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Hereditary Melanoma: Update on Syndromes and Management - Emerging melanoma cancer complexes and genetic counseling

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Abstract

Recent advances in cancer genomics have enabled the discovery of many cancer predisposing genes that are being used to classify new familial melanoma/cancer syndromes. In addition to *CDKN2A* and *CDK4*, germline variants in *TERT*, *MITF*, and *BAP1* have been added to the list of genes harboring melanoma-predisposing mutations. These newer entities may have escaped earlier description in part due to more advanced technologies and also in part due to their mixed cancer phenotype as opposed to a melanoma-focused syndrome. Dermatologists should be aware of, and able to recognize, the clinical signs exhibited by high-risk patients in different contexts. Personal and family history of cancer should always be sought in patients with multiple nevi, or positive history for melanoma, and should be updated yearly. Various features that are unique to specific disorders, such as the appearance of melanocytic BAP1-mutated atypical intradermal tumors (MBAITs) in cases of BAP1 melanoma syndrome, should also be recognized early. Such patients should be offered regular screenings with the use of dermoscopy and total body photography, as needed. More importantly, referral to other specialists may be needed if internal malignancy risk is suspected. It is important to have in mind that these patients tend to develop multiple melanomas,

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along with various internal organ malignancies, often at younger ages, therefore, a multidisciplinary approach to their cancer screening and treatment is ideal.

Keywords

familial melanoma syndromes; mixed cancer syndromes; BAP1; MITF; TERT; PTEN; melanoma genetics

2.1 General considerations for emerging melanoma cancer complexes

KEY POINTS

- A number of melanoma susceptibility genes have been discovered during recent years. These include mutations in BAP1, MITF, Shelterin complex and PTEN

During the last few years sequencing efforts in the field of melanoma research have led to a number of scientific breakthroughs. These include the elucidation of unknown molecular pathways and the discovery of new susceptibility genes. These discoveries hold great value since they may assist in identification of possible molecular therapeutic targets or could even serve as biomarkers for melanoma development and progression. Although the identification of new susceptibility genes may shed a light on the complexity of the genetic landscape of melanoma, at this point it is uncertain on how these genes influence patient phenotypes. Overall, it is estimated that about 10% of melanoma patients present with a positive family history for melanoma.¹ However, true hereditary melanoma syndromes are much rarer. Patients often present with early onset melanomas, multiple primary melanomas and a family history where multiple cases of melanoma in several generations on one side of the family are reported.² In addition, a number of those patients, and their families, may present with other internal organ malignancies. These patients fall under the category of “mixed cancer syndrome” patients, where melanoma may appear in the context of a more general predisposition for malignancy. Familial atypical multiple mole-melanoma syndrome is one of the most comprehensively described melanoma tumor syndromes. However, in recent years, mutations in BAP1, Shelterin complex, MITF and PTEN have also been associated with melanoma and internal organ cancers. In Part II we summarize the current knowledge on these emerging cancer complexes, their pathogenetic mechanisms and the known data on patient phenotypes. We also attempt to provide information on how these patients should be managed.

2.2. BAP1 tumor syndrome

KEY POINTS

- The *BAP1* tumor syndrome is associated with the appearance of cutaneous melanoma, uveal melanoma, and various internal malignancies
- Up to 67% of patients with *BAP1* cancer complex present with multiple atypical melanocytic proliferations called “MBAITs”

- Patients presenting with metastatic UM or concurrent UM and cutaneous melanoma have a higher possibility of exhibiting *BAP1* mutations compared to other melanoma patients

Somatic mutations of the BRCA1-associated Protein 1 (*BAP1*) gene were first described in 26 of 31 aggressive (class 2) cases of ocular (i.e. uveal) melanomas (UM).^{3, 4} Subsequently, germline *BAP1* mutations were also reported in multi-cancer families. Since cutaneous/ocular melanomas, melanocytic proliferations, and other internal neoplasms are a part of the *BAP1* cancer complex, the term “COMMON” syndrome has also been proposed.⁵ This cancer complex is phenotypically characterized by the appearance of clinically benign, but histologically-aggressive, melanocytic skin tumors (Figure 1a, b) at a young age, and a high incidence of mesothelioma, UM, cutaneous melanoma, and possibly other cancers, at an older age. Although a single germline *BAP1* mutation was reported in the original paper by Harbour and colleagues,⁴ the association of germline *BAP1* mutations with a multitude of cancers was independently described in families with uveal melanoma and mesothelioma,⁶ and in kindreds with both uveal melanoma and cutaneous melanoma.⁷

