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Association of *DRD2* and *DRD3* Polymorphisms with Parkinson's Disease in a Multiethnic Consortium

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Abstract

Objective—To examine genetic associations of polymorphisms in the dopamine receptor D2 (*DRD2*) and D3 (*DRD3*) genes with risk of Parkinson's disease (PD).

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Methods—The study included 1325 newly diagnosed patients with PD and 1735 controls from a consortium of five North American case-control studies. We collected risk factor information by in-person or telephone interview. Six *DRD2* and two *DRD3* polymorphisms were genotyped using a common laboratory. Odds ratios were estimated using logistic regression.

Results—Among non-Hispanic whites, homozygous carriers of Taq1A *DRD2* (rs1800497) polymorphism had an increased risk of PD compared to homozygous wildtype carriers (OR=1.5, 95% CI 1.0–2.3). In contrast, the direction of association for Taq1A polymorphism was opposite for African Americans, showing an inverse association with PD risk (OR=0.10, 95% CI 0.2–0.7). Among white Hispanics who carried two alleles, the Ser9Gly *DRD3* (rs6280) polymorphism was associated with a decreased risk of PD (OR=0.4, 95%CI 0.2–0.8). The inverse association of smoking with PD risk was not modified by any of the *DRD2* or *DRD3* polymorphisms.

Conclusions—DRD2 polymorphisms are unlikely to be true disease-causing variants; however, three *DRD2* polymorphisms (including Taq1A) may be in linkage disequilibrium with possible disease associated variants in the *DRD2-ANKK1-NCAM1-TTC12* gene cluster.

Keywords

Parkinson's disease; dopamine receptor genes; case-control studies; epidemiology

1. Introduction

Genetic polymorphisms of the dopamine D2 receptor (*DRD2*) and D3 receptor (*DRD3*) genes may be associated with PD, either due to their influence on dopamine regulation [1] or to their association with cigarette smoking, which is inversely related to the risk of PD [2]. Numerous association studies have reported that the *DRD2* Taq1A polymorphism is associated with taking up the smoking habit, with earlier onset and current smoking, and with fewer attempts to quit smoking [1]. However, two recent meta-analyses of the effect of *DRD2* polymorphisms on smoking behavior reported conflicting results, with one study reporting a higher prevalence of Taq1A allele in smokers [3], and the other finding no association of *DRD2* polymorphisms with any measures of smoking [4].

Several case-control studies have investigated the association of certain polymorphisms in *DRD2* and *DRD3* genes with PD, with varying results [5–13]. None of these studies assessed whether dopamine receptor polymorphisms modify the influence that smoking has on PD risk. To address these disparate results, we investigated whether polymorphisms in the *DRD2* and *DRD3* genes are associated with PD and whether they modify the association of smoking with risk of PD in a large multiethnic consortium study.

2. Materials and Methods

2.1. Study Design and Populations

We created a research consortium, Parkinson's Epidemiology and Genetics Association Studies in the U.S. (PEGASUS), which combined DNA and risk factor data from five epidemiologic studies of PD, two of which were nested within a cohort study [14–19]. Table 1 summarizes the characteristics of the study populations including the research diagnostic criteria for PD [20, 21].

2.2. Data Collection Methods

Professional interviewers conducted structured clinic, in-home or telephone interviews to collect risk factor data from study subjects, including detailed information on race/ethnicity and cigarette smoking. Race/ethnicity was self-reported according to one of the following

categories: Hispanic white, non-Hispanic white, Asian or African American. Questions pertaining to cigarette use allowed the construction of the following exposure measures: broad categories of smoking (never, former, current), cumulative duration of cigarette smoking and average daily number of cigarettes, and cigarette pack-years. The Human Subjects Committees at the various institutions approved the study, and informed consent was obtained from all cases and controls.

2.3. Laboratory Methods

Study sites sent their DNA samples to the Stanford Human Genome Center (SHGC) for genotyping. Laboratory personnel were blinded to the identity and case-control status of the samples. *DRD2* and *DRD3* genes were sequenced in 24 early-onset PD patients from the PEAK study to identify variants that occur at frequencies greater than 1% in the functional regions (exons, intron-exon junctions, and approximately 500 bp of 5' and 3' UTR regions) [22]. The *DRD2* and *DRD3* polymorphisms from the sequencing analyses and public SNP databases were prioritized for genotyping assay design on the basis of function, frequency and linkage disequilibrium. We genotyped six *DRD2* polymorphisms and two *DRD3* polymorphisms on PEGASUS samples (Table 2). PCR assays were run in TaqMan Universal Master Mix (Applied Biosystems). Fluorescence data files from each plate were analyzed by automated allele calling software (ABI Prism 7900 HT Sequence Detection System 2.1). A small number of individual genotypes that were ambiguous (i.e., did not fall clearly into a genotype cluster) were designated as missing data, with less than 1% excluded on this basis.

