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Dissection of the genetics of Parkinson’s disease identifies an additional association 5’ of SNCA and multiple associated haplotypes at 17q21

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We performed a genome-wide association study (GWAS) in 1705 Parkinson’s disease (PD) UK patients and 5175 UK controls, the largest sample size so far for a PD GWAS. Replication was attempted in an additional cohort of 1039 French PD cases and 1984 controls for the 27 regions showing the strongest evidence of association (P < 10^{-14}). We replicated published associations in the 4q22/SNCA and 17q21/MAPT chromosome regions (P < 10^{-10}) and found evidence for an additional independent association in 4q22/SNCA. A detailed analysis of the haplotype structure at 17q21 showed that there are three separate risk groups within this region. We found weak but consistent evidence of association for common variants located in three previously published associated regions (4p15/BST1, 4p16/GAK and 1q32/PARK16). We found no support for the previously reported SNP association in 12q12/LRRK2. We also found an association of the two SNPs in 4q22/SNCA with the age of onset of the disease.

INTRODUCTION

Parkinson’s disease (PD) is the second most common neurodegenerative disease after Alzheimer’s disease. It affects over 1% of the elderly population and despite effective symptomatic therapies is progressive and disabling. The motor phenotype is characterized by variable severity of bradykinesia, rigidity and tremor. The age at onset varies, but for the ‘typical sporadic’ patients it is in the seventh decade and beyond. As our population ages so the prevalence of PD is increasing. The clinical definition of the disease is based on the core features listed above and includes initial responsiveness to levodopa. This clinical phenotype correlates very highly with the pathological phenotype of Lewy body neurodegeneration.

Previous genetic studies of familial forms of PD have identified rare, highly penetrant variants in several chromosome regions, in particular 4q22/SNCA, 12q12/LRRK2 1p36/Pink1, 1p36/DJ-1 and 6q26/parkin (1,2). However, our knowledge of the genetic factors underlying the sporadic form of PD remains poor. The advent of rapid, robust and cost-effective approaches to a systematic genome-wide association analysis has enabled appropriately powered large-scale studies to be undertaken for the first time. Recently, two groups (3,4) have reported their PD genome-wide association results. These two studies provided strong evidence of association at two chromosome regions: 4q22/SNCA and 17q21/MAPT. In addition, they present suggestive evidence of association for common variants in three chromosome regions 4p15/BST1, 1q32/PARK16 and 12q12/LRRK2. Edwards et al. (5) have since confirmed the associations at 4q22/SNCA and 17q21/MAPT in a meta-analysis totalling 1752 cases and 1745 controls, but they did not find evidence for any other loci associated with PD. Identification of new associations requires additional genome-wide association study (GWAS) using larger sample sizes to provide the required statistical power to detect subtle effects on PD risk.

RESULTS

To further understand the genetic basis of PD, we undertook a PD GWAS in the UK population as part of the Wellcome...
Trust Case Control Consortium 2 (WTCCC2). Our initial sample size consisted of 5667 UK control samples and 2190 UK PD cases passing the aforementioned phenotype criteria (Supplementary Material, Table S1). UK PD cases were randomly selected from population and hospital-based clinics with an emphasis on sporadic cases with no family history for this disease. Half of the cases had been screened for the known, rare, highly penetrant G2019S mutation (1) in the LRKK2 gene (see Materials and Methods). We identified 14 G2019S carriers, a frequency consistent with previous reports of G2019S frequency in UK PD cases. Owing to our focus on common rather than rare variants, we excluded these 14 individuals from the GWA scan.

Case samples were genotyped on the Illumina Human660-Quad platform and control samples were genotyped on the Illumina 1.2 m Duo platform; the overlap SNP set was used in this analysis. Following sample quality control (Supplementary Material, Table S2), our final data set consisted of 1705 cases and 5175 controls. We attempted replication of the top findings in a French PD case–control collection of 1039 cases and 5175 controls. Among these loci, only the established associations 4q22/SNCA and 17q21/MAPT successfully replicated at \( P < 10^{-4} \) (Supplementary Material, Table S3). The third strong association in our GWAS at 7q32 (rs10447854) showed marginal evidence of association in the replication set but in the opposite direction to that of our initial finding. Thorough checks did not find genotyping errors or allele switches and we therefore assume that in spite of the convincing statistical evidence in our GWAS, this result is a false positive.

