



Published in final edited form as:

*Hum Genet.* 2009 January ; 124(6): 593–605. doi:10.1007/s00439-008-0582-9.

## Genomewide association study for susceptibility genes contributing to familial Parkinson disease

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### Abstract

Five genes have been identified that contribute to Mendelian forms of Parkinson disease (PD); however, mutations have been found in fewer than 5% of patients, suggesting that additional genes contribute to disease risk. Unlike previous studies that focused primarily on sporadic PD, we have

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performed the first genomewide association study (GWAS) in familial PD. Genotyping was performed with the Illumina HumanCNV370Duo array in 857 familial PD cases and 867 controls. A logistic model was employed to test for association under additive and recessive modes of inheritance after adjusting for gender and age. No result met genomewide significance based on a conservative Bonferroni correction. The strongest association result was with SNPs in the *GAK/DGKQ* region on chromosome 4 (additive model:  $p = 3.4 \times 10^{-6}$ ; OR = 1.69). Consistent evidence of association was also observed to the chromosomal regions containing *SNCA* (additive model:  $p = 5.5 \times 10^{-5}$ ; OR = 1.35) and *MAPT* (recessive model:  $p = 2.0 \times 10^{-5}$ ; OR = 0.56). Both of these genes have been implicated previously in PD susceptibility; however, neither was identified in previous GWAS studies of PD. Meta-analysis was performed using data from a previous case-control GWAS, and yielded improved  $p$  values for several regions, including *GAK/DGKQ* (additive model:  $p = 2.5 \times 10^{-7}$ ) and the *MAPT* region (recessive model:  $p = 9.8 \times 10^{-6}$ ; additive model:  $p = 4.8 \times 10^{-5}$ ). These data suggest the identification of new susceptibility alleles for PD in the *GAK/DGKQ* region, and also provide further support for the role of *SNCA* and *MAPT* in PD susceptibility.

## Background

Parkinson disease (PD [MIM 168600]) is the second most common neurodegenerative disease. Mutations in five genes have been identified to influence PD risk in fewer than 5% of those with PD (Pankratz and Foroud 2007). Three, *PARK2* (*parkin*), *PARK7* (*DJ1*), and *PINK1*, are typically transmitted with autosomal recessive inheritance and two, *SNCA* and *LRRK2*, are inherited in an autosomal dominant fashion. Mutations in all but *LRRK2* are typically found in early onset PD.

Two genomewide association studies (GWAS) to identify susceptibility genes contributing to the risk for PD have been performed previously. The first employed a discordant sibling design with 443 families to identify a set of associated SNPs that were then confirmed with 332 cases and a similar number of controls (Maraganore et al. 2005). The second study utilized a case-control design and included 267 PD cases and 270 controls (Fung et al. 2006). Unfortunately, there was little overlap in results between the two studies, and a few independent studies published following Maraganore et al. have not confirmed the initially associated regions or SNPs [reviewed in (Myers 2006)].

Notably, both previous GWAS studies utilized primarily or exclusively sporadic PD participants. While the majority of people with PD do not report a family history of disease, 15–25% report a first degree relative with PD (Sellbach et al. 2006). It is likely that the genetic contribution to disease risk is greatest in this subset of patients with a positive family history of disease. Therefore, to maximize the power to detect genes affecting PD susceptibility, we performed a GWAS utilizing only PD patients with a family history of PD, primarily in a first degree relative. We hypothesize that the homogeneity with regards to family history of disease may provide us greater power to detect unique loci influencing familial PD.

## Methods

### Sample selection

PD cases negative for the *LRRK2* G2019S mutation ( $n = 935$ ) were selected from two ongoing studies of familial PD. Additional genes, such as *PARK2* (*parkin*), *PARK7* (*DJ1*), and *NR4A2*, were screened for many, but not all subjects (Foroud et al. 2003; Karamohamed et al. 2005; Nichols et al. 2004, 2007; Pankratz et al. 2006; Sun et al. 2006); no subjects were included who had known disease producing mutation(s). Both studies (PROGENI and GenePD) initially ascertained multiplex PD families consisting of at least a sibling pair, both of whom were reported to be affected with PD. In a small proportion (9%), the PD case may have had another

affected relative rather than an affected sibling. On average, each PD participant had an additional 1.8 relatives who were reported to have PD. Only a single individual per family was genotyped ensuring sample independence. Both studies ascertained primarily Caucasian, non-Hispanic participants. PD cases underwent a uniform neurological evaluation that employed PD diagnostic criteria based broadly on the United Kingdom PD Society Brain Bank Criteria (Gibb and Lees 1988), although modified by both studies. A detailed description of the inclusion and exclusion criteria has been previously published for both the PROGENI (Pankratz et al. 2002) and GenePD (Maher et al. 2002) studies.

Control samples ( $n = 895$ ) were obtained from the NINDS Human Genetics Resource Center at the Coriell Institute Coriell Cell Repositories (Camden, NJ); older individuals were preferentially selected in an effort to have the mean age at recruitment of the controls be similar to the mean age at onset of the PD cases. All selected control samples were reported to be Caucasian, non-Hispanic. Based on self-report, the control subjects did not have a personal history of PD, and none reported a positive family history of PD (family history data was available for 91% of controls). Appropriate written informed consent was obtained for all samples included in this study.

### Microarray genotyping and quality assessment

Genotyping was performed by the Center for Inherited Disease Research (CIDR). DNA sources included blood ( $n = 905$ ), lymphoblastoid cell lines (LDL,  $n = 895$ ; all control samples) and whole genome amplified DNA ( $n = 30$ ). Genotyping was performed using Illumina HumanCNV370 version1\_C BeadChips (Illumina, San Diego, CA, USA) and the Illumina Infinium II assay protocol (Gunderson et al. 2006). In addition, intensity data was collected for 23,573 probes specifically designed to detect copy number variation (CNV). Allele cluster definitions for each SNP were determined using Illumina BeadStudio Genotyping Module version 3.1.14 and the combined intensity data from 96% of study samples (for details see Supplemental Methods I). The resulting cluster definition file was used on all study samples to determine genotype calls and quality scores. Genotype calls were made when a genotype yielded a quality score (Gencall value) of 0.25 or higher. The final raw dataset released by CIDR to the investigators and to dbGaP contained 344,301 SNPs with genotype calls and the 1,888 samples used in the current study (for details see Supplemental Methods I). Blind duplicate reproducibility was 99.98%. Data are available at dbGaP (<http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap>; Accession number: phs000126.v1.p1).

Samples having genotypes for at least 98% of the SNPs were considered for inclusion in analyses. These samples were rigorously checked for cryptic relatedness, population stratification, and related issues (Fig. 1 and Supplemental Methods II), and consequently, a total of 106 samples were removed from further analyses. The final sample used in analyses included 857 PD cases and 867 controls ( $n = 1,724$  individuals). A supplemental analysis using broader inclusion criteria was also performed with a sample of 902 PD cases and 881 controls ( $n = 1,783$  individuals, this sample is described in Supplemental Methods III).

SNPs with a call rate of 98% or greater were included for further quality control analyses ( $n = 336,537$ ). SNPs were removed if: (1) the minor allele frequency was less than 0.01 in the combined case and control dataset ( $n = 7,667$ ); (2) there were differential rates of missing genotypes in the cases and controls ( $n = 75$ ) or males and females ( $n = 271$ ), or (3) significant deviation from Hardy–Weinberg equilibrium was observed in the control sample ( $n = 906$ ). Many markers failed multiple tests. The final dataset consisted of 328,189 SNPs that passed all quality control measures (94.6% of all attempted SNPs).

