REVIEW
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Melanoma Management

Familial risk of melanoma and links with other cancers

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Practice points

Background

- Several genes have been implicated in familial melanoma and associated tumors.

CDKN2A* & *CDK4

- *CDKN2A* and *CDK4* are the most well studied, and are implicated in up to 40% of cases of familial melanomas.

BAP1*, *TERT* & *POT1

- Use of whole-exome sequencing has helped scientists to identify several new genes responsible for familial melanoma and associated tumors over the past 5 years.
- *BAP1*, *TERT* and *POT1* are recently identified genes associated with melanoma and other tumors.

Future perspective

- Identification of mutations in individuals with cutaneous melanoma should prompt both cancer screening for tumors associated with that specific gene.
- Because only a small number of families with these gene mutations have been identified thus far, clear recommendations for cancer screening have not been established. Thus, a thorough patient and family history is imperative in a patient suspected of having familial melanoma, as well as referral to a geneticist with expertise in inherited tumor syndromes.
- Identification of these new genes causing familial melanoma and associated tumors theoretically offers possible targets for new drug therapies in the future.

SUMMARY The genetic risk factors for melanoma are complex and involve both familial and environmental components. Of the thousands of melanomas diagnosed each year, only a fraction are due to familial causes. These melanomas typically present in younger individuals, and may be associated with genetic factors that put these individuals at risk for other tumors. *CDKN2A* and *CDK4* are the most well-characterized mutations, as they have been identified in up to 40% of familial melanomas. Individuals with *CDKN2A* are also at risk for pancreatic cancer. The *BRCA2* mutation has also been implicated in familial melanomas, breast and ovarian cancer. The *BAP1*, *TERC* and *POT1* mutations are associated with melanomas and several other familial tumors.

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The incidence of melanoma has increased steadily over the past 20 years, drawing increased focus to this skin cancer and associated tumors [1–3]. Although approximately 2% of the population will be diagnosed with melanoma in their lifetime, only a handful of these people will develop melanoma due to familial syndromes [4,5]. Familial melanoma is estimated to account for approximately one-tenth of all newly diagnosed cases [6]. Over the past decade, development of linkage analysis, positional cloning and genome-wide molecular sequences techniques have allowed researchers to identify mutations in new target genes responsible for familial melanomas. Understanding specific gene mutations provide potential targets for drug therapies, guiding researchers responsible for developing novel medications for melanoma.

Of the genes responsible for melanoma associated with familial tumors, *CDKN2A* was one of the earliest identified [5,7,8]. This melanoma susceptibility gene, along with CDK4, accounts for the majority of familial melanoma cases. In recent years, *BRCA2*, *BAP1*, *TERT* and *POT1* have also been identified as playing a significant role in familial melanoma syndromes. The objective of this study is to review familial melanoma and associated cancers.

Molecular basis for development of melanoma

On the cellular level, melanoma arises from uncontrolled mitosis of melanocytes, which are derived from neural crest cells. In addition to the skin, melanocytes are found in the uveal tract (choroid, ciliary body, iris), cochlear and leptomeninges. Through use of extensive genome analysis and other laboratory technologies, scientists have elucidated several pathways and high-risk loci which contribute to the development of melanoma. Alternations in these pathway and loci are categorized as genetic, such as amplifications, deletions, mutations, translocations and epigenetic, such as promoter hypermethylation [5]. The development of melanoma initiates with a 'driver' event in which an instigating epigenetic or genetic factor initiates tumor development [9]. Afterwards, 'passenger' events represent additional insults to the genome or molecular pathways which propagate the erroneous sequence of events leading to the development of melanoma [5]. The interplay between the molecular basis of melanoma and environmental factors such as UV light still remains to be elucidated [10,11]. Mutations in melanogenesis pathways result in a high familial risk of tumor development.

CDKN2A

• Epidemiology

The CDKN2A pathway was one of the first pathways elucidated to be related to melanoma development [12]. On the molecular level, CDKN2A is a tumor suppressor that encodes two different proteins produced by alternative reading frames: p16INK4a and p14ARF. P16INK4a (exons 1a, 2, 3) is a cell cycle inhibitory protein, whereas p14ARF (exons 1b, 2, 3) induces cell cycle arrest and apoptosis [6]. Mutations in this gene are inherited in an autosomal dominant pattern, albeit with variable penetrance. Exons 1a and 2 are most commonly mutated in those with melanoma [6].

Worldwide, approximately 40% of familial melanoma cases have *CDKN2A* mutations. Geographically, this mutation was found in 20% of families with melanoma in Australia, 45% of families with melanoma in North America, and 57% of families with melanoma in Europe [13,14]. Approximately 10–15% of people with melanoma and no family history were also found to have germline *CDKN2A* mutations [15].