Next, we examined other reported PD associations for evidence of association in our data. We observed \( P \)-values < 0.05 for SNPs in 4p15/BST1 and 4p16/GAK (Table 1). We found no conclusive support for the published association in the 1q32/PARK16 chromosome region (4) (Table 1) and, unlike both previously published PD GWAS of non-familial cases, we found no evidence of association in the 12q12/LRRK2 chromosome region (Table 1).

To identify further risk variants, which may not be well correlated with any single SNP in our data, we used the program IMPUTE2 (7) to impute an additional 1,200,917 SNPs. To do so, we exploited data from both the HapMap project (www.hapmap.org) and additional WTCCC2 genotyping available for the control collections (see Materials and Methods). Association analysis of this enriched data set did not yield any compelling additional signals of association.

Next, we further investigated the signal at the loci showing strong evidence for association in our data. An association analysis in the 4q22/SNCA region conditional on the most associated SNP (rs356220) revealed a second independent association at rs7687945, which is located 5′ of SNCA. The

Figure 1. Genome-wide association plot. Genome-wide association results for PD at 532, 616 SNPs. Alternating chromosomes are show in shades of blue. Previously identified loci that also replicate in this study are highlighted in green.
We assessed this in the phased data and parameter related to the way in which the SNP alleles combine effects for these two SNPs or whether it requires an additional increase in risk relative to individuals homozygote for the G allele (1.08 (1.00–1.17)).

It is natural to ask whether the best statistical model just has an odds ratio shown for the risk allele.

A previous study reported additional PD associations in the 5′ region upstream of SNCA (10). However, the LD between our second signal, rs7687945, and these previously reported variants is low ($r^2 = 0.24, 0.26$ with rs2736994 and rs2737026, respectively, calculated in the imputed 58C data) and AA haplotypes in Table 2. To pursue this possibility, we examined whether any of the SNPs in the 1000 Genomes data did not identify additional signals at two SNPs in our data, this could, in principle, arise if disease risk depended on a single, untyped SNP: for example, if the risk allele at the untyped SNP occurred with increasing frequencies on the GG, GA, AG and AA haplotypes in Table 2. To pursue this possibility, we examined whether any of the SNPs in the 1000 Genomes data (March 2010 release) in the association region was a better predictor than either rs356220 or rs7687945, but none was. In addition, the analysis of the 1000 Genomes data did not identify non-synonymous SNPs in strong LD ($r^2 > 0.5$) with either rs356220 or rs7687945. It is therefore unlikely that the effect on PD risk is mediated by a protein coding change.
and these previous associations were only found in female and young onset cases. Further analysis is required to determine whether these observations represent an independent association signal.

The 17q21 hit region falls on a known polymorphic 900 kb inversion. The two forms of the inversion, often termed H1 and H2, vary in frequency globally, with the minor H2 haplotype found almost exclusively in Southwest Asian and European populations, at a frequency of 5–30% (11–13). There is some evidence that H2 is under selection in Europe, where it has been linked to higher recombination rate and greater fertility (12). Suggestive associations of the region with Crohn’s disease and type 1 diabetes have recently been reported (14). There is very little evidence of recombination between the two orientations of the inversion, but within these, H1 shows relatively normal recombination and variation patterns, whereas there is very little variation within the H2 haplotype (15). Analyses of the age of the inversion event and its history have led to differing conclusions (11,12,16,17). The inversion encompasses several genes, and the most associated SNP in our GWAS, rs7215239, is located in the promoter region of the MAPT gene. The minor allele at rs7215239 (G) is protective for PD and is in LD with multiple SNPs over a large region tagging the H2 and H1 haplotypes, an association result consistent with a previous study (18). Within the H1 haplotype, there is genetic diversity, and many sub-haplotype have been determined (12). To date, results for associations of these sub-haplotype with PD have shown contradictory findings (19), with one study showing distinct H1 sub-haplotype associate with PD and supranuclear palsy (18,19) and another study indicating that the PD association at the MAPT gene is not due to the different sub-haplotype of H1 but explained by the H1/H2 inversion (18). However, it has been demonstrated that a subset of H1 haplotypes (referred to as H1c) is associated with increased MAPT expression (20).

In order to further investigate the association at this locus, we used a recently published software package, GENECLUSTER (21), to find evidence for causal mutation(s). GENECLUSTER looks for evidence of potential additional association signals by examining the clustering of case and control haplotypes at the tips of a genealogical tree estimated from reference-panel data (here HapMap CEU) at a fine grid of locations. Differential clustering under a particular branch of the tree suggests the possibility of a mutation on that branch which affects disease risk. GENECLUSTER assesses evidence for association in a Bayesian framework, and investigates models where there is one, and separately two, disease-predisposing mutation in the region.

