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Germline mutations predisposing to melanoma

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Abstract

Nearly 15% of melanomas occur in patients with a family history and a subset of these patients have a germline mutation in a melanoma predisposing gene. *CDKN2A* mutations are responsible for the majority of hereditary melanoma, but many other susceptibility genes have been discovered in recent years, including *CDK4*, *TERT*, *ACD*, *TERF2IP*, *POT1*, *MITF*, *MC1R*, and *BAP1*. Additionally, melanoma risk is increased in mixed cancer syndromes caused by mutations in *PTEN*, *BRCA2*, *BRCA1*, *RB1*, and *TP53*. While early onset, multiple tumors, and family cancer history remain the most valuable clinical clues for hereditary melanoma, characteristic epithelioid cytology of melanocytic tumors may suggest an underlying *BAP1* mutation. Herein, we review the clinical and histopathologic characteristics of melanocytic tumors associated with these germline mutations and discuss the role of genetic counseling.

Keywords

CDKN2A; germline mutation; hereditary; melanocytic nevus; melanoma

1 | INTRODUCTION

A subset of melanoma, approximately 7% to 15%, occurs in individuals with a family history.¹ The factors influencing melanoma risk in a family include shared sun exposure experiences, geographic location, skin phototype, and genetic variants.¹ Approximately 22% of familial cases are caused by a mutation in a currently known single high-risk tumor predisposition gene, *CDKN2A*, and over half of individuals with multiple primary melanomas carry mutations in the gene.¹ Melanoma may either be the dominant cancer in the family, such as in families with *CDKN2A* mutation, or be a part of a mixed cancer syndrome such as in families with Cowden syndrome caused by *PTEN* mutations. Generally,

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CONFLICT OF INTEREST

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the mutations in tumor predisposition genes cause multiple tumors with earlier onset than in the general population and occur in those with a positive family history.

While only a small subset of melanoma patients have a tumor syndrome predisposing to cancer, understanding the causes of hereditary melanoma has led to the discovery of a role for several key genes, many of which are also somatically mutated in melanoma, including *CDKN2A*, *TERT*, *MITF* and *PTEN*.² This review discusses the genetic background and clinical and histopathologic features of hereditary syndromes characterized by predisposition to melanoma, melanocytic nevi, and other melanocytic tumors. While most of these tumors are histopathologically indistinguishable from their sporadic counterparts, a subset shows characteristic features such as those caused by *BAP1* germline mutations. Awareness of these syndromes will facilitate early diagnosis and improve patient care.

2 | GERMLINE MUTATIONS

2.1 | CDKN2A

CDKN2A is by far the most commonly mutated gene causing hereditary melanoma (Table 1).¹ Germline mutations in *CDKN2A* increase the risk of melanoma by 65-fold.³ This tumor syndrome was first described in the 1960s by Lynch and Krush⁴ as familial atypical multiple mole and melanoma syndrome (FAMMM) and by Clark and colleagues as B-K mole syndrome⁵ or dysplastic nevus syndrome. Both groups described families with multiple clinically atypical nevi, melanomas and, in a subset of patients, pancreatic cancer. The disease gene was later identified in the 1990s as *CDKN2A*.^{6,7}

CDKN2A is a tumor suppressor gene encoding two transcripts, p16 and p14(ARF), that regulate two critical cell cycle pathways. p16 inhibits CDK4 and, therefore, phosphorylation of RB. p14ARF inhibits HDM2 and, therefore, ubiquitination of p53. In addition to germline mutations, *CDKN2A* is commonly somatically mutated in sporadic melanoma.¹ Somatic biallelic inactivation of *CDKN2A* occurs exclusively within invasive melanomas^{8,9} and can be assessed with immunohistochemical staining for p16 protein. Utility and recommendations for p16 staining as a prognostic and diagnostic marker are variable.¹⁰

A family with *CDKN2A* mutation often includes multiple individuals with numerous atypical melanocytic nevi, sometimes more than 50.¹¹ Patients with nevi on the buttocks or dorsal feet have the highest risk of being mutation carriers.¹¹ Nevi are variable in appearance, ranging from banal to atypical, with large size, irregular and indistinct borders, and variable colors.¹ Histologically, they exhibit features of a dysplastic nevus, including cytologic atypia, asymmetry, papillary dermal fibroplasia, lentiginous melanocytic hyperplasia, variable lymphocyte infiltration, and “shouldering” phenomenon.¹²

Melanoma occurs approximately 15 years earlier in *CDKN2A* mutation carriers than in the general population,¹³ with a median age of onset around 33 to 45 years compared to 53 to 61 years in the general population.^{14,15} Melanoma may occur in adolescence or early adulthood with some of the youngest reported cases at 13 years of age.^{16,17} Conversely, in a population-based series of 20 childhood melanomas, only one *CDKN2A* mutation was identified.¹⁸ A recent study performed in an Italian population demonstrated no difference

between overall survival or melanoma-specific survival in patients with and without *CDKN2A* germline mutations,¹⁹ contradicting prior reports based on Swedish Cancer Registry data.³ However, these studies were performed in different populations with possible underlying differences, necessitating caution when interpreting the results.

