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Susceptibility Loci for Pigmentation and Melanoma in Relation to Parkinson's disease

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Abstract

Growing evidence suggests that Parkinson's disease (PD) patients have a lower risk for most types of cancer except for melanoma, which has a modest positive association with PD. Pigmentation genes has been hypothesized to contribute to this association. We therefore examined whether genetic susceptibility loci for pigmentation or melanoma were associated with PD risk in two large independent datasets. In the Parkinson's Genes and Environment (PAGE) Study, we examined 11 SNPs identified from previous GWAS studies of pigmentation or melanoma in relation to PD among 808 PD cases and 1,623 controls; further, we also examined the colors of hair, eye, or skin, and melanoma in relation to PD. In the International Parkinson's Disease Genomic Consortium (IPDGC), we examined a broader selection of 360 pigmentation or melanoma GWAS SNPs in relation to PD among 5,333 PD cases and 12,019 controls. All participants were non-Hispanic Whites. As expected, in the PAGE study, most SNPs were associated with one or more pigmentation phenotypes. However, neither these SNPs nor pigmentation phenotypes were associated with PD risk after Bonferroni correction with the exception of rs4911414 at the *ASIP* gene (P=0.001). A total of 18 PD cases (2.2%) and 26 controls (1.6%) had a diagnosis of melanoma with an odds ratio of 1.3 (95% confidence interval: 0.7-2.4). In the IPDGC analysis, none of the 360 SNPs, including rs4911414, were associated with PD risk after adjusting for multiple comparisons. In conclusion, we did not find significant associations between GWAS SNPs of pigmentation or melanoma and the risk for PD.

1. Introduction

Growing evidence suggests that Parkinson's disease (PD) patients have a lower risk of most types of cancer (Bajaj, et al., 2010). Melanoma is a notable exception in that the risk appears to be higher among PD patients and vice versa (Bertoni, et al., 2010, Ferreira, et al., 2010, Inzelberg and Israeli-Korn, 2009, Liu, et al., 2011). The explanation for this epidemiologic observation remains elusive, but shared genetic or environmental risk factors have been

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suspected. In particular, it has been hypothesized that pigmentation and genes related to pigmentation and melanoma may contribute to this link (Herrero Hernandez, 2009). We therefore examined susceptibility loci for pigmentation and melanoma in relation to PD risk in the Parkinson's Genes and Environment (PAGE) study and in the International Parkinson's disease Genomic Consortium (IPDGC).

2. Methods

The PAGE study was a nested case-control study within the NIH-AARP Diet and Health cohort (Gao, et al., 2011). The current analyses included 808 physician-confirmed PD cases and 1,623 controls that provided saliva samples for genotyping. All subjects are non-Hispanic Whites. Among them, 606 cases and 1,340 controls further provided information on the color of hair, eye, and skin. Further, melanoma cases in the cohort were identified along with cases with other cancers by probabilistic record linkage with state cancer registries.(Lin, et al., 2012). The IPDGC represents an international collaboration of genome-wide association studies (GWAS) to understand the genetic causes of PD with participants from the US, UK, Germany and France (Nalls, et al., 2011). The current analysis used data from the discovery phase of 5,333 cases and 12,019 controls (Nalls, et al., 2011). Details of IPDGC are provided in Supplementary table 1.

In the PAGE study, we successfully genotyped 11 SNPs which were associated with pigmentation phenotypes or the risk of melanoma in previous GWAS (Supplementary Table 1). The genotyping was performed by BioServe Biotechnologies, Ltd (Beltsville, MD), using Sequenom MassARRAY iPLEXTM platform with an average call rate of 95.1% (Supplementary Table 2). All participating cohorts of the IPDGC used Illumina platform for genotyping (Nalls, et al., 2011) and the Markov Chain based haplotyper (MACH; version 1.0.16) to impute genotypes for all participants of European ancestry with haplotypes derived from initial low coverage sequencing of 112 European ancestry samples in the 1000 Genomes Project (as of August, 2009). A total of 7,689,524 SNPs were either genotyped or imputed. In the IPDGC analysis, we included more pigmentation and melanoma susceptiblity SNPs with an updated search for all SNPs that were in high linkage disequilibrium ($r^2 > 0.8$) with reported GWAS loci of pigmentation phenotypes of melanoma via SNAP (http://www.broadinstitute.org/mpg/snap/ldsearch.php). A total of 483 SNPs were found and 360 were either genotyped or imputed in the IPDGC (Supplementary Table 3).

