

REVIEW

Comprehensive Study of the Clinical Phenotype of Germline BAP1 Variant-Carrying Families Worldwide

Sebastian Walpole, Antonia L. Pritchard, Colleen M. Cebulla, Robert Pilarski, Meredith Stautberg, Frederick H. Davidorf, Arnaud de la Fouchardière, Odile Cabaret, Lisa Golmard, Dominique Stoppa-Lyonnet, Erin Garfield, Ching-Ni Njauw, Mitchell Cheung, Joni A. Turunen, Pauliina Repo, Reetta-Stiina Järvinen, Remco van Doorn, Martine J. Jager, Gregorius P.M Luyten, Marina Marinkovic, Cindy Chau, Miriam Potrony, Veronica Höiom, Hildur Helgadóttir, Lorenza Pastorino, William Bruno, Virginia Andreotti, Bruna Dalmaso, Giulia Ciccicarese, Paola Queirolo, Luca Mastracci, Karin Wadt, Jens Folke Kiilgaard, Michael R. Speicher, Natasha van Poppelen, Emine Kilic, Rana'a T. Al-Jamal, Irma Dianzani, Marta Betti, Carsten Bergmann, Sandro Santagata, Sonika Dahiya, Saleem Taibjee, Jo Burke, Nicola Poplawski, Sally J. O'Shea, Julia Newton-Bishop, Julian Adlard, David J. Adams, Anne-Marie Lane

See the Notes section for the full list of authors and their affiliations.

*These authors co-led this study.

Correspondence to: Nicholas K. Hayward, PhD, Oncogenomics Group, QIMR Berghofer Medical Research Institute, 300 Herston Rd, Herston, Brisbane 4006, Australia (e-mail: Nick.Hayward@qimrberghofer.edu.au); or Mohamed H. Abdel Rahman, MD, PhD, Department of Ophthalmology, The Ohio State University Comprehensive Cancer Center, 400 W 12th Ave, Room 202 Wiseman Hall, Columbus, OH 43210 (e-mail: Mohamed.Abdel-Rahman@osumc.edu).

Abstract

Background: The BRCA1-associated protein-1 (BAP1) tumor predisposition syndrome (BAP1-TPDS) is a hereditary tumor syndrome caused by germline pathogenic variants in BAP1 encoding a tumor suppressor associated with uveal melanoma, mesothelioma, cutaneous melanoma, renal cell carcinoma, and cutaneous BAP1-inactivated melanocytic tumors. However, the full spectrum of tumors associated with the syndrome is yet to be determined. Improved understanding of the BAP1-TPDS is crucial for appropriate clinical management of BAP1 germline variant carriers and their families, including genetic counseling and surveillance for new tumors.

Methods: We collated germline variant status, tumor diagnoses, and information on BAP1 immunohistochemistry or loss of somatic heterozygosity on 106 published and 75 unpublished BAP1 germline variant-positive families worldwide to better characterize the genotypes and phenotypes associated with the BAP1-TPDS. Tumor spectrum and ages of onset were compared between missense and null variants. All statistical tests were two-sided.

Results: The 181 families carried 140 unique BAP1 germline variants. The collated data confirmed the core tumor spectrum associated with the BAP1-TPDS and showed that some families carrying missense variants can exhibit this phenotype. A variety of noncore BAP1-TPDS-associated tumors were found in families of variant carriers. Median ages of onset of core tumor types were lower in null than missense variant carriers for all tumors combined ($P < .001$), mesothelioma ($P < .001$), cutaneous melanoma ($P < .001$), and nonmelanoma skin cancer ($P < .001$).

Received: April 19, 2018; Revised: July 17, 2018; Accepted: August 31, 2018

© The Author(s) 2018. Published by Oxford University Press. All rights reserved. For permissions, please email: journals.permissions@oup.com

Conclusions: This analysis substantially increases the number of pathogenic *BAP1* germline variants and refines the phenotype. It highlights the need for a curated registry of germline variant carriers for proper assessment of the clinical phenotype of the *BAP1*-TPDS and pathogenicity of new variants, thus guiding management of patients and informing areas requiring further research.

BRCA1-associated protein-1 (*BAP1*) is a deubiquitinating hydrolyase identified in a yeast two-hybrid screen in 1998 as binding to the RING finger domain of the BRCA1 protein (1). Although *BAP1* has been categorized as a tumor suppressor, it is not known if a single function, or multiple roles, confers this activity (2,3). *BAP1* has roles in numerous cellular processes, including DNA damage response, cell cycle regulation, cell growth, metabolism, and the regulation of inflammatory responses (4–10). Although functional domains and binding partners of *BAP1* are still being identified, it is known to bind to a number of proteins via specific domains, including ASXL1/2, HCFC1, YY1, and FOXK1/2 (11) as indicated in Figure 1.

Germline null variants of *BAP1* underlie the *BAP1* tumor predisposition syndrome (*BAP1*-TPDS, OMIM 614327) (12). The first null variant was described in a patient with uveal melanoma (UM) enrolled in a study that investigated somatic mutations of *BAP1* in UM metastases (13). The *BAP1*-TPDS was subsequently established by three independent research groups that proposed UM, malignant mesothelioma, and cutaneous melanoma (CM) as the core component tumors of the syndrome (14–16). Renal cell carcinoma (RCC) was added to the core tumor spectrum shortly thereafter (17). A new form of cutaneous melanocytic tumor was also associated with this syndrome (16), described variously as BAP-oma, atypical Spitz tumor, melanocytic *BAP1*-associated intradermal tumor, nevoid melanoma-like proliferation, or *BAP1*-inactivated melanocytic nevus/melanocytoma (18). The latter term is proposed in the upcoming fourth edition of the WHO Classification of Skin Tumours and will thus be used throughout this article. Unfortunately, these tumors could not be included in the analyses because it is unknown how many patients underwent full-body skin examinations.

There is growing evidence that meningioma, basal cell carcinoma (BCC), and cholangiocarcinoma may form part of the *BAP1*-TPDS spectrum (19–23); additional tumor types have been proposed as potentially linked to germline *BAP1* variants, but a higher burden of proof is required (14,19–21,24–29). *BAP1* is somatically mutated in a diverse array of tumors (30,31), suggesting *BAP1* is important in the tumorigenesis of several additional types of cancer, including some of those speculatively associated with the *BAP1*-TPDS (19–22). A paucity of molecular analyses of tumor specimens from *BAP1* variant carriers further confounds the definitive linking of these additional tumor types to the *BAP1*-TPDS. Therefore, clear definition of the *BAP1*-TPDS phenotype requires further studies, such as this collaborative analysis, to assemble and investigate a large cohort of affected families.

A review of the *BAP1*-TPDS in 2017 by Haugh and colleagues summarized 87 families worldwide with 71 unique *BAP1* germline variants (32). Reviews so far have assessed only variant carriers and have not considered untested relatives who may exhibit similar phenotypes (32,33). In many cases, further genetic testing may not be possible but could provide support for an expansion, or restriction, to the spectrum of tumors associated with the *BAP1*-TPDS. This compounds uncertainty surrounding the functional impact of germline missense substitutions in *BAP1*, to date classified mostly as variants of

unknown significance (VUS). Consideration of the tumor spectrum within the family of missense VUS carriers can help inform variant classification. Thus, there are several gaps in our knowledge of the *BAP1*-TPDS critically affecting patient management, including, but not limited to, definition of the full spectrum of tumors associated with the syndrome; establishing genotype-phenotype associations; establishing which of the VUS are pathogenic; and determining the penetrance of the pathogenic variants, that is, the lifetime risks of developing each tumor type.

The aim of this analysis was to collate and analyze data within the global cohort of published and unpublished families carrying *BAP1* variants to better characterize the phenotype of the syndrome and classification of missense VUS. Improved understanding of the *BAP1*-TPDS is crucial for appropriate management of *BAP1* germline variant carriers, including genetic counseling and surveillance for early diagnoses of new tumors. This is vital, because the American College of Medical Genetics and Genomics (ACMG) guidelines state those working in specific disease groups should develop more focused guidance given that the applicability and weight assigned to certain criteria may vary by gene and disease (34).

Methods

Database

A Microsoft Access database was created for the purpose of collating *BAP1* germline variants. This is a relational database that summarizes information on individual carriers, their relationships to family members, and their tumor diagnoses, allowing for standardized inputs and outputs. The database included variant carriers proven through sequencing or linkage, as well as tumor-affected relatives who were not genotyped. As described in detail below, data were either taken directly from published material or provided by various authors of this review, if unpublished. In some cases, updates on tumor development and/or *BAP1* carrier status in families from published data were also provided by authors. Variants were recorded using reference sequence NM_004656.3, and chromosome positions were mapped using genomic build GRCh37/hg19. Tumors were assigned codes according to the International Statistical Classification of Diseases and Related Health Problems 10th edition for body site and the International Classification of Diseases for Oncology 3rd edition for morphology (35,36). Tumor analysis of *BAP1* immunohistochemistry (IHC) or loss of heterozygosity (LOH) was recorded, if available.

Literature Review

A literature review was conducted on all articles available in PubMed up until December 1, 2017. The search of PubMed was dictated by keywords “*BAP1*” and “BRCA1-associated protein-1.” Forty-one articles were found describing patients with germline *BAP1* variants; these were reviewed and relevant data extracted for 106 families.

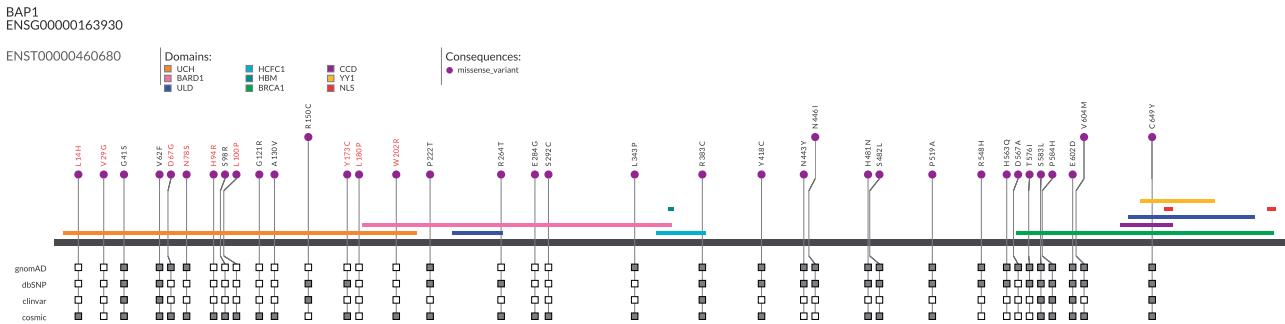


Figure 1. Reported missense variants plotted proportional to their frequency along the BAP1 gene with the functional domains shown. Variants that have evidence supporting pathogenicity are marked as red. The four blocks underneath each variant indicate their presence in the indicated databases. Database versions used for these metadata were: ClinVar 20170705, COSMIC v81 20170508, dbSNP 20170710, and gnomAD r2.0.1. BARD1 = BARD1 binding domain; BRCA1 = BRCA1 binding domain; cosmic = Catalogue of Somatic Mutations in Cancer; CCD = coiled-coil domain; dbSNP = Database of Single-Nucleotide Polymorphisms; gnomAD = Genome Aggregation Database; HBM = HCF binding motif (minimal tetrapeptide HCF1 binding motif); HCFC1 = HCFC1 binding domain; NLS = nuclear localization signal; UCH = ubiquitin carboxy-terminal hydrolase; ULD = Uch37-like domain; YY1 = YY1 binding domain.

