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Review

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 Helgadottir, Lorenza Pastorino, William Bruno, Virginia Andreotti, Bruna Dalmasso, 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

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tumor diagnoses, and information on BAP1 immunohistochemistry or loss of somatic heterozygosity on 106 published and 75 unpublished *BAP1* germline variant-positive families worldwide to better characterize the genotypes and phenotypes associated with the *BAP1*-TPDS.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 ($P < .001$).

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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 hydrolase 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.

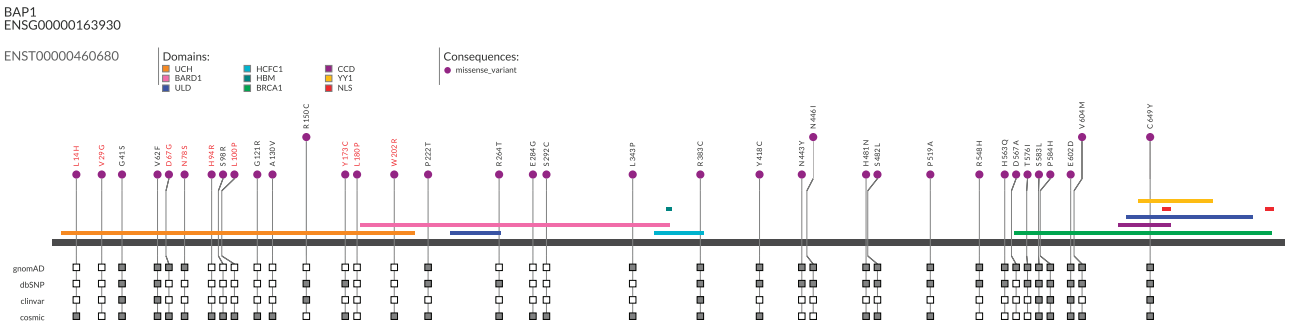

Figure 1. Reported missense variants plotted proportional to their frequency along the *BAP1* gene with the functional domains shown. Variants that have evidence supporting pathogenicity are marked as red. The four blocks underneath each variant indicate their presence in the indicated databases. Database 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

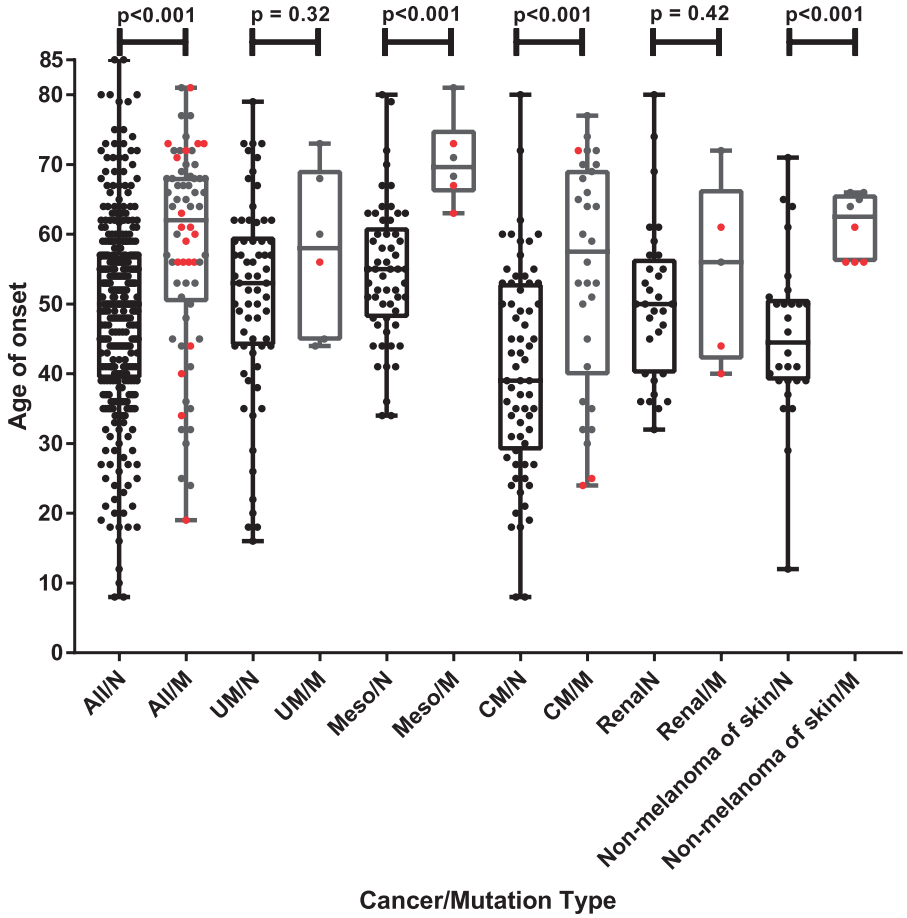

Figure 2. The age of onset of all tumors presenting in variant carriers included in this study shown as box and whisker plots. Tumors are grouped together in the "all" group and then broken down into subgroups of the main BAP1-associated tumors. CM = cutaneous melanoma; Meso = mesothelioma; Renal = nonmelanoma 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† (37)	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)	—	—	—	11/51 (21.6)	Deng et al. 2016 (30)
C18-20	Colorectal	2/141 (1.4)	0/183	31/522 (5.9)	—	—	4.3%	—	
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	Nasophraynx	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)	—	—	—	0/3	Forbes et al. 2017 (31)
C54.1	Endometrium	0/71	1/103 (1)	1/261 (0.4)	—	—	—	12/658 (1.8)	Forbes et al. 2017 (31)
C55	Uterus	0/71	0/103	3/261 (1.2)	—	—	2.9%	—	
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	—	—	1.0%	32/2115 (1.5)	Forbes et al. 2017 (31)
C25.9	Pancreas	0/40	0/10	1/113 (0.9)	—	—	1.6%	11/1907 (0.6)	Forbes et al. 2017 (31)
C40-41	Bone	0/40	0/10	1/113 (0.9)	—	—	—	3/594 (0.5)	Forbes et al. 2017 (31)
C49	Soft tissue	0/40	0/10	2/113 (1.8)	—	—	—	5/572 (0.9)	Forbes et al. 2017 (31)
C51.9	Vulva	0/27	0/10	1/46 (2.2)	—	—	—	0/3	Forbes et al. 2017 (31)
C53.9	Cervix	0/27	0/10	3/46 (6.5)	—	—	0.6%	4/329 (1.2)	Forbes et al. 2017 (31)
C54.1	Endometrium	0/27	0/10	1/46 (2.2)	—	—	—	12/658 (1.8)	Forbes et al. 2017 (31)
C55	Uterus	0/27	0/10	3/46 (6.5)	—	—	2.9%	—	
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 missense 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 tumors 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). Supplemenatry 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 (Supplemenatry Table 2, available online); however, we identified six additional variants that have evidence suggesting pathogenicity outside the criteria (Supplemenatry 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 $240/729^9$. 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.

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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 Dalmasso, 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,

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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 of Biopathology, 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 (MJJ, 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); 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