Germline CDKN2A Mutations in Childhood Melanoma

Cutaneous melanoma, primarily a disease of adulthood, does occur in children and displays similar biologic behaviors, including invasion, metastasis, and death (1). The proposition that those who develop melanoma during childhood harbor a strong predisposition to melanocyte neoplasia is consistent with Knudson’s hypothesis that cancers arising in the very young may result from mutations to key regulatory genes passed through the germline (2). Evidence from melanoma kindreds indicates that germline mutations in the CDKN2A tumor-suppressor gene are causally related to the development of a subset of these cancers (3). CDKN2A would also be expected to have a role in the etiology of some early-onset melanomas. To test this hypothesis, we screened a population-based series of childhood melanoma cases for evidence of germline CDKN2A mutations.

During the interval January 1, 1987, through June 30, 1994, 61 histologically confirmed cases of cutaneous melanoma occurring in children less than 15 years of age were notified to the Queensland Cancer Registry. As part of a larger case–control study (4), blood samples were subsequently obtained from 31 of these children (males:females, 20:11; age range at diagnosis, 3–14 years). Written informed consent was obtained from the parents of each subject, and the study was approved by our institutional ethics review board.

DNA was extracted from lymphocytes of each case and the three exons of CDKN2A that encode p16 (3) were screened for mutations by single-strand conformation polymorphism analysis following amplification by polymerase chain reaction (5). Samples that showed aberrant mobility patterns (Fig. 1) were sequenced (5) to identify specific nucleotide changes.

Of the 31 cases, 10 had a family history of melanoma and were a priori considered to have a greater likelihood of inherited disease susceptibility; the remainder were ‘sporadic’ cases. Among the familial cases, one germline mutation was observed in a female (case No. 140090) with a history of two primary melanomas before age 13 years. The mutation was a thymidine-to-cytosine transition, resulting in a leucine-to-proline substitution at codon 16. No disease-associated CDKN2A mutations were detected among the sporadic cases, although one individual carried the well-characterized alanine-to-threonine polymorphism at codon 148.

The prevalence of CDKN2A mutation among childhood cases as a whole (one of 31) was lower than anticipated; however, the finding that one of 10 familial melanoma cases harbored a germline mutation accords with the prevalence among melanoma kindreds (3). These data indicate that mutations of CDKN2A are not commonly associated with childhood melanoma. Although this finding does not preclude a central role for CDKN2A in the evolution of some pigment cell cancers (3), it suggests that other genes are important in the genesis of early-onset melanomas.


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Fig. 1. Autoradiograph of a single-strand conformation polymorphism gel showing mobility shifts in exon 1 of CDKN2A. Lanes 1, 2, 9, and 10 are wild-type polymerase chain reaction products; lanes 4–8 are positive controls from melanoma cell lines with known exon 1 mutations; lane 3 is from melanoma case No. 140090.

References


Notes

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Erratum: “Aspartame Consumption in Relation to Childhood Brain Tumor Risk: Results From a Case–Control Study,” by Gurney et al. [J Natl Cancer Inst 1997;89:1072–4 (Issue 14)]. In paragraph 2, line 11, the sentence should read, in part, “Briefly, case patients were 19 years of age or younger. . . .” The Journal regrets the error.

Erratum: “Association Between Human Papillomavirus Type 18 Variants and Histopathology of Cervical Cancer,” by Lizano et al. [J Natl Cancer Inst 1997;89:1227–31 (Issue 16)]. There is a discrepancy between the text on page 1229 (column 2, sentence beginning on line 20) and data shown in Table 1, B, concerning HPV18 variant 1. The information in the table is correct, and the sentence in the text should read as follows: “The other HPV18 variant (var-1) was observed in all histologic types except small-cell carcinoma.” The Journal regrets the error.