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Genome-wide association study confirms BST1 and suggests a locus on 12q24 as risk loci for Parkinson’s disease in the European population

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Abstract

We performed a three-stage genome-wide association study to identify common PD risk variants in the European population. The initial genome-wide scan was conducted in a French sample of 1,039 cases and 1,984 controls, using almost 500K SNPs. Two SNPs at SNCA were found associated with PD at the genome-wide significance level (P < 3 x 10^{-8}). An additional set of promising and new association signals was identified and submitted for immediate replication in two independent case-control studies of subjects of European descent. We first carried-out an in-silico replication study using GWAS data from the WTCCC2 PD study sample (1,705 cases, 5,200 WTCCC controls). Nominally replicated SNPs were further genotyped in a third sample of 1,527 cases and 1,864 controls from France and Australia. We found converging evidence of association with PD on 12q24 (rs4964469, combined P = 2.4x10^{-7}) and confirmed the association on 4p15/BST1 (rs4698412, combined P = 1.8x10^{-6}), previously reported in Japanese data. The 12q24 locus includes RFX4, an isoform of which, named RFX4_v3, encodes a brain specific transcription factors that regulates many genes involved in brain morphogenesis and intracellular calcium homeostasis.
INTRODUCTION

Parkinson’s disease (PD) is the second most common degenerative disease, affecting 1-2% of individuals older than 65 years. Clinical features of PD result primarily from loss of dopaminergic neurons in the substantia nigra. Although the common form of PD is sporadic, six genes have been identified, mainly by linkage analyses of Mendelian forms of the disease. Two genes, SNCA (encoding a-synuclein) and LRRK2, have an autosomal dominant inheritance and four other genes, PARK2 (parkin), PARK6 (PINK1), PARK7 (DJ-I) and PARK13 (ATP13A2) have an autosomal recessive inheritance (1). Frequently, mutations in these genes are found in early onset patients with PD, particularly those with autosomal recessive inheritance. However, in most populations, Mendelian forms of parkinsonism are rare compared with the most common form of PD, a frequent and complex disorder likely explained by the interaction between genetic and environmental factors. The first two first GWASs in PD (2, 3) provided evidence of association with several loci but most often not at the genome-wide significant level, and most initial association findings were not confirmed by subsequent replication analyses (4). Two recent GWASs (5, 6) reported strong or genome-wide significant associations with one or more of the known PD genes (i.e., SNCA, MAPT and/or LRRK2). So far, only two ‘new’ loci have been identified, 1q32/PARK16 and 4p15/BST1, in the Japanese data (5). The US/UK/German GWAS (6) replicated positive association with variants at PARK16 but failed to replicate the association at BST1.

To identify additional variants that affect PD risk in the European population, we designed a three-stage genome-wide association study of PD in three case-control samples from France, UK and Australia (total of >13,300 subjects). A set of 50 top association signals was identified in the scan sample (1,039 cases and 1,984 controls from France) using the Illumina-610Quad chip. Promising and new signals were followed-up for stepwise replication in two further UK and French/Australian case-control studies (>3,200 cases and 7,000 controls).

RESULTS

The genome-wide association results from logistic test corrected for genomic inflation (GC) revealed two SNPs with $P_{GC}<10^{-7}$, and a substantial number of SNPs with strong ($P_{GC}<10^{-4}$) evidence of
association (Figure 2 & Table 2). For practical reasons, we focus our attention on the 50 best associated SNPs to prioritize for immediate in-silico replication (Table 2). Secondary logistic analyses, adjusted for the first two PCs, led to similar rank order of SNPs, albeit slightly weaker association signals (Table 2). This suggests that the significant results, revealed by our primary analyses, are not biased by residual population substructure within our French scan sample. The 50 best associated SNPs spanned 23 distinct genomic loci, and were associated with $P_{GC} < 5.6 \times 10^{-5}$. Sixteen associations were found within 2 well-known PD genes, including SNCA (4q22, 4 SNPs) and MAPT (17q12-q21, 11 SNPs), or within BST1 (4p15, one SNP) a recently reported PD risk locus established at genome-wide significance level in a Japanese population (5). The remaining 34 SNPs were located in 20 distinct previously unreported putative PD loci. The 2 genome-wide significant SNPs were located on 4q22/SNCA (rs356220, $P_{GC} = 2.82 \times 10^{-8}$, OR=1.37; 95% CI [1.22-1.53] and rs2736990, $P_{GC} =2.88 \times 10^{-8}$, OR=1.35 [1.22-1.50]). The next most significant SNP was on chromosome 12q21/LOC401725 (rs=7954761, $P_{GC} =2.09 \times 10^{-7}$, OR= 1.34 [1.20-1.50]).

