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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 12-019 control samples, with genotyped and imputed data at 7-689-524 SNPs. The replication phase consisted of 7053 case and 9007 control samples. We identified 11 loci that surpassed the threshold for genome-wide significance ($p < 5 \times 10^{-8}$). 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.

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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

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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.

Conflicts of interest

KSt has received grants from deCODE. JH has received consulting fees or honoraria from Eisai and his institute has received consulting fees or honoraria from Merck-Serono. TG has received consultancy fees from Cephalon and Merck-Serono; grants from Novartis; payments for lectures including service on speakers' bureaus from Boehringer Ingelheim, Merck-Serono, UCB, and Valeant; and holds patents NGFN2 and KASPP. MAN, VP, DGH, MSh, U-MS, MSa, JS-S, CS, SL, SS, KS, MM, PH, ABr, ABS, and NWW declare that they have no conflicts of interest.

Parkinson's disease. MAPT and SNCA^{1, 2, 3, 4 and 5} have consistently shown associations in genome-wide association studies (GWAS). BST1, LRRK2, GAK, and HLA-DRB5^{1, 2, 3, 5, 6 and 7} 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.⁸ 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^{1, 2, 3 and 9} 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.^{5 and 10} 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.^{1, 2, 3, 5, 9 and 11}

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 Chain based haplotyper (MACH; version 1.0.16) on every dataset to impute genotypes for all participants of European ancestry with haplotypes derived from initial low coverage sequencing of 112 European ancestry samples in the 1000 Genomes Project (as of August, 2009).^{12 and 13} For all datasets, data were imputed by a two-stage design. The first stage generated error and crossover maps as parameter estimates for imputation on a random subset of 200 samples per study over 100 iterations of the initial statistical model. We used these parameter estimates to generate maximum likelihood estimates of allele numbers per SNP on the basis of reference haplotypes for the datasets during the second stage of the imputation. SNPs with RSQR quality estimates of less than 0.30 as indicated by MACH were excluded from analyses of the datasets, because imputed genotypes below this threshold are probably of poor quality.

We did genome-wide dataset analyses at every site with MACH2DAT.¹² 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 $p < 1 \times 10^{-5}$) 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 ($I^2 > 75\%$).¹⁴ and ¹⁵ 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),¹⁶ and ¹⁷ 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.¹⁸ 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.¹⁹ 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 χ^2 tests for heterogeneity (Cochran's Q) with METAL and we generated I^2 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 ($\log_{\text{odds ratio}}$). 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 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.²⁰ 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.

Webappendix pp 10–13 and a previous study²¹ provide 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 1×10^{-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 7-689-524 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 ($p < 5 \times 10^{-8}$; table 2).¹⁸ One locus on chromosome 17 from 18-601-523 to 18-602-998 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 I^2 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. Webappendix pp 15–31 provides more detailed results for every region.

We confirmed the Parkinson's disease associations at the SNCA and MAPT loci^{1, 2, 3, 4 and 5} and at BST1, LRRK2, GAK, and HLA-DRB5 (table 2).^{1, 2, 3, 5, 6 and 7} 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. Webappendix pp 7–8 provides 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.²² 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 SYT11 locus is

independent of GBA mutations (webappendix pp 9–10 and pp 32–33). Similarly, we did an analysis that controlled for the known common LRRK2 mutation G2019S in the replication phase, and showed that the association detected in the meta-analysis close to LRRK2 might be caused by variation independent of this mutation (webappendix pp 9–10 and 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%.² 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.

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 and arrays in this region. For the MAPT locus, risk estimates were positively associated with quantitative trait locus effects, leading to increased gene expression (cerebellum r^2 0.1366; frontal cortex r^2 0.8042; both tissues $p < 2 \times 10^{-16}$). We noted the opposite effect in the methylation quantitative trait loci at MAPT, with minor alleles associated with increased risk and with decreased methylation (cerebellum r^2 0.9268, $p < 2 \times 10^{-16}$; frontal cortex r^2 0.4667, $p = 3.68 \times 10^{-6}$). The MAPT locus showed associations for multiple probes within MAPT and probes within proximal genes, including ARL17A and PLEKHM1. 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 locus 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 BTNL2, HLA-DQB2, and SLC44A4. 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 0.4977, $p < 2 \times 10^{-16}$).