2.2.a. Aspects on the pathogenesis of *BAP1* tumor syndrome

The *BAP1* gene is located on chromosome 3 (3p21.3) and it encodes the 90-kDa BRCA1-associated protein-1 (*BAP1*; Figure 2a). Enzymatically, *BAP1* has an ubiquitin carboxy-terminal hydrolase domain suggesting that it serves as an intracellular deubiquitinase.⁸ Ubiquitin groups are small peptides used to post-translationally modify proteins in order to target them for degradation by proteosomes or to regulate its function. *BAP1* has roles in many important cellular processes, including: cell division, gene expression, signal transduction, protein trafficking, dsDNA repair, and DNA repair regulation, among others (reviewed in ref^{8, 9}). The pathogenetic mechanisms through which *BAP1* mutations (rearrangements, homozygous deletions, and missense mutations) directly or indirectly promote melanomagenesis have not been fully elucidated. Some authors have suggested that patients with the mutation may exhibit altered patterns of gene expression through histone 2A modification¹⁰ or impaired DNA damage repair in response to UV-induced damage.⁸ However, the role of UV radiation in the appearance of UM is debatable.¹¹ *BAP1* is also a UV-inducible substrate of the ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR) kinases. These two kinases inhibit cell cycle progression after UV damage in order to allow for either DNA repair or the induction of apoptosis.¹² Interestingly, recent studies by Kumar et al. showed that *BAP1* may have a tumor maintenance role in sporadic CMM.¹³ More studies are needed in order to fully understand the precise carcinogenic mechanisms of *BAP1* mutations.

2.2.b. Phenotype of patients with *BAP1* tumor syndrome

Patients with *BAP1* tumor syndrome develop multiple, distinct, melanocytic lesions. These lesions have been described as skin-colored to reddish-brown, dome-shaped to pedunculated, well-circumscribed papules that appear progressively after the first decades of life (Figure 1b).⁹ They have been described to be 2–10 mm in diameter and may number from 5 to more than 50.⁷ These skin tumors have been reported to resemble dermal nevi

clinically and nevoid melanomas⁵ or atypical Spitz tumors (ASTs) histologically. However, Carbone et al. evaluated the histological and molecular characteristics of these tumors and reported that their morphology was that of a conventional junctional, compound, or dermal nevus composed of small melanocytes which lack BAP1 staining.⁸ Additionally, a dermal lesion composed of large epithelioid BAP1-negative and, occasionally BRAF-mutated, melanocytes (no mitoses, negative Ki67 immunostaining) have been described adjacent to these lesions though no Kamino bodies have been observed. The authors proposed the term melanocytic BAP1-mutated atypical intradermal tumors (MBAITs) to describe these latter lesions.⁸ These characteristics may be useful in differentiating ASTs from MBAITs, although, the line of distinction is often blurred. Wiesner et al., after investigating 32 sporadic ASTs, reported that nine (28%) showed loss of BAP1 expression, of which 8 (89%) had concomitant BRAF mutations, and exhibited a very similar histologic picture to that of MBAITs.¹⁴ Thus, some dermatopathologists consider MBAITs a subgroup of ASTs that exhibit BAP1 loss.

In a recent study, 66.7% of patients with germline *BAP1* mutations had MBAITs, compared to none of the controls. Also, some of the investigated patients that were positive for MBAITs had already been diagnosed with CMM.¹⁵ Interestingly, these tumors are considered to be slow growing, benign, and possess low metastatic potential.^{9, 15} Unfortunately, no data exist regarding the median age of onset for MBAITs and CMM in this cohort. However, since these lesions can appear early in life, they should be viewed as potential markers of germline *BAP1* mutagenesis. Furthermore, there is insufficient experience to fully exonerate these lesions as pre-malignant.