The 50 top SNPs were tested for in-silico replication in the WTCCC2 PD study data (Table 2). For the sake of clarity, ORs values are reported as a function of the number of risk alleles as identified in the stage-1 data. Associations for all fifteen SNPs in SNCA and MAPT genes were replicated at nominal $P$ values < $4 \times 10^{-5}$. Association with the BST1 variant was also replicated but at a weaker significance level (OR=1.08, $P=0.025$). For all SNPs at SNCA, MAPT and BST1, the results in the French scan and the UK replication samples were highly congruent in terms of risk alleles and allele frequencies. As expected, ORs estimated in our scan study tend to be higher than those obtained in the replication stage data, especially for BST1. Of the remaining 20 loci, association signals at 3 loci (4 SNPs) were replicated with nominal $P<5\%$ and with same direction of effect. These SNPs were located on chromosomes 2q21.3 (rs621341, OR=1.08, $P=0.028$ and rs6723108, OR=1.11, $P=0.005$), 12p13.3 (rs11064524, OR=1.08, $P=0.045$) and 12q24 (rs4964469, OR=1.11, $P=0.0045$). Differences in allele frequencies across the FR and UK data were notable for the 2q21-q22 SNPs. Indeed, the region encompasses the LCT (lactase) gene whose SNPs are known to vary in frequency.
across Europe, and rs6723108 has been shown to have different allele frequencies in the French and the UK-Irish populations (7).

We further followed-up the 5 replicated SNPs (from 3 newly identified loci and from BST1) in the second replication dataset (1,527 cases and 1,864 controls from France and Australia) (Table 3). In stage-3, evidence of association was assessed with the Mantel-Haenszel test to control for the potential confounding due to the different geographical origins (France vs Australia). Evidence of association was replicated for 2 SNPs, located on 12q24 (rs4964469, OR=1.12, P=0.0175) and on 4p15/BST1 (rs4698412, OR=1.10, P=0.029). Association signals from joint analysis of the 2 replication datasets were improved for the same 2 SNPs only: at 4p15/BST1 (stage2+stage3, P=0.0033) and at 12q24 (stage2+stage3, P=0.00036) loci. Notably, joint analysis of the 3 datasets showed a consistently greater support for association for the newly identified locus on chromosome 12q24 (P=2.38x10^-7) than for 4p15/BST1 (P=1.79x10^-6). Additional analyses showed that our initial association signals were not confounded by age and they did not appear to be driven neither by the subgroup of cases having an early age (<50) of onset of the disease nor by those having a positive family history of PD (results not shown). The population attributable risk (PAR) associated with SNCA, MAPT, BST1 and the 12q24 locus estimated in stage-1 data was 11%, 20%, 13% and 8%, respectively; in the combined data, PAR was 7% and 4% for BST1 and 12q24, respectively.

Finally, we also examined 18 SNPs from 5 loci, previously reported to be associated with PD at a genome-wide significance level from two published GWAS of PD (5, 6) (Table 4). We added three SNPs (at SNCA and BST1) that were found strongly associated in our stage-1 data. The table also shows the results for a suggestive PD risk locus (GAK) reported by the published GWAS of PD from familial cases (8). As for the previously reported PD loci, two loci only (SNCA and MAPT) have been identified with genome-wide significance at the screen stage: SNCA in both the Japanese and European populations and MAPT in the European population only. The two newly PD risk loci (BST1 and PARK16) were identified
in the Japanese population: association signals were strong \((P<10^{-6})\) in the discovery sample, and exceeded \(P<10^{-8}\) in the combined data \((5)\). As already reported here, our GWAS provided genome-wide significance for two SNCA variants and replicated positive associations for variants at MAPT and BST1 loci. It is worth to note that allele frequencies may differ markedly between the Japanese and the European datasets, especially for SNPs at the SNCA and BST1 loci. Saliently, the directions of effects (i.e., risk allele) and effect sizes at SNCA variants are rather congruent across the European and Japanese datasets. For the remaining 3 PD loci, evidence of association was nominal (PARK16, \(P_{GC}=0.03\); LRKK2, \(P_{GC}=0.04\); GAK \(P_{GC}=0.008\)) in the FR-GWAS data.

