Uveal Melanoma in *BAP1* Tumor Predisposition Syndrome: Estimation of Risk

NAKUL SINGH, RAHUL SINGH, RANDY CHRIS BOWEN, MOHAMED H. ABDEL-RAHMAN, AND ARUN D. SINGH

• PURPOSE: To estimate point prevalence of uveal melanoma in the patients with germline *BAP1* pathogenic variant.
• DESIGN: Cohort study with risk assessment using Bayesian analysis.
• METHODS: The point prevalence estimate was obtained by Bayes's rule of reverse conditional probabilities. The probability of uveal melanoma given that *BAP1* mutation exists was derived from the prevalence of uveal melanoma, prevalence of germline *BAP1* pathogenic variants, and the probability of germline *BAP1* pathogenic variant given that uveal melanoma is present. Confidence intervals (CIs) for each variable were calculated as the mean of Bernoulli random variables and for the risk estimate, by the delta method. The age at diagnosis and the gender of the uveal melanoma patients with *BAP1* germline pathogenic variants obtained from previous publications or from authors' unpublished cohort was compared with those in the Surveillance, Epidemiology, and End Results (SEER) database.
• RESULTS: The point prevalence of uveal melanoma in patients with the germline *BAP1* pathogenic variants in the US population was estimated to be 2.8% (95% CI, 0.88%-4.81%). In the SEER database, the median age at diagnosis of uveal melanomas was 63 (range 3-99 years) with a male-to-female ratio of 1.01:1. In comparison, uveal melanoma cases with *BAP1* germline pathogenic variants from the US population (n = 27) had a median age at diagnosis of 50.5 years (range 16-71).
• CONCLUSIONS: Quantification of the risk of developing uveal melanoma can enhance counseling regarding surveillance in patients with germline *BAP1* pathogenic variant. (Am J Ophthalmol 2021;224:172–177. © 2020 Elsevier Inc. All rights reserved.)

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THE *BAP1* TUMOR PREDISPOSITION SYNDROME (*BAP1*-TPDS, MIM 614327)[1,2] is a recently recognized autosomal dominant syndrome with predisposition to uveal melanoma and other primary cancers.[3] Meta-analysis of a global cohort of 181 families from the United States, United Kingdom, Australia, and several European countries carrying *BAP1* pathogenic (null) variants has confirmed 4 primary core tumor types of this syndrome that include uveal melanoma, mesothelioma, cutaneous melanoma, and renal cell carcinoma.[4] The reported frequencies are likely to represent a selection bias of the family and probands (for uveal melanoma; 36% in the proband, 15.9% in nonproband carriers, and 10.7% in relatives who were not genotyped) as the data are derived from the individuals or families with multiple cancer phenotypes.[4] Several recent reviews and comprehensive reports have emphasized decreasing frequency of tumors with increasing numbers of tested individuals.[4-6]

Uveal melanoma is not only the most frequent tumor observed in *BAP1*-TPDS, but it manifests in several distinct phenotypes such as bilateral tumors,[7] earlier age of onset,[4,6,8,9] and familial inheritance pattern (Table 1).[2,4,8,10-14] Even if there is selection bias in which the frequency of reported cases is overestimated, all these attributes are otherwise uncommon in uveal melanoma and should trigger genetic counseling and testing for *BAP1*-TPDS and other emerging genetic mutations.[8] Specifically, patients who have ≥2 *BAP1*-TPDS-associated tumors (uveal melanoma, cutaneous melanoma, mesothelioma, or renal cell carcinoma) or a single *BAP1*-TPDS-associated tumor and a first- or second-degree relative with ≥1 of these tumors should undergo germline *BAP1* mutation analysis to detect pathogenic variants.[15] Furthermore, germline *BAP1* pathogenic variants should be evaluated in uveal melanoma patients younger than 40 years, cutaneous melanoma less than 18 years, mesothelioma younger than 50 years, or renal cell carcinoma younger than 46 years.[15] Even so, only 20% to 25% of the familial cases can be attributed to the *BAPI* pathogenic variant, suggesting the role of other as yet unidentified genes.[10,16]