2.2.c. Melanomas in BAP1 tumor syndrome and management of patients

The BAP1 tumor syndrome has been clearly associated with a higher incidence of CMM and UM. Njauw et al. have demonstrated that *BAP1* mutations are more frequent among metastatic UM cases compared to non-metastatic UM controls (8% vs. 0%, $p = 0.059$), which has subsequently been confirmed in a separate cohort of 507 patients with OM.^{5, 16} In addition, *BAP1* mutations were more common in families with both CMM and UM compared to those with only CMM (29% vs. 0.52%; $p = 0.003$).⁵ Gupta et al. have recently reported that patients with UM, positive for germline BAP1 mutations, developed larger tumors (mean diameter, 15.9 vs 12.3 mm), exhibited higher rates of ciliary body involvement (75.0% vs 21.6%), had a higher metastatic potential (71.4% vs 18.0%) and had an increased frequency of family cancer history (especially for CM and OM) compared to controls.¹⁶ Carbone et al. have also reported that 17.7% and 12.9 % of the *BAP1*-mutant patients in their study developed CMM and UM, respectively, compared to none of the controls.¹⁵ Beyond these select studies, many more have demonstrated an association between CMM and *BAP1* mutations.^{7, 17–20} Given the aggressive histologic appearance of MBAITs, some of these CMMs could have been misdiagnosed MBAITs. More studies are needed to understand the clinical features and course of BAP1-associated CMMs.

Given the rarity of the BAP1 tumor syndrome, there are no codified recommendations for the management of patients with BAP1 mutations. It is extremely important for known *BAP1* mutation carriers to be closely monitored with at least bi-annual skin examinations

accompanied by removal of all changing lesions.^{9, 15} (Level of evidence IV) The MBAITs can appear completely banal (Figure 1b), but should be completely excised given the frequently atypical histology. If a patient presents with multiple MBAITs, those lesions that show atypia or morphological changes over time should be excised. (Level of evidence IV). Moreover, an annual ophthalmologic screening starting from early adulthood would be appropriate (Level of evidence IV).

2.2.d. BAP1 tumor syndrome and other cancers

An example of a BAP1 mutation positive family pedigree is shown in Figure 1c. BAP1 mutations have also been associated with a number of other types of malignancy (Table 1). Overall, Carbone et al. have reported that 63.5% of patients with *BAP1* mutations, compared to 9.1% of controls, developed at least one cancer (OR 17.39, 95% CI: 6.07–49.83).¹⁵ As with other cancer syndromes, these patients are also at risk for developing malignancies at a younger age. No specific screening protocols for internal malignancies have been currently established for individuals who carry a germline *BAP1* variant.

2.3. Telomeres and melanoma risk

KEY POINTS

- The shelterin complex and telomerase protect telomeres from gradual erosion, a process that leads to cell senescence
- Mutations in *TERT*, the protein component of telomerase, and in various components of the shelterin complex have been associated with a higher incidence of melanoma and other internal malignancies
- The association of these mutations with inherited melanoma syndromes remains to be elucidated

Telomeres are DNA protein structures comprised of tandem repeats of the six-nucleotide unit sequence TTAGGG that extend for thousands of bases at chromosome ends. As DNA replication mechanisms are unable to fully copy end DNA, a progressive shortening of telomeres is observed with subsequent cycles, which eventually leads to cell senescence. However, various mechanisms exist in order to counter this gradual telomere erosion.²¹ The shelterin complex physically protects telomeres and also regulates the function of *TERT*. The shelterin complex contains 6 proteins: TRF1, TRF2, and TPP1, which can specifically recognize and bind to double-stranded TTAGGG repeats; POT1, which binds to the single-stranded telomeric overhang; and TIN2 and RAP1 (Figure 3).²² POT1 mutations lead to insufficient capping of telomeres by shelterin. In addition, overexpression of POT1 leads to inhibition of telomerase function. Interestingly, POT1 and TPP1 may have the ability to serve as enhancers of telomerase processivity.²³

TERT, a reverse transcriptase, and *TERC*, an RNA fragment which acts as a template for telomere addition, are the main components of telomerase, a large multi-subunit ribonucleic protein (Figure 2b). Telomerase protects telomeres by elongating them via a strict, cell cycle-regulated process. In addition, telomerase can preferentially elongate the shortest

telomeres, which leads to only a subset of telomeres being elongated in any given cell cycle. Telomerase levels and the balance between its components play an important role in appropriate telomere length maintenance.²⁴