**DISCUSSION**

Our genome-wide association analyses in the French scan data revealed two SNPs with genome-wide significance \((P_{GC}<10^{-7})\), and a number of additional SNPs with suggestive evidence \((P_{GC}<10^{-4})\). Here, we focused on the 50 top associated SNPs for immediate replication in two independent case-control samples. We used a stepwise replication design. To refine the set of most promising results, we first conducted \textit{in-silico} replication for the 50 SNPs in the WTCCC2 PD data \((1,705\text{ cases and } 5,200\text{ WTCCC controls})\). Replicated SNPs were genotyped and tested in a third dataset of 1,527 cases and 1,864 controls from France and Australia. Our scan stage showed genome-wide significance of association with PD for 2 SNPs at 4q22/SNCA locus \((P_{GC}<2.88 \times 10^{-8})\). Indeed, out of the 50 top associated SNPs, 15 are located in genomic regions of 2 known PD genes (SCNCA, MAPT) and one is located on 4p15/BST1, a risk locus recently reported with genome-wide significance in Japanese samples. SNPs at SNCA and MAPT were all significantly associated with PD in the UK-GWAS data \((SNCA, P< 8 \times 10^{-5};\text{ MAPT, } P<2.75 \times 10^{-6})\). Evidence of association with 4p15/BST1 was also replicated in the UK sample but at a lower \((rs4698412, P=0.025)\) significance level. Out of the remaining 34 SNPs, 4 SNPs (3 loci) showed significant \((P<0.05)\) and consistent evidence of association in the UK data. A total of 5 SNPs (4 loci: 2q21.3, 12p13.3, 12q24 and BST1) were followed-up for replication in the third case-control sample. Two of the 4 tested regions were
replicated: 4p15/BST1 (P=0.03) and 12q24 (P=0.018). Of the 4 regions, only one (12p13.3) showed no evidence of association from combined analysis of the 2 replication datasets. Overall, evidence of association was consistently stronger with the region of the newly identified PD risk locus than with BST1, in each replication sample as well as in the combined (genome-wide and two replication samples) data (12q24, P=2.38x10^{-7}; BST1, P=1.79x10^{-6}).

The evidence of association (P_GC<1.35 x10^{-5}, Tables 2 & 4), that we detected with several SNPs in the 3’block of LD of the SNCA locus (Figure 3.A), including the two SNPs reaching genome-wide significance in our scan sample, is highly consistent with previous PD GWAS studies (5, 6).

MAPT is located in a large block of LD on chromosome 17q12-q22 which contains several additional genes (Figure 3.B). Previous studies (9, 10) have identified a large haplotypic block associated to PD, with H1 and H2 being the at-risk and the protective haplotype, respectively. Our two most associated SNPs in the 17q12-q22 region are located within this haplotypic block: rs17690703 (P_GC=3.9 x 10^{-6}) and rs17563986 (P_GC =1.3 x 10^{-5}), the later being at MAPT. In addition, H2 is tagged by the minor alleles of 4 of our genotyped SNPs: rs12185268/G, rs12373139/A, rs1981997/A, and rs8070723/G. In our scan data, we found same H1/H2 association signals, with all minor alleles of these 4 SNPs being significantly associated (P_GC < 3.44 x 10^{-5}) with a decreased risk of PD (Table 2).

The BST1 gene has previously been associated with PD in a GWAS Japanese study at a genome-wide significance level (5). Strong evidence of association for rs4698412 was found in the Japanese scan (P=5.3x10^{-5}, OR=1.25) and in the combined (scan + replication) data (P=1.8x10^{-8}, OR=1.24) (5). A much weaker signal was obtained in the US/UK/German data, in both the scan (P=0.09, OR=1.07) and the combined (P=0.03, OR=1.06) data (6). Here, we report strong evidence of association of PD with BST1 (combined P=1.79x10^{-6}, OR=1.14). The most associated SNP (rs4698412) maps to a 15kb LD-block (Figure 3.C) and is in high LD (r2=0.74/0.79) with the next top two BST1 variants (Table 4). Despite the variation in the allele frequency of the risk allele between the Japanese (RAF=0.33) and the European (RAF=0.52-0.56) samples (Table 4 & Table 3), we found marked homogeneity in
the direction of effects across the groups, but effect sizes seemed to be lower in European than in
Japanese samples. BST1 has been proposed to play a role in generating cyclic ADP-ribose that serves
as a second messenger for Ca2+ mobilization in endoplasmic reticulum and thus Ca homeostasis-
related BST1 could be a cause of selective vulnerability of dopaminergic neurons in PD (11).