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,²³ 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^{1, 2, 3, 4, 5, 6, 7 and 9} 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, 2, 3, 5, 6 and 9}

Panel. Research in context

Systematic review—As part of the International Parkinson Disease Genomics Consortium we had access to several genome-wide association datasets for Parkinson's disease, including both published and unpublished studies. To identify other studies, we searched PubMed with no date restrictions for published genome-wide association studies in Parkinson's disease with the following terms: Parkinson's disease, genome wide association. The search returned studies already included through the consortium members,^{1, 2, 3, 9 and 11} For those studies outside the existing framework of the consortium, we used all studies that included more than 300-000 single nucleotide polymorphisms and for which the underlying genetic data were available for download. This resulted in one additional dataset being added to the meta-analysis.⁵

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.

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 homeostasis 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, 26 and 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, 30 and 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 functionally involved in intrinsic cell-death pathways and interacted with huntingtin to modulate polyglutamine-induced neuronal dysfunction in transgenic worm and mouse models.³³ Finally, the association detected at the SYT11 locus includes a gene that has been investigated previously in a negative mutation screening study in 393 patients with familial or sporadic Parkinson's disease³⁴ and in a cell biology study that showed an interaction between the protein products of SYT11 and PARK2 in patients with Parkinson's disease.³⁵

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Saad M, Lesage S, Saint-Pierre A, et al. for the French Parkinson's Disease Genetics Study Group. Genome-wide association study confirms BST1 and suggests a locus on 12q24 as risk loci for Parkinson's disease in the European population. *Hum Mol Genet.* 2011; 20:615–627. [PubMed: 21084426]
2. Simon-Sanchez J, Schulte C, Bras JM, et al. Genome-wide association study reveals genetic risk underlying Parkinson's disease. *Nat Genet.* 2009; 41:1308–1312. [PubMed: 19915575]
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 5ÅL of SNCA and multiple associated haplotypes at 17q21. *Hum Mol Genet.* 2011; 20:345–353. [PubMed: 21044948]
4. Edwards TL, Scott WK, Almonte C, et al. Genome-wide association study confirms SNPs in SNCA and the MAPT region as common risk factors for Parkinson disease. *Ann Hum Genet.* 2010; 74:97–109. [PubMed: 20070850]
5. Pankratz N, Wilk JB, Latourelle JC, et al. Genomewide association study for susceptibility genes contributing to familial Parkinson disease. *Hum Genet.* 2009; 124:593–605. [PubMed: 18985386]
6. Satake W, Nakabayashi Y, Mizuta I, et al. Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease. *Nat Genet.* 2009; 41:1303–1307. [PubMed: 19915576]
7. Hamza TH, Zabetian CP, Tenesa A, et al. Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson's disease. *Nat Genet.* 2010; 42:781–785. [PubMed: 20711177]
8. Singleton AB, Hardy J, Traynor BJ, Houlden H. Towards a complete resolution of the genetic architecture of disease. *Trends Genet.* 2010; 26:438–442. [PubMed: 20813421]
9. Simón-Sánchez J, van Hilten JJ, van de Warrenburg B, et al. Genome-wide association study confirms extant PD risk loci among the Dutch. *Eur J Hum Genet.* 2011 published online Jan 19. DOI: 10.1038/ejhg.2010.254.
10. Mailman MD, Feolo M, Jin Y, et al. The NCBI dbGaP database of genotypes and phenotypes. *Nat Genet.* 2007; 39:1181–1186. [PubMed: 17898773]
11. Fung HC, Scholz S, Matarin M, et al. Genome-wide genotyping in Parkinson's disease and neurologically normal controls: first stage analysis and public release of data. *Lancet Neurol.* 2006; 5:911–916. [PubMed: 17052657]

