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Driver Mutations in Uveal Melanoma:

Associations With Gene Expression Profile and Patient Outcomes

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Abstract

IMPORTANCE—Frequent mutations have been described in the following 5 genes in uveal melanoma (UM): *BAP1*, *EIF1AX*, *GNA11*, *GNAQ*, and *SF3B1*. Understanding the prognostic significance of these mutations could facilitate their use in precision medicine.

OBJECTIVE—To determine the associations between driver mutations, gene expression profile (GEP) classification, clinicopathologic features, and patient outcomes in UM.

DESIGN, SETTING, AND PARTICIPANTS—Retrospective study of patients with UM treated by enucleation by a single ocular oncologist between November 1, 1998, and July 31, 2014.

MAIN OUTCOMES AND MEASURES—Clinicopathologic features, patient outcomes, GEP classification (class 1 or class 2), and mutation status were recorded.

RESULTS—The study cohort comprised 81 participants. Their mean age was 61.5 years, and 37% (30 of 81) were female. The GEP classification was class 1 in 35 of 81 (43%), class 2 in 42 of 81 (52%), and unknown in 4 of 81 (5%). *BAP1* mutations were identified in 29 of 64 (45%),

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Study concept and design: Garg, Bowcock, Harbour
Acquisition, analysis, or interpretation of data: Decatur, Ong, Garg, Anbunathan, Bowcock, Field
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GNAQ mutations in 36 of 81 (44%), *GNA11* mutations in 36 of 81 (44%), *SF3B1* mutations in 19 of 81 (24%), and *EIF1AX* mutations in 14 of 81 (17%). Sixteen of the mutations in *BAP1* and 6 of the mutations in *EIF1AX* were previously unreported in UM. *GNAQ* and *GNA11* mutations were mutually exclusive. *BAP1*, *SF3B1*, and *EIF1AX* mutations were almost mutually exclusive with each other. Using multiple regression analysis, *BAP1* mutations were associated with class 2 GEP and older patient. *EIF1AX* mutations were associated with class 1 GEP and the absence of ciliary body involvement. *SF3B1* mutations were associated with younger patient age. *GNAQ* mutations were associated with the absence of ciliary body involvement and greater largest basal diameter. *GNA11* mutations were not associated with any of the analyzed features. Using Cox proportional hazards modeling, class 2 GEP was the prognostic factor most strongly associated with metastasis (relative risk, 9.4; 95% CI, 3.1–28.5) and melanoma-specific mortality (relative risk, 15.7; 95% CI, 3.6–69.1) ($P < .001$ for both). After excluding GEP class, the presence of *BAP1* mutations was the factor most strongly associated with metastasis (relative risk, 10.6; 95% CI, 3.4–33.5) and melanoma-specific mortality (relative risk, 9.0; 95% CI, 2.8–29.2) ($P < .001$ for both).

CONCLUSIONS AND RELEVANCE—*BAP1*, *SF3B1*, and *EIF1AX* mutations occur during UM tumor progression in an almost mutually exclusive manner and are associated with different levels of metastatic risk. These mutations may have value as prognostic markers in UM.

Uveal melanoma (UM) is the most common primary cancer of the eye and has a propensity for fatal hematogenous metastasis.[1] Uveal melanomas can be stratified by gene expression profile (GEP) classification into 2 prognostically significant molecular classes. Class 1 UMs have a low metastatic risk, whereas class 2 UMs have a high metastatic risk.[2] Class 1 tumors retain a differentiated melanocytic phenotype, whereas class 2 tumors exhibit a dedifferentiated stem cell–like phenotype.[3] After it was shown by multiple groups that the prognostic accuracy of GEP outperforms clinicopathologic features and chromosomal gains and losses,[4–6] our group developed a GEP classifier for routine clinical use in which expression of 12 discriminating genes and 3 control genes is measured by quantitative polymerase chain reaction (PCR) on a microfluidics platform after targeted amplification. The result was an ultrahigh-performance assay that accurately measures gene expression from fine-needle biopsy samples that are too small to be reliably assessed using chromosome-based assays.[7] A prospective multicenter study[8] was performed, which confirmed the assay's prognostic accuracy and showed it to be superior to chromosome 3 testing. To date, this assay is the only prognostic test for UM ever to undergo prospective multicenter validation, which is required for a cancer biomarker to achieve the highest level I evidence according to the National Comprehensive Cancer Network Task Force on cancer biomarkers and the Tumor Marker Utility Grading System.[9]