Our most associated SNP, on 12q24, (combined P=2.38x10^{-7}, OR=1.16) is 26kb centromeric of RFX4
(Regulatory factor X4) (Figure 3.D). Two other closest genes, POLR3B (Polymerase RNA III
polypeptide B) and RIC8B (Resistance to inhibitors of cholinesterase 8 homolog B) are 200kb
centromeric and telomeric of the 12q24 SNP, respectively. The RFX proteins belong to the winged-
helix subfamily of helix-turned-helix transcription factor. The RFX4_v3 transcript variant is the only
RFX4 isoform that is significantly expressed in the fetal and adult brain, and its expression is
restricted to brain. In addition, it is involved in the transcription of many genes involved in brain
morphogenesis, such as the signaling components in the wnt, bone morphogenetic protein (BMP) and
retinoic acid (RA) pathways. In particular, cx3cl1, a CX3C-type chemokine gene that is highly
expressed in brain in response to injury or infection and regulates intracellular calcium concentration,
was down regulated in the RFX4_v3-null mice (12). This allows speculating that RFX4 and BST1 are
functionally linked and indirectly involved in the regulation of intracellular Ca+ concentrations,
which plays an important role in various cellular functions and cell death. Finally, polymorphisms in
RFX4 have been shown to be risks factors for the bipolar disorder, manic-depressive illness (13). A
recent study showed that a substantial proportion (10-15%) of top GWAS hits, so far identified, are e-
Quantitative Trait Loci i.e., associated to gene expression levels (14). We have initiated eQTLs
analysis using an existing brain expression database (15), but so far, failed to identify any association
of the PD-associated rs4964469 SNP with the expression of known genes contained within the 12q24
region.

In conclusion, we have conducted a large GWAS of PD in three case-control samples from France,
UK, and Australia. The GWAS stage has 75% and 33% power to detect loci of the effect sizes
observed in stage-1 data for the 12q24 variant (OR=1.27) at a significance of P<5x10^{-5} and P<10^{-7},
respectively. In the scan-step, we detected genome-wide significance of association with PD for 2 SNPs on 4q22, and strong evidence of association with 17q12-q22 SNPs. The two regions encompass previously reported loci: SNCA and MAPT, respectively. In addition, we confirmed, for the first time in subjects of European ancestry, the association of PD with 4p15/BST1, recently identified in Japanese samples. Finally, we identified a new locus on 12q24, potentially associated to PD. Further replication studies conducted in large case-control samples are warranted to evaluate the contribution of this locus on PD risk.

MATERIAL AND METHODS

1. Samples ascertainment and diagnostic criteria

The main characteristics of the three case-control samples are shown in table 1. Stage-1 Subjects: The total number of cases and controls from France included in stage-1 was 1,070 and 2,023 controls, respectively.

- PD subjects: Patients were recruited through the French network for the study of Parkinson’s disease Genetics (PDG) that regroups 15 university hospitals across France. Definite and probable PD were defined according to standard criteria. Definite PD required at least 2 of 3 cardinal signs (akinesia and/or rigidity and/or tremor) and absence of exclusion criteria (ophthalmoplegia, pyramidal or cerebellar signs, early dementia, urinary incontinence or postural instability and prior exposure to neuroleptic drugs), and a positive and sustained response to levodopa therapy. Probable PD required at least two of the 5 following criteria: the parkinsonian triad, a good response to levodopa therapy and asymmetrical onset. Most (>80%) of PD cases fulfilled the criteria for definite PD. Patients were selected in an effort to enrich for individuals that may have greater genetic predisposition to Parkinson’s disease, through selection of cases with a positive family history of PD (see Table 1). Cases were of European origin, mostly French (n=930). Subjects diagnosed genetically with known PARK mutations (SNCA, LRRK2, parkin, and PINK1) were excluded.