2.4. Statistical Methods

Statistical analyses were performed using SAS® statistical software (SAS Institute, Cary NC, 2007). Case-control data were analyzed using stratified data analysis methods and unconditional logistic regression to estimate the odds ratios (OR) and the 95% confidence intervals (CI). All models were adjusted for age, sex, race/ethnicity (non-Hispanic white, white Hispanic, African-American and Asian) and study site. The association of each *DRD2* and *DRD3* polymorphism with PD was estimated by examining differences in allele frequencies using the additive model. When examining genotype frequencies; we compared heterozygous and homozygous carriers of the polymorphism with wildtype homozygotes. We assigned the minor allele based on the largest group (non-Hispanic white subjects) and assigned this designation to all subjects, regardless of whether the minor allele was the more frequent allele in these other ethnicities. We evaluated whether variants in *DRD2* and *DRD3* were modified by the smoking PD association (never/ever, packs per day, duration of smoking and pack-years). We compared the likelihood ratio chi-square test statistic in the logistic regression model with and without the interaction term to determine its significance. We also conducted analyses examining the association of risk of PD with haplotypes created with the six *DRD2* polymorphisms and the two DRD3 polymorphisms.

We used a permutation approach to adjust *p*-values for multiple testing [23]. We randomly permuted cases and controls within strata defined by age group (≤ 60, > 60 years), sex, race/ethnicity and site. For each of the 10,000 permutated datasets, we used logistic regression to compute an age-, sex-, race- and site-adjusted per allele effect estimate for each polymorphism. The resulting empirical *p*-value distribution of 10,000 minimum *p*-values was used to estimate multiple comparison adjusted *p*-values.

Since associations with genetic variants may vary according to factors such as age at disease onset (≤ 60, > 60 years), race/ethnicity and family history of PD in first degree relatives, we conducted subgroup analyses to examine the association of *DRD2* and *DRD3* polymorphisms with PD in each of these groups. For analyses of the newly discovered

SNPs, we excluded the 24 early onset cases that were included in the discovery sample. For the consortium effort, we also excluded subjects who identified their race/ethnicity as other (n=18), and those whose genotyping assay results could not be called (n=58). The final analyses included 1325 cases and 1735 controls.

For each polymorphism, we examined the association of cigarette smoking and risk of PD, stratified by copies of the variant allele. Several aspects of cigarette smoking were examined: smoking (never/ever), and packs per day, duration of smoking and number of pack-years as continuous variables. For the smoking analyses, we adjusted for age, sex, race/ethnicity and study site.

3. Results

The cases and controls differed with respect to age, race/ethnicity, family history of PD and smoking status. The case group was slightly younger and had a higher proportion of non-Hispanic whites (Table 3); however, these variables were controlled for in the analysis. Cases were more likely to have a family history of PD and were less likely than controls to have been ever smokers or be current smokers.

We examined Hardy Weinberg equilibrium (HWE) within each ethnic group within each site and noted a few instances of polymorphisms out of HWE at $p < 0.01$ (HAAS study rs6279, rs2134655; and PEAK study Hispanics rs6278, rs1800497) (Table 2). However, association analyses carried out excluding these samples did not differ significantly from those in which all samples were included. The prevalence of the minor alleles differed by race/ethnicity (Table 2). Most notably, the minor allele frequency (MAF) for *DRD2* rs6279 allele was higher among African-Americans and Asians than among whites and the MAF for *DRD2* rs1799732 polymorphism was much higher among African Americans than the other racial groups.

After adjusting for age, sex, and site, only one *DRD2* polymorphism was associated with an increased risk of PD among non-Hispanic whites, which comprised the largest number of subjects in the study (1035 cases and 1279 controls) (Table 4). For *DRD2* Taq1A (rs1800497) polymorphism, the odds ratios varied significantly by race/ethnicity (*p* for interaction=0.001). Non-Hispanic white subjects, homozygous variant for Taq1A, showed a 1.5-fold increased risk for PD compared to homozygous wildtype (95% CI 1.0–2.3), but the per allele effect was not significant for trend (uncorrected *p*-value 0.18, permutation adjusted *p*=0.65). In contrast, African-Americans had an 80% to 90% decreased risk for PD if they carried one or two copies of the Taq1A variant allele (heterozygous OR=0.2, 95% CI 0.1–0.6; homozygous mutant OR=0.1, 95% CI 0.02–0.7) with a significant inverse per allele effect (uncorrected *p*-value 0.001, permutation adjusted *p*=0.01). The number of African Americans who were carriers of the Taq1A variant allele was based on relatively small numbers (among PD cases: 8 heterozygotes and 2 homozygotes; among controls: 32 heterozygotes and 12 homozygotes), but the confidence intervals and test for trend were highly significant when using Fisher's exact tests ($p < 0.05$).