Additional factors can predict a higher risk in those carrying this gene mutation for people living in sun-exposed countries. These risk factors include UV exposure, increased number of family members with melanoma, early median age at melanoma diagnosis, history of pancreatic cancer in a family member and multiple melanomas in the same patient [14,16–19]. The penetrance in individuals with *CDKN2A* mutations also varies geographically, with varying clinical features and melanoma risk [16,20,21]. However, vigilance with monitoring at-risk patients is necessary, given the high risk of developing an aggressive melanoma [22].

• Associated tumors

Clinically, carriers of germline *CDKN2A* mutations may display increased nevi, as CDKN2A is nevogenic. Those with *CDKN2A* mutations were also found to have more freckling and increased number of nevi on the buttocks and feet. Overall nevi number on the whole body is typically >100 [23]. A *CDKN2A* mutation is associated with the familial atypical mole and melanoma (FAMMM syndrome), in which individuals are at a higher risk of developing both multiple melanomas and pancreatic cancer [24]. In families with the

CDKN2A mutation, the diversity of clinical presentation is impressive. While multiple melanomas predominated as the primary tumor type in some families, early- or late-onset pancreatic cancer predominated in other families. Some individuals with *CDKN2A* mutations may also develop primary sarcomas, lung, head and neck, breast and esophageal cancers [25–27]. Individuals may also be more susceptible to tobacco-related carcinogens, given the elevated risks of lung, head and neck and esophageal tumors [26].

CDK4

• Epidemiology

The *CDK4* gene is closely related to the *CDKN2A* gene, as both act on the same molecular pathway. As a result, both confer high risks for development of melanoma. *CDK4* encodes a serine/threonine protein kinase, which functions in controlling progression through the cell cycle (G1 phase) [28]. Most mutations in CD4K have been reported on codon 24 of exon 2, resulting in a substitution of arginine for histadine. This substitution results in a defective p16INK4a binding domain, leading to progression of the cell cycle since P16INK4a normally acts to inhibit the cell cycle [29]. Similar to *CDKN2A*, mutations in *CDK4* are inherited in an autosomal dominant manner. In contrast, germline mutations of CDK4 are rare, with less than 20 known families in the literature [29,30].

• Associated tumors

Phenotypically, individuals with *CDK4* mutations cannot be distinguished from those with *CDKN2A* mutations [29,31]. Both mutations are characterized by numerous atypical nevi and multiple primary melanomas. Due to the rarity of germline *CDK4* mutations, the data on associated tumors are based on only 17 families with 103 members. Tumors afflicting these 17 families include keratinocyte carcinomas (basal and squamous cell carcinoma), breast, ovarian, cervical, gastrointestinal (including pancreatic), lung, prostate cancer and lymphomas [29].

BRCA

• Epidemiology

Although the *BRCA1/2* genes are better known to be associated with breast cancer, *BRCA2* carriers are also at increased risk for ocular and cutaneous melanoma [32]. *BRCA2* is a tumor suppressor gene involved in DNA repair. It was first identified in the mid-1990s from large cohorts of women with a history of breast cancer [33]. Since then, these genes have been associated with a variety of tumors, and *BRCA2* is estimated to play a role in approximately 3% of individuals who develop ocular melanoma [34].

• Associated tumors

In an analysis of the Breast Cancer Linkage Consortium, *BRCA2* carriers had an 84% risk of developing breast cancer and a 27% probability of developing ovarian cancer by the age of 70 [35]. Furthermore, *BRCA2* has been associated with prostate, pancreatic, gallbladder/bile duct, nasopharyngeal and stomach tumors. Of these tumors, the risk of gallbladder/bile duct tumors is the highest, with a relative risk of 5. The relative risk of developing prostate cancer is 4.7, while the risk of developing hepatic cancer is 4.2 [32,36].

BAP1

• Epidemiology

BAP1 is a recently described gene in which mutations are associated with a high risk of melanoma and other tumors [37,38]. Truncating mutations on chromosome 3 are responsible for a significant number of cases reported in the literature. This tumor suppressor gene likely has a role in cell proliferation and inhibition of growth [39]. Its interaction with host-cell factor-1 may play a role in its inhibition of growth [39]. Additionally, germline mutations have identified mutations in the C-terminus of the protein, suggesting that the interaction with the BRCA1 binding domain may also play a key role in carcinogenesis [40].

BAP1 mutations are associated with uveal melanomas, with mutations seen in almost 50% of uveal melanomas [6,39,41]. Affected individuals tend to develop tumors at an early age. Additionally, the *BAP1* mutation is found in more than 80% of uveal melanoma metastasis [6]. Recent studies have also shown associations with cutaneous melanomas and atypical nevoid melanoma-like melanocytic proliferations, melanocytic intradermal proliferations, Spitz tumors and cutaneous nevoid melanomas [40,42,43].

• Associated tumors

In addition to cutaneous and uveal melanomas, individuals with *BAP1* mutations can develop a wide variety of tumors. These include mesothelioma, cutaneous basal cell carcinoma, clear cell renal cell carcinoma, breast cancer, lung cancer, colon cancer, meningiomas and neuroendocrine

carcinomas [39,42,44,45]. Of these tumors, the association with melanomas and mesotheliomas appear to be the strongest. In a study of two American families with mesotheliomas and no known environmental risk factors, both were found to have frameshift *BAP1* mutations [46]. These families also presented with a history of uveal melanomas and cutaneous melanomas. In another study of 53 subjects with *BAP1* mutations, several were also found to have mesotheliomas and melanomas [39]. Several other studies have also supported this association [43,46,47].

