Comprehensive research synopsis and systematic meta-analyses in Parkinson's disease genetics: The PDGene database

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Text S1 (Supplementary material)

Supplementary Methods

Literature Searches

Inclusion criteria: For inclusion in PDGene, a study has to meet three criteria:
1) It must evaluate the association between a bi-allelic genetic polymorphism (minor allele frequency [MAF] ≥0.01 in the healthy control population of at least one study) and Parkinson's disease (PD) risk in datasets comprised of both affected (defined as clinically and/or neuropathologically diagnosed "Parkinson's disease") and unaffected individuals.
2) It must be published in a peer-reviewed journal. This criterion specifically excludes studies reported only in abstract format, e.g. at scientific meetings.
3) The study must be published in English.
Exclusion criteria: While studies using family-based methods were included in the qualitative gene summary pages on PDGene, genotype distributions were excluded from the statistical analyses (except when raw genotype data were available, which was applicable for the LEAPS GWAS) [1]. Of note, case-control studies that were enriched for family history were not excluded. Genetic association studies published in non-English studies were excluded due to practical reasons. The percentage of published non-English genetic association studies in PD is small, and more than half of these non-English papers are also published in an English language journal (and hence included in PDGene if there were otherwise eligible). For instance, an exploratory Pubmed search for all PD genetic association papers published between 2009 and 2010 yielded a total of two potentially eligible, non-English publications [2,3] (out of 177), thus representing ~1% of all studies published during this time period. Furthermore, based on the content of the abstracts, the same authors had previously reported identical or largely overlapping results in an English journal [4,5]. Studies examining genotype-phenotype correlations in PD subjects only (but not examining "healthy" controls), or studies exclusively using PD dementia as their "case" definition were not included. Whenever a sample contains patients suffering from both PD with and without dementia, only data on PD subjects without dementia were utilized if they were given separately for this group. Studies using only "diseased" controls, e.g. hospital-based controls suffering from other diseases, were excluded. Studies on polymorphisms with three or more alleles were usually excluded from the meta-analyses. Proxy SNPs, i.e. SNPs tagging other variants, were generally not combined in the meta-analysis due to potentially different linkage disequilibrium patterns across different populations and ethnicities. An exception was made for the *MAPT* H1H2 haplotype, where frequencies were determined based on tagging-variants (mostly SNPs) as described in the original publications. However, this excluded tagging microsatellites. Variants in mitochondrial DNA tested in association studies were included in the qualitative gene summaries on PDGene but were not subjected to meta-analysis because of the multicopy nature of the mitochondrial genome, and the high frequency of somatic mutation events that vary substantially across tissues [6], which may introduce a potential bias into the meta-analyses. Studies using a "pooled DNA approach" were included in the qualitative gene summary pages on PDGene, but data were excluded from the PDGene meta-analyses. For exclusion criteria of data from analyses due to errors in study conduct or presentation, please see the section about additional quality control below.
Search strategies: To identify potential association studies eligible for inclusion in PDGene, we performed a PubMed search using the terms "parkinson* AND associat*" before January 1st 2007, and performed daily searches for "parkinson*" thereafter until March 31st 2011. This search yielded 27,210 articles, which were screened for eligibility using the title, abstract, or full-paper, as necessary. Additional screening of bibliographies in reviews, published meta-analyses, and original genetic association studies were also performed. Overall, full text versions of 1,534 articles were obtained. Following the inclusion and exclusion criteria outlined above, 828 articles were included in PDGene until March 31st 2011 (also see Figure 1).

Data Management

Demographic variables: Details extracted for each included study consisted of the first author name, year of publication, and PubMed-identifier, along with key population-specific details extracted from each study (if provided), such as ascertainment design (family-based or case-control), ethnic background and population (i.e. country) of origin, as well as source (clinic-, or population-based) of the samples, the number of cases with gender ratio, age at onset, age at examination, and method of diagnosis (see below), the number of controls with gender ratio and age at examination, and the reported study results. All data were first entered into a local, offline database, after which all entries were double-checked by an independent member of our group against the original publications.
Genetic association data: Whenever possible, "dbSNP" identifiers ("rs-ID") were used to designate polymorphism identity throughout the database. If these were not specified in the original articles, we attempted to resolve rs-IDs using bioinformatics tools such as NCBI's "BLAST" (http://www.ncbi.nlm.nih.gov/BLAST/) and Ensembl (http://www.ensembl.org/index.html), which allowed us to determine rs-IDs for ~80% of all polymorphisms initially not published with an rs-ID. If an rs-ID