- 3C neurologically normal controls: The French Three-City (3C) cohort is a population-based, prospective (4-years follow-up) study of the relationship between vascular factors and dementia, carried out in three French cities: Bordeaux (Southwest France), Dijon (central eastern France) and
Montpellier (Southeast France) (16). Participants (>9,000) are non-institutionalised subjects, over-65 years of age, randomly selected from the electoral rolls of each city. Patients with Alzheimer’s disease or other types of dementia, and individuals for whom information on their dementia status during the 4-year follow-up was missing were further excluded. Here, we used a sample of 2,023 neurologically normal subjects matched on gender with PD cases, randomly selected from all the participants.

**Stage-2 subjects:** - *In-silico* replication sample: We exchanged genome-wide association data with the WTCCC2 PD study group (Spencer et al., submitted). This case-control study consisted of 1,705 PD cases and 5,200 controls from the 1958 Birth Cohort and from the OK Blood Services Controls (17).

**Stage-3 subjects:** De novo-genotyping was conducted in two independent case-control datasets from France (872 PD, 1,440 controls) and Australia (655 PD, 424 controls). The subjects from France were combined from three French studies: TERRE (207 cases, 468 controls), PARTAGE (313 cases, 593 controls), and an extension of PDG (352 cases, 378 controls). The extension PDG study includes patients that were not available at the time of the stage-1 genotyping execution and neurologically normal spouses of PDG patients. In cases, the mean age at examination and the mean age of onset of PD is 59 (30 to 86) and 50 (20 to 84) years, respectively. The mean age of controls is 60 (31 to 85) years. In PARTAGE, patients and controls were identified among affiliates to the Mutualité Sociale Agricole (MSA) from five French districts. parkinsonism was defined as the presence of at least two cardinal signs (rest tremor, bradykinesia, rigidity, impaired postural reflexes); PD was defined as the presence of parkinsonism after exclusion of other causes of parkinsonism. Controls were randomly selected from all MSA affiliates in the same districts and matched for sex, age (± 2 years). DNA was collected from saliva (Oragene kit). Cases and controls have a mean age of 67 (37 to 79) years, and the mean age of onset of disease is 63 (35 to 75) years. TERRE is based on a similar protocol (18), but DNA was collected from blood; the mean age in cases and controls is 73 (46 to 82) years, and the mean age of onset is 66 (39 to 80) years in cases. --- Australian study: Subjects with PD were recruited from one private and two public movement disorders clinics in Brisbane. Controls were electoral roll volunteers and patient spouses, excluding the subjects demonstrating signs of
parkinsonism (19). The mean age is 72 (34 to 105) and 74 (33 to 107) years in controls and cases, respectively; the mean age of onset is 59 (23 to 96) years in cases. Only Caucasian subjects were included in stage-3; in the Australian study, analyses were restricted to participants who reported to have 4 European grand-parents (>85% British). There was no overlap between the subjects used in the replication datasets and those included in the stage-1 data. Written informed consent was obtained for all participating subjects and research protocols were approved by local ethic committees.

2. Genotyping

Stage 1 Genotyping: DNA samples of GPD cases and 3C controls were transferred to the French Centre National de Génotypage. First stage samples that passed DNA quality control (1,064 PD cases and 2,023 controls) were genotyped with Illumina Human610-Quad BeadChip and subjected to standard quality control procedures.

Stage-2 genotyping: This WTCCC2 PD study sample was genotyped by the Welcome Trust Case Control Consortium using the Illumina 650Y genotyping array (Spencer et al., submitted).

Stage-3 genotyping: Genotyping in the extended GPD sample was carried out in the UMR/S 975 lab, using predesigned TaqMan probes (C_537709_10/ rs621341; C_29330880_10/ rs6723108; C_12096605_10/ rs11064524; C_2775670_10/ rs4964469; C_1216796_10/ rs4698412) on an ABI 7500 Real-Time PCR system Applied Biosystems, Foster City, CA, USA), according to the manufacturer’s instructions. Data were then analyzed using the 7500 software v2.0.1. The TERRE/PARTAGE and Australian samples were genotyped using the Sequenom MassARRAY platform, with the iPLEX protocol (Genoscreen, France). The basic protocol involves a multiplex primer extension followed by matrix-assisted laser desorption ionization-time of flight mass spectroscopy detection. In order to avoid any genotyping bias, cases and controls were randomly mixed when genotyping and, laboratory personnel were blinded to case/control status.