TERT

• Epidemiology

Mutations in the promoter region of *TERT*, or telomerase reverse transcriptase, can lead to multiple cutaneous melanomas. *TERT* encodes a catalytic subunit of telomerase. Mutations in TERT creates new binding motifs for Ets transcription factors and ternary complex factors close to the start of transcription. When mutated, it can result in up to a twofold increase in transcription [48]. *TERT* promoter mutations were identified in linkage studies of families with a high incidence of metastatic melanoma. UV signature mutations (cytidine to thymidine at a dipyrimidine motif) were also detected in the *TERT* promotor regions in families with a strong history of melanoma [38,39].

TERT promotor region dysregulation may serve as the 'driver' event in the development of melanoma. These mutations also showed a combined frequency that was higher than *BRAF* and *NRAS* mutations, which are well-known melanoma drivers [49]. Additionally, telomerase's role in tumorigenesis has previously been well-established, although its exact function in dvelopment of melanoma is unclear.

• Associated tumors

In addition to melanoma, several tumors have been associated with *TERT* promotor region mutations, including hematological malignancies, gliomas, lung cancer, keratinocyte carcinomas, pancreatic cancer, prostate breast, ovarian cancer, bladder cancer and hepatocellular carcinoma [48,50–53]. Cutaneous basal and squamous cell carcinomas with *TERT* mutations show UV signature mutations, suggesting a significant role

Table 1. Associated tumors of various genes linked to melanoma.

	CDK2N	*CDK4*	*BRCA2*	*BAP1*	*TERT*	*POT1*
Astrocytoma						X
Bladder					X	
Breast	X	X	X	X	X	X
Cervical		X				
Colon				X		
Esophageal	X					
Gallbladder/bile duct tumors			X			
Gliomas					X	
Head and neck	X					
Hematological		X			X	X
Hepatocellular					X	
Keratinocyte carcinomas		X		X	X	
Lung	X	X		X	X	X
Meningioma				X		
Mesothelioma				X		
Nasopharyngeal			X			
Neuroendocrine carcinomas				X		
Ovarian		X	X		X	
Pancreatic	X	X	X		X	
Prostate		X	X		X	X
Renal (clear cell)				X		
Sarcoma	X					
Stomach			X			
Uterine						X

for UV exposure in the pathogenesis of TERT-related cutaneous malignancies [50]. It is unclear whether melanoma predisposes patients to other high-risk tumors, or whether these tumors are solely a result of the underlying *TERT* mutation.

POT1

• Epidemiology

This high-risk melanoma susceptibility gene was identified using whole-exome sequencing of five affected families living in Romagna, Italy [54]. A missense variant in the protection of telomeres 1 gene (*POT1*) was identified in all individuals with cutaneous melanoma. *POT1* is inherited in an autosomal dominant manner with incomplete penetrance [54]. Carriers of *POT1* mutations showed increased telomere lengths, suggesting that telomere maintenance is affected in these individuals [54].

• Associated tumors

In families with *POT1* mutations, several associated tumors have been reported. These include uterine cancer, astrocytoma, prostate cancer, breast cancer, small cell lung cancer and chronic lymphocytic leukemia (CLL) [55]. The link between *POT1* and CLL is the most well established, and was identified through whole exome sequencing in patients with CLL. In a study of 214 individuals with CLL, 5% of subjects were found to have recurrent *POT1* somatic mutations, making it one of the most frequently mutated genes in this hematologic malignancy [56]. In CLL cells with the *POT1* mutation, telomeric instability and chromosomal abnormalities were identified [56–58].

Conclusion

Over the past 5 years, our knowledge of genetic causes of melanoma and associated tumors has significantly increased given the use of new technologies such as whole exome sequencing [18]. Previously, families prone to melanoma and other tumors could only be tested for known mutations, such as *CDKN2A* or *CDK4*. If they lacked these mutations, scientists had few tools to definitively identify whether other germline or somatic mutations may be involved.

With the use of whole exome sequencing, it is likely that new genes will be continued to be identified in families with a strong history of melanoma and other tumors. Of the genes that have recently been identified, such as *BAP1*, *TERT* and *POT1*, we can expect continued research into their role in tumorigenesis of both melanoma and other cancers **(Table 1)**. These genes have also identified telomeres as an area of interest for tumorigenesis. Because these genes were only recently identified, it is difficult to determine whether other tumors occurring in the family are a direct result of the gene mutation, or whether they occurred incidentally. Therefore, caution needs to be exercised before drawing definitive conclusions of tumor association with these genes. Identification of these genes and pathways as a causative factor in melanoma allows for improved health screening practices and the theoretically possible new drug targets in the future.

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