could not be determined unequivocally, we adopted the most commonly used nomenclature of the primary publications. Genotype distributions or published allelic odds ratios (ORs) and confidence intervals (CIs) were extracted for each polymorphism from the publications where provided. Published allelic ORs and CIs were used if they were calculated either without adjustment for covariates, or if they had been adjusted for age and/or sex and/or for population substructure, and/or corrected for genomic inflation; effect size estimates based on adjustment for other covariates were not included. In cases where allele frequencies, but not genotype distributions or allelic ORs, were presented in a publication, genotype distributions were calculated from reported allele frequencies and sample sizes (assuming no violation of Hardy Weinberg equilibrium [HWE] unless reported otherwise in the original paper). First and last authors of studies with missing genetic association data were generally contacted twice via e-mail and asked to supply their genotype/allele distributions for the investigated polymorphisms.

Additional quality control of genetic association data: Potential errors in study conduct and reporting of results (e.g. erroneous genotyping/sequencing protocols, genotype/allele counts that did not match the effective sample size provided in the demographic description of the respective publications, allele mismatches, erroneous rs-identifiers, etc.) were carefully investigated by cross-checking of relevant data extracted from the publications, and, where applicable, by automated comparison to public databases (NCBI's dbSNP [http://www.ncbi.nlm.nih.gov/sites/entrez], UCSC Genome Browser [http://genome.ucsc.edu/]). Deviations from allele frequencies in controls of more than 10% in comparison to ethnicity-specific allele frequency data of the International HapMap Consortium and 1000G were flagged as a potential error. Upon identification of these and other potential errors, the authors of the respective publications were generally contacted for clarification. In rare events, the discrepancies could not be resolved, the study was included in the qualitative overview pages on PDGene, but data were excluded from the meta-analyses. For studies reporting association results on polymorphisms without providing NCBI's rs-identifiers or applying non-commercial, custom-made genotyping and sequencing protocols, the genotyping protocol was carefully re-evaluated by comparison to the appropriate human reference sequence, and, as outlined above, the investigated variant was assigned an existing rs-identifier, if available.

Duplicate publications: In many cases, authors report the same association results in identical or largely overlapping samples in separately published articles. Whenever such overlap between two (or more) studies was evident by information provided in the original publication, or suspected overlap was confirmed by the authors, duplicate or overlapping datasets were excluded from the meta-analyses. Where possible the dataset with the largest sample size was included in the meta-analysis. Data on additional polymorphisms provided in the overlapping studies that were not investigated in the other study were still included in the respective meta-analyses.

Large-scale association studies. The extent of data integration from large-scale genotyping studies (e.g. GWAS) was based on the availability of the data. Whenever possible, individual-level data was obtained (via NCBI's "dbGaP" database), and study-specific ORs determined after data-cleaning and adjustment for age, sex and population stratification (outlined below). In cases where only summary-level genotype data were available (e.g. the extended "NINDS/Germany" sample, see below), we used the allelic ORs and 95% CIs supplied by the original investigators. If neither individual-level or summary-level genome-wide genotype data were available, we extracted as much of the data as possible from the primary publications. Generally, preference was given to include allelic ORs and CIs adjusted for population stratification as reported in the primary publications. If these were not available or not eligible, crude ORs were calculated from the provided genotype/allele summary data.

Statistical Analyses:

Statistical analysis for this manuscript were performed in SAS v9.2, the PLINK toolset v1.07 [7] and the R programming language, version 2.10.0, using packages HardyWeinberg, version 1.4 and rmeta, version 2.16, with the exception of the GWAS-only meta-analyses (see below).