Asians and Hispanic whites were also at decreased risk for PD if they carried two copies of the Taq1A variant allele, but the risk estimates for these groups were imprecise (Asians, OR=0.7, 95% CI 0.3–1.4; Hispanics, OR=0.5, 95% CI 0.2–1.2).

Among African-Americans, we noted several interesting associations with two other *DRD2* polymorphisms (Table 4). African-Americans who carried one or two copies of *DRD2* variant rs6279 had an increased risk of PD compared to African Americans who carried no polymorphisms (heterozygous OR=14.5, 95% CI 1.6–133; homozygous mutant OR=12.0, 95% CI 1.2–115; uncorrected *p*-value=0.05). The results reflect the small number of

homozygous wildtype cases (1 case versus 18 controls). We also applied Fisher's exact tests to rs6279 (not adjusted for confounders) and noted highly significant confidence intervals and tests for trend ($p<0.05$). The association of *DRD2* rs6279 polymorphism among Asians was modestly increased (OR=1.5, 95% CI 0.8–2.8). African-Americans who carried one or two copies of the *DRD2* −141CIns/Del (rs1799732) polymorphism were at increased risk for PD (heterozygous OR=3.7, 95%CI 1.0–13.1; homozygous mutant OR=3.6, 95% CI 0.9–14.3; uncorrected *p*-value 0.08); however, the risk was not significant after adjustment for multiple comparisons ($p=0.36$).

Of the two *DRD3* polymorphisms, only Hispanic whites showed an association of PD risk with the non-synonymous Ser9Gly (rs6280) polymorphism (heterozygous OR=0.8, 95% CI 0.5–1.4; homozygous mutant OR=0.4, 95% CI 0.2–0.8); but per allele effect was of borderline significance ($p=0.11$) (Table 4). When we stratified on age at diagnosis and family history, neither of these factors modified the association of *DRD2* or *DRD3* polymorphisms with PD risk.

We assessed the association of *DRD2* and DRD3 haplotypes with the risk of PD and found no association with any of the six haplotypes (data not shown). Race/ethnicity did not modify the *DRD2* or DRD3 haplotype-PD associations.

We examined the association between cigarette smoking and risk of PD. We found an inverse association of PD risk among ever cigarette smokers compared to never smokers (OR=0.7, 95% CI 0.6–0.8), after adjusting for age, sex, race/ethnicity and site. The smoking-PD association was not significant for African Americans (OR=0.9, 95% CI 0.3–2.4) or Asians (OR=0.8, 95% CI 0.35–1.2). When we stratified by genotype, we did not find any differences in the strength of the smoking-PD association among non-Hispanic white subjects who carried zero, one or two copies (Table 5). This was true for all racial/ethnic groups; however, the gene-environment interaction analyses are imprecise in some groups due to small numbers (data not shown). The associations of packs per day, duration of smoking, or pack years and risk of PD were also not affected by genotype status.

4. Discussion

In the PEGASUS multiethnic consortium, we observed significant associations of three *DRD2* polymorphisms with the risk of PD (Taq1A, rs6279, −141CIns/Del). Taq1A was positively associated with PD in non-Hispanic Caucasians and inversely associated with PD in other racial and ethnic groups. Among African American subjects, we noted significant positive associations for two other *DRD2* polymorphisms (rs6279, −141CIns/Del).

Non-Hispanic whites who carried two Taq1A alleles had a 50% increased risk of PD, replicating associations observed in three recent PD studies conducted in non-Hispanic white populations. One large study conducted in five European centers (767 cases, 1989 controls) reported an OR of 1.4 for homozygous carriers of the Taq1A *DRD2* polymorphism (95% CI 1.0–2.0) [11]. Significant positive associations were also observed in a study of Norwegians (homozygous Taq1A OR=2.2, 95% CI 1.1–4.4) [7] and a study of Italians (among carriers of at least one Taq1A allele, OR=1.7, 95% CI 1.1–2.7) [6]. Although two other smaller studies found no association of the Taq1A SNP with PD risk [5, 10], the preponderance of evidence strongly supports an association between Taq1A homozygosity and PD risk among non-Hispanic white subjects. PDGene database allows a meta-analysis of the association of the Taq1A *DRD2* allele and risk of PD [24]. The allelic association of *DRD2* Taq1A was 1.1 (95% CI 0.96–1.2) [24], indicating that a genotypic analysis is essential for identifying the specific association of the *DRD2* homozygous state with PD.

In contrast to the finding of a positive association of Taq1A homozygosity and PD risk among non-Hispanic whites, we found that African Americans who carried one or two Taq1A alleles had a significant 80%–90% decreased risk for PD. Similarly, Asian and Hispanic carriers of the Taq1A allele were at decreased risk for PD, but the results were not statistically significant. The sample sizes in these ethnic groups were relatively small; therefore our results need replication in future studies. Ours is the first study to include African Americans, but three other studies have examined the association of Taq1A and PD risk in Asian populations. Singh et al. reported a decreased risk in PD among those who were homozygous for the Taq1A polymorphism (OR=0.3, 95% CI 0.1–1.0) [12], while another study in India [9] and one in Singapore [8] found no association.