3. Quality control of FR-GWAS scan data.

Various stringent quality control (QC) filters were applied to remove poorly performing SNPs and samples using tools implemented in PLINK version 1.7 (20). -- SNP QC. Markers were removed if they had a genotype-missing rate >0.03 or a minor allele frequency (MAF) <0.05 or a Hardy-
Weinberg $P \leq 10^{-5}$. This SNP QC step led to the removal of 74,660 autosomal SNPs. Thus, subsequent analyses were based on 492,929 SNPs. **Individual QC.** Samples were removed based on standard exclusion criteria: call rate of less than 96% (22 subjects), inconsistencies between reported gender and genotype-determined gender (11 subjects) and genetic relatedness (identity-by-descent estimate $>0.14$; 6 subjects). Applying these QC filters led to the removal of 39 subjects (14 cases, 25 controls). **Population stratification and principal components analysis:** To detect individuals of non-European ancestry, we thinned the SNPs to reduce linkage disequilibrium (LD) to a set of 55,193 SNPs. To this end, we removed SNPs in extensive regions of LD (CHR2, CHR5, CHR6, CHR8, CHR11) (21), and excluded SNPs if any pair within a 1000-SNPs window had $r^2>0.2$. Our stage-1 genotype data were then merged with genotypes at the same SNPs from 381 unrelated European (CEU), Yoruban (YRI) and Asian (CHB and JPT) samples from the HapMap project. Principal components analysis was applied using EIGENSTRAT (22). The two principal components (PCs) clearly separated the HapMap data into three distinct clusters according to ancestry, and most of our stage-1 samples were clustered with the HapMap European samples (Figure 1). Thirty-two samples appeared to be ethnic outliers (including 1 subject clearly sharing African ancestry) from the European cluster and were excluded from further analysis. The final post-QC scan sample comprised 1,039 PD cases and 1,984 controls.

4. Statistical analysis.

Association analysis of the genotype data was conducted with PLINK (20).

**Stage-1 association analyses:** Logistic regression was used to study the allelic association between each SNP and PD assuming an additive genetic model. Our analysis was based on 492,929 SNPs, and on a conservative genome-wide significance threshold of $0.05/492,929=10^{-7}$. The distribution of the association results was found marginally inflated (median chi-square=0.521); genomic inflation factor $\lambda=1.14$ ($\lambda_{1000}=1.10$). Logistic regression analysis adjusted for the two first PCs of the EIGENSTRAT analysis, revealed a genomic inflation of 1.03 (median chi-square=0.472). As for our primary analyses, we applied the genomic inflation correction method (23); the median of the GC-corrected chi-square value was 0.447. Sensitivity analyses: Two further analyses were conducted to assist in interpretation of results of the identified GWAS SNPs. We performed age-adjusted regression
analysis and conducted subgroup analyses of two subtypes of cases against all controls. Cases with a disease onset before 50 years (n=428) were classified as “early AOO”, and cases having at least one first degree relative with PD (n=452) were classified as “FH+”.

**Stage-2 in silico association analyses:** Statistical data (ORs, effective sample sizes and nominal P-values for each of the 50 top SNPs) in the UK sample were obtained from the WTCC2 PD study group which used similar analytical methods (Spencer et al., submitted).

**Stage-3 association analyses:** For de novo replication stage, we computed association statistics with the Mantel-Haenszel test to control for the potential confounding due to the geographical centre (France vs Australia) for the 5 SNPs replicated at stage-2. Using raw genotypes from all study samples we computed similar stratified (FR vs Australia vs UK) association statistics in the combined (stage-2 + stage-3 and stage-1+ stage-2+ stage-3) data.

The population-attributable risk (PAR) associated with the detected variants was estimated with the following formula: \( PAR = \frac{p \times (OR-1)}{p \times (OR-1) + 1} \), where \( p \) is the frequency of the risk allele in controls, and \( OR \) is the odds ratio associated with the risk allele.

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**CONFLICT OF INTEREST:**

The authors declare no competing financial interests.
AUTHOR CONTRIBUTIONS

SL supervised DNA sampling; JCC, MV, EB, FD, PP, PD, FT, AD, AB recruited patients; JCC, AD, AB supervised clinical work; DZ and ML supervised PD and 3C GWAS genotyping and DNA QC work; SL and JCL supervised genotyping of stage-3 samples. AE, JCL, MAL, CT, GDM, and PAS contributed to stage-3 replication; MS, ASP and MM executed QC analyses and performed statistical association analyses; AE, AB and MM were involved in obtaining funding; MM drafted the manuscript and SL, AB, AE contributed to the writing of the final version; AB and MM conceived and oversaw the design and execution of the GWAS.
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**Figure 1:** Principal Components for our genome-wide stage-1.