Meta-analyses: For all variants with minor allele frequencies>0.01 in at least one control population meeting our inclusion criteria (see above) crude study-specific ORs and 95% CIs were calculated for each dataset using allelic contrasts (usually comparing minor vs. major allele). For studies with no available genotype or allele distributions, we used allelic ORs and CIs as given in the original publication where provided. Random-effects allelic meta-analyses [8] were performed if a minimum of four independent datasets existed per polymorphism. This procedure was first performed on all studies irrespective of ethnicity. Summary ORs and 95% CIs were also calculated for studies of distinct ethnic groups, i.e. Caucasians, and Asians, if three or more such studies exist.

Sensitivity analyses and between-study heterogeneity: Sensitivity analysis entailed calculating summary ORs and 95% CIs for all studies after excluding the initial report, and after excluding smaller-scale studies that violated HWE according to a chi-square test implemented in the "HardyWeinberg" R package at $p \leq 0.05$. In case of cell counts below 5 Fisher's exact test was used instead of the chi-square test. Between-study heterogeneity was assessed by calculating the I^2 heterogeneity metric. I^2 is estimated based on the Q

statistic (Q-(df)/Q), and it takes values from 0 to 100% that show the extent of the heterogeneity that is beyond chance. In contrast to Q, which cannot be compared across meta-analyses with different numbers of studies, I^2 is comparable regardless of the number of studies meta-analyzed. Generally values above 50% are considered to represent large heterogeneity [9,10]. When there are only few studies, both Q and I^2 carry considerable uncertainty and should be interpreted cautiously [11].

Evaluating the credibility of significant associations: Each nominally significant meta-analysis result was assessed based on two different approaches:

1) Calculation of Bayes factors (BF): BFs were calculated assuming an average non-null odds ratio of 1.15 as approximation of a typical "complex disease effect size" based on a spike and smear prior distribution of effects [12], and expressed as the ratio of the probability of H1 vs. H0. That is, the higher the BF, the higher the odds that H1 is true vs. H0, while a BF of 1 suggests that both hypotheses are equally likely. BFs are expressed as $\log_{10}$(BF) (abbreviated as "logBF") throughout our paper. Generally, a logBF≥5, which suggests that the data increase over 100,000-fold the odds of a given finding being true vs. not true, is considered as "sufficiently convincing" support in the context of genetic association studies [13].

2) Grading based on Human Genome Epidemiology Network (HuGENet) interim criteria for the assessment of cumulative evidence of genetic associations [14,15]. These criteria take into account "amount of evidence" (i.e. sample size, measured as "N minor"), "consistency of replication" (i.e. heterogeneity across studies, measured as "I^2"), and "protection from bias" ("Bias reason"). For amount of evidence, grade A is when the total number of minor alleles of cases and controls combined in the meta-analyses exceeds 1000, B when it is between 100 and 1000, and C when it is less than 100. Consistency of replication, was assessed by determining the I^2 heterogeneity metric (see above). I^2 point estimates<25% obtain grade A, values of 25-50% are rated grade B, and I^2 exceeding 50% is rated C. This criterion does not apply to meta-analyses with a *P*-value<$1x10^{-7}$ after exclusion of the initial studie(s), as described in Khoury et al, 2009 [15]. For protection from bias, the following potential reasons for bias in the meta-analysis results are systematically assessed: summary OR<1.15 ("Low OR"), loss of significance after exclusion of first study ("F", see above), loss of significance after exclusion of studies violating HWE in control populations ("HWE", see above), evidence for publication/small-study bias using a modified regression test ("Regr") [16]. If none of the latter conditions are met grade "A" is assigned, otherwise grade "C". This criterion does not apply to meta-analyses with a *P*-value<$1x10^{-7}$ (including all data for prospective analyses, e.g. GWAS, and after exclusion of the initial studie(s) for retrospective analyses), as described in Khoury et al, 2009 [15]. The overall epidemiological credibility is graded as "A" (=strong) if associations received three A grades, "B" (=moderate) if they received at least one B grade but no C grades, and "C" (=weak) if they received a C grade in any of the three assessment criteria.

