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Pediatric Melanoma in Melanoma-prone Families

Alisa M. Goldstein, Ph.D.[*], **Kelsey C. Stidd, B.S.**, **Xiaohong R. Yang, Ph.D., M.P.H.**, **Mary C. Fraser, R.N., M.A.**, and **Margaret A. Tucker, M.D.**

Human Genetics Program, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA

Abstract

Background: In the United States, only 0.4% of all melanomas are diagnosed in patients <20 years. Melanoma in pediatric members of melanoma-prone families has not been fully investigated. The study goal was to evaluate pediatric melanoma patients with extensive follow-up in melanoma-prone families with and without *CDKN2A* mutations.

Methods: For this non-population-based study, families were followed prospectively for up to 40 years. Sixty families with ≥3 melanoma patients were included for analysis: 30 *CDKN2A* mutation positive (*CDKN2A*+) and 30 *CDKN2A* negative (*CDKN2A*-). Age at first melanoma and number of melanomas were obtained for each patient and summarized by family or sets (*CDKN2A*+ vs *CDKN2A*-). For set comparisons and categorical variables (occurrence of melanoma in pediatric patients, number of melanomas, number of patients with single or multiple melanomas), Pearson chi-square or Fisher exact test was used.

Results: Regardless of *CDKN2A* status, melanoma-prone families had 6–28-fold higher proportions of patients with pediatric melanoma compared to the general population of melanoma patients in the United States. Within *CDKN2A*+ families, pediatric melanoma patients were significantly more likely to have multiple melanomas than their relatives who were diagnosed at >20 years (71% vs 38%, respectively; p=0.004). *CDKN2A*+ families had significantly higher percentages of pediatric melanoma patients (11.1% versus 2.5%, p=0.004) compared to *CDKN2A*- families.

Conclusions: These observations have implications for prevention of melanoma as well as clinical care for early detection of melanoma. Children in melanoma-prone families should have careful sun protection from an early age and skin surveillance to reduce their risk of melanoma.

Precis:

[*]Corresponding Author: Dr. Alisa M. Goldstein, Clinical Genetics Branch, HGP, DCEG, NCI, NIH, 9609 Medical Center Dr, Rm 6E438, MSC 9772, Bethesda, MD 20892-9772, Tel: 240-276-7233, goldstea@mail.nih.gov.

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Regardless of *CDKN2A* status, melanoma-prone families had 6–28-fold higher proportions of patients with pediatric melanoma compared to the general population of melanoma patients in the United States. Children in melanoma-prone families should have careful sun protection from an early age and skin surveillance to reduce their risk of melanoma.

Keywords

melanoma; *CDKN2A*; pediatrics; family research; genetics; sun protection

Introduction

Cutaneous malignant melanoma (CMM) is a potentially fatal form of skin cancer, resulting from a combination of environmental, host, and genetic factors.[1–3] Multiple high-, intermediate- and low-risk susceptibility genes are linked to CMM, with cyclin-dependent kinase inhibitor 2A (*CDKN2A*) being the major high-risk susceptibility gene.[4] *CDKN2A*, a tumor suppressor gene, located on chromosome 9p21, encodes two distinct proteins translated in alternate reading frames (ARF), from alternatively spliced transcripts. The alpha transcript encodes p16, a protein that inhibits the cyclin-D1-cyclin-dependent kinase 4 (CDK4) or cyclin D1-CDK6 complex. The p16 protein arrests cell growth at the G_1 stage of the cell cycle, acting as a tumor suppressor.[1,4] The smaller beta transcript specifies p14ARF; this protein induces cell cycle arrest or apoptosis acting through the p53 pathway. Germline mutations in *CDKN2A* have been found in ~20–40% of melanoma-prone families worldwide.[1,4]

In the United States general population, melanoma is the fifth most common cancer in men and sixth most common in women. The median age at melanoma diagnosis is 64 years and only 0.4% of all melanomas are diagnosed in patients less than 20 years of age.[5] The major environmental risk factor for melanoma is exposure to ultraviolet (UV) radiation, either natural exposure or artificial exposure usually via tanning beds. Host factors associated with melanoma include fair skin, hair, and eye color, poor tanning ability, and the presence of multiple melanocytic nevi.[1]