## Statistical analysis

Logistic regression covarying for gender and age (age at evaluation for controls and onset for cases) was employed to test for the association of each SNP with PD susceptibility. An additive model was implemented, and because the additive model may not adequately identify recessive causal alleles (Lettre et al. 2007) and these cases were largely ascertained as affected sibling pairs, a recessive model was also implemented. Odds ratios and  $p$  values were computed to assess the strength of the association. All analyses were performed using PLINK (Purcell et al. 2007).

To further prioritize findings within our GWAS, we employed meta-analysis methods to combine  $p$  values from our study with those from the only comparable study that tested similar hypotheses. We obtained from dbGaP the publicly available genotype level data from the Fung et al. study. This study consisted of PD cases and controls available from the NINDS Human Genetics Resource Center at the Coriell Institute Coriell Cell Repositories (Camden, NJ). There was no overlap between the subjects used in Fung et al. and those included in this study. Genotyping for Fung et al. was performed with the Illumina Infinium I and the Infinium HumanHap300 SNP chip (Illumina, San Diego, CA, USA). A total of 408,803 unique SNPs were genotyped across these two arrays. We performed quality assessment similar to that performed for the data generated by CIDR for this study (Supplemental Methods IV) and removed eight samples (4 cases, 4 controls) due to quality control issues and three due to self reported African American or Hispanic ancestry. The final analytic sample included 262 cases and 260 controls.

In contrast with the initial report (Fung et al. 2006), we tested for association between the SNPs and disease susceptibility using a logistic regression model (both additive and recessive effects) incorporating an age (at evaluation for controls and onset for cases) and sex adjustment. For those SNPs genotyped in both studies ( $n = 310,160$  markers), the  $p$  values obtained in each study for the two relevant models were combined as implemented in METAL (Abecasis and Willer 2007). Specifically, for each SNP a  $Z$  statistic was computed for each study based on the study specific  $p$  value and direction of the estimated effect. An overall  $Z$  statistic (and then corresponding  $p$  value) was computed as a weighted average of the study specific  $Z$  statistics, with the weights proportional to the square root of the number of individuals within each study. Given the substantially larger size of our sample, proportional weighting of each study (1,724 for this study; 537 for the Fung et al. study) was performed.

## Role of the funding sources

The funding sources did not have any involvement in the collection, analysis, interpretation or writing of this report.

## Results

The familial PD participants recruited from the two studies had quite similar demographic characteristics (Table 1). Gender and age (age at onset for cases and age at exam for controls) were each significantly associated with affection status ( $p < 1 \times 10^{-15}$ ). The overall average call rate for the final analytic dataset was 0.9986 (standard deviation was 0.0023 when called by sample and 0.0040 when called by SNP).

Association results are summarized in Fig. 2 and Tables 2, 3. No result met genomewide significance based on a conservative Bonferroni correction for multiple testing ( $p < 1.5 \times 10^{-7}$  based on 328,189 SNPs considered in this study). The strongest evidence of association ( $p \leq 6 \times 10^{-6}$ ) was obtained with three SNPs within a 112 kb region on chromosome 4p in the genes *DGKQ* and *GAK* (Fig. 3a). Multiple SNPs met a  $p < 1 \times 10^{-4}$  threshold within a

chromosomal region on chromosome 4q which encompassed *SNCA*, *GPRIN3*, and *MMRN1* (Fig. 3b). This nearly 600 kb region has long range LD and previous studies have provided evidence supporting an association of *SNCA* with PD susceptibility (Maraganore et al. 2006; Winkler et al. 2007). Under the recessive model, the most significant SNP ( $p = 2 \times 10^{-5}$ ) was near *C17orf69* and the region of chromosome 17 that includes *MAPT* and a common inversion polymorphism (Fig. 3c). This SNP also provided evidence of association with the additive model.

To further prioritize our association results, we performed a meta-analysis combining association results (direction of effect and  $p$  values) from this study with those from Fung et al. Under an additive model, the evidence for association increased for the *DGKQ/GAK* and the *C17orf69/MAPT* regions (Table 2). No other regions or genes identified using the additive model (Table 2) had smaller  $p$  values following meta-analysis. In contrast, several chromosomal regions had lower  $p$  values when meta-analyses were performed combining results generated under the recessive model of disease inheritance. These included the *C17orf69/MAPT* region, *PIK3CD*, *LOC643954/HS3ST5* and *FIGN* (Table 3).

To ensure that SNPs providing modest but consistent evidence of association in both case-control studies were not overlooked, we summarize the top meta-analysis results for both the additive (Table 4) and recessive (Table 5) models. In addition to the *GAK/DGKQ* region and the *MAPT* region, a region on chromosome 2 encompassing SNPs in *LY75/PLA2R1* also had smaller  $p$  values under the additive model when meta-analysis was performed.

## Discussion

We performed the largest GWAS to date in PD. Unlike previous studies, we focused exclusively on cases having a positive family history of PD, which we hypothesize reflects an increased genetic contribution to disease risk. Using this approach, we detected consistent evidence of association to several chromosomal regions. Notably, we detected association to SNPs within or near two candidate genes previously associated with PD: *SNCA* and *MAPT*. Neither of these genes was identified in the two previous GWAS studies of PD.

*SNCA* was the first gene in which mutations were identified as causing PD (Polymeropoulos et al. 1997). It is thought that aberrant aggregation of the  $\alpha$ -synuclein protein results in cell damage and ultimately neuronal death. Subsequent analyses have showed that point mutations (Kruger et al. 1998; Zarranz et al. 2004) as well as gene duplications (Chartier-Harlin et al. 2004; Ibanez et al. 2004) and triplications (Singleton et al. 2003) can result in PD; however, mutations in *SNCA* are a quite rare cause of autosomal dominant PD. More recently, several studies reported that variation in the promoter region of *SNCA*, specifically the dinucleotide repeat polymorphism known as Rep1, acts as a susceptibility factor for PD, increasing the risk for disease (Kruger et al. 1999; Maraganore et al. 2006). Association has also been reported at the 3' end of the gene (Mueller et al. 2005), and a 3' SNP (rs356219) was identified to be associated with *SNCA* mRNA levels in substantia nigra and cerebellum (Fuchs et al. 2008). The evidence of association we detected ( $p < 1 \times 10^{-4}$ ) with several SNPs in *SNCA* is within intron 4 and the 3' region of the gene. The rs356229 SNP that we report with a minor allele increasing risk of PD (OR = 1.35) exhibits modest LD with rs356219 (HapMap CEPH  $D' = 0.65$ ,  $r^2 = 0.39$ ). The evidence that alpha-synuclein levels in the brain are influenced by genetic variability in the 3' region of the gene (Fuchs et al. 2008) and the LD between the reported SNPs in *SNCA* provide a link between our GWAS results and *SNCA* gene expression.

*MAPT* encodes microtubule-associated protein tau, which regulates microtubule dynamics and assembles microtubules into parallel arrays within axons. Aggregation of tau is a pathological hallmark of several neurodegenerative disorders collectively known as tauopathies, including

Pick disease and Alzheimer disease, as well as several disorders with parkinsonian features such as progressive supranuclear palsy, corticobasal degeneration, and fronto-temporal dementia with parkinsonism. Linkage of PD to the *MAPT* region was previously reported (Scott et al. 2001) and several studies have indicated that a large haplotype block containing *MAPT* is associated with a small but significant increase in risk for PD (Healy et al. 2004; Tobin et al. 2008; Zabetian et al. 2007; Zhang et al. 2005). The deleterious haplotype (H1) and the protective haplotype (H2) actually represent groups of subhaplotypes that arose from an inversion of 900 kb on chromosome 17 several million years ago (Stefansson et al. 2005); however, associations with these subhaplotypes have not been replicated (Zabetian et al. 2007). The SNPs that define the parent haplotypes of H1 and H2 are in complete linkage disequilibrium with each other ( $r^2 = 1$ ), indicating that the functional variation could be anywhere within this large 900 kb region and not necessarily within the *MAPT* gene. Complex permutations of alternative splicing lead to many different isoforms of tau; so if the association with H1 is due to variation that were to upset this delicate balance of isoforms, it may help to explain the variety of different neurodegenerative phenotypes that exhibit tau pathology.

