VOLUME 36 · NUMBER 28 · OCTOBER 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Frequency of Germline Mutations in Cancer Susceptibility Genes in Malignant Mesothelioma

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Published at jco.org on August 16, 2018.

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0732-183X/18/3628w-2863w/$20.00

ABSTRACT

Purpose
The aim of the current study was to determine the prevalence and clinical predictors of germline cancer susceptibility mutations in patients with malignant mesothelioma (MM).

Methods
We performed targeted capture and next-generation sequencing of 85 cancer susceptibility genes on germline DNA from 198 patients with pleural, peritoneal, and tunica vaginalis MM.

Results
Twenty-four germline mutations were identified in 13 genes in 23 (12%) of 198 patients. *BAP1* mutations were the most common (n = 6; 25%). The remaining were in genes involved in DNA damage sensing and repair (n = 14), oxygen sensing (n = 2), endosome trafficking (n = 1), and cell growth (n = 1). Pleural site (odds ratio [OR], 0.23; 95% CI, 0.10 to 0.58; $P < .01$), asbestos exposure (OR, 0.28; 95% CI, 0.11 to 0.72; $P < .01$), and older age (OR, 0.95; 95% CI, 0.92 to 0.99; $P = .01$) were associated with decreased odds of carrying a germline mutation, whereas having a second cancer diagnosis (OR, 3.33; 95% CI, 1.22 to 9.07; $P = .02$) significantly increased the odds. The odds of carrying a mutation in *BAP1* (OR, 1,658; 95% CI, 199 to 76,224; $P < .001$), *BRCA2* (OR, 5; 95% CI, 1.0 to 14.7; $P = .03$), *CDKN2A* (OR, 53; 95% CI, 6 to 249; $P < .001$), *TMEM127* (OR, 88; 95% CI, 1.7 to 1,105; $P = .01$), *VHL* (OR, 51; 95% CI, 1.1 to 453; $P = .02$), and *WT1* (OR, 20; 95% CI, 0.5 to 135; $P = .049$) were significantly higher in MM cases than in a noncancer control population. Tumor sequencing identified mutations in a homologous recombination pathway gene in 52% (n = 29 of 54).

Conclusion
A significant proportion of patients with MM carry germline mutations in cancer susceptibility genes, especially those with peritoneal MM, minimal asbestos exposure, young age, and a second cancer diagnosis. These data support clinical germline genetic testing for patients with MM and provide a rationale for additional investigation of the homologous recombination pathway in MM.

J Clin Oncol 36:2863-2871. © 2018 by American Society of Clinical Oncology

INTRODUCTION

Malignant mesothelioma (MM) is an aggressive malignancy with poor survival.[1,2] MM develops in the pleura (MPM; 80% to 95%), the peritoneum (MPeM; 5% to 20%), and, rarely, the pericardium and tunica vaginalis of the testis.[3,4] Globally, MM mortality has been estimated at 9.9 per million with large regional variations that correlate with asbestos use.[5] Both MPM and MPeM are strongly associated with prior asbestos exposure.[2] Heavy occupational exposure or long-standing, low-level environmental exposure increases the risk, yet only a fraction of exposed individuals develop MM.[6,7] Other patients with MM have no identifiable history of exposure to asbestos or asbestiform minerals. These data suggest that individuals who are not resistant to the carcinogenic effects of asbestos and those who develop MM with minimal or no asbestos exposure may have an underlying inherited susceptibility.

Identification of germline mutations in *BAP1* in families with multiple relatives with MM[8] and studies that have demonstrated more frequent and accelerated MM development in mice that carry one abnormal copy of *Bap1* exposed to even low levels of asbestos compared with wild-type mice[9,10] provide a proof of principle that germline

DOI: https://doi.org/10.1200/JCO.2018.78.5204

genetics contribute to MM risk. More recently, germline mutations in other cancer susceptibility genes, including *ATM*, *CDKN2A*, *BRCA1*, *BRCA2*, *MSH6*, *MLH1*, *PALB2*, and *TP53*, have been reported in individual patients[11-16]; however, the prevalence and causative role of germline mutations in known cancer susceptibility genes in MM remain unknown.

