Published in final edited form as:

Clin Genet. 2016 March ; 89(3): 285–294. doi:10.1111/cge.12630.

Comprehensive review of *BAP1* tumor predisposition syndrome with report of two new cases

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Abstract

The *BRCA1-associated protein-1 (BAP1)* tumor predisposition syndrome (*BAP1*-TPDS) is a recently identified hereditary cancer syndrome. Germline mutations in this tumor suppressor gene predispose families to the development of various malignancies. The molecular functions of the gene as well as the clinical phenotype of the syndrome are still being clarified. We sought to conduct a comprehensive review of published research into *BAP1*-TPDS to more thoroughly delineate the clinical implications of germline *BAP1* mutations. We also report two additional families with germline *BAP1* mutations. Current evidence demonstrates that germline *BAP1* mutations predispose families to uveal melanoma, renal cell carcinoma, malignant mesothelioma, cutaneous melanoma, and possibly to a range of other cancers as well. Some of these cancers tend to be more aggressive, have a propensity to metastasize, and onset earlier in life in patients with *BAP1* mutations as compared to non-predisposed patients with equivalent cancers. Although further research is necessary, this information can aid in the management, diagnosis, and therapy of these patients and their families, and highlights the importance of genetic counseling.

Keywords

BAP1; cutaneous melanoma; germline; mesothelioma; renal cell carcinoma; uveal melanoma

Germline mutation in *BRCA1-associated protein-1 (BAP1)* underlies the recently identified tumor predisposition syndrome (*BAP1*-TPDS) OMIM 614327 (1). The work identifying this hereditary cancer syndrome came simultaneously from three independent research groups focused on uveal melanoma (UM), mesothelioma (MMe), and cutaneous melanoma (CM)

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Conflict of interest

No conflicts of interest exist for any author.

Supporting Information

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(2–4). Shortly after this, renal cell carcinoma (RCC) was also associated with the syndrome (5). An increasing number of patients with germline *BAP1* mutations have been reported since (Appendix S1, Supporting Information). Although the full phenotype of the syndrome is still being characterized, the literature suggests that several other cancers reported in patients and relatives of patients with germline *BAP1* mutations may also be associated and that some cancers associated with this syndrome may have a poorer prognosis. A complete understanding of the disease penetrance as well as gene function and phenotypic spectrum of *BAP1* has also not yet been established.

BAP1 is a deubiquitinating hydrolase identified in 1998 that binds to the RING finger domain of the BRCA1 protein (6). Although earlier reports suggested that the *BAP1* tumor suppressor function was through its deubiquitinating activity upon BRCA1, this was refuted and later studies have indicated that it is an independent tumor suppressor (7). Further studies revealed its involvement in various biologic processes including chromatin dynamics, DNA damage response, cell cycle regulation, and cell growth (8–10). Several recent reviews have detailed the different molecular functions of *BAP1* (8, 11–15). The complex functional roles of BAP1 are partially through its deubiquitinase activity and interactions with several other proteins, in particular HCFC1, YY1, OGT, ASXL1/2 and FOXK1/2 (15–17). However, the structural architecture and stoichiometry of BAP1 complexes have not been fully characterized. The impact of different *BAP1* mutations on the function of these complexes and whether genotype–phenotype correlation exists is still unclear.

The aim of this review was to compile all reported research into *BAP1*-TPDS to help establish counseling, testing, and management guidelines. Further, we introduce two new families with germline *BAP1* mutations and provide updates on several previously reported families.