In PAGE, we first evaluated the relationships of candidate SNPs with pigmentation phenotypes using linear regression model or with melanoma using logistic regression model, adjusting for year of birth and sex. Pigmentation phenotypes were coded as ordinal variables as did in published studies (Han, et al., 2008). We then evaluated candidate SNPs or related pigmentation phenotypes and melanoma in relation to PD risk. Odds ratios (ORs) and 95% confidence intervals (CIs) were derived from multivariate logistic regression models, adjusting for year of birth, sex, caffeine intake, and smoking status. For the analysis in IPDGC, logit additive genetic effect was first estimated in each cohort and then meta-analyzed, adjusting for sex and the first two principal components of population structure. All statistical analyses were performed using Plink v1.07 and R software (version 2.11.1; The R Foundation for Statistical Computing).

All PAGE study participants provided written consent and the study protocol was approved by the Institutional Review Board of the National Institute of Environmental Health Sciences and the Special Studies Institutional Review Board of the National Cancer Institute. The discovery phase of IPDGC was approved by the institutional review boards of

participating cohorts. The detailed Methods section is available in the online Supplementary data.

3. Results

Demographic characteristics of PD cases and controls in the PAGE study are shown in Table 1. As expected, PD patients were less likely to be smokers and drank less coffee as compared to controls.

In the PAGE study, most of the selected SNPs from previous GWAS studies were associated with one or more of the pigmentation phenotypes in the directions that were expected, although some did not reach statistical significance (at $P<0.05$) (Table 2). For both hair color and eye color, rs12896399 at the *SLC24A4* showed the strongest association ($P=1.07\times10^{-10}$ for hair color and 7.11×10^{-7} for eye color), and for skin color, rs258322 at the *CDK10* showed the strongest association ($P=1.24\times10^{-7}$).

In the PAGE study, we identified 18 PD cases (2.2%) and 26 (1.6%) controls with first primary melanoma. Several SNPs showed ORs that were consistent with a modest to strong association with melanoma. For example, the minor allele of rs4911414 at the *ASIP* had an OR of 4.74 ($P=0.022$), followed by rs1805008 at the *MC1R* (OR=3.79, $P=0.22$), and rs12203592 at the *IRF4* (OR=2.49, $P=0.16$). However, with the exception of rs4911414 at the *ASIP*, none of these SNPs were statistically associated with melanoma due to small sample size.

In the PAGE study, neither pigmentation phenotypes nor melanoma were statistically associated with PD risk. A modest association of melanoma and PD was suggested with an OR of 1.32 (95%CI: 0.71-2.44) that was consistent with the literature; however, this association did not reach statistical significance probably due to the few melanoma cases in the analysis. Further, with the exception of the rs4911414 at the *ASIP* ($P=0.001$), none of the SNPs for pigmentation phenotypes or melanoma was associated with PD risk after correcting for multiple comparison (Table 3). However, this SNP was not associated with PD risk in the larger dataset of IPDGC ($P=0.43$), and none of the other 359 SNPs selected for analysis in the IPDGC dataset showed statistical significance with PD (Table 4 and supplementary Table 3).

4. Discussion

In this large and comprehensive analysis, we confirmed the associations of these susceptibility loci with pigmentation phenotypes and/or melanoma; however, we did not identify any association between these SNPs and PD risk. While the statistical power in the PAGE study was limited, the IPDGC had 5,333 cases and 12,019 controls and thus adequate statistical power.

Human pigmentation phenotypes such as the colors of hair, eye, and skin, are polygenic quantitative traits with high heritability, and the link between certain pigmentation phenotypes and susceptibility genes and melanoma have been well-established (Mitra, et al., 2012). Recent GWAS studies (Bishop, et al., 2009, Gudbjartsson, et al., 2008, Han, et al., 2008, Sulem, et al., 2008, Sulem, et al., 2007) identified approximately a dozen susceptibility loci for pigmentation, some shared by phenotypes and others are distinctive. Some of these, such as *MC1R* and *ASIP* genes, also confer a higher risk for melanoma. In the PAGE study, we replicated most reported associations between these SNPs and pigmentation phenotypes. The analysis on melanoma was obviously limited by sample size, but the directions and magnitudes of associations with these SNPs were mostly comparable

to published reports (Bishop, et al., 2009, Sulem, et al., 2008). Also consistent with previous reports, we found a modest positive association between melanoma and PD (Liu, et al., 2011), but the statistical test was not significant, possibly due to the few melanoma cases in the study.

To the best of our knowledge, only one previous study has directly examined the hypothesis that pigmentation genes may underlie the association between PD and melanoma. The study included 298 PD cases and focused on one SNP (*MC1R* rs1805007) that encodes red hair (Gao, et al., 2009b). The study reported that compared with the wild type, the homozygous mutant genotype was associated with three-fold higher risk for PD. Correspondingly, participants with red hair were four times more likely to have PD than those with black hair. On the other hand, Meng *et al*. examined PD susceptibility loci identified from GWAS studies (e.g. *SNCA* and *MAPT*) in relation to melanoma in two large GWAS datasets and reported null findings. Three other studies took an indirect approach by examining whether relatives of melanoma patients had a higher risk for PD than individuals without a family history of melanoma or the converse. Two reported positive associations (Gao, et al., 2009a, Kareus, et al., 2012) but the other did not (Olsen, et al., 2011).