Although several studies have quantified the frequency of *BAP1* germline pathogenic variants in patients with uveal melanoma of approximately 2% (Table 2),[2,14,16,19–21] the frequency is higher in studies that have enriched the population of uveal melanoma patients with family histories of uveal melanoma, mesothelioma, cutaneous

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TABLE 1. *BAP1* Germline Pathogenic (Null) Variants: Phenotypes of Uveal Melanoma

Feature	Subtype
Tumor characteristics	
Multiple	Multifocal primary uveal melanoma[17]
Bilateral	Bilateral primary uveal melanoma[7]
Clinical features	
Occurrence at an earlier age	Uveal melanoma in young individual[4,6,8,9]
Familial occurrence	Familial uveal melanoma[2,4,8,10-13]
Metastasis	High risk of metastasis[2,4,11,14]
Systemic associations	
Skin lesions	BAP1-Inactivated Melanocytic Tumors (BIMT)[a]
Systemic tumors (RCC, Mesothelioma	Renal cell carcinoma, mesothelioma, skin melanoma, other cancers[2-4,8,12,13,18]
Family history	
Other cancers	Uveal melanoma, renal cell carcinoma, mesothelioma, skin melanoma and other cancers[2,4,8,12,13,18]

[a]Other nomenclatures: nevoid melanomas and highly atypical nevoid melanoma-like melanocytic proliferations (NEMMPs),[2] melanocytic BAP1-mutated atypical intradermal tumor (MBAIT), and atypical Spitz tumor (AST).[4,12,13]

melanoma, and related cancers (4.7%-8.0%).[4,10,22] What is not known, however, is the risk of developing uveal melanoma in a patient identified to have germline *BAP1* pathogenic variant. Such estimates are relevant for patients' counseling and to develop surveillance recommendations. In this study, using previously published data and available databases, we have mathematically estimated point prevalence of uveal melanoma in the patients with germline *BAP1* pathogenic variant.

METHODS

• **POINT PREVALENCE ESTIMATE:** The point prevalence estimate was obtained by Bayes' rule, which applies to reverse conditional probabilities (Supplement A). In simple terms, conditional occurrence of 2 events as A (uveal melanoma) and B (*BAP1* mutation), that is, probability of uveal melanoma given that *BAP1* mutation exists, represented as Pr(A | B) can be derived if the probability or prevalence of uveal melanoma [Pr(A)] and probability or prevalence of germline *BAP1* pathogenic variants [Pr(B)] are known. Additional variable necessary for calculation of Pr(A | B) is the reverse conditional probability of Pr(B | A), which is the probability of germline *BAP1* pathogenic variant given that uveal melanoma is present. Such a relationship can be written as the following equation$\Pr(A \mid B) = \Pr(B \mid A) \times \Pr(A)/\Pr(B)$

• **CONFIDENCE INTERVALS:** Standard errors for each quantity on the right-hand side was calculated as the mean of Bernoulli random variables (Supplement B). The standard error Pr(A | B) was the calculated by delta method (Supplement C).

• **AGE AND GENDER DISTRIBUTION:** The age at diagnosis and the gender of the uveal melanoma patients with *BAP1* germline pathogenic variants from the United States (n = 27) were obtained from previous publications or from Abdel-Rahman's unpublished cohort (Table 3) and was compared with those in the Surveillance, Epidemiology, and End Results (SEER) database (n = 10,678).[23]

RESULTS

THE QUANTITIES ON THE RIGHT-HAND SIDE OF THE ABOVE equation were obtained as follows.

Pr(B | A) is the probability of a *BAP1* germline pathogenic variants in an unselected uveal melanoma population, which was tabulated from the published values that ranged from 1.6% to 2% (Table 2).[2,14,16,19–21] We used the value of 8/507 (1.6%), which corresponded to a report from a United States based population.[14] The 95% CI was calculated as 0.80-3.08.