Compared to the general population, melanoma-prone families have a reduced age at melanoma diagnosis and increased frequency of multiple primary melanomas (MPM).[6,7] However, the occurrence of melanoma in pediatric (<20 years) members of these families has not been fully investigated. The goal of the current study was to evaluate the occurrence and clinical and genetic characteristics of young onset (i.e. pediatric) melanoma cases with extensive follow-up in melanoma-prone families with and without *CDKN2A* mutations. Better understanding of pediatric melanoma will help to ensure UV protection from an early age and classification of nevus status; it would also be useful for helping to decide surveillance approaches.

Subjects and Methods

Data for this study came from a non-population-based family study from the Division of Cancer Epidemiology and Genetics at the National Cancer Institute (NCI). Families were

ascertained through self or health professional referrals, and have been followed prospectively for up to 40 years, starting in the 1970s. For this analysis, eligibility criteria included documented cutaneous melanoma, invasive and/or in situ, in at least 3 family members, with at least two of the required melanoma patients being first-degree relatives. Age at melanoma diagnosis was not a criterion for ascertainment. After initial confirmation of family eligibility, all identified living family members were invited to the NIH Clinical Center for detailed skin examinations to document susceptibility phenotypes. If families/individuals could not travel to the NIH, we organized field trips near individuals' homes to collect biospecimens, conduct skin examinations, and photograph nevi. Written informed consent for each participant or each participant's guardian for this observational study was obtained prior to participation under an NCI Institution Review Board approved protocol (NCI 02–0211; Clinicaltrials.gov ID NCT00040352). Willing participants provided blood primarily for genetic studies. All participating families were Caucasian and resided in various regions of the United States. Variables collected and examined in this study included gender, study period, age at melanoma diagnosis, melanoma subtype and site, thickness, precursor nevus status, number of melanomas, and *CDKN2A* mutation status. Study period for time of melanoma occurrence was defined as "retrospective" if the melanoma in a study participant occurred prior to the participant's initial clinical examination and "prospective" if the melanoma occurred after the initial clinical examination of the participant. All diagnoses of melanoma were confirmed by review of pathology materials/reports, medical records, or death certificates. All melanoma diagnoses were confirmed using the above review strategy except for one pediatric patient (patient #23 from family D7) for whom it was not possible to retrieve medical records or death certificate. Sixty families were included in this study, 30 of which were *CDKN2A* mutation positive (denoted *CDKN2A*+) and 30, *CDKN2A* mutation negative (*CDKN2A*-). These 60 families included more than 1300 clinically evaluated participants (melanoma cases, unaffected relatives, and spouses).

The Surveillance Epidemiology and End Results (SEER) Program was used to obtain data regarding the general population (https://seer.cancer.gov/statfacts/html/melan.html; https://seer.cancer.gov/csr/1975_2014)[5] of melanoma patients for comparison with proportion of pediatric melanoma patients and age at diagnosis in the melanoma-prone families.

The median age at first diagnosis of melanoma and number of melanomas were obtained for each subject with melanoma and then summarized by family or sets of families (*CDKN2A*+ vs *CDKN2A*-). For comparisons between sets (*CDKN2A*+ vs. *CDKN2A*- families; melanoma patients from *CDKN2A*+ vs. *CDKN2A*- families) and different categorical variables (occurrence of melanoma in pediatric patients, number of melanomas, number of patients with single or multiple melanomas), the Pearson chi-square or Fisher exact test was used depending on sample sizes. Because of the relatively small number of patients available for analysis, we assumed independence of melanoma patients within families for patient-level analyses. As a sensitivity analysis to reduce effects of bias from family referral, selection, or correlation, we performed the same comparisons after exclusion of the probands (the melanoma patients who led to ascertainment of a family) from each family. All statistical analyses were conducted using Excel, StataSE 11.2, or SAS 9.4. All p-values were two-sided and considered significant at the 0.05 level.

