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Germline *BAP1* Alterations in Familial Uveal Melanoma

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Abstract

Uveal melanoma (UM) is the most commonly diagnosed primary intraocular tumor in adults. Familial UM (FUM), defined as two or more family members diagnosed with UM, is rare and estimated at less than 1% of all UM. Currently, *BAP1* is the only gene known to contribute significant risk for UM. In this study we aimed to estimate the frequency of *BAP1* mutation in FUM and to characterize the family and personal histories of other cancers in these families. We identified 32 families with FUM, including seven families previously reported by our group. *BAP1* mutation testing was carried out by direct sequencing of the coding exons and the adjacent untranslated regions of the gene. Germline deletion and duplication analysis of *BAP1* was assessed by multiplex ligation-dependent probe amplification (MLPA). Germline *BAP1* mutations were found in 6/32 (19%) families. No deletions or duplications were identified in any of the 24 samples tested by MLPA. Combined with published studies, the frequency of *BAP1* mutations was 14/64 (22%) in FUM. FUM families without *BAP1* mutations have distinct family histories with high rates of prostate cancer in first- and second-degree relatives. It is likely that additional genes conferring risk for FUM exist. It is important to understand key shared features of FUM to focus future research on identifying these additional tumor predisposition syndromes. Though *BAP1* should be tested first in these families, FUM families without *BAP1* mutation should be explored for additional predisposition genes.

INTRODUCTION

Uveal melanoma (UM) is the most commonly diagnosed primary intraocular cancer in adults (Singh et al., 2011). While the disease is relatively rare in the general population, with an incidence rate of 5.1 per million, there is strong support for the role of heredity in familial UM (FUM), defined as two or more family members diagnosed with UM (Singh et al., 1996b, 2011; Abdel-Rahman et al., 2010). The chance of two or more first degree relatives

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with UM occurring in a family by chance is very low and estimated at 0.00018 (Singh et al., 1996c). Approximately 12% of patients with UM have family history characteristics suggestive of a hereditary syndrome (Abdel-Rahman et al., 2010), and evidence of an autosomal dominant mode of inheritance has been suggested (Singh et al., 1996b). In addition, multiple reports have described the association of UM and other cancers, especially cutaneous melanoma (CM) and breast cancer (Henkind and Roth, 1971; Rednam et al., 1981;Harvey and Brinton, 1985; van Hees et al., 1998; Hemminki and Jiang, 2001; Diener-West et al., 2005b; Bergman et al., 2006). Only a few genes that play a role in FUM have been identified, of which the BRCA-associated-protein 1 (*BAP1*) gene appears to have the strongest association. The frequency of *BAP1* mutations in FUM is currently unknown, however, complicating genetic testing decisions in high-risk families. Furthermore, currently known genes account for only a fraction of hereditary UM, and it is likely that additional genes exist. A close analysis of families with multiple UM diagnoses can uncover shared features that may point to new cancer predisposition syndromes. Thus, the aims of this study were to estimate the prevalence of *BAP1* mutations and deletions or duplications in FUM, and to demonstrate features of these families that may aid in the discovery of new genes predisposing to UM and other cancers.

MATERIALS AND METHODS

Germline Mutation Testing

Data on 25 previously unreported families with multiple individuals diagnosed with UM were included (Table 1). Three of these 25 families were accrued at the Cole Eye Institute at the Cleveland Clinic Foundation and the remaining families were accrued at The Ohio State University. Probands were accrued prospectively and personal and family cancer histories were collected in addition to peripheral blood. Samples were sequenced for all coding exons of *BAP1* and the 5'untranslated region (UTR) according to our previously described protocol (Abdel-Rahman et al., 2011a). The following three primer sets were used to sequence the 3'UTR (F1 ACATTCCTTCCATCGTGCCC, R1 TGGGACACCCTACTCCCAAC, F2 AGGTCCTTGTATCATGCCACG, R2: GCAACCCTGTCTCTGCTACC, F3: GTT CTAGGGCTCTTCGCCTTC and R3: AGCAACCACAGGAGGGTTCAT). Sequences were aligned per the reference sequence provided by GenBank accession number NM_004656.2. All research was approved by the Institutional Review Boards at The Ohio State University and Cole Eye Institute and informed consents were obtained prior to testing. Results were combined with those from five FUM families previously reported by our group (Abdel-Rahman et al., 2011a; Pilarski et al., 2014; Cebulla et al., 2015) for a total $n = 32$.