Within this *MAPT* region, which exhibits wide ranging LD, are several additional genes including *C17orf69*, *CRHR1* and *IMP5*. A SNP between *C17orf69* and *CRHR1* provided the strongest evidence of association using the recessive model and had an even smaller  $p$  value when included as part of our meta-analysis. Evidence of association to this region was also strengthened when meta-analysis was performed using the additive model. Minor alleles of SNPs genotyped in this study that tag the H2 haplotype include rs12185268/G, rs12373139/A, rs1981997/A, and rs8070723/G, all of which were highlighted in the results of the additive meta-analysis (Table 4). Both SNPs in *IMP5* identified in the meta-analysis (Table 4) are missense polymorphisms. Given the complex LD structure within this chromosomal region, it is not yet clear whether it harbors multiple susceptibility genes (or alleles) within this region or, conversely, whether the evidence of association with multiple SNPs in different genes reflects a single susceptibility allele. We favor the former hypothesis, although further genotyping and analysis are clearly warranted to resolve this issue. Nonetheless, both the primary GWA analysis and meta-analysis support the existing hypothesis that the complex genomic region around *MAPT* is related to PD risk.

In order to evaluate replication of our top findings and to identify SNPs with modest  $p$  values that may nonetheless be true associations, we performed a meta-analysis. The focus of the present study is a comparison of PD cases and controls, a design also employed by Fung et al. In contrast, a previous GWAS by Maraganore and colleagues (Maraganore et al. 2005) initially employed a discordant sibling design. As noted by others (Defazio et al. 2006), a discordant sibling design is less powerful than a case-control design since the unaffected sibling may have still inherited susceptibility alleles that as a result of incomplete penetrance are not expressed. Therefore, we thought it most appropriate to include in our meta-analysis only the study of Fung et al. which like our own study was an analysis of unrelated cases and controls. We considered combining the genotypic datasets from Fung et al. with our study and testing for association on the combined dataset; however, due to the potential variation introduced by genotyping in differing laboratories with unique control samples and protocols and the different ascertainment scheme of the cases (familial vs. sporadic), we elected to perform a conservative meta-analysis using the results of association tests performed in each study separately. The meta-analysis results have provided support for association to several novel genes and regions not previously reported in GWAS of PD.

To prioritize among these novel genes and regions, we carefully reviewed the evidence for association from nearby SNPs, any published literature about the function of the gene or its potential role in PD susceptibility, and the meta-analysis results. The evidence for a possible association with the LD block region containing *GAK* (cyclin G associated kinase, a cell cycle

regulator) and *DGKQ* (diacylglycerol kinase, theta) increased following meta-analysis. *GAK* is a particularly promising candidate because it is one of 137 genes shown to be differentially expressed in PD, with a 1.56-fold change in expression in the substantia nigra pars compacta of PD patients as compared to controls (Grunblatt et al. 2004). No SNPs within the other 136 differentially expressed genes (or within 50 kb of these genes) highlighted in this expression study (Grunblatt et al. 2004) were significantly associated with PD susceptibility in our sample ( $p < 0.0001$ ). Less is known about *DGKQ*; however, it is thought to be involved in the phosphatidylinositol signaling system (KEGG pathway ID: hsa04070) and is expressed in the brain. The gene *PIK3CD*, identified among top recessive model results, is involved in the same pathway as *DGKQ*. There is another gene (*TMEM175*) in between *GAK* and *DGKQ*; however, while there were SNPs genotyped in this gene, none showed suggestive evidence of association with PD (Fig. 3a). Nevertheless, it is possible that a disease risk modifying variant could be present in any of the genes in this region.

For the SNPs presented in Tables 2, 3, we performed a secondary analysis in a broader set of individuals encompassing 902 cases (PROGENI,  $n = 491$ ; GenePD,  $n = 411$ ) and 881 controls (see Supplemental Methods III and Supplemental Table 1) including 40 cases and 14 controls of Hispanic or Asian descent and 19 cases from whole genome amplified samples. Results were largely similar to those obtained in the primary sample (see Supplemental Tables 2A, B).

One limitation of our study is the difference in ascertainment that resulted in differences in the age and gender distribution between our case and control populations. Because the age at exam for the controls was on average 7 years younger than the average age of onset of the cases, it is possible that a small number of the controls might develop PD as they age. However, the lifetime risk of PD is only approximately 1%; therefore, if a few controls were to develop PD, this would have little effect on the power of the current study. As with any association study, the greatest concern is the possibility of population stratification within cases and controls. We have employed stringent criteria and did not detect evidence suggesting that any of the first 10 MDS components (a proxy for population stratification) were significantly associated with disease status in the final sample. These results indicate that the sample is relatively homogenous and unlikely to be biased due to admixture.

The results obtained from this study do not meet genomewide significance based on a conservative Bonferroni correction for multiple testing ( $1.5 \times 10^{-7}$ ). Although our sample size is more than twice the size of previous GWAS studies, we still have limited power to detect, at a genomewide significant level, the small to moderate effect sizes often seen in susceptibility alleles for complex diseases such as PD. It is likely that some of the true association results will not lie among the most significant association results. We, therefore, turned to other lines of evidence to discern which among our strongest association results are most likely to be true positive results. Notably, two of our strongest association results were in the regions that include *SNCA* and *MAPT*; both genes have been previously reported as associated with PD susceptibility and therefore independent replication has been demonstrated in the existing literature. Meta-analysis demonstrates consistency of the *DGKQ/GAK* region in two independent studies.

It is possible that genes related to familial PD may be different than sporadic PD and vice versa. Finding an appropriate sample to directly replicate our association results is hindered by the dearth of samples enriched for familial PD. Future directions include the recruitment and analysis of an independent sample of familial PD patients and collaborating with investigators that have already collected large samples of sporadic PD that can be used for replication. In addition we will perform analyses utilizing CNVs. The methodology for best calling CNVs is still evolving and we will apply new and existing algorithms to ensure we obtain consistent, robust results prior to dissemination of findings.

In summary, we have performed the largest GWAS to date in PD. We have limited our PD cases to only those with a family history of PD, thereby potentially increasing the contribution of genetic risk factors. Using this case-control design, we detected evidence of association to two chromosomal regions that encompassed previously reported genes: *SNCA* and *MAPT*. In addition, we found consistent evidence of association to *DGKQ/GAK*. Further analyses are warranted in these and additional chromosomal regions nominated in this study to evaluate the evidence of association in both familial and sporadic PD cohorts.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