12. Li Y, Willer C, Sanna S, Abecasis G. Genotype imputation. *Annu Rev Genomics Hum Genet.* 2009; 10:387–406. [PubMed: 19715440]
13. University of Michigan Center for Statistical Genetics. [accessed Dec 1, 2009] 1000G 2009–08 download. <http://www.sph.umich.edu/csg/abecasis/MACH/download/1000G-Sanger-0908.html>
14. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003; 327:557–560. [PubMed: 12958120]
15. Ioannidis JP, Patsopoulos NA, Evangelou E. Heterogeneity in meta-analyses of genome-wide association investigations. *PLoS One.* 2007; 2:e841. [PubMed: 17786212]
16. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient metaanalysis of genomewide association scans. *Bioinformatics.* 2010; 26:2190–2191. [PubMed: 20616382]
17. University of Michigan Centre for Statistical Genetics. [accessed Dec 1, 2009] Metal—meta-analysis helper. <http://www.sph.umich.edu/csg/abecasis/metal>
18. de Bakker PI, Ferreira MA, Jia X, Neale BM, Raychaudhuri S, Voight BF. Practical aspects of imputation-driven meta-analysis of genome-wide association studies. *Hum Mol Genet.* 2008; 17:R122–R128. [PubMed: 18852200]
19. R Development Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2008.
20. Zollner S, Pritchard JK. Overcoming the winner's curse: estimating penetrance parameters from case-control data. *Am J Hum Genet.* 2007; 80:605–615. [PubMed: 17357068]
21. Gibbs JR, van der Brug MP, Hernandez DG, et al. Abundant quantitative trait loci exist for DNA methylation and gene expression in human brain. *PLoS Genet.* 2010; 6:e1000952.
22. Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. *N Engl J Med.* 2009; 361:1651–1661. [PubMed: 19846850]
23. Singleton A, Gwinn-Hardy K. Parkinson's disease and dementia with Lewy bodies: a difference in dose? *Lancet.* 2004; 364:1105–1107. [PubMed: 15451205]
24. Garavaglia S, Perozzi S, Galeazzi L, Raff aelli N, Rizzi M. The crystal structure of human alpha-amino-beta-carboxymuconateepsilon-semialdehyde decarboxylase in complex with 1,3-dihydroxyacetonephosphate suggests a regulatory link between NAD synthesis and glycolysis. *FEBS J.* 2009; 276:6615–6623. [PubMed: 19843166]
25. Ramoz N, Cai G, Reichert JG, Silverman JM, Buxbaum JD. An analysis of candidate autism loci on chromosome 2q24-q33: evidence for association to the STK39 gene. *Am J Med Genet B Neuropsychiatr Genet.* 2008; 147B:1152–1158. [PubMed: 18348195]
26. Wang Y, O'Connell JR, McArdle PF, et al. From the cover: whole-genome association study identifies STK39 as a hypertension susceptibility gene. *Proc Natl Acad Sci USA.* 2009; 106:226–231. [PubMed: 19114657]
27. Cunnington MS, Kay C, Avery PJ, Mayosi BM, Koref MS, Keavney B. STK39 polymorphisms and blood pressure: an association study in British caucasians and assessment of cis-acting influences on gene expression. *BMC Med Genet.* 2009; 10:135. [PubMed: 20003416]
28. Malosio ML, Giordano T, Laslop A, Meldolesi J. Dense-core granules: a specific hallmark of the neuronal/neurosecretory cell phenotype. *J Cell Sci.* 2004; 117:743–749. [PubMed: 14734658]
29. Lincoln MR, Ramagopalan SV, Chao MJ, et al. Epistasis among HLA-DRB1, HLA-DQA1 and HLA-DQB1 loci determines multiple sclerosis susceptibility. *Proc Natl Acad Sci USA.* 2009; 106:7542–7547. [PubMed: 19380721]
30. Cano P, Klitz W, Mack SJ, et al. Common and well-documented HLA alleles: report of the ad-hoc committee of the American Society for Histocompatibility and Immunogenetics. *Hum Immunol.* 2007; 68:392–417. [PubMed: 17462507]
31. Handel AE, Handunnetthi L, Berlanga AJ, Watson CT, Morahan JM, Ramagopalan SV. The effect of single nucleotide polymorphisms from genome wide association studies in multiple sclerosis on gene expression. *PLoS One.* 2010; 5:e10142. [PubMed: 20405052]
32. Wersinger C, Sidhu A. An inflammatory pathomechanism for Parkinson's disease? *Curr Med Chem.* 2006; 13:591–602. [PubMed: 16515523]
33. Parker JA, Metzler M, Georgiou J, et al. Huntingtin-interacting protein 1 influences worm and mouse presynaptic function and protects *Caenorhabditis elegans* neurons against mutant polyglutamine toxicity. *J Neurosci.* 2007; 27:11056–11064. [PubMed: 17928447]

34. Glass AS, Huynh DP, Franck T, et al. Screening for mutations in synaptotagmin XI in Parkinson's disease. *J Neural Transm Suppl.* 2004; 68:21–28. [PubMed: 15354386]
35. Huynh DP, Scoles DR, Nguyen D, Pulst SM. The autosomal recessive juvenile Parkinson, parkin interacts with and ubiquitinates synaptotagmin XI. *Hum Mol Genet.* 2003; 12:2587–2597. [PubMed: 12925569]