In the current study, we screened patients with MPM, MPeM, or tunica vaginalis mesothelioma for germline mutations in 85 cancer susceptibility genes. We describe the prevalence and spectrum of germline mutations in MM, report disease features that predict the presence of a germline mutation, and compare the prevalence of germline mutations with that of a control population.

METHODS

Study Population

Unrelated patients with MM who attended The University of Chicago Medicine (UCM) MM clinic from April 2016 to August 2017 were prospectively consented. Saliva, peripheral blood, and tumor specimens were collected. A detailed personal and family history of malignancy and asbestos exposure were obtained in person by trained interviewers using a standardized questionnaire. Asbestos exposure was self-reported as definite, probable, possible, or no known exposure and categorized as primary for those with known occupational or environmental exposure and as secondary for those exposed through family members' exposures. Deceased patients who had previously consented to an historical tumor banking protocol from whom germline DNA was available were also included. Clinical information was abstracted from the medical record. The UCM Institutional Review Board approved this study.

Germline Mutation Detection and Interpretation

Germline variants were identified in DNA that was extracted from saliva or peripheral blood using a customized, Clinical Laboratory Improvement Amendments–certified targeted gene panel designed by The University of Chicago Genetic Services Laboratory to capture and sequence the coding and flanking intronic regions of 85 cancer susceptibility genes[17] (Data Supplement). All variants were analyzed by two independent reviewers and interpreted according to the American College of Medical Genetics and Genomics and Association for Molecular Pathology consensus guidelines (Data Supplement).[18] Pathogenic and likely pathogenic variants—hereafter termed germline mutations—including nonsense, frameshift, splice site, and missense variants, in genes with known moderate-to-high penetrance cancer susceptibility were reported. For missense variants, only those with published evidence of a damaging effect on protein function were included. All germline mutations were validated by Sanger sequencing, correlated with clinical and family history, and segregated in family members when possible.

Population Frequency Estimates

We estimated the population frequency of germline mutations in each gene using the publicly available noncancer exome sequencing data set from the Exome Aggregation Consortium[19] (ExAC; Data Supplement). Individual variant data for each gene were analyzed and interpreted according to American College of Medical Genetics guidelines.[18]

Somatic Mutation Detection

Somatic mutations were identified in DNA that was extracted from fresh-frozen, paraffin-embedded MM specimens using one of two next-generation sequencing platforms, UCM-OncoPlus[20] (n = 147 gene panel; Data Supplement) and Foundation Medicine[21,22] (n = 315 gene panel).

Functional Tumor Studies

Microsatellite instability was assessed using a polymerase chain reaction–based assay with fluorescently labeled primers to five DNA mononucleotide repeat markers, and/or a clinically validated method using 336 loci on UCM-OncoPlus. We performed immunohistochemistry

Table 1. Patient Characteristics

Characteristic	No. (%)
Total	198 (100)
Sex	
Male	136 (69)
Age at diagnosis, median (IQR)	67 (59-73)
Ethnicity	
Non-Hispanic white	192 (97)
Black	3 (2)
Asian	3 (2)
Site of origin	
Pleura	148 (75)
Peritoneum	44 (22)
Pleura and peritoneum	3 (2)
Tunica vaginalis	3 (2)
Histology	
Epithelioid	157 (79)
Sarcomatoid	13 (7)
Biphasic	23 (12)
Unknown	5 (3)
Additional cancer primary*	
Yes†	27 (14)
Hematologic	8 (4)
Breast	7 (4)
Prostate	5 (3)
Melanoma	4 (2)
Colon	2 (1)
Renal	2 (1)
Other	3 (2)
FDR with cancer*	
Yes	142 (72)
No	54 (27)
Unknown	2 (1)
FDR and/or SDR with cancer *	
Yes	173 (87)
No	23 (12)
Unknown	2 (1)
Asbestos exposure	
Definite	104 (53)
Probable	22 (11)
Possible	35 (18)
None	35 (18)
Unknown	2 (1)
Type of asbestos exposure‡	
Primary	98 (49)
Secondary	32 (16)
Primary and secondary	31 (16)
Smoking status	
Current	1 (1)
Former	89 (45)
Never	106 (54)
Unknown	2 (1)
Treatments received for MM	
Curative intent surgery	100 (51)
Chemotherapy	165 (83)
Platinum-based chemotherapy	159 (80)