Materials and methods

Literature review

A literature review was conducted on all peer-reviewed English language articles on *BAP1* and its *Drosophila* homolog, *Calypso*, published through 18 May 2015. A search on PubMed was directed with the keywords ‘BRCA1 associated protein-1’, ‘BAP1’, and ‘Calypso’. Unpublished material was not included. Eighty-seven articles pertaining to *BAP1* and its association with cancer were obtained. Of these, 27 articles described patients with germline *BAP1* mutations. The articles were collated and data were extracted via an article-by-article systematic review. Online supplemental material was consulted if available. Data extracted from the review included clinical information, molecular testing results, and method of molecular analysis. All reported mutations were reviewed and updated to the current standard nomenclature. All data were analyzed and calculated by the authors to produce relevant statistics. Cancer frequency statistics in the general population were derived from the Surveillance, Epidemiology and End Results (SEER) database for comparison.

Screening guidelines from syndromes with similar phenotypes were adapted to develop management recommendations for *BAP1*-TPDS. Interval follow-up data from our previously reported families are included herein (2, 18, 19).

Germline mutation detection

Data on two new families identified by the authors are included. Sequencing was done according to our previously reported protocol and aligning with the reference sequence provided by Genbank accession number NM_004656.2 (2). Confirmation of the splice variant detected in one family was carried out using a primer set with forward primer 5'TGCTCGTG GAAGATTTTCGGTG in exon 3 and reverse primer 5'GGCATGGCTATTATGGGCCT in exon 6. RNA was extracted from peripheral blood leukocytes utilizing Trizol reagent with phenol chloroform precipitation according to the manufacturer's protocol (Life Technologies, Grand Island, NY). Reverse transcription was carried out utilizing SuperScript VILO cDNA synthesis Kit (Life Technologies). Splice variants detected by reverse transcription polymerase chain reaction (RT-PCR) were individually isolated and purified from agarose gel using a gel purification kit according to manufacturer's protocol (Qiagen, Valencia, CA), and then sequenced using forward and reverse primers. The research on our patients was approved by the Institutional Review Board of The Ohio State University and informed consent was obtained from all subjects before testing.

Results

Report of two new families

Germline *BAP1* mutations were detected in two new families. The proband of FUM124 presented with MMe between the rib cage and chest wall at age 71, multiple basal cell carcinomas (BCC) beginning age 56, and CM of the hand diagnosed at age 72. Family history of UM, CM, BCC and multiple other cancers was reported (Fig. 1). A germline missense mutation (c.539T>C, p.L180P) was detected in the proband and an unaffected niece (59 years). The mutation, located in the ubiquitinase domain of *BAP1*, is predicted to be deleterious by both SIFT and POLYPHEN protein modeling software (Fig. 1). According to ACMG guidelines, the mutation classification is most consistent with 'likely pathogenic' (20). The proband's brother (an obligate mutation carrier) was diagnosed with UM at age 60 and with several BCC on his face starting age 61, but passed away from liver metastasis at age 65 without being tested. Ten other family members tested negative for the mutation including five unaffected relatives and five relatives with CM, breast carcinoma, liposarcoma, schwannoma, and prostate cancer. Because the mutation does not unconditionally track with the disease, it is possible that there is a modifier or another gene mutation concurrently affecting this family's cancer risk.

The proband of FUM128 presented with epithelioid peritoneal MMe at age 60 and family history of UM, MMe, and other cancers (Fig. 1). A germline intronic variant (c.256-4_256-2del) was detected. No family members were available for testing. Both NetGene 2 version 2.42 and NNSPLICE version 0.9 software indicated that this variant is a potential splice-site mutation. Sequencing of the RT-PCR product utilizing primers in exons

3 and 6 confirmed the aberrant splicing with formation of two splice products, one with splicing-out of 253 base pairs of exons 4–5 and the other with inclusion of intron 4 (393 base pairs) (Fig. 1; Fig. S1).