Results

Among the 60 families (30 *CDKN2A*+, 30 *CDKN2A*-) in the current study, there were 311 confirmed melanoma patients, of whom 24 (7.7%) were diagnosed before age 20 years. Table 1 shows the clinical characteristics of the 24 pediatric melanoma patients, 21 from thirteen *CDKN2A*+ families and 3 from three *CDKN2A*- families. All pediatric melanoma patients from *CDKN2A*+ families for whom biologic specimens were available (n=19) carried their respective family's mutation. The median age at first melanoma diagnosis was 16.5 years (range: 9–19 years). Thirteen patients (54%) were female. For most patients (16/20 with known classification), the first melanoma was a superficial spreading melanoma; more than half of the melanomas had a precursor nevus, the clear majority being a dysplastic nevus (DN). Overall, the 24 pediatric patients had a median of two melanomas (range: 1–32 over the time of follow-up). Fifteen patients, all from *CDKN2A*+ families, had multiple primary melanomas (MPM). Seven of the 15 MPM patients had multiple melanomas before age 20 years.

Table 2 shows the age at diagnosis, thickness, study period, and nevus status for each melanoma, and clinical DN and age at last status for the 24 pediatric melanoma patients. Similar to the situation for first melanomas, most subsequent melanomas also had precursor lesions (67/83=80.7%) with about 70% being DN. Among the 21 examined patients, all but one patient (#21) had clinical DN. Patient #21, however, had small atypical nevi that did not meet criteria for DN. For five patients (#2, 4, 15, 19, 21), their first tumor was melanoma-in-situ (MIS). Two of these patients (#19, 21) have not yet developed any additional melanomas although both are still young (age 22 and 33 years, respectively, at last follow-up) and therefore may develop additional melanomas in the future. Of the 15 MPM patients, half developed additional melanomas at least ten years after their initial melanomas. Three patients (#2, 5, 10) were diagnosed with >10 melanomas, invasive or in-situ, during their follow-ups of more than 30 years. Of interest, the two patients who developed the most melanomas used tanning beds during part of the follow-up period.[8]

Among the 60 families evaluated, 43% of *CDKN2A*+ families had at least one pediatric CMM case and 10% of *CDKN2A*- families had at least one pediatric CMM case (Table 3). Further, one-third (10/30) of *CDKN2A*+ families had pediatric CMM cases who developed multiple primary melanoma tumors. In contrast, no *CDKN2A*- families had pediatric MPM cases. Eleven percent of the CMM cases (21/189) in *CDKN2A*+ families and 2.5% of CMM cases (3/122) in *CDKN2A*- families were diagnosed before age 20 years (Table 3). Although these percentages differed significantly (p=0.004), both percentages were substantially greater than in the United States general population (0.4% occurring in patients diagnosed before 20 years).[5] Specifically, the melanoma-prone families in this study had 6–28-fold (.025/.004 for pediatric melanoma patients from *CDKN2A*- families; .111/.004 for pediatric melanoma patients from *CDKN2A*+ families) higher proportions of patients with pediatric melanoma compared to the NCI's SEER-based melanoma patient population.[5] The sensitivity analyses excluding probands showed similar results to analyses that included all melanoma patients (including probands) with significant differences between family sets for the pediatric cases (Table 3). Finally, within *CDKN2A*+ families, pediatric melanoma

patients were significantly more likely to have MPM than their relatives who were diagnosed at greater than 20 years of age (71% vs 38%, respectively; p=0.004).