Compared with the general population, melanomas are thinner in mutation carriers,²⁰ possibly confounded by increased surveillance of individuals with inherited susceptibility to melanoma. Superficial spreading melanoma is most common in *CDKN2A* mutation carriers, including on the head and neck.²¹ In a case-control comparison of 81 sporadic melanomas, 123 melanoma families with the *CDKN2A* mutation, and 120 melanoma families without, histopathological features specific to *CDKN2A* mutation positive melanomas included higher pigmentation, pagetoid scatter, and spindle cell morphology in the vertical growth phase.²² No differences were found in ulceration, epidermal nesting, the presence of an associated nevus or lentigo, fibroplasia, solar elastosis, regression, or associated lymphocytes, or cell shape, cytologic grade, and mitotic figures of the radial growth phase.²² Others have found that sparser inflammation and lack of regression may be associated features.¹⁵ Similar to sporadic melanoma, somatic mutations in melanomas associated with germline *CDKN2A* mutation include *BRAF* and *NRAS*, although *BRAF* tends to be less common and *NRAS* mutations more common in *CDKN2A* germline mutation associated melanoma.^{23,24}

Notably, a subset of patients, 28%, develops pancreatic cancer.¹ Survival rates in patients with *CDKN2A* mutations who develop pancreatic cancer are lower compared to those without the mutation (22 vs 35 months).²⁵ In addition, *CDKN2A* mutation carriers have an increased risk of upper digestive cancer and cancers involving the respiratory tract, especially in ever-smokers, suggesting that *CDKN2A* increases sensitivity to carcinogens in tobacco.^{26,27} Therefore, *CDKN2A* mutation carriers should be counseled about smoking cessation.

2.2 | *CDKN2A* mutations affecting p14ARF transcript

Through alternatively spliced variants involving exon 1 alpha and 1 beta, *CDKN2A* encodes two major proteins, p16 and p14(ARF), respectively. p14(ARF) regulates the cell cycle through p53 dependent apoptotic pathways.^{28,29}

Interestingly, families with *CDKN2A* mutations that affect the p14 (ARF) transcript develop tumors of the central nervous system, including astrocytoma, and nerve sheath tumors, including neurofibromas and schwannomas, in addition to melanoma (Figure 1A–C; melanoma astrocytoma syndrome).^{30–36} Thus far, missense mutations or deletions at exon 1 beta have been reported in at least three families.^{37,38} Therefore, exon 1 beta should be considered in genetic testing of hereditary melanoma, especially if neural tumors are present.

2.3 | *CDK4*

CDK4 germline mutations are rare, with fewer than 20 families reported in the literature.³⁹ *CDK4* is an oncogene that, when mutated, inhibits binding of p16, leading to phosphorylation of RB and cell cycle progression. Similar to *CDKN2A* mutations, *CDK4*

germline mutations predispose to early onset multiple primary melanomas and increased numbers of atypical nevi.^{40,41} *CDK4* mutation-associated melanomas often occur on the limbs, with average age of onset at 39 years (range of 18-86 years).

In a study of 17 families that included 103 individuals with melanoma, the most common histological subtype was superficial spreading melanoma.⁴¹ The average tumor thickness is 0.32 mm.¹² A longitudinal study by Clark and colleagues demonstrated that a precursor nevus, either intradermal or dysplastic nevus, is often present.¹² Melanocytes, sometimes heavily pigmented, are arranged as single cells and nests with upward scatter of single cells and associated with epidermal hyperplasia.¹² In some tumors, epithelioid cell morphology and lesser pigmentation are noted.¹²

In addition to melanomas, *CDK4* mutation carriers may be at higher risk of developing non-melanoma skin cancers, breast cancer, pancreatic cancer, ovarian cancer, cervical cancer, and stomach cancer, among others.^{1,41}

2.4 | TERT

The role of telomeres is highly implicated in tumorigenesis; germline and somatic mutations in *TERT*, encoding for one of the main components of telomerase, are common in human tumors, including melanoma. Somatic *TERT* promoter mutations are considered one of the earliest secondary mutations following *BRAF* and *NRAS* driver mutations, and are found in 30% to 70% of sporadic melanomas, especially nodular or superficial spreading melanomas.^{8,42,43}

TERT encodes a reverse transcriptase that, together with *TERC*, creates a template for telomere addition, and forms the main components of telomerase. While short telomeres ultimately lead to cell senescence, longer telomeres are associated with cancer, including cutaneous melanoma.⁴⁴

Germline mutations in the *TERT* promoter are rare but predispose to early-onset melanoma and other tumor types.⁴⁵ In a study of 675 families known for high penetrance mutations (*CDKN2A*, *CDK4*, *BAP1*, *POT1*, *ACD*, and *TERF2IP*), only one family with a *TERT* promoter mutation was found.⁴⁶ Horn et al reported *TERT* c.-57T(G) cosegregating with melanoma in a family characterized by early-onset melanoma diagnosed between ages 18 and 46 (mean of 34).⁴⁵ Most of these individuals died within 3 years of diagnosis, suggesting the possibility of a more aggressive clinical course. Two family members were diagnosed with multiple cancers, including one with ovarian cancer and melanoma, and another with renal cell, bladder, breast, and bronchial cancer. In another family with *TERT* c.-57T(G) promoter mutation, seven cases of melanoma diagnosed between ages 15 and 50 were reported.⁴⁶ Melanocytic nevi, basal cell carcinomas, and a bladder tumor were also reported.⁴⁶

