Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

No Association between Parkinson Disease Alleles and the Risk of Melanoma

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Abstract

Background: Recent data showed that melanoma was more common among patients with Parkinson disease than individuals without Parkinson disease and vice versa. It has been hypothesized that these two diseases may share common genetic and environmental risk factors.

Methods: We evaluated the association between single-nucleotide polymorphisms (SNP) selected on the basis of recent genome-wide association studies (GWAS) on Parkinson disease risk and the risk of melanoma using 2,297 melanoma cases and 6,651 controls.

Results: The Parkinson disease SNP rs156429 in the chromosome 7p15 region was nominally associated with melanoma risk with *P* value of 0.04, which was not significant after the Bonferroni correction for multiple comparisons. No association was observed between the remaining 31 Parkinson disease SNPs and the risk of melanoma. The genetic score based on the number of Parkinson disease risk allele was not associated with melanoma risk [OR for the highest genetic score quartile (30–35) vs. the lowest (15–20), 1.13, 95% confidence interval (CI), 0.47–2.70].

Conclusion: The Parkinson disease SNPs identified in published GWAS do not seem to play an important role in melanoma development.

Impact: The Parkinson disease susceptibility loci discovered by GWAS contribute little to the observed epidemiologic association between the Parkinson disease and melanoma. *Cancer Epidemiol Biomarkers Prev; 21(1); 243–5. ©2011 AACR.*

Introduction

A large number of epidemiologic studies have reported that melanoma occurs with higher-than-expected frequency among patients with Parkinson disease and vice versa (1). It has been hypothesized that these 2 conditions may have shared environmental and genetic risk factors or common pathogenic pathways, although direct evidence is largely lacking. Gao and colleagues, in 2009, reported an increased risk of Parkinson disease associated with fair hair color, a strong phenotypic risk factor for melanoma, and a family history of melanoma in first-degree relatives (2, 3). In addition, tobacco smoking, longer duration of rotating night shift, and shorter telomere length are associated with decreased risk for both diseases (4–6). Although the preliminary evidence is supportive, more research needs to be carried out to better understand the potential link between the 2 conditions. We, therefore, evaluated the association between published Parkinson disease risk variants selected from recent genome-wide association studies (GWAS) and melanoma risk.

Material and Methods

We combined data from 2 GWAS on melanoma: the nested case–control study within the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS; 493 cases and 5,625 controls) and the MD Anderson Cancer Center melanoma case–control study (1,804 cases and 1,026 controls). Detailed description on these 2 studies and the genotyping procedure and quality control are presented in the online Supplementary text. Single-nucleotide polymorphisms (SNP) significantly associated with Parkinson disease in Caucasian populations were selected from 11 existing GWAS (Supplementary Methods). Studies on candidate genes were not included. A total of 37 SNPs were selected and marked into 2 groups:

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Table 1. Association between Parkinson disease SNPs and melanoma risk

				NHS and HPFS set					MD Anderson set		Meta-analysis		
SNP	CHR	Gene	Reference number	Risk	Ref	Allele frequency	OR	*P*	OR	*P*	OR	95% CI	*P*
rs708723[a]	1	*RAB7L1/PARK16*	18	T	C	0.56	1.05[c]	0.45	1.03	0.61	1.04	0.95–1.13	0.38
rs156429[a]	7	*GPNMB*		T	C	0.60	1.14[c]	0.07	1.06[c]	0.25	1.09	1.00–1.19	0.04
rs6812193[a]	4	*STBD1*	19	C	T	0.64	1.01[c]	0.83	0.94	0.25	0.97	0.88–1.05	0.45
rs4889603[a]	16	*STX1B*		G	A				0.99	0.91			
rs591323[a]	8	*FGF20*		G	A				1.10[c]	0.14			
rs11868035[b]	17	*SREBF1/RAI1*		G	A				0.92	0.15			
rs2942168[a]	17	*MAPT*	20	G	A	0.78	0.93[c]	0.39	1.05	0.45	1.00	0.90–1.10	0.98
rs356219[a]	4	*SNCA*		G	A				1.02[c]	0.76			
rs11724635[a]	4	*BST1*		A	C				1.11[c]	0.06			
rs1491942[a]	12	*LRRK2*		G	C				1.06[c]	0.35			
rs34372695[a]	1	*SYT11*		A	G				1.06	0.78			
rs356220[a]	4	*SNCA*	21	T	C	0.38	0.96[c]	0.61	1.02	0.75	1.00	0.91–1.09	0.94
rs4964469[b]	12	*Intergenic*		A	G	0.38	0.93[c]	0.32	1.04	0.48	1.00	0.91–1.09	0.93
rs3129882[a]	6	*HLA-DRA*	17	G	A	0.43	0.93[c]	0.27	0.94	0.31	0.93	0.86–1.02	0.14
rs11248051[a]	4	*GAK*		T	C	0.10	0.87[c]	0.24	1.15	0.16	1.02	0.88–1.19	0.75
rs11012[b]	17	*PLEKHM1, MAPT*	16	C	T	0.81	0.96[c]	0.80	1.08	0.30	1.05	0.93–1.19	0.43
rs11931074[a]	4	*SNCA*	14	T	G	0.08	1.32[c]	0.14	1.12[c]	0.28	1.18	0.97–1.42	0.09
rs947211[a]	1	*PARK16, SLC45A3*		G	A	0.76	0.98[c]	0.80	1.02[c]	0.74	1.00	0.90–1.10	0.92
rs1994090[a]	12	*LRRK2*		G	T	0.22	0.89[c]	0.13	0.97	0.69	0.93	0.85–1.04	0.21
rs2708453[b]	12	*LRRK2*		T	G	0.16	0.86[c]	0.13	1.02	0.78	0.96	0.85–1.08	0.48
rs7304279[b]	12	*LRRK2*		T	C	0.16	0.87[c]	0.16	1.05[c]	0.53	0.98	0.87–1.10	0.70
rs4768212[b]	12	*LRRK2*		C	T	0.07	0.86	0.26	1.13	0.26	0.98	0.83–1.16	0.84
rs6532194[b]	4	*SNCA*		T	C	0.09	1.02[c]	0.85	1.13	0.23	1.08	0.93–1.25	0.30
rs3857059[b]	4	*SNCA*		G	A	0.07	1.06[c]	0.62	1.14[c]	0.26	1.10	0.93–1.30	0.24
rs708730[b]	1	*SLC41A1*		A	G	0.83	1.11[c]	0.25	1.07	0.37	1.08	0.97–1.21	0.16
rs823122[b]	1	*NUCKS1*		T	C	0.94	0.89[c]	0.39	1.07	0.57	0.99	0.83–1.18	0.90
rs894278[b]	4	*SNCA*		T	G	0.94	1.03[c]	0.85	0.89	0.34	0.95	0.78–1.14	0.56
rs823156[b]	1	*SLC41A1*		A	G	0.82	1.08[c]	0.40	1.08	0.28	1.08	0.97–1.21	0.17
rs393152[a]	17	*MAPT, C17orf69*	15	A	G	0.78	0.93[c]	0.37	1.05[c]	0.45	1.00	0.90–1.11	1.00
rs199533[a]	17	*NSF*		G	A	0.80	0.98[c]	0.85	1.07	0.30	1.05	0.95–1.16	0.36
rs823128[b]	1	*CYP17A1, C10orf32*		A	G	0.96	0.72[c]	0.03	1.03	0.83	0.87	0.70–1.07	0.19
rs2736990[a]	4	*SNCA*		G	A	0.47	0.98[c]	0.72	1.02	0.75	1.00	0.92–1.09	0.98