Deletion/Duplication Analysis

Deletions and duplications were assessed in 24 patients with no detected germline *BAP1* sequence mutation utilizing multiplex ligation-dependent probe amplification analysis (SALSA MLPA P417 *BAP1* probemix, MRC-Holland) according to the manufacturer's protocol.

Literature Review

We conducted a literature review of all English language peer-reviewed articles on FUM. A PubMed search was directed with the key words “familial uveal melanoma,” “familial ocular melanoma,” and “familial eye melanoma”. Excluding reports by our own group, a total of 28 articles describing 115 independent families with multiple UM diagnoses were identified (https://docs.google.com/spreadsheets/d/1rb0qu-4d_rPjW7qs6G1-GyfE-sepWtas40QM230_4Dfg/edit?usp=sharing: Lynch et al., 1968; Green et al., 1978; Oosterhuis et al., 1982; Canning and Hungerford, 1988; Jay and McCartney, 1993; Young et al., 1994; Wang et al., 1996; Singh et al., 1996a, 1996b, 2000; van Hees et al., 1998; Soufir et al., 2000; Krygier et al., 2001; Hearle et al., 2003b; Kodjikian et al., 2003; Barker-Griffith and Streeten, 2004; Jonsson et al., 2005; Smith et al., 2007; Njauw et al., 2012; Wadt et al., 2012, 2014; Aoude et al., 2013; Cheung et al., 2013; Hoiom et al., 2013; Popova et al., 2013; Maerker et al., 2014; Gupta et al., 2015; Turunen et al., 2016). Out of those, 39 families had undergone *BAP1* testing; seven of these were single case reports. Single case reports were excluded from our assessment of the frequency of *BAP1* mutation in familial cases to avoid introducing selection and testing bias. Thus, 32 FUM families with known *BAP1* mutation status, from three published series of unselected families, were combined with our series for a meta-analysis to estimate the frequency of *BAP1* mutation in FUM.

Out of the 115 reported families no genetic testing was reported in 59 probands; genetic testing results for one or more of other candidate genes (*CDKN2A, CDKN2B, CDK4* and *BRCA2*), but not *BAP1*, were available in 16 additional probands (Singh et al., 1996a; Soufir et al., 2004; Hearle et al., 2003a). No mutation was identified in any of these candidate genes. In one familial case a mutation in *TP53* was suggested based on immunohistochemistry assessment (Jay and McCartney, 1993). To evaluate the frequency of other cancers in FUM and effect of *BAP1* mutation status, we combined data from our series with that from the literature. We excluded the family with putative *TP53* mutation as well as those missing full reports of family histories. As such, only 53 out of the 115 families from the literature were used in the family history analysis (Lynch et al., 1968; Green et al., 1978; Oosterhuis et al., 1982; Young et al., 1994; Singh et al., 1996b, 2000; van Hees et al., 1998; Soufir et al., 2000; Krygier et al., 2001; Hearle et al., 2003b; Kodjikian et al., 2003; Jonsson et al., 2005; Smith et al., 2007; Njauw et al., 2012; Wadt et al., 2012, 2014; Aoude et al., 2013; Cheung et al., 2013; Hoiom et al., 2013; Popova et al., 2013; Maerker et al., 2014; Gupta et al., 2015; Turunen et al., 2016). A two-tailed Fisher’s exact test was used to measure the statistical significance of variance in family cancer histories.

Systematic data abstraction from the articles included family history of cancer, age of cancer diagnosis, degree of relation, and genetic testing results. Unpublished material was not consulted and supplemental material was consulted if available. Data were collated and analyzed by the authors to produce relevant results.

RESULTS

Frequency of *BAP1* Alterations in FUM

The mean age of primary uveal melanoma diagnosis in probands in our cohort of 32 families was 54 years (range 18–76). Our cohort had 56% female probands. Among probands, 11/32 (34%) had a second primary cancer diagnosis in addition to UM.

Out of the 25 unreported FUM we identified two patients FUM327 and FUM340 with germline truncating mutation in *BAP1* (Table 1). Combined with our previously published families the overall *BAP1* mutations frequency in our cohort was 6/32 (19%; Table 1). Deletions and duplications were successfully assessed by MLPA in 24 patients, with no such alterations detected in *BAP1.* A variant in the 3'UTR, rs123598, was identified in 3/28 (11%) patients. The variant has been reported in the 1000 Genomes Project with a global minor allele frequency (MAF) of 0.03 (A) and Caucasian MAF of 0.06 suggesting that this is a benign variant.