Identification of New Families

Several genetic counseling and clinical variant testing services in Australia, Europe, and the United States (US) as well as the groups that had published on germline variants were contacted to identify BAP1 germline variant carriers. Of the 181 total families collated, 75 were previously unpublished. Written informed consent was obtained from each subject or from his or her guardian, and all human subjects research was performed with approval by local institutional ethics review boards and, where appropriate, in accordance with an assurance filed with and approved by the US Department of Health and Human Services.

Evidence for Pathogenicity of Variants

All variants were evaluated for pathogenicity under ACMG guidelines for interpretation of sequence variants (34). Variants were split into two categories: null and missense. All nonsense, frameshift, and canonical splice site variants, as well as functionally validated cryptic splice site variants, were classified as null variants, because they are assumed to result in a truncated protein. All missense variants were assessed together regardless of their classification under ACMG criteria, with the exception of two variants, which were shown to alter splicing and were thus included as null variants.

Lifetime Cancer Risks

Lifetime risk of cancer statistics were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database for comparison (37). When lifetime risk for relevant tumors was not present in the SEER database, published data were used.

Somatic Mutation Frequencies

The proportion of various tumor types with somatic BAP1 mutations was retrieved from either The Cancer Genome Atlas (<https://cancergenome.nih.gov/>) or Catalogue of Somatic Mutations in Cancer (<http://cancer.sanger.ac.uk/cosmic>) databases (30,31).

Statistical Analysis

Age of onset distributions of tumors with at least five records were compared using the Mann-Whitney test. The sex

distribution of individuals diagnosed with mesothelioma was compared using a binomial test. All statistical tests were two-sided and P less than .05 was considered statistically significant.

Results

Metadata

Germline BAP1 null and missense variants identified worldwide, including previously published and unpublished individuals ($n = 804$) or families ($n = 181$), are documented in [Supplementary Tables 1 and 2](#) (available online), respectively. Some countries reported several carrier families (or probands) to this analysis: US (69), France (34), Australia (18), United Kingdom (14), Finland (8), the Netherlands (8), Denmark (6), Italy (8), and Austria (4).

Variants Identified

In total, there are 141 (104 unique) null variants and 40 (36 unique) missense variants. Notable founder variants are evident, for example, p.G594Vfs*48 in Finland and p.L573Wfs*2 in the US, the latter of which can be traced back to a Swiss origin in the 16th century (38). A recurrent variant previously reported, p.R60*, has been proven through haplotype studies to have arisen independently multiple times (20) and was observed in three more families, yielding a total of seven families from four different countries. In null variant families, a mean of 2.3, a median of 1, and a range of 1 to 11 individual family members were screened for each variant.

We identified three missense variants (p.H94R, p.L100P, p.Y173C) in this analysis that could be regarded as being likely pathogenic under ACMG criteria (34) based on segregation within the family (criterion PP1), observation of carriers with core BAP1-TPDS tumors (PP4), and computational evidence (PP3), as well as the variant not being observed in population controls (PM1) ([Supplementary Table 2](#), available online). We also identified an additional six variants (p.L14H, p.V29G, p.D67G, p.N78S, p.L180P, p.W202R) that have some evidence of pathogenicity (ie, all have PM1 and PP3 and some have varying levels of PP1 and PP4) but do not reach the likely pathogenic ACMG threshold ([Supplementary Table 2](#), available online; see also [Figures 1 and 2](#)). The differential evidence that elevated these families into this group is phenotypical evidence in the proband or their family, independent of computational

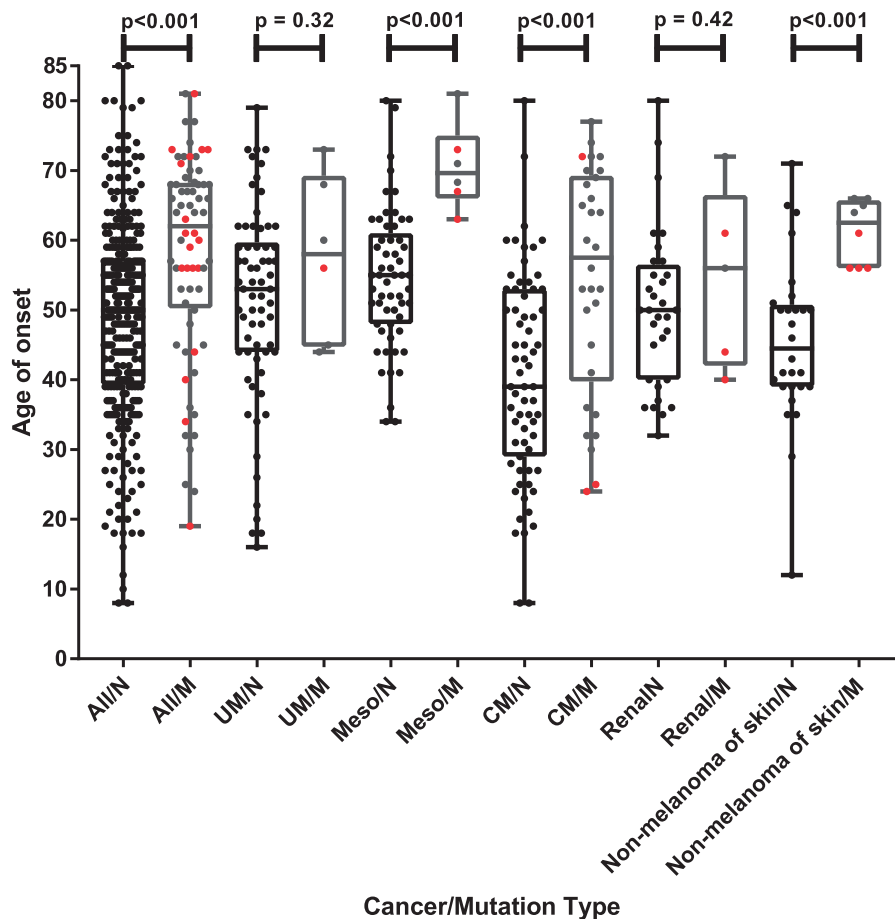


Figure 2. The age of onset of all tumors presenting in variant carriers included in this study shown as box and whisker plots. Tumors are grouped together in the “all” group and then broken down into subgroups of the main BAP1-associated tumors. CM = cutaneous melanoma; Meso = mesothelioma; Renal = nonmelanoma of skin, liver, and meningioma; UM = uveal melanoma. All tumors are separated into the type of variant of the individual. M = missense; N = null. Tumors of carriers with missense variants that have evidence supporting pathogenicity (ie, those asterisked in [Supplementary Table 2](#), available online) are marked red. P values were calculated using a two-sided Mann-Whitney test.

evidence (eg, segregation of core BAP1-TPDS tumors not meeting ACMG criteria; unusual incidence of rare core tumors [UM/mesothelioma] in the family without segregation; multiple primary BAP1-TPDS core tumors in the proband, or a combination of these). No VUS even if deemed likely pathogenic under ACMG criteria are grouped with null variants unless functionally validated.

[Tables 1](#) and [2](#) summarize the overall frequency of tumors observed in null and missense variant-carrying probands and other variant carriers as well as relatives who were not genotyped, respectively. SEER or published data when SEER data were not available are presented for comparison. SEER was used because it is one of the largest population-based datasets and because the greatest proportion of families in this study resides in the US.

Overall Tumor Spectrum

The tumors occurring in families that carry a BAP1 variant were tabulated using the accumulated information either from the original publication or after further information was obtained from the authors. Because information on the BAP1-inactivated melanocytic nevus/melanocytoma has not been routinely and systematically collected, their frequency was not assessed, but

because several studies used individuals with these benign tumors to identify BAP1 carrier families, some of the probands do not have another type of tumor. All relatives who were not genotyped had at least one tumor, because this was the criterion for being included in the database. The vast majority of tumors in the diverse affected tissues that might be associated with the syndrome have no reported molecular analysis or are present in relatives who were not genotyped.

Tumor Spectrum in Null Variant Carriers

At the time of sampling, 87.9% of probands ($n = 141$) and 82.5% ($n = 183$) of nonproband variant carriers were found to have at least one tumor. The frequency of the tumors previously associated with the BAP1-TPDS in null variant-positive families was: UM (proband: 36.2%; nonproband variant carriers: 15.9%; relatives who were not genotyped: 10.7%), mesothelioma (24.8%, 16.9%, 13.2%), CM (23.4%, 12.0%, 10.2%), RCC (5.7%, 4.9%, 4.0%), nonspecific/other kidney (7.8%, 2.7%, 2.5%), total renal (13.5%, 7.7%, 6.5%), nonmelanoma skin cancer (10.6%, 8.2%, 6.7%), and meningioma (8.5%, 2.2%, 1.3%) ([Table 1](#)). Among the tumors not previously associated with the BAP1-TPDS, two are the most common cancers in the general population, breast cancer (9.9%, 10.7%, 21.1%) and lung cancer (2.8%, 3.8%, 7.7%), with both