Clinical findings in families with germline *BAP1* mutation

Including the two new families reported herein, there have been 57 families with 174 individuals reported to carry *BAP1* mutations; 67 are male (39%), 95 are female (55%), and 12 patients have no gender information reported. UM is the most common cancer diagnosed with a total of 54 patients (31%) (2–5, 18, 19, 21–31). Fifty-six of the 57 families presented with one or more of four main cancers (UM, MMe, CM, and RCC). The distribution of these cancers in these families is summarized with Venn diagrams (Fig. 2). Median age of cancer diagnosis in these patients was age 50 (range 16–85). It should be noted that many reported cancers were not confirmed by records review. In addition, a comparison of cancer frequency is imperfect as our cohort includes patients reported internationally while SEER compiles data from patients in the United States (Appendix S1).

Common *BAP1*-TPDS tumors

Uveal melanoma—Both germline and somatic *BAP1* mutations have been found in patients with UM, the most common ocular malignancy in adults (Table 1). Fifty-four of 174 (31%) reported *BAP1* mutation carriers had a diagnosis of UM (2–5, 18, 19, 21–31). The incidence of UM in the general population is 5.1 diagnoses per million population (32).

The earliest reported age of cancer onset in a germline *BAP1* mutation carrier is for UM at age 16, and there have been a total of four UM diagnosed by age 20 (19, 22, 27, 30). Median age of onset is earlier in UM patients with germline *BAP1* mutation (51 years, range 16–72) compared with the general population (62 years) (32).

Beyond epidemiologic data, there is good molecular evidence of UM's association with the *BAP1*-TPDS. Genetic analysis of UM tumor tissue from seven patients with germline *BAP1* mutations showed loss-of-heterozygosity (LOH) or loss of expression of the wild-type allele (2, 4, 22, 26, 27, 30). Somatic *BAP1* mutations have also been widely reported in sporadic UM, and protein expression studies have also shown lack of BAP1 expression in UM tumors (Table 1) (44–47).

Malignant mesothelioma—A total of 39/174 patients (22%) with germline mutations have been diagnosed with MMe with median age of onset earlier than that in the general population (Table 1) (2, 3, 5, 18, 30, 31, 33–36). Twenty-six patients (67%) had pleural MMe, 12 patients (31%) had peritoneal MMe, and 1 patient had diagnoses of both. Interestingly, all 13 patients reported to have diagnoses of peritoneal MMe are female, while peritoneal MMe is more commonly diagnosed in males in the general population (48).

Another finding in this subset of patients is the high frequency of multiple cancers. Excluding cases of multiple MMe, 14 patients (36%) have been diagnosed with another primary cancer in addition to MMe. Of the second cancers, UM occurred in 5/39 (13%) of the MMe patients.

Asbestos exposure is a strong predisposing factor for MMe development in the general population, but its role in *BAP1*-TPDS is unclear. Testa et al. detected asbestos traces in homes of all affected family members in both of the families they report with germline mutations (3). Arzt et al., however, found no statistically significant effect of asbestos exposure on BAP1 protein expression *in vitro*; any potential mechanism of how asbestos and BAP1 may interact is unknown (49).

MMe tumors from seven germline *BAP1* mutation carriers have been shown to have loss of the wild-type *BAP1* allele or its expression (3, 35). Somatic *BAP1* mutations and loss of BAP1 expression have also been reported in presumably sporadic MMe (Table 1) (3, 44, 50–52).

Cutaneous melanoma—There are 23/174 (13%) reported patients with germline *BAP1* mutations diagnosed with CM; median age of onset is earlier than in the general population (Table 1) (2, 4, 5, 22, 24, 27, 29–31, 35, 37). Notably, 5/23 (22%) of these patients had multiple primary CM with a maximum of seven in a single patient (5, 29, 30). Further, 11 (48%) had CM diagnosed in addition to another cancer (4, 5, 24, 29, 31, 35). Tumors from four of these patients show LOH and/or loss of expression of BAP1 as well (4, 29, 35). Njauw et al. noted three families carrying germline mutations had diagnoses of ‘nevroid CM’, a rare subtype. Analysis of these irregular tumors in one family revealed semitranslucent orange-red pigmentation and high levels of Ki67 staining. These lesions were distinct from traditional CM and may be related to atypical Spitz tumors (ASTs) (29).