This project was supported by R01 NS37167, R01 NS036711, the Robert P. & Judith N. Goldberg Foundation, the Bumpus Foundation and the Harvard NeuroDiscovery Center. This study used samples from the NINDS Human Genetics Resource Center DNA and Cell Line Repository (<http://ccr.coriell.org/ninds>), as well as clinical data. DNA samples contributed by the Parkinson Institute—Istituti Clinici di Perfezionamento, Milan, Italy were from the “Human genetic bank of patients affected by PD and parkinsonisms”, supported by Italian Telethon grant n. GTB07001 and by the “Fondazione Grigioni per il Morbo di Parkinson”. Genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University, contract number HHSN268200782096C. We particularly thank Justin Paschall from the NCBI dbGaP staff for his assistance in developing the dataset available at dbGaP. The data generated from this case-control study are available at <http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap> through dbGaP accession number: phs000126.v1.p1. Data from the Fung et al. study were obtained from dbGaP. Funding support for “NINDS-Genome-Wide Genotyping in Parkinson's Disease: First Stage Analysis and Public Release of Data” was provided by intramural programs of the National Institute on Aging and the National Institute on Neurological Disorders and Stroke (NINDS) and the genotyping of samples was provided by NINDS. The dataset used for the meta-analyses described in this manuscript were obtained from the NINDS Database found at <http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap> through dbGaP accession number phs000089.v1.p1. The following are members of the PROGENI Steering Committee. University of Tennessee Health Science Center: R. F. Pfeiffer; University of Rochester: F. Marshall, D. Oakes, A. Rudolph, A. Shinaman; Columbia University Medical Center: K. Marder; Indiana University School of Medicine: P. M. Conneally, T. Foroud, C. Halter; University of Kansas Medical Center: K. Lyons; Eli Lilly & Company: E. Siemers; Medical College of Ohio: L. Elmers; University of California, Irvine: N. Hermanowicz. The following are members of the GenePD Steering Committee. University of Virginia Health System: G. F. Wooten; UMDNJ-Robert Wood Johnson Medical School: L. Golbe; Center for Human Genetic Research, Massachusetts General Hospital, Harvard Medical School: J. F. Gusella; Boston University School of Medicine: R. H. Myers. We thank the subjects for their participation in this research study.

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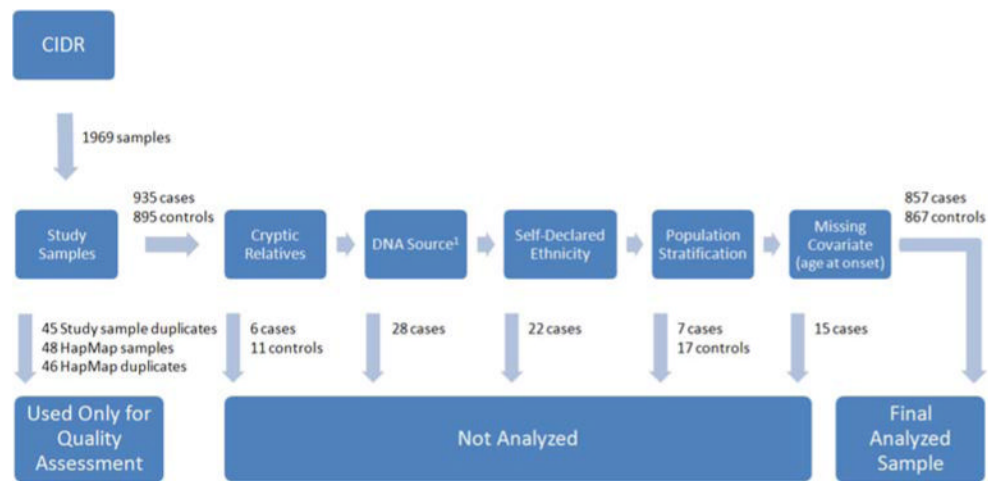
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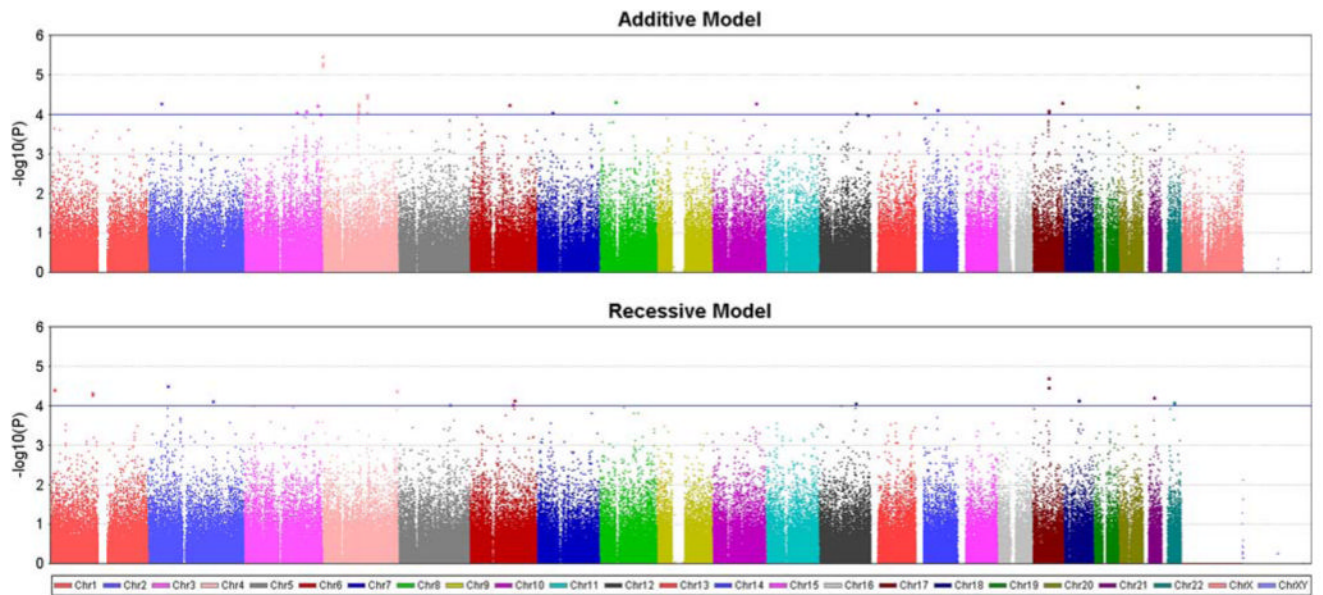
Zarranz JJ, Alegre J, Gomez-Esteban JC, Lezcano E, Ros R, Ampuero I, Vidal L, Hoenicka J, Rodriguez O, Atares B, Llorens V, Gomez Tortosa E, del Ser T, Munoz DG, de Yebenes JG. The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. *Ann Neurol* 2004;55:164–173. [PubMed: 14755719]

Zhang J, Song Y, Chen H, Fan D. The tau gene haplotype h1 confers a susceptibility to Parkinson's disease. *Eur Neurol* 2005;53:15–21. [PubMed: 15627775]