The *BAP1* mutation frequency in our cohort is similar to the frequency of *BAP1* mutations in FUM (20–29%) found by other groups in smaller cohorts. Popova et al. found a *BAP1* mutation frequency of 29% in a cohort of 14 families, while Gupta et al. and Turunen et al. found frequencies of 20% and 25% in cohorts of 10 and eight families respectively (Popova et al., 2013; Gupta et al., 2015; Turunen et al., 2016). These previous reports sequenced the coding region of *BAP1* and no reports of germline deletions or duplications were available. When our data are combined with these previous reports the frequency of *BAP1* mutation in FUM is estimated to be approximately 22% (95% CI 21–23%).

Family Cancer History in FUM

Family history information collected in our prospective cohort of 32 families ranged from three to five generations. Thirteen out of all 32 families (41%) and 10 out of our 26 *BAP1* mutation-negative families (38%) had a second UM diagnosis in a first-degree relative. This is approximately consistent with an autosomal dominant inheritance pattern as has been suggested (Singh et al., 1996b). Fifteen of the 53 FUM families in the literature with adequate family cancer history information had a *BAP1* mutation, 10 families tested negative, and 28 families were untested. Table 2 summarizes the cancer family histories reported in families with and without *BAP1* mutations, in our cohort and in the literature. As expected, families with *BAP1* mutations have significantly higher rates of malignant mesothelioma (MMe, $p = 0.0001$) and renal cell carcinoma (RCC, $p = 0.0003$). Interestingly, higher rates of lung cancer approached significance ($p = 0.09$) in families with *BAP1* mutation while higher rates of CM, a cancer with known predisposition conferred by *BAP1*, did not reach statistical significance ($p = 0.2114$). In FUM families without *BAP1* mutation, the family history rates of MMe and RCC are significantly lower.

DISCUSSION

BAP1 has been identified as a significant UM predisposition gene. However, until now there have been few estimates as to the prevalence of germline *BAP1* mutations in FUM. We estimate that *BAP1* mutations are present in approximately 22% of FUM families overall,

compared with 2–4% in unselected UM (Gupta et al., 2015; Turunen et al., 2016). However, the history of other cancers in the family can significantly alter the chance of finding a *BAP1* mutation. In FUM families with no other history of *BAP1*-associated cancers, the chance of *BAP1* mutation may be as low as 8%. Conversely, the chance of *BAP1* mutation in FUM families with additional family history of CM, MMe, and/or RCC can be as high as 50%. Families with multiple UM diagnoses should be referred for germline genetic testing for *BAP1*, even though it explains only a subset of FUM. We did not identify deletions or duplications in any of the samples tested, suggesting that large gene rearrangement is not a major contributor to germline *BAP1* alterations.

There are a number of characteristics that FUM families share that point to the existence of hereditary cancer syndromes beyond *BAP1*. Approximately 38% of the *BAP1* negative families have two UM diagnoses in first-degree relatives, consistent with autosomal dominant inheritance and suggesting that relatives are at high-risk for developing tumors. In addition, FUM families appear to have a higher cancer burden overall. For instance, the rate of second primary cancers in the probands was about 3-fold higher than in unselected UM (31% versus 10%; Diener-West et al., 2005a). The tumor spectrum reported in the family histories is distinct between those that have germline *BAP1* mutations and those that do not. Specifically, families without *BAP1* mutations have lower rates of MMe and RCC as compared to those with *BAP1* mutations. Comparison to rates of these cancers expected in family histories in the general population is difficult, however. It is also unclear if there is a strong association between FUM, breast cancer, and CM in these families, though this has been previously reported (Henkind and Roth, 1971; Rednam et al., 1981; Harvey and Brinton, 1985; van Hees et al., 1998; Hemminki and Jiang, 2001; Diener-West et al., 2005b; Bergman et al., 2006). Interestingly, lung cancer may be a minor phenotype of the *BAP1* syndrome, though this should be confirmed in future studies. One of the major challenges in evaluating published data on FUM is that many of the publications either listed only UM patients, UM but no other cancers or described only *BAP1* positive FUM but provided no information on those with no *BAP1* mutation. Establishing a registry for this rare cancer that captures such crucial information is highly warranted. Fortunately, there is a serious effort in the ocular oncology community in the US and other parts of the world to establish such a registry.