Somatic mutations and lack of staining for BAP1 via immunohistochemistry have also been noted in CM tissues from patients *without* germline mutations, indicating *BAP1* may be involved in some aspects of CM pathogenesis (Table 1) (4, 44, 53, 54).

Renal cell carcinoma—Eighteen of 174 (10%) of the reported patients with germline *BAP1* mutations had RCC with median age of diagnosis earlier than that seen in the general population (Table 1) (3, 5, 18, 25, 29, 37–40). Tumor tissue studies demonstrating LOH, somatic *BAP1* mutations, and IHC staining all support an association between germline *BAP1* mutation and RCC (Table 1) (39, 40, 44, 55–60).

Cutaneous melanocytic lesions—*BAP1*-TPDS is associated with a distinct subset of benign skin lesions located on the head and neck, trunk, and limbs. A range of names has been given to these lesions, including melanocytic *BAP1*-mutated atypical intradermal tumors (MBAITs), ASTs, Wiesner nevi, and nevroid melanoma-like melanocytic proliferations (NEMMPs) (29, 61–63). Herein, we will refer to them as ASTs as these lesions fit closest clinically and pathologically to this designation. These lesions are well-circumscribed dome shaped, skin-colored or reddish-brown nodules, with average sizes of 5 mm, and range widely in number. Morphologically, the lesions are mostly intradermal with occasional involvement of the junctional epidermis, and show cytological features resembling atypical Spitz nevi (64). They are characterized by biallelic inactivation of *BAP1* and frequent *BRAF*^{V600E} mutation; both of which can be reliable markers for aiding in the diagnosis (63).

The prevalence of ASTs in *BAP1*-TPDS is unclear as they were not assessed in a majority of reported patients. Of 43 germline *BAP1* patients who were assessed via full body skin exams with biopsy of suspicious lesions, 31 patients (72%) were diagnosed with ASTs (4, 27–31, 35, 61, 65). Eleven of 31 (35%) of these patients had multiple lesions, with a range of 2 to over 50 (4, 5, 24, 29, 35, 65). Median age of diagnosis was 42 years. Although their natural history is unknown, Busam et al. found ASTs to be present since childhood in one germline *BAP1* mutation carrier (65, 66). LOH in the tumor was confirmed in 22 ASTs in 3 germline mutation carriers from one family (4).

Lesions with similar morphological and molecular characteristics have also been reported in patients *without* germline *BAP1* mutation (4, 14, 63). The clinical significance of these lesions and any possible relation to CM is yet to be determined.

Possible *BAP1*-TPDS tumors

A number of other tumor types including a range of sarcomas and carcinomas have been reported in germline *BAP1* mutation carriers; however, there are limited data supporting their inclusion in *BAP1*-TPDS (Table 1; Appendix S1) (2, 3, 5, 18, 22, 24, 25, 27–31, 41–44, 67–75). The most commonly reported cancers include breast cancer and BCC with 9 and 11 patients with germline mutations diagnosed, respectively. Tumor testing in these patients has shown LOH. Although BCC is common in the general population, these molecular data suggest an association. *BAP1*'s association with breast cancer has been suspected, given its interaction with the *BRCA1* tumor suppressor. Conflicting reports regarding the association have been published, however, as germline *BAP1* mutations are not common in breast cancer, including in patients with family histories consistent with hereditary cancer predisposition (5, 76, 77). The recent addition of *BAP1* to multigene panels offered by several clinical laboratories, including those for breast cancers, will help elucidate any association.

Germline *BAP1* mutation and tumor aggressiveness

Current data suggest that germline mutations in patients with UM, CM, and RCC are associated with more aggressive disease, while in MMe they are associated with less aggressive disease, as discussed below.