While somatic *TERT* promoter mutations are associated with poor prognostic factors, including increased tumor thickness, ulceration, a high mitotic rate, and lymph node metastasis, and co-occur with *BRAF* and *CDKN2A* alterations, reports on histopathologic features of melanomas associated with germline *TERT* mutations are lacking.⁴⁷⁻⁴⁹

2.5 | Shelterin complex genes: *POT1*, *ACD*, and *TERF2IP*

The shelterin family of genes, *ACD*, *TERF2IP*, *TERF1*, *TERF2*, *TINF2*, and *POT1*, regulates telomere processing and stability. Germline mutations in *ACD*, *TERF2IP*, and *POT1* cause hereditary melanoma.⁵⁰ Like *TERT*, these genes are implicated in telomere maintenance and their mutations can increase telomere length and fragility.⁵¹ They bind to telomeric repeats thereby regulating their function.⁵¹

Aoude et al found that of 510 melanoma families, 6 families had *ACD* mutations and 4 had *TERF2IP* mutations.⁵⁰ In a study of 694 patients including high-risk melanoma, 8 variants of *POT1* were found exclusively in the high-risk population.⁵² In a large cohort of patients with first or second-degree relatives with melanoma, four families were identified with *POT1* mutations (frequency of 1.7%).⁵³ Families with *POT1* mutations typically have between one and eight melanomas per family, which occur in individuals between the ages of 25 and 80.⁵³

Of the 510 melanoma families that Aoude et al studied, most cases of *ACD* and *TERF2IP* mutations were superficial spreading melanomas and lentigo maligna melanomas,⁵⁰ although data are sparse. *POT1* variants are typically superficial spreading melanomas.⁵²

ACD and *TERF2IP* mutations also predispose individuals to breast, ovarian, cervical, uterine, thyroid, colon, lung, renal, urinary, prostate, and esophageal cancers as well as lymphomas and leukemias.¹ Additionally, brain tumors are common in families with *POT1* germline mutations.⁵⁴ In a study of 55 families with *POT1* mutations, all families had members with gliomas.⁵⁴ Colorectal cancer, chronic lymphocytic leukemia, breast cancer, and small cell lung cancer are also seen.^{53,55,56}

2.6 | MITF

In 2005, a germline variant *MITF*p.E318K was shown to predispose to melanoma^{57,58} and later, to melanoma and renal cell carcinoma.⁵⁹ This variant is present in approximately 1% of individuals of European descent and is associated with 3- to 5-fold risk of melanoma.⁶⁰ However, individuals with the variant, who also have a personal or family history of pancreatic or renal cell cancer have a 31-fold or 8-fold increased risk of developing melanoma, respectively.¹

As part of the *Myc* family of genes, *MITF* encodes a melanocytic-lineage-specific transcription factor that regulates the differentiation, proliferation, and survival of melanocytes.⁶¹ *MITF*p.E318K is a gain-of-function variant that causes impaired sumoylation of the protein, and therefore, aberrant regulation of downstream, target pathways.⁵⁸ In addition, *MITF* stimulates hypoxia inducible factor 1A (HIF1A), part of the key pathway in renal cell carcinoma development.

Interestingly, *MITF* variants are associated with darker hair, fair skin, and non-blue eye color among other phenotypic characteristics⁶⁰ as well as an increased nevus count, atypical nevi, depigmented nevi, and amelanotic melanomas.⁶² Histopathologically, nodular melanoma and thicker tumors may be more common in some populations,⁶³ although these findings are not supported by Australian/UK data sets.^{58,62}

2.7 | MC1R

Variants of *MC1R* are relatively common, found in up to 11% of individuals,^{64,65} although with lower penetrance. A recent study demonstrated that 66% of a large cohort of melanoma patients were carriers of *MC1R* variants and 28% of the melanomas were attributable to the *MC1R* gene.⁶⁶ Individuals with two *MC1R* variants have a higher melanoma risk compared to those with single variants.⁶⁷ One can expect a 1.5- to 4-fold increased risk of melanoma, and a 3- to 4-fold risk of thick melanomas in *MC1R* variants.^{64,68} Overall, these variants appear to considerably contribute to melanoma burden.⁶⁹

MC1R, or melanocortin-receptor 1, is a G protein coupled receptor that regulates both hair and skin pigmentation. When activated by ultraviolet (UV) radiation, the receptor is bound by alpha melanocyte-stimulating hormone, resulting in melanin upregulation within melanocytes and stimulation of DNA repair mechanisms.⁷⁰ *MC1R* variants generally correlate with phenotypes such as red hair, freckling, UV sensitivity, and melanoma risk,⁷⁰ although *MC1R* variants with darker phenotypes exist and also confer an increased risk of melanoma.⁶⁴

In a study of 2160 patients, no significant associations were discovered between *MC1R* variants and histopathologic variables, including tumor thickness, Clark level, presence of mitotic figures, ulceration, pigmentation, vertical growth phase, regression, tumor infiltrating lymphocytes, or solar elastosis, although further stratification based on sun-sensitive vs sun-resistant phenotypes revealed associations with tumor thickness, presence of mitotic figures, ulceration, and tumor infiltrating lymphocytes.⁷¹ There was an association between more than one high-risk variant and predisposition to melanoma on the arms, although overall trunk was the most common anatomic site.⁷¹

2.8 | BAP1

BAP1 is a tumor suppressor gene on 3p21 that encodes a deubiquitinating enzyme and a binding partner to BRCA1, implicated in chromatin modulation, transcriptional regulation, and DNA damage repair.^{72,73} Characteristic for a tumor suppressor gene, tumors show loss of heterozygosity of *BAP1*.⁷⁴