In the 17q21 region, the strongest GENECLUSTER evidence for association results in a log10(Bayes factor) of 6.22 under the two-mutation model. At the same position, the one-mutation model log10(Bayes factor) is much smaller at 5.23, which strongly suggests that more than one variant is needed to explain the association.

The most likely two-mutation model identified three haplotype risk backgrounds, corresponding to H2 and two subsets of H1 (Fig. 2). These three groups are well tagged by four SNPs (rs9303521, rs11079711, rs12938476, rs1880756) with the TGCC haplotype defining H2, and GATT, TGTC or TGTT haplotypes defining a subset of H1 haplotypes partitioning it into two risk groups. We phased the study genotypes across the region and labelled individuals according to the alleles carried at the four tagging SNPs at the H2 haplotype, a two-group model separating just H1 and H2 (likelihood ratio test \( P = 0.003 \)). Relative to the risk of the H2 haplotype, we estimate one subset of H1 haplotypes (Fig. 2, coloured red) to have a risk of 1.18 (95% CI 1.07–1.30), and the other set of H1 haplotypes (Fig. 2, coloured blue) to have a risk of 1.36 (95% CI 1.23–1.50). For replication, we tested the same three-group model defined by the sets of haplotypes at these SNPs in the French data and

![Figure 2. Haplotype tagging of three risk groups identified at the 17q21 locus.](image-url)
found it significant at \( P = 0.026 \) (OR = 1.18, 95% CI 1.03–1.35 for the low-risk H1 haplotype and OR = 1.37, 95% CI 1.19–1.58 for the high risk H1 haplotype).

We also investigated whether the two main associations at SNCA and MAPT showed evidence of interaction, i.e. a departure from the simple model in which the risks for the main SNP at each locus combine multiplicatively. Using a one degree-of-freedom case only test for genotype correlations (22) between the MAPT SNP and each of the two SNCA SNPs, we found no evidence of interaction (\( P > 0.05 \)).

A further association study was carried out in the PD data, treating the age of onset as a quantitative trait. No SNP passed a stringent significance threshold (\( P = 10^{-7} \)). However, motivated by the higher prior belief of a potential association with the age of onset for PD-associated loci, we used a less stringent significance threshold for the PD-associated SNPs in the MAPT and SNCA chromosome regions. This analysis identified an age at onset association for both PD-associated SNPs in SNCA. As with the case–control analysis, the evidence at these SNPs is the strongest when they are both included in the model: \( F \)-test of the two-SNP model gives a \( P \)-value of \( 6.37 \times 10^{-4} \) compared with either rs7687945 (\( P = 0.0049 \)) or rs356220 (\( P = 0.189 \)) when tested separately. The direction of risk at these SNPs is the same as in the case–control analysis (Table 3). Individuals carrying homozygote A alleles at both SNPs have an average 5.48 year earlier onset of PD than those carrying homozygote G alleles at both SNPs. The association of the pair of SNPs with the age of onset was replicated in the French data (\( P = 0.02 \), with rs2301134 used as a proxy for rs7687945). However, while the direction of effects is the same, the individual effects and marginal significance of the two SNPs differ somewhat in the discovery and replication data sets (Table 3), so we would recommend some caution pending further replication.

**DISCUSSION**

We undertook a GWAS for PD in 1705 cases and 5175 controls. We found strong support for previously reported associations at 4q22 and 17q21, and support at \( P < 0.05 \) at 4p15 and 4p16. An earlier reported association around LRRK2 did not replicate in our study.

We undertook additional analyses at the two major GWAS loci, 4q22/SNCA and 17q21/MAPT, and in each case uncovered additional signals. At 4q22/SNCA, association analysis conditioned on the top SNP revealed a second independent signal which was masked in single-SNP analyses. The presence of the additional signal substantially increases the size of the genetic effect at the locus, with each additional copy of the risk allele at both loci increasing disease risk by a factor of 1.65. SNCA is a likely candidate in this region: SNCA is a major component of Lewy bodies, the abnormal inclusions in the brain which are important in PD pathology, and previous studies have linked PD risk with SNCA overexpression caused by triplications of this gene (2). Our results suggest that SNCA risk alleles for PD may well also be associated with earlier disease onset. Previous reports have associated rare copy number variants in SNCA with the age of onset, whereby duplications are associated with late onset and triplications associated with early onset (23). Together these observations suggest a key role for SNCA in PD susceptibility and progression, which is potentially directly related to gene expression and therefore α-synuclein concentrations (2).

