

CURATION

GWAS Source

High-Resolution Whole-Genome Association Study of Parkinson's Disease

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We performed a two-tiered, whole-genome association study of Parkinson disease (PD). For tier 1, we individually genotyped 198,345 uniformly spaced and informative single-nucleotide polymorphisms (SNPs) in 443 sibling pairs discordant for PD. For tier 2a, we individually genotyped 329 PD-associated SNPs (P < .05 in tier 1) and 300 genomic control SNPs in 332 matched case-unrelated control pairs. We identified 11 SNPs that were associated with PD (P < .05) in both tier 1 and tier 2 samples and had the same direction of effect. For these SNPs, we combined data from the case-unrelated sibling pair (tier 1) and case-unrelated control pair (tier 2) samples and employed a liberalization of the sibling transmission disequilibrium test to calculate odds ratios, 95% confidence intervals, and P values. A SNP within the semaphorin 5A gene (SEMA5A) had the lowest combined P value (P = 7.42 × 10⁻⁷). The protein encoded by this gene plays an important role in neurogenesis and in neuronal apoptosis, which is consistent with existing hypotheses regarding PD pathogenesis. A second SNP tagged the PARK11 late-onset PD susceptibility locus (P = 2.52 × 10⁻⁵). In tier 2b, we also selected for genotyping, additional borderline significant (P < .05) in tier 1 but that tested a prior biological or genetic hypothesis (P < .05) in tier 2b. In analysis of the combined tier 1 and tier 2b data, the two SNPs with the lowest P values (P = 9.07 × 10⁻⁶; P = 2.96 × 10⁻⁵) tagged the PARK10 late-onset PD susceptibility locus. Independent replication across populations will clarify the role of the genomic loci tagged by these SNPs in conferring PD susceptibility.

Introduction

Association-based genome-wide approaches that search across over a few thousand base pair subregions from linkage disequilibrium (LD) have been used to identify genetic variants associated with many human diseases (Klein et al., 2009). Here, we report the results of a high-resolution, whole-genome association study of Parkinson disease (PD) (MIM:168600). Our findings support the existence of a genetic predisposition map for PD, and we illustrate a novel genotyping approach that can be applied to the study of other complex diseases.

Material and Methods

We performed a high-resolution, whole-genome association study of PD, using a two-tiered genotyping approach. In tier 1, we individually genotyped 198,345 uniformly spaced and informative single-nucleotide polymorphisms (SNPs) in 443 sibling pairs discordant for PD. For tier 2a, we individually genotyped 329 PD-associated SNPs (P < .05 in tier 1) and 300 genomic control SNPs in 332 matched case-unrelated control pairs. We identified 11 SNPs that were associated with PD (P < .05) in both tier 1 and tier 2 samples and had the same direction of effect. For these SNPs, we combined data from the case-unrelated sibling pair (tier 1) and case-unrelated control pair (tier 2) samples and employed a liberalization of the sibling transmission disequilibrium test to calculate odds ratios, 95% confidence intervals, and P values. A SNP within the semaphorin 5A gene (SEMA5A) had the lowest combined P value (P = 7.42 × 10⁻⁷). The protein encoded by this gene plays an important role in neurogenesis and in neuronal apoptosis, which is consistent with existing hypotheses regarding PD pathogenesis. A second SNP tagged the PARK11 late-onset PD susceptibility locus (P = 2.52 × 10⁻⁵). In tier 2b, we also selected for genotyping, additional borderline significant (P < .05) in tier 1 but that tested a prior biological or genetic hypothesis (P < .05) in tier 2b. In analysis of the combined tier 1 and tier 2b data, the two SNPs with the lowest P values (P = 9.07 × 10⁻⁶; P = 2.96 × 10⁻⁵) tagged the PARK10 late-onset PD susceptibility locus. Independent replication across populations will clarify the role of the genomic loci tagged by these SNPs in conferring PD susceptibility.

Results

We performed a two-tiered, whole-genome association study of Parkinson disease (PD). For tier 1, we individually genotyped 198,345 uniformly spaced and informative single-nucleotide polymorphisms (SNPs) in 443 sibling pairs discordant for PD. For tier 2a, we individually genotyped 329 PD-associated SNPs (P < .05 in tier 1) and 300 genomic control SNPs in 332 matched case-unrelated control pairs. We identified 11 SNPs that were associated with PD (P < .05) in both tier 1 and tier 2 samples and had the same direction of effect. For these SNPs, we combined data from the case-unrelated sibling pair (tier 1) and case-unrelated control pair (tier 2) samples and employed a liberalization of the sibling transmission disequilibrium test to calculate odds ratios, 95% confidence intervals, and P values. A SNP within the semaphorin 5A gene (SEMA5A) had the lowest combined P value (P = 7.42 × 10⁻⁷). The protein encoded by this gene plays an important role in neurogenesis and in neuronal apoptosis, which is consistent with existing hypotheses regarding PD pathogenesis. A second SNP tagged the PARK11 late-onset PD susceptibility locus (P = 2.52 × 10⁻⁵). In tier 2b, we also selected for genotyping, additional borderline significant (P < .05) in tier 1 but that tested a prior biological or genetic hypothesis (P < .05) in tier 2b. In analysis of the combined tier 1 and tier 2b data, the two SNPs with the lowest P values (P = 9.07 × 10⁻⁶; P = 2.96 × 10⁻⁵) tagged the PARK10 late-onset PD susceptibility locus. Independent replication across populations will clarify the role of the genomic loci tagged by these SNPs in conferring PD susceptibility.