Germline mutations in *BAP1* predispose carriers to the *BAP1* tumor predisposition syndrome (*BAP1*-TPDS), characterized by *BAP1*-inactivated nevi (BINs), uveal melanoma, cutaneous melanoma, mesothelioma, renal cell carcinoma, and other tumors.^{59,75–79} BINs are highly penetrant, present in up to 90% of mutation carriers, and typically present as multiple, skin colored or reddish-brown, dome-shaped melanocytic tumors (also or previously called *BAP1*-inactivated melanocytic tumors, Wiesner nevi, BAPomas, nevoid melanoma-like melanocytic proliferations, *BAP1* mutant Spitz nevi, and melanocytic *BAP1*-mutated atypical intradermal tumors).^{73,80} BINs develop early in life (median 31 years, range 10-56 years) and increase in number with age.^{81,82}

The most common malignancy associated with this syndrome is uveal melanoma, occurring in up to 29% of patients, followed by mesothelioma (22%), cutaneous melanoma (18%), and renal cell carcinoma (9%).^{73,81} Additionally, basal cell carcinoma, meningioma, cholangiocarcinoma, breast cancer, lung adenocarcinoma, pancreatic cancer, and thyroid

cancer have been reported.⁸¹ A quarter of patients with melanoma typically have multiple primary cutaneous melanomas.⁷⁹

Morphologically, BINs feature a dome-shaped, exclusively or predominantly intradermal melanocytic tumor, with epithelioid melanocytes that have round to oval vesicular nuclei and abundant amphophilic cytoplasm with a nodular or sheet-like growth pattern (Figure 2A–C).^{77,78,83} An associated common nevus component is commonly present, characteristic of a combined nevus containing two or more melanocytic nevus components.⁸⁴ A review of 102 BINs revealed that 69% of cases exhibit spitzoid epithelioid cytomorphology while 31% of cases had smaller epithelioid cells without abundant eosinophilic cytoplasm.⁷⁸ Additionally, rhabdoid features may be present.⁷⁸ In this series, 12% of BINs were associated with a germline *BAP1* mutation.⁷⁸ No significant differences in clinical or histopathologic features were found between tumors with a confirmed germline mutation vs tumors without, except for the presence of extensive junctional component more commonly seen with *BAP1* germline mutation.⁷⁸ Some lesions may exhibit atypical features, including nuclear pleomorphism, and are thus termed *BAP1*-inactivated melanocytomas.⁷⁷ Lastly, transformation of BIN to melanoma has been documented.⁸²

Awareness of BIN and its histopathologic features will enable identification of patients and families with a high probability of germline *BAP1* mutations. When pathologists encounter melanocytic tumors with epithelioid features characteristic of BIN, immunohistochemical testing for *BAP1* should be considered as a screening tool for *BAP1* inactivation. Because normal *BAP1* protein is nuclear, cells with biallelic inactivation will show lack of nuclear staining (Figure 3A–C).⁸¹ In such cases, genetic counseling and/or testing for *BAP1* germline mutation in the patient and family may be appropriate, depending on the clinical setting, i.e., multiple immunohistochemically confirmed BINs at a young age, and personal and family history of cancer.^{83,85,86}

2.9 | Mixed cancer syndromes with melanoma

Mixed cancer syndromes (or melanoma-subordinate syndromes) have an increased risk of melanoma, but lower than that of other cancers seen in the syndrome. These syndromes are caused by mutations in *PTEN*, *TP53*, *BRCA1*, *BRCA2*, and *RBI*, as well as xeroderma pigmentosum genes (Figure 4A–C) and are discussed in Table 2.

3 | SCREENING, GENETIC TESTING, AND GENETIC COUNSELING

Screening for hereditary melanoma begins with obtaining a detailed personal and family history of cancer. As a general guide, multiple tumors of early onset are seen in hereditary cancer syndromes and the “rule of threes” can be applied: patients with a personal or family history of three or more primary melanomas and/or pancreatic cancer should be referred for genetic counseling and testing. In geographic areas with lower prevalence of melanoma, the threshold for testing is two or more primary melanomas or melanoma in situ.⁸⁷ A genetic counselor or other genetics specialist can best guide the patient through this process, including education and obtaining informed consent; appropriate test selection; and post-test counseling that includes recommendations for management of extra-cutaneous cancer risks.⁸⁸

Historically, individual testing of susceptibility genes was performed, but in the recent decade, next-generation sequencing technologies have enabled affordable and timely testing of multiple genes (panel testing).⁸⁷ Panel testing is tailored based on the personal and family history, as thoroughly reviewed by Leachman et al.⁸⁷

Generally, in mutation carriers, full-body skin exams every 6 to 12 months should be performed, and digital dermoscopy, total body photography, and further screening for visceral cancers considered as appropriate.⁸⁹

4 | SUMMARY

In conclusion, a subset of familial melanoma is caused by germline mutations in high-risk melanoma susceptibility genes, many of which are also somatically mutated in melanoma. In general, early onset, multiple tumors, and family history are clues to an underlying tumor syndrome. Pathologists can enable identification of patients at risk by recognizing *BAP1*-inactivated nevi. Identification of patients with a germline mutation predisposing to cancer enables genetic counseling, genetic testing of family members, and appropriate surveillance, reducing morbidity and mortality in these patients.