Mutations in the promoter region of the telomerase reverse transcriptase (*TERT*) gene have been described both at the germline level and at the somatic level in sporadic cases of melanoma.^{25, 26} These mutations have been found in the promoter region of the *TERT* isoform that encodes a catalytic reverse transcriptase subunit of telomerase responsible for telomere length maintenance (Figure 2b). Indeed, an association between longer telomere length and CMM risk has been demonstrated;²⁷ telomerase over-expression may be responsible for the cellular immortality associated with cancer.^{25, 26} Horn et al. have described *TERT* mutations in a kindred with 14 CMM patients, yet they also described somatic mutations of *TERT*, which bore a clear UV-signature, in sporadic CMMs.²⁵ A paucity of data exists on the phenotypes of patients carrying *TERT* mutations, although co-existence of numerous nevi has been reported.²⁵ Several studies have demonstrated UV-signature mutations at various positions in the *TERT* promoter.^{25, 26} These alterations may increase the transcription of *TERT* by creating novel Ets transcription factor binding sites. The GA binding protein (GABP) transcription factor, an Ets family member, has now been shown to be recruited to the sites of *TERT* promoter mutations.²⁸ As reported in a recent study, melanomas with *TERT* promoter variants were more likely to be nodular and superficial spreading in subtype and had increased thickness, ulceration, high mitotic rate, and frequent BRAF^{V600E} mutations.²⁹ It is uncertain whether these characteristics also apply to familial cases, but they do imply a more aggressive course for these CMMs.²⁹ In a recent study by Gibbs et al. a significant association between multiple primary melanomas and mutations in *TERT* has been demonstrated (*TERT*/CLPTM1L rs401681, (P = 0.004)).³⁰ Besides CMM, a number of other malignancies have been attributed to *TERT* mutations (Table 1). Interestingly, similar mutations were seen in 16% of various established cancer cell lines, suggesting this might be a common activating mutation in multiple cancer types.²⁶ In addition, Vinagre et al. observed recurrent *TERT* promoter somatic mutations in 43% of central nervous system cancers, 59% of bladder cancers and 10% of thyroid (follicular cell-derived) cancers, in a total of 741 tumors screened.³¹

Other studies have also connected the *TERT* locus or telomere biology with melanoma risk.³² Nan et al. researched the role of 39 single-nucleotide polymorphisms (SNPs) associated with telomere length in 218 patients with CMM and found a positive association with telomere length and CMM risk. In addition, two SNPs in the *TRF2* gene, rs153045 and rs251796, showed significant associations with both total number of moles and the number of raised moles on upper extremities.³³ This finding is consistent with those of previous studies.³⁴ Iles et al. studied 7 SNPs, previously associated with telomere length,³⁵ in 11,108 CMM patients and 13,933 control patients from various areas in the world. A strong association between increased telomere score and increased risk of melanoma ($P = 8.92 \times 10^{-9}$) was consistent across geographic regions, and 4 SNPs with a p value <0.05 were reported (rs10936599 (*TERC*), p=0.0003; rs2736100 (*TERT*), p=0.02; rs7675998 (*NAFI*), p=0.03, rs9420907 (*OBFC1*), p=0.001).³⁵ The frequency of these mutations in melanoma kindreds has not yet been investigated.

Beyond telomerase, other components of the telomeric apparatus have also been shown to harbor mutations in melanoma-prone families. POT1 is a critical member of the shelterin complex, which resides at the telomeres and protects the ends of chromosomes. Mutations in the *POT1* gene have been described in a small number of unrelated Italian, French, and U.S. melanoma families.^{36, 37} In addition to *POT1* mutations, other mutations affecting the function of the shelterin complex have also been described. For instance, mutations in the adrenocortical dysplasia (*ACD*) protein gene have been observed in a small number of melanoma families. This gene not only increases the affinity of POT1 for telomeric single-stranded DNA, but, together with POT1, mediates the interaction between shelterin and TERT as well. Other mutations of the shelterin complex observed in CMM families include mutations in the *TERF2IP* gene. Families harboring such mutations may present with early onset melanomas (appearing in patients as young as 15 years), as well as multiple primary melanomas. Other types of cancer were also observed, including breast, prostate, and lung, among others.³⁸ (Table 1)