Discussion

Cutaneous melanoma is predominantly an adult onset disease with median age at diagnosis of 64 years in the United States.[5] Pediatric melanoma, defined here as occurring before 20 years of age, is rare and found in only 0.4% of melanoma patients in the United States. In contrast, regardless of *CDKN2A* mutation status, the melanoma-prone families in this study had 6–28-fold higher proportions of patients with pediatric melanoma compared to the NCI's SEER-based melanoma patient population.[5] Moreover, in the general population, melanoma occurring in this age range shows a female predominance, whereas in the families the occurrence of pediatric melanoma was close to equal in both genders.[5,9] In addition, 71% of pediatric melanoma patients in *CDKN2A*+ families had multiple melanomas with almost half of these patients (7/15) having multiple melanomas before age 20 years. Pediatric melanoma patients from *CDKN2A*+ families were also significantly more likely than their non-pediatric melanoma relatives (i.e. diagnosed at 20 years or greater) to have multiple melanomas. This observation is consistent with what is seen in the general population of melanoma patients in which individuals who develop melanoma at an early age are also at higher risk of developing subsequent melanomas than older individuals. The risk of second primary melanoma in individuals less than 30 years of age is 15.4-fold increased; in those 30–49 years, it is 9.6-fold increased, and in those over age 50 years, 8-fold increased.[10]

The incidence of cutaneous melanoma has been continuing to rise in the United States for the past several decades with increasing incidence in young onset melanoma in recent years.[5,11,12] Among patients diagnosed before 20 years of age, the clear majority (>90%) are diagnosed in the teen years[13] similar to what was observed in the melanoma-prone families in the current study. Although numerous studies have investigated the prevalence of *CDKN2A* mutations in adult onset melanoma cases from families and the general population[14–18] less is known about the prevalence of mutations in *CDKN2A* in young onset melanoma cases. A study using the Swedish Cancer Register evaluated 51 histopathologically confirmed melanoma patients diagnosed before age 20 years for germline mutations in *CDKN2A* and found only one *CDKN2A* mutation in a patient with a strong family history of melanoma.[19] A recent study of 23 clinic-based American, Spanish, and Dutch melanoma patients diagnosed before 20 years of age found no germline mutations in the known melanoma-predisposing genes including *CDKN2A*.[13] Although based on relatively small numbers, these studies suggest that germline *CDKN2A* mutations are rare in pediatric melanoma patients outside of the familial melanoma setting. The current study could not evaluate the prevalence of *CDKN2A* mutations in pediatric melanoma patients from the general population but showed that melanoma-prone families, with and without *CDKN2A* mutations, have an increased frequency of pediatric melanoma compared to the general population of melanoma patients.

All but one of the pediatric melanomas in the current study were confirmed by review of pathology material/reports, medical records, or death certificates. For the pediatric

melanoma patient from family D7 (patient #23), it was not possible to confirm her melanoma diagnosis because we were unable to obtain medical records or death certificate. Exclusion of this patient and family from the study had minimal effect on the results. Family U was included among the families without a *CDKN2A* mutation. The pediatric melanoma patient in this family was diagnosed with melanoma at age 12 years. His father was diagnosed with melanoma at age 23 years and his paternal grandmother was diagnosed at age 36 years. The paternal grandmother was negative for a *CDKN2A* mutation. However, the unaffected paternal grandfather, who self-identified as Latino, carried a *CDKN2A* variant p.I49T that has conflicting interpretations of pathogenicity (ClinVar[20]) and occurs at an allele frequency in the Latino population from gnomAD (0.0044) that is above the threshold considered too common to plausibly cause disease.[21,22] Therefore, this variant was excluded from consideration as disease-causing and family U was considered *CDKN2A*- for this (and all our previous) studies.