In UM, patients with germline *BAP1* mutations tend to have more aggressive cancers with higher tumor staging and a greater likelihood of metastasis (29). Tumors with somatic *BAP1* mutations have also demonstrated larger tumor sizes, more aggressive disease with poorer outcomes, and higher rates of metastasis, and they may represent a precursor event to the more aggressive 'class 2' UM (26, 39, 55, 59, 78). Mean survival in UM patients with tumors that lacked BAP1 protein expression was 4.74 years as compared to 9.97 years in patients with BAP1 protein expression (45).

Similar somatic findings were reported in RCC as Hakimi et al. found an average of 31.2 month survival in RCC patients with somatic *BAP1* mutations compared to 78.2 month survival in patients without in a cohort of 421 patients (56). Kapur et al. determined similar survival rates with an average of 1.9-year survival in RCC patients with tumors with somatic

BAP1 mutations vs 5.4-year survival in patients with tumors with *PBRM1* mutations in a cohort of 327 patients (79). A smaller cohort in the study showed 4.6-year survival in *BAP1* mutant tumors vs 10.6-year survival in *PBRM1* mutant tumors.

In CM, a small pilot study has suggested the tumors with low *BAP1* expression tends to have shorter disease-free survival and melanoma-specific survival (53). However, *in vitro* and *in vivo* studies of primary melanomas and non-transformed melanoma cell lines suggested a pro-survival role of *BAP1*. This could be partially explained through its effect on survivin protein expression (80).

In contrast, a cohort of 23 MMe patients with germline *BAP1* mutations appeared to have sevenfold longer overall survival as compared with sporadic MMe patients (81). Patients with germline *BAP1* mutations had improved survival in both peritoneal and pleural MMe (81). de Reynies et al. found a distinct, less aggressive subset of MMe through molecular profiling that was characterized by a high prevalence of somatic *BAP1* mutation (82).

The molecular mechanism of such variation in aggressiveness between *BAP1*-associated cancers is not clear. A potential explanation could be differences in treatment response in tumors with and without *BAP1* inactivation. Another explanation could be the well-differentiated morphology of some MMe in patients with germline *BAP1* mutations in contrast to high grade tumors in other patients, although the mechanism for this is unknown. Also, the increased rate of peritoneal MMe in *BAP1* carriers, which has a better prognosis than pleural MMe, may be causing the increase in overall survival (83).

Penetrance of *BAP1*-TPDS

Current evidence suggests that the penetrance of *BAP1* mutations is high with 148/174 (85%) reported mutation carriers affected with cancer. Although ages for unaffected individuals were not reported, estimates based on the pedigrees placed an average unaffected age in the late 50's (5, 18, 27, 29, 30). It should be noted, however, that several unaffected carriers are young and therefore may yet develop cancer. One *BAP1* patient (FUM036, III.9) previously reported as unaffected by our group subsequently developed MMe at age 60 and passed away (2). Additionally, two newly tested members of families previously reported by our group were found to carry the family mutations and remain unaffected at ages 47 and 35, respectively (FUM103, III.3; FUM152, III.2) (18, 19).

It is likely, however, that these penetrance data are inflated by test bias since the patients and family members who get tested are generally those affected by cancer. Of the 57 reported families, only the affected proband was tested in 30, and only 17 families had more than 3 individuals tested. Thus, the true penetrance for *BAP1* mutations may well be lower than currently estimated.

Genotype–phenotype correlation

Of 57 families, 46 had unique mutations, two families had the c.2050C>T, p.Q684* mutation, two families had the c.1882_1885delTCAC, p.S628Pfs*8 mutation, two families had the c.1717delC, p.L573Wfs*3 mutation, two families had the c.588G>A, p.Trp196* mutation, while three families had the c.178C>T, p.R60* mutation. Discussions between the

authors concluded that the families carrying the c.2050C>T, p.Q684* and c.1882_1885delTCAC, p.S628Pfs*8 mutations were unrelated. However, discussions and haplotype analysis suggested that the two families from Denmark carrying the c.178C>T, p.R60* mutation were related, whereas the family carrying this mutation from the United States was not (3, 18, 19, 29, 31).