We found that there are at least three haplotype groups at 17q21 with differing risk. Further characterizing these haplotypes and determining the mechanisms behind the several associations reported at the 17q21 locus is an important priority for further work. While MAPT is a strong PD candidate gene in 17q21 and MAPT has differential expression in the H1 and H2 haplotypes, with higher expression in H1 compared with H2 (20,24), the PD association could well involve another gene. In particular, the H1/H2 genotype is weakly associated with type 1 diabetes and Crohn’s disease risk (14) which indicates that variants on this large haplotype may affect multiple pathways.

For the \( P \)-value threshold of \( 10^{-4} \) that we used to select loci for replication, our sample size provides 93% power to detect an allele with a minor allele frequency (MAF) of 20% and an effect size of 1.3. Given the good genome coverage of the Illumina Human660-Quad platform that was used in this study, the absence of additional replicated associations suggests that 4q22/SNCA and 17q21/MAPT may be the only common variants with effects of this magnitude on PD risk in the UK population. However, and in addition to the well-documented contribution of highly penetrant rare variants for PD risk, our results cannot rule out the presence of a significant number of common associations but with smaller odds ratio. Future pooling of existing case–control studies into large meta-analyses is required to increase the statistical power to detect weaker associations and improve our understanding of the genetic architecture of PD.

**MATERIALS AND METHODS**

**Case and control samples**

Prior to any exclusion, the full data set comprised 2190 individuals with idiopathic PD, and 5667 population controls. Known familial cases and individuals with known Mendelian mutations (including LRRK2 mutations) were excluded. The samples were collected through five UK-wide centres (Supplementary Material, Table S1). Case samples collected in London and Cardiff were screened for the previously reported highly penetrant and rare G0219S mutation in the LRRK2 gene. The 14 G0219S carriers that we identified were excluded from the GWA study. The control data set was that of the previously described WTCCC2 study (25)—totalling 2930 samples from the 1958 Birth Cohort (58C) and 2737 samples from the UK Blood Services Controls (NBS).

**Phenotype definition**

All case subjects met the UK Brain Bank Clinical Criteria for PD (26). Of the 1705 samples that progressed through to analysis, age of onset was available for 1439 samples. The mean age of disease onset, as defined by reported age of first motor symptom, was 65.8, with the youngest at age 29 years and the oldest at age 105 years. The male-to-female
Genotyping methodology and quality control

Genotyping of the samples was carried out at the WTSI on the Illumina BeadArray platform. Cases were genotyped on the Illumina Human660-Quad array and the controls were genotyped on the Illumina 1.2M Duo array. Normalized probe intensities were exported using the BeadStudio program and genotypes called separately in the 58C, NBS and PD data sets using the program Illuminus (27). For the purposes of quality control, SNPs were excluded from analysis if, in any of the data sets (58C, NBS or PD), they had a MAF less than 0.01%, a significant departure from Hardy Weinberg equilibrium ($P < 10^{-20}$) or a significant association with the plate on which the samples were assayed ($P < 10^{-6}$). We also excluded SNPs for which the observed statistical (Fisher) information about the allele frequency was less than 98% of the information contained in a hypothetical sample of the same size and expected MAF but with no missing data. An additional 39 SNPs were removed following visual inspection of cluster plots. In total, 61,636 SNPs were removed from the overlap set on the two genotyping chips, leaving 532,588 for association analysis. Sample exclusions were based on four genome-wide summary statistics of the genotyping data designed to be sensitive to possibly sources of heterogeneity: fraction of missing genotypes, autosomal heterozygosity, a measure of African and Asian ancestry (defined by a principal component analysis of the HapMap 2 data) and the average difference in the probe intensities across SNPs. By modelling the distribution of each of these summaries as a mixture, we inferred outlying individuals and excluded them from analysis. Furthermore, we exclude one of each pair of individuals showing greater than 5% identity by descent by inferring chromosomal sharing at a genome-wide subset of 11,547 SNPs. To reduce the risk of errors through sample swaps, we also removed samples for which the reported gender and genetically determined gender were discordant, or where Illumina array-based genotypes disagreed with more than 10% of the Sequenom genotypes which were typed as part of sample preparation described above. After sample quality control, 1705 cases and 5175 controls sample remained for analysis (Supplementary Material, Table S2).