Consequently, this assay has been made commercially available (DecisionDX-UM; Castle Biosciences, Inc), which has become the standard care for molecular prognostic testing in many ocular oncology centers.[10] The class 2 profile is strongly associated with inactivating mutations in the *BAP1* (OMIM 603089) tumor suppressor gene.[11] Four other genes are frequently mutated in UM, including *EIF1AX* (OMIM 300186), *GNA11* (OMIM 139313), *GNAQ* (OMIM 600998), and *SF3B1* (OMIM 605590).[12–16] Herein, we describe the associations between mutations in these 5 genes, GEP molecular class, clinicopathologic features, and patient outcomes in 81 primary UMs treated by enucleation.

Methods

Tissue Samples

This study was conducted in a Health Insurance Portability and Accountability Act of 1996-compliant manner in accord with the tenets of the Declaration of Helsinki. Approval was obtained from the Institutional Review Board of the University of Miami. Written informed consent was attained from each patient. Tumor samples were taken at enucleation between November 1, 1998, and July 31, 2014, from patients with UMs arising from the ciliary body, choroid, or both. Samples were snap frozen and stored at −80°C. Baseline clinical and pathologic information, as well as patient outcomes, were recorded.

Molecular Analyses

Molecular prognostic class assignments (class 1 or class 2) were obtained using a prospectively validated 12-gene classifier, as previously reported.[8] Genomic tumor DNA was prepared for sequencing with a purification kit (Wizard Genomic DNA; Promega) following the manufacturer's protocol, and target regions were amplified using PCR. The PCR was performed on a thermal cycler (Veriti; Applied Biosystems) in a reaction volume of 25 μL. Thermocycling was performed in the following conditions: initial denaturation at 95°C for 3 minutes and 30 rounds of amplification at 95°C for 15 seconds, touchdown PCR ramping from 65 to 55°C for 30 seconds, 72°C for 45 seconds, and a final extension step at 72°C for 7 minutes. The PCR products were visualized on a 2% agarose gel, and the remaining volume was purified using resin (SOPE; Edge BioSystems). One microliter of clean PCR product was then sequenced using a cycle sequencing kit (BigDye Terminator, version 3.1; Applied Biosystems) according to the manufacturer's protocol. Products were combined with a plate (Sephadex; GE Healthcare Bio-Sciences AB) for purification and loaded on a sequencer (ABI 3730; Applied Biosystems) for 25 cycles. Mutations in *BAP1* and *SF3B1* were initially identified with exome sequencing in a subset of tumors, and then the mutation status of additional samples was determined by Sanger sequencing, as previously described.[11] For this study, sequencing of *BAP1* included all coding regions and splice junctions, as previously described.[11] For *GNAQ* and *GNA11*, the 2 mutation hot spots at *R183* and *Q209* were sequenced.[14] For *SF3B1*, the mutation hot spot at *R625* was sequenced.[15] For *EIF1AX*, the hot spot regions containing reported mutations within exons 1 and 2 were sequenced.[16] Mutation calling was performed by aligning the genomic sequence traces using sequence analysis software to the hg19 genome build (Sequencher, version 4.1.2; Gene Codes).

Statistical Analysis

Statistical analysis was performed using a computer program (MedCalc, version 14.10.2; MedCalc Software bvba). The Fisher exact test was used to evaluate discrete dichotomous variables, Cox proportional hazards modeling was used to assess variables associated with metastasis and melanoma-specific mortality, and multiple regression was used for identifying clinicopathologic features associated with mutations in *BAP1*, *EIF1AX*, *GNA11*, *GNAQ*, and *SF3B1*. $P \leq .05$ was considered statistically significant.