Abbreviations: FDR, first-degree relative; IQR, interquartile range; MM, malignant mesothelioma; SDR, second-degree relative.
*Excludes nonmelanoma skin cancer.
†Twenty-seven patients had 31 total additional cancer primaries. Other includes ovarian cancer (n = 1), Wilms tumor (n = 1), and GI stromal tumor (n = 1).
‡Asbestos exposure type with possible, probable, or definite exposure (n = 161).

(IHC) on fresh-frozen, paraffin-embedded tumor sections to assess for the presence of BAP1, MLH1, MSH6, MSH2, and PMS2 proteins (Data Supplement).

Statistical Analysis

Two-sided Fisher's exact tests and Wilcoxon rank-sum tests were used to test the difference between categorical and continuous variables, respectively. We used logistic regression to assess associations between clinical characteristics and the presence of a germline mutation. Nested models were compared using likelihood ratio tests. Two-sided exact binomial tests were used to compare the frequencies of germline mutations in genes that were identified in our patients with MM versus those in the noncancer population in ExAC. P values $< .05$ were considered significant. Statistical analyses were performed with STATA software (version 15; STATA, College Station, TX; Computing Resource Center, Santa Monica, CA).

RESULTS

Study Population

Of 250 unrelated, eligible patients, 186 prospectively consented and 12 historical patients had sufficient germline DNA available for sequencing and were included (Data Supplement). Among these 198 patients, median age at MM diagnosis was 67 years (range, 24 to 88 years). The majority of patients were male (n = 136; 69%), had pleural disease (n = 148; 75%), epithelioid histology (n = 157; 79%), a history of occupational asbestos exposure (n = 129; 65%), and were never smokers (n = 106; 54%; Table 1). Twenty-seven patients (14%) had additional primary cancer diagnoses, with hematologic (n = 8; 4%), breast (n = 7; 4%), prostate (n = 5; 3%), and melanoma (n = 4; 2%) as the most frequent. Most had a family history of first-degree relatives (FDRs) and/or second-degree relatives (SDRs; n = 173; 87%) with cancer. Breast, lung, colorectal, and prostate cancers accounted for the majority of cancers in FDRs or SDRs (n = 67, 53, 46, 40 relatives, respectively), but hematologic malignancies (n = 34) were also frequent (Data Supplement). Thirteen probands had one or more FDR or SDR with MM (Data Supplement).

Germline Mutations

Twenty-three (12%) of 198 patients with MM carried a germline mutation, including one patient (UC049) who carried two mutations, one in *BAP1* and one in *TMEM127* (Fig 1A, Table 2, and Data Supplement). The 24 mutations were distributed among 13 genes. *BAP1* mutations were the most common, accounting for 25% (n = 6). The remaining were in genes involved in cell-cycle and DNA repair (n = 14), oxygen sensing (n = 2), endosome trafficking (n = 1), and cell growth and development (n = 1).