2.4. Other melanoma cancer syndromes

KEY POINTS

- Cowden syndrome belongs to the family of PTEN hamartoma tumor syndromes and is characterized by the appearance of trichilemmomas, papillomatous papules, mucosal lesions (papules) and palmar-plantar keratosis within the 3 first decades of life
- Newer data suggest that Cowden syndrome patients have a higher risk of presenting with melanoma compared to healthy controls
- Patients that harbor *MITF* mutations may exhibit a high atypical nevus count and have a tendency to develop melanomas at young age
- Patients with pancreatic or renal cancer who harbor *MITF* mutations have a higher risk of developing CMM

PTEN hamartoma tumor syndrome (PHTS) is a rare condition that encompasses four major, clinically distinct entities associated with germline mutations in the tumor suppressor gene *PTEN*. These include Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome, and Proteus-like syndrome. Phenotypically, all of them are characterized by formation of multiple hamartomas due to unregulated cellular proliferation, but only Cowden syndrome seems to be associated with an increased risk for malignancy.^{39, 40} Cowden syndrome is rare, with an estimated prevalence of approximately 1 case per 200,000 population.⁴⁰

Cowden syndrome (CS) exhibits a very distinct phenotype which includes the appearance of trichilemmomas, papillomatous papules, mucosal lesions (papules) and palmar-plantar keratosis. These features are pathognomonic, since 99% of the patients develop them before the 3rd decade of life (diagnostic criteria can be found ref^{39, 40}). Although CS has been associated in the past with various types of malignancies, recent data also show an

association with melanoma. Tan et al. investigated 368 individuals carrying *PTEN* mutations and demonstrated an elevated standardized incidence ratio (SIR) for CMM of 8.5 (95% CI, 4.1–15.6), with an estimated lifetime risk of 6%.⁴¹ Similarly, Bubien et al. reported a SIR for melanoma of 28.3 for women (95% CI, 7.6–35.4), and 39.4 for men (95% CI, 10.6–100.9) ($P < .001$) in 154 investigated patients.⁴² At this point the exact incidence of melanoma in Cowden syndrome patients has not been clearly defined. Thus, an annual dermatologic examination should be considered for all CS patients. (Level of evidence IV) For those with documented germline *PTEN* mutations, referral to specialized centers for coordinated cancer care (e.g. annual thyroid gland ultrasound, mammography, or endometrial biopsy) is recommended.³⁹ (Level of evidence IV) Given the fact that Cowden syndrome is very rare, most recommendations are supported on anecdotal data, or small studies.

A single codon 318 Glu-to-Lys (E318K) mutation in the Microphthalmia-associated transcription factor (*MITF*) was recently described and shown to increase CMM risk.^{43–45} *MITF* has been demonstrated to act both as a master transcription factor, involved in cell cycle regulation, and a transcriptional repressor.⁴⁶ The E318K mutation affects *MITF* sumoylation (Figure 2c), therefore altering *MITF*'s transcriptional properties.⁴³ Recently, Bartolotto et al. reported that *MITF*(E318K) mutations are associated with a 5-fold increase in risk for developing CMM, renal cancer, or both.⁴³ Ghiorzo et al. similarly reported that *MITF*(E318K) mutation carriers have a 3-fold increase in CMM risk; the authors also determined there was a positive association with the development of other types of cancer besides CMM (Table 1). Interestingly, carriers with personal and/or family history of PC or renal cancer had a 31- and 8-fold increase in risk, respectively, for developing CMMs.⁴⁴ Yokoyama et al. studied the phenotypic traits of *MITF*(E318K)-mutation carriers and reported an association with a higher nevus count, CMM onset before 40 years of age, and non-blue eye color; no association was found with freckling, skin color, or hair color.⁴⁵ These findings were corroborated by Sturm et al., in addition to a reportedly higher incidence of amelanotic melanoma and an association with fair skin. These patients exhibited not only a higher nevus count, but also more nevi larger than 5 mm in diameter, compared to controls. The most common location of CMM development was found to be the back, followed by the limbs, which as the authors suggested, may indicate a propensity for UVR-exposed sites. The predominant dermoscopic pattern for the nevi in *MITF*(E318K)-mutation carriers was reticular.⁴⁷ The exact incidence of *MITF* (E318K)-mutation is not defined in the overall population. However this variant has been found to be augmented in cases displaying multiple primary melanomas and in those with a family history of melanoma.⁴⁸ Although most studies largely corroborate one another, additional studies are needed in order to fully understand the way that these mutations alter the risk for cancer development and the clinical utility of testing for this single variant. A summary of the basic known clinical characteristics for emerging melanoma syndromes can be seen in table 2.

