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Variants in estrogen-related genes and risk of Parkinson's disease

Sun Ju Chung, MD, PhD[1,2], **Sebastian M. Armasu, MS**[3], **Joanna M. Biernacka, PhD**[3], **Timothy G. Lesnick, MS**[3], **David N. Rider, MSE**[3], **Julie M. Cunningham, PhD**[4], and **Demetrius M. Maraganore, MD**[5]

[1]Department of Neurology, Mayo Clinic, Rochester, MN

[2]Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

[3]Department of Health Sciences Research, Mayo Clinic, Rochester, MN

[4]Department of Laboratory Medicine, Mayo Clinic, Rochester, MN

[5]Department of Neurology, NorthShore University HealthSystem, Evanston, IL

Abstract

Address correspondence to Dr. Demetrius M. Maraganore, Ruth Cain Ruggles Chairman, Department of Neurology, NorthShore University HealthSystem, 2650 Ridge Avenue, Evanston, IL 60201., (work): dmaraganore@northshore.org, (personal): dmaraganore@me.com, Telephone: 847 570 1678, Fax: 847 733 5565.

Author Roles: Sun Ju Chung– Dr. Chung was involved in Research Project (Execution), Statistical Analysis (Review and Critique), Manuscript (Writing of the first draft); Sebastian M. Armasu–Mr. Armasu was involved in Statistical Analysis (Design, Execution, Review and Critique), Manuscript (Review and Critique); Joanna M. Biernacka–Dr. Biernacka was involved in Statistical Analysis (Design, Review and Critique), Manuscript (Review and Critique); Timothy G. Lesnick–Mr. Lesnick was involved in Research Project (Conception, Organization, and Execution), Statistical Analyses (Design, Execution, and Review and Critique), Manuscript (Writing of the first draft, Review and Critique); David N. Rider–Mr. Rider was involved in Statistical Analysis (Execution, Review and Critique), Manuscript (Review and Critique); Julie M. Cunningham–Dr. Cunningham was involved in Manuscript (Review and Critique); Demetrius M. Maraganore–Dr. Maraganore was involved in Research Project (Conception, Organization, Execution), Statistical Analysis (Design, Execution, Review and Critique), Manuscript (Writing of the first draft, Review and Critique).

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Incidence rates of Parkinson's disease (PD) are higher in men than women at all ages, and these differences may be due to the neuroprotective effects of estrogen on the nigrostriatal pathway. We investigated the association of common variants in four estrogen-related genes with PD. Tagging single nucleotide polymorphisms (SNPs) in the *CYP19A1*, *ESR1*, *ESR2*, and *PRDM2* genes were selected from the International Haplotype Map and genotyped in 1,103 PD cases from the Upper Midwest, USA and in 1,103 individually matched controls (654 unaffected siblings, and 449 unrelated controls from the same region). Out of 137 informative SNPs, two *PRDM2* SNPs were significantly associated with an increased risk of PD at the Bonferroni-corrected significance level of 0.0004 (rs2744690: OR = 1.54, 99.96% CI = 1.05 – 2.26, uncorrected *P* = 0.0001; rs2744687: OR = 1.53, 99.96% CI = 1.03 – 2.29, uncorrected *P* = 0.0002); the association was significant in the women only stratum but not in the men only stratum. An additional six SNPs in *PRDM2*, two in *ESR1*, one in *ESR2*, and one in *CYP19A1* had significant *P*-values in the overall sample before Bonferroni correction. None of the SNPs were significantly associated with age at onset of PD after Bonferroni correction. Our results confirm the association of *PRDM2* variants with PD susceptibility, especially in women.

INTRODUCTION

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder that affects 2% of men and 1.3% of women during their life.[1] Epidemiological studies report higher incidence rates of PD in men compared with women at all ages,[2, 3] which may be due to the neuroprotective role of female sex hormones such as estrogen.

There is evidence for a neuroprotective effect of estrogen on the nigrostriatal pathway in mice.[4–15] The neuroprotective properties of estrogen have also been demonstrated in primate models.[16] Those laboratory findings are consistent with clinical and epidemiologic studies documenting possible neuroprotective roles of estrogen.[17–19] We recently reported that both unilateral and bilateral oophorectomy performed prior to menopause may be associated with an increased risk of PD.[20]

Common variants of the estrogen receptor 1 gene (*ESR1*) are associated with earlier age at natural menopause and increased risk of surgical menopause.[21] We previously failed to observe significant associations of two estrogen receptor gene variants with PD susceptibility in a smaller study.[22] However, our genome-wide association study highlighted a significant association of the single-nucleotide polymorphism (SNP) rs2245218 in the estrogen-related *PRDM2* gene with PD susceptibility.[23] We expanded the scope of our earlier genetic studies to include multiple SNP variants in four estrogen-related genes in a much larger sample.

