Large Scale Meta Analysis of Genome-wide Association Data in Parkinson's Disease Reveals 28 Distinct Risk Loci

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We conducted a meta analysis of extant genome-wide association studies for Parkinson disease (PD) using a common set of 7,893,274 variants across 13,728 cases and 95,282 controls. Twenty-six loci yielding genome-wide significant evidence for association were identified in this analysis. These and six additional

previously reported loci were then tested in an independent set of 5,353 PD cases and 5,551 controls. Of the 32 tested SNPs, 24 replicated, including 6 novel loci. In an attempt to determine whether more than one independent risk allele exists at each locus we performed a reanalysis conditioning on genome wide associated SNPs. This showed that four loci including *GBA*, *GAK/DGKQ*, *SNCA*, and *HLA* each contain a secondary independent risk variant. Thus in total we identified and replicated 28 independent risk variants for PD. While the effect of each individual locus is small, a risk profile analysis revealed a substantial alteration in risk for the 20% of individuals with the highest burden of genetic risk compared to the lowest 20% of genetic risk (OR=3.31, 95% CI: 2.55, 4.30; p-value = $2x10^{-16}$). Analysis of brain tissue quantitative trait locus (QTL) data revealed 6 of 28 PD risk loci were associated with an alteration in proximal gene expression or DNA methylation. These findings provide extensive evidence for a substantial genetic component to PD.

Increasing evidence supports the extensive and complex genetic contribution to PD. Genome-wide association (GWA) studies have shed light on the genetic basis of this disease, with the identification and replication of risk loci that fit the common disease common variant hypothesis.[1–17] The loci identified have both affirmed the central role of genes previously linked to PD and implicated new proteins in the pathogenic cascade.[18] These data have also shown that thus far only a small portion of the heritable component of PD has been identified.[19] Experience in other complex diseases and traits demonstrates that ever greater resolution of genetic risk can be

achieved through larger sample sizes and that common genetic variability may play a more substantial role in complex traits than previously anticipated.[20–22] With each of these factors in mind, we performed a meta-analysis of all existing European ancestry PD GWA study data and a replication study in an independent data set.

We performed a meta-analysis of genome-wide SNP data from 13,728 PD patients and 95,282 controls. This approach required imputation using the August 2010 release of the 1000 Genomes Project European ancestry haplotype reference set to standardize data to over 11 million variants.[23] Only markers that were successfully imputed in at least three datasets and that had a meta-analysis wide sample size weighted minor allele frequency of 0.1% or more were included (n=7,893,274). The genomic inflation factor for each of the datasets ranged from 0.889 to 1.056 (based on lambda values standardized to a scale of 1000 cases and 1000 controls, see Table S1 for study specific details). Fixed-effect meta-analysis of the summary statistics from each set revealed 26 loci associated with risk for disease in the discovery phase, based on a widely-accepted genome-wide p-value threshold of $5x10^{-8}$ (Table 1).[24]

To identify which of the putatively associated loci were truly disease-related, we attempted to replicate each locus in an independent sample series using a semi-custom genotyping array called NeuroX. This array typed >240,000 exonic variants available on Illumina's Infinium HumanExome BeadChip and an additional ~24,000 variants proven or hypothesized to be relevant in neurodegenerative disease [Nalls et al., in preparation]. Within the custom content we included the 26 genome-wide

significant candidate loci implicated in PD from the primary meta-analysis. For each independent locus the most significantly associated SNP and a series of proxy variants were included in the array design. Following stringent quality control, high quality genotype data were available for a sample set of 5,353 cases and 5,551 controls (see supplemental online methods for complete details). Association analysis revealed replication of 22 of 26 loci tested based on a nominal 1-sided p-value of <0.05 and consistent direction of association which incorporates the premise of prior knowledge for most loci based on previous meta-GWAS (Table 1); of these loci, six were novel *(SIPA1L2, INPP5F, MIR4697, GCH1, VPS13C, DDRGK1*). In addition we examined association at six loci previously reported to be associated with risk for PD but that did not show association at $p<5x10^{-8}$ in the discovery phase.[1,2,4,25] While these loci have been reported in samples derived from some of the cohorts included in the discovery phase of this meta-analysis, individuals in the replication samples were distinct from those used to nominate these loci. We found evidence for association based on a nominal 1-sided p-value of <0.05 in the replication data at two of these loci in our replication phase analyses (*FGF20* and *SREBF/RAI1*; Table 1).