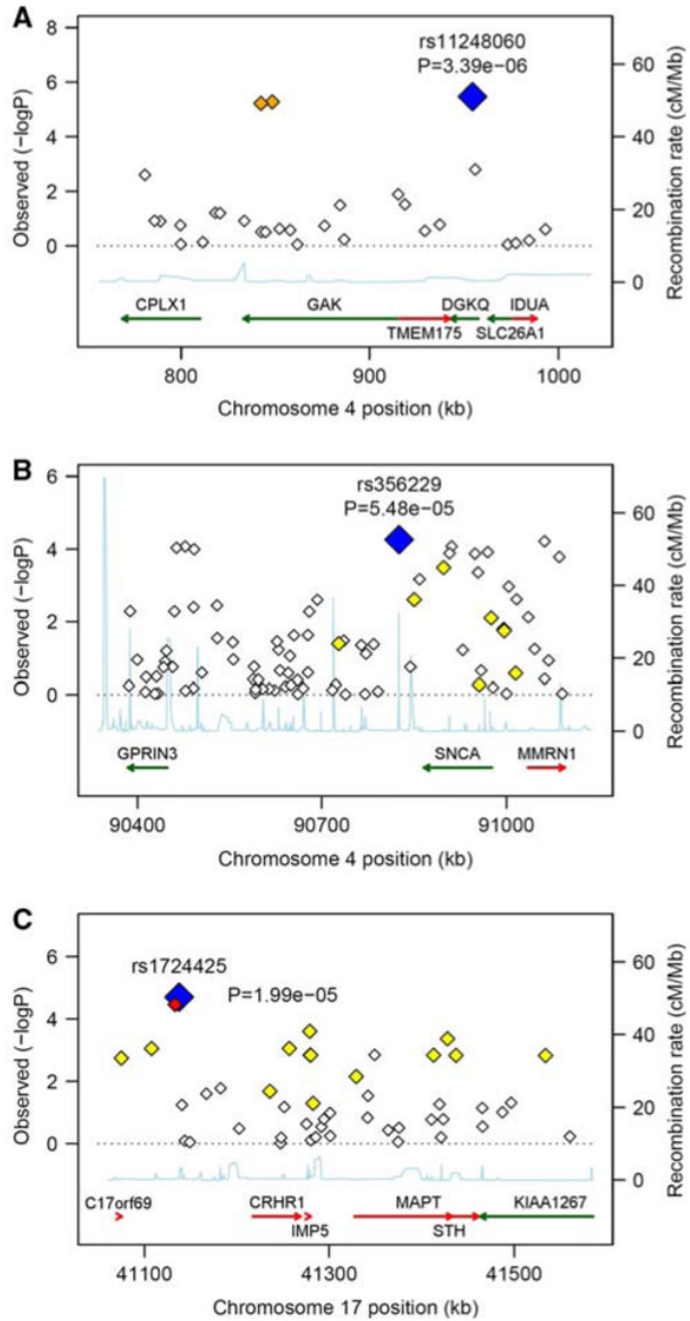


**Fig. 1.** Sample processing. Diagram of sample processing from initial receipt of samples from CIDR to the final analyzed dataset. <sup>1</sup>Samples from whole genome amplified (WGA) DNA had lower call rates, particularly near the telomeres, and for a subset of the SNPs the minor allele frequency estimates from WGA DNA differed significantly from that obtained from other sources of DNA ( $p < 1 \times 10^{-7}$  for 65 markers)





**Fig. 2.** Additive and recessive models. Results from genomewide association analysis modeling two modes of inheritance (additive and recessive). The X-axis indicates the chromosomal position of each SNP while the Y-axis denotes the evidence of association [shown as  $-\log(p \text{ value})$ ]. The line indicates the inclusion threshold for the results presented in the Tables ( $p < 10^{-4}$ )



**Fig. 3.** Evidence of association in particular chromosomal regions. Along the X-axis is the physical position in the region (in kb) with known genes shown in their orientation. The left Y-axis denotes the association test result as  $-\log(p)$  value corresponding to diamonds in the figure. The blue diamond identifies the primary SNP result labeled with an rs# and  $p$  value. The color of additional diamonds depicts the pairwise linkage disequilibrium with the primary SNP: red indicates  $r^2 > 0.8$ , orange  $0.5 < r^2 < 0.8$ , yellow  $0.2 < r^2 < 0.5$ , white  $r^2 < 0.2$ .  $r^2$  values were obtained from the control sample genotyped as part of this study using Haploview (Barrett et al. 2005). The right Y-axis indicates the recombination rate, obtained from the available HapMap data in the CEPH Caucasians, and shown within the figure by the solid blue line. **a**

Additive results around *GAK/DGKQ*; **b** additive results around *GPRIN3/SNCA/MMRN1*; **c**  
Recessive results around *C17orf69/MAPT/IMP5/STH*



**Table 2**  
Additive model: SNPs providing the strongest association results ( $p < 0.0001$ )

| #  | Gene region <sup>d</sup>     | Chr | SNP  | Minor allele     | Position <sup>b</sup>                                | MAF case                                       | MAF control                                    | Odds ratio <sup>c</sup>                    | p value  | Meta-analysis p value <sup>d</sup>   |
|----|------------------------------|-----|--|------------------|--|--|--|--|--|--|
| 1  | <i>GAK/DGKQ</i>              | 4   | <b>rs1564282</b><br>rs11248051<br><b>rs11248060</b><br>rs4811072 | T<br>T<br>T<br>G | <b>842313</b><br>848332<br><b>954359</b><br>48519524 | <b>0.131</b><br>0.132<br><b>0.145</b><br>0.291 | <b>0.087</b><br>0.087<br><b>0.097</b><br>0.238 | <b>1.70</b><br>1.70<br><b>1.69</b><br>1.40 | <b><math>6.0 \times 10^{-6}</math></b><br>$5.2 \times 10^{-6}$<br><b><math>3.4 \times 10^{-6}</math></b><br>$6.5 \times 10^{-5}$ | <b><math>6.7 \times 10^{-7}</math></b><br>$2.5 \times 10^{-7}$<br><b><math>4.7 \times 10^{-4}</math></b><br>$4.7 \times 10^{-4}$ |
| 2  | <i>COX6CP2/PTPN1</i>         | 20  | rs19197791<br>rs2654735  | G<br>A           | 48529835<br>112618062                                | 0.297<br>0.391                                 | 0.461<br>0.459                                 | 1.43<br>0.75                               | $1.9 \times 10^{-5}$<br>$9.0 \times 10^{-5}$   | $5.9 \times 10^{-5}$<br>$1.3 \times 10^{-3}$   |
| 3  | <i>LOC729075</i>             | 4   | rs1806506<br>rs11729080  | C<br>A           | 112686700<br>112723321                               | 0.386<br>0.135                                 | 0.459<br>0.187                                 | 0.74<br>0.66                               | $3.7 \times 10^{-5}$<br>$3.3 \times 10^{-5}$   | $6.3 \times 10^{-4}$<br>$1.8 \times 10^{-2}$   |
| 4  | <i>LOC727725/ZMAT4</i>       | 8   | rs4736788<br>rs10094981  | T<br>C           | 40947586<br>40950451                                 | 0.223<br>0.223                                 | 0.276<br>0.276                                 | 0.70<br>0.70                               | $4.9 \times 10^{-5}$<br>$4.8 \times 10^{-5}$   | $9.9 \times 10^{-4}$<br>$9.7 \times 10^{-4}$   |
| 5  | <i>HRNBP3</i>                | 17  | rs898528   | T                | 74678398   | 0.296  | 0.368  | 0.74                                       | $4.9 \times 10^{-5}$   | $1.7 \times 10^{-4}$   |
| 6  | <i>LAMP1</i>                 | 13  | rs12871648   | C                | 113018663  | 0.376  | 0.316  | 1.36                                       | $5.0 \times 10^{-5}$   | $9.4 \times 10^{-4}$   |
| 7  | <i>LTBP1</i>                 | 2   | rs4670322  | G                | 33309246   | 0.323  | 0.256  | 1.38                                       | $5.1 \times 10^{-5}$   | $2.0 \times 10^{-3}$   |
| 8  | Gene desert                  | 10  | rs11592212   | C                | 110407383  | 0.085  | 0.052  | 1.80                                       | $5.2 \times 10^{-5}$   | $6.5 \times 10^{-3}$   |
| 9  | <i>SNCA/GPRIN3/MMRN1</i>     | 4   | rs4106153<br>rs1504489<br>rs356229                               | C<br>T<br>G      | 90463499<br>90477611<br>90825620                     | 0.167<br>0.362<br>0.435                        | 0.219<br>0.424<br>0.369                        | 0.70<br>0.75<br>1.35                       | $9.2 \times 10^{-5}$<br>$8.4 \times 10^{-5}$<br>$5.5 \times 10^{-5}$   | $1.1 \times 10^{-3}$<br>$5.1 \times 10^{-3}$<br>$3.5 \times 10^{-4}$   |
| 10 | <i>PRDM13/MCHR2</i>          | 6   | rs356188<br>rs3775478  | G<br>G           | 90910560<br>91061863                                 | 0.177<br>0.102                                 | 0.225<br>0.069                                 | 0.70<br>1.69                               | $8.4 \times 10^{-5}$<br>$6.1 \times 10^{-5}$   | $3.5 \times 10^{-4}$<br>$1.6 \times 10^{-4}$   |
| 11 | <i>VPS8</i>                  | 3   | rs4431442  | G                | 100320236  | 0.322  | 0.262  | 1.39                                       | $5.6 \times 10^{-5}$   | $3.2 \times 10^{-3}$   |
| 12 | <i>CGRFR1/SAMD4A</i>         | 14  | rs10937194<br>rs4901519  | G<br>C           | 186201412<br>54088930                                | 0.192<br>0.115                                 | 0.241<br>0.152                                 | 0.70<br>0.65                               | $5.9 \times 10^{-4}$<br>$7.6 \times 10^{-5}$   | $6.5 \times 10^{-4}$<br>$1.3 \times 10^{-4}$   |
| 13 | <i>C17orf69/PLEKHH1/MAPT</i> | 17  | <b>rs11012</b><br>rs1724425                                      | <b>A</b><br>T    | <b>40869224</b><br>41137530                          | <b>0.143</b><br>0.387                          | <b>0.196</b><br>0.449                          | <b>0.68</b><br>0.75                        | <b><math>8.8 \times 10^{-5}</math></b><br>$7.8 \times 10^{-5}$   | <b><math>4.8 \times 10^{-5}</math></b><br>$8.2 \times 10^{-5}$   |
| 14 | <i>LEKRI</i>                 | 3   | rs12638253   | C                | 158108785  | 0.447  | 0.524  | 0.75                                       | $8.3 \times 10^{-5}$   | $5.0 \times 10^{-4}$   |
| 15 | <i>POU6F2</i>                | 7   | rs9655034  | T                | 39258636   | 0.483  | 0.414  | 1.33                                       | $8.8 \times 10^{-5}$   | $5.1 \times 10^{-4}$   |
| 16 | <i>TMEM108</i>               | 3   | rs1197313  | T                | 134583142  | 0.393  | 0.451  | 0.75                                       | $8.9 \times 10^{-5}$   | $3.8 \times 10^{-4}$   |
| 17 | <i>LOC728328/PCTK2</i>       | 12  | rs7312607  | C                | 93550301   | 0.487  | 0.434  | 1.33                                       | $9.3 \times 10^{-5}$   | .  |
| 18 | <i>FGF12</i>                 | 3   | rs9859577  | T                | 193571219  | 0.125  | 0.172  | 0.67                                       | $9.9 \times 10^{-5}$   | .  |
| 19 | <i>LOC652429/TMEM132B</i>    | 12  | rs2108521  | C                | 124901417  | 0.219  | 0.271  | 0.72                                       | $1.0 \times 10^{-4}$   | $4.4 \times 10^{-4}$   |