SUBJECTS AND METHODS

Cases and Controls

We conducted case-control (PD susceptibility) and case-only (age at onset) analyses. Cases were patients with PD referred sequentially to the Department of Neurology of the Mayo Clinic in Rochester, MN, from June 1, 1996 through June 30, 2007, who resided in the 5-

state region including Minnesota, Wisconsin, Iowa, North Dakota, and South Dakota. The diagnosis of PD was made by a movement disorder specialist using previously reported criteria.[2] Control subjects consisted primarily of unaffected siblings of PD cases who screened negative for PD or parkinsonism via telephone interview, or siblings who screened positive but were free of parkinsonism at clinical examination.[24, 25] Cases were matched to a single participating sibling first by sex (when possible) and then by closest age. Cases without an available sibling were matched to unrelated controls living in the same 5-state region and of same sex and age (same year of birth ± 2 years). Controls of age 65 or older were randomly selected for contact from the Centers for Medicare and Medicaid Services (CMS) lists, while those younger than 65 years were selected for contact using random digit dialing, according to standard techniques.[26, 27]

Because unrelated controls screening positive for PD or parkinsonism could not be examined as part of the study, they were excluded from the list of potential controls. All examinations (cases and siblings screening positive) were performed in a standardized fashion by neurologists specialized in Movement Disorders, and employing a protocol for clinical assessment. The Institutional Review Board of the Mayo Clinic approved the study, and all subjects provided written informed consent.

Genotyping

For all subjects, genomic DNA was collected, extracted, and stored as previously described.[28, 29] We studied the estrogen receptor 1 (*ESR1*) and estrogen receptor 2 (*ESR2*) genes because they encode the receptors to which estrogen binds. The genes that estrogens regulate via their cognate receptors are considered to include apoptotic/antiapoptotic genes, neurotrophins and growth factors, and genes that mediate structural alterations in neurons and synaptogenesis.[30] We studied the cytochrome P450, family 19, subfamily A, polypeptide 1 (*CYP19A1*) gene because it encodes the rate-limiting step in estrogen metabolism (the enzyme aromatase). Finally, we studied the PR domain containing 2, with ZNF domain (*PRDM2*) gene in light of our prior genome-wide association study findings and because it encodes a protein that binds to the estrogen receptor and functions as a specific effector of estrogen action. SNPs were selected for these 4 estrogen-related genes using the International HapMap Project unrelated Centre d'Etude du Polymorphisme Humain collection (CEPH) samples.[31]

The LDSelect program was used to identify tag SNPs using a linkage disequilibrium (LD) r^2 threshold of 0.8 and with minor allele frequencies of 5% or higher. Two tag SNPs were selected for each LD bin when the number of SNPs in the bin was 10 or more. We excluded SNPs with Illumina platform design scores < 0.4 and those within 60 bp of another SNP that had already been chosen.

We genotyped 141 SNPs using an Illumina GoldenGate custom SNP panel (Illumina Inc., San Diego, California, USA). This included 38 SNPs in *CYP19A1*, 58 SNPs in *ESR1*, 18 SNPs in *ESR2*, and 27 SNPS in *PRDM2*. Four SNPs failed genotyping (one in *CYP19A1*, one in *ESR1*, and two in *PRDM2*), whereas 137 SNPs were successfully genotyped and included in our analyses. The average call rate for these SNPs was 99.1%. Quality control was monitored by inclusion of DNA from a CEPH family trio in each plate (Father, mother,

daughter from CEPH/UTAH pedigree 1347 from the Coreill Institute for Medical Research); concordance was 100%.

Haploview was used to generate LD maps for each gene using data from the controls.[32] Only variants with minor allele frequencies > 0.01 and in Hardy-Weinberg equilibrium (P > 0.001) were included. Figure 1 shows the LD map for the *PRDM2* gene. Supplementary Figure 1 provides the LD maps for all four genes.