GWAS-only meta-analyses

Datasets: Three independent sets of individual-level and/or summary genotype data were obtained via the dbGaP repository (http://www.ncbi.nlm.nih.gov/gap) and used in the GWAS meta-analyses. The **first dataset** contained individual-level genotype data from the "Mayo-Perlegen Linked Efforts to Accelerate Parkinson's Solutions (hereafter referred to as "LEAPS") Collaboration" (phs000048.v1.p1; health research consent; embargo release March 3, 2008) [1]. Genotyping was performed using a Perlegen platform (198,345 SNPs). This family-based dataset consists of 443 discordant sibling pairs (DSP; prior to data cleaning), such that each sibling pair has one member affected with PD and one unaffected. **The second dataset** is part of the National Institute of Neurological Disorders and Stroke-Genome-Wide Genotyping in Parkinson's Disease (hereafter referred to as "NINDS") [17]. Genotyping was performed using HumanHap550 BeadChips (Illumina, Inc.). For this study, individual-level genotype data for subjects from the United States were available on dbGaP under accession phs000089.v3.p2 ("Individual genotype-calls of common SNP loci"; consent group: general research use; embargo release: April 09, 2010) for 545,066 SNPs in a total of 940 PD cases and 801 controls (prior to data cleaning). This dataset was used for genome-wide genotype imputation after data cleaning (see below). The investigators also released genotype summary data for 463,185 SNPs in a larger sample comprising 1,713 PD cases and 3,978 controls from the United States and Germany (hereafter referred to as "NINDS/Germany"; accession pha002868.1 [Analysis data files for associations between genotype and phenotype variables; consent group: general research use; embargo release: January 11, 2010]) [17]. Quality control filtering for these data was performed by the GWAS investigators prior to release of the data. Since this latter sample was considerably larger than phs000089.v3.p2, we used the ORs provided by the GWAS investigators in the GWAS meta-analyses where applicable, i.e. for SNPs with data in the US-only and US/Germany datasets, results from the latter were used. The **third dataset** contained individual-level genotype data from the "Parkinson's Research: The Organized Genetics Initiative (PROGENI)" and "Genome-wide scan for Parkinson's disease" (GenePD) Initiative (hereafter referred to as "PROGENI/GenePD", phs000126.v1.p1; general research use and Parkinson's Disease and related disorders consent groups, embargo release February 13, 2009) [18]. Genotypes from the Illumina HumanCNV 370v1 (344,301 SNPs) were available on 900 PD cases and 867 controls (prior to data cleaning).

Data Cleaning: Data cleaning was performed with the PLINK toolset v1.07 [7]. Duplicate and related samples: Prior to any analysis, we excluded samples found to overlap or to represent either 1st or 2nd degree relatives within or across the NINDS (n=19 samples) and PROGENI/GenePD (n=10 samples) datasets (provided by Drs. N. Pankratz and T. Foroud). Subsequent genome-wide pairwise IBS estimation on the combined NINDS and PROGENI/GenePD datasets confirmed that no sample pairs existed in the resulting dataset with PI-HAT values>0.2. No overlapping or related samples were found between LEAPS and the other two datasets. Genotyping quality: The remaining samples were cleaned on the basis of genotyping efficiency and quality by excluding all SNPs with a MAF<0.01, missing rates>2%, or HWE violations with *P*-values<$1x10^{-6}$. In addition, individual samples with genotyping efficiency<95% were excluded. This resulted in 149,817 (across 433 PD and 428 controls), 508,861 (931 PD, 790 controls), and 328,529 (888 PD, 857 controls) analyzable SNPs from the LEAPS, NINDS, PROGENI/GenePD datasets, respectively. Outlier detection and population stratification: For the two case-control datasets (NINDS, PROGENI/GenePD) we used genome-wide pairwise IBS estimations to determine outlying samples, and multidimensional scaling (MDS) to create a set of MDS co-variates for adjustment for population stratification in the subsequent genetic association analyses. First, we determined a set of low-LD SNPs from each GWAS dataset (using the "indep-pairwise" command in PLINK on windows of 100 SNPs, a stepsize of 5 and maximum r^2 threshold of 0.2). This resulted in 109,114 and 86,516 SNPs for the NINDS and PROGENI/GenePD datasets, respectively. Second, we determined outlying samples by identifying the five nearest neighbors of each sample based on pairwise IBS distances (using the "neighbor" command in PLINK) and excluded samples deviating -4 or more standard deviations, i.e. 23 and 9 samples in the NINDS and PROGENI/GenePD datasets, respectively. Third, we extracted MDS dimensions from the genome-wide pairwise IBS distances of the remaining samples (using the "mds-plot" option in PLINK). The first two MDS dimensions from these analyses were used to account for population stratification in the subsequent association analyses (see below).