*bold* indicates entries where results from the meta-analysis had smaller  $p$  values than the initial results from this study. *a period* (.) indicates that the marker was not genotyped in the Fung et al. study, a "gene desert" is defined here as being more than 500 kb from any gene listed in RefSeq

<sup>a</sup> Genes taken from the NCBI mRNA reference sequences collection (RefSeq)

<sup>b</sup> From NCBI Build 36 reference

<sup>c</sup> Odds ratios were computed for the minor allele

<sup>d</sup> Meta-analysis with Fung et al.

**Table 3** Recessive model: SNPs providing the strongest association results ( $p < 0.0001$ )

| #  | Gene region <sup>a</sup>       | Chr | SNP              | Minor allele | Position <sup>b</sup> | MAF case     | MAF control  | Odds ratio <sup>c</sup> | p value                                | Meta-analysis p value <sup>d</sup>     |
|----|--------------------------------|-----|------------------|--------------|-----------------------|--------------|--------------|-------------------------|--|--|
| 1  | <i>C17orf69/MAPT</i>           | 17  | rs1724422        | G            | 41133096              | 0.403        | 0.462        | 0.58                    | $3.4 \times 10^{-5}$                   | $6.0 \times 10^{-5}$                   |
| 2  | <i>F5HR</i>                    | 2   | <b>rs1724425</b> | T            | <b>41137530</b>       | <b>0.387</b> | <b>0.449</b> | <b>0.56</b>             | <b><math>2.0 \times 10^{-5}</math></b> | <b><math>9.8 \times 10^{-6}</math></b> |
| 3  | <i>PIK3CD</i>                  | 1   | rs7578654        | C            | 49363677              | 0.470        | 0.423        | 1.73                    | $3.1 \times 10^{-5}$                   | $9.3 \times 10^{-4}$                   |
| 4  | <i>LOC728284/F11</i>           | 4   | <b>rs4240910</b> | C            | <b>9673044</b>        | <b>0.515</b> | <b>0.449</b> | <b>1.65</b>             | <b><math>3.9 \times 10^{-5}</math></b> | <b><math>5.4 \times 10^{-6}</math></b> |
| 5  | Gene desert                    | 1   | rs2889188        | G            | 187552805             | 0.268        | 0.233        | 2.49                    | $4.3 \times 10^{-5}$                   | $5.1 \times 10^{-4}$                   |
|    |                                |     | rs11184419       | C            | 105439944             | 0.333        | 0.362        | 0.53                    | $5.3 \times 10^{-5}$                   | $3.1 \times 10^{-4}$                   |
|    |                                |     | rs4128942        | C            | 105447249             | 0.331        | 0.362        | 0.52                    | $4.8 \times 10^{-5}$                   | $2.7 \times 10^{-4}$                   |
| 6  | GPXP2                          | 21  | rs969988         | A            | 27474523              | 0.469        | 0.421        | 1.71                    | $6.2 \times 10^{-5}$                   | $5.1 \times 10^{-4}$                   |
| 7  | <b><i>LOC643954/HS3ST5</i></b> | 6   | <b>rs1519686</b> | T            | <b>114553816</b>      | <b>0.245</b> | <b>0.223</b> | <b>2.62</b>             | <b><math>7.1 \times 10^{-5}</math></b> | <b><math>4.4 \times 10^{-5}</math></b> |
| 8  | <i>SYT4/RIT2</i>               | 18  | rs4890430        | A            | 38951528              | 0.447        | 0.387        | 1.72                    | $7.1 \times 10^{-5}$                   | $7.4 \times 10^{-5}$                   |
| 9  | <i>FIGN</i>                    | 2   | <b>rs2083482</b> | A            | <b>164146021</b>      | <b>0.504</b> | <b>0.465</b> | <b>1.62</b>             | <b><math>7.6 \times 10^{-5}</math></b> | <b><math>6.8 \times 10^{-6}</math></b> |
| 10 | SYN3                           | 22  | rs1159220        | T            | 31410753              | 0.391        | 0.423        | 0.58                    | $8.2 \times 10^{-5}$                   | $4.7 \times 10^{-2}$                   |
|    |                                |     | rs3788483        | C            | 31414345              | 0.393        | 0.425        | 0.58                    | $9.1 \times 10^{-5}$                   | $4.9 \times 10^{-2}$                   |
| 11 | <i>LOC283398/TMCC3</i>         | 12  | rs10859725       | C            | 93468003              | 0.206        | 0.173        | 2.93                    | $8.5 \times 10^{-5}$                   | .                                      |
| 12 | <i>CDC2L6</i>                  | 6   | rs6912010        | A            | 111003337             | 0.283        | 0.245        | 2.18                    | $9.2 \times 10^{-5}$                   | $1.9 \times 10^{-3}$                   |
| 13 | <i>LOC728637/ACSL6</i>         | 5   | rs1355095        | G            | 131276668             | 0.165        | 0.211        | 0.23                    | $9.4 \times 10^{-5}$                   | $5.4 \times 10^{-4}$                   |
| 14 | <i>LOC651011/OXSM/NGLY1</i>    | 3   | rs9310784        | C            | 25905208              | 0.403        | 0.462        | 0.20                    | $1.0 \times 10^{-4}$                   | $6.0 \times 10^{-5}$                   |

*Bold* indicates entries where results from the meta-analysis had smaller  $p$  values than the initial results from this study, *a period* (.) indicates that the marker was not genotyped in the Fung et al. study, a “gene desert” is defined here as being more than 500 kb away from any gene listed in RefSeq

<sup>a</sup> Genes taken from the NCBI mRNA reference sequences collection (RefSeq)

<sup>b</sup> From NCBI Build 36 reference

<sup>c</sup> Odds ratios were computed for the minor allele

<sup>d</sup> Meta-analysis with Fung et al.