Statistical Analyses

In the case-control analyses, we studied the association of each genetic variant with PD susceptibility in the overall sample, using conditional logistic regression with a log additive genotype coding scheme.[33] We also performed analyses using dominant or recessive coding schemes. A log additive coding specifies that the log odds ratio for heterozygotes falls midway between the log odds ratios for the homozygotes, whereas dominant or recessive coding combines the heterozygotes with one or the other of the homozygote groups. The analyses were adjusted for age at study (continuous variable) and sex to remove possible residual confounding. For each genetic variant, we calculated an odds ratio (OR), a 95% confidence interval (CI), and a two-tailed P value. In addition, we performed similar analyses separately in strata defined by type of control (case-unaffected sibling pairs versus case-unrelated control pairs), sex, and age at onset of PD. Analyses in the sex-specific strata excluded 216 sib pairs of discordant sex, since not every case had an available sibling of the same sex.

In the case-only analyses, we studied the association of each genetic variant with age at onset of PD using Cox proportional hazard models and the same coding schemes described earlier.[34] The analyses were adjusted for sex. For each genetic variant we calculated a hazard ratio (HR), a 95% CI, and a two-tailed P value. We performed similar analyses of age at onset of PD in men and women separately.

The P values from primary analyses were assessed for significance using a Bonferroni corrected significance level of 0.05/137=0.0004. However, because the Bonferroni correction may be conservative due to residual LD between the selected tag-SNPs, we also used permutation techniques to correct for multiple testing in the primary analyses.[35] Case-control status was randomly permuted within matched pairs and each permuted data set was re-analyzed. This procedure was repeated 5000 times. Correction for multiple testing of each p-value in the original data analysis was achieved by counting the proportion of permutations in which at least one of the SNPs had a smaller p-value. The statistical packages SAS® (version 9.1; SAS Institute Inc., Cary, NC) and S-Plus® (version 8.0.1; MathSoft, Seattle, WA) were used for all analyses.

RESULTS

Sample

There were 1,103 cases and 1,103 controls included in the study (654 case-unaffected sibling pairs and 449 case-unrelated control pairs). There were 555 men-men pairs (290 case-sibling pairs and 265 case-unrelated control pairs), 332 women-women pairs (173 case-

sibling pairs and 159 case-unrelated control pairs), and 216 men-women pairs (case-sibling pairs only). Patients with PD were more often men (64.1%) than women (35.9%). Approximately 17% of cases reported having a first degree relative with PD. The demographic characteristics of the sample are summarized in Table 1.

Case-Control Analyses of Genetic Variants and PD Susceptibility

For the overall sample, 12 of the 137 SNPs were associated with PD susceptibility at an uncorrected significance level of 0.05, with a log-additive model for allele effects (Table 2). These included eight SNPs in *PRDM2*, two SNPs in *ESR1*, one SNP in *CYP19A1*, and one SNP in *ESR2*. The main effects of these variants were modest, with ORs ranging between 0.75 and 1.54. Two SNPs in the *PRDM2* gene remained significantly associated with PD susceptibility when using the Bonferroni corrected significance level of 0.0004 (rs2744690: OR = 1.54, 95% CI = 1.24 – 1.90 (99.96% CI = 1.05 – 2.26), $P = 0.0001$; rs2744687: OR = 1.53, 95% CI = 1.23 – 1.91, $P = 0.0002$, log additive model). With a less conservative permutation-based correction for multiple testing, one additional *PRDM2* SNP was significantly associated with PD susceptibility (rs2697962: OR = 1.45, 95% CI = 1.18 – 1.79 (99.96% CI = 1.03 – 2.29), p=0.0005, corrected $P = 0.0436$).

For the 12 SNPs significantly associated with PD at the uncorrected level of $p<0.05$, ORs in the case-unaffected sibling pairs were similar in magnitude to ORs in the case-unrelated control pairs. An interaction analysis confirmed that the ORs did not differ significantly for the different types of controls. Similarly, the ORs obtained using men-men pairs and women-women pairs did not differ significantly, as demonstrated by an interaction analysis. However, we note that, although the differences were not significant, the ORs for the 12 SNPs in men-men pairs were considerably different from ORs in women-women pairs. In particular, SNPs in *PRDM2* tended to show larger effects in the stratum of women, whereas SNPs in *ESR1* and *ESR2* tended to show larger effects in men. Supplementary Table 1 provides detailed results for the association with PD susceptibility of all genotyped SNPs in all four estrogen-related genes, including results for multiple coding schemes in the overall sample, and in strata defined by type of control, sex, and age at onset.