In our study, we did not find an association of *DRD2* −141CIns/Del polymorphism with PD among non-Hispanic whites or Asians, a finding similar to those of two other case-control studies, one in a non-Hispanic white population [7] and another in India [9]. However, African-Americans in PEGASUS had a nearly four-fold increase in risk of PD if they carried one or two alleles of the *DRD2* −141 Ins/Del polymorphism, and a thirteen-fold increase in risk of PD if they carried one or two alleles of the rs6279 polymorphism.

Of note is that the minor allele frequencies (MAF) of *DRD2* SNPs vary widely among racial/ethnic groups. In our study, the prevalence of the *DRD2*-141 Ins/Del polymorphism was much higher in African Americans (57% of cases, 39% of controls) compared to the other racial groups. Gelernter et al. [25] noted a similar result in community volunteer subjects where the MAF for the −141CIns/Del polymorphism was 39% for African Americans, compared to 11% for non-Hispanic whites and 21% for Japanese Americans.

Together these findings suggest that Taq1A is unlikely to be a true disease-causing variant, but that Taq1A and other *DRD2* polymorphisms (particularly among African Americans) may be in linkage disequilibrium with possible disease associated variants. Taq1A actually resides in the coding region of a neighboring gene *ANKK1* (ankyrin repeats and kinase domaine containing 1 gene) approximately 10 kb downstream of *DRD2*. *ANKK1* is a serine/threonine kinase involved in signal transduction, thought to affect dopaminergic reward processes [26], and is located with a cluster of genes, which includes not just *DRD2*, but neural cell adhesion molecule 1 (*NCAM1*) and tetratricopeptide repeat domain 12 (*TTC12*) [27]. In this gene cluster, *DRD2* maps molecularly close to *NCAM1*, and both are functional candidates for Alzheimer's disease risk [27].

The *DRD2* Taq1A polymorphism has been associated with the propensity to engage in addictive behaviors including cigarette smoking [1]. Gelernter et al. [28] reported a strong association between a haplotype spanning *TTC12* and *ANKK1* and nicotine dependence, in both non-Hispanic white and African American populations. Although *DRD2* Taq1A was not associated with nicotine dependence, the authors noted that two of the four SNPS selected for haplotype analysis were in linkage disequilibrium with *DRD2* Taq1A [28]. Huang et al. [29] also noted a significant association between a functional polymorphism in *ANKK1* and nicotine dependence in African-Americans. In PEGASUS, we examined the relation between smoking and the Taq1A polymorphism in control subjects and found no association with any of the cigarette smoking measures. Nor did the Taq1A polymorphism modify the smoking-PD association in our study in any of the racial/ethnic groups. All four of these genes in the *ANKK1* cluster are considered candidate loci for substance dependence [28], and complexities of this genomic region may explain the inconsistency in *DRD2* associations with nicotine dependence across studies. The three other genes in this cluster have not been taken into consideration in our study nor in other previous studies of PD. Given the consistent finding of an inverse association between smoking and PD, future genetic association studies with markers in this four-gene cluster with PD could be fruitful.

DRD3 genetic polymorphisms (rs6280 and rs2134655) were not associated with PD risk in most racial/ethnic groups. The only significant result was a 60% decrease in risk for PD among Hispanic white subjects who carried two polymorphisms for Ser9Gly (rs6280), a nonsynomous coding region variant. Other case-control studies have found no association between this polymorphism and PD [9, 12, 13], none of which included Hispanic populations. When we examined the smoking and PD association, none of the *DRD3* polymorphisms modified the effect of smoking. The Ser9Gly (rs6280) polymorphism lies within the region not thought to be involved with ligand binding or signal transduction [30]. Thus, the variant may itself be functional or may be in linkage disequilibrium with other markers involved in susceptibility to PD and other neurologic conditions.

Our consortium study has a number of strengths, including (a) the methodologic rigor of the individual studies, (b) the large number of well characterized PD patients, most of whom have newly diagnosed PD, (c) the quality and comparability of information on tobacco exposure and (d) a greater degree of racial/ethnic diversity of subjects than any one study can usually provide. However, we did not have sufficient numbers of individuals other than non-Hispanic whites to provide precise odds ratio estimates for any of the groups. The significant associations noted in racial/ethnic groups other than white non-Hispanics may also be a reflection of population admixture.