**Table 4**  
 Meta-analysis—additive model: SNPs providing the strongest association results ( $p < 0.0001$ )

| #  | Gene region <sup>a</sup>       | Chr | SNP        | Minor allele | Position <sup>b</sup> | MAF case | MAF control | Odds ratio <sup>c</sup> | p value              | Meta-analysis p value <sup>d</sup> |
|----|--------------------------------|-----|------------|--------------|-----------------------|----------|-------------|-------------------------|----------------------|------------------------------------|
| 1  | DGKQ/GAK                       | 4   | rs1564282  | T            | 842313                | 0.131    | 0.087       | 1.70                    | $6.0 \times 10^{-6}$ | $6.7 \times 10^{-7}$               |
| 2  | LOC728667/C14orf165            | 4   | rs11248060 | T            | 954359                | 0.145    | 0.097       | 1.69                    | $3.4 \times 10^{-6}$ | $2.5 \times 10^{-7}$               |
| 3  | LOC387882                      | 14  | rs12050360 | T            | 23372513              | 0.195    | 0.247       | 0.73                    | $4.2 \times 10^{-4}$ | $9.7 \times 10^{-6}$               |
| 4  | PIK3CD                         | 12  | rs11112522 | G            | 104345578             | 0.136    | 0.181       | 0.72                    | $8.1 \times 10^{-4}$ | $1.3 \times 10^{-5}$               |
| 5  | GRB10                          | 1   | rs4240910  | C            | 9673044               | 0.515    | 0.449       | 1.31                    | $2.3 \times 10^{-4}$ | $1.6 \times 10^{-5}$               |
| 6  | LY75/PLA2R1                    | 7   | rs1978208  | G            | 50752942              | 0.161    | 0.197       | 0.75                    | $2.2 \times 10^{-3}$ | $1.6 \times 10^{-5}$               |
|    |                                | 2   | rs12692575 | G            | 160478277             | 0.250    | 0.197       | 1.34                    | $7.9 \times 10^{-4}$ | $2.3 \times 10^{-5}$               |
|    |                                | 2   | rs1995950  | G            | 160508874             | 0.243    | 0.193       | 1.33                    | $1.4 \times 10^{-3}$ | $4.4 \times 10^{-5}$               |
|    |                                | 2   | rs3792161  | T            | 160517469             | 0.244    | 0.194       | 1.33                    | $1.4 \times 10^{-3}$ | $2.9 \times 10^{-5}$               |
|    |                                | 2   | rs1511217  | C            | 160523339             | 0.245    | 0.194       | 1.33                    | $1.3 \times 10^{-3}$ | $3.3 \times 10^{-5}$               |
| 7  | SH3GL2                         | 9   | rs2145656  | C            | 17598784              | 0.213    | 0.172       | 1.36                    | $9.5 \times 10^{-4}$ | $3.0 \times 10^{-5}$               |
| 8  | CAST                           | 5   | rs1559085  | C            | 96104458              | 0.159    | 0.117       | 1.46                    | $4.9 \times 10^{-4}$ | $3.8 \times 10^{-5}$               |
| 9  | DHFRP1                         | 2   | rs7586694  | A            | 82511859              | 0.299    | 0.338       | 0.77                    | $1.0 \times 10^{-3}$ | $7.9 \times 10^{-5}$               |
|    |                                | 2   | rs1549582  | C            | 82542491              | 0.301    | 0.340       | 0.77                    | $9.3 \times 10^{-4}$ | $4.5 \times 10^{-5}$               |
|    |                                | 2   | rs2902376  | G            | 82644916              | 0.270    | 0.306       | 0.78                    | $1.7 \times 10^{-3}$ | $7.5 \times 10^{-5}$               |
|    |                                | 2   | rs7608203  | G            | 82706135              | 0.266    | 0.300       | 0.78                    | $2.3 \times 10^{-3}$ | $8.3 \times 10^{-5}$               |
|    |                                | 2   | rs6731289  | A            | 82746305              | 0.228    | 0.270       | 0.75                    | $5.8 \times 10^{-4}$ | $3.9 \times 10^{-5}$               |
| 10 | C17orf69/PLEKHM1/MAPT/IMP5/STH | 17  | rs11012    | A            | 40869224              | 0.143    | 0.196       | 0.68                    | $8.8 \times 10^{-5}$ | $4.8 \times 10^{-5}$               |
|    |                                | 17  | rs393152   | G            | 41074926              | 0.178    | 0.230       | 0.72                    | $2.4 \times 10^{-4}$ | $1.1 \times 10^{-4}$               |
|    |                                | 17  | rs1724425  | T            | 41137530              | 0.387    | 0.449       | 0.75                    | $7.8 \times 10^{-5}$ | $8.2 \times 10^{-5}$               |
|    |                                | 17  | rs12185268 | G            | 41279463              | 0.176    | 0.228       | 0.71                    | $1.9 \times 10^{-4}$ | $1.1 \times 10^{-4}$               |
|    |                                | 17  | rs12373139 | A            | 41279910              | 0.175    | 0.228       | 0.71                    | $1.5 \times 10^{-4}$ | $4.2 \times 10^{-5}$               |
|    |                                | 17  | rs1981997  | A            | 41412603              | 0.176    | 0.229       | 0.71                    | $1.6 \times 10^{-4}$ | $1.1 \times 10^{-4}$               |
|    |                                | 17  | rs8070723  | G            | 41436901              | 0.177    | 0.229       | 0.71                    | $1.6 \times 10^{-4}$ | $1.1 \times 10^{-4}$               |
|    |                                | 20  | rs1997791  | G            | 48529835              | 0.297    | 0.238       | 1.43                    | $1.9 \times 10^{-5}$ | $5.9 \times 10^{-5}$               |
| 11 | COX6CP2/PTPNI                  | 10  | rs2151173  | A            | 36911902              | 0.129    | 0.092       | 1.48                    | $7.3 \times 10^{-4}$ | $6.2 \times 10^{-5}$               |
| 12 | LOC646309                      | 15  | rs8041610  | C            | 24559357              | 0.304    | 0.357       | 0.75                    | $1.6 \times 10^{-4}$ | $6.4 \times 10^{-5}$               |
| 13 | GABRB3                         | 5   | rs3756616  | T            | 179333453             | 0.339    | 0.396       | 0.76                    | $4.3 \times 10^{-4}$ | $6.5 \times 10^{-5}$               |
| 14 | RNF130                         | 14  | rs8021486  | A            | 43803554              | 0.225    | 0.179       | 1.39                    | $2.3 \times 10^{-4}$ | $6.9 \times 10^{-5}$               |
| 15 | YWHAZP                         | 15  | rs4476132  | C            | 92937185              | 0.347    | 0.296       | 1.31                    | $5.7 \times 10^{-4}$ | $7.7 \times 10^{-5}$               |
| 16 | MCTP2                          | 19  | rs7245958  | G            | 37673142              | 0.121    | 0.088       | 1.54                    | $2.7 \times 10^{-4}$ | $9.0 \times 10^{-5}$               |
| 17 | DPIY19L3                       | 20  | rs6045766  | G            | 18947826              | 0.413    | 0.357       | 1.28                    | $8.6 \times 10^{-4}$ | $9.2 \times 10^{-5}$               |
| 18 | C20orf79/SLC24A3               | 6   | rs9275184  | C            | 32762692              | 0.077    | 0.107       | 0.64                    | $3.2 \times 10^{-4}$ | $9.5 \times 10^{-5}$               |
| 19 | HLA-DQB1                       | 6   | rs884742   | T            | 160727422             | 0.494    | 0.448       | 1.21                    | $7.8 \times 10^{-3}$ | $9.5 \times 10^{-5}$               |
| 20 | SLC22A3                        | 7   | rs6957669  | A            | 138038319             | 0.243    | 0.194       | 1.38                    | $2.9 \times 10^{-4}$ | $9.5 \times 10^{-5}$               |
| 21 | LOC647123                      | 20  | rs6129005  | T            | 59022667              | 0.305    | 0.345       | 0.78                    | $1.3 \times 10^{-3}$ | $9.6 \times 10^{-5}$               |
| 22 | LOC731917/CDH4                 | 8   | rs39765    | A            | 90872865              | 0.376    | 0.321       | 1.30                    | $6.0 \times 10^{-4}$ | $9.7 \times 10^{-5}$               |
| 23 | RIPK2                          |     |            |              |                       |          |             |                         |                      |                                    |