All eight *PRDM2* SNPs associated with PD susceptibility map to blocks 2 and 3 of the LD map (Figure 1). The two *PRDM2* SNPs (rs2744690 and rs2744687) that were significant after correction for multiple testing are in strong LD with each other (haplotype block 2). The additional *PRDM2* SNP (rs2697962) that was significant after permutation testing is in block 3, and is also in LD with the two significant SNPs in block 2 ($r^2 > 0.78$). All of these SNPs are also in high LD with the *PRDM2* SNP rs2245218 that was significantly associated with PD in our previous genome-wide wide study (rs2744690: $r^2 = 0.636$, $D' = 1.0$; rs2744687: $r^2 = 0.578$, $D' = 0.824$; and rs2697962: $r^2 = 1.0$, $D' = 1.0$).[23]

In analyses stratified by sex, 11 SNPs were associated with PD susceptibility in men (eight in *ESR1*, two in *ESR2*, and one in *CYP19A1*) and 11 SNPs in women (eight in *PRDM2*, two in *CYP19A1*, and one in *ESR2*) at an uncorrected level of $P < 0.05$ (Table 3). Of these, two *PRDM2* SNPs (rs2744690 and rs2744687) were significant after Bonferroni correction in women only. The SNPs significantly associated with PD susceptibility were different for men and women. In women, six of the seven SNPS in *PRDM2* significantly associated with

PD susceptibility in the overall sample remained significant and had stronger effects (ORs more remote from 1.0).

Case-Only Analyses of Genetic Variants and Age at Onset of PD

Nine SNPs (four in *CYP19A1*: rs8031463, rs16964258, rs730154, and rs10459592; four in *ESR1*: rs1709183, rs9322335, rs6912184, and rs2347923; one in *ESR2*: rs1256063; and none in *PRDM2*) were associated with age at onset of PD in the overall sample. However, none of these associations remained significant after Bonferroni correction. Fourteen SNPs had significant uncorrected *P* values in analyses restricted to men and nine SNPs in analyses restricted to women. Supplementary Table 1 provides the details for associations of all SNPs in the four genes with age at onset of PD, including results for multiple coding schemes in the overall sample, and for men and women separately.

DISCUSSION

This study confirmed the association of common variations in the *PRDM2* gene with PD susceptibility, but showed limited evidence of association of common variations in other estrogen-related genes with PD. Three SNPs in *PRDM2* (rs2744690, rs2744687, and rs2697962) that were significantly associated with PD susceptibility in the overall sample after permutation-based correction for multiple testing, were also significant (uncorrected *P* values) in the women only stratum but not in the men only stratum. The mechanism of this potentially sex-specific difference in genetic architecture relating to PD susceptibility remains uncertain. Nevertheless, the sex-specific nature of these associations is interesting and warrants further investigation of the functional role of these genetic variations in the susceptibility to PD in men and women.

The present findings are consistent with the findings from our previous genome-wide association study that included 443 PD cases and 443 matched controls genotyped for 198,345 informative genomic SNPs (tier 1 sample); and an additional 332 PD cases and 332 matched controls (tier 2 sample) genotyped for the SNPs that were significantly associated with PD in the tier 1 sample. That study yielded suggestive findings for the *PRDM2* SNP rs2245218 (OR = 1.67, 95% CI = 1.29 – 2.14, *P* value = 4.61×10^{-5}); however, the association was not significant after correction for multiple testing.[23] In the current study, three SNPs in *PRDM2* (rs2744690, rs2744687, and rs2697962) were associated with PD susceptibility in the overall sample (corrected *P* values), and in the stratum of women (uncorrected *P* values). These *PRDM2* SNPs were in LD with the *PRDM2* SNP rs2245218 highlighted by our previous genome-wide association study.[23] The results presented here are not an independent replication because 374 case-control pairs and an additional 69 cases included in this study had also been included in the prior genome-wide study, and 11 of the 143 SNPs investigated here were included in the prior study. However, the current study had a considerably larger sample size and a greater coverage of genetic variation in the four estrogen-related genes. Furthermore, the significantly associated SNPs remained nominally significant even after removing the cases and controls that had been included in the prior GWAS study ($p<0.005$ for the two PRDM2 SNPs that were significant after Bonferroni-correction).