The majority (32/51, 63%) of the reported mutations were truncating, 11 (22%) were missense mutations thought to be pathogenic, and 8 (15%) were splice-site variations. Five of the splice-site variations also caused protein truncation. Thus, 22% of the reported germline mutations are missense mutations and 73% cause protein truncation. All the truncating mutations were proximal to the nuclear localizing regions of BAP1.

With the exception of one patient, all reported pathogenic mutations in *BAP1*, including truncating, missense, and splice-site mutations, were associated with at least one of the four main cancers in the family (Fig. 3). All four cancers were observed with all classes of mutations. Taken together, the available data suggest no clear genotype–phenotype correlation between type or location of the mutation and the type of cancer in patients.

Discussion

Genetic counseling and patient management

Of the 174 reported patients with *BAP1* mutations 130 (75%) were diagnosed with UM, MMe, CM, RCC, and/or BAP1-deficient ASTs, and 90% of these families had at least two of these tumors in first or second-degree relatives. Five families reported histories of only one of the main tumors. Thus, we recommend that genetic assessment and testing for *BAP1* mutations should be considered in patients with two or more of these tumors in themselves and/or first or second-degree relatives, with the exclusion of families with only multiple CM cases, given its frequency in the general population. We recognize, however, that if a melanoma-only family is undergoing *CDKN2A* testing for hereditary melanoma, it may be reasonable and cost effective to also test them for mutations in *BAP1* at the same time. Although it has been suggested elsewhere that *BAP1* testing be conducted in families with histories of one UM and two or more primary cancers of any type, we feel this is overly broad as there is not sufficient evidence supporting the involvement of other cancers (84).

Families in which a germline *BAP1* mutation is found should receive counseling regarding cancer risk management options and risks to family members. Testing of at-risk family members is indicated because the syndrome follows an autosomal dominant inheritance pattern. Although evidence-based management recommendations have not been established, the cancer risks in these families cannot be ignored. As such, regular examinations, particularly for eye and skin tumors, to facilitate early diagnosis, and thereby improved prognosis, are necessary. Although imperfect, we recommend that screenings follow guidelines based on other TPDS with similar phenotypes (Table 2) (53, 85–91). The recommended ages to begin screening given are based on currently reported ages of diagnoses; however, if an individual family has members diagnosed at an even earlier age for a specific cancer, screening for that cancer should begin for other members of that family about 5 years before that age of diagnosis. ASTs have a unique clinical, morphological, and

molecular characterization and their high frequency in patients with germline *BAP1* mutation indicate they might serve as a potential marker of *BAP1*-TPDS. It is highly recommended that ASTs, in particular those with a prominent epithelioid component, be screened for BAP1 status by immunohistochemistry. If BAP1 loss is detected, referral for genetic counseling and germline *BAP1* testing should be considered (14). There are currently no Food and Drug Administration (FDA)-approved targeted treatments for *BAP1*-driven malignancies. Intriguingly, preliminary attempts at discovering therapies have shown modest success in UM *in vitro* (90).

Conclusions

UM, MMe, CM, RCC, and ASTs are clearly established as part of the phenotypic spectrum associated with germline *BAP1* mutations. Although other cancers, in particular breast cancer and BCC might be associated, further studies are needed. Although UM, CM, and RCC tumors in patients with germline *BAP1* mutations tend to be more aggressive and have poorer outcomes, patients with MMe appear to have longer survival. There appears to be no genotype–phenotype correlation with this syndrome. Penetrance for the gene appears to be high, but ascertainment bias makes it difficult to currently establish accurate estimates of cancer risk. Nonetheless, increased screening is indicated, particularly for skin and eye cancers.

