

BRIEF COMMUNICATION

Sun-Related Risk Factors in Melanoma-Prone Families With CDKN2A Mutations

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The CDKN2A gene encodes a low-molecular-weight protein, p16, that inhibits the activity of the cyclin D1-cyclin-dependent kinase 4 complex (1). This enzyme complex phosphorylates the retinoblastoma protein, allowing the cell to progress through the G₁ phase of the cell cycle. CDKN2A germline mutations have been detected in approximately 25% of melanoma-prone families. Deletions or mutations of the CDKN2A gene are common in melanomas grown in culture but less frequent in primary melanoma tumors (1–12). The identification of an unaffected individual homozygous for CDKN2A gene mutations (11) in addition to other mutation carriers without melanomas (12,13) suggests that other gene(s) and/or environmental factors are involved in the pathogenesis of melanoma. To identify these other factors, we evaluated the risk of melanoma in relation to clinical, environmental, and genetic factors in American families with germline CDKN2A mutations that co-segregated with melanoma (13,14; Goldstein AM, Sikorski RS, Tucker MA: unpublished data).

The study subjects came from 13 kindreds with invasive melanoma in at least two first-degree relatives (13–15). Melanoma diagnoses were confirmed using histologic review, pathology reports, or death certificates. Written informed consent was obtained prior to participation under an Institutional Review Board-

approved protocol. These same families have been followed prospectively for 4–20 years. All family members willing to participate in the study were clinically evaluated. Variables recorded during the clinical examination included the type and total number of nevi, extent of freckling, skin complexion, evidence for solar injury of the skin, and hair and eye color. A self-administered questionnaire obtained information from 70% of the clinically evaluated subjects on sun-related variables, such as skin reaction

Table 1. Categories of clinical, environmental, and genetic variables used for analysis

Variable	No. of case subjects	No. of control subjects
Complexion*		
Medium/dark	6	77
Pale/fair	42	156
Dysplastic nevi		
Absent	2	100
Indeterminate	17	71
Present	51	76
Freckles†		
None/few/moderate	28	176
Many	22	59
Hair color		
All others	40	187
Red/blonde	12	44
Mutation, CDKN2A		
Absent	4	87
Unknown/untyped	16	116
Present	50	44
Total nevi		
<100	22	206
≥100	29	29
Skin response to sun		
First exposure		
Tan/little burn	19	95
Painful burn/little tan	19	67
Repeated exposure		
Moderate/deep tan	25	117
Mild/no tan	13	45
Solar injury‡		
Absent	15	144
Present	34	88
No. of sunburns		
At ages 0–9 y		
0–1	28	131
≥2	10	22
At ages 10–19 y		
0–2	24	113
≥3	14	40
Lifetime		
0–4	24	111
≥5	14	41

*Clinically assessed on unexposed skin.

†Categorical distribution on limbs and trunk; none = 0; few = 1–100; moderate = 101–500; and many = greater than 500.

‡Clinician assessment of absence/presence of solar keratosis, wrinkling, and telangiectasia on backs of shoulders.

to sun exposure and number of bad blistering sunburns.

The measure of association between melanoma risk and the clinical, genetic, and environmental variables was the odds ratio (OR). Point estimates and 95% confidence intervals of adjusted ORs were calculated using logistic regression analysis as implemented in the EPICURE software package (16). We conducted two analyses. The first analysis [PECAN program (16)] conditioned on family membership using the entire dataset (70 melanoma case patients; 247 unaffected relatives/control subjects). We also conducted an unconditional logistic regression analysis [GMBO program (16)] on the subset of confirmed CDKN2A mutation carriers (50 case patients; 44 control subjects).

Because of the small numbers of study subjects, most categorical variables were reduced to the referent/unexposed and risk/exposed categories (Table 1) using the values leading to the highest or smallest unadjusted OR as the risk category and pooling the others in the referent category. Dysplastic nevi (DN) were divided into three categories: absent, indeterminate, or present. Indeterminate was used for prepubertal subjects less than 16 years of age and for subjects greater than 60 years of age without definite clinical or histologic evidence of DN (17). Two variables defined mutation status: mutation present versus absent and mutation status known versus unknown. For all other variables, individuals with missing data for the variable under study were excluded from the analyses. The calculated ORs were very similar whether age was included as a categorical or a continuous

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Table 2. Odds ratios between melanoma and selected clinical, environmental, and genetic variables