By contrast, four other genome-wide association studies highlighted no associations of estrogen-related genes with PD.[36–39] The study by Fung and colleagues employed more SNP markers than our original genome-wide association study, but included only 276 PD cases and 276 unmatched controls. The study of Pankratz and colleagues employed more SNP markers than our original genome-wide association study and more subjects (857 PD cases and 867 controls); however, their sample included only familial PD cases. Neither of those two studies highlighted any of the estrogen-related genes independently or in pooled analyses. However, both of these studies had a smaller sample size than the current study. The studies of Simon-Sanchez and Satake included 7,208 PD cases and 27,184 controls collectively, and genotyped more than 500,000 SNPs. However our candidate gene study approach required a much smaller multiple-testing correction because we had a focused a priori hypothesis. Also, by selecting tagSNPs based on patterns of linkage disequilibrium, our candidate gene approach provided high coverage of the four estrogen-related genes. By contrast to this study, none of the five genome-wide studies selected genetic variants to comprehensively cover the four estrogen-related genes, nor did they report analyses stratified by sex.

We also studied the association of common variants in estrogen-related genes with age at onset of PD. We observed associations for nine SNPs at an uncorrected significance level of 0.05 (four in *CYP19A1*, four in *ESR1*, and one in *ESR2*). Thus far, there has been only one genome-wide association study of age at onset of PD that showed no significant genomic SNP associations after Bonferroni correction.[40] Additional studies are needed to determine whether common variations in these estrogen-related genes are associated with age at onset of PD.

While our most significant findings (significant after Bonferroni correction) were for two *PRDM2* SNPs (rs2744690 and rs2744687), it remains unknown whether these intronic SNPs have a functional effect or whether they are markers of other functional variants. An additional SNP (rs2697962) that was significant with permutation testing maps to the 3′ untranslated region of the *PRDM2* gene. It is not known whether that SNP modifies gene expression. Further studies are needed to replicate our association findings for these *PRDM2* gene SNPs with PD susceptibility and to fine map and define functional variants within the gene.

This study has several strengths. First, our large sample size (1,103 PD cases and 1,103 controls) provided sufficient statistical power to detect a wide range of ORs (and HRs) for a range of minor allele frequencies (log additive model). Second, we studied four estrogen-related genes that have plausibility as candidate genes for PD. Third, we studied multiple LD tagging SNPs in each gene. Fourth, we observed a strong concordance of ORs of each variant associated with PD susceptibility between case-unaffected sibling and case-unrelated control pairs (internal replication). Fifth, we studied the association of genetic variants with age at onset of PD as well as with susceptibility.

Our study also has some limitations. First, our sample was not population-based. However, population-based case-control studies are often not large enough to detect the small effects of common genetic variants. We tried to limit sampling bias by recruiting cases

prospectively from a defined geographic region (the upper Midwest, USA). We previously showed that for approximately half of our patients with PD (residing within 120 miles of the Mayo Clinic in Rochester, MN), the demographic characteristics are similar to those of an incidence cohort of PD patients from Olmsted County, MN. By contrast, the other half of our patients with PD (residing within a broader five-state region) were younger, possibly increasing the genetic load.[2, 41, 42] Although all PD patients were recruited from a single tertiary specialty clinic, the risk of referral bias is expected to be minimal unless clinical characteristics of referred PD patients have a different genetic basis from non-referred patients. Notably, frequency of family history was similar in our study to that observed in other population-based studies, which suggests the role of genetic factors may not differ greatly between this population and other populations with PD. However, the genetic associations and corresponding effect sizes observed in this study are based on cases seen in a tertiary clinic, and may not generalize to all patient populations

Second, our controls were primarily unaffected siblings to limit possible population stratification bias and to maximize participation rates. Unaffected sibling controls may be overmatched for genetic and environmental factors, leading to false negative findings (reduced statistical power). For this reason, we performed sensitivity analyses, which showed similar ORs in separate analyses for case-unaffected sibling pairs or case-unrelated control pairs.

Third, while our overall sample size was large, our sample size within strata defined by type of control or by sex were more modest. Fourth, we did not re-sequence the four genes in all subjects to detect rare point mutations or copy number variations that were associated with PD. Such studies are expected to become feasible in the coming years when the costs for next-generation sequencing technologies will decline.[43, 44] Fifth, we performed multiple statistical tests, increasing the likelihood of chance findings. Therefore, we employed Bonferroni correction for our primary analysis to identify genetic associations that exceeded chance expectations.