Imputation and haplotype phasing

Haplotyping phasing and imputation was performed using IMPUTE2 (7), which adopts a two-stage approach using both haploid and diploid reference panels. For the haploid reference panel, we used HapMap2 and HapMap3 SNP data for the 120 non-related CEU trios (see www.hapmap.org), and for the diploid reference we used 58C and NBS control data, merging genotypes from the Illumina 1.2 m Duo chip and Affymetrix Genome Wide Human SNP array 6.0. Prior to analysis with IMPUTE2, we applied standard quality control filters akin to those described above. To further protect against potential errors misleading the imputation and phasing, we checked that each genotype conformed to local patterns of LD in HapMap by employing a leave-one-out imputation strategy. Specifically, we ran IMPUTE (7) on each of the study samples in turn, both cases and controls, re-imputing known genotypes. Control individuals for which the imputed genotypes were more than 4.5% discordant with the original genotype were removed. The same rule was applied to case individuals with a discordance threshold of 6%. SNPs for which IMPUTE was confident of the imputation call but the genotyped data were discordant (and therefore indicative of genotyping error) were also removed if the difference between measure of information and error rate was greater than 0.05.

Statistical analysis

Genome-wide case–control analysis was performed using frequentist tests, under a missing data logistic regression model, as implemented in the program SNPTTEST (6). Unless otherwise stated, we assumed a multiplicative model for allelic risk by encoding the genotypes at each SNP as a discrete explanatory variable with an indicator of case status as the binary response. We note that an analogous analysis using the Cochran–Armitage trend test in PLINK (29), ignoring the uncertainty in genotype calls, gave very similar results (data not shown). To look for secondary independent signals...
within associated loci, we included the SNP with the lowest trend test P-value in the logistic regression model as a discrete covariate using PLINK (28). Likelihood ratio tests were used to compare one SNP to two SNP models in order to identify SNPs within the loci with independent effects on risk. For the analysis of haplotypes in the 4q22 and 17q21 regions, we employed logistic regression models to estimate the risk associated with carrying each of the haplotypes or where relevant set of haplotypes, by including a set of indicator variables denoting the haplotypes carried by each study individual. To formally compare the two-group haplotype model to the three-group model at 17q21, we re-encoded haplotypes to form a nested model and tested the need for an indicator of membership of the two risk groups within the H1 background. These analyses were carried out in the statistical package R.

Age of onset analysis was carried out by treating it as a continuous quantitative response in a linear regression model. Genome-wide analysis was performed using frequentist tests in SNPTTEST calculated using missing data likelihoods. To look in detail at the combined effect of the two SNPs in 4q22, we reanalysed the data in R. Meta analysis results for both age of onset and case–control analysis were obtained assuming a standard fixed effects model to combine estimates of the odds ratio and standard errors across studies.

It has become standard practice in GWAS to refer to the odds ratio associated with a particular allele or haplotype, which we estimate to be the $e^\beta$, where $\beta$ is the maximum likelihood estimate of the coefficient describing the effect of each predictor on the response in the assumed model. We note however that, as is of true this study and many others, where the controls are taken at random from the population without reference to case status, $\beta$ is actually the log of the relative risk and not the log of the odds ratio.

Replication strategy
For in silico replication, we exchanged genotype data with a study carried out in the French population using a similar study design. The French data set consisted of a total of 1039 cases and 1984 controls (see Saad et al., manuscript in preparation). These samples were typed on the Illumina 610 platform, which has an overlap of 473892 SNPs with our study. Selecting only from the subset of SNPs which passed quality control in both studies, association test data for 100 SNPs were exchanged. This SNP replication list included the 55 top hit SNPs from our study (Supplementary Material, Table S3), 20 randomly selected control SNPs and 25 SNPs from the two most recently published PD GWAS studies (3,4). Owing to the significant level of population structure in the French GWA scan, the association test included covariates for population structure computed from a principal component analysis (29).

AUTHOR CONTRIBUTIONS
N.W.W., P.F.C., D.B., R.A.B., A.J.L., K.B., C.E.C., K.E.M. were involved in establishing DNA collections, assembling phenotypic data and/or recruiting patients; J.H., N.W.W., N.W.W. supervised clinical and laboratory work; WTCCC2 DNA, Genotyping, Data QC and Informatics group executed GWAS sample handling, genotyping and QC; WTCCC2 Data and Analysis group, M.G., C.C.A.S., A.S., V.P. and P.D. performed statistical analyses; V.P., C.C.A.S., A.S., J.H., P.D. and N.W.W. contributed to writing the manuscript. WTCCC2 Management Committee conceived and oversaw the design and execution of the GWAS. WTCCC2 group memberships are specified in the full author list.

SUPPLEMENTARY MATERIAL
Supplementary Material is available at HMG online.

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APPENDIX
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