1. This study was supported by the Medical Research Council and Wellcome Trust disease centre (grant WT089698/Z/09/Z to NW, JH, and AS). This study was also supported by Parkinson’s UK (grants 8047 and J 0804) and the Medical Research Council (G0700943). We thank Jeffrey Barrett for assistance with the design of the ImmunoChip. DNA extraction work that was done in the UK was undertaken at University College London Hospitals, University College London, who received a proportion of funding from the Department of Health’s National Institute for Health Research Biomedical Research Centres funding. This study was supported in part by the Wellcome Trust/Medical Research Council Joint Call in Neurodegeneration award (WT089698) to the Parkinson’s Disease Consortium (UKPDC), whose members are from the UCL Institute of Neurology, University of Sheffield, and the Medical Research Council Protein Phosphorylation Unit at the University of Dundee.

References


3 The UK Parkinson’s Disease Consortium and The Wellcome Trust Case Control Consortium 2. Dissection of the genetics of Parkinson’s disease identifies an additional association 5’ of SNCA and multiple associated haplotypes at 1q21. Hum Mol Genet 2011; 20: 345–53.