Sixth, we did not study gene-gene or gene-environment interactions (beyond the scope of this initial exploratory study). Finally, we did not replicate our significant findings in independent samples (also beyond the scope of this initial exploratory study). Large-scale replications of genetic association studies of PD are feasible within existing large consortia.[45, 46]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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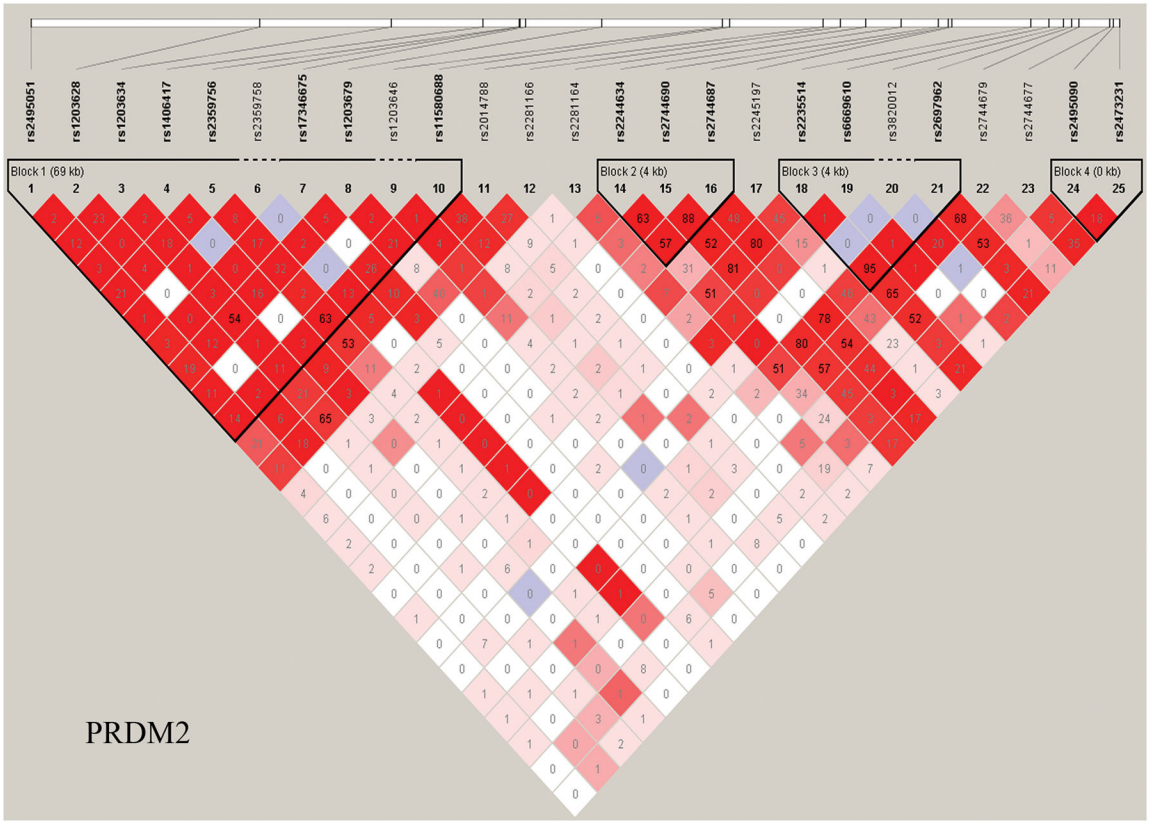

Figure 1. Linkage disequilibrium (LD) maps

Haplotype blocks of the *PRDM2* gene. The LD values measured using r^2 are given by numbers and the LD values measured by D′ are shown by color intensity (red squares indicate strong LD, pink squares indicate intermediate LD, and white squares indicate low LD, with evidence for ancestral recombination; blue indicates limited data).

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Table 1

Demographic Characteristics of Parkinson's Disease (PD) Cases, Unaffected Siblings, and Unrelated Controls