Genome-wide genotype imputations: Genotypes for uncovered autosomal SNPs were inferred from the cleaned LEAPS, NINDS, and PROGENI/GenePD datasets using the IMPUTE program v2.0 [19]. Before imputation, all genotypes were recoded to reflect alignment to the "plus" strand using information provided along with the GWAS datasets from dbGaP. As reference for the imputations, we used the precompiled "HapMap 3 + 1000GP CEU+TSI" panels from the IMPUTE website (obtained on June 2nd, 2010). These contain HapMap 3 data (from release #2, Feb 2009) and 1,000 Genomes Project data from Pilot 1 genotypes (released in August 2009) for autosomal SNPs. In the two case-control datasets (NINDS, PROGENI/GenePD) only SNPs with an average maximum posterior genotype call probability across all samples (i.e. a "certainty" score) ≥0.4 and an estimated minor allele frequency of 0.01 were considered further. In the family-based dataset (LEAPS), individual-level genotypes were assigned according to the genotype called with 0.9 or greater posterior call probability, or coded as missing if the posterior call probability fell below 0.9. Next, imputed genotyped datasets were cleaned following the same thresholds as outlined above (i.e. exclusion of SNPs with MAF<0.01, HWE *P*-value<$1x10^{-6}$, genotyping efficiency<0.98, and exclusion of samples with average missing genotype rates>5%). Overall, this led to final datasets of 735,746 SNPs (in 431 PD and 427 controls; LEAPS), 7,050,115 SNPs (in 905 PD and 782 controls; NINDS), and 7,319,987 SNPs (in 861 PD and 852 controls; PROGENI/GenePD). **Within-Study Association Analyses:** Association analyses were performed in SAS v9.2 for the LEAPS and SNPTEST v2 [19] for the NINDS and PROGENI/GenePD datasets. For the family-based dataset (LEAPS) we used a conditional logistic regression approach stratifying on family to estimate the additive (copies of minor allele) OR for autosomal SNPs [20]. For the case-control datasets (NINDS and PROGENI/GenePD), we used the frequentist under an additive transmission model adjusted for age, sex and population stratification (using the first two MDS dimensions) and an EM model to adjust for genotype uncertainty following imputation to estimate sample-specific ORs for each SNP. For the NINDS dataset, 463,185 quality cleaned SNPs were released as summary data for an extended dataset ("NINDS/Germany", see above). Since this extended dataset was substantially larger than the sample released with individual-level genotype data, we used the reported ORs for these SNPs in the subsequent meta-analyses.

Meta-Analyses of GWAS results: Meta-analyses based on random-effects and fixed-effect models were performed in PLINK v1.07 [7] using the study-specific ORs and standard errors (SE's; scaled by the square root of each sample's genomic inflation factor) calculated as outlined above. Overall, there were a total of 7,723,931 unique SNPs, 7,123,920 of which were present in at least two, 711,271 in at least three datasets. In addition, we used the METAL software [21] (Aug 2010 version) to perform P-value based meta-analyses weighted by sample size. Both methods led to comparable results although the random-effects meta-analyses tended to be more conservative. The genomic-inflation factor did not exceed 1.007 after removal of the established PD susceptibility genes *SNCA*, *LRRK2*, *MAPT*, and *DGKQ*/*GAK* (see Figure S1).