Results

Baseline Data

Clinicopathologic and patient outcome data are summarized in Table 1. Molecular and genetic data are summarized in Figure 1. Among 81 participants, the GEP classification was class 1 in 35 (43%), class 2 in 42 (52%), and unknown in 4 (5%). Among those with DNA samples available for sequencing, *BAP1* mutations were identified in 29 of 64 (45%), *GNAQ* mutations in 36 of 81 (44%), *GNA11* mutations in 36 of 81 (44%), *SF3B1* mutations in 19 of 81 (24%), and *EIF1AX* mutations in 14 of 81 (17%). Sixteen of the mutations in *BAP1* were previously unreported in UM or any other cancer (Table 2). Six of the mutations in *EIF1AX*, found in 10 tumors, were novel in UM, and 2 of the 6 mutations were not previously reported in any cancer (Table 3). One of the novel mutations was a splicing change predicted to lead to loss of exon 2. During a mean follow-up of 34.1 months (median, 24.4 months) among 81 participants, metastasis was detected in 28 (35%), and melanoma-specific mortality occurred in 21 (26%). Among primary tumors that metastasized, mutations were detected in *BAP1* in 17 of 24 (71%), *GNAQ* in 13 of 28 (46%), *GNA11* in 12 of 28 (43%), *SF3B1* in 3 of 28 (11%), and *EIF1AX* in none.

Associations Between Mutations

Statistical analysis for the associations between different mutated genes was performed using the Fisher exact test, and the results are shown in Figure 2. Mutations in *GNAQ* and *GNA11* were mutually exclusive ($P < .001$). Mutations in *BAP1* and *SF3B1* were almost mutually exclusive ($P = .007$), as were mutations in *BAP1* and *EIF1AX* ($P = .03$). Mutations in *SF3B1* and *EIF1AX* were also almost mutually exclusive, with only one tumor having a mutation in both, but this association did not achieve statistical significance ($P = .17$).

Mutations vs Clinicopathologic Features

The associations between mutations and clinicopathologic features were analyzed for statistical significance using multiple regression analysis (eTable in the Supplement). *BAP1* mutations were associated with class 2 GEP ($P < .001$) and older patient age ($P = .007$). *EIF1AX* mutations were associated with class 1 GEP and the absence of ciliary body involvement ($P = .03$ for both). *SF3B1* mutations were associated with younger patient age ($P = .006$). *GNAQ* mutations were associated with the absence of ciliary body involvement ($P = .008$) and greater largest basal diameter ($P = .04$). *GNA11* mutations were not associated with any of the analyzed features.

Survival Analysis

Cox proportional hazards modeling was used to analyze the prognostic value of GEP class, gene mutations, and clinicopathologic features vis-à-vis time to metastasis and to melanoma-specific mortality (eTable in the Supplement). When all of these variables were considered together, class 2 GEP was the prognostic factor most strongly associated with metastasis (relative risk, 9.4; 95% CI, 3.1–28.5) and melanoma-specific mortality (relative risk, 15.7; 95% CI, 3.6–69.1) ($P < .001$ for both). After excluding GEP class, the presence of *BAP1* mutations was the factor most strongly associated with metastasis (relative risk, 10.6;

95% CI, 3.4–33.5) and melanoma-specific mortality (relative risk, 9.0; 95% CI, 2.8–29.2) ($P < .001$ for both).

Discussion

The identification of driver mutations has become a centerpiece of cancer precision medicine for diagnostic, prognostic, and therapeutic decision making in individual patients with cancer.[17] Thus far, only the following 5 genes have been found to be commonly mutated in UM: *GNAQ*, *GNA11*, *BAP1*, *SF3B1*, and *EIF1AX*. In this study, we found mutation frequencies of 89% (72 of 81) for *GNAQ* and *GNA11*, 45% (29 of 64) for *BAP1*, 23% (19 of 81) for *SF3B1*, and 17% (14 of 81) for *EIF1AX*, which is similar to previous reports.[11–16,18,19] Sixteen mutations in *BAP1* and 6 mutations in *EIF1AX* were previously unreported in UM. *GNAQ* and *GNA11* mutations were mutually exclusive with each other, they were present in similar proportions in class 1 and class 2 UMs, and they showed no association with tumor size or patient outcomes, suggesting that these mutations occur early in tumorigenesis.[12] Mutations in *BAP1*, *SF3B1*, *EIF1AX* were almost mutually exclusive with each other, suggesting that they may represent alternative downstream molecular events during tumor progression. Of particular interest, *BAP1* mutations were associated with poor prognostic factors (class 2 GEP and older patient age) and high metastatic risk. In contrast, *EIF1AX* and *SF3B1* mutations were associated with good prognostic factors (*EIF1AX* mutations with class 1 GEP and the absence of ciliary body involvement and *SF3B1* mutations with younger patient age).