2.5. Conclusion

During recent years, a number of genes associated with melanoma have been described. However, the pathogenesis of melanoma is complicated and multifactorial, and it is likely that many contributory genes remain to be elucidated. With high throughput next generation

sequencing and big data analysis, the science of melanoma syndromes is fluid and changing. Thus, dermatologists need to be constantly aware of new cancer complexes involving CMM in order to provide early diagnosis for cutaneous malignancies and referral to specialized centers for preventive interventions to screen for possible internal malignancies. Recognizing and treating such patients requires a multidisciplinary approach that includes, among others, dermatologists, pathologists, and oncologists. More epidemiological, clinical, and genetic studies are needed in order to fully understand the way that these syndromes are inherited, the role of environmental factors in gene penetrance, the influence of gene-gene interactions, and the importance of these genes in patient prognosis. Furthermore, such studies may also assist in identifying new, druggable targets for the treatment of melanoma.

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Learning Objectives for the CME titled:

HEREDITARY MELANOMA: UPDATE ON NEW SYNDROMES AND MANAGEMENT

Part II: Emerging melanoma cancer complexes and genetic counseling

After completing this Journal CME activity, the learner should be able to:

More efficiently identify and manage patients with possible MTS

Understand the genetic basis of melanoma predisposition, in light of novel susceptibility genes identified recently in genomic studies

Review the current role of genetic counseling in patients with familial melanoma

Part 2 Questions

Question 1: A 25 year old patient presents with multiple rose colored dome-shaped melanocytic lesions. He mentions that these appeared gradually during the last 10 years. Biopsy of one of the lesions shows a highly atypical melanocytic proliferation with features suggestive of nevoid melanoma. He also mentions a positive family history for cutaneous and ocular melanoma. The patient is most likely a mutation carrier in which of the following genes?

- a. CDKN2A
- b. MITF
- c. BAP1
- d. CDK4
- e. PTEN

Answer: C

Question 2: The patient is most prone to which of the following cancers given his personal and family history?

- a. Mesothelioma
- b. Astrocytoma
- c. Esophageal cancer
- d. Colorectal carcinoma
- e. Prostate cancer

Answer: A

Question 3: Which of the following is considered appropriate regarding the follow-up planning for the previous patient?

- a. Annual full skin examinations are considered sufficient for this patient

- b. MBAITs need not be excised since they are banal looking and possess a low metastatic potential
- c. There should not be a low threshold for excising new or changing lesions
- d. Bi- annual ophthalmologic examination should be strongly recommended
- e. Full skin examination should be offered to all first degree relatives of the patient

Answer: E

Question 4: Which of the following alterations has been most frequently observed in melanoma tumor specimens?

- a. UV signature changes in the TERT promoter region
- b. Nonsense mutations in the TERT exons
- c. Frequent deletions of the TERT locus
- d. Missense mutations of the TERT protein that cause aberrant sumoylation
- e. Promoter mutations in the TERC gene

Answer: A

Question 5: A patient with a strong family history of melanoma and other internal malignancies presents for a dermatological checkup. He has no prior history of skin cancer or atypical skin lesions. His mother had a uveal melanoma while his brother was recently treated for mesothelioma. If his mother and brother share a melanoma-causing mutation, what is the patient's probability of being a carrier?

- a. 0%
- b. 12.5%
- c. 25%
- d. 50%
- e. 100%

Answer: D

Figure 1. The BAP1 tumor syndrome phenotype

(a) Patient with germline BAP1 mutation. Clinically atypical moles may or may not be present. (b) Typical MBAITs. These lesions are usually round, dome-shaped and orange-red. (c) Pedigree of a BAP1 kindred. Proband (arrow) had multiple BAMPs along with early onset CM (MEL) and SCC and BCC. Her brother had early onset kidney cancer (KID) and CM along with many BAMPs. Her sister has had multiple BAMPs and CM while her father had lung cancer (LUNG CA) and ocular melanoma (OC MEL). Carriers are indicated by (m). This family was published in the manuscript (Njauw et al, 2012) (d) Patients with the BAP1 tumor syndrome are at risk for cutaneous melanoma, MBAITs, ocular melanoma, mesothelioma and possibly other lung cancers and possibly renal cell cancer.

