Family history of melanoma and Parkinson disease risk

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ABSTRACT

Background: Co-occurrence of Parkinson disease (PD) and melanoma has been reported in numerous studies. If this was due to common genetic mechanisms, a positive family history of melanoma would be associated with an excessive PD risk, independent of environmental risk factors for PD.

Methods: We prospectively examined associations between a family history of melanoma and PD among 157,036 men and women free of PD at baseline (1990 for men and 1982 for women) who participated in 2 ongoing US cohorts: the Health Professional Follow-up Study and the Nurses' Health Study. Information on family history of melanoma in parents or siblings was assessed via questionnaire. Relative risks and 95% confidence intervals were estimated using Cox proportional hazards models and pooled using a fixed-effects model.

Results: During 14–20 years follow-up, we identified 616 incident PD cases. A family history of melanoma in a first-degree relative was associated with a higher risk of PD (multivariate relative risk = 1.85; 95% confidence interval: 1.2, 2.8; $p = 0.004$), after adjusting for smoking, ethnicity, caffeine intake, and other covariates. In contrast, we did not observe significant associations between a family history of colorectal, lung, prostate, or breast cancer and PD risk. Interactions between melanoma family history and age, smoking, or caffeine intake were not significant and subgroup analyses according to these factors generated similar results.

Conclusions: Our findings support the notion that melanoma and Parkinson disease (PD) share common genetic components. The genetic determinants of melanoma could therefore be explored as susceptibility candidate genes for PD. *Neurology*® 2009;73:1286–1291

GLOSSARY

BMI = body mass index; **CDK** = cyclin dependent kinase; **CI** = confidence interval; **HPFS** = Health Professional Follow-up Study; **NHS** = Nurses' Health Study; **OR** = odds ratio; **PD** = Parkinson disease; **RR** = relative risk; **SER** = standardized event ratio.

Co-occurrence of Parkinson disease (PD) and melanoma has been reported in numerous studies.^{1–6} Most convincingly, in a large-scale study including over 8,000 PD cases from the national Danish Hospital Register, it was found that a diagnosis of melanoma was associated with an approximately 50% increased risk of subsequently developing PD (odds ratio [OR] = 1.44; 95% confidence interval [CI] 1.0, 2.0),¹ whereas individuals with PD had a twofold increase in risk of subsequently developing melanoma.²

Different hypotheses have been put forward to interpret the co-occurrence of PD and melanoma. Administration of levodopa has been thought to be a culprit since 1972 when it was described for the first time that a patient with PD had recurred melanoma after 3–4 months levodopa treatment.³ Levodopa serves as a substrate for tyrosine hydroxylase, and might therefore accelerate melanoma tumor growth.^{4,6} However, 3 systematic reviews of case reports regarding levodopa treatment and melanoma did not support this hypothesis.^{4–6} An alternative hypothesis is that the co-occurrence between PD and melanoma is due to environmental

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confounders (e.g., smoking or social class) or some common genetic components.^{1,7-9} We recently reported that pigmentation, which is an important determinant for melanoma risk, is associated with PD risk; individuals with red hair color or homozygous for the melanocortin 1 receptor (MC1R) Arg151Cys variant allele were ~2–3 times more likely to develop PD than those without these traits.⁷

A positive family history is one of the most important and consistent risk factors for melanoma¹⁰⁻¹²; individuals with a family history of melanoma are twice more likely to develop melanoma.^{10,11} If PD shares common genetic components with melanoma, individuals with a family history of melanoma would thus be expected to have an excessive PD risk relative to those without the family history, independent of environmental risk factors for PD. We, therefore, examined the associations between a family history of melanoma in a first-degree relative and PD risk among ~160,000 men and women participating in 2 large-scale, ongoing prospective cohorts in the United States: the Health Professional Follow-up Study (HPFS) and the Nurses' Health Study (NHS). To determine whether the results are specific for family history of melanoma, we also examined the associations between a family history of 4 other common cancers not known to be genetically related to PD risk.