In general, melanocytic neoplasms in children (diagnosed before 20 years of age) have been classified into three main subtypes: in association with a large congenital melanocytic nevus, spitzoid melanocytic tumors which include spitzoid melanoma and atypical Spitz tumours, and adult-like (or 'conventional) melanoma.[9,13] Most melanomas developing in pediatric subjects after puberty, designated adolescents, tend to show clinical features consistent with adult melanoma.[9,23] About one-quarter of the pediatric melanoma patients in the current study developed their initial melanomas before/during puberty with the youngest pediatric melanoma patient being diagnosed at nine years of age, however, all the melanoma tumors in pediatric patients were adult-like in their clinical and histologic characteristics, with the predominant histologic type being superficial spreading melanoma. Further, about one-quarter of the initial tumors were MIS/microinvasive and thus associated with excellent prognosis, whereas one-quarter were at least 1.50 mm thick (three being >2 mm thick) with a much less favorable prognosis. Children in melanoma-prone families should be protected from UV exposure from birth to reduce their risk of melanoma. Further, given the earliest diagnosis of melanoma at only nine years of age, regular skin surveillance including the scalp for early detection of features associated with increased risk for melanoma including occurrence of DN should be considered for children from melanoma-prone families before they enter their teen years.[23,24] Usually, the first indication that children may develop DN is an increased number of nevi, some of which may be slightly irregular in outline or variable in color. Anecdotally, dysplastic nevi may become more apparent around the time of puberty. Some of these pediatric patients also continue to develop melanomas throughout their lives and therefore need to practice sun protection, carefully monitor their skin for changes both in nevi and normal skin that occur in a manner worrisome for melanoma, and continue to have regular professional skin surveillance throughout their lives.

Whether children from melanoma-prone families should undergo genetic testing is complicated. In a position paper published in 2015, the American Society of Human Genetics recommended use of predictive genetic testing in minors only for conditions in which a clinical intervention could be delivered in childhood and for which benefits of early intervention outweighed potential psychological harms.[25,26] Stump et al[26] recently investigated whether genetic counseling and test reporting for *CDKN2A* mutations improved sun protection without inducing distress. In a very small initial study of nine carriers and

nine noncarriers, the authors reported significantly fewer sunburns and a greater proportion reporting sun protection adherence between baseline and one-year post-disclosure. The results, however, did not differ by mutation status suggesting that the education provided during the counseling session may have itself contributed to the changes in behavior. Although the authors suggested that this small initial study provided support for the clinical utility of genetic testing and counseling for melanoma risk among minors from families with known familial predisposition mutations, they also noted the importance of confirming the findings in a much larger sample.[26] Although mutation positive members of *CDKN2A*+ families have increased risks for melanoma, we recently reported that among American and Swedish *CDKN2A*+ families, members who tested negative for their family's mutation remained at moderately increased risk for melanoma.[27] Therefore, mutation negative family members should also be encouraged to follow sun safety recommendations and practice skin self-exams in addition to being considered for continuing dermatologic surveillance.[27] Given that the occurrence of pediatric melanoma in both *CDKN2A*+ and *CDKN2A*- families in the current study was significantly increased compared to the general population of US melanoma patients, education and counseling plus skin surveillance for prevention/early detection of melanoma may be the most important proposed strategies for children in melanoma-prone families.

The current study was not population-based and therefore might be prone to referral bias. It was also limited by relatively small number of patients with melanoma diagnosed before 20 years. Given the relatively small number of pediatric melanoma patients, analyses comparing melanoma patients in families with and without *CDKN2A* mutations were conducted assuming independence of these patients. Results were similar, however, with (patient-based) or without (family-based) this independence assumption. To reduce any effects of bias from family referral, selection, or correlation, we conducted a sensitivity analysis from which the melanoma patients who led to ascertainment of each family, i.e. the probands, were excluded from the analyses. The sensitivity analyses showed results consistent with the full analyses suggesting that ascertainment did not bias the results. Since this study was a non-population-based family study, it was not possible to examine the prevalence of *CDKN2A* mutations in pediatric melanoma patients from the general population. Large population-based studies would be required for such an evaluation.

The occurrence of pediatric melanoma is significantly increased in melanoma-prone families, with and without *CDKN2A* mutations, compared to the general population of melanoma patients in the United States. These observations have implications for prevention of melanoma as well as clinical care for early detection of melanoma. Children in melanoma-prone families should have careful sun protection from an early age and skin surveillance to reduce their risk of melanoma.

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Table 1.