[a]SNPs reached genome-wide significance level ($P = 5 \times 10^{-8}$) with risk of Parkinson disease.
[b]SNPs did not reach *P* value of 5×10^{-8}.
[c]Imputed genotype, $r^2 > 0.8$ in the MD Anderson set and >0.95 in the NHS and HPFS set.

those associated with Parkinson disease risk with *P* value $\leq 5 \times 10^{-8}$ were in group 1 and those highly associated with Parkinson disease risk but did not reach *P* value of 5×10^{-8} were in group 2. For SNPs with high linkage disequilibrium (LD), which was characterized by $r^2 > 0.8$ according to the HapMap 3 (release 2), only the ones with the smallest *P* value were chosen for the genetic score summary. We used unconditional logistic regression to calculate OR and 95% confidence interval (CI) adjusting for age, gender, and 5 eigenvectors (EV) which were calculated for all individuals on the basis of approximately 10,000 unlinked markers with the EIGENSTRAT software. Power calculations showed that our combined samples had 80% power to detect variants conferring an OR of 1.18 with an allele frequency of 10%. Betas from each study were combined by a meta-analysis with weights proportional to the inverse variance of the beta in each study. We calculated a genetic score on the basis of the presence of total copy number of 21 independent Parkinson disease risk alleles in the NHS and HPFS set. The score was logistically regressed against the disease status adjusting for age, gender, and 5 EVs.

Results

A total of 37 SNPs were initially selected from 11 published Parkinson disease GWAS to date. Five SNPs were excluded because of the lack of information in both melanoma data sets (rs12817488, rs6599388, rs11711441, rs2102808, and rs6710823). SNP rs156429 in the 7p15 region reached nominal significance with OR = 1.09, 95% CI (1.00–1.19) in the meta-analysis. The *P* value was 0.04 which was not significant after adjusting for multiple comparisons. We did not observe significant association for the remaining 31 SNPs (Table 1). We also examined the potential cumulative effects of the 21 independent SNPs in the NHS and HPFS by examining the genetic score and melanoma risk. The genetic scores in our data set ranged from 15 to 35. No significant association was observed between the presence of Parkinson disease risk alleles and melanoma risk (OR for the highest genetic score quartile 30–35 vs. the lowest 15–20, 1.13, 95% CI, 0.47–2.70).

Discussion

Despite growing epidemiologic and clinical evidence of a link between the Parkinson disease and melanoma, we did not observe an association between Parkinson disease GWAS SNPs and melanoma risk. Although several genes have been identified responsible for the early onset or familial forms of the Parkinson disease, large portion of Parkinson disease cases are sporadic and may be due to low-penetrance genetic variations, environmental factors, or gene–environment interactions. Thus, our null result may be partially because the selected SNPs represent very small portion of genetic susceptibility and do not cover those genes involved in both Parkinson disease and melanoma. In addition, Parkinson disease and melanoma have long been recognized as results of combined genetic and environmental risk factors. As a response to environmental exposure, posttranscriptional regulation may play a large role in the development of both diseases. The changes of gene expression could be regulated through various mechanisms such as epigenetic or miRNA regulation. This could partially explain the null association between Parkinson disease and melanoma at SNP level. Furthermore, mitochondrial DNA has been implicated in the pathogenesis of both Parkinson disease and melanoma, which also increases the complexity of identifying the true pathways shared between Parkinson disease and melanoma (7, 8). In summary, we did not find evidence of associations between the selected Caucasian Parkinson disease risk alleles and the risk of melanoma. Future work is needed to screen more novel Parkinson disease variants and investigate the association between Parkinson disease and melanoma at gene expression level as well as in the mitochondrial pathways.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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