We tested whether multiple independent risk alleles existed at any of the 26 genome-wide significant loci identified in the discovery phase. For each locus we tested all variants within 1 million base pairs of the index SNP with the most extreme p-value. To identify risk alleles independent of the primary effect, the index SNP was included as a covariate in the model (0, 1 or 2 copies of the minor allele). Additional independent risk variants were identified at 8 of the loci ($9.31x10^{-6}$ to $7.09x10^{-19}$) and were also included

on the replication array. Four of these variants revealed significant association upon conditional analysis of the replication phase data (Table 2).

Risk profiles were generated incorporating three groups of SNPs. The first group included genome-wide significant index SNPs (or their proxies) from the discovery phase that replicated in the independent replication phase (n=22). The second group comprised conditional SNPs that validated in the replication phase (n=4). The third group consisted of previously reported SNPs that did not quite meet genome-wide significance in the discovery phase but provided evidence of association in the replication phase (n=2). These 28 SNPs were used to compute genetic risk profile scores (for additional risk profiling methods, please see supplemental text). In brief, genetic risk scores were scaled on a per SNP basis using effect estimates from the discovery phase then applied to the genotype data generated for the samples in the replication phase to create the dataset for analyses of the risk profiles. Similar to previous studies we showed marginal predictive power for genetic risk profile scores, with areas under the receiver operator curves of 0.616 without age and sex included as covariates and 0.633 with age and sex (Table 3, Figure 2a).[3] As expected, those individuals with a genetic risk profile score above one standard deviation from the population mean, indicative of a roughly 34% increase in genetic risk scores above the control mean, had a significantly higher risk of PD (from meta-analysis odds ratio = 1.51, 95% CI = 1.38-1.66, $p=2x10^{-16}$). When comparing the 5th quintile of genetic risk scores to the 1st quintile of genetic risk as a reference, the odds ratio was 3.31 (95% CI = 2.55-4.30, $p=2x10^{-16}$). These odds ratios are larger compared to earlier

publications and may be due to finer scale imputation used in the discovery phase of this project, as well as the inclusion of additional loci and to some degree differing distributions of cumulative genetic risk scores across populations in the analysis.[3,4] Cohort level summary statistics were significantly heterogeneous for both trend based analyses (I2 = 0.74, heterogeneity p-value = 0.003) and the comparisons of the highest versus lowest risk quintiles (I2 = 0.70, heterogeneity p-value = 0.01). Therefore, a random effects model was used to account for the heterogeneity of effect.

For each of the 28 SNPs included in the risk profile analyses, we attempted to infer functional consequences in frontal cortex and cerebellar tissue samples from neurologically normal individuals that were assayed for both genome-wide methylation and expression levels.[26] These analyses may shed light on potential disease mechanisms for follow-up in future studies. We tested *cis* associations (any methylation or expression probes +/- 1Mb from each SNP) in each of the datasets. After quality control, 25 SNPs of interest from our meta-analysis passed quality control in the mRNA expression datasets and all 28 SNPs of interest passed quality control the CpG methylation datasets. We tested multiple probes per SNP in each set of analyses. A total of 336 unique SNP-probe pairs were tested in the frontal cortex mRNA expression dataset, 865 pairs in the frontal cortex CpG methylation dataset, 333 pairs in the cerebellar mRNA expression dataset and 1,097 pairs in the cerebellar CpG methylation dataset. Associations were tested using linear regression adjusting for appropriate covariates and resulting p-values adjusted based on the false-discovery rate correction (see online methods for details).