The results of this study warrant further research in order to gain an understanding of the role that *DRD2* and *DRD3*, and other genes in the *DRD2* genomic region, might play in the etiology of PD. Future studies of genetic associations will greatly benefit from the inclusion of sufficiently large numbers of individuals in racial and ethnic groups other than Caucasians and better characterisation of the *DRD2-ANKK1-NCAM1-TTC12* gene cluster.

ABBREVIATIONS

CI	confidence interval
DRD2	dopamine receptor D2
DRD3	dopamine receptor D3
FAME	Farming and Movement Evaluation
HAAS	Honolulu Aging Asia Study
KPMCP	Kaiser Permanente Medical Care Program
MAF	minor allele frequency
OR	odds ratio
PD	Parkinson's disease
PEAK	Parkinsonism Epidemiology at Kaiser
PEG	Parkinson’s disease Epidemiology and Genetics
PEGASUS	Parkinson’s Epidemiology and Genetics Association Studies in the US

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Author Appendix

In addition to the main authors listed above, the following individuals also contributed to the study as members of the PEGASUS Consortium:

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Table 1

Description of study populations in the Parkinson's Epidemiology and Genetics Association Studies in the U.S (PEGASUS)

Study	Parkinsonism Epidemiology at Kaiser (PEAK) Studies I & II[18]	Parkinson's disease Environment & Genes (PEG) Study[23]	Columbia University (Washington Heights/ Inwood) Studies I[20] & II[21]	Agricultural Health Study of Farming and Movement Evaluation (FAME) [19]	Honolulu Asia Aging Study (HAAS) [22]
	Case-control study	**Case-control study**	**Case-control studies (2)**	**Nested case-control study**	**Nested case-control study**
Study Population	Kaiser Permanente Medical Care Program of Northern California (3 million members)	Residents of Fresno, Kern, & Tulare, who resided in CA in last 5 yrs before recruitment	Residents of Washington-Heights-Inwood Section of northern Manhattan	Cohort of licensed pesticide applicators and their spouses in Iowa and N. Carolina	Men of Japanese and Okinawan ancestry born between 1900 –1919, resided on Oahu, Hawaii in 1965
Case Identification	Cases ascertained by treating neurologist or computerized inpatient, outpatient and pharmacy databases	Recruitment through rural health care providers and neurologists. Cases ascertained by treating neurologist or physician	Community-based PD patients and PD cases seen at referral/senior centers, all living in same geographical area in northern Manhattan	Multistage screening method that includes in-person evaluation and diagnosis by expert consensus	Ongoing search of hospital records, review of death certificates, and medical records of local neurologists
Number of PD cases, controls with DNA	n = 584 PD cases n = 639 controls	n = 279 PD cases n = 254 controls	From 2 studies total: n = 296 PD cases n = 299 controls	n = 100 PD cases n = 367 controls	n = 72 PD cases n = 185 controls
Method of Case Definition	Medical record review by movement disorder specialist, case definition according to CAPIT/Hughes criteria [24,25]	Examined by movement disorder specialists, case definition according to CAPIT/Hughes criteria [24,25]	Neurology clinic record review, neurologic exam and diagnosis confirmed by study neurologist*	Diagnosed by movement disorder specialist based on neurologic exam, structured videotape, and medical records review; according to CAPIT/Hughes criteria, [24,25]	Neurologist case confirmation, according to CAPIT/Hughes criteria, [24,25]
Time period of case/control ascertainment	1994–1995 and 2000–2003	Jan 1st, 1998 thru Aug 31st, 2004	1988–1996	2000–2005	1965–1991
Control Selection	Controls randomly selected from Kaiser membership rolls, matched to cases by gender and year of birth	Age-sex matched population controls from Medicare and random sample from residential tax assessors' parcels (residents of CA for the past 5 yrs)	Healthy community volunteers living in same geographical area in northern Manhattan	Selected from all non affected pesticide applicators in the AHS cohort	Selected from all non affected men in study cohort

* Diagnostic criteria (a) bradykinesia, (b) one of the following: rigidity, rest tremor or postural instability, (c) at least 3 of the following (unilateral onset, persistent asymmetry of signs or symptoms, good response to levodopa, progressive course, levodopa-induced chorea) and (d) no evidence of drug-induced parkinsonism.

Table 2

Polymorphic variants in the *DRD2* and *DRD3* genes genotyped in PEGASUS control subjects

SNP Name	Location		Minor/Major Allele	Minor Allele Frequency (%)			
				Non-Hispanic White N=1279	Hispanic White N=164	Asian N=226	African-American N=66
DRD2							
rs1076563	5’	503 5’ Tr start	T/G	38.9	57.1	89.4	65.9
rs6279	exon 8	3’ UTR	C/G	30.8	39.6	54.1*	56.2
rs6278	exon	3’ UTR	T/G	15.1	20.2*	36.5	9.1
rs273482	exon	3’ UTR	C/G	31.0	42.9	53.5	65.9*
rs1800497	exon	10 kb exon 8	T/C	19.4	29.6*	36.6	43.0
rs1799732	5’	−141 5’ exon 1	Del/C	9.3	18.6	13.6	39.4
DRD3							
rs6280	exon	Ser/Gly	G/A	32.6	48.8	25.3	73.5
rs2134655	intron	146 3’ exon 5	A/G	27.7	21.3	29.7*	8.3