General Characteristics	PD Case-Sibling Pairs		PD Case-Unrelated Control Pairs		All PD Case-Control Pairs	
	PD Cases	Sibling Controls	PD Cases	Unrelated Controls	PD Cases	All Controls
Total sample, n	654	654	449	449	1,103	1,103
Men, n (%)	417 (63.8)	329 (50.3)	290 (64.6)	290 (64.6)	707 (64.1)	619 (56.1)
Women, n (%)	237 (36.2)	325 (49.7)	159 (35.4)	159 (35.4)	396 (35.9)	484 (43.9)
Age at onset of PD, median year (range)	60.4 (28.2 – 86.9)	—	64.7 (23.3 – 88.0)	—	62.2 (23.3 – 88.0)	—
Age at study, median year (range)[a]	66.3 (30.8 – 91.4)	65.1 (32.0 – 90.4)	70.3 (44.5 – 90.4)	71.8 (44.9 – 92.8)	68.0 (30.8 – 91.4)	67.6 (32.0 – 92.8)
Duration of PD, median year (range)	3.2 (0.1 – 23.6)	—	3.9 (0 – 54.2)	—	3.4 (0 – 54.2)	—
Region of origin of parents[b]						
Both parents of European origin, n (%)	570 (87.2)	557 (85.2)	361 (80.4)	391 (87.1)	931 (84.4)	948 (85.9)
Both parents Northern European, n (%)	154 (27.0)	148 (26.6)	116 (32.1)	126 (32.2)	270 (29.0)	274 (28.9)
Both parents Central European, n (%)	233 (40.9)	219 (39.3)	119 (33.0)	124 (31.7)	352 (37.8)	343 (36.2)
Both parents Southern European, n (%)	3 (0.5)	3 (0.5)	3 (0.8)	4 (1.0)	6 (0.6)	7 (0.7)
Both parents European, mixed region, n (%)	180 (31.6)	187 (33.6)	123 (34.1)	137 (35.0)	303 (32.5)	324 (34.2)
Only one parent of European origin, n (%)[c]	53 (8.1)	61 (9.3)	60 (13.4)	41 (9.1)	113 (10.2)	102 (9.2)
One parent declared "American", n (%)[d]	2 (0.3)	1 (0.2)	1 (0.2)	4 (0.9)	3 (0.3)	5 (0.5)
Both parents declared "American", n (%)[d]	19 (2.9)	20 (3.1)	13 (2.9)	7 (1.6)	32 (2.9)	27 (2.4)
Both parents Asian, n (%)	3 (0.5)	3 (0.5)	5 (1.1)	0 (0.0)	8 (0.7)	3 (0.3)
Both parents Mexican, n (%)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.2)	2 (0.2)
Unknown, n (%)	6 (0.9)	11 (1.7)	8 (1.8)	5 (1.1)	14 (1.3)	16 (1.5)

[a] Age at blood draw.

[b] Self-reported by subjects. "Northern European" includes Scandinavian, Swedish, Norwegian, Finnish, Danish, Irish, or British origins. "Central European" includes French, Belgian, Dutch, Swiss, Luxemburgian, German, Austrian, Hungarian, Polish, Czechoslovakian, or Russian origins. "Southern European" includes Italian, Spanish, Portuguese, Greek, or Yugoslavian origins.

[c] Includes subjects for whom origin of one parent is unknown.

[d] These subjects were all Caucasians and not Native Americans.

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Table 2

Single Nucleotide Polymorphisms (SNPs) in Estrogen-related Genes Significantly Associated with PD Susceptibility in the Overall Sample (n = 12)[a]

Gene	SNP	Chromosome	Position[b]	Type of Variant SNP[c]	Allele	Minor Allele Frequencies		Log Additive Model OR (95% CI)[d]	Log Additive Model *P* value[e]
						Cases %	Controls %		
PRDM2	rs2744690	1	14010388	Intronic	A/C	16.5	12.3	1.54 (1.24 – 1.90)	0.0001
PRDM2	rs2744687	1	14011400	Intronic	T/G	15.1	11.4	1.53 (1.23 – 1.91)	0.0002
PRDM2	rs2697962	1	14023579	3′ UTR	C/T	16.7	13.0	1.45 (1.18 – 1.79)	0.0005
PRDM2	rs2744679	1	14024257	Near 3′ UTR	A/G	20.4	16.6	1.39 (1.15 – 1.67)	0.0006
PRDM2	rs2244634	1	14006741	Intronic	T/G	21.5	17.7	1.38 (1.14 – 1.66)	0.0009
PRDM2	rs2235514	1	14019522	Intronic	A/G	16.7	13.1	1.41 (1.15 – 1.73)	0.001
PRDM2	rs2245197	1	14011783	Intronic	C/T	23.6	19.9	1.34 (1.12 – 1.61)	0.002
ESR1	rs3778099	6	152460268	Intronic	C/T	10.8	9.1	1.37 (1.07 – 1.76)	0.01
CYP19A1	rs2470157	15	49377192	Intronic	A/G	9.0	11.0	0.75 (0.59 – 0.94)	0.01
ESR2	rs12434245	14	63761606	Intronic	C/T	9.2	7.6	1.32 (1.03 – 1.69)	0.03
ESR1	rs2813543	6	152466171	Near 3′ UTR	A/G	22.4	24.3	0.83 (0.70 – 0.99)	0.03
PRDM2	rs2744677	1	14027310	Near 3′ UTR	A/C	22.5	20.0	1.19 (1.00 – 1.42)	0.05

[a] The SNPs are listed in order of decreasing statistical significance as indicated by the uncorrected *P* values.