METHODS **Study population and assessment of exposures and potential covariates.** The HPFS was established in 1986, when 51,529 male US health professionals (dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians) aged 40–75 years completed a mailed questionnaire regarding their medical history and lifestyle. The NHS cohort was established in 1976, when 121,700 female registered nurses responded to a similar questionnaire. The overall response rate is greater than 94% in the HPFS and the NHS follow-up has been 95% of potential person-years in the overall cohort.

A question regarding melanoma in a father, mother, or sibling (i.e., a first-degree relative) was included in the 1990 questionnaire for the men (i.e., the HPFS), and updated in 1992. A similar question was asked in the 1982 questionnaire for the women (i.e., the NHS), and the information was updated in 1992, 1996, and 2000. In the HPFS, we also asked about family history of colon or rectal cancer, and prostate cancer in 1990, of lung cancer in 1992, and of breast cancer in 1996. In the NHS, we asked about family history of colon or rectal cancer, and breast cancer in 1982, of prostate cancer in 1996, and of lung cancer in 2000.

Dietary intakes were assessed with semiquantitative food frequency questionnaires validated for use with these popula-

tions.^{13,14} Information on age, weight, height, smoking status, ethnicity, use of nonaspirin nonsteroidal antiinflammatory drugs, natural hair color, and childhood tan and sunburn reaction was collected through questionnaires. Body mass index (BMI) was calculated as weight (kg)/height (m).²

In the present study, we used 1990 as baseline for the HPFS and 1982 for the NHS. Participants who had been previously diagnosed with PD or those who did not report their family history of melanoma were excluded, leaving 46,911 men and 110,125 women for further analyses.

Standard protocol approvals, registrations, and patient consents. The institutional review board at Brigham and Women's Hospital reviewed and approved this study, and receipt of each questionnaire implies participant's consent.

Ascertainment of PD. We identified new PD cases by biennial self-reported questionnaires.¹⁵ We then asked the treating neurologists to complete a questionnaire to confirm the diagnosis of PD or to send a copy of the medical records. A case was confirmed if a diagnosis of PD was considered definite or probable by the treating neurologist or internist, or if the medical record included either a final diagnosis of PD made by a neurologist, or evidence of at least 2 of the 3 cardinal signs (rest tremor, rigidity, bradykinesia) in the absence of features suggesting other diagnoses. The review of medical records was conducted by the investigators, blind to the exposure status. Overall, the diagnosis was confirmed by the treating neurologist in 81% of the cases, by review of the medical records in 3%, and by the treating internist without further support in the remaining 16%. We also requested the death certificates of the deceased study participants and identified PD diagnoses that were not reported in the regular follow-up (less than 2%). If PD was listed as a cause of death on the death certificate, we requested permission from the family to contact the treating neurologist or physician and followed the same procedure as for the nonfatal cases. In this analysis, we used only definite and probable PD as in our previous reports.^{7,16,17}

Statistical analysis. We computed person-time of follow-up for each participant from the return date of the baseline questionnaires (1990 for the HPFS and 1982 for the NHS) to the date of the occurrence of the PD (PD first symptom), death from any cause, or end of follow-up (2004 for men and 2002 for women), whichever came first. In the primary analyses, we categorized participants into 2 groups based on presence of family history of melanoma at baseline and calculated relative risks (RRs) using a Cox proportional hazards model, controlling for age (in months), smoking status (never smoker, past smoker, current smoker with 1–14 cigarettes/day, or current smoker with ≥ 15 cigarettes/day), BMI (<23, 23–24.9, 25–26.9, 27–29.9, or ≥ 30 kg/m²), ethnicity (Caucasian, African American, or Asian and others), use of nonsteroid antiinflammatory drugs (yes/no), and intake of total caffeine (quintiles), lactose (quintiles), and alcohol (none, 1–4.9, 5–9.9, 10–14.9, or ≥ 15 g/day for women; none, 1–9.9, 10–19.9, 20–29.9, or ≥ 30 g/day for men). All covariates were derived from baseline data. Log RRs from the 2 cohorts were pooled by a fixed-effects model, weighted by the inverse of their variances as significance tests did not suggest heterogeneity between cohorts ($p > 0.1$ for all tests).¹⁸