Clinical characteristics of first melanoma and total number of melanomas in pediatric melanoma patients from melanoma-prone families with (Positive) and without (Negative) *CDKN2A* mutations

Patient No.	Family ID	Gender	Age	Melanoma Type	Site	Thickness (mm)	Precursor Lesion (Pathology)	Period	Multiple Primary Melanoma	No. Mel before age 20 years	Total No. of Mel	Family Mutation Status
1	AN	Male	16	NM	Chest	2.10	No	Retrospective	Yes	1	2	Positive
2	AN	Female	13	SSM	Back	MIS	Yes/DN	Retrospective	Yes	9	13	Positive
3	A	Female	19	SSM	Knee	0.72	Yes/DN	Prospective	Yes	2	2	Positive
4	E	Female	13	SSM	Calf	MIS	Yes/DN	Prospective	Yes	1	2	Positive
5	D	Male	14	Unclassified	Back	Unknown	Yes/DN	Retrospective	Yes	1	23	Positive
6	BB	Female	19	SSM	Foot	1.50	Yes/Not DN	Retrospective[a]	No	1	1	Negative
7	F	Male	19	SSM	Scalp	2.42	Yes/DN	Retrospective	Yes	1	4	Positive
8	F	Male	17	Unknown	Neck	Unknown	Unknown	Retrospective	No	1	1	Positive
9	U	Male	12	Unclassified	Face	0.88	Yes/Not DN	Retrospective	No	1	1	Negative
10	G	Female	18	SSM	Forearm	Microinvasive	Yes/DN	Retrospective	Yes	1	32	Positive
11	G	Female	19	NM	Forearm	1.65	Yes/DN	Prospective	Yes	1	7	Positive
12	G	Female	17	SSM	Shoulder	0.30	No	Prospective	Yes	3	3	Positive
13	G	Female	16	SSM	Scalp	0.70	No	Prospective	Yes	2	2	Positive
14	J	Male	17	NM	Upper arm	1.66	No	Retrospective	Yes	1	2	Positive
15	J	Female	17	SSM	Calf	MIS	De Novo	Retrospective	Yes	1	2	Positive
16	O	Female	14	SSM	Back	0.52	Yes/DN	Retrospective	Yes	5	8	Positive
17	AH	Male	9	SSM	Shoulder	0.34	Yes/DN	Prospective	Yes	2	3	Positive
18	AH	Male	11	SSM	Back	0.47	No	Prospective	No	1	1	Positive
19	P	Female	13	LMM	Hip	MIS	No	Prospective	No	1	1	Positive
20	P	Male	18	SSM	Scalp	6.50	Yes/DN	Prospective	No	1	1	Positive
21	AS	Male	18	SSM	Breast	MIS	No	Prospective	No	1	1	Negative
22	AP	Male	15	SSM	Face	0.32	Yes/DN	Retrospective[a]	Yes	5	5	Positive
23	D7	Female	13	Unknown	Unknown	Unknown	Unknown	Retrospective[a]	No	1	1	Positive
24	A9	Female	17	SSM	Back	0.60	Yes/DN	Retrospective[a]	No	1	1	Positive

Abbreviations: No., Number; NM, nodular melanoma; SSM, superficial spreading melanoma; LMM, lentigo maligna melanoma; mm, millimeters; DN, dysplastic nevus; Mel, melanoma; MIS, melanoma-in-situ

[a]Patient was a proband, i.e., one of the melanoma patients who led to ascertainment of family

Table 2.

Clinical characteristics of each melanoma, overall clinical dysplastic nevus (DN) status, and age at last status in the 24 pediatric melanoma patients.