Table 1. Tumors in families with null variants

ICD-10	Description	Occurrence in probands (%)	Occurrence in nonproband variant carriers (%)	Occurrence in ungenotyped relatives* (%)	Reported tumor loss of BAP1 IHC† (n)	Reported tumor LOH† (n)	Lifetime risk‡ (§)	Somatic mutation rate§ (%)	Reference
C-	All cancers†	124/141 (87.9)	151/183 (82.5)	522/522	Yes (34)	Yes (17)	38.5%	—	
C69	Uveal melanoma	51/141 (36.2)	29/183 (15.9)	56/522 (10.7)	Yes (1)	Yes (6)	—	25/80 (31.3)	Deng et al. 2016 (30)
C45	Mesothelioma	35/141 (24.8)	31/183 (16.9)	69/522 (13.2)	Yes (13)	Yes (5) No (1)	0.04%	23/82 (28.1)	Deng et al. 2016 (30)
C43	Cutaneous melanoma§	33/141 (23.4)	22/183 (12.0)	53/522 (10.2)	Yes (3)	Yes (1)	2.2%	16/469 (3.4)	Deng et al. 2016 (30)
C44	Nonmelanoma of skin	15/141 (10.6)	15/183 (8.2)	35/522 (6.7)	Yes (7)	Yes (1)	—	—	
C50.9	Breast	7/71 (9.9)	11/103 (10.7)	55/261 (21.1)	Yes (3)	—	6.4%	16/2939 (0.5)	Forbes et al. 2017 (31)
C70	Meningioma	12/141 (8.5)	4/183 (2.2)	7/522 (1.3)	Yes (3)	Yes (2) No (1)	—	5/93 (5.9)	Forbes et al. 2017 (31)
C64	Nonspecified/other kidney	11/141 (7.8)	5/183 (2.7)	13/522 (2.5)	Yes (2)	—	1.6%	183/2389 (7.7)	Forbes et al. 2017 (31)
C64/8312	Renal cell carcinoma	8/141 (5.7)	9/183 (4.9)	21/522 (4.0)	—	—	—	—	
C34.9	Lung	4/141 (2.8)	7/183 (3.8)	40/522 (7.7)	Yes (2)	Yes (1)	6.4%	15/2578 (0.6)	Forbes et al. 2017 (31)
C73	Thyroid	3/141 (2.1)	0/183	7/522 (1.3)	—	—	1.2%	6/773 (0.8)	Forbes et al. 2017 (31)
C40-41	Bone	3/141 (2.1)	1/183 (0.6)	6/522 (1.2)	—	—	—	3/594 (0.5)	Forbes et al. 2017 (31)
C61	Prostate	1/61 (1.6)	1/76 (1.3)	12/249 (4.9)	—	—	—	8/1869 (0.4)	Forbes et al. 2017 (31)
C22.1.2	Cholangiocarcinoma	2/141 (1.4)	0/183	5/522 (1.0)	—	—	4.3%	11/51 (21.6)	Deng et al. 2016 (30)
C18-20	Colorectal	2/141 (1.4)	0/183	31/522 (5.9)	—	—	—	—	
C74-76	Other endocrine glands	2/141 (1.4)	1/183 (0.6)	3/522 (0.6)	—	—	—	—	
C53.9	Cervix	1/71 (1.4)	1/103 (1)	2/261 (0.8)	—	—	0.6%	4/329 (1.2)	Forbes et al. 2017 (31)
C22	Nonspecified/other liver	1/141 (0.7)	3/183 (1.6)	12/522 (2.3)	—	—	1.0%	32/2115 (1.5)	Forbes et al. 2017 (31)
C47.2	Nerve	1/141 (0.7)	0/183	0/522	—	—	—	—	
C49	Soft tissue	1/141 (0.7)	1/183 (0.6)	2/522 (0.4)	—	No (1)	—	5/572 (0.9)	Forbes et al. 2017 (31)
C68.9	Unknown urinary organ	1/141 (0.7)	0/183	0/522	—	—	—	—	
C67.9	Bladder	1/141 (0.7)	0/183	11/522 (2.1)	—	—	2.4%	—	
C85	Non-Hodgkin lymphoma	1/141 (0.7)	0/183	9/522 (1.7)	—	—	2.1%	—	
C06.9	Mouth	1/141 (0.7)	0/183	1/522 (0.2)	—	—	1.1%	—	
C02.9	Tongue	0/141	1/183 (0.6)	1/522 (0.2)	—	—	—	—	
C09.9	Oropharynx	0/141	0/183	1/522 (0.2)	—	—	—	—	
C11.9	Nasopharynx	0/141	1/183 (0.6)	0/522	—	—	—	—	
C15.9	Esophagus	0/141	0/183	4/522 (0.8)	—	—	0.5%	19/1291 (1.5)	Forbes et al. 2017 (31)
C16.9	Stomach	0/141	3/183 (1.6)	15/522 (2.9)	—	—	0.8%	15/1027 (1.5)	Forbes et al. 2017 (31)
C21	Anus	0/141	0/183	0/522	—	—	—	—	
C25.9	Pancreas	0/141	2/183 (1.1)	18/522 (3.5)	—	—	1.6%	11/1907 (0.6)	Forbes et al. 2017 (31)
C30.1	Middle ear	0/141	0/183	1/522 (0.2)	—	—	—	—	
C31.9	Sinus	0/141	0/183	1/522 (0.2)	—	—	—	—	
C38.0	Heart	0/141	1/183 (0.6)	0/522	—	Yes (1)	—	—	
C48.2	Peritoneum	0/141	1/183 (0.6)	2/522 (0.4)	—	—	—	—	
C51.9	Vulva	0/71	0/103	1/261 (0.4)	—	—	—	—	
C54.1	Endometrium	0/71	1/103 (1)	1/261 (0.4)	—	—	—	0/3	Forbes et al. 2017 (31)
C55	Uterus	0/71	0/103	3/261 (1.2)	—	—	2.9%	12/658 (1.8)	Forbes et al. 2017 (31)
C56	Ovary	0/71	3/103 (2.9)	11/261 (4.2)	—	—	1.3%	6/913 (0.7)	Forbes et al. 2017 (31)
C60.9	Penis	0/61	1/76 (1.3)	0/247	—	—	—	—	
C62.9	Testis	0/61	0/76	2/249 (0.8)	—	—	—	0/169	Forbes et al. 2017 (31)
C71.9	Brain	0/141	2/183 (1.1)	16/522 (3.1)	—	—	—	—	

(continued)

Table 1. (continued)

ICD-10	Description	Occurrence in probands (%)	Occurrence in nonproband variant carriers (%)	Occurrence in ungenotyped relatives* (%)	Reported tumor loss of BAP1 IHC† (n)	Reported tumor LOH† (n)	Lifetime risk‡ (37)	Somatic mutation rate§ (%)	Reference
C72.9	CNS	0/141	0/183	2/522 (0.4)	—	—	—	4/2424 (0.2)	Forbes et al. 2017 (31)
C76.0	Head and neck	0/141	1/183 (0.6)	5/522 (1.0)	—	—	—	—	—
C76.2	Abdomen	0/141	1/183 (0.6)	2/522 (0.4)	—	—	—	—	—
C78.2	Pleura	0/141	0/183	1/522 (0.2)	—	—	—	—	—
C80.0	Unknown cancer	0/141	11/183 (7.7)	36/522 (6.9)	—	—	—	—	—
C81	Hodgkin lymphoma	0/141	1/183 (0.6)	5/522 (1.0)	—	—	0.2%	—	—
C90.0	Multiple myeloma	0/141	0/183	2/522 (0.4)	—	—	0.8%	—	—
C91-95	Leukemia	0/141	0/183	9/522 (1.7)	—	—	1.5%	—	—

*A requirement for an ungenotyped relative to be recorded in the database is a diagnosis of a tumor that explains the 100% penetrance of tumors in that subpopulation.
 †Where available, IHC = immunohistochemistry; LOH = loss of heterozygosity.

‡A total of 124 probands, 151 nonproband variant carriers, and 522 ungenotyped relatives had 236, 199, and 598 tumors, respectively. CNS = central nervous system.

§A total of 33 probands, 22 nonproband variant carriers, and 53 ungenotyped relatives had 48, 29, and 55 cutaneous melanomas, respectively.

||A total of 15 probands, 15 nonproband variant carriers, and 35 ungenotyped relatives had 31, 35, and 41 nonmelanoma skin cancers, respectively.

showing that the frequency in carriers was markedly lower than in ungenotyped family members. In contrast, the frequency of thyroid cancer (2.1%, 0%, 1.3%) and bone cancer (2.1%, 0.6%, 1.2%) was elevated in BAP1 variant carriers compared with ungenotyped relatives. Notably, in this study, we report the first family with a heterozygous whole-gene deletion of BAP1, with carriers presenting with UM, meningioma, BCC, and pancreatic cancer.

In null variant carriers, there was a statistically significant ($P = .04$) predominance of females diagnosed with mesothelioma (42/66 [63.6%]; 95% confidence interval [CI] = 51 to 75). Additionally, mesothelioma was the only tumor for which there were enough data to comment on different presentations, with 24/66 (36.4%) being peritoneal tumors, 17/66 (25.8%) being pleural, and 25/66 (37.9%) unspecified.

Tumor Spectrum in Missense Variant Carriers

Overall, 97.5% of probands ($n = 40$) and 60.0% of nonproband ($n = 10$) missense variant carriers developed at least one tumor. In missense variant-positive families, the frequency of the tumors previously associated with the BAP1-TPDS were: UM (22.5%, 30.0%, 3.5%), mesothelioma (15.0%, 10.0%, 8.0%), CM (45.0%, 0%, 11.5%), RCC (10.0%, 10.0%, 11.5%), nonspecified/other kidney (2.5%, 0%, 1.8%), total renal (12.5%, 10.0%, 13.3%), and nonmelanoma of the skin (15.0%, 10.0%, 8.0%) (Table 2). Of the tumors not previously associated with the BAP1-TPDS, the most common are: breast cancer (20.0%, 0%, 19.6%), prostate cancer (10.0%, 0%, 2.0%), ovarian cancer (7.4%, 0%, 2.2%), bladder cancer (2.5%, 0%, 1.8%), and non-Hodgkin lymphoma (2.5%, 0.9%).

In the nine families with missense variants we have classified as “likely pathogenic” under our recommended modification of the ACMG criteria, there were five families with UM (six cases), two with renal cancer (three cases), four with mesothelioma (four cases), two with cholangiocarcinoma (two cases), two with breast cancer (two cases), and one family with CM and nonmelanoma skin cancer (Supplementary Table 2, available online). There were not enough mesothelioma cases ($n = 7$) in missense variant carriers to draw conclusions about the gender and presentation of mesothelioma.

Genotype-Phenotype Correlation

The null variants are distributed along the entire length of the encoded protein (Supplementary Table 1, available online), with no obvious association between the tumor type developed in carriers and variant location, suggesting the relative position of truncation does not have any effect on the development of specific tumors. The family with the large deletion had a presentation similar to that of the other null variants.