In one of the FUM families we confirmed *BAP1* mutation in two family members (FUM036). In other families another family member with UM was not available for testing; however in several we confirmed *BAP1* mutations in family members with other cancers. One of the mutations identified c.1717_1717delC, p.Leu573fs_3 (FUM152) was recently reported as a founder mutation in several families in North America (Carbone et al., 2015; Cebulla et al., 2015). A synonymous rare variant rs71651686 in linkage disequilibrium with the founder mutation was also observed in the proband of FUM152 suggesting that the FUM152 is linked to the same founder mutation. We should note that we recently identified another family with the same founder mutation and the rs71651686 variant (unpublished data) and the family presented with UM and other cancers linked to the *BAP1*-tumor predisposition syndrome. This suggests that this founder mutation is likely underdiagnosed in the US.

Few genes have previously been implicated in predisposition for UM. The best described is *BAP1*, with UM risk estimated at up to 29% (Rai et al., 2016). UM is the most frequent and earliest presenting cancer (age 16) reported in the *BAP1* tumor predisposition syndrome. Interestingly, although UM was the first cancer-type associated with the gene, several other cancers were found to be associated with the syndrome upon further research (Harbour et al., 2010; Abdel-Rahman et al., 2011a; Testa et al., 2011; Wiesner et al., 2011). As such, what first appeared as a narrow phenotype was actually a rather broad tumor predisposition syndrome. *BRCA2*, although primarily associated with breast and ovarian cancer risk, has been implicated in risk for UM (Sinilnikova et al., 1999; Iscovich et al., 2002; Scott et al., 2002; Hearle et al., 2003b; Liede et al., 2004), with estimated risk between 0 and 4.8% in males (Liede et al., 2004). The CM gene *CDKN2A* has also been implicated in predisposition to UM, with a single case of a pathogenic mutation in a UM patient with family history of CM (Kannengiesser et al., 2003). Eight of our families were also tested for *CDKN2A, CDKN2B* and *CDK4*, Table 1. One of them, FUM011, showed a variant of uncertain significance that is predicted benign (Abdel-Rahman et al., 2011b). There has been one case report associating *TP53* with UM (Jay and McCartney, 1993), but the specific mutation was not identified. In addition, linkage studies have also identified a locus at 9q21.32 that may segregate with the UM phenotype (Jonsson et al., 2005; Bishop et al., 2009).

In conclusion, the overall frequency of *BAP1* mutation in FUM is estimated at 22%, although this can vary between 8% and 50% depending on additional family history of CM, MMe, and/or RCC. While *BAP1* is the most frequent known genetic cause of FUM, it is likely that other genes exist. Future research should focus on FUM families to identify novel cancer predisposition syndromes and genes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Summary of Personal History of Cancer and Family History of Uveal Melanoma in Patients Included in the Study

Family/ Case #	Proband UM (age/sex)	Proband (other cancer/age)	Family history UM (Age/Sex)	BAP1 Status	Reference
FUM036[a]	52/F	Lung Ca	Maternal first cousin (50F), Maternal first cousin once removed (N/A M)	c. 799C>T, p. Gly267*, c.650-26T>A c. 931 170A>G, c.931 1117_118delCC, rs28997577, c. 1891-30G>C	Abdel-Rahman et al., 2011
FUM064[a]	41/F	Liver Ca (42), Soft Tissue Carcinoma (42)	Father (49M), Paternal 3rd cousin (N/A F)	c.2050C>T, p.Gln684*	Pilarski et al., 2014
FUM104	67/F	Colon Ca (71)	Son (49M), Maternal uncle (N/A M)	c.1180_1183delACTC, p.Tyr627Tyrfs* 9	Pilarski et al., 2014
FUM152	18/F	None	Father (45M)	c. 1717delC, p.L573fs* 3, rs71651686	Cebulla et al. 2015
FUM327	62/M	None	Maternal first cousin (N/A F), Maternal grandfather (N/A M)	c.1938T>A, Y646*	This study
FUM340	22/F	None	Paternal great uncle (40's M), Paternal great uncle (40's M), Paternal second cousinonce-removed (40's F)	c.458_459delCT P153Rfs* 7	This study
FUM011[a]	55/M	Cutaneous melanoma (63)	Mother (62F)	WT	Abdel-Rahman et al., 2010
FUM012[a]	27/M	None	Maternal 1st cousin once removed (10–19M)	WT	Abdel-Rahman et al., 2011
FUM033[a]	37/F	None	Paternal aunt (N/A F)	WT	Abdel-Rahman et al., 2011
FUM058[a]	74/F	None	Maternal first cousin (50's M)	WT	This study
FUM062	42/F	None	Paternal first cousin once removed (58M)	WT	This study
FUM073	72/M	None	Brother (62M)	WT	This study
FUM074	73/M	None	Father (58M)	WT	This study
FUM075	51/M	None	Maternal aunt (N/A F)	WT	This study
FUM144[a]	76/M	None	Paternal second cousin (N/A F)	WT	This study
FUM230	67/F	Renal Cell Ca (57)	Unknown relative (N/A M)	WT	This study
FUM306	46/F	Uterine Ca (51)	Maternal aunt (55F)	WT	This study
FUM312	64/F	None	Maternal first cousin (50F)	WT	This study
FUM315	66, 78/F (ipsilateral)	None	Paternal first cousin (N/A M), Paternal first cousin (N/A M)	WT	This study
FUM317	38/F	Uterine Ca (68)	Father (75M)	WT	This study
FUM318	51/M	None	Paternal 2nd cousin once removed (N/A M)	WT	This study