To take advantage of repeated assessment of family history of melanoma in both cohorts, in secondary analyses, we used the updated (i.e., the most recent) family history of melanoma in relation to the incidence of PD. To test robustness of our results, we conducted sensitivity analyses by restricting the analyses to PD cases diagnosed by neurologists, and to Caucasians. We also

Table 1 Basic characteristics according to family history of melanoma status at baseline in the Health Professionals Follow-up Study (1990) and the Nurses' Health Study (1982)

	Men Family history of melanoma		Women Family history of melanoma	
	No	Yes	No	Yes
No.	46,109	802	107,538	2,587
%	98.3	1.7	97.7	2.3
Age, y	58.0	57.6	48.6	48.9
Caucasian, %	95.7	97.9	96.2	98.2
Current smokers, %	8.1	6.6	27.4	23.8
Past smokers, %	46.3	47.0	28.9	30.2
Body mass index, kg/m ²	25.7	25.7	24.7	25.1
Red natural hair, %	2.7	3.3	3.5	5.1
Painful sunburn in childhood, %	24.6	30.0	14.5	17.2
Alcohol intake, g/d	10.1	10.0	6.3	6.2
Caffeine intake, mg/d	233	230	397	394
Lactose intake, g/d	15.4	14.9	13.6	13.4
Use of nonaspirin nonsteroidal antiinflammatory drugs, %	8.3	10.8	4.8	6.1

conducted a sensitivity analysis by censoring of participants with malignant melanoma onset during the follow-up at the date of diagnosis of the melanoma. Because there is a possibility that some patients with PD may not be diagnosed during the early stage, we therefore conducted a lag analysis by excluding PD cases with onset during the first 4 years of follow-up.

We also examined interactions between family history of melanoma and age at onset (< vs ≥ 70 y, based on approximately median value), smoking status (never vs ever), and caffeine intake (low vs high, based on median intake) by adding

multiplicative terms in the Cox models, adjusting for other potential confounders. We used the SAS statistical package (version 9; SAS Institute, Cary, NC) for all analyses.

RESULTS During 14–20 years of follow-up, we identified 616 incident PD cases (315 men and 301 women). Within each cohort, the patterns of smoking history, dietary intake, BMI, and use of non-steroid antiinflammatory drugs were similar in the groups of participants with and without a family history of melanoma (table 1). However, participants with a family history of melanoma were more likely to be Caucasian, to have red hair color, and to have experienced painful sunburn during childhood, relative to those without a family history. Age-adjusted ORs of having a family history of melanoma were 1 (ref) for individuals with black hair, 1.28 for brown hair, 1.24 for blonde hair, and 1.63 (95% CI: 1.3, 2.1; $p < 0.001$) for red hair, and 1.31 (95% CI: 1.2, 1.4; $p < 0.0001$) for individuals who experienced painful sunburn during childhood, relative to those without sunburn.

A positive family history of melanoma in a first-degree relative was associated with a higher risk of developing PD. The age-adjusted RR for a family history of melanoma was 2.10 (95% CI: 1.1, 3.9) for men and 1.75 (95% CI: 1.0, 3.1) for women. Further adjustment for smoking, caffeine intake, ethnicity, and other potential covariates did not materially change the magnitude of the associations (table 2). There was no evidence that the association between a

Table 2 Relative risk (95% confidence interval) of Parkinson disease according to a family history of melanoma in the Health Professionals Follow-up Study (HPFS) (1990) and the Nurses' Health Study (NHS) (1982)