Similarly, the missense variants are present throughout the protein (Supplementary Table 2, available online); Figure 1 shows the distribution of the missense variants relative to the functional domains of the BAP1 protein. The nine variants (p.L14H, p.V29G, p.D67G, p.N78S, p.H94R, p.L100P, p.Y173C, p.L180P, p.W202R) we have classified as likely pathogenic under our recommended modification of the ACMG criteria all occur in the ubiquitin carboxyl hydrolase (UCH) domain (highlighted in red in Figure 1), suggesting altered deubiquitinase activity is important for pathogenicity of certain missense variants. Although this group represents a small

Table 2. Tumors in families with missense variants

ICD-10	Description	Occurrence in probands (%)	Occurrence in nonproband variant carriers (%)	Occurrence in ungenotyped relatives* (%)	Reported tumor loss of BAP1 IHC† (n)	Reported tumor LOH† (n)	Lifetime risk‡ (37)	Somatic mutation rate§ (%)	Reference
C-	All cancers‡	39/40 (97.5)	6/10 (60.0)	113/113*	Yes (4)	Yes (5)	38.5%	—	
C43	Cutaneous melanoma§	18/40 (45.0)	0/10	13/113 (11.5)	—	—	2.2%	16/469 (3.4)	Deng et al. 2016 (30)
C69	Uveal melanoma	9/40 (22.5)	3/10 (30.0)	4/113 (3.5)	Yes (1)	Yes (2)	—	25/80 (31.3)	Deng et al. 2016 (30)
C50.9	Breast	3/15 (20.0)	0/10	9/46 (19.6)	Yes (1)	Yes (1) No (1)	6.4%	16/2939 (0.5)	Forbes et al. 2017 (31)
C45	Mesothelioma	6/40 (15.0)	1/10 (10.0)	9/113 (87.96)	—	—	0.04%	23/82 (28.1)	Deng et al. 2016 (30)
C44	Nonmelanoma of skin	6/40 (15.0)	1/10 (10.0)	9/113 (8)	—	—	—	—	
C64/8312	Renal cell carcinoma	4/40 (10.0)	1/10 (10.0)	13/113 (11.5)	Yes (2)	Yes (2)	—	—	
C61	Prostate	1/10 (10.0)	0/10	1/49 (2)	—	—	—	8/1869 (0.4)	Forbes et al. 2017 (31)
C56	Ovary	2/27 (7.4)	0/10	1/46 (2.2)	—	—	1.3%	6/913 (0.7)	Forbes et al. 2017 (31)
C22.1.2	Cholangiocarcinoma	2/40 (5.0)	0/10	0/113	—	—	—	11/51 (21.6)	Deng et al. 2016 (30)
C34.9	Lung	2/40 (5.0)	0/10	6/113 (5.3)	—	—	6.4%	15/2578 (0.6)	Forbes et al. 2017 (31)
C64	Nonspecified/other kidney	1/40 (2.5)	0/10	2/113 (1.8)	—	—	1.6%	183/2389 (7.7)	Forbes et al. 2017 (31)
C67.9	Bladder	1/40 (2.5)	0/10	2/113 (1.8)	—	—	2.4%	—	
C85	Non-Hodgkin lymphoma	1/40 (2.5)	1/10 (10.0)	1/113 (0.9)	—	—	2.1%	—	
C05.9	Palate	0/40	0/10	1/113 (0.9)	—	—	1.1%	—	
C11.9	Nasopharynx	0/40	0/10	1/113 (0.9)	—	—	—	—	
C16.9	Stomach	0/40	0/10	7/113 (6.2)	—	—	0.8%	15/1027 (1.5)	Forbes et al. 2017 (31)
C18-20	Colorectal	0/40	0/10	9/113 (8)	—	—	4.3%	—	
C21.0	Anus	0/40	0/10	1/113 (0.9)	—	—	—	—	
C22	Nonspecified/other liver	0/40	0/10	0/113	—	—	—	—	
C25.9	Pancreas	0/40	0/10	1/113 (0.9)	—	—	1.0%	32/2115 (1.5)	Forbes et al. 2017 (31)
C40-41	Bone	0/40	0/10	1/113 (0.9)	—	—	1.6%	11/1907 (0.6)	Forbes et al. 2017 (31)
C49	Soft tissue	0/40	0/10	2/113 (1.8)	—	—	—	3/594 (0.5)	Forbes et al. 2017 (31)
C51.9	Vulva	0/27	0/10	1/46 (2.2)	—	—	—	5/572 (0.9)	Forbes et al. 2017 (31)
C53.9	Cervix	0/27	0/10	3/46 (6.5)	—	—	0.6%	0/3	Forbes et al. 2017 (31)
C54.1	Endometrium	0/27	0/10	1/46 (2.2)	—	—	0.6%	4/329 (1.2)	Forbes et al. 2017 (31)
C55	Uterus	0/27	0/10	3/46 (6.5)	—	—	2.9%	12/658 (1.8)	Forbes et al. 2017 (31)
C57.0	Fallopian tube	0/27	0/10	2/46 (4.4)	—	—	—	—	
C62.9	Testis	0/16	0/10	1/49 (2.0)	—	—	—	0/169	Forbes et al. 2017 (31)
C68.9	Other urinary organs	0/40	1/10 (10.0)	1/113 (0.9)	—	—	—	—	
C70	Meningioma	0/40	0/10	1/113 (0.9)	—	—	—	5/93 (5.9)	Forbes et al. 2017 (31)
C71.9	Brain	0/40	0/10	2/113 (1.8)	—	—	—	—	
C80.0	Unknown cancer	0/40	0/10	12/113 (10.6)	—	—	—	—	
C91-95	Leukemia	0/40	0/10	4/113 (3.5)	—	—	1.5%	—	

*A requirement for an ungenotyped relative to be recorded in the database is a diagnosis of a tumor that explains the 100% penetrance of tumors in that subpopulation.

†Where available. IHC = immunohistochemistry, LOH = loss of heterozygosity.

‡A total of 39 probands, 6 nonproband variant carriers, and 113 ungenotyped relatives had 74, 7, and 124 tumors, respectively.

§A total of 18 probands and 13 ungenotyped relatives had 33 and 15 cutaneous melanomas, respectively.

||A total of 6 probands and 9 ungenotyped relatives had 9 and 12 nonmelanoma skin cancers, respectively.

number of families and individual carriers, all core BAP1-TPDS tumors are represented.

Age of Tumor Onset

Age of tumor onset was recorded if available. The ages of onset of tumors previously linked to the BAP1-TPDS in variant carriers are plotted in [Figure 2](#), split between null and missense variants. For all tumors with sufficient data, the median age of onset associated with null variants was younger than that for missense variants and statistically significant for all besides UM and renal tumors, as shown in [Figure 2](#): all tumors (50 years, interquartile range [IQR] = 39–57 years vs 62 years, IQR = 50–68 years; $P < .001$); UM (53 years, IQR = 44–60 years vs 58 years, IQR = 45–69 years; $P = .32$); mesothelioma (55 years, IQR = 48–61 years vs 69 years, IQR = 66–75 years; $P < .001$); CM (39 years, IQR = 29–53 years vs 57 years, IQR = 40–69 years; $P < .001$); renal tumors (50 years, IQR = 40–57 years vs 56 years, IQR = 42–67 years; $P = .42$); and nonmelanoma skin cancer (44 years, IQR = 39–51 years vs 62 years, IQR = 56–66 years; $P < .001$). Ages of onset for tumors that arose in carriers of missense variants that we have classified as pathogenic under our modified ACMG criteria are marked with red dots in [Figure 2](#). Furthermore, both null and missense carriers showed a lower age of onset in comparison to the general US population published by SEER for: all tumors (66 years), UM (61 years), mesothelioma (74 years), CM (58 years), and renal (64 years) (37). The cumulative frequencies of the age of onset of the core tumors are plotted in [Supplementary Figures 1 to 5](#) (available online), comparing null and missense variants.

Tumor Analysis

BAP1 IHC was performed on 40 tumors from carriers, with 38 showing loss of nuclear BAP1 protein expression. This includes tumors established as part of the BAP1-TPDS as well as breast and lung cancers and nonmelanocytic tumors of the skin ([Tables 1 and 2](#)); one of five breast cancers retained BAP1 expression and was from a carrier of a nonsense variant. BAP1 LOH was assessed in 26 tumors from carriers (eight UM, six mesotheliomas, three meningiomas, two RCC, two breast cancers plus one each of CM, nonmelanoma skin cancer, lung cancer, cardiac tumor [no histology available], and fibrous histiocytoma), with 22 showing loss of the wild-type allele. The four tumors that retained wild-type alleles were a mesothelioma (in a p.G684* carrier), a fibrous histiocytoma (in a p.L570_splice carrier), a breast cancer (in a p.W202R carrier), and a meningioma (in a p.Y173* carrier) ([Tables 1 and 2](#)). These tumor analyses are from multiple sources (published and unpublished), with no explicit details collated on consistency of methodologies used.

Discussion

A review of BAP1-TPDS in 2016 documented 51 families with variants worldwide (33); an updated review in 2017 increased this to 87 (32). Our analysis increases the number of families carrying a BAP1 variant to 181 and the number of unique variants to 140, of which 104 are null and 9 missense variants in the UCH domain are likely pathogenic under our recommended modification of the ACMG criteria ([Supplementary Tables 1 and 2](#), available online). This steadily increasing number suggests these variants may be more common than initially thought, as further confirmed with ClinVar (39), reporting 581 variants in

BAP1, with 68 classified as pathogenic and 278 VUS as of June 2018. Of all the variants reported in this study, ClinVar reports on only 16 of the null variants and 7 of the missense variants, indicating the critical need for this analysis, which provides a substantive update of available clinically annotated variant information. Further evidence of this is shown by a recent publication on BAP1 germline variants in ExAC that suggested that the syndrome is underreported (40). The vast majority of samples reported in ClinVar are from clinical laboratories with very limited or no information on the clinical presentation and segregation analysis, thus limiting the utility of the data. Development of a dedicated, curated registry for patients with germline variants in BAP1 will be essential for proper assessment of the clinical phenotype of the syndrome and the pathogenicity of each variant. There are multiple founder variants, with the most prevalent being a variant, p.L573Wfs*2, observed in 11 families from the US (38,41). This founder variant was traced back nine generations to a common ancestor in four families through haplotype analysis that identified a cosegregating rare synonymous SNP (rs71651686; MAF = 0.002) (38). De novo germline variants are possible; however, only a single variant carrier (p.G340Hfs*46) was thought to have a de novo germline variant with both parents testing negative for the variant.

From the collated data, it is clear that on average only a few family members are screened upon identification of a null variant. This indicates a high likelihood that carriers exist within the families who are not being appropriately clinically managed, particularly given that 84.9% of null variant carriers developed at least one tumor.

An important consideration when analyzing penetrance is that the data collated on tumor development are independent of age. Many young pathogenic variant carriers unaffected at the time of testing may potentially develop tumors as they age. Because the current analysis shows an occurrence of one or more tumors in 84.9% carriers of null variants, it is conceivable that penetrance of developing at least one tumor type may approach 100% over a lifetime. The cumulative frequency plots provided ([Supplementary Figures 1–5](#), available online) help to estimate the risk of developing each of the four core tumors, or any tumor, for an unaffected carrier tested at any given age. A similar assessment is not possible for missense variants because of the method of their ascertainment, which was predominantly through screening of probands, with just 10 nonproband variant carriers being tested (most likely because they had developed a tumor).