Variable	Measure of association*					
	Univariate results conditioning on family membership†		Results adjusted for CDKN2A mutation (conditioned on family membership)‡		Results from subset analysis of CDKN2A mutation carriers§	
	OR	95% CI	OR	95% CI	OR	95% CI
Complexion	2.5	1.0–7.4	3.1	0.8–13.4	5.1	1.6–16.2
Dysplastic nevi	25.0	7.3–157.4	10.2	2.6–67.4	8.0	1.6–41.1
Freckling	1.5	0.7–3.3	2.0	0.6–6.3	1.9	0.7–5.3
Hair color	2.0	0.8–4.9	2.0	0.6–6.2	2.6	0.8–8.6
Mutation, CDKN2A	56.5	17.0–258.5	—	—	—	—
Total nevi	14.9	6.1–41.1	12.6	3.5–58.6	11.9	3.7–38.3
Skin response to sun, first exposure	2.1	0.9–4.9	2.8	0.9–8.5	2.6	0.8–8.2
Skin response to sun, repeated exposure	1.6	0.6–3.8	3.0	0.9–10.8	5.4	1.4–21.2
Solar injury	2.4	1.1–5.7	4.5	1.4–16.2	3.4	1.1–10.0
No. of sunburns, 0–9 y	2.4	0.9–7.0	1.9	0.5–7.4	1.6	0.4–6.1
No. of sunburns, 10–19 y	2.2	0.9–5.3	1.6	0.5–4.9	1.2	0.4–3.6
No. of sunburns, lifetime	1.7	0.7–4.1	1.3	0.4–4.2	0.9	0.3–2.7

*Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated as described in the text.

†All ORs adjusted for age and conditioned on family membership.

‡All ORs adjusted for age and CDKN2A mutation and conditioned on family membership.

§All ORs adjusted for age; analysis restricted to CDKN2A mutation carriers.

variable. Therefore, we have presented only the data where age was a continuous variable.

Table 2 shows the associations between melanoma risk and selected clinical, environmental, and genetic variables. Results from the univariate conditional analyses (Table 2, column 2) showed that the presence of a CDKN2A mutation, DN, and total nevi had the strongest associations with melanoma. Even after adjusting for CDKN2A mutation (Table 2, column 3), complexion, DN, total nevi, and solar injury each showed a significant association with melanoma. However, freckling, red/blonde hair color, childhood, teenage or lifetime sunburns, and the skin's response to first or repeated sun exposure were each not significantly associated with melanoma. The results from the subset analysis of mutation carriers (Table 2, column 4) were similar to the entire dataset results. Overall, individuals with melanoma were more likely than their unaffected relatives to have these characteristics: a pale/fair complexion, DN, greater than or equal to 100 total nevi, poor tanning ability, or solar injury to the skin.

The major epidemiologic factors associated with melanoma are increased numbers of melanocytic nevi, both clinically banal and dysplastic, intermittent intense sun exposure, and the skin's response to sun exposure (18,19). Despite the high number of melanoma cases

per family (average, 6.4 ± 2.9) in the current study, the variables that were identified, namely dysplastic and increased numbers of nevi and sun-related host characteristics (pale complexion, solar injury, poor tanning ability), were consistent with results from the general population. Our inability to identify sunburning, freckling, and hair color as significant risk factors may result from: 1) increased sharing of these factors among relatives, 2) inaccurate estimation of sunburning, 3) difficulty in clinically separating sun exposure from sun-related host characteristics, or 4) the fact that the variables may not be risk determinants in the families under study.

The study was also limited by the small number of confirmed mutation carriers. This small sample size precluded adjustment for family membership in the subset analysis and may have prevented the detection of every relevant risk factor. Differential inclusion of mutation carriers, deceased melanoma cases, or relatives with certain exposures may also have influenced the results. It is difficult, however, to predict whether the ORs would decrease or increase as a result of this potential participation bias.

For families in this study, we determined that variables other than CDKN2A gene mutations may influence melanoma risk. Exposure to UV radiation contributes to some variables associated with melanoma risk. There-

fore, CDKN2A mutation carriers may be able to reduce their disease risks by limiting their sun exposure. The pattern of CDKN2A gene mutations seen in melanoma tumors (7,20–22) also suggests a possible role for UV radiation in the tumorigenic process. Increased knowledge about the p16/retinoblastoma protein pathway may lead to the development of better diagnostic and therapeutic regimens. However, until that time, management of melanoma-prone families should include efforts to prevent melanoma by reducing the risk factors that promote tumorigenesis and to detect melanomas early by obtaining a biopsy sample from suspicious lesions. Although CDKN2A gene mutations confer substantial risk for melanoma, sun-related exposures also appear to further enhance the disease risk. Identification of clinical and environmental factors, such as those shown in the current study, should assist in further reducing the risk of melanoma in susceptible families with CDKN2A gene mutations.

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Notes

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