Histologic features of melanoma associated with *CDKN2A* genotype

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Background: Inherited susceptibility genes have been associated with histopathologic characteristics of tumors.

Objective: We sought to identify associations between histology of melanomas and *CDKN2A* genotype.

Methods: This was a case-control study design comparing 28 histopathologic tumor features among individuals with sporadic melanomas (N = 81) and cases from melanoma families with (N = 123) and without (N = 120) *CDKN2A* germline mutations.

Results: Compared with *CDKN2A*$^-$ cases, mutation carriers tended to have histologic features of superficial spreading melanoma subtype including higher pigmentation (P_{trend} = .02) and increased pagetoid scatter (P_{trend} = .07) after adjusting for age at diagnosis, sex, and American Joint Committee on Cancer thickness category. Similar associations were observed when comparing mutation carriers with a combined group of *CDKN2A*$^-$ (wild type) and sporadic melanomas. The presence of spindle cell morphology in the vertical growth phase was also an important predictor of genotype. Of the 15 cases with this phenotype, none were observed to harbor a *CDKN2A* mutation.

Limitations: Our study examined rare mutations and may have been underpowered to detect small, but biologically significant associations between histology and genotype.

Conclusion: Familial melanomas with *CDKN2A* mutations preferentially express a histologic phenotype of dense pigmentation, high pagetoid scatter, and a non-spindle cell morphology in the vertical growth phase. (J Am Acad Dermatol 2015;72:496-507.)

Key words: *CDKN2A*; classification and regression tree analysis; familial melanoma; genetic testing; histology; pagetoid scatter; pigmentation; sporadic melanoma.

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Melanoma clusters within families in about 5% to 10% of cases, and *CDKN2A* germline mutations are found in 20% to 40% of familial melanoma kindreds.[1] In contrast, the prevalence of a *CDKN2A* germline mutation in sporadic melanomas is low ranging from 0.2% to 2.0%.[2-5] The *CDKN2A* locus codes for 2 proteins, p16INK4 and p14ARF, that function as tumor suppressors in the Rb/E2F and HDM2/p53 pathways, respectively.[6,7] Previous research has shown that specific histopathologic features are associated with inherited genetics. Female *BRCA1* and *BRCA2* carriers are predisposed to medullary and lobular carcinomas of the breast, respectively, and the 6q22.2 and 6p21.32 genetic regions are associated with adenocarcinomas of the lung.[8-12]

CAPSULE SUMMARY

- It is unknown whether *CDKN2A* mutations are associated with specific histopathological features of melanomas arising within melanoma families.
- Familial melanomas with *CDKN2A* mutations preferentially express a non-spindle cell morphology, dense pigmentation, and high pagetoid scatter.
- If these findings are validated, clinicians can use histology to help determine which patients should be offered *CDKN2A* genetic testing.

To date, there has been limited information published as to the clinicopathologic subtypes of melanoma most likely to occur in familial melanoma kindreds, which are defined by the presence of 2 or more melanomas among first-degree relatives or 3 or more melanomas irrespective of degree of relationship.[5] Previous descriptive series have reported an overrepresentation of superficial spreading morphology among familial melanomas, but these studies were relatively small in size and did not report whether specific histologic features were associated with genotype.[13-16] Bastian and colleagues recently reported good correlation between melanoma histology and somatic mutation status of the oncogenes *BRAF* and *NRAS*, whose profiles broadly resembled those of superficial spreading and lentigo maligna type melanomas, respectively.[17] Among melanomas arising in individuals with *CDKN2A* germline mutations, the prevalence of *NRAS* and *BRAF* mutations is 16% and 37%, respectively.[16]

The purpose of this study was to determine if histologic features of melanoma are associated with inherited *CDKN2A* mutations, which are the most prevalent genetic alterations observed in melanoma families. We hypothesized that the majority of the melanomas diagnosed in *CDKN2A* mutation carriers would be melanomas of the superficial spreading subtype, and that histologic markers of this tumor subtype would be observed at higher proportions in this group. This hypothesis is based on our experience and that of others that suggest an increased prevalence of this subtype of melanoma in familial melanoma kindreds.[13-16,18]

METHODS

Study design

We performed a case-control study of the histopathologic features of familial melanomas from family members with (N = 123) and without (N = 120) *CDKN2A* germline mutations and sporadic melanomas (N = 81). Hereinafter, melanomas from family members who carry a *CDKN2A* mutation are referred to as "*CDKN2A*$^+$" and those from family members testing negative for a *CDKN2A* mutation are referred to as "*CDKN2A*$^-$". Familial melanoma cases were obtained from individuals in families with 2 first-degree relatives given the diagnosis of melanoma or families with 3 or more cases of melanoma irrespective of degree of relationship.[5] Tumor samples were collected from Philadelphia, PA; Bethesda, MD; Barcelona, Spain; Brisbane and Sydney, Australia; Genoa, Italy; Leeds, United Kingdom; and Leiden, The Netherlands, for use in this Melanoma Genetics Consortium (GenoMEL, www.genomel.org) study. Institutional review board approval was obtained at each participating institution. All melanoma specimens were fixed in formalin, stored in paraffin blocks, and slides were subsequently cut for pathologic review. For each melanoma family, only 1 case was selected for use in this study. All slides were stripped of patient identifiers to protect patient privacy. GenoMEL centers contributing tumor slides were asked to match sporadic and familial *CDKN2A*$^-$ melanomas to familial *CDKN2A*$^+$ melanomas on age at diagnosis, sex, and American Joint Committee on Cancer (AJCC) thickness categories to the best of their abilities. In practice however, matching was inconsistently applied across centers. This resulted in a collection of tumor slides that ranged from those selected without regard to any matching criteria to those matched to varying degrees dependent on the number of familial melanoma specimens and/or availability of sporadic melanoma cases at a given center. The distribution of age at diagnosis, sex, and AJCC thickness category across the 3 comparison groups is presented in Supplementary Table I (available at http://www.jaad.org).