This analysis agrees with previous studies indicating that UM, mesothelioma, CM, and RCC are the four core tumor types associated with the BAP1-TPDS; however, as the number of tested individuals has increased, the proportion of all variant carriers with these tumors has fallen (32,33). The occurrence of the main BAP1-TPDS tumor types in carriers of null and missense variants respectively are, in decreasing order, UM (24.7% and 24%), mesothelioma (20.4% and 14.0%), CM (17.0% and 36%), and renal (10.2% and 12.0%). The frequency of these tumors in variant carriers was higher than the lifetime risks reported in SEER data for the US population, which are: CM (2.2%), renal (1.6%), and mesothelioma (0.04%) (37); or the published incidence data for UM, which suggest a lifetime risk of approximately 0.02% (42), which was not reported by SEER. Furthermore, both null and missense carriers showed a lower age of onset in comparison with the general US population published by SEER (37), suggesting pathogenic BAP1 variants not only influence tumor susceptibility but also the age at which tumors develop. We did not calculate standardized incidence

ratios in comparison with population data because we believe that the ascertainment biases in our cohort would result in misleading standardized incidence ratios estimates.

Analyses of rare genetic syndromes are plagued with ascertainment bias because carriers are identified based on the presence of symptoms or diseases associated with the syndrome, meaning that unaffected carriers, or carriers with unusual clinical presentation, are less likely to be described. Ascertainment bias is therefore likely an important caveat in the studies comprising this analysis in which candidates were often screened because of a family history of several tumors on the BAP1-TPDS spectrum, with few variant carriers without a tumor being reported in families and the testing schedule of nontumor-bearing relatives often not being stated. For example, it is plausible that the observation of 36.2% of probands and 15.9% of nonproband variant carriers having a diagnosis of UM in part arises because of increased screening for BAP1 in families with two cases of UM, rather than this being a defining feature of BAP1-TPDS families. Similarly, mesothelioma occurred in 24.8% and 16.9% of proband and nonproband variant carriers, respectively, compared with a lifetime risk of 0.04% in the general population (37). Complete investigation of all available members within BAP1 variant-positive families and systematic screening of all patients presenting with one of the “core” or potential BAP1-TPDS tumors would provide a more complete picture and reduce the effects of ascertainment bias as well as help assess the segregation criteria for evaluation of pathogenicity of mis-sense variants.

Some core tumors in the BAP1-TPDS have risks associated with environmental exposures, for example, ultraviolet radiation (UVR) exposure in CM and BCC as well as asbestos exposure in mesothelioma. It is difficult to properly document how these exposures may have influenced tumor development in this cohort because such data were not documented by the majority of publications and centers contributing to this study. Although BAP1 is phosphorylated following UVR exposure *in vitro* (7), there is currently no research describing the role of UVR exposure in modulating tumorigenesis in BAP1 germline variant carriers. This is similarly seen in mesothelioma where *in vivo* data show that asbestos exposure, even minimal exposure (43–45), in germline *Bap1* heterozygous mice increases risk of mesothelioma. However, *in vitro* studies of cells derived from germline variant carriers suggest that BAP1 may have a more global role in response to environmental stressors through its cytoplasmic functions (46,47). Further research is warranted to assess the impact of environmental mutagens on modulating penetrance of BAP1 germline mutations.

A limitation consistently found in the reporting of the BAP1-TPDS families is that the exact histological subtype of some tumor types (eg, RCC, lung cancer) is often not provided, which, given that the predisposition pertains to specific cell types or body sites (eg, clear cell RCC and pleural mesothelioma), confounds interpretation of tumor spectrum data. This highlights the need for better pathological annotation of tumors provided under personal or family history.

The classically described core tumor spectrum for the BAP1-TPDS includes UM, mesothelioma, CM, and RCC. This can now be expanded to include nonmelanoma tumors of the skin (predominantly BCC) (in 24.9% of families in this study), meningioma (in 9.4% of families), and cholangiocarcinoma (in 5.6% of families in this study). The reason we believe these tumors should be included in the BAP1-TPDS spectrum is primarily based on molecular evidence (IHC/LOH) observed in tumors of carriers as well as the substantially higher incidence of the two

rarer tumor types [meningioma (48) and cholangiocarcinoma (49)] than in the general population.

For mesothelioma we show here a female predominance (63.6%) in the BAP1-TPDS, which is in stark contrast to data on mesothelioma in the general population (50). However, the presentation of mesothelioma in the BAP1-TPDS seems to be starkly different from that of the general population, in which pleural mesothelioma makes up about 90.0% of mesothelioma cases and peritoneal mesothelioma is a rare disease (51). In null variant carriers, we found that peritoneal mesothelioma (36.4%) was more common than pleural mesothelioma (25.8%), although the location of a large proportion of all cases was unspecified (37.9%).

Unfortunately, we were not able to address questions relating to pathologies of interest in other tumor types, such as clear cell RCC or rhabdoid meningioma, because the numbers ($n < 5$) were too low to draw any conclusions. A worldwide central pathology review of all cases is outside the scope of this study; however, it represents an important consideration for the future. We highly recommend that more specific details of tumor histopathology be included in all publications reporting on BAP1-TPDS families.

The long tail of the observed tumor spectrum is highlighted in Tables 1 and 2, with many tumors from diverse tissues being observed in families carrying a BAP1 germline variant. It is unclear what proportion of these may be sporadic cases not influenced by BAP1 variants. Certain tumors with lifetime risks greater than 2%, such as breast, stomach, and colorectal cancer (37), are inherently difficult to confidently link to the BAP1-TPDS in the absence of IHC or LOH data because they commonly present in the relatives who were not genotyped and cannot be firmly linked to BAP1-TPDS without further genetic and experimental evidence. On the other hand, tumors present in this large tail of tumors cannot be ruled out as being associated with the BAP1-TPDS, particularly for tumors that are known to harbor somatic BAP1 mutations, including liver, stomach, colorectal, and bladder cancers (30,31). We recommend all tumors in variant carriers be evaluated through the framework produced by ClinGen to identify somatic alteration in addition to the germline variant to provide more evidence to further establish the tumor spectrum (52).

Somatic analysis of BAP1 expression by IHC and LOH provides evidence of contribution to tumorigenesis, or is indicative of prognosis, in a variety of tumor types (19,53–59). In the 1237 tumors recorded for this study, only 40 were reported to have BAP1 IHC performed, and 26 were documented to have been tested for BAP1 LOH. This highlights an important focus for future research, particularly collection and assessment of tumors in germline variant carriers. In addition, a variety of methodologies was used to assess the tumors by IHC, and the data included in this study were derived from in-house experimental analyses and pathology service centers. A source of variation across reports may therefore be protocols or antibodies used.

We recommend that all tumors in variant carriers be analyzed for evidence of loss of protein expression or LOH, which contributes to the ClinGen framework to enable further associations to be defined in the future. Furthermore, the results of these analyses should be routinely included in publications referring to these families. It should be noted that BAP1 somatic inactivation is a common event in “sporadic” tumors of three of the “core” BAP1-TPDS spectrum (UM, mesothelioma, and RCC). Therefore, loss of BAP1 expression/LOH in an isolated UM, RCC, or mesothelioma case with no family history of other tumors associated with the BAP1-TPDS is insufficient evidence for a

pathogenic germline variant. Moreover, the use of standardized methodologies and antibodies across groups worldwide would allow a more consistent evaluation of protein expression or LOH.

A recent comprehensive evaluation (32) of 53 germline variant carriers showed that 40 (75.5%) who had a full-body skin examination presented with at least one BAP1-inactivated melanocytoma/nevus. Conversely, among 49 patients who had at least one BAP1-inactivated melanocytic tumor, 25 (51.0%) were wild type for BAP1 germline variants (60). Epidemiological studies that address areas like the prevalence of these tumors in the general population are vital to understand their biological relevance in the BAP1-TPDS and to make an informed recommendation on genetic testing of patients that present with BAP1-inactivated melanocytic tumors. We agree with the recommendations proposed by previous studies (32,60) whereby if these lesions are biopsied, then BAP1 IHC should be performed and together with family history they are indications for germline genetic testing.

The tumor suppressor property of BAP1 has been linked to several functions of the protein, including deubiquitination activity, DNA damage response, cell cycle regulation, interactions with the polycomb group-like protein ASXL2, and apoptosis, which can each be assessed using specific assays (2,5,29,61,62). [Supplementary Table 3](#) (available online) shows the array of functional assays that have been utilized to date. There is no clear consensus on the mechanism by which BAP1 acts as a tumor suppressor, and this might differ between associated tumor types, meaning none of these functional assays can definitively assess potential pathogenicity of the VUS. Determining the mechanism, followed by establishment of an in vitro functional assay or a collection of assays, used in combination to evaluate all functions of BAP1 as a robust surrogate for in vivo tumorigenicity is therefore critically important for the evaluation of VUS. Until this has occurred, we recommend that the results of any current functional tests not be used as definitive proof of pathogenicity of a given BAP1 VUS and that the ACMG criteria be adhered to.

Classification of nonsense, frameshift, and canonical splice variants as null pathogenic variants is straightforward for BAP1, but this is much less so for missense variants. Given the lack of understanding of the function of BAP1 as a tumor suppressor, the value of in silico predictions of a deleterious effect of missense VUS is limited. For example, a recently published in silico mutation predictor that claims to be more conservative in calling of pathogenic variants predicts that 35/40 (87.5%) of the missense variants in our cohort are at least likely pathogenic (63). This seems improbable in light of a recent analysis of in silico prediction of the pathogenicity of BRCA1 and BRCA2 missense variants, which concluded that the vast majority of variants predicted to be deleterious are false positives (64). Although in other disorders in silico prediction of the effect of an amino acid alteration on a protein can provide a useful indication of deleterious effect on structure and/or function, the seemingly complex mechanism of action(s) of BAP1 as a tumor suppressor makes these generic in silico tools unsuitable for assessing VUS in BAP1. A better understanding of the vital functions of BAP1 and the use of evidence from other aspects of the ACMG criteria is clearly needed to establish pathogenicity.