Germline Mutations and Clinical Characteristics

Germline mutation frequency was highest in patients with peritoneal MM (n = 11 [25%] of 44 *v* n = 11 [7%] of 148 for pleural), no known asbestos exposure (n = 9 [26%] of 35 *v* n = 7 [7%] of 104 for those with definite exposure), those with a second cancer diagnosis (n = 7 [26%] of 27 *v* n = 16 [9%] of 171 in those without), and epithelioid histology (n = 21 [13%] of 157 *v* n = 1 [4%] of 23 [biphasic] and n = 0 [0%] of 13 [sarcomatoid]; Fig 1B). The proportion of patients who carried a germline mutation significantly increased with decreasing age from 4% of those older than 75 years to 20% of those age 55 years or younger at diagnosis (test of trend; $P = .01$). Sex, histology, FDR with cancer, FDR/SDR with MM, and smoking status did not significantly differ between those patients with a germline mutation and those without (Table 3).

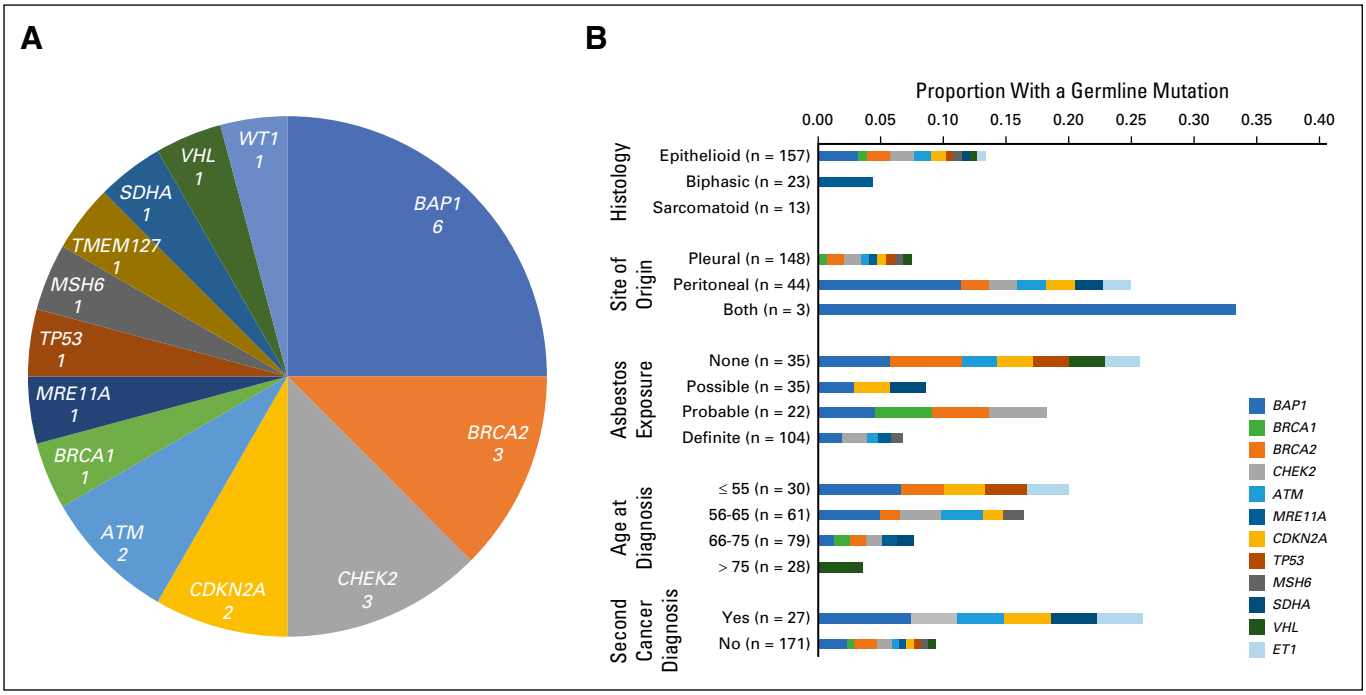

Fig 1. Germline cancer susceptibility gene mutations identified in patients with malignant mesothelioma. (A) Distribution of the 24 mutations identified in 23 patients among 13 genes. (B) Proportions of patients with a germline mutation by specific clinical characteristics.