Pr(B) is the prevalence of *BAP1* pathogenic variants, which was estimated using gnomAD database,[24] a database of exome/whole genome sequences. Pathogenic variants were identified based on the ACGM/AMP (American College of Medical Genetics and Genomics and the Association for Molecular Pathology) criteria. These include nonsense, frameshift, canonical ±1 or 2 splice sites, and initiation codon variants.[25] We used a noncancer cohort as representation of population controls

TABLE 2. Frequency of Germline *BAP1* Pathogenic (Null) Variants in Uveal Melanoma

Author	Country	Year	Positive/Total n	Frequency, %	Selection Criteria
Aoude[19]	Australia	2012	2/66	3	Uveal melanoma at <50 years of age or bilateral uveal melanoma
Njauw[2]	USA	2012	4/100	4	Metastatic and non metastatic uveal melanoma
Repo[16]	Finland	2019	4/16	25	Familial uveal melanoma
			9/433	2	Unselected uveal melanoma
Turunen[20]	Finland	2016	3/148	2	Unselected uveal melanoma
Gupta[14]	USA	2015	8/507	1.6	Unselected uveal melanoma
Ewens[21]	USA	2018	11/142	8	Unselected uveal melanoma (N = 90), personal or family history of *BAP1*-TPDS (N = 52)
Boru[22]	USA	2019	6/34	18	Familial uveal melanoma.
			2/138	1.4	Uveal melanoma patients with strong personal or family history of cancer

BAP1-TPDS = *BAP1* tumor predisposition syndrome.

than with inclusion of the TCGA (The Cancer Genome Atlas) data set.

There were 134,187 noncancer subjects, with 5 of them having pathogenic variants, at the time of the search in May 2020 (Supplementary Table).[8,26] The frequency of the variants in non-Finnish European noncancer controls was 2/59,095. Therefore, the carrier frequency was calculated as 2/59,095 = 0.0034%. The 95% CI was calculated as 0.0009-0.0123.

Pr(A) is the prevalence of uveal melanoma, which was obtained from the SEER13 database using the statistical package, SEER*Stat 8.3.6.1.[27] The 24-year limited duration prevalence estimate was 0.0061% (2664/43,675,957) with a 95% CI of 0.0058%-0.0063%.

Pr(A | B) is the probability of a person developing uveal melanoma if they have a *BAP1* germline pathogenic variants.

$$= \Pr(B \mid A) \times \Pr(A)/\Pr(B)$$
$$= (8/507) \times (2664/43{,}675{,}957)/(2/59{,}095)$$
$$= 0.028$$
$$= 2.8\%$$

After calculating the standard errors for each quantity on the right-hand side of the above equation (Supplement B), the 95% CI for Pr(A | B) was 0.88%-4.81% (Supplement C) (Table 4).

In the SEER database, the median age at diagnosis of uveal melanomas was 63 (range 3-99 years) with a male-to-female ratio of 1.01:1. In comparison, uveal melanoma cases with *BAP1* germline pathogenic variants from the US population (n = 27) had median age at diagnosis of 50.5 (range 16-71 years) and male-to-female ratio of 0.69:1.0. and those reported by Walpole and associates[4] was 53.0 years in null variants carriers (Figure).

DISCUSSION

IN THIS STUDY, WE COMBINED THE ROBUST SEER CANCER registry data with the Genome Aggregation Database (gnomAD) and used Bayes's rule of reverse conditional probabilities to estimate point prevalence 2.8% (95% CI, 0.88%-4.81%) of uveal melanoma in patients with the germline *BAP1* pathogenic variants in the US population. We have calculated point prevalence estimate which is the prevalence of disorder at a specific point in time whereas values in the published literature refers to frequency estimates (lifetime prevalence) of uveal melanoma in patients with germline *BAP1* pathogenic variants. However, there are several reasons to consider our estimate only as the first step in risk assessment. Our results must be interpreted knowing the sources, methods, and underlying assumptions.