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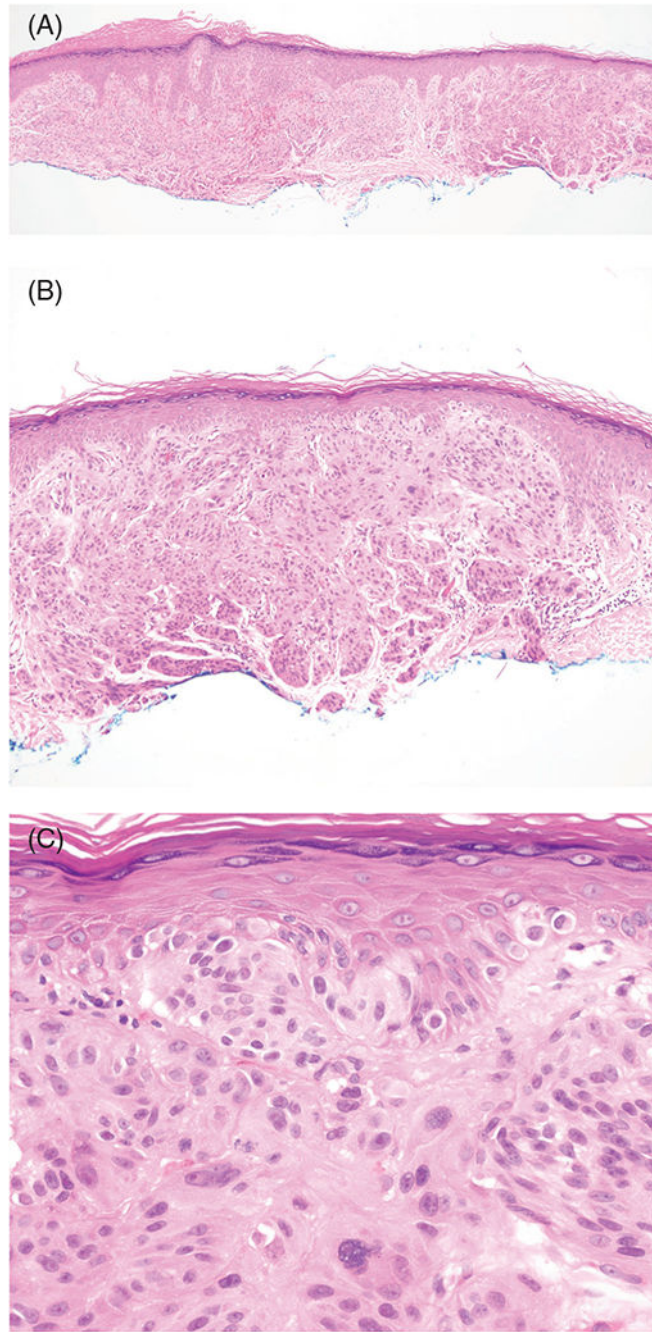


FIGURE 1. Melanoma associated with a germline deletion of exon 1B of *CDKN2A* gene. The patient had a history of multiple primary cutaneous melanomas and visceral metastases. A, Hemotoxylin and eosin (H&E), ×40. B, H&E, ×100. C, H&E, ×400