Evaluation of VUS in BAP1 to date includes accumulation of experimental genetic and functional evidence (52). A framework can be drawn up to assess VUS based on family cancer history and somatic analysis of the tumor for BAP1 expression and LOH. A patient presenting with a missense variant that is diagnosed

with a BAP1-TPDS-associated tumor that has LOH, shows negative BAP1 protein staining by IHC, or both, has some evidence of pathogenicity independent of family history. We identified three missense variants in this analysis that could be regarded as likely pathogenic under ACMG criteria ([Supplementary Table 2](#), available online); however, we identified six additional variants that have evidence suggesting pathogenicity outside the criteria ([Supplementary Table 2](#), available online; see also [Figures 1 and 2](#) and [Methods](#)). Some of these families have tumor analyses available as supportive evidence, as suggested above, but all families with VUS would be better evaluated if these data were available. One of these additional variants (p.N78S) we identified was highlighted in the recent publication by the Cancer Genome Atlas authors in its Pan-Cancer Atlas of Splice-Site-Creating article where they found this missense variant in two RCC samples (65). In the sample with available protein data, they found that the sample had statistically significantly ($P = .04$) lower expression of BAP1 at the translational level, which they concluded means that the missense variant had caused an alternatively spliced transcript. Interestingly, all nine of the missense variants we considered to show some evidence of pathogenicity occur in the UCH domain of BAP1, and the chance of this occurring randomly is 240/729⁹. Previous studies provide further support, with experimentally pathogenic missense variants in the UCH domain inducing amyloidogenic aggregation, causing adverse outcomes (66). Additionally, many missense variants cluster in the ASX binding motif region, which is an obligate binding partner for deubiquitinating enzyme activity (62,66). However, not all missense variants identified in the UCH domain in this study have evidence for pathogenicity, indicating that the presence of a variant in the UCH domain alone is not sufficient to infer pathogenicity. The need for greater collection of comprehensive clinical and family data that can be used as a reference for VUS, as well as the analysis of tumors from VUS carriers, is clear and further strengthens the argument that all tumors in BAP1 variant carriers should undergo IHC and LOH analysis.

There is compelling evidence to show that the identification of BAP1 germline variants and somatic mutations have a role in the development and clinical behavior of a number of tumors (15,19,53–56,58,59,67–71). Routine clinical surveillance of carriers for tumors associated with the BAP1-TPDS is important for their early detection and appropriate management (33,72). We recommend the guidelines published in [GeneReviews](#) (73), which include biannual/annual skin and eye exams, physical examinations, and ultrasound/MRI imaging. As the tumor spectrum associated with the BAP1-TPDS expands, so too will the need for the addition of different surveillance modalities.

The advent of massively parallel sequencing has resulted in the increased number of identified germline variants in BAP1 and an improved understanding of the BAP1-TPDS syndrome. Our results confirm that there are four main tumor types strongly associated with the BAP1-TPDS (UM, mesothelioma, CM, and renal). In addition, there is an extended spectrum of tumors that includes meningioma, BCC, and cholangiocarcinoma and a wide range of less frequent tumors with varying degrees of evidence linking them to the syndrome. Further evaluation of BAP1-inactivated melanocytic tumors and their degree of involvement in the BAP1-TPDS is an important area for future studies. An increase in surveillance of BAP1 tumors via IHC and LOH analysis is warranted to better evaluate the extended tumor spectrum in the BAP1-TPDS. Without calibrated functional assays yet available, this will play an important role in the evaluation of missense variants that can be reliably used to assess

Box 1. Authors' consensus recommendations for suspected/confirmed carriers of and for the BAP1-TPDS.

- BAP1 should be included in all germline cancer panels for genetic testing (which should include copy number variation assessment), particularly in patients with tumors associated with the BAP1-TPDS, and as many family members should be genotyped as possible to aid segregation analysis, which will directly inform on surveillance of carriers and assessment of mutation penetrance.
- Use of the ClinGen disease-gene association framework to evaluate tumor spectrum and more consistency in reporting of tumor histopathology, in particular, site/histology of mesotheliomas, histology of RCCs, and histology of meningiomas (52).
- IHC and LOH analysis performed on all tumors in all carriers regardless of variant type.
- Conduct epidemiological studies evaluating BAP1-inactivated melanocytic tumors in the general population and use recommendations proposed by Haugh et al. and Cabaret et al. (32, 60) in the evaluation of these tumors.
- Although a useful aid, do not use functional assays as a definitive evaluation of pathogenicity of BAP1 variants until proof of that function is linked to tumorigenesis in vivo.
- Pathogenicity of missense variants needs to be evaluated beyond in silico prediction and single functional assays; currently, family assessment (eg, segregation of core BAP1-TPDS tumors; core rare tumors [UM/mesothelioma]) in the family without segregation data; multiple primary BAP1-TPDS core tumors in the proband, or a combination of these) and tumor analysis are the most important tools.
- Implementation and expansion of current and appropriate surveillance measures for variant carriers. The current suggested guidelines are published in GeneReviews (73).

impact on BAP1 tumor-suppressor activity. It is also critical to form an international collaborative effort to define the optimal surveillance and prevention strategy for the BAP1-TPDS. Moving forward, the targeting of these key areas and efforts to functionally evaluate BAP1 will be critical in garnering a greater understanding of the mechanism by which it acts as a tumor suppressor in each key tumor type. The consensus recommendations of our group for the evaluation of families and individuals with suspected/confirmed BAP1 germline variants and the tumors they present with, the management of these carriers, and future publications on the BAP1-TPDS, are presented in Box 1.

Funding

This work was supported by an Australian Government Research Training Program Scholarship (SW); the National Health and Medical Research Council of Australia (NH, AP, JP, MH, HH, JS, SW, BG, SW, PJ); the Patti Blow Research Fund in Ophthalmology (MHA and FHD); the National Eye Institute of the National Institutes of Health under Award number K08EY022672 (CMC); R21CA191943 Grant from the

National Cancer Institute (MHA); The Ohio Lions Eye Research Foundation (MHA and CMC); the Dutch Cancer Society (UL2012-5489) to R van Doorn; the Italian Ministry of Health 5×1000 per la Ricerca Corrente to Ospedale Policlinico San Martino to PG; The Helsinki University Hospital Research Funds (TYH2017218), The Sigrid Jusélius Foundation, The Finnish Cancer Foundation, The Eye and Tissue Bank Foundation, The Folkhälsan Research Foundation, The Evald and Hilda Nissi Foundation, The Paulo Foundation, and The Mary and Georg C. Ehrnrooth Foundation (TK, JT); the National Institutes of Health (K24CA149202) (H Tsao, CN Njauw); generous donations to the Massachusetts General Hospital; the research at the Melanoma Unit in Barcelona is partially funded by Spanish Fondo de Investigaciones Sanitarias grants PI15/00716 and PI15/00956; CIBER de Enfermedades Raras of the Instituto de Salud Carlos III, Spain, cofinanced by the European Development Regional Fund “A way to achieve Europe” ERDF; AGAUR 2014_SGR_603 and 2017_SGR_1134 of the Catalan Government, Spain; European Commission under the 6th Framework Programme, contract no. LSHC-CT-2006-018702 (GenoMEL) and by the European Commission under the 7th Framework Programme, Diagnostics; The National Cancer Institute (NCI) of the National Institutes of Health (NIH) (CA83115); a grant from “Fundació La Marató de TV3” 201331-30, Catalonia, Spain; a grant from “Fundación Científica de la Asociación Española Contra el Cáncer” GCB15152978SOEN, Spain, and CERCA Programme/Generalitat de Catalunya. Part of the work was carried out at the Esther Koplowitz Center, Barcelona. Miriam Potrony is the recipient of a PhD Fellowship FI14/00231 from Instituto de Salud Carlos III, Spain; the National Institutes of Health, National Cancer Institute Grant R01 (CA175691) (JRT); the Dutch Cancer Society (2014–6905) and the Collaborative Ophthalmic Research Rotterdam (1.1.1) (NvP, EK, and AdK); grants from Wealthon, Bontius Stichting, LSBS, Stichting Blinden Penning, ANVVB, and Oogfonds (MJJ, GPML, and AdK). Karolinska Institutet's foundation grants for eye research and the Carmen and Bertil Regnérs foundation for eye research (VH, HH); the NIH/NCI Cancer Center Support Grant P30 CA008748 (RM); a COACYT PhD fellowship (RO); Wellcome Trust 204562/Z/16/Z (CDRE); UNAM PAPIIT 200318 (CDRE); Miguel Aleman Medical Science stimulus (CDRE).

Notes

Authors: Sebastian Walpole, Antonia L. Pritchard, Colleen M. Cebulla, Robert Pilarski, Meredith Stautberg, Frederick H. Davidorf, Arnaud de la Fouchardière, Odile Cabaret, Lisa Golmard, Dominique Stoppa-Lyonnet, Erin Garfield, Ching-Ni Njauw, Mitchell Cheung, Joni A. Turunen, Pauliina Repo, Reetta-Stiina Järvinen, Remco van Doorn, Martine J. Jager, Gregorius P.M. Luyten, Marina Marinkovic, Cindy Chau, Miriam Potrony, Veronica Höiom, Hildur Helgadottir, Lorenza Pastorino, William Bruno, Virginia Andreotti, Bruna Dalmaso, Giulia Ciccarese, Paola Queirolo, Luca Mastracci, Karin Wadt, Jens Folke Kiilgaard, Michael R. Speicher, Natasha van Poppelen, Emine Kilic, Rana'a T. Al-Jamal, Irma Dianzani, Marta Betti, Carsten Bergmann, Sandro Santagata, Sonika Dahiya, Saleem Taibjee, Jo Burke, Nicola Poplawski, Sally J. O'Shea, Julia Newton-Bishop,

Julian Adlard, David J. Adams, Anne-Marie Lane, Ivana Kim, Sonja Klebe, Hilary Racher, J. William Harbour, Michael L. Nickerson, Rajmohan Murali, Jane M. Palmer, Madeleine Howlie, Judith Symmons, Hayley Hamilton, Sunil Warriar, William Glasson, Peter Johansson, Carla Daniela Robles-Espinoza, Raul Ossio, Annelies de Klein, Susana Puig, Paola Ghiorzo, Maartje Nielsen, Tero T. Kivelä, Hensin Tsao, Joseph R. Testa, Pedram Gerami, Marc-Henri Stern, Brigitte Bressac-de Paillerets, Mohamed H. Abdel-Rahman, Nicholas K. Hayward