Patient No.	Mel No.	Age at Mel Diagnosis, years	Thickness, mm	Study Period	Precursor Lesion	Patient Clinical DN Status	Age at last status, years
1	1	16	2.1	Retrospective	No	Yes	47
	2	34	2.85	At Exam	Yes/not DN		
2	1	13	MIS	Retrospective	Yes/DN	Yes	49
	2	13	MIS	Retrospective	Yes/DN		
	3	16	0.43	Prospective	Yes/DN		
	4	16	MIS	Prospective	Yes/DN		
	5	16	MIS	Prospective	Yes/DN		
	6	16	MIS	Prospective	Yes/DN		
	7	16	0.35	Prospective	Yes/DN		
	8	18	MIS	Prospective	Yes/DN		
	9	18	MIS	Prospective	Yes/DN		
	10	21	Microinvasive	Prospective	Yes/DN		
	11	42	MIS	Prospective	Yes/DN		
	12	45	MIS	Prospective	Clinical nevus[b]		
	13	46	0.28	Prospective	Yes/DN		
3	1	19	0.72	Prospective	Yes/DN	Yes	45
	2	19	0.94	Prospective	No		
4	1	13	MIS	Prospective	Yes/DN	Yes	36
	2	36	MIS	Prospective	Yes/DN		
5	1	14	Unknown	Retrospective	Yes/DN	Yes	63
	2	24	0.4	Retrospective	Yes/DN		
	3	24	0.22	Retrospective	No		
	4	26	0.41	Prospective	Yes/DN		
	5	26	Microinvasive	Prospective	Yes/DN		
	6	27	MIS	Prospective	Yes/DN		
	7	31	0.25	Prospective	Yes/DN		
	8	31	0.39	Prospective	Yes/DN		
	9	32	0.38	Prospective	Yes/DN		
	10	33	0.35	Prospective	No		
	11	35	Microinvasive	Prospective	No		
	12	37	0.5	Prospective	No		
	13	41	0.45	Prospective	Yes/not DN		
	14	41	0.55	Prospective	Yes/DN		
	15	41	0.33	Prospective	No		

Patient No.	Mel No.	Age at Mel Diagnosis, years	Thickness, mm	Study Period	Precursor Lesion	Patient Clinical DN Status	Age at last status, years
	16	42	MIS	Prospective	No		
	17	48	0.42	Prospective	No		
	18	48	MIS	Prospective	Yes/DN		
	19	48	MIS	Prospective	No		
	20	55	MIS	Prospective	Yes/DN		
	21	55	MIS	Prospective	Unknown		
	22	56	MIS	Prospective	Yes/DN		
	23	62	0.84	Prospective	Clinical nevus[b]		
6	1	19	1.5	Retrospective[a]	Yes/not DN	Unknown (Not Examined)	21
7	1	19	2.42	Retrospective	Yes/DN	Yes	25
	2	22	1	Retrospective	Yes/DN		
	3	22	0.4	Retrospective	Yes/DN		
	4	23	0.54	Retrospective	Yes/DN		
8	1	17	Unknown	Retrospective	Unknown	Unknown (Not Examined)	20
9	1	12	0.88	Retrospective	Yes/not DN	Yes	25
10	1	18	Microinvasive	Retrospective	Yes/DN	Yes	60
	2	21	Microinvasive	Retrospective	Yes/DN		
	3	21	0.88	Retrospective	Yes/DN		
	4	21	0.15	Retrospective	Yes/DN		
	5	22	Microinvasive	Retrospective	Yes/not DN		
	6	23	0.56	Retrospective	Yes/DN		
	7	24	Microinvasive	Prospective	Yes/DN		
	8	24	MIS	Prospective	No		
	9	26	MIS	Prospective	Yes/not DN		
	10	26	0.59	Prospective	Yes/DN		
	11	27	MIS	Prospective	No		
	12	28	MIS	Prospective	No		
	13	28	MIS	Prospective	Yes/DN		
	14	28	Microinvasive	Prospective	Yes/DN		
	15	29	0.33	Prospective	Yes/DN indeterminate		
	16	29	Microinvasive	Prospective	No		
	17	29	Microinvasive	Prospective	No		
	18	29	MIS	Prospective	Yes/not DN		
	19	35	MIS	Prospective	No		
	20	36	Unknown	Prospective	Unknown		
	21	38	0.33	Prospective	Yes/DN		