*p-value < 0.01 for Hardy-Weinberg Equilibrium chi-square

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Table 3

Characteristics of PD cases and controls in PEGASUS

Characteristic	Overall		PEAK		PEG		COLUMBIA		FAME		HAAS	
	Cases	Ctrls	Cases	Ctrls	Cases	Ctrls	Cases	Ctrls	Cases	Ctrls	Cases	Ctrls
Total Number*	1325	1735	578	630	279	254	296	299	100	367	72	185
Male (%)	61.1	65.4	61.8	63.0	54.5	52.0	52.4	47.2	74.0	76.3	100.0	100.0
Age at diagnosis (yrs.) (%)												
≤ 60	37.2	24.2	43.3	42.1	22.6	29.5	41.9	6.0	49.0	10.9	9.7	11.4
> 60	62.8	75.9	56.8	57.9	77.4	70.5	58.1	94.0	51.0	89.1	90.3	88.7
Mean age (yrs.) (%)	64.9	68.4	64.3	64.6	67.6	65.8	61.9	72.9	62.0	69.6	75.2	75.5
Race/ethnicity												
African American (%)	2.2	3.8	2.8	5.7	1.1	3.5	2.7	5.0	2.0	1.6	0.0	0.0
Asian (%)	9.1	13.0	7.4	5.1	1.8	3.5	0.0	0.0	0.0	0.0	100.0	100.0
Hispanic White	10.6	9.5	8.3	7.3	10.4	7.5	21.3	32.4	1.0	0.5	0.0	0.0
Non-Hispanic White (%)	78.1	73.7	81.5	81.9	86.7	85.4	76.0	62.5	97.0	97.8	0.0	0.0
Family history of PD† (%)	10.4	5.9	10.4	2.9	12.5	11.8	6.0	5.2	13.7	7.9	4.4	5.3
Smoking status												
Never (%)	54.3	46.8	52.1	45.8	52.9	40.6	56.1	43.6	74.5	61.8	43.1	34.4
Former (%)	41.2	41.3	44.3	41.2	40.3	51.2	39.5	41.8	24.5	31.5	45.8	45.9
Current (%)	4.7	12.0	3.6	13.0	6.8	8.3	4.4	14.5	1.0	6.7	11.1	19.7

*The totals for some variables may not equal the number of cases and controls because of missing values.

†One or more first degree relatives with PD

Table 4

Adjusted odds ratios (OR) and 95% (CI) for the association between *DRD2* and *DRD3* polymorphisms and PD in PEGASUS, by race/ethnicity*.

	Race-Specific							
	Non-Hispanic White				Hispanic White			
Polymorphism	**Cases % n=1035**	**Controls % n=1279**	**OR†**	**95% CI†**	**Cases % n=141**	**Controls % n=164**	**OR†**	**95% CI†**
DRD2								
rs1076563								
GG	34.9	36.9	1.0		20.6	21.5	1.0	
GT	49.4	48.3	1.1	0.9–1.3	44.0	42.9	1.0	0.5–1.9
TT	15.7	14.8	1.1	0.8–1.4	35.5	35.6	0.9	0.5–1.8
rs6279								
GG	49.3	47.6	1.0		42.9	37.8	1.0	
GC	40.6	43.1	0.9	0.7–1.0	41.4	45.1	1.0	0.6–1.6
CC	10.1	9.2	1.0	0.7–1.3	15.7	17.1	1.0	0.5–2.1
rs6278								
GG	70.8	72.1	1.0		58.9	68.7	1.0	
GT	26.0	25.5	1.1	0.9–1.3	35.5	22.1	1.5	0.9–2.7
TT	3.1	2.4	1.3	0.8–2.1	5.7	9.2	0.5	0.2–1.3
rs273482								
GG	49.3	47.4	1.0		38.3	35.0	1.0	
GC	39.9	43.1	0.9	0.7–1.0	44.7	44.2	1.1	0.6–1.8
CC	10.8	9.4	1.1	0.8–1.4	17.0	20.9	0.9	0.5–1.9
DRD2								
rs1800497								
(*Taq1A*)								
CC	64.1	64.9	1.0		46.8	52.4	1.0	
CT	30.2	31.4	1.0	0.8–1.2	46.1	36.0	1.3	0.8–2.2
TT	5.7	3.7	1.5	1.0–2.3	7.1	11.6	0.5	0.2–1.2
rs1799732								
(−*141CIns*/Del)								