Family/ Case #	Proband UM (age/sex)	Proband (other cancer/age)	Family history UM (Age/Sex)	BAP1 Status	Reference
FUM319	44/M	Skin Ca (30's)	Maternal great uncle (60's–70's M), Maternal 1st cousin (50's M)	WT	This study
FUM326	54/F	None	Maternal grandfather (70'sM)	WT	This study
FUM328	76/M	None	Brother (50's M)	WT	This study
FUM330	48/F	None	Father (50M)	WT	This study
FUM331	51/M	Thyroid Ca	Maternal grandmother (N/A F)	WT	This study
FUM332	49/F	Breast Ca	Brother (45M)	WT	This study
FUM329	75/M	None	Maternal 3rd cousin (75F)	WT	This study
FUM313	36/M	None	Paternal aunt (N/A F)	WT	This study
CCE 4516	69/M	None	Mother (80F)	WT	This study
CCE 4518	N/A/F	Breast Ca (N/A)	Mother (N/A F)	WT	This study
CCE 4587	62/M	None	Son (32M)	WT	This study

WT:wild type, Ca: Cancer.

[a]These patients were also tested for *CDKN2A*, *CDKN2B* and *CDK4*. FUM011 showed a VUS in *CDKN2A* (chr9:21994399G>A).

TABLE 2

Non-UM Cancer Prevalence in Proband and First- and Second-Degree Relatives in Familial UM Families, With Comparison of Overall Cancer Rates Between *BAP1*-Positive and *BAP1*-Negative Families

	Prospective cohort (*n* = 32)		Literature (*n* = 53)[a]			Combined (*n* = 57)		
Family history	***BAP1*+ Mut (*n* = 6)**	***BAP1* WT (*n* = 26)**	***BAP1* + Mut (*n* = 15)[b]**	***BAP1* WT (*n* = 10)[c]**	**Untested (*n* = 28)**	***BAP1* + Mut (*n* = 21)**	***BAP1* WT (*n* = 36)**	**p-value (Fisher's exact test)**
Basal cell carcinoma	0	12%	27%	0	7%	19%	8%	0.4042
Breast cancer	33%	19%	20%	20%	14%	24%	19%	0.7439
CM	33%	15%	40%	30%	21%	38%	19%	0.2114
Cholangiocarcinoma	0	0	7%	0	4%	5%	0	0.3684
Colon cancer	17%	19%	7%	10%	7%	10%	17%	0.6966
Lung cancer	67%	23%	40%	30%	14%	48%	25%	0.0918
Malignant Mesothelioma	50%	0	33%	0	4%	38%	0	**0.0001**
Meningioma	17%	0	0%	0	0	5%	0	0.3684
Pancreatic cancer	17%	0	0%	10%	0	5%	3%	1
Prostate cancer	17%	35%	7%	20%	0	10%	31%	0.1027
Renal cell carcinoma	17%	4%	47%	0	0	43%	3%	**0.0003**

[a] 115 families were reported in the literature, however, sufficient family history to assess other cancers in the family was only available for 53 families (Aoude et al., 2013; Cheung et al., 2013; Green et al., 1978; Gupta et al., 2015; Hearle et al., 2003a,b; Hoiom et al., 2013; Jonsson et al., 2005; Kodjikian et al., 2003; Krygier et al., 2001; Lynch et al., 1968; Maerker et al., 2014; Njauw et al., 2012; Oosterhuis et al., 1982; Popova et al., 2013; Singh et al., 2000; Singh et al., 1996b; Smith et al., 2007; Soufir et al., 2000; Turunen et al., 2016; van Hees et al., 1998; Wadt et al., 2012; Wadt et al., 2014; Young et al., 1994).

[b] Seven studies didn't report family histories of cancer other than uveal melanoma.

[c] Only one study reported family histories of *BAP1* negative familial UM patients. Mut: mutant, WT: wild type.