Patient No.	Mel No.	Age at Mel Diagnosis, years	Thickness, mm	Study Period	Precursor Lesion	Patient Clinical DN Status	Age at last status, years
	22	42	MIS	Prospective	Clinical nevus[b]		
	23	45	MIS	Prospective	Unknown		
	24	47	0.24	Prospective	Yes/DN		
	25	48	MIS	Prospective	Yes/DN		
	26	50	0.4	Prospective	Yes/DN indeterminate		
	27	51	MIS	Prospective	Unknown		
	28	52	MIS	Prospective	Unknown		
	29	52	0.25	Prospective	Unknown		
	30	54	0.5	Prospective	Unknown		
	31	56	0.34	Prospective	Clinical nevus[b]		
	32	57	0.2	Prospective	Clinical nevus[b]		
11	1	19	1.65	Prospective	Yes/DN	Yes	51
	2	30	MIS	Prospective	Yes/not DN		
	3	35	MIS	Prospective	Unknown		
	4	40	MIS	Prospective	Yes/DN		
	5	42	MIS	Prospective	Yes/DN		
	6	46	0.4	Prospective	Unknown		
	7	49	MIS	Prospective	Unknown		
12	1	17	0.3	Prospective	No	Yes	26
	2	18	0.35	Prospective	Yes/DN		
	3	19	0.33	Prospective	Yes/DN		
13	1	16	0.7	Prospective	No	Yes	20
	2	18	0.55	Prospective	Yes/DN indeterminate		
14	1	17	1.66	Retrospective	No	Yes	27
	2	20	MIS	Prospective	Yes/DN		
15	1	17	MIS	Retrospective	No	Yes	44
	2	39	0.53	Prospective	Yes/not DN		
16	1	14	0.52	Retrospective	Yes/DN	Yes	25
	2	14	0.46	Retrospective	Unknown		
	3	16	0.37	Retrospective	Yes/DN		
	4	16	0.4	Retrospective	Yes/DN		
	5	16	0.32	Retrospective	Yes/DN		
	6	20	2.4	Retrospective	Yes/DN		
	7	21	1	Retrospective	Yes/DN		
	8	21	MIS	Retrospective	Unknown		
17	1	9	0.34	Prospective	Yes/DN	Yes	30

Patient No.	Mel No.	Age at Mel Diagnosis, years	Thickness, mm	Study Period	Precursor Lesion	Patient Clinical DN Status	Age at last status, years
	2	10	0.49	Prospective	Yes/not DN		
	3	30	MIS	Prospective	Clinical nevus[b]		
18	1	11	0.47	Prospective	No	Yes	23
19	1	13	MIS	Prospective	No	Yes	22
20	1	18	6.5	Prospective	Yes/DN	Yes	32
21	1	18	MIS	Prospective	No	Indeterminate	33
22	1	15	0.32	Retrospective[a]	Yes/DN	Yes	31
	2	15	0.64	Retrospective	No		
	3	15	MIS	Retrospective	Yes/not DN		
	4	16	0.43	Retrospective	Yes/not DN		
	5	16	0.45	Retrospective	Yes/not DN		
23	1	13	Unknown	Retrospective[a]	Unknown	Unknown (Not Examined)	39
24	1	17	0.6	Retrospective[a]	Yes/DN	Yes	44

Abbreviations: No., Number; Mel, melanoma; mm, millimeters; DN, dysplastic nevus; MIS, melanoma-in-situ

[a]Patient was a proband, i.e., one of the melanoma patients who led to ascertainment of family

[b]Clinical nevus means that on a previous exam, or by history, a nevus was present but it was not detected in pathology report

Table 3.

Proportion of pediatric melanoma patients by family and by melanoma patients in *CDKN2A*+ and *CDKN2A*- families

	***CDKN2A*+ Families**	***CDKN2A*- Families**	***P* value**
No. families with pediatric cases (%)	13/30 (43.3)	3/30 (10.0)	0.007
No. pediatric cases among all melanoma patients (%)	21/189 (11.1)	3/122 (2.5)	0.004
Excluding Probands:			
No. families with pediatric cases (%)	10/24 (41.7)	1/16 (6.2)	0.027
No. pediatric cases among all melanoma patients (%)	18/109 (16.5)	1/39 (2.6)	0.026