Figure 2. New melanoma predisposition pathways

(a) In the BAP1 pathway, the deubiquitinase activity of BAP1 removes ubiquitin groups (Ub) from transcriptional regulators and histone 2A (H2A) thereby regulating gene expression. Inactivating mutations in BAP1 leads to loss of nuclear BAP1 activity. (b) Both telomerase (TERT) and the shelterin complex maintain normal telomeric structure. Inherited or somatic variants in the TERT promoter region recruits GABP transcription factor to the TERT promoter thereby stimulating TERT transcription. Inactivating mutations in other shelterin complex genes (e.g. POT1) can be inherited, disrupt normal telomere structure and predispose individuals to melanoma. (c) Lastly, the E318K mutation in MITF removes a normal sumoylation (Su) site in MITF thereby altering the occupancy and transcription of MITF target genes. Presumably, changes in the expression pattern of MITF target genes, which can regulate the survival and the pigment synthetic genes in melanocytes, increase melanoma risk.

Table 1

Malignancies (besides melanoma) associated with familial melanoma syndromes or cancer syndromes with higher incidence of melanoma^{1–6,13,17,22,23,32,35,39,40,46–51}

BAP1	PTEN	TERT	MITF	Shelterin Complex (ACD, TERF2IP)
Uveal melanoma	N/A	N/A	N/A	N/A
Basal cell carcinoma	N/A	N/A	N/A	N/A
Breast Cancer	Breast cancer	Breast cancer	Breast cancer	Breast cancer
Ovarian tumors		Ovarian tumors	N/A	Ovarian tumors
N/A	Endometrial cancer	N/A	N/A	Cervical cancer
Pancreatic cancer	N/A	Pancreatic cancer	Pancreatic cancer	N/A
N/A	N/A	N/A	N/A	N/A
Colon Cancers	Colorectal carcinomas	Colon cancers	N/A	Colon cancers
Mesothelioma Lung cancer	N/A	Lung cancer	N/A	Lung cancer
N/A	N/A	Acute myeloid leukemia Chronic lymphocytic leukemia Myelodysplastic syndrome	N/A	Leukemia
N/A	N/A	N/A	Lymphoma	B cell lymphoma
Meningioma Paraganglioma Neuroendocrine carcinoma	N/A	CNS tumors	N/A	Meningioma Brain tumors
Renal Cell Carcinoma	Renal Cell Carcinoma	Renal Cell Carcinoma	Renal cell carcinomas	Renal Cell Carcinoma
N/A	N/A	Urinary bladder carcinoma	N/A	Urinary bladder carcinoma
N/A	N/A	Prostate cancer	N/A	Prostate cancer
N/A	N/A	Testicular cancer	N/A	N/A
Hepatic cholangiocarcinoma	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	Uterus tumors
N/A	N/A	N/A	N/A	Ovarian tumors
N/A	N/A	N/A	N/A	Cancer of the esophagus
N/A	Thyroid gland carcinomas (follicular and papillary types)	N/A	N/A	N/A

Summary of known data on the phenotypic appearance of patients with possible melanoma tumor syndromes^{5,7,15,30,33,38-40,45,47,48}

Table 2

Characteristics	BAP1	TERT	POT1	PTEN (Cowden syndrome)	MITF
Incidence	Unknown	Unknown	Unknown	1:200,000	Unknown
Phenotype	Multiple MBATIS (appear at first decades of life)	Multiple atypical nevi (possible)	Not clearly defined (mutation is very rare)	trichilemmomas, papillomatous papules, mucosal lesions (papules) palmar-plantar keratosis	Fair skin type (debated) Multiple atypical nevi
Characteristics of melanoma	<ul style="list-style-type: none"> Melanoma: clinical appearance remains undefined Uveal melanoma: aggressive course with high metastatic potential 	nodular or superficial spreading types	clinical appearance remains undefined	clinical appearance remains undefined	Amelanotic melanoma may be more common in this population
Age of onset	Current data do not indicate earlier age of onset	Age of onset is not described	Early age of onset	Age of onset is not described	Early age of onset
Multiple primary melanomas	Yes	Yes	Yes	Unknown	Yes