The current study directly and comprehensively evaluated multiple pigmentation phenotypes, melanoma, and related SNPs in relation to the risk for PD in two independent datasets. Compared with the previous study (Gao, et al., 2009b), we had a much larger sample size and included many more SNPs and pigmentation phenotypes. In the PAGE study, neither these SNPs nor the pigmentation phenotypes were associated with PD risk. More importantly, the results were also null in a broader analysis of 360 SNPs using the very large dataset of IPDGC. In the IPDGC, rs1805007 at *MC1R*, the SNP that showed significant association with PD in the previous study (Gao, et al., 2009b) had an OR of 1.06 (95%CI: 0.94-1.19, P=0.37). Our analysis, however, focused on SNPs identified from GWAS and did not include other genetic variations such as mutations in high-penetrance genes (e.g. *CDKN2* and *CDK4*). Thus, we cannot exclude the possibility that other genes may explain the association between melanoma and PD.

Taken together, evidence to date remains elusive on what may be responsible for the link between melanoma and PD. The explanations are likely to be multifactorial and other possibilities, such as environmental factors, should also be considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

Disclosure statement The authors have no conflicts of interest.

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Table 1

Characteristics of participants of the Parkinson's Genes and Environment Study

Variables	Case (%) (n=808)	Control (%) (n=1623)	OR (95%CI)*	*P* *
Year of Birth (mean± SD)	1932±5	1932±5	-	-
Sex				
Female	189 (23.4%)	346 (21.3%)	-	-
Male	619 (76.6%)	1277 (78.7%)	-	-
Caffeine intake				
≤ median (≤ 216.54 mg)	452 (55.9%)	764 (47.1%)	ref.	
> median (> 216.54 mg)	356 (44.1%)	859 (52.9%)	0.72(0.61-0.85)	<0.001
Smoking status				
Never	373 (46.2%)	569 (35.1%)	ref.	
Ever	404 (50.0%)	946 (58.3%)	0.68(0.57-0.81)	<0.001
Current	31 (3.8%)	108 (6.6%)	0.47(0.31-0.71)	<0.001

*Adjusted for year of birth, sex, caffeine intake and smoking status as appropriate.

Table 2

SNPs in relation to pigmentation and melanoma in the Parkinson's Genes and Environment Study

CHR	Gene	SNP	Minor allele	MAF	Hair color (black to red)			Eye color (blue to black)			Skin color (light to dark)			Melanoma	
					beta	s.e.	*P*	beta	s.e.	*P*	beta	s.e.	*P*	OR (95%CI)	*P*
6	*IRF4*	rs12203592	T	0.17	−0.26	0.04	1.67×10^{-10}	−0.14	0.05	1.02×10^{-2}	−0.1	0.02	1.51×10^{-5}	2.49 (0.77-0.83)	1.55×10^{-1}
11	*TYR*	rs1126809	A	0.27	0.07	0.03	4.52×10^{-2}	−0.15	0.05	1.15×10^{-3}	−0.09	0.02	1.22×10^{-5}	1.22 (0.45-3.33)	7.47×10^{-1}
11	*TPCN2*	rs35264875	T	0.17	0.05	0.04	2.08×10^{-1}	−0.06	0.05	2.39×10^{-1}	0.00	0.02	8.52×10^{-1}	1.73 (0.58-5.22)	3.54×10^{-1}
11	*TPCN2*	rs3829241	A	0.38	0.09	0.03	6.44×10^{-3}	−0.09	0.04	3.86×10^{-2}	−0.05	0.02	1.09×10^{-2}	0.55 (0.18-1.69)	2.62×10^{-1}
12	*KITLG*	rs12821256	C	0.09	0.10	0.05	7.28×10^{-2}	0.08	0.07	2.76×10^{-1}	−0.03	0.03	2.68×10^{-1}	1.26 (0.29-5.23)	7.81×10^{-1}
14	*SLC24A4*	rs12896399	T	0.43	0.2	0.03	1.07×10^{-10}	−0.2	0.04	7.11×10^{-7}	−0.05	0.02	6.53×10^{-3}	0.56 (0.22-1.40)	1.86×10^{-1}
16	*MC1R*	rs1805008	T	0.07	0.39	0.06	1.60×10^{-9}	−0.08	0.08	3.34×10^{-1}	−0.14	0.04	1.11×10^{-4}	3.79 (0.57-25.06)	2.20×10^{-1}
16	*CDK10*	rs258322	T	0.10	0.34	0.05	2.00×10^{-10}	0.01	0.07	8.32×10^{-1}	−0.16	0.03	1.24×10^{-7}	1.35 (0.31-5.95)	7.41×10^{-1}
20	*ASIP*	rs1015362	A	0.28	−0.06	0.03	7.59×10^{-2}	0.00	0.05	9.85×10^{-1}	0.01	0.02	7.96×10^{-1}	4.74 (1.24-18.2)	2.20×10^{-2}
20	*ASIP*	rs4911414	T	0.33	0.01	0.03	7.19×10^{-1}	−0.05	0.04	2.75×10^{-1}	−0.04	0.02	4.22×10^{-2}	1.97 (0.75-5.18)	1.90×10^{-1}
20	*PIGU*	rs910873	A	0.07	0.18	0.06	2.53×10^{-3}	−0.06	0.08	4.17×10^{-1}	−0.13	0.03	1.90×10^{-4}	0.55 (0.09-3.35)	5.12×10^{-1}