Conclusion

We performed a two-tiered, whole-genome association study of Parkinson disease (PD). For tier 1, we individually genotyped 198,345 uniformly spaced and informative single-nucleotide polymorphisms (SNPs) in 443 sibling pairs discordant for PD. For tier 2a, we individually genotyped 329 PD-associated SNPs (P < .05 in tier 1) and 300 genomic control SNPs in 332 matched case-unrelated control pairs. We identified 11 SNPs that were associated with PD (P < .05) in both tier 1 and tier 2 samples and had the same direction of effect. For these SNPs, we combined data from the case-unrelated sibling pair (tier 1) and case-unrelated control pair (tier 2) samples and employed a liberalization of the sibling transmission disequilibrium test to calculate odds ratios, 95% confidence intervals, and P values. A SNP within the semaphorin 5A gene (SEMA5A) had the lowest combined P value (P = 7.42 × 10⁻⁷). The protein encoded by this gene plays an important role in neurogenesis and in neuronal apoptosis, which is consistent with existing hypotheses regarding PD pathogenesis. A second SNP tagged the PARK11 late-onset PD susceptibility locus (P = 2.52 × 10⁻⁵). In tier 2b, we also selected for genotyping, additional borderline significant (P < .05) in tier 1 but that tested a prior biological or genetic hypothesis (P < .05) in tier 2b. In analysis of the combined tier 1 and tier 2b data, the two SNPs with the lowest P values (P = 9.07 × 10⁻⁶; P = 2.96 × 10⁻⁵) tagged the PARK10 late-onset PD susceptibility locus. Independent replication across populations will clarify the role of the genomic loci tagged by these SNPs in conferring PD susceptibility.

Top-level summary

Marker details

Phenotype summary

GWAS Central Identifier HGVPM126

Phenotype Parkinson's disease

Used in Study GWAS of Parkinson's disease (HGVST83)

Description Sibling pairs that are discordant for Parkinson's Disease.

Variable type Not supplied

Variable unit Not supplied

Related links Not supplied

Phenotype annotation MeSH: Parkinson Disease (D010300)

Phenotypes inferred from OMIM PARKINSON DISEASE (168600)
 HPO: Mask-like facies (HP:0000298)
 HPO: Depression (HP:0000716)
 HPO: Dementia (HP:0000726)
 HPO: Personality changes (HP:0000751)
 HPO: Dysarthria (HP:0001260)
 HPO: Parkinsonism (HP:0001300)
 HPO: Tremor (HP:0001337)
 HPO: Soft voice (HP:0001621)
 HPO: Rigidity (HP:0002063)
 HPO: Bradykinesia (HP:0002067)
 HPO: Hyposmia (HP:0004409)
 HPO: Short stepped shuffling gait (HP:0007311)

Phenotype details

Phenotype summary

The following Phenotypes are defined in this Study. What is a Phenotype?

Phenotype	Description
Parkinson's disease	Sibling pairs that are discordant for Parkinson's Disease.
Parkinson's disease	Not provided

Summary | View | Panels | Phenotypes | Analysis experiments | Association results

GWAS Central Identifier HGVST83

Study name GWAS of Parkinson's disease

Total markers imported 195,214

Phenotype(s) tested Parkinson's disease

Study design Case and control

Genotype platforms Not supplied

Abstract We performed a two-tiered, whole-genome association study of Parkinson disease (PD). For tier 1, we individually genotyped 198,345 uniformly spaced and informative single-nucleotide polymorphisms (SNPs) in 443 sibling pairs discordant for PD. For tier 2a, we individually genotyped 1,793 PD-associated SNPs (P < .01 in tier 1) and 300 genomic control SNPs in 332 matched case-unrelated control pairs. We identified 11 SNPs that were associated with PD (P < .01) in both tier 1 and tier 2 samples and had the same direction of effect. For these SNPs, we combined data from the case-unrelated sibling pair (tier 1) and case-unrelated control pair (tier 2) samples and employed a liberalization of the sibling transmission disequilibrium test to calculate odds ratios, 95% confidence intervals, and P values. A SNP within the semaphorin 5A gene (SEMA5A) had the lowest combined P value (P = 7.62 × 10⁻⁶). The protein encoded by this gene plays an important role in neurogenesis and in neuronal apoptosis, which is consistent with existing hypotheses regarding PD pathogenesis. A second SNP tagged the PARK11 late-onset PD susceptibility locus (P = 1.70 × 10⁻⁵). In tier 2b, we also selected for genotyping additional SNPs that were borderline significant (P < .05) in tier 1 but that tested a prior biological and genetic hypotheses regarding susceptibility to PD (n=941 SNPs). In analysis of the combined tier 1 and tier 2b data, the two SNPs with the lowest P values (P = 9.07 × 10⁻⁶; P = 2.96 × 10⁻⁵) tagged the PARK10 late-onset PD susceptibility locus. Independent replication across populations will clarify the role of the genomic loci tagged by these SNPs in conferring PD susceptibility.