Acknowledgments

This work was supported by the Patti Blow Research Fund in Ophthalmology, Grant #IRG-67-003-47 from the American Cancer Society, and funding from the Ohio Lions Eye Research Foundation, Ocular Melanoma Foundation, Melanoma Know More Foundation, the R21CA191943 Grant from the National Cancer Institute (PI: Abdel-Rahman, MH), and the National Eye Institute grant K08EY022672 (C. M. C.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, National Cancer Institute, or National Eye Institute. We thank Brandon Massengill for his work in sample sequencing and other investigative experiments.

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Fig. 1.

Two new families with germline *BAP1* mutation. **(a, b)** In FUM124, the proband (III-7) and his niece IV-8 showed a germline heterozygous c.539T>C, p.L180P. The proband presented with pleural malignant mesothelioma (MMe), basal cell carcinomas (BCC) and cutaneous melanoma (CM), a brother (obligate carrier) had uveal melanoma (UM) and BCC while the niece was unaffected at age 59. Five other individuals in the family with cancer (II-3: prostate Ca, III-2: liposarcoma, IV-3: CM, IV-6: Breast Ca and V-4: Schwannoma) tested negative for the mutation. Five unaffected relatives also tested negative for mutation (only three are shown). **(c)** In FUM, 128 the proband (III-2) presented with peritoneal MMe, other cancer in the families were peritoneal MMe, UM, pancreatic and bladder cancers. **(d)** Germline 2 bp deletion (c.256-4_256-2del) in intron 4. **(e)** The deletion causes aberrant splicing of the *BAP1* (first lane genomic DNA, second lane patients cDNA and third lane a control individual cDNA). In both families, *BAP1* mutation status is denoted as mutated (*BAP1* +ve) or wild-type (*BAP1* -ve). Some of the unaffected *BAP1* -ve individuals are not shown.

Fig. 2.

Venn diagrams of the cancers identified in *BAP1* patients and families. **(a)** Individuals with *BAP1* mutations diagnosed with uveal melanoma (UM), renal cell carcinoma (RCC), cutaneous melanoma (CM), and/or malignant mesothelioma (MMe). There are 118 patients who were diagnosed with at least one of the above cancers. Thirty individuals were only diagnosed with another cancer uncertain to be *BAP1* related. Twelve individuals were diagnosed with atypical Spitz tumors (ASTs) only. Fourteen individuals were unaffected. **(b)** Families with *BAP1* mutations with mutation-positive members diagnosed with UM, RCC, CM, and MMe. There were 57 families reported, of which 54 had at least member with one of the above diagnoses testing positive. One family presented with only ASTs and another cancer uncertain to be *BAP1* related. Two families had a history of one of the above diagnoses, but those members were not tested.

Fig. 3. Gene location and mutation type of the reported germline pathogenic variants in *BAP1* in the four main cancers associated with *BAP1*-TPDS. No genotype–phenotype correlation was observed. One mutation was found in a family not reporting a uveal melanoma (UM), malignant mesothelioma (MMe), cutaneous melanoma (CM), or renal cell carcinoma (RCC). Two family mutations were not tested in a member with a personal history of UM, MMe, CM, or RCC. ▲, splice-site mutation; ★, truncating mutation; ●, missense mutation; UCH, ubiquitin C-terminal hydrolase; BARD1, BARD1 binding domain; HCF1, HCF1 binding motif; BRCA1, BRCA1 binding domain; N, nuclear localization signal.

Table 1

Summary of clinical and molecular feature of tumor types reported more than once in patients with germline *BAP1* mutations