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	Race-Specific							
	Non-Hispanic White				Hispanic White			
Polymorphism	**Cases % n=1035**	**Controls % n=1279**	**OR†**	**95% CI†**	**Cases % n=141**	**Controls % n=164**	**OR†**	**95% CI†**
CC	81.4	81.7	1.0		75.0	68.3	1.0	
Cd	18.3	17.9	1.0	0.8–1.3	18.6	26.2	0.6	0.3–1.1
dd	0.4	0.4	0.9	0.2–3.6	6.4	5.5	1.4	0.5–3.8
DRD3								
rs6280								
(*Ser9Gly*)								
AA	43.0	44.9	1.0		34.0	25.6	1.0	
AG	46.9	45.1	1.1	0.9–1.3	51.1	51.2	0.8	0.5–1.4
GG	10.1	10.1	1.0	0.7–1.3	14.9	23.2	0.4$^{\delta}$	0.2–0.8
rs2134655								
GG	49.3	52.5	1.0		57.4	64.0	1.0	
GA	40.6	40.4	1.0	0.9–1.2	37.6	29.3	0.5	0.9–2.5
AA	10.1	7.1	0.9	0.7–1.3	5.0	6.7	0.8	0.3–2.3
DRD2								
rs1076563								
GG	4.2	1.8	1.0		13.8	9.1	1.0	
GT	20.2	17.7	0.6	0.1–2.6	31.0	50.0	0.4	0.1–1.9
TT	75.6	80.5	0.6	0.1–2.7	55.2	40.9	0.9	0.2–3.9
rs6279								
GG	22.9	26.6	1.0		3.4	27.7	1.0	
GC	43.2	38.5	1.5	0.8–2.7	51.7	32.3	14.5	1.6–133
CC	33.9	34.9	1.5	0.8–2.9	44.8	40.0	12.0‡	1.2–115
rs6278								
GG	48.3	43.7	1.0		100.0	81.8	1.0	
GT	38.1	39.6	0.8	0.5–1.3	0.0	18.2	---	---
TT	13.6	16.7	0.7	0.3–1.3	0.0	0.0	---‡	---
rs273482								

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	Race-Specific							
	Non-Hispanic White				Hispanic White			
Polymorphism	**Cases % n=1035**	**Controls % n=1279**	**OR†**	**95% CI†**	**Cases % n=141**	**Controls % n=164**	**OR†**	**95% CI†**
GG	25.2	25.2	1.0		0.0	19.7	1.0	
GC	45.4	42.5	1.2	0.7–2.2	48.3	28.8	---	--
CC	29.4	32.3	1.2	0.6–2.3	51.7	51.5	---‡	--
DRD2								
rs1800497								
(*Taq1A*)								
CC	46.2	44.1	1.0		65.5	32.8	1.0	
CT	40.3	38.6	0.9	0.5–1.5	27.6	48.4	0.2	0.07–0.6
TT	13.4	17.3	0.7	0.3–1.4	6.9	18.8	0.1‡§	0.02–0.7
rs1799732								
(*−141CIns/Del*)								
CC	72.0	75.5	1.0		17.2	42.4	1.0	
Cd	25.4	21.8	1.2	0.7–2.1	51.7	36.4	3.7	1.0–13.1
dd	2.5	2.7	1.3	0.3–5.5	31.0	21.2	3.6	0.9–14.3
DRD3								
rs6280								
(*Ser9Gly*)								
AA	52.5	57.7	1.0		17.2	10.6	1.0	
AG	39.0	34.0	1.2	0.8–2.0	27.6	31.8	0.5	0.11–2.1
GG	8.5	8.4	0.9	0.4–2.2	55.2	57.6	0.5	0.10–2.0
rs2134655								
GG	51.4	53.5	1.0		79.3	84.8	1.0	
GA	34.2	33.7	1.1	0.7–1.9	17.2	13.6	1.4	0.4–4.78
AA	14.4	12.9	1.4	0.7–2.8	3.4	1.5	2.7	0.1–47.8

*Minor allele based on the largest group (white, non-Hispanic subjects) and assigned to all subjects, regardless of whether minor allele more frequent allele in these other race/ethnicities

†OR, odds ratio; 95% CI, confidence interval, adjusted for age, sex and site

‡Fisher's exact test: p<0.05; analyses did not include adjustment for other variables.

§p for trend=0.001, adjustment for multiple comparisons $p = 0.01$

δp for trend=0.02, adjustment for multiple comparisons $p = 0.11$

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Table 5

Adjusted odds ratios (OR) and 95% (CI) for the association between cigarette smoking and PD in non-Hispanic white PEGASUS subjects, by *DRD2* and *DRD3* polymorphisms by race.