Affiliations of authors: QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia (SW, ALP, JMP, MH, JS, HH, PJ, NKH); University of Queensland, Brisbane, QLD, Australia (SW); The University of the Highlands and Islands, Inverness, UK (ALP); Department of Ophthalmology and Visual Science, The Ohio State University, Columbus, OH (CMC, FHD, MHAR); Division of Human Genetics, Department of Internal Medicine and Comprehensive Cancer Center, The Ohio State University, Columbus, OH (RP, MS, MHAR); Département de Biopathologie, Centre Leon Bérard, Lyon, France (AdlF); Département de Biopathologie, Gustave Roussy, Université Paris-Saclay, Villejuif, France (OC, BBP); Département De Biologie Des Tumeurs, Institut Curie, Paris, France (LG, DSL, MHS); Institut Curie, PSL Research University, INSERM U830, DNA Repair and Uveal Melanoma (D.R.U.M.), Equipe labellisée par la Ligue Nationale contre le Cancer, Paris, France (DSL, MHS); Sorbonne Paris Cité, University Paris-Descartes, Paris, France (DSL); Department of Dermatology, Feinberg School of Medicine, Northwestern University, Chicago, IL (EG, PG); Department of Dermatology, Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA (CNN, HT); Cancer Biology Program, Fox Chase Cancer Center, Philadelphia, PA (MC, JRT); Folkhälsan Institute of Genetics, Helsinki, Finland (JAT, PR, RSJ); Department of Ophthalmology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland (JAT, PR, RSJ, TTK); Department of Dermatology, LUMC, Leiden, The Netherlands (RvD); Department of Ophthalmology, LUMC, Leiden, The Netherlands (MJ), GPML, MM, CC); Dermatology Department, Melanoma Unit, Hospital Clinic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Spain (MP); Centro de Investigación Biomédica en Red (CIBER) de Enfermedades Raras, Instituto de Salud Carlos III, Barcelona, Spain (MP, SP); Department of Oncology-Pathology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden (VH, HH, SP); Department of Internal Medicine and Medical Specialties and Genetics of Rare Cancers, University of Genoa, Ospedale Policlinico San Martino, Genoa, Italy (LP, WB, VA, BD, GC, PG); Medical Oncology Unit, Ospedale Policlinico San Martino, Genoa, Italy (PQ); Department of Surgical and Diagnostic Sciences, Pathology Unit, University of Genoa and Ospedale Policlinico San Martino, Genoa, Italy (LM); Department of Clinical Genetics, University Hospital of Copenhagen, Copenhagen, Denmark (KW); Department of Ophthalmology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark (JFK); Institute of Human Genetics, Diagnostic and Research Center for Molecular Biomedicine, Medical University of Graz, Graz, Austria (MRS); Department of Ophthalmology (NvP) and Department of Clinical Genetics (NvP, EK, AdK), Erasmus University Medical Center, Rotterdam, the Netherlands; Department of Ophthalmology, Ocular Oncology Service, Helsinki University Central Hospital, Helsinki, Finland (RTAJ); Department of Health Sciences, Università del Piemonte Orientale, Novara, Italy (ID, MB); Bioscientia Center for Human Genetics, Ingelheim, Germany (CB); Department of Medicine IV,

Faculty of Medicine, Medical Center—University of Freiburg, University of Freiburg, Freiburg, Germany (CB); Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (SS); Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO (SD); Department of Dermatology, Dorset County Hospital NHS Foundation Trust, Dorchester, UK (ST); Tasmanian Clinical Genetics Service, Royal Hobart Hospital, TAS, Australia (JB); Adult Genetics Unit, Medicine Directorate, Royal Adelaide Hospital, Adelaide, SA, Australia (NP); University Department of Paediatrics, University of Adelaide, Adelaide, SA, Australia (NP); Dermatology Department, Mater Private Hospital Cork, Citygate, Mahon, Cork, Ireland (SJO); Yorkshire Regional Genetics Service, Chapel Allerton Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, UK (JNB, JA); Experimental Cancer Genetics, Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Cambridge, UK (DJA, CDRE); Department of Ophthalmology, Ocular Melanoma Center and Retina Service, Massachusetts Eye and Ear, Harvard Medical School, Boston, MA (AML, IK); Department of Anatomical Pathology, Flinders University and SA Pathology at Flinders Medical Centre, Adelaide, SA, Australia (SK); Impact Genetics, Bowmanville, Ontario, Canada (HR); Bascom Palmer Eye Institute, Sylvester Comprehensive Cancer Center and Interdisciplinary Stem Cell Institute, University of Miami Miller School of Medicine, Miami, FL (JWH); Laboratory of Translational Genomics, National Cancer Institute, Bethesda, MD (MLN); Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY (RM); Queensland Ocular Oncology Service, The Terrace Eye Centre, Brisbane, QLD, Australia (SW, WG); Laboratorio Internacional de Investigación sobre el Genoma Humano, Universidad Nacional Autónoma de México, Juriquilla, Santiago de Querétaro, Mexico (CDRE, RO); Department of Clinical Genetics, LUMC, Leiden, The Netherlands (MN); Massachusetts General Hospital Cancer Center, Boston, MA (HT); The Robert H. Lurie Cancer Center, Northwestern University, Chicago, IL (PG); INSERM UMR 1186, Integrative Tumor Immunology and Genetic Oncology, Gustave Roussy, EPHE, PSL, Faculté de Médecine, Université Paris-Sud, Université Paris-Saclay, Villejuif, France (BBdP); and Department of Pathology, Menoufiya University, Shebin El-Kom, Egypt (MHAR).

The funders had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

The authors have no conflicts of interest to disclose.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We acknowledge the contributions of the patients, their families, and the many clinicians, geneticists, genetic counsellors, and allied health professionals involved in their management, in particular: Caroline Abadie, Jean-Philippe Arnault, Séverine Audebert-Bellanger, Marie-Françoise Avril, Philippe Bahadoran, Pascaline Berthet, Françoise Boitier, Valérie Bonadona, Marie-Noëlle Bonnet-Dupeyron, Olivier Caron, Frédérique Carre-Pigeon, Estelle Cauchin, Tara Clancy, Carole Corsini, Isabelle Coupier, Stéphane Dalle, François Eisinger, Patricia Fergelot, Paul Gesta, Olivier Ingster, Bertrand Isidor, Nicolas Janin, Fiona Laloo, Sophie Lejeune, Dominique Leroux, Alain Lortholary, Delphine Lutringer, Tanguy Martin-Denavit, Christine Maugard, Gwenael Nadeau, Jill A. Ohar, Laurence Olivier-Faivre, Clotilde Penet, Marie-Françoise Petit, Fabienne Prieur, Stéphane Richard, Caroline Robert, Hélène Schuster, Luc Thomas, Julie Tinat, Pierre

Vabres, Hélène Zattara, Helen Schmid, and Graham Mann. We also thank the following people for their contributions to this study: Andrew Stark, Olivia Rolfe, and Matthew D'Mellow for data acquisition at Terrace Eye Centre, Queensland Ocular Oncology Service; James B. Massengill for molecular analysis at The Ohio State University; Annalia Cianflone for her help in referring, interviewing families, and molecular analysis; Charlotta All Eriksson for help in referring families; and Rainer Tuominen for molecular analysis. We are grateful for the support of the Gustave Roussy Biobank (no. BB-0033-00074).