	Without a family history of melanoma	With a family history of melanoma	Parents had melanoma	Siblings had melanoma
HPFS (1990–2004)				
Case no.	304	11	5	6
Age and smoking adjusted	1 (ref)	2.07 (1.12, 3.81)	1.66 (0.68, 4.06)	2.36 (1.03, 5.40)
Multivariate 1*	1 (ref)	2.11 (1.14, 3.90)	1.73 (0.71, 4.26)	2.34 (1.02, 5.37)
Multivariate 2*	1 (ref)	2.08 (1.12, 3.86)	1.73 (0.70, 4.25)	2.29 (1.00, 5.27)
NHS (1982–2002)				
Case no.	288	13	9	4
Age and smoking adjusted	1 (ref)	1.69 (0.96, 2.95)	1.77 (0.91, 3.45)	1.40 (0.52, 3.76)
Multivariate 1*	1 (ref)	1.66 (0.95, 2.90)	1.76 (0.90, 3.42)	1.35 (0.50, 3.63)
Multivariate 2*	1 (ref)	1.67 (0.95, 2.93)	1.77 (0.91, 3.46)	1.36 (0.50, 3.66)
Pooled†	1 (ref)	1.85 (1.22, 2.79)	1.75 (1.02, 2.99)	1.86 (0.99, 3.52)

*Adjustment for age (in months), smoking status (never smoker, past smoker, current smoker with 1–14 cigarettes/d, or current smoker with ≥ 15 cigarettes/d), body mass index (<23, 23–24.9, 25–26.9, 27–29.9, or ≥ 30 kg/m²), ethnicity (Caucasian, African American, or Asian and others), use of nonsteroid antiinflammatory drugs (yes/no), and intake of caffeine (quintiles), lactose (quintiles), and alcohol (none, 1–4.9, 5–9.9, 10–14.9, or ≥ 15 g/d for women; none, 1–9.9, 10–19.9, 20–29.9, or ≥ 30 g/d for men). Cox proportional hazard models were used to calculate relative risk.

*Further adjusted for hair color (black, brown, blonde, or red) and experience of painful sunburn in childhood.

†Based on multivariate model 1.

Table 3 Relative risk (RR) (95% confidence interval) of Parkinson disease according to family history of colorectal, lung, prostate, and breast cancers and Parkinson disease risk in the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS)

	Family history of colorectal cancer		Family history of lung cancer		Family history of prostate cancer		Family history of breast cancer	
	No	Yes	No	Yes	No	Yes	No	Yes
HPFS (1990-2004)								
%	91.3	8.7	94.8	5.2	93.9	6.1	88.8	11.2
Case no.	288	27	291	17	298	17	270	28
Multivariate RR*	1 (ref)	0.84 (0.56, 1.25)	1 (ref)	1.21 (0.74, 1.99)	1 (ref)	0.84 (0.51, 1.37)	1 (ref)	0.79 (0.53, 1.17)
NHS (1982-2002)								
%	92.5	7.5	89.3	10.7	93.8	6.2	93.6	6.4
Case no.	280	21	247	26	263	30	275	26
Multivariate RR*	1 (ref)	0.70 (0.45, 1.09)	1 (ref)	0.91 (0.60, 1.36)	1 (ref)	1.42 (0.97, 2.07)	1 (ref)	1.09 (0.73, 1.64)
Pooled RR	1 (ref)	0.77 (0.57, 1.04)	1 (ref)	1.02 (0.74, 1.39)	1 (ref)	1.17 (0.86, 1.58)	1 (ref)	0.92 (0.70, 1.22)

*Adjustment for age (in months), smoking status (never smoker, past smoker, current smoker with 1-14 cigarettes/d, or current smoker with ≥ 15 cigarettes/d), body mass index (< 23 , 23-24.9, 25-26.9, 27-29.9, or ≥ 30 kg/m²), ethnicity (Caucasian, African American, or Asian and others), use of nonsteroid antiinflammatory drugs (yes/no), and intake of caffeine (quintiles), lactose (quintiles), and alcohol (none, 1-4.9, 5-9.9, 10-14.9, or ≥ 15 g/d for women; none, 1-9.9, 10-19.9, 20-29.9, or ≥ 30 g/d for men). Cox proportional hazard models were used to calculate RR.

family history of melanoma and PD risk was different between men and women (p for heterogeneity = 0.57). The pooled multivariate RR was 1.85 (95% CI: 1.2, 2.8; p = 0.004). When we additionally adjusted for hair color and childhood reaction to tan and sunburn, associations between a family history of melanoma and PD were attenuated slightly but remained significant (table 2). As a comparison, we did not observe significant associations between a family history of colorectal, lung, prostate, or breast cancer and PD risk (table 3). Nonsignificant association between a family history of lung cancer and PD risk was virtually identical with and without adjustment for smoking status (data not shown).