Additional data
For 147 SNPs of the 867 PDGene core meta-analyses yielding P-values of ≤0.1, we obtained additional summary data from all remaining Caucasian GWAS datasets. For the established loci *SNCA*, *MAPT*, and *LRRK2* only the SNPs reported by the recent GWAS meta-analysis [22] were requested. In addition, we obtained data from the newly identified SNP rs7077361 in *ITGA8* from the Japanese GWAS dataset [23]. Furthermore, we obtained summary data for ten SNPs reported in the recent GWAS meta-analysis [22] generated in datasets of the GEO-PD Consortium [24]. Details on sample characteristics, data cleaning, and, if applicable, imputation protocols as well as statistical analyses can be found in the individual publications [22–30] . Briefly, data of the following additional datasets were provided to us by investigators from the respective sites:
1) 23andMe [25]**:** 112 SNPs in 3,426 PD cases and 29,624 controls;
2) UK (WTCCC2) [26]**:** 140 SNPs in 1,705 PD cases and 5,175 controls, genotyped on the Illumina Human660-Quad platform (cases) and on the Illumina 1.2M Duo platform (controls);
3) USA (NGRC) [27]**:** 135 SNPs in 1,956 PD cases and 1,982 controls, genotyped on the Illumina HumanOmni1-Quad platform;
4) France [28]**:** 140 SNPs in 1,039 PD cases and 1,984 controls, genotyped on the Illumina Human610-Quad platform;
5) Netherlands [29]**:** 138 SNPs in 824 PD cases and 2,082 controls, genotyped on the Illumina Human660W-Quad platform (cases);
6) Iceland [22]**:** 124 SNPs in 479 PD cases and 1,427 controls, genotyped on Illumina Bead Arrays;
7) Germany [17]**:** 138 SNPs in 742 PD cases and 944 controls, genotyped on Illumina 550Kv1 arrays; and the Human610K platform (controls);
8) USA (HIHG) [30]**:** 120 SNPs in 579 PD cases and 619 controls, genotyped on the Illumina Human610-Quad platform (cases),and the Illumina Human610-Quad, Illumina HumanHap550, and 1M-Duo Infinium HD BeadChip platforms (controls).
9) GEO-PD [24]**:** 10 SNPs in 5,702 PD cases and 4,973 controls of Caucasian descent (excluding DNA samples from the UK and France overlapping with the GWAS datasets used by the recent GWAS-meta-analysis [22]), and 1,022 PD cases and 874 controls of Asian descent.
10) Japan [23]**:** 1 SNP in 988 PD cases and 2,521 controls, genotyped on Illumina HumanHap550 platforms.

Online Database Structure
PDGene database. After completion of the data entering, processing and analyses described in detail above, all study-specific variables, genotype data (except for GWAS), and meta-analysis plots are posted on a dedicated, publicly available, online adaptation of the PDGene database using the same software and code as our databases for Alzheimer's disease [31] and schizophrenia [32]. The online database is hosted by the "Alzheimer Research Forum", a non-profit, internet-based community portal dedicated to furthering collaboration among researchers to help in the search for causes, treatments, and understanding of Alzheimer's disease. The PDGene site can be accessed via its own designated URL (http://www.pdgene.org).
Summaries of large-scale studies: In addition to systematically including association results from GWAS, large-scale studies are summarized in a dedicated section on PDGene. This section distinguishes between "GWAS" (≥100,000 independent markers) and "Other large-scale association studies" (≥1,000 independent genetic markers; this latter section also includes re-analyses or meta-analyses of previous GWAS). In addition to providing the main characteristics of each study, this section also provides a hyperlinked list of "featured genes", i.e. those loci or pathways highlighted by the primary authors as the main outcome of their study after having completed all analyses. Note that the criteria used to define of "featured genes" varies across publications.
Display of meta-analysis results on UCSC Genome Browser. All meta-analysis results were compressed into "BigWig" format (i.e. indexed binary files) [33] displayed as custom track on the UCSC Genome Browser (URL: http://genome.ucsc.edu/cgi-bin/hgTracks?org=human&db=hg18&position=chr4&hgt.customText=http://xgene.molgen.mpg.de/ucsc/pdgenetracks.txt). This feature plots random-effects meta-analysis $-\log_{10}$ *P*-values (on the y-axis), against genomic location (based on build NCBI36/hg18; on the x-axis). This includes the results of all 7,123,920 GWAS meta-analyses as well as the results of all 867 meta-analyses included in PDGene proper. Whenever SNPs from the GWAS meta-analyses overlapped with those from PDGene, *P*-values from the latter were used for display as these were always based on larger sample sizes. SNP names were based on dbSNP build 131, transcribed to build NCBI36/hg18.

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