References

- Jensen DE, Proctor M, Marquis ST, et al. BAP1: a novel ubiquitin hydrolase which binds to the BRCA1 RING finger and enhances BRCA1-mediated cell growth suppression. *Oncogene*. 1998;16(9):1097–1112.
- Ventii KH, Devi NS, Friedrich KL, et al. BRCA1-associated protein-1 is a tumor suppressor that requires deubiquitinating activity and nuclear localization. *Cancer Res*. 2008;68(17):6953–6962.
- Yu H, Mashtalir N, Daou S, et al. The ubiquitin carboxyl hydrolase BAP1 forms a ternary complex with YY1 and HCF-1 and is a critical regulator of gene expression. *Mol Cell Biol*. 2010;30(21):5071–5085.
- Zarrizi R, Menard JA, Belting M, et al. Deubiquitination of gamma-tubulin by BAP1 prevents chromosome instability in breast cancer cells. *Cancer Res*. 2014;74(22):6499–6508.
- Yu H, Pak H, Hammond-Martel I, et al. Tumor suppressor and deubiquitinase BAP1 promotes DNA double-strand break repair. *Proc Natl Acad Sci USA*. 2014; 111(1):285–290.
- Ji Z, Mohammed H, Webber A, et al. The forkhead transcription factor FOXK2 acts as a chromatin targeting factor for the BAP1-containing histone deubiquitinase complex. *Nucleic Acids Res*. 2014;42(10):6232–6242.
- Eletr ZM, Yin L, Wilkinson KD. BAP1 is phosphorylated at serine 592 in S-phase following DNA damage. *FEBS Lett*. 2013;587(24):3906–3911.
- Daou S, Hammond-Martel I, Mashtalir N, et al. The BAP1/ASXL2 histone H2A deubiquitinase complex regulates cell proliferation and is disrupted in cancer. *J Biol Chem*. 2015;290(48):28643–28663.
- Baughman JM, Rose CM, Kolumam G, et al. NeuCode proteomics reveals Bap1 regulation of metabolism. *Cell Rep*. 2016;16(2):583–595.
- Gezgin G, Dogrusöz M, van Essen TH, et al. Genetic evolution of uveal melanoma guides the development of an inflammatory microenvironment. *Cancer Immunol Immunother*. 2017;66(7):903–912.
- Chittock EC, Latwiel S, Miller TC, et al. Molecular architecture of polycomb repressive complexes. *Biochem Soc Trans*. 2017;45(1):193–205.
- Online Mendelian Inheritance in Man, OMIM[®]. Baltimore, MD: Johns Hopkins University. <https://omim.org/>. Accessed October 14, 2018.
- Harbour JW, Onken MD, Roberson ED, et al. Frequent mutation of BAP1 in metastasizing uveal melanomas. *Science*. 2010;330(6009):1410–1413.
- Abdel-Rahman MH, Pilarski R, Cebulla CM, et al. Germline BAP1 mutation predisposes to uveal melanoma, lung adenocarcinoma, meningioma, and other cancers. *J Med Genet*. 2011;48(12):856–859.
- Testa JR, Cheung M, Pei J, et al. Germline BAP1 mutations predispose to malignant mesothelioma. *Nat Genet*. 2011;43(10):1022–1025.
- Wiesner T, Obenaus AC, Murali R, et al. Germline mutations in BAP1 predispose to melanocytic tumors. *Nat Genet*. 2011;43(10):1018–1021.
- Popova T, Hebert L, Jacquemin V, et al. Germline BAP1 mutations predispose to renal cell carcinomas. *Am J Hum Genet*. 2013;92(6):974–980.
- World Health Organization. WHO Classification of Skin Tumours. 4th Ed. Geneva, Switzerland: World Health Organization; 2018.
- Shankar GM, Abedalthagafi M, Vaubel RA, et al. Germline and somatic BAP1 mutations in high-grade rhabdoid meningiomas. *Neuro Oncol*. 2016; doi: 10.1093/neuonc/nov235.
- Wadt KA, Aoude LG, Johansson P, et al. A recurrent germline BAP1 mutation and extension of the BAP1 tumor predisposition spectrum to include basal cell carcinoma. *Clin Genet*. 2015;88(3):267–272.
- de la Fouchardiere A, Cabaret O, Savin L, et al. Germline BAP1 mutations predispose also to multiple basal cell carcinomas. *Clin Genet*. 2015;88(3): 273–277.
- Pilarski R, Cebulla CM, Massengill JB, et al. Expanding the clinical phenotype of hereditary BAP1 cancer predisposition syndrome, reporting three new cases. *Genes Chromosomes Cancer*. 2014;53(2):177–182.
- Cheung M, Kadariya Y, Talarckek J, et al. Germline BAP1 mutation in a family with high incidence of multiple primary cancers and a potential gene-environment interaction. *Cancer Lett*. 2015;369(2):261–265.
- Rawson RV, Watson GF, Maher AM, et al. Germline BAP1 mutations also predispose to cutaneous squamous cell carcinoma. *Pathology*. 2017; doi: 10.1016/j.pathol.2017.03.005.
- de la Fouchardiere A, Cabaret O, Petre J, et al. Primary leptomeningeal melanoma is part of the BAP1-related cancer syndrome. *Acta Neuropathol*. 2015; 129(6):921–923.
- Ribeiro C, Campelos S, Moura CS, et al. Well-differentiated papillary mesothelioma: clustering in a Portuguese family with a germline BAP1 mutation. *Ann Oncol*. 2013;24(8):2147–2150.
- Farley MN, Schmidt LS, Mester JL, et al. A novel germline mutation in BAP1 predisposes to familial clear-cell renal cell carcinoma. *Mol Cancer Res*. 2013; 11(9):1061–1071.
- McDonnell KJ, Gallanis GT, Heller KA, et al. A novel BAP1 mutation is associated with melanocytic neoplasms and thyroid cancer. *Cancer Genet*. 2016; 209(3):75–81.
- Ohar JA, Cheung M, Talarckek J, et al. Germline BAP1 mutational landscape of asbestos-exposed malignant mesothelioma patients with family history of cancer. *Cancer Res*. 2016;76(2):206–215.
- Deng M, Bragelmann J, Schultze JL, et al. Web-TCGA: an online platform for integrated analysis of molecular cancer data sets. *BMC Bioinformatics*. 2016;17: 72.
- Forbes SA, Beare D, Boutselakis H, et al. COSMIC: somatic cancer genetics at high-resolution. *Nucleic Acids Res*. 2017;45(D1):D777–d783.
- Haugh AM, Njauw CN, Bubleja JA, et al. Genotypic and phenotypic features of BAP1 cancer syndrome: a report of 8 new families and review of cases in the literature. *JAMA Dermatol*. 2017; doi:10.1001/jamadermatol.2017.2330.
- Rai K, Pilarski R, Cebulla CM, et al. Comprehensive review of BAP1 tumor predisposition syndrome with report of two new cases. *Clin Genet*. 2016;89(3): 285–294.
- Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405–424.
- World Health Organization. *International Classification of Diseases for Oncology, ICD-O-3*. Geneva, Switzerland: World Health Organization; 2000.
- World Health Organization. *International Statistical Classification of Diseases and Related Health Problems, ICD-10*. 10th ed. Geneva, Switzerland: World Health Organization; 1996.
- Surveillance Epidemiology and End Results Program (SEER). In: Howlander NA, Krapcho M, Miller D, et al., eds. *SEER Cancer Statistics Review, 1975–2014*. Bethesda, MD: National Cancer Institute. Based on November 2016 SEER data submission, posted to the SEER website, April 2017.
- Carbone M, Flores EG, Emi M, et al. Combined genetic and genealogic studies uncover a large BAP1 cancer syndrome kindred tracing back nine generations to a common ancestor from the 1700s. *PLoS Genet*. 2015;11(12): e1005633.
- Landrum MJ, Lee JM, Benson M, et al. ClinVar: improving access to variant interpretations and supporting evidence. *Nucleic Acids Res*. 2018;46(D1): D1062–D1067.
- Massengill JB, Sample KM, Pilarski R, et al. Analysis of the Exome Aggregation Consortium (ExAC) database suggests that the BAP1-tumor predisposition syndrome is underreported in cancer patients. *Genes Chromosomes Cancer*. 2018;57(9):478–481.
- Turunen JA, Markkinen S, Wilska R, et al. BAP1 germline mutations in Finnish patients with uveal melanoma. *Ophthalmology*. 2016;123(5): 1112–1117.
- Jovanovic P, Mihajlovic M, Djordjevic-Jocic J, et al. Ocular melanoma: an overview of the current status. *Int J Clin Exp Pathol*. 2013;6(7):1230–1244.
- Napolitano A, Pellegrini L, Dey A, et al. Minimal asbestos exposure in germline BAP1 heterozygous mice is associated with deregulated inflammatory response and increased risk of mesothelioma. *Oncogene*. 2016;35(15): 1996–2002.
- Xu J, Kadariya Y, Cheung M, et al. Germline mutation of Bap1 accelerates development of asbestos-induced malignant mesothelioma. *Cancer Res*. 2014; 74(16):4388–4397.
- Kadariya Y, Cheung M, Xu J, et al. Bap1 is a bona fide tumor suppressor: genetic evidence from mouse models carrying heterozygous germline Bap1 mutations. *Cancer Res*. 2016;76(9):2836–2844.
- Bononi A, Giorgi C, Patergnani S, et al. BAP1 regulates IP3R3-mediated Ca(2+) flux to mitochondria suppressing cell transformation. *Nature*. 2017;546(7659): 549–553.
- Bononi A, Yang H, Giorgi C, et al. Germline BAP1 mutations induce a Warburg effect. *Cell Death Differ*. 2017;24(10):1694–1704.
- Ostrom QT, Gittleman H, Liao P, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2010–2014. *Neuro Oncol*. 2017;19(suppl 5):v1–v88.
- Saha SK, Zhu AX, Fuchs CS, et al. Forty-year trends in cholangiocarcinoma incidence in the U.S.: intrahepatic disease on the rise. *Oncologist*. 2016;21(5): 594–599.
- Hyland RA, Ware S, Johnson AR, et al. Incidence trends and gender differences in malignant mesothelioma in New South Wales, Australia. *Scand J Work Environ Health*. 2007;33(4):286–292.
- Sharma H, Bell I, Schofield J, et al. Primary peritoneal mesothelioma: case series and literature review. *Clin Res Hepatol Gastroenterol*. 2011;35(1):55–59.
- Strande NT, Riggs ER, Buchanan AH, et al. Evaluating the clinical validity of gene-disease associations: an evidence-based framework developed by the clinical genome resource. *Am J Hum Genet*. 2017;100(6):895–906.
- Tang J, Xi S, Wang G, et al. Prognostic significance of BRCA1-associated protein 1 in colorectal cancer. *Med Oncol*. 2013;30(2):541.

54. Nickerson ML, Dancik GM, Im KM, et al. Concurrent alterations in TERT, KDM6A, and the BRCA pathway in bladder cancer. *Clin Cancer Res*. 2014;20(18):4935–4948.
55. Al-Shamsi HO, Anand D, Shroff RT, et al. BRCA-associated protein 1 mutant cholangiocarcinoma: an aggressive disease subtype. *J Gastrointest Oncol*. 2016;7(4):556–561.
56. Gossage L, Murtaza M, Slatter AF, et al. Clinical and pathological impact of VHL, PBRM1, BAP1, SETD2, KDM6A, and JARID1c in clear cell renal cell carcinoma. *Genes Chromosomes Cancer*. 2014;53(1):38–51.
57. Farquhar N, Thornton S, Coupland SE, et al. Patterns of BAP1 protein expression provide insights into prognostic significance and the biology of uveal melanoma. *J Pathol Clin Res*. 2018;4(1):26–38.
58. Pulford E, Huilgol K, Moffat D, et al. Malignant mesothelioma, BAP1 immunohistochemistry, and VEGFA: does BAP1 have potential for early diagnosis and assessment of prognosis? *Dis Markers*. 2017;2017:1310478.
59. Wang XY, Wang Z, Huang JB, et al. Tissue-specific significance of BAP1 gene mutation in prognostic prediction and molecular taxonomy among different types of cancer. *Tumour Biol*. 2017;39(6):101042831769911.
60. Cabaret O, Perron E, Bressac-de Paillerets B, et al. Occurrence of BAP1 germline mutations in cutaneous melanocytic tumors with loss of BAP1-expression: a pilot study. *Genes Chromosomes Cancer*. 2017;56(9):691–694.
61. Ismail IH, Davidson R, Gagne JP, et al. Germline mutations in BAP1 impair its function in DNA double-strand break repair. *Cancer Res*. 2014;74(16):4282–4294.
62. Peng H, Prokop J, Karar J, et al. Familial and somatic BAP1 mutations inactivate ASXL1/2-mediated allosteric regulation of BAP1 deubiquitinase by targeting multiple independent domains. *Cancer Research*. 2017;78(5):1200–1213.
63. Salgado D, Desvignes JP, Rai G, et al. UMD-predictor: a high-throughput sequencing compliant system for pathogenicity prediction of any human cDNA substitution. *Hum Mutat*. 2016;37(5):439–446.
64. Ernst C, Hahnen E, Engel C, et al. Performance of in silico prediction tools for the classification of rare BRCA1/2 missense variants in clinical diagnostics. *BMC Med Genomics*. 2018;11(1):35.
65. Jayasinghe RG, Cao S, Gao Q, et al. Systematic analysis of splice-site-creating mutations in cancer. *Cell Rep*. 2018;23(1):270–281.e3.
66. Bhattacharya S, Hanpude P, Maiti TK. Cancer associated missense mutations in BAP1 catalytic domain induce amyloidogenic aggregation: a new insight in enzymatic inactivation. *Sci Rep*. 2015;5:18462.
67. Arzt L, Quehenberger F, Halbwedl I, et al. BAP1 protein is a progression factor in malignant pleural mesothelioma. *Pathol Oncol Res*. 2014;20(1):145–151.
68. Baumann F, Flores E, Napolitano A, et al. Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival. *Carcinogenesis*. 2015;36(1):76–81.
69. Kapur P, Peña-Llopis S, Christie A, et al. Effects on survival of BAP1 and PBRM1 mutations in sporadic clear-cell renal cell carcinoma: a retrospective analysis with independent validation. *Lancet Oncol*. 2013;14(2):159–167.
70. Hakimi AA, Ostrovskaya I, Reva B, et al. Adverse outcomes in clear cell renal cell carcinoma with mutations of 3p21 epigenetic regulators BAP1 and SETD2: a report by MSKCC and the KIRC TCGA research network. *Clin Cancer Res*. 2013;19(12):3259–3267.
71. Njauw CN, Kim I, Piris A, et al. Germline BAP1 inactivation is preferentially associated with metastatic ocular melanoma and cutaneous-ocular melanoma families. *PLoS One*. 2012;7(4):e35295.
72. Star P, Goodwin A, Kapoor R, et al. Germline BAP1-positive patients: the dilemmas of cancer surveillance and a proposed interdisciplinary consensus monitoring strategy. *Eur J Cancer*. 2018;92:48–53.
73. Pilarski R, Rai K, Cebulla C, et al. BAP1 tumor predisposition syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews*[®]. Seattle, WA: University of Washington, Seattle; 2016.