Plot of first two principal components from analysis of our stage-1 (post-QC) data combined with HapMap data. Ethnicity of HapMap samples indicated by color: Africa (YRI) in green, Japan (JPT) in brown, Chinese (CHB) in yellow and Europe (CEU) in red. Study samples identified to be non-European or not clustering with European samples (outliers) are colored in blue and the remaining study samples assumed to be of European origin are colored in black.

**Figure 2:** Manhattan plot of the genome-wide association results for 492,929 SNPs

Logistic analysis corrected for genomic inflation (GC results)

**Figure 3:** Regional association plots and Linkage Disequilibrium structure for the four PD risk loci (A) 4q22/SNCA (B) 17q12-q22/MAPT (C) 4p15/BST1 and (D) 12q24/RFX4.

The –log10 P values (logistic regression tests corrected for genomic inflation) in the GWAS stage. In each panel, the blue horizontal line indicates a P value of $5 \times 10^{-5}$. Pairwise Linkage Disequilibrium ($D'$) values are displayed and the SNPs with strongest association signals are circled. SNPs are color-coded for LD relationships ($r^2$) to the best (colored in black) SNP: red: $0.8 \leq r^2 < 1$; green: $0.6 \leq r^2 < 0.8$; grey: $0.4 \leq r^2 < 0.6$; blue: $0 \leq r^2 < 0.4$. Positions are NCBI build 36 coordinates. Intron and exon structure of genes are taken from the UCSC Genome Browser.
Table 1: Samples used (post-quality control) in this study

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<th>Center</th>
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<tr>
<td>FH+</td>
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<td>0%</td>
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|                      | Controls     |                   |                   |                   |
|----------------------|--------------|-------------------|-------------------|
| Sex ratio (M/F)      | 1.33         | 1.02              | 1.05              |
| Age: mean ±sd (n*)   | 73.7 ±5.4 (1,984) | 51                | 68.1 ±10.0        |

|                      | Total        |                   |                   |                   |
|----------------------|--------------|-------------------|-------------------|
|                     | 3,023        | 6,905             | 3,391             | 13,319             |

*number of subjects for which age/age of onset of disease is known
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*Risk allele in stage-1 data; **Risk allele frequency in controls; $SL$ Logistic tests corrected for genomic inflation; $P$Logistic tests including 2PCs as covariates; $p$ Values shown when direction of effect in stage-1 and stage-2 data are consistent; *** 1-tailed P<0.5
Table 3: GWAS and replication: Loci considered to follow-up

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<th>Pos (bp)</th>
<th>SNP</th>
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<th>OR (95% CI)</th>
<th>P (2-tailed)</th>
<th>Stage-2 (UK)</th>
<th>OR (95% CI)</th>
<th>P (2-tailed)</th>
<th>Stage-3 (FR/AUS)</th>
<th>OR (95% CI)</th>
<th>P (2-tailed)</th>
<th>Combined</th>
<th>OR (95% CI)</th>
<th>P (2-tailed)</th>
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*Risk allele in stage-1 data; $Risk allele frequency in controls; %Odds ratio computed for the stage-1 risk allele; ^P values shown when direction of effect in stage-1 and each replication data are consistent; &P values from stratified association tests**1-tail P >0.05
**Table 4:** Association results of previously reported PD loci.

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<th>Position</th>
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<th>Haplotype (minor allele)</th>
<th>Japanese (Scan Phase)</th>
<th>European (Scan Phase)</th>
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**A. Genome-wide significant loci**

1q32 (PARK16)

12q12 (LRRK2)

**B. Suggestive Loci**

4p16 (GAK)

*SNP bp* GWAS Risk

**P** OR P

*GWAS Risk All RAF OR P OR P

**P** OR F

**GWAS Risk All RAF OR P OR P

**P** OR P

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*Table 1 from Satake et al., Nat Genet, 2009; Japanese data -- Scan Phase (1,078 PD / 2,521 controls)

**Table 2 from Simon-Sanchez et al., Nat Genet, 2009; US/GE/UK data -- Scan Phase (1,745 PD / 4,047 controls)

**Table 2 from Pankratz et al., Hum Genet, 2009; US (PROGENI + GenePD) data -- (857 familial PD cases / 867 controls)

** genome-wide significant (<10^-7) are underlined