Consistent with previous work,[8] class 2 GEP demonstrated prognostic accuracy that was superior to all other variables that were examined. After excluding GEP class, the next most accurate prognostic factor was the presence of *BAP1* mutations for both time to metastasis and to melanoma-specific mortality. These findings suggest that mutational analysis of *BAP1* may have value as a biomarker for poor prognosis, whereas *EIF1AX* and *SF3B1* may be useful markers of good prognosis, as previously suggested.[20] Our group recently reported that expression of the oncogene *PRAME* identifies class 1 UMs with intermediate metastatic risk, and these class 1 *PRAME*-positive UMs often harbor *SF3B1* mutations.[21] As such, we anticipate that *SF3B1* mutations will be associated with a newly identified subclass of UM associated with metastatic risk that is intermediate between UMs with *BAP1* mutations (high risk) and UMs with *EIF1AX* mutations (low risk).

A limitation of this study was that it included only UMs treated by enucleation, which was a matter of necessity to obtain adequate amounts of tumor tissue for the various molecular analyses that were performed. As such, the findings of our study and others that are limited to enucleation specimens may not be representative of smaller UMs that are treated by globe-sparing procedures. With recent advances in next-generation sequencing technology, all of these mutations can be detected from a single fine-needle aspiration biopsy sample. A second limitation was that tumor DNA adequate for sequencing all coding regions of the entire *BAP1* gene (which was not required for the other 4 genes) was available in only 64 of 81 (79%) participants. However, most other studies have relied on immunohistochemistry for the presence of the BAP1 protein as a surrogate marker for *BAP1* mutations,[22] which is associated with considerable false-positive and false-negative results, so our study provides

important new insights based on validated mutations. A third limitation was that we performed targeted sequencing of only the 5 commonly mutated genes. With multiple groups reporting their whole-exome sequencing results for UM, rare mutations in other genes have been found and will likely continue to be discovered.[11,16,23] The importance of these additional infrequent events will need to be assessed in future studies. A fourth limitation was the retrospective design and its effect on the clinical outcomes obtained. We are planning a prospective multicenter study to evaluate these and other genetic abnormalities in UM.

Conclusions

Five common mutations in UM have been identified to date. Two of these mutations (*GNAQ* and *GNA11*) occur early in tumor formation and are not associated with prognosis, whereas the other 3 (*BAP1*, *SF3B1*, and *EIF1AX*) likely occur later in tumor progression and are prognostically significant. These findings suggest that the mutation status of *BAP1*, *SF3B1*, and *EIF1AX* is of clinical value in the application of precision medicine in UM. Because the GEP classification was prognostically superior to the mutation status of these genes, the role of mutational analysis for prognostication will likely be as a supplement to GEP. While GEP remains the most accurate prognostic biomarker, it is possible that continued research will show that the inclusion of mutational information with GEP could increase the prognostic accuracy or suggest specific treatment choices, such as an MEK inhibitor for *GNAQ* and *GNA11* mutations or an epigenetic modulator for *BAP1* mutations.[24,25]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question

What are the associations between driver mutations, gene expression profile classification, clinicopathologic features, and patient outcomes in uveal melanoma?

Findings

This retrospective study of patients with uveal melanoma treated by enucleation found that *BAP1*, *SF3B1*, and *EIF1AX* mutations were almost mutually exclusive with each other. *BAP1* mutations were associated with poor prognostic factors, and *EIF1AX* and *SF3B1* mutations were associated with good prognostic factors.

Meaning

BAP1, *SF3B1*, and *EIF1AX* mutations may have value as prognostic markers in uveal melanoma.