	Wildtype				Heterozygote				Homozygote			
Smoking Variable	**Cases**	**Controls**	**OR***	**95% CI***	**Cases**	**Controls**	**OR***	**95% CI***	**Cases**	**Controls**	**OR***	**95% CI***
DRD2												
rs1076563												
Never	189	212	1.00		265	294	1.00		79	85	1.00	
Ever	164	257	0.62	0.46–0.83	229	317	0.74	0.57–0.95	81	104	0.64	0.40–1.01
Packs per day			0.74	0.59–0.93			0.72	0.59–0.88			1.00	0.72–1.38
Duration (decades)			0.86	0.79–0.94			0.86	0.80–0.93			0.85	0.75–0.98
Pack years (by 10)			0.90	0.84–0.96			0.90	0.85–0.96			1.01	0.91–1.11
rs6279												
Never	268	285	1.00		223	247	1.00		43	60	1.00	
Ever	229	322	0.63	0.49–0.82	184	297	0.62	0.47–0.81	59	58	1.23	0.70–2.18
Packs per day			0.68	0.55–0.83			0.79	0.64–0.98			1.03	0.71–1.50
Duration (decades)			0.86	0.79–0.93			0.83	0.77–0.90			0.96	0.80–1.14
Pack years (by 10)			0.89	0.84–0.94			0.92	0.87–0.98			0.98	0.87–1.10
rs6278												
Never	374	419	1.00		140	158	1.00		20	13	1.00	
Ever	338	494	0.70	0.57–0.87	122	166	0.61	0.42–0.87	12	17	0.38	0.12–1.25
Packs per day			0.77	0.65–0.90			0.79	0.60–1.04			0.57	0.24–1.38
Duration (decades)			0.86	0.80–0.91			0.86	0.77–0.96			0.77	0.51–1.16
Pack years (by 10)			0.90	0.86–0.94			0.95	0.87–1.03			0.88	0.66–1.17
rs273482												
Never	267	280	1.00		209	249	1.00		47	61	1.00	
Ever	218	323	0.59	0.46–0.77	183	294	0.66	0.50–0.87	59	59	1.11	0.63–1.94
Packs per day			0.71	0.58–0.87			0.78	0.63–0.97			1.00	0.69–1.45
Duration (decades)			0.86	0.79–0.92			0.84	0.77–0.91			0.92	0.78–1.09
Pack years (by 10)			0.90	0.85–0.96			0.92	0.86–0.98			0.97	0.86–1.08
rs1800497 (*Taq1A*)												

	Wildtype				Heterozygote				Homozygote			
Smoking Variable	**Cases**	**Controls**	**OR***	**95% CI***	**Cases**	**Controls**	**OR***	**95% CI***	**Cases**	**Controls**	**OR***	**95% CI***
Never	340	385	1.00		165	183	1.00		31	24	1.00	
Ever	307	438	0.72	0.58–0.90	140	216	0.56	0.40–0.77	27	23	0.72	0.31–1.69
Packs per day			0.75	0.63–0.89			0.77	0.60–0.99			0.89	0.49–1.60
Duration (decades)			0.86	0.80–0.92			0.84	0.76–0.93			0.96	0.74–1.26
Pack years (by 10)			0.90	0.85–0.94			0.93	0.86–1.00			1.02	0.87–1.21
rs1799732 (*141Ins/Del*)												
Never	436	489	1.00		97	99	1.00		2	1	1.00	
Ever	382	545	0.66	0.54–0.81	88	128	0.68	0.45–1.03	2	4	--	--
Packs per day			0.74	0.64–0.86			0.85	0.62–1.19			--	--
Duration (decades)			0.84	0.79–0.90			0.90	0.80–1.01			--	--
Pack years (by 10)			0.90	0.86–0.94			0.96	0.87–1.05			--	--
DRD3												
rs6280 (*Ser9Gly*)												
Never	218	276	1.00		267	254	1.00		49	63	1.00	
Ever	215	294	0.82	0.63–1.06	206	318	0.51	0.39–0.66	53	64	1.06	0.60–1.85
Packs per day			0.89	0.73–1.08			0.61	0.50–0.76			1.09	0.72–1.67
Duration (decades)			0.86	0.80–0.93			0.82	0.76–0.89			1.03	0.87–1.22
Pack years (by 10)			0.93	0.87–0.99			0.88	0.82–0.93			1.04	0.93–1.17
rs2134655												
Never	283	294	1.00		212	260	1.00		40	39	1.00	
Ever	237	374	0.57	0.45–0.73	208	252	0.89	0.68–1.18	31	51	0.49	0.25–0.96
Packs per day			0.70	0.58–0.85			0.84	0.68–1.04			0.96	0.57–1.63
Duration (decades)			0.84	0.78–0.90			0.90	0.83–0.98			0.79	0.65–0.95
Pack years (by 10)			0.91	0.86–0.96			0.93	0.87–0.98			0.91	0.76–1.09

*OR, odds ratio; 95% CI, confidence interval; adjusted for age, sex, and site