[b] NCBI build 36 of the human genome.

[c] SNP = single nucleotide polymorphism; UTR = untranslated region.

[d] Log additive model; OR = odds ratio, CI = confidence interval

[e] Log additive model; uncorrected *P* values. Only two *PRDM2* gene variants remained significant after Bonferroni correction (rs2744690 and rs2744687) and three *PRDM2* gene variants remained significant after permutation correction (rs2744690, rs2744687, and rs2697962).

Table 3

Single Nucleotide Polymorphisms (SNPs) in Estrogen-related Genes Significantly Associated with PD Susceptibility in Sex-Specific Analyses[a]

Gene	SNP	Chromosome	Position[b]	Type of Variant SNP[c]	Allele	Minor Allele Frequencies		Log Additive Model OR (95% CI)[d]	Log Additive Model *P* value[e]
						Cases %	Controls %		
Men-Men Pairs (n = 555 pairs)									
ESR1	rs10484922	6	152174010	Intronic	C/T	9.7	8.7	1.64 (1.17 – 2.31)	0.004
ESR2	rs12434245	14	63761606	Intronic	C/T	9.2	7.6	1.58 (1.13 – 2.22)	0.007
ESR1	rs7761133	6	152193556	Intronic	C/T	15.8	14.8	1.44 (1.09 – 1.90)	0.01
ESR1	rs9322331	6	152204010	Intronic	C/T	32.8	34.2	0.78 (0.64 – 0.95)	0.02
ESR2	rs7159462	14	63828629	Intronic	C/T	9.4	8.0	1.49 (1.07 – 2.07)	0.02
ESR1	rs3778099	6	152460268	Intronic	C/T	10.8	9.2	1.48 (1.06 – 2.06)	0.02
ESR1	rs7761846	6	152254201	Intronic	C/T	7.8	9.0	0.65 (0.44 – 0.96)	0.03
ESR1	rs1514348	6	152224008	Intronic	T/G	40.4	41.8	0.81 (0.66 – 0.99)	0.04
ESR1	rs985694	6	152328318	Intronic	C/T	15.7	15.0	1.32 (1.01 – 1.71)	0.04
CYP19A1	rs3751591	15	49394002	Intronic	A/G	17.1	16.3	1.31 (1.01 – 1.70)	0.04
ESR1	rs2813543	6	152466171	Near 3′ UTR	A/G	22.4	24.3	0.78 (0.61 – 0.99)	0.04
Women-Women Pairs (n = 332 pairs)									
PRDM2	rs2744690	1	14010388	Intronic	A/C	16.5	12.3	1.98 (1.34 – 2.92)	0.0006
PRDM2	rs2744687	1	14011400	Intronic	T/G	15.1	11.4	1.97 (1.31 – 2.96)	0.001
PRDM2	rs2744679	1	14024257	Near 3′ UTR	A/G	20.4	16.6	1.75 (1.24 – 2.46)	0.001
PRDM2	rs2697962	1	14023579	3′ UTR	C/T	16.7	13.0	1.81 (1.25 – 2.62)	0.002
PRDM2	rs2235514	1	14019522	Intronic	A/G	16.7	13.1	1.80 (1.25 – 2.59)	0.002
PRDM2	rs2244634	1	14006741	Intronic	T/G	21.5	17.7	1.64 (1.16 – 2.32)	0.005
PRDM2	rs6669610	1	14021343	Intronic	C/T	6.8	7.8	0.52 (0.32 – 0.84)	0.008
CYP19A1	rs2470157	15	49377192	Intronic	A/G	9.0	11.0	0.58 (0.37 – 0.89)	0.01
PRDM2	rs2473231	1	14028265	—	C/G	41.1	39.2	1.37 (1.06 – 1.77)	0.02
CYP19A1	rs730154	15	49378496	Intronic	C/T	14.4	16.2	0.68 (0.48 – 0.97)	0.03
ESR2	rs1255998	14	63763624	3′ UTR	C/G	10.2	9.9	1.68 (1.01 – 2.78)	0.04

[a] The SNPs are listed in order of decreasing statistical significance as indicated by the uncorrected *P* values. None of the SNPs had significant interactions with sex after correction for multiple testing.

[b] NCBI build 36 of the human genome.

[c] UTR = untranslated region.

[d] Log additive model; OR = odds ratio, CI = confidence interval.

[e] Log additive model; uncorrected *P* values. No SNPs remained significant after Bonferroni correction or after permutation correction for multiple comparisons.