Adjusted for year of birth and sex.

Table 3

Pigmentation / melanoma in relation to Parkinson's Disease risk in the Parkinson's Genes and Environment Study

variables	Case	Control	Adjusted OR (95%CI)*	Adjusted *P**	*P* for trend*
Hair color					0.202
Black	60	156	ref.		
Brown	424	861	1.25 (0.90-1.73)	0.179	
Auburn	19	38	1.28 (0.68-2.44)	0.442	
Blonde	79	236	0.87 (0.58-1.29)	0.475	
Red	14	27	1.36 (0.66-2.79)	0.406	
Eye color					0.759
Blue/Gray	255	585	ref.		
Green	60	124	1.08 (0.77-1.53)	0.654	
Light brown/Hazel	144	316	1.05 (0.82-1.35)	0.691	
Brown/Black	131	292	1.03 (0.80-1.33)	0.819	
Skin color					0.088
Light	244	580	ref.		
Medium	340	704	1.22 (0.99-1.49)	0.057	
Dark	16	36	1.11 (0.60-2.06)	0.736	
Melanoma					0.276
No	790	1597	Ref		
Yes	18	26	1.32 (0.71-2.44)	0.375	

*Adjusted for year of birth, sex, smoking status and caffeine intake.

Table 4

SNPs in relation to Parkinson's disease in the Parkinson's Genes and Environment Study and in the International PD Genomic Consortium

					Parkinson's Gene Environment Study				International PD Genomic Consortium **	
CHR	**Gene**	**SNP**	**Minor allele**	**MAF in controls**	**Case**	**Control**	**Adjusted OR (95%CI)***	***P*** *	**Meta OR (95%CI)**	**meta_*P***
6	*IRF4*	rs12203592	T	0.16	25/222/539	54/404/1107	1.05 (0.89-1.23)	0.555	0.88 (0.80-0.96)	0.004
11	*TYR*	rs1126809	A	0.27	62/282/399	123/572/799	1.01 (0.88-1.16)	0.910	1.01 (0.95-1.07)	0.816
11	*TPCN2*	rs35264875	T	0.17	21/236/526	47/438/1070	1.04 (0.88-1.22)	0.640	0.98 (0.91-1.05)	0.586
11	*TPCN2*	rs3829241	A	0.38	106/363/302	221/716/601	0.99 (0.87-1.12)	0.825	0.99 (0.94-1.04)	0.615
12	*KITLG*	rs12821256	C	0.09	10/125/647	22/250/1287	1.00 (0.82-1.23)	0.982	1.02 (0.94-1.11)	0.666
14	*SLC24A4*	rs12896399	T	0.43	154/368/248	283/746/499	1.04 (0.92-1.17)	0.576	1.00 (0.95-1.05)	0.926
16	*MC1R*	rs1805008	T	0.06	7/99/671	6/188/1356	1.14 (0.89-1.44)	0.295	0.98 (0.89-1.07)	0.624
16	*CDK10*	rs258322	T	0.09	8/134/633	22/247/1264	1.03 (0.84-1.27)	0.764	1.10 (1.01-1.20)	0.030
20	*ASIP*	rs1015362	A	0.29	61/265/432	137/618/789	0.84 (0.73-0.96)	0.011	1.04 (0.98-1.10)	0.195
20	*ASIP*	rs4911414	T	0.35	86/302/395	190/700/660	0.80 (0.70-0.91)	0.001	1.02 (0.97-1.08)	0.374
20	*PIGU*	rs910873	A	0.08	5/87/653	8/221/1305	0.82 (0.64-1.05)	0.120	0.90 (0.82-0.99)	0.039

* Adjusted for year of birth, sex, smoking status and caffeine intake.

** Other SNPs from the IPDGC were not statistically significantly associated with PD risk.