When we used the most updated information of a family history of melanoma as exposure variable, results were similar. The pooled multivariate RR was 1.66 (95% CI: 1.2, 2.4; p = 0.004). In the sensitivity analyses, we saw similar associations between a family history of melanoma and PD risk when analyses were restricted to the PD cases diagnosed by neurologists (pooled multivariate RR = 1.94; 95% CI: 1.3, 3.0; p = 0.003), to Caucasians (RR = 1.99, 95% CI: 1.3, 3.0; p = 0.001), to individuals without natural red hair (RR = 1.97, 95% CI: 1.3, 3.0; p = 0.001), or to those without experience of sunburn during childhood (RR = 1.78, 95% CI: 1.1, 2.8; p = 0.01). The results were not materially changed in further sensitivity analyses, which included censoring participants with melanoma onset during follow-up at diagnosis of the disease (pooled multivariate RR = 1.68, 95% CI: 1.1, 2.6; p = 0.02); adjustment for updated age, use of nonsteroidal antiinflammatory drugs, BMI,

and intake of alcohol, caffeine, and lactose (RR = 1.63, 95% CI: 1.1, 2.5; p = 0.03); and exclusion of PD cases with onset during the first 4 years of follow-up (RR = 1.69, 95% CI: 1.0, 2.7; p = 0.03).

We did not find significant interactions between a family history of melanoma and age, smoking status, or caffeine intake. The association between a family history and a higher PD risk was evident in subgroup analyses according to age, smoking status, and caffeine intake (figure e-1 on the *Neurology*[®] Web site at www.neurology.org).

DISCUSSION In this prospective analysis, we found an approximately twofold increase in risk of PD among individuals who reported a family history of melanoma in a first-degree relative, as compared with those without such a family history. The significant association was independent of several known risk factors for PD, including smoking and caffeine intake. In contrast, we did not observe significant associations between a family history of 4 other common cancers and PD risk.

Our findings do not support the notion that melanoma in patients with PD is due to adverse effects of levodopa treatment. These are consistent with results from 2 recent epidemiologic studies. In a case-control study of 314 patients with PD (45 of them had melanoma), no effect of levodopa on the risk of melanoma was reported; the OR for each 1,000 g cumulative intake of the drug was 1.0 (95% CI: 0.8, 1.3).¹⁹ In the DATATOP (deprenyl and tocopherol antioxidative therapy of parkinsonism) trials, incidence of melanoma was significantly higher than ex-

pected in the general population, with a standardized event ratio (SER) of 3.3 (95% CI: 1.1, 7.8), but the incidence rates of melanoma before and after initiation of levodopa were similar (SER 3.2 vs 3.4).²⁰

Our finding that a family history of melanoma was associated with a higher risk of PD is unlikely to be explained by smoking or socioeconomic variations, which were thought to confound the association between melanoma and PD observed in previous studies.^{1,8} Several observational studies reported that individuals who smoked or had a lower socioeconomic status had a lower risk of PD^{21,22} and melanoma.²³⁻²⁶ However, in the current study, adjustment for smoking status did not materially change our results. In a subgroup analysis, we also observed a similar association between family history of melanoma and PD among nonsmokers. Our populations are rather homogenous in respect to their educational level and socioeconomic status. Further, exclusion of non-Caucasian participants generated similar significant results.

Family history represents a combination of an increased genetic susceptibility and environmental factors, such as lifestyle and dietary factors. In the present analysis, however, the excess risk of PD associated with a family history of melanoma did not change materially after controlling for smoking, intake of caffeine and lactose, ethnicity, and other known or suspected environmental risk factors for PD. Although we cannot completely rule out a possibility that other unknown environmental factors may partially contribute the observed associations between a family history and melanoma and PD risk, our results suggest the existence of important genetic contributions.