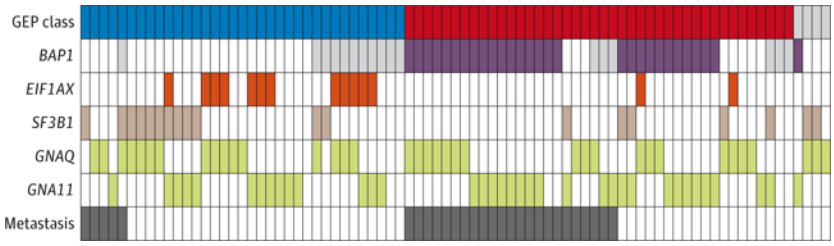

Figure 1. Overview of Driver Mutations in Uveal Melanoma, Gene Expression Profile (GEP) Classification, and Metastatic Status in 81 Uveal Melanomas

White boxes indicate mutation absent (wild type); colored boxes, mutation present; and gray box, information not available. For GEP class, blue boxes indicate class 1, and red boxes indicate class 2.

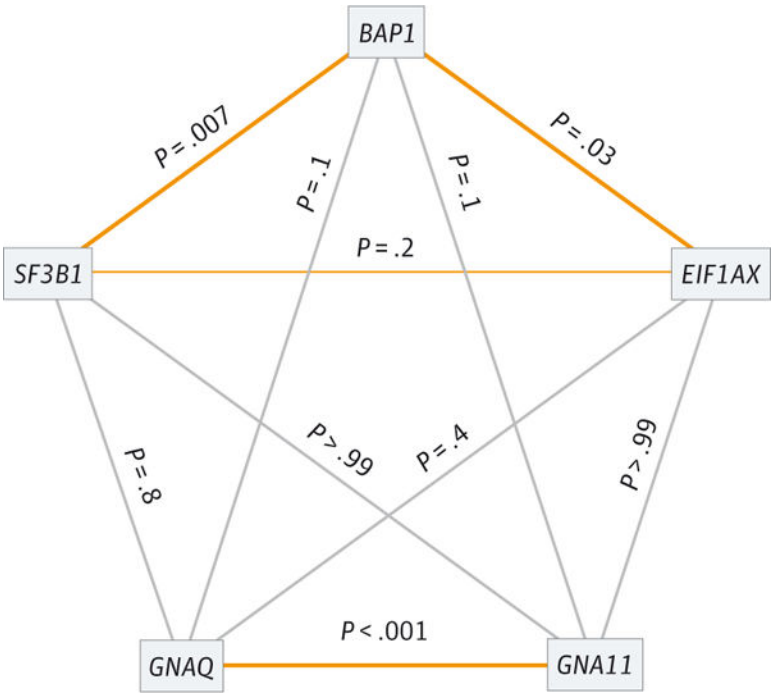

Figure 2. Molecular Association Plot Summarizing Statistical Associations Between Driver Mutations

P values indicate statistical significance of association between mutations in 2 genes connected by a given line. Thick orange lines indicate statistically significant inverse associations ($P \leq 05$), and gray lines indicate no statistically significant association ($P > .05$). The thin orange line indicates that mutations in *SF3B1* and *EIF1AX* were almost mutually exclusive, with only one tumor having a mutation in both, but this association did not achieve statistical significance ($P = .17$).

Table 1

Summary of Clinical and Pathologic Features in 81 Primary Uveal Melanomas

Variable	Summary Statistic (N = 81)
Age at diagnosis, y	
Mean	61.5
Median (range)	64.1 (18–92)
Sex, No. (%)	
Female	30 (37)
Male	51 (63)
Ciliary body involvement, No. (%)	
Yes	55 (68)
No	23 (28)
Not available	3 (4)
Pathologic cell type, No. (%)	
Spindle	17 (21)
Mixed	35 (43)
Epithelioid	22 (27)
Not available	7 (9)
Extraocular extension, No. (%)	
Yes	23 (28)
No	58 (72)
Largest basal tumor diameter, mm	
Mean	16.6
Median (range)	17.4 (5–24)
Tumor thickness, mm	
Mean	9.7
Median (range)	10.1 (1–22)
Metastasis, No. (%)	
Yes	28 (35)
No	53 (65)
Melanoma-specific mortality, No. (%)	
Yes	21 (26)
No	60 (74)
Follow-up, mo	
Mean	34.1
Median (range)	24.4 (0–241)