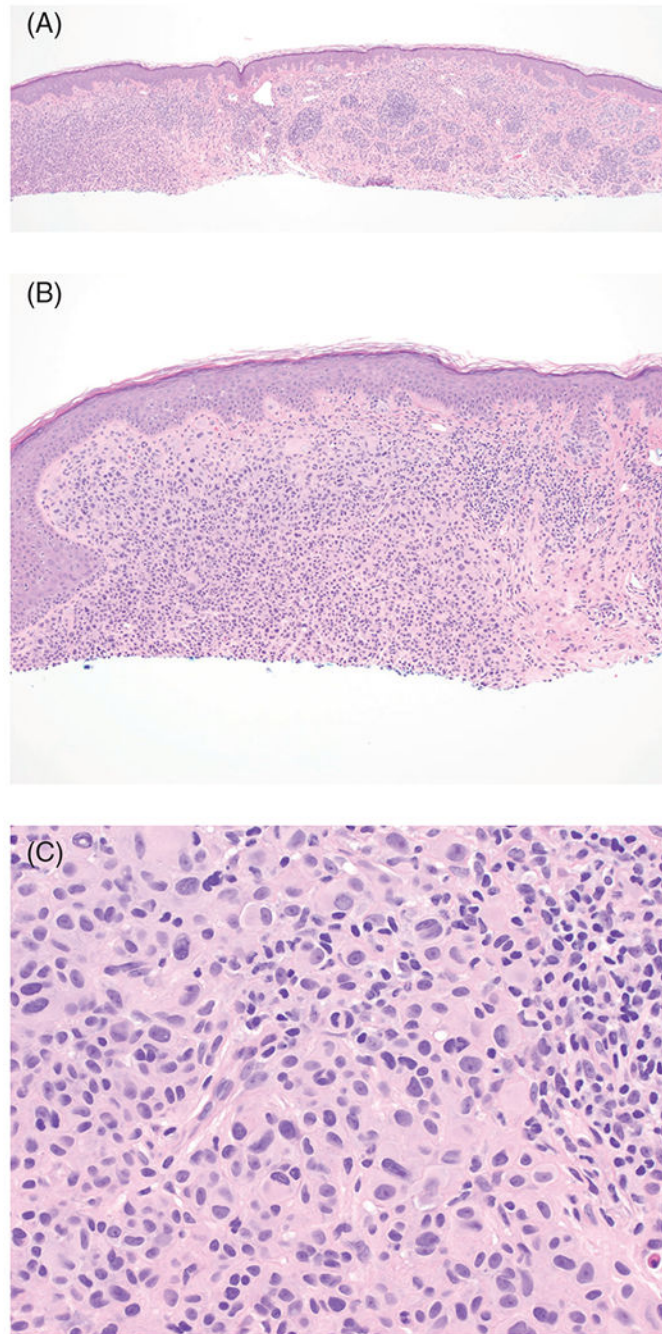


FIGURE 2. BAP1-inactivated nevus with epithelioid melanocytes. This adolescent patient had multiple BAP1-inactivated nevi. A, Hematoxylin and eosin (H&E), $\times 40$. B, H&E, $\times 100$. C, H&E, $\times 400$

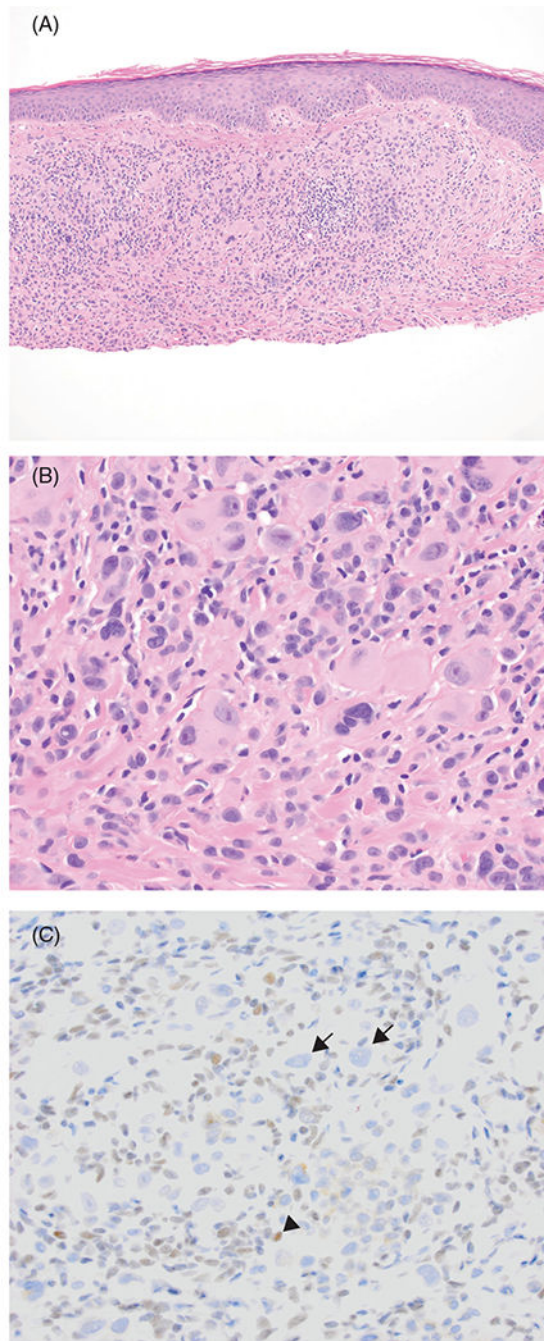


FIGURE 3. Loss of nuclear BAP1 expression in a BAP1-inactivated melanocytoma. This tumor displays nuclear pleomorphism. A, Hematoxylin and eosin (H&E), $\times 100$. B, H&E, $\times 400$. C, BAP1 immunohistochemistry, $\times 400$. Large epithelioid tumor cells have lost BAP1 expression (arrow). Lymphocytes show normal nuclear expression of BAP1 (arrowhead)