The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) provides cancer incidence, prevalence, and survival data through a broad geographic population-base registry that covers currently 35% of the US population. SEER database is the only comprehensive population-based data in the United States that provides the stage of cancer at the time of diagnosis and patient survival data. Consequently, within the United States, SEER contains the greatest longevity for population-based cancer statistics.[28] The database provided a 24-year prevalence of uveal melanoma of 0.0061% (61 per million) from more than 43 million patients in the SEER registry. Uveal melanoma was predominantly reported in Caucasians (96.9%).[29] When compared with incidence, the prevalence is approximately 10 times higher,[29] similar to previously published estimates (73 per million) derived using probability arguments.[30]

TABLE 3. The Age at Diagnosis and the Gender of the Uveal Melanoma Patients With *BAP1* Germline Pathogenic (Null) Variants in the United States (n = 31)

Age, y	Gender	Mutation Type	PubMed ID
50	Male	Frameshift deletion	26719535
58	Male	Frameshift insertion	22545102
53	Female	Nonsense	22545102
37	Male	Frameshift deletion	22545102
30	Female	INDEL-multiexon deletion	Unpublished
29	Male	Nonsense	30883995
18	Female	Frameshift deletion	25687217
67	Female	Frameshift deletion	4041196
49	Male	Frameshift deletion	4041196
62	Male	Nonsense	27718540
63	Female	Nonsense	27718540
Unknown	Unknown	Frameshift	25974357
Unknown	Unknown	Frameshift insertion	25974357
Unknown	Unknown	Frameshift insertion	25974357
59	Female	Nonsense	21874000
48	Female	Frameshift deletion	1005633
71	Male	Frameshift deletion	1005633
53	Female	Frameshift insertion	21051595
41	Female	Nonsense	4041196
62	Male	Frameshift insertion	22545102
51	Female	Nonsense	22545102
55	Male	Nonsense	22545102
57	Female	Nonsense	22545102
Unknown	Male	Nonsense	22545102
49	Male	Nonsense	4041196
22	Female	Frameshift deletion	27718540
52	Female	Nonsense	21941004
50	Female	Nonsense	21941004
16	Female	Whole Gene deletion	30883995
34	Female	Nonsense	Unpublished
64	Male	Frameshift	Unpublished

Age of onset of the disease was not available for 4 patients.
None of the variants were identified in the gnomAD database.

Somatic pathogenic variants in *BAP1* was initially identified as a marker for metastatic uveal melanoma.[11] Identifying a pathogenic variant in a family with multiple uveal melanoma cases as well as other cancers helped characterization of a novel hereditary cancer predisposition syndrome.[18] Overall, cancer patients have a significantly higher frequency of germline *BAP1* pathogenic variants than the general population, and there are data to suggest under-reporting of *BAP1-TPDS*.[26] The relative high-prevalence of the 4 cancers associated with BAP1-TPDS compared with the general population is likely due to genetic testing ascertainment bias, given that these families were screened for pathogenic variants because of strong family history of several tumors, including those associated with BAP1-TPDS.[4]

As yet, prevalence of *BAP1* pathogenic variants in population-based studies has not been determined. As a close approximation, we have used the Genome Aggregation Database (gnomAD) that harmonizes large-scale exome and genome sequencing data sets, which allowed us to identify the prevalence of *BAP1* mutant carriers.[24] Only pathogenic variants based on the ACGM/AMP criteria were included.[25] We chose the noncancer cohort as it is a more appropriate representation of population controls than the gnomAD cohort with inclusion of TCGA. Because the Finnish are one of the "founder populations," with enrichment of certain genetic alterations, we limited our analysis to non-Finnish European noncancer controls as a close match to the US population.