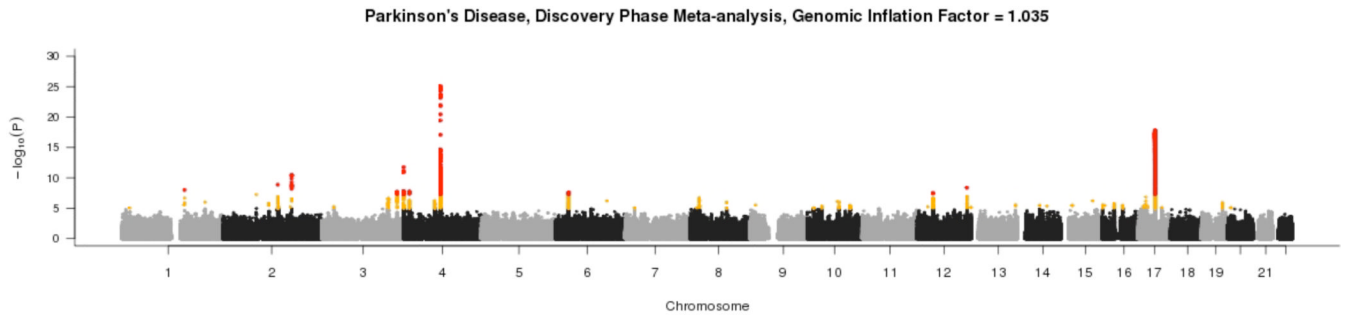


Figure 1.

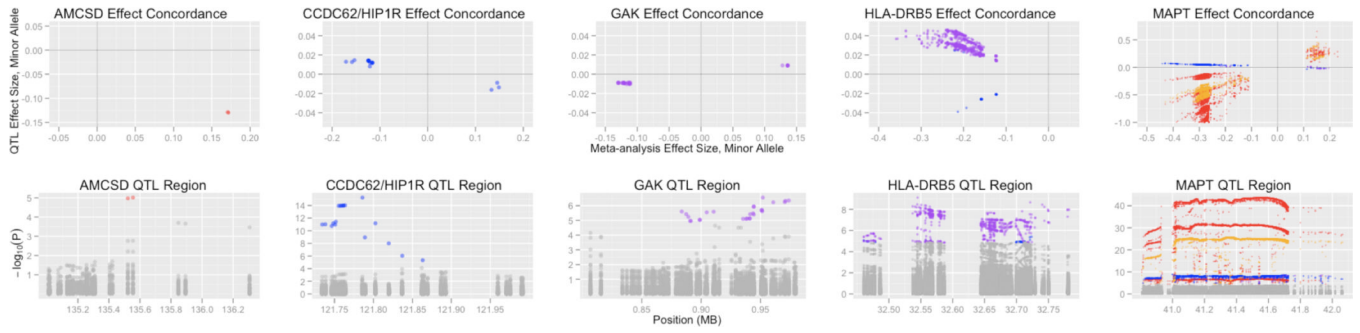


Figure 2.

Table 1

Study characteristics

Study	Cases				Controls				GWAS		
	Sample Size	Mean AAO (SD)	Percent Female	Sample Size	Mean AAE (SD)	Percent Female	Number of Successfully Genotyped SNPs	Number of Successfully Imputed SNPs	Covariates in GWAS	Genomic Inflation Factor (λ)	
USA-NIA	971	55.9 (15.1)	40.5	3034	62 (15.6)	52.8	463187	7590773	Population structure*	1.043	
UK	1705	65.8 (10.8)	43.3	5200	NA	49.5	598821	7678643	None	1.048	
Germany	742	56 (11.6)	39.8	944	NA	48.0	463187	7589890	Population structure*	1.029	
France	1039	48.9 (12.8)	41.2	1984	73.7 (5.4)	33	493081	7340040	Population structure*	1.029	
USA-dbGAP	876	61.5 (9.2)	40.4	857	NA	60.2	334513	7482040	Population structure*	1.023	
Meta-analysis	5333			12019			547951	7689524#	Genomic control\$	1.042	