Table 2

Somatic *BAP1* Mutations Previously Unreported in Primary Uveal Melanoma

Tumor ID	GEP Class	Metastasis	Mutation Position	Mutation Nucleotide Change (hg19)	Predicted Functional Change	Mutation Type	Exon Involved
MM004	NA	No	3:52437275	T→A	p.Q590L	Missense	14
MM129	2	Yes	3:52442047	A→C	p.L101R	Missense	5
MM137	2	Yes	3:52443889–52443927	delATTCATCTTCCCGCGGGGCGGCCCCTCAGCGCCATGTCC	Removal of start site	Deletion	5′ Untranslated region, exon 1
MM144	2	No	3:52442595	delG	p.F50LfsX22	Premature termination	4
MM151	2	Yes	3:52440918–52440925	delAGGGCCCT	Deletion of splice donor and 6 base pair of exon	In-frame deletion	Splice donor, exon 8
MM161	2	No	3:52439813–52439814	delCT	p.R300GfsX6	Premature termination	10
MM162	2	Yes	3:52537431; 3:52437433	C→G; delA		Missense	Splice donor, exon 14
MM173	2	No	3:52441415	C→A	p.R146M	Missense	7
MM175	2	No	3:52439825–52439845	delAGCACCAGCGGGGACTTGTTG	p.S289RfsX41	Premature termination	10
MM179	2	Yes	3:52443876	C→A	p.E007*	Premature termination	1
UMM002	2	Yes	3:52437252–52437291	delGGCTGCTGGACCCCTGGCTGCCTTGGATTGGTCTGATGGA	p. S585Qfs*19	Deletion	14
UMM004	2	No	3:52442542	T→C	p.D68G	Missense	4
UMM006	2	No	3:52441943–52442093	delTGTGAGCCAGGATGAAGGCACTGCAGCCTACCTCAGGGCT-GAAACCCTTG GTGAAGTCCTTCATGCGACTCAGGGTGGGTCCCAGGTCCAC-GCTGCTGCA GTTCAGGAGCACGCTCAGCAAGGCATGAGTTGCACAAGAGTTGGGTATCAG	p.(L86_E125del)	Deletion	5
UMM007	2	No	3:52438516	A→C	p.Y401*	Premature termination	12
UMM009	2	No	3:52439927	delA	p.L262Rfs*2	Premature termination	10
UMM010	2	No	3:52441215	delC	p.L186*	Premature termination	7

Abbreviations: fs, frameshift; GEP, gene expression profile; ID, identification; NA, not available; p, protein.

Table 3

Somatic *EIF1AX* Mutations Previously Unreported in Primary Uveal Melanoma

Tumor ID	GEP Class	Metastasis	Mutation Position	Mutation Nucleotide Change	Predicted Functional Change	Mutation Type	Exon Involved	Cosmic ID
MM041	1	No	X:20156731	C→A	p.G9V	Missense	2	NA
MM068	1	No	X:20156732	C→G	p.G9R	Missense	2	COSM3372214
MM074	1	No	X:20156732	C→G	p.G9R	Missense	2	COSM3372214
MM078	2	No	X:20156731	C→A	p.G9V	Missense	2	NA
MM082	1	No	X:20156731	C→T	p.G9D	Missense	2	COSM3372213
MM094	1	No	X:20156737	T→C	p.K7R	Missense	2	COSM3560352
MM105	1	No	X:20156742	T→C	Splice acceptor	Splice site	Intron 1	NA
MM131	1	No	X:20156731	C→T	p.G9D	Missense	2	COSM3372213
UMM003	1	No	X:20156734	C→T	p.G8E	Missense	2	COSM4829462
UMM009	2	No	X:20156732	C→G	p.G9R	Missense	2	COSM3372214

Abbreviations: GEP, gene expression profile; ID, identification; NA, not available.