<sup>a</sup> Genes taken from the NCBI mRNA reference sequences collection (RefSeq)

<sup>b</sup> From NCBI Build 36 reference

<sup>c</sup> Odds ratios were computed for the minor allele

<sup>d</sup> Meta-analysis with Fung et al.

**Table 5** Meta-analysis—recessive model: SNPs providing the strongest association results ( $p < 0.0001$ )

| #  | Gene region <sup>a</sup> | Chr | SNP        | Minor allele | Position <sup>b</sup> | MAF case | MAF control | Odds ratio <sup>c</sup> | p value              | Meta-analysis p value <sup>d</sup> |
|----|--------------------------|-----|------------|--------------|-----------------------|----------|-------------|-------------------------|----------------------|------------------------------------|
| 1  | <i>PIK3CD</i>            | 1   | rs4240910  | C            | 9673044               | 0.515    | 0.449       | 1.65                    | $3.9 \times 10^{-5}$ | $5.4 \times 10^{-6}$               |
| 2  | <i>FIGN</i>              | 2   | rs2083482  | A            | 164146021             | 0.504    | 0.465       | 1.62                    | $7.6 \times 10^{-5}$ | $6.8 \times 10^{-6}$               |
| 3  | <i>C17orf69/MAPT</i>     | 17  | rs1724422  | G            | 41133096              | 0.403    | 0.462       | 0.58                    | $3.4 \times 10^{-5}$ | $6.0 \times 10^{-5}$               |
| 4  | <i>MYBBP1A</i>           | 17  | rs1724425  | T            | 41137530              | 0.387    | 0.449       | 0.56                    | $2.0 \times 10^{-5}$ | $9.8 \times 10^{-6}$               |
| 5  | <i>LOC643954/HSS3T5</i>  | 6   | rs3816686  | G            | 4401915               | 0.227    | 0.196       | 2.83                    | $3.1 \times 10^{-5}$ | $3.1 \times 10^{-5}$               |
| 6  | <i>LOC387941/SOX21</i>   | 6   | rs11752866 | C            | 114455213             | 0.338    | 0.302       | 1.96                    | $1.2 \times 10^{-4}$ | $7.2 \times 10^{-5}$               |
| 7  | <i>DHFRP1</i>            | 13  | rs1519686  | T            | 114553816             | 0.245    | 0.223       | 2.62                    | $7.1 \times 10^{-5}$ | $4.4 \times 10^{-5}$               |
|    |                          | 13  | rs9524596  | G            | 94166840              | 0.417    | 0.450       | 0.69                    | $4.1 \times 10^{-3}$ | $4.4 \times 10^{-5}$               |
|    |                          | 2   | rs1549582  | C            | 82542491              | 0.301    | 0.340       | 0.53                    | $2.5 \times 10^{-4}$ | $4.5 \times 10^{-5}$               |
|    |                          | 2   | rs7586694  | A            | 82511859              | 0.299    | 0.338       | 0.52                    | $2.1 \times 10^{-4}$ | $8.7 \times 10^{-5}$               |
|    |                          | 2   | rs1365951  | T            | 82519187              | 0.341    | 0.375       | 0.59                    | $6.9 \times 10^{-4}$ | $7.7 \times 10^{-5}$               |
| 8  | <i>ZNF345</i>            | 19  | rs826278   | A            | 42058972              | 0.313    | 0.296       | 1.78                    | $1.4 \times 10^{-3}$ | $5.4 \times 10^{-5}$               |
| 9  | <i>FLJ46257</i>          | 22  | rs386300   | G            | 46488923              | 0.349    | 0.365       | 0.59                    | $7.7 \times 10^{-4}$ | $5.4 \times 10^{-5}$               |
| 10 | <i>LOC728274</i>         | 4   | rs4974767  | A            | 4031034               | 0.446    | 0.407       | 1.46                    | $3.8 \times 10^{-3}$ | $5.5 \times 10^{-5}$               |
| 11 | <i>LOC730572/RIPK2</i>   | 8   | rs39770    | T            | 90905380              | 0.393    | 0.337       | 1.68                    | $7.5 \times 10^{-4}$ | $6.0 \times 10^{-5}$               |
| 12 | <i>MAP3K7</i>            | 6   | rs1498249  | C            | 92586434              | 0.183    | 0.166       | 2.91                    | $1.8 \times 10^{-4}$ | $8.7 \times 10^{-5}$               |
|    |                          | 6   | rs2454275  | C            | 92605303              | 0.183    | 0.166       | 2.98                    | $1.7 \times 10^{-4}$ | $6.3 \times 10^{-5}$               |
| 13 | <i>SYT4/RIT2</i>         | 18  | rs4890430  | A            | 38951528              | 0.447    | 0.387       | 1.72                    | $7.1 \times 10^{-5}$ | $7.4 \times 10^{-5}$               |
|    |                          | 18  | rs1878680  | C            | 38979393              | 0.396    | 0.345       | 1.71                    | $4.4 \times 10^{-4}$ | $2.0 \times 10^{-4}$               |
| 14 | <i>SBF2</i>              | 11  | rs780382   | A            | 9838051               | 0.363    | 0.411       | 0.63                    | $1.5 \times 10^{-3}$ | $7.6 \times 10^{-5}$               |
| 15 | <i>FNDC1</i>             | 6   | rs12526577 | G            | 159554596             | 0.470    | 0.427       | 1.61                    | $2.2 \times 10^{-4}$ | $7.7 \times 10^{-5}$               |
| 16 | <i>HS322B1A</i>          | 22  | rs140289   | T            | 22666327              | 0.266    | 0.231       | 2.41                    | $1.2 \times 10^{-4}$ | $8.8 \times 10^{-5}$               |
| 17 | <i>CLECL3</i>            | 12  | rs521040   | G            | 10039117              | 0.266    | 0.279       | 0.49                    | $3.5 \times 10^{-4}$ | $8.9 \times 10^{-5}$               |
| 18 | <i>PDCL3</i>             | 2   | rs4261746  | A            | 100588062             | 0.459    | 0.428       | 1.47                    | $3.0 \times 10^{-3}$ | $9.8 \times 10^{-5}$               |

<sup>a</sup> Genes taken from the NCBI mRNA reference sequences collection (RefSeq)

<sup>b</sup> From NCBI Build 36 reference

<sup>c</sup> Odds ratios were computed for the minor allele

<sup>d</sup> Meta-analysis with Fung et al.