Table 2

Summary of Significant Loci

Most Significant SNP in Region	Locus information				Discovery Phase Results				Replication Phase Results				Combined Risk Estimate				
	CHR	Position (bp)	MAF in Discovery Phase	Minor/Major Alleles	Candidate Gene	Odds Ratio per Minor Allele Dose	Standard Error	Fixed Effects P -value	Random Effects P -value	I ² Index of Heterogeneity	Heterogeneity P-value	Odds Ratio per Minor Allele Dose	Standard Error	Fixed Effects P-value	Population Attributable Risk Estimate (%)	Lower 95% Confidence Interval	Upper 95% Confidence Interval
chr1:154105678	1	154105678	0.02	T/C	SYT11	1.67	0.09	1.02E-08	5.70E-09	0	0.77	1.44	0.08	1.18E-06	1.21	0.34	1.47
rs6710823	2	135308851	0.19	A/G	AMCSD	1.38	0.05	1.35E-09	1.61E-05	48.26	0.11	1.07	0.02	0.003161	4.05	1.66	6.82
rs2102808	2	168825271	0.13	T/G	STK39	1.28	0.04	3.31E-11	1.54E-11	0	0.72	1.12	0.04	0.001639	2.29	1.11	2.98
rs11711441	3	184303969	0.14	A/G	MCCCI/LAMP3	0.82	0.04	2.10E-08	1.17E-08	0	0.97	0.87	0.03	6.92E-05	13.71	9.05	17.70
chr4:911311	4	911311	0.28	C/G	GAK	1.21	0.03	1.80E-12	2.96E-07	51.58	0.09	1.14	0.02	7.46E-08	4.87	2.68	6.38
rs11724635	4	15346199	0.45	C/A	BST1	0.87	0.03	1.85E-08	0.001407	74.77	4.05E-03	0.87	0.02	2.43E-09	7.82	5.30	9.47
rs356219	4	90856624	0.39	G/A	SNCA	1.30	0.03	7.90E-26	1.11E-26	0	0.58	1.27	0.02	4.23E-23	9.71	6.68	10.27
chr6:32588205	6	32588205	0.15	G/A	HLA-DR	0.70	0.06	2.58E-08	1.44E-08	0	0.88	0.80	0.04	9.30E-08	17.68	11.04	23.00
rs1491942	12	38907075	0.21	G/C	LRRK2	1.19	0.03	3.23E-08	5.24E-06	35.52	0.20	1.30	0.05	1.06E-08	2.09	1.00	2.50
rs12817488	12	121862247	0.46	A/G	CCDC62/HIP1R	1.16	0.03	4.43E-09	2.99E-06	34.97	0.20	1.13	0.03	9.06E-07	5.56	3.20	7.37
rs2942168	17	41070633	0.22	A/G	MAPT	0.76	0.03	1.62E-18	3.91E-19	0	0.74	0.80	0.03	1.37E-13	17.57	12.92	20.78

Study	Trend P-value	AUC	OR	95% CI, Upper Bound		2nd Risk Quintile		3rd Risk Quintile		4th Risk Quintile		5th Risk Quintile					
				95% CI, Lower Bound	95% CI, Upper Bound	OR	95% CI, Lower Bound	95% CI, Upper Bound	OR	95% CI, Lower Bound	95% CI, Upper Bound	OR	95% CI, Lower Bound	95% CI, Upper Bound			
USA	<2E-16	0.584	1	--	--	1.49	1.25	1.78	1.67	1.40	2.00	1.90	1.59	2.27	2.25	1.88	2.70
UK	<2E-16	0.631	1	--	--	1.63	1.27	2.08	2.26	1.77	2.88	2.65	2.09	3.38	3.30	2.60	4.21
Germany	1.44E-08	0.69	1	--	--	1.16	0.86	1.57	1.55	1.14	2.11	1.68	1.23	2.29	2.06	1.51	2.82
France	6.15E-09	0.644	1	--	--	1.24	0.72	2.16	2.13	1.26	3.66	2.84	1.68	4.88	4.31	2.51	7.55
Netherlands	8.34E-04	0.576	1	--	--	1.21	0.74	2.00	1.12	0.68	1.84	1.50	0.93	2.42	1.89	1.17	3.07
Combined	<2E-16	0.63	1	--	--	1.43	1.27	1.62	1.77	1.55	1.99	2.03	1.80	2.32	2.51	2.23	2.83
% Cases per Quintile (N cases)				39.00			47.13			52.16			55.93			61.17	
				(886)			(1069)			(1185)			(1268)			(1394)	