For calculating Pr(B|A), the probability of a *BAP1* germline pathogenic variants in an unselected uveal melanoma population, we used the value of 8/507 (1.6%) from a report from the United States (Table 2).[14] Although the race of individuals with uveal melanoma was not specified

TABLE 4. Estimation of Point Prevalence of Uveal Melanoma in Patients With *BAP1* Germline Pathogenic Variants

Variable	Symbol	Value		95% CI (%)	Source
		Original Fraction	Converted (%)		
Probability of *BAP1* germline mutation in unselected uveal melanoma population	Pr(B|A)	8/507	1.6%	0.80-3.08	Published value[14]
Prevalence of *BAP1* germline pathogenic variant in general population	Pr(B)	2/59095	0.0034%	0.0009-0.0123	gnomAD database[24]
Prevalence of uveal melanoma	Pr(A)	2664/43675957	0.0061%	0.0058-0.0063	SEER13 database[27]
Probability of uveal melanoma given that *BAP1* germline pathogenic variant exists	Pr(A|B)	0.0284	2.8%	0.88-4.81	Calculated

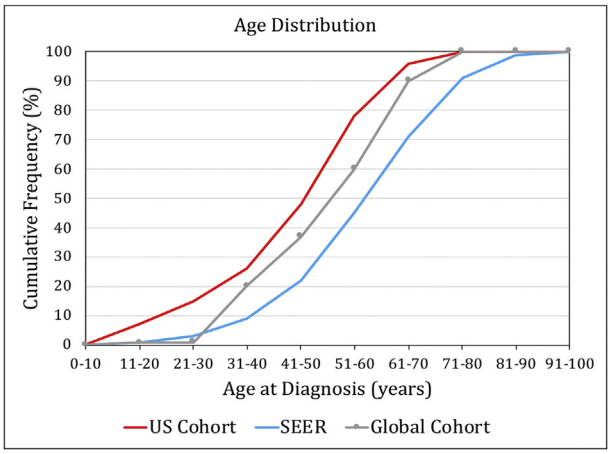

FIGURE. Cumulative frequency of age and at diagnosis. Uveal melanoma with *BAP1* germline pathogenic variants (US cohort, n = 27) manifested at younger age than those registered in the SEER database and those reported in the global cohort of null variant carriers (Walpole and associates[4]).

in the report, we can assume them all to be white because uveal melanoma is much more prevalent in the white population (98%).[29] Therefore, the point prevalence estimate is most applicable to the US white population.

In an international collaboration study, the age of onset in uveal melanoma with *BAP1* mutation was separated into variant carriers of either variants of uncertain significance or pathogenic variants.[4] Young patients (≤20 years of age) had pathogenic variants whereas patients with variants of uncertain significance did not develop *BAP1*-associated uveal melanoma until after the age of 40 years.[4] Compared with those in the SEER database,[29] the patients in the *BAP1* consortium group were younger, with a median age of 50.5 years (range 16-71), similar to that reported (53.0 years) in the meta-analysis by Walpole and associates (Figure).[4]

Given that uveal melanoma manifests predominantly in adults (with or without *BAP1* germline pathogenic variants), the effect of age on reported lifetime prevalence (as some variant carriers in the reported families were too young to have developed uveal melanoma) is probably an underestimation of the true lifetime prevalence, which would have a similar effect of underestimating the point prevalence. Given the small number patients in various age groups, we are unbale to generate age-specific point prevalence estimates. The point prevalence reported herein is most accurate when applied to a 50½-year-old patient (median age) with *BAP1* germline pathogenic variant. The point prevalence may underestimate or overestimate the true risk in patients who are younger or older than 50.5 years, respectively.

Estimation of the point prevalence of uveal melanoma in patients with *BAP1* germline pathogenic variants reported herein provides general guidance for surveillance for early detection of uveal melanoma. The screening guidelines are still evolving.[15] Current recommendation for ophthalmic screening is driven by early age of tumor diagnosis in at least 3 patients at age 16 years. All 3 were diagnosed with large tumors. This has led to recommendation of annual fundus examinations starting at age 11 years, which is 5 years earlier than the youngest diagnosed case.[1,6] Another group has suggested fundus examination starting at age 16 years (younger age considered if family member with early onset uveal melanoma) and biannual examination starting at age 30 years.[31]

In conclusion, we estimate point prevalence of uveal melanoma in patients with germline *BAP1* pathogenic variant at 2.8% (95% CI, 0.88%-4.81%). Quantification of the risk of developing uveal melanoma can enhance counseling regarding surveillance.

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