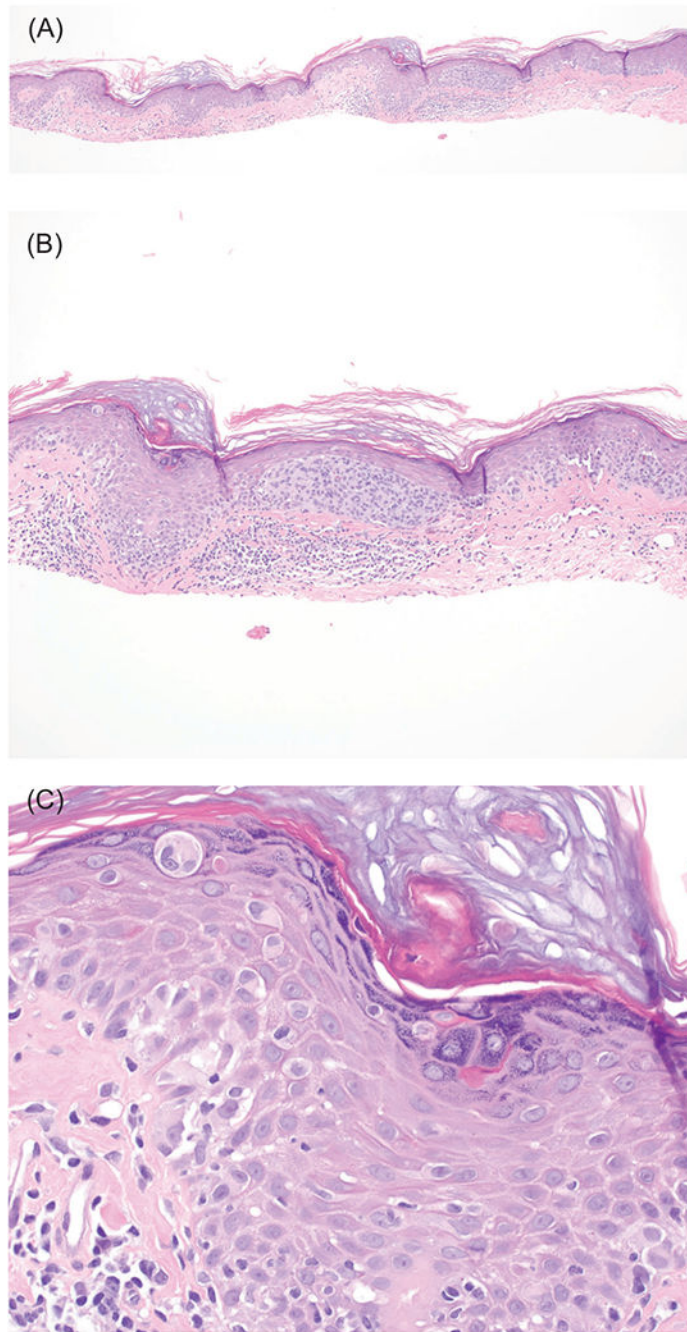


FIGURE 4. Melanoma in situ in a patient with xeroderma pigmentosum. This 22-year old patient had a history of multiple melanomas (invasive and in situ) and numerous basal cell carcinomas. A, Hemotoxylin and eosin (H&E), $\times 40$. B, H&E, $\times 100$. C, H&E, $\times 400$

Germline mutations associated with melanocytic tumors. The relevant gene and its function, clinical phenotype, and histopathological features of melanoma are summarized here.

TABLE 1

Gene ^a	Gene/protein function	Phenotype	Histopathologic features or most common histopathologic subtype of melanoma
Cyclin dependent kinase inhibitor 2A (<i>CDKN2A</i>)	<ul style="list-style-type: none"> Tumor suppressor Two main alternate transcripts: <ul style="list-style-type: none"> (a) p16 inhibits CDK4 and phosphorylation of RB; (b) p14ARF inhibits HDM2 and ubiquitination of p53 	<ul style="list-style-type: none"> Melanocytic nevi, melanoma, pancreatic, upper GI, and respiratory cancers; astrocytoma, neurofibromas and schwannomas (mutation affecting p14ARF) 	<ul style="list-style-type: none"> Superficial spreading melanoma Pigmentation, pagetoid scatter, and spindle cell morphology in vertical growth phase
Cyclin dependent kinase 4 (<i>CDK4</i>)	<ul style="list-style-type: none"> Oncogene Inhibits binding of p16 tumor suppressor leading to phosphorylation of RB and cell cycle progression 	<ul style="list-style-type: none"> Melanocytic nevi, melanoma, pancreatic cancer 	<ul style="list-style-type: none"> Superficial spreading melanoma Pigmentation and pagetoid scatter
Telomerase reverse transcriptase (<i>TER1</i>)	<ul style="list-style-type: none"> Telomerase reverse transcriptase, a component of telomerase Normally repressed in postnatal somatic cells leading to shortening of telomeres 	<ul style="list-style-type: none"> Melanoma, melanocytic nevi, other reported cancers (ovarian, renal cell, bladder, breast, and bronchial cancer) 	<ul style="list-style-type: none"> Nodular and superficial spreading melanoma
Protection of telomeres 1 (<i>POT1</i>)	<ul style="list-style-type: none"> Constituent of shelterin complex that regulates telomere processing and stability 	<ul style="list-style-type: none"> Melanoma, other reported cancers (glioma, chronic lymphocytic leukemia, colorectal, breast, and lung cancers) 	<ul style="list-style-type: none"> Superficial spreading melanoma
ACD shelterin complex subunit and telomerase recruitment factor (<i>ACD</i>)	<ul style="list-style-type: none"> Constituent of shelterin complex that regulates telomere processing and stability 	<ul style="list-style-type: none"> Melanoma, other reported cancers (breast, ovarian, cervical, uterine, thyroid, colon, lung, renal, urinary, prostate and esophageal cancers, lymphomas and leukemias) 	<ul style="list-style-type: none"> Superficial spreading melanoma, and lentigo maligna melanoma
TERF2 interacting protein (<i>TERF2IP</i>)	<ul style="list-style-type: none"> Constituent of shelterin complex that regulates telomere processing and stability 	<ul style="list-style-type: none"> Melanoma, other reported cancers (breast, ovarian, cervical, uterine, thyroid, colon, lung, renal, urinary, prostate and esophageal cancers, lymphomas and leukemias) 	<ul style="list-style-type: none"> Superficial spreading melanoma, and lentigo maligna melanoma
Melanocyte inducing transcription factor (<i>MITF</i>)	<ul style="list-style-type: none"> A melanocytic lineage-specific transcription factor, regulating differentiation, proliferation and survival of melanocytes 	<ul style="list-style-type: none"> Melanoma, renal cell carcinoma Darker hair, fair skin, and non-blue eye color 	<ul style="list-style-type: none"> Amelanotic Thicker tumors (in some populations) Nodular melanoma
Melanocortin-1 receptor (<i>MCL1R</i>)	<ul style="list-style-type: none"> G protein coupled receptor for melanocyte-stimulating hormone Controls melanogenesis and thus skin and hair color 	<ul style="list-style-type: none"> Melanoma Red hair, freckling, light skin, and UV sensitivity (loss-of-function variants) 	<ul style="list-style-type: none"> Anatomic site (arms; in carriers of more than one high-risk variant)
BRCA1 associated protein 1 (<i>BAP1</i>)	<ul style="list-style-type: none"> Deubiquitinating enzyme, BRCA1 binding partner Implicated in chromatin modulation, transcriptional regulation, and DNA damage repair 	<ul style="list-style-type: none"> <i>BAP1</i>-inactivated nevi, uveal melanoma, cutaneous melanoma, mesothelioma, and renal cell carcinoma Other reported tumors (basal cell carcinoma, meningioma, cholangiocarcinoma, breast, lung, pancreatic, and thyroid cancer) 	<ul style="list-style-type: none"> <i>BAP1</i>-inactivated nevi: <ul style="list-style-type: none"> Exclusively or predominantly intradermal Associated common nevus component often present (a combined nevus) Epithelioid melanocytes with round to oval vesicular nuclei and abundant amphiphilic cytoplasm May show smaller epithelioid cells without abundant eosinophilic cytoplasm May show rhabdoid features