The metabolism of pigments, and genes that encode the proteins in this process, may, at least in part, explain the observed association between a family history of melanoma and PD risk.^{7,9} One clinical characteristic of PD is an abnormal loss of neuromelanin-containing cells within the substantia nigra. We previously reported that light hair color, an important phenotype of human pigmentation and a well-established risk factor for melanoma,²⁷ is significantly associated with PD risk in the HPFS and the NHS.⁷ In a case-control study including 509 newly diagnosed patients with PD in Northern California, individuals with darker skin color were found to have a lower PD risk, both among Caucasians (OR = 0.46; 95% CI: 0.28, 0.78) and among African Americans (OR = 0.60; 95% CI: 0.38, 0.94).²⁸ In addition, we found that carriers of the MC1R Arg151Cys polymorphism, a key genetic determinant for human pigmentation and red hair color, had a higher PD risk than noncarriers in a case-control

study nested in the HPFS and the NHS.⁷ MC1R Arg151Cys variants are associated with an increased melanoma risk, independent of skin type and hair color.²⁷

Other genes, such as cyclins and cyclin dependent kinases (CDKs), could also have a role in the observed association between a family history of melanoma and PD risk. CDKs are often overexpressed in melanoma cells as compared to benign nevi.²⁹ It has been suggested recently that an increased expression of proteins involved in the cell cycle (e.g., CDKs) may have a critical role in neuronal cell death in patients with PD.^{30,31} Animal studies have shown that 1-methyl-4-phenylpyridinium (MPP⁺) induces neuronal apoptosis and could be attenuated by flavopiridol, a broad-spectrum CDK inhibitor.³⁰

Because of the prospective design, our results are unlikely to be significantly affected by recall or selection bias. We also carried out several sensitivity analyses that generated similar significant results. Although known PD risk factors were adjusted in our analysis, we cannot exclude the possibility of residual confounding by unknown risk factors. However, the magnitude of the observed association was rather large and might not be totally explained by these unknown confounders. Data on family history were self-reported by study participants, and no formal validation study was conducted to assess accuracy. Because the participants were all health care professionals, the accuracy of the reports is likely to be high. This was supported by the significant associations of a self-reported family history of melanoma with red natural hair color and a history of painful sunburn. In the NHS and the HPFS cohorts, a family history of melanoma was associated with an increased risk of melanoma.³² Further, prior studies showed that self-reported family history of several common cancers, including colorectal, breast, and prostate cancer, is reliable.^{33,34} Nevertheless, some degree of nondifferential misclassification in reported family history of cancers cannot be excluded, which could attenuate rather than exaggerate risk estimates.

AUTHOR CONTRIBUTIONS

Dr. Gao conducted the statistical analysis. He received a master's degree in Epidemiology & Biostatistics in 2001.

DISCLOSURE

Dr. Gao serves on the Monitoring Committee of the Parkinson Study Group and received the Mentored Clinical Research Award (PI) supported by the Parkinson Study Group and the Parkinson's Disease Foundation's Advancing Parkinson's Treatments Innovations Grant. Dr. Simon reports no disclosures. Dr. Han serves as an Associate Editor of *Cancer Causes and Control*. Dr. Schwarzschild has in the past 2 years received non-industry-sponsored speaker honoraria and research support from the NIH/NINDS [K24NS060991 (PI), R01NS054978 (PI), and R21NS058324 (PI)] and the US Department of Defense [W81XWH-04-1-0881 (PI)], and from the Michael J. Fox Foundation, the Parkinson

Disease Foundation, the RJG Parkinson's Disease Foundation, the American Parkinson Disease Association, and the American Federation for Aging Research. Dr. Ascherio serves on the scientific advisory board of the Michael J. Fox Foundation; serves as an associate editor of *American Journal of Epidemiology* and serves on the editorial boards of *Neurology*[®] and *Annals of Neurology*; has received speaker honoraria from Merck Serono; and receives research support from the Michael J. Fox Foundation (coinvestigator), the US Department of Defense (Army) [W81XWH-05-1-0117 (PI)], and the NIH [R01 NS045893 (PI), R01 NS047467 (PI), R01 NS48517 (PI), NINDS R01 NS042194 (PI) and R01 NS046635 (PI)].

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