Tumor type	Tumor features in patients with <i>BAP1</i> germline mutation				Tumor characteristics in general population			Sporadic tumors Somatic mutation frequency (32)
	Reported frequency	Sex ratio M:F	Median age of onset in <i>BAP1</i> patients (range)	Tumor biallelic inactivation reported (n)	References	Lifetime risk (reference)	Median age of onset (reference)	
Uveal melanoma	54/174	23:25	51 (16–72)	Yes (7)	2–5, 18, 19, 21–31	0.00051% (31)	62	54/233
Mesothelioma	39/174	12:27	56 (34–85)	Yes (7)	2, 3, 5, 18, 30, 31, 33–35	0.13% (33) ^a	74 (36)	26/153
Cutaneous melanoma	23/174	13:10	46 (25–72)	Yes (4)	2, 4, 5, 22, 24, 27, 29–31, 35	3.25% (37) ^a	58 (37) ^b	15/820
Renal cell carcinoma	18/174	8:7	47 (36–72)	Yes (5)	3, 5, 18, 25, 29, 38–40	1.60% (37) ^a	64 (37) ^b	138/1508
Abdominal cancer	2/174	0:2	64 (57–64)	N/A	18, 22	–	–	21/1934
Basal cell carcinoma	11/174	4:7	50 (42–65)	Yes (9)	3, 5, 22, 24, 31	–	–	–
Breast cancer	9/95	9	58 (37–85)	Yes (2)	3, 5, 18, 29–31	12.33% (37) ^a	61 (37) ^b	11/1688
Cholangiocarcinoma	4/174	2:2	66 (47–71)	N/A	18, 28, 29, 31	0.83% (37) ^a	50 (41)	16/113
Colorectal cancer	2/174	1:1	62 (53–71)	N/A	18, 25	4.96% (37) ^a	71 (37) ^b	42/1132
Lung cancer	6/174	3:3	56 (46–59)	Yes (1)	2, 22, 29, 30	6.99% (37) ^a	70 (37) ^b	9/1031
Meningioma	3/174	0:3	44 (35–52)	Yes (2)	2, 31, 42	–	65 (43)	0/65
Neuroendocrine cancer	2/174	1:1	47 (42–52)	Yes (1)	2, 30	–	–	5/2545
Ovarian cancer	3/95	3	59 (34–69)	N/A	2, 3	1.12% (37) ^a	63 (37) ^b	6/890
Prostate cancer	2/67	2	65 (63–67)	N/A	25, 27	16.15% (37) ^a	68 (37) ^b	5/861
Sarcoma	4/174	1:3	45 (42–64)	N/A	3, 18, 30	–	–	0/353
Thyroid cancer	2/174	0:2	38 (34–41)	No	5, 42	0.90% (37) ^a	47 (37) ^b	1/535

F, female; M, male; N/A, not applicable; SEER, Surveillance, Epidemiology and End Results.

^a Age-adjusted SEER data from 2007 to 2009.

^b SEER data from 2000 to 2003.

Table 2Proposed management recommendations for families with germline *BAP1* mutation

Risk	Age of earliest reported case	Screening recommendations
Uveal melanoma (UM)	16	<ul style="list-style-type: none"> Yearly dilated eye exams and ophthalmic imaging by ocular oncologist^a beginning age 11^b If UM is diagnosed, consider a 'high risk' patient monitoring protocol for systemic metastatic surveillance (e.g. liver-directed imaging every 3–6 months, pulmonary imaging every 6–12 months)
Malignant mesothelioma	34	<ul style="list-style-type: none"> None exist (85) Yearly physical examinations recommended
Cutaneous melanoma, basal cell carcinoma and atypical Spitz tumors	25	<ul style="list-style-type: none"> Yearly dermatology full body skin exam beginning age 20^b (86, 87) Self-skin exam following ABCDE characteristics of melanoma Use of sun protection If atypical Spitz tumors are detected, <i>BRAF</i> mutation testing and immunostaining for <i>BAP1</i> should be performed (53)
Renal cell carcinoma	36	<ul style="list-style-type: none"> None exist Protocol for von Hippel-Lindau (VHL) syndrome renal screening could be considered (yearly abdominal ultrasound exam, MRI every 2 years) (88)

MRI, magnetic resonance imaging.

^a <http://www.eyecancer.com/find-a-doctor>.^b Five years earlier than earliest reported case.