^a Gene symbols and nomenclature obtained from the HUGO Gene Nomenclature Committee.

Melanoma-subordinate syndromes. The genes of melanoma-subordinate syndromes are summarized here, alongside the clinical phenotype or tumor spectrum^{90–96}

TABLE 2

Gene	Syndrome	Phenotype and tumor spectrum
Phosphatase and tensin homolog (<i>PTEN</i>)	Cowden syndrome	<ul style="list-style-type: none"> • Mucocutaneous findings: trichilemmomas, acral keratoses, and oral papillomas sometimes with cobblestone appearance • Thyroid abnormalities (multinodular goiter, thyroiditis, and adenomas) • Macrocephaly • Breast cancer (most common malignancy) • Thyroid cancer • Genitourinary cancers (endometrial cancer and renal cell cancer) • GI tumors, including polyps and colorectal cancer • Neurologic tumors • Vascular tumors • Melanoma
Tumor protein p53 (<i>TP53</i>)	Li-Fraumeni syndrome	<ul style="list-style-type: none"> • Multiple cancers, lifetime risk of cancer 70% to 100% • Sarcomas (all types of soft tissue and bone sarcomas, including but not limited to osteosarcoma and rhabdomyosarcoma), except for Ewing sarcoma • Breast cancer • Brain tumors, including high-grade gliomas and medulloblastoma • Adrenocortical carcinoma • Melanoma
BRCA1 DNA repair associated (<i>BRCA1</i>), BRCA2 DNA repair associated (<i>BRCA2</i>)	Hereditary breast and ovarian cancer	<ul style="list-style-type: none"> • Breast and ovarian cancer • Other gynecologic cancers (Fallopian tubal, peritoneal, endometrial, and uterine papillary serous) • Pancreatic cancer • Prostate cancer • Colorectal cancer • Stomach and biliary cancer • Melanoma, including uveal melanoma (mainly <i>BRCA2</i> mutation carriers)
RB transcriptional corepressor 1 (<i>RB1</i>)	Hereditary retinoblastoma	<ul style="list-style-type: none"> • Retinoblastoma, typically under the age of three • Pineoblastoma • Osteosarcoma • Soft tissue sarcomas • Melanoma
mutL homolog 1 (<i>MLH1</i>) mutS homolog 2 (<i>MSH2</i>) Epithelial cell adhesion molecule (<i>EPCAM</i>) mutS homolog 6 (<i>MSH6</i>) PMS1 homolog 2, mismatch repair system component (<i>PMS2</i>)	Hereditary non-polyposis colorectal cancer (HNPCC; Lynch syndrome)	<ul style="list-style-type: none"> • Colorectal cancer • Endometrial cancer • Cancer of small intestine • Other genitourinary cancers (ureteral, uterine, and renal pelvis) • Melanoma
Damage specific DNA binding protein 2 (<i>DDB2</i>) ERCC excision repair 1, endonuclease non-catalytic subunit (<i>ERCC1</i>) ERCC excision repair 2, TFIIH core complex helicase subunit (<i>ERCC2</i>)	Xeroderma pigmentosum	<ul style="list-style-type: none"> • Extreme sensitivity to UV light • Freckling (solar lentigines) in early childhood, poikiloderma • Skin cancers in first decade of life • Basal cell carcinoma • Squamous cell carcinoma • Melanoma • Brain tumors

Gene	Syndrome	Phenotype and tumor spectrum
ERCC excision repair 3, TFIIH core complex helicase subunit (<i>ERCC3</i>) ERCC excision repair 4, endonuclease catalytic subunit (<i>ERCC4</i>)		<ul style="list-style-type: none"> • Lung cancer • Neurological abnormalities
ERCC excision repair 5, endonuclease (<i>ERCC5</i>) DNA polymerase eta (<i>POLH</i>) XPA, DNA damage recognition, and repair factor (<i>XPA</i>)		