Submission information

Contributor	Date Submitted	Author?	Submitter?	Source?
GWAS Central	2002-12-09	✗	✓	✗
Maraganore DM et al.	2002-12-09	✓	✗	✓

Author communication

Corresponding author	Date of contact	Response received	Date of response	Type of response
Dennis G. Ballinger	2011-03-17	✓	2011-03-17	E-mail bounce

Links Supplementary data from PMID16252231

Experiment details

Summary | View | Panels | Phenotypes | Analysis experiments | Association results

The Study contains 2 Analysis Experiments. What is an Analysis Experiment?

Expand All | Collapse All

Experiment HGVE138

Association analysis experiment (Tier 1) for Parkinson's disease

Phenotype Parkinson's disease

Total no. markers imported 192,227

Genotype platform(s)

Analysis summary

Analysis Method	Result Set
log-additive method	Trend analysis (HGVR137)

Assayed panels used in Experiment

Assayed panel name	No. Individuals	Selected from Sample panel(s)
Cases (Tier 1: PD)	344	Tier 1 cohort (Discordant sibling-pairs)
Controls (Tier 1: Sibling pairs discordant for Parkinson's disease)	443	Tier 1 cohort (Discordant sibling-pairs)

Related links Supplementary file 1

Individual-level data statement Access to individual-level data must be made to the study authors

Comments None

Association results

Summary | View | Panels | Phenotypes | Analysis experiments | Association results

Top results to show in data sets: 50

Export all top results as: --choose a format-- Go

Expand All | Collapse All

Data set HGVR137

Top 50 associations for Parkinson's disease (HGVPM126) from data set HGVR137(192,227 in database)

Export as: --choose a format-- Go

Experiment: Association analysis experiment (Tier 1) for Parkinson's disease (HGVE138)

Data set: Trend analysis (HGVR137)

Rank	Identifier	Accession	Region	p-value	-log p-value	Effect size	Risk allele	Related data	Links
1	HGVM2262419	rs3746736	chr20:23424613..23424613	1.301e-05	4.886	Not supplied	Not supplied	Details	Not supplied
2	HGVM420277	rs1472402	chr12:42263030..42263030	1.4409e-05	4.841	Not supplied	Not supplied	Details	Not supplied
3	HGVM3067273	rs10197606	chr2:41878796..41878796	1.9528e-05	4.709	Not supplied	Not supplied	Details	Not supplied
4	HGVM13206713	rs17463995	chr15:49003772..49003772	3.4967e-05	4.456	Not supplied	Not supplied	Details	Not supplied
5	HGVM18052891	rs16887478	chr8:38442043..38442043	3.6351e-05	4.439	Not supplied	Not supplied	Details	Not supplied
6	HGVM4532217	rs11887431	chr2:42267462..42267462	3.6577e-05	4.437	Not supplied	Not supplied	Details	Not supplied
7	HGVM4319177	rs11674789	chr2:41911100..41911100	3.7598e-05	4.425	Not supplied	Not supplied	Details	Not supplied
8	HGVM1020790	rs1984279	chr20:23313192..23313192	3.8852e-05	4.411	Not supplied	Not supplied	Details	Not supplied
9	HGVM3521330	rs10815285	chr9:5814424..5814424	4.6376e-05	4.334	Not supplied	Not supplied	Details	Not supplied
10	HGVM19101008	rs17344386	chr1:83541990..83541990	4.7053e-05	4.327	Not supplied	Not supplied	Details	Not supplied

Marker details

Summary | Association results

GWAS Central marker ID HGVM2262419

Marker accession ID rs3746736

Variation type SNP

Observed alleles 5' upstream 30bp (allele seq) 3' downstream 30bp

GTGGAGTATATAGTCACCTGTGAAGATTGGC (C) GGACCAAAATGCAAGAGGAATGACACGAGCA

GTGGAGTATATAGTCACCTGTGAAGATTGGC (T) GGACCAAAATGCAAGAGGAATGACACGAGCA

Genomic location chr20:23,424,613..23,424,613 (view in genome browser: Ensembl | UCSC)

Mapped gene CSTL1[exonic]

Marker status and Revision History This marker is currently ACTIVE (no revision history)

Cross-references None available

Links OMIM
SNPedia
dbSNP