After correcting for multiple tests, we found 30 significant associations between SNPs of interest and either CpG methylation or mRNA expression (Table S2) across six loci. Of particular interest were associations at rs199347 on chromosome 7 and rs823118 on chromosome 1, as both SNPs are significantly associated with both methylation and expression changes in each brain region. The risk allele (A) at rs199347 on chromosome 7 was associated with increased expression of two probes tagging *NUPL2* as well as with decreased methylation of *GPNMB* in both brain regions. These data suggest that risk at the locus containing rs199347 might be due to increased transcription of *NUPL2* further bolstered by decreased methylation. On chromosome 1, the risk allele (T) at rs823118 was associated with decreased expression of *NUCKS1* and increased expression of *RAB7L1*, as well as increased DNA methylation detected by two probes close to *FLJ32569* in both brain tissues. These data suggest a complicated risk locus at the *NUCKS1/RAB7L1/ FLJ32569* region, where the same risk allele is associated with both increased expression of *RAB7L1* as well as increased regulation of nearby genes *NUCKS1* and *FLJ32569*. The possibility of multiple functionally active risk variants at this locus seems likely and is evident in the results of our conditional phase of analyses (Table 2). The complicated nature of this locus may be suggestive of some type of interaction or epistatic effect as well and it is likely that future functional and deep sequencing studies will be required to understand the basis of association at this region.

In total here we have identified 28 independent risk loci for PD; 22 found in the discovery phase and confirmed by replication, two previously reported loci confirmed in the replication phase, and four loci identified by a second risk allele exerting an effect independent of the primary risk allele.

URL's

MACH2QTLv1.11 (http://www.sph.umich.edu/csg/abecasis/MaCH/download/)

MiniMac (http://genome.sph.umich.edu/wiki/Minimac)

1000 Genomes haplotypes (http://www.sph.umich.edu/csg/abecasis/MaCH/download/)

PDGene database (http://www.pdgene.org)

METHODS

Methods and any associated references are available in the online version of the paper. Supplementary information is available in the online version of the paper. . Summary statistics of this study have been made available at http://www.pdgene.org *(Note to the editor/reviewers: Summary statistics of the discovery and replication phase of this study will be made available to the community at the listed URL upon publication of this study)*

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COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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FIGURES AND TABLES

Figure 1: Manhattan plot of discovery phase meta-analyses.

Figure 2a: ROC curve for genetic risk profiles across cohorts adjusting for cohort membership, age and gender.

Figure 2b: Forest plots describing cohort level and summary effects of risk profile analyses.

Table 1: Results of discovery and replication association analyses.

C - Chromosome; OR - odds ratio; I2 - heterogeneity

*replication genotyping for these SNPs failed assay design or quality control and a suitable proxy variant was selected (rs35749011, proxy rs71628662; rs1474055, proxy rs1955337; rs115185635, proxy rs62267708; rs9275326, proxy rs115462410; rs117896735, proxy rs118117788; rs3793947, proxy rs12283611; rs1555399, proxy rs1077989; rs62120679, proxy rs10402629; rs8118008, proxy rs55785911). Note, only replication phase p-values are one-sided. Nearest gene or previously published proximal gene names included in table.

Table 2: Results of conditional association analyses.

Replication genotyping for these SNPs failed assay design or quality control and a suitable proxy variant was selected (rs1596117, proxy rs4859430; rs7681154, proxy rs3910105; rs13201101, proxy rs8192591; based on discovery series comparison, the minor allele for rs3910105 tags the major allele of rs7681154 therefore risk is consistent across proxy and discovery SNP, see Table S2 for proxy statistics

comparisons across phases). Note, only replication phase p-values are one-sided. Nearest gene or previously published proximal gene names included in table.

Table 3: Summary statistics for risk profile scoring analyses.

Table S1: Studies contributing to the discovery phase meta-analysis.* denotes genomic inflation estimates (lambda) scaled to 1000 cases and 1000 controls.[24]

Table S2: Genome-wide significant SNPs are associated with distinct changes in methylation and expression levels in proximal genomic regions across multiple brain regions.

Supplemental figures 1-32.

SNPs from discovery phase analyses +/- 1 Mb from most significant SNP per locus in Table 1. The r2 pattern is based on most significant SNP per locus, based on the 283 European ancestry samples from the August 2010 release of the 1000 genomes project dataset. Secondary signals are annotated in text as per their description in the conditional analysis section of Table 2. Recombination rates are as per HapMap phase 2 European ancestry samples. Nearest gene or previously published proximal gene names included in table.

Supplemental figures 33-72.

Forest plots of SNPs from discovery and conditional phases described in Tables 1 and 2. Nearest gene or previously published proximal gene names included in table.