Table 2. Detailed Clinical Characteristics of Patients With Malignant Mesothelioma and a Germline Cancer Predisposition Mutation

Patient ID	Sex	Age at Diagnosis, Years	Site of Origin	Histology	Second Cancer Diagnosis	Cancer in FDR or SDR	Personal or Family History Meets Clinical Criteria for Germline Genetic Testing†	Asbestos Exposure	Type of Asbestos Exposure	Germline Gene Mutated	Protein Change	Acquired Mutation(s) or Other Tumor Findings
Moderate-to-high penetrance risk alleles												
UC170	Female	57	Peritoneum	Epithelioid	Breast	Uterus, lung, colorectal, prostate	Family history meets Lynch syndrome criteria	None	None	*ATM*	p.? (c.4909+1G>T)	*BAP1* (p.Val247fs*2)
UC258	Male	59	Pleura	Epithelioid	None	Lung, breast, basal cell skin cancer	Personal and family history meet BAP1 criteria	Definite	Primary	*ATM*	p.Arg2763*	NA
UC041	Male	37	Peritoneum	Epithelioid	None	Leukemia	No	Probable	Secondary	*BAP1*	p.Val27Glyfs*42	*BAP1* (c.68-2A>C in trans); BAP1 loss by IHC
UC102	Male	65	Peritoneum	Epithelioid	None	Ovarian, lung (n = 3), urinary tract	Family history meets HBOC criteria	Definite	Primary	*BAP1*	p.Ser126Glnfs*16	*BAP1* (c.437+2T>A); CSF1R (p.Leu756fs*23)
UC060	Male	61	Peritoneum	Epithelioid	None	Breast, lymphoma, lung, MM, hepatic, uterus	Personal and family histories meet BAP1 criteria, and family history meets HBOC criteria	Definite	Primary	*BAP1*	p.Tyr173Leufs*10	NA; BAP1 loss by IHC
UC049	Male	61	Pleura and peritoneum	Unknown	Melanoma	MM (n = 2), renal (n = 2), basal cell skin cancer	Personal and family histories meet BAP1 criteria	Possible	Secondary	*BAP1*	p.Gln260*	NA
UC221	Female	55	Peritoneum	Epithelioid	None	MM	Personal and family histories meet BAP1 criteria	None	None	*BAP1*	p.Leu573Trpfs*3	NA
UC238	Female	74	Peritoneum	Epithelioid	Breast	Colorectal	Personal history meets HBOC criteria	None	None	*BAP1*	p.Gln684*	NA
UC264	Male	75	Pleura	Epithelioid	None	Lung, liver	No	Probable	Primary	*BRCA1*	p.Glu352*	NA
UC169	Male	65	Pleura	Epithelioid	None	Pancreas, breast, melanoma	Personal and family histories meet BAP1 criteria	Probable	Secondary	*BRCA2*	p.Gln1429Serfs*9	NA
UC191	Female	72	Pleura	Epithelioid	None	Breast	Family history meets HBOC criteria	None	None	*BRCA2*	p.Val1681Glufs*7	NA
UC241	Female	56	Peritoneum	Epithelioid	None	Breast	No	None	None	*BRCA2*	p.Ser1720Phefs*7	NA
UC061	Female	32	Peritoneum	Epithelioid	Melanoma	Breast (n = 2), pancreas, colorectal (n = 3), lung, lymphoma	Family history meets HBOC criteria,‡ and Personal history meets BAP1 criteria	Possible	Primary and secondary	*CDKN2A*	p.Ala4_Pro11dup	NA
UC265	Male	64	Pleura	Epithelioid	None	Head and neck, colorectal, esophageal	No	None	None	*CDKN2A*	p.Arg24Pro	NA
UC016	Male	61	Pleura	Epithelioid	None	Lymphoma, colorectal	No	Probable	Primary and secondary	*CHEK2*	p.Ile157Thr	None; BAP1 loss by IHC
UC064	Male	62	Pleura	Epithelioid	None	Lymphoma	No	Definite	Primary	*CHEK2*	p.Ile157Thr	NA
UC129	Male	76	Peritoneum	Epithelioid	Colorectal, prostate	None	No	Definite	Primary	*CHEK2*	p.Gly306Ala	NA
UC201	Male	66	Pleura	Biphasic	None	Unknown	No	Definite	Primary	*MRE11A*	p.? (c.1326+2T>G)	NA
UC081	Male	56	Pleura	Epithelioid	None	Melanoma (n = 2), lung, colorectal	Personal and family histories meet BAP1 criteria	Definite	Primary and secondary	*MSH6*	p.Phe1088Leufs*5	MSI stable, MMR proteins all intact by IHC
UC242	Female	71	Peritoneum	Epithelioid	Breast, ovarian, GIST	Lung, breast (n = 2)	Personal history meets HBOC criteria§	Possible	Secondary	*SDHA*	p.Glu230Serfs*10	NA
UC049	Male	61	Pleura and peritoneum	Unknown	Melanoma	MM (n = 2), renal (n = 2), basal cell skin cancer	Personal and family histories meet BAP1 criteria	Possible	Secondary	*TMEM127*	p.Leu155*	NA
UC124	Female	27	Pleura	Epithelioid	None	Prostate (n = 4), gastric	No‖	None	None	*TP53*	p.Arg248Trp	NA
UC240	Female	78	Pleura	Epithelioid	None	Prostate, hepatic	No	None	None	*VHL*	p.Leu188Val	NA
UC059	Male	37	Peritoneum	Epithelioid	Wilms tumor	Colorectal, lung (n = 2), brain	No¶	None	None	*WT1*	p.Ser165*	*BAP1* (p.Lys425fs*5); complex karyotype on tumor cytogenetics
Low-penetrance risk alleles												
UC139	Female	57	Pleura	Epithelioid	None	Lung, breast (n = 2)	No	None	None	*APC*	p.Ile1307Lys	NA
UC230	Female	66	Pleura	Biphasic	None	Breast (n = 2)	Family history meets HBOC criteria	Definite	Secondary	*APC*	p.Ile1307Lys	NA
UC102	Male	65	Peritoneum	Epithelioid	None	Ovarian, lung (n = 3), urinary tract	Family history meets HBOC criteria	Definite	Primary	*MITF*	p.Glu318Lys	*CSF1R* (p.Leu756fs*23); *BAP1* (c.437+2T>A)
UC114	Female	60	Pleura	Epithelioid	None	Leukemia, multiple myeloma	No	Definite	Primary and secondary	*MITF*	p.Glu318Lys	NA
UC249	Male	77	Pleura	Epithelioid	Prostate	Lymphoma, lung	No	Definite	Primary and secondary	*MUTYH*	p.Gly382Asp	*BAP1* (p.Gln684*); *DDX3X* (p.Gln360*)

NOTE. Of the 198 patients tested, saliva from 183 patients (92%) and peripheral blood from 15 patients (8%) were used as the germline sample source. The Data Supplement provides details.

Abbreviations: FDR, first-degree relative; GIST, GI stromal tumor; HBOC, hereditary breast and ovarian cancer syndrome; IHC, immunohistochemistry; MM, malignant mesothelioma; NA, not available; SDR, second-degree relative.

†Family history is as obtained at the time of first patient interview. Clinical criteria for germline genetic testing include National Comprehensive Cancer Network guidelines[23, 24] as well as BAP1 tumor predisposition syndrome clinical testing recommendations.[26]

‡This patient's family had a known *BRCA2* mutation in the family, which UC061 did not carry, as well as the *CDKN2A* mutation identified here.

§This patient had clinical panel–based testing for hereditary breast and ovarian cancer genes that was negative; this panel did not include *SDHA*.

‖This patient had prior clinical genetic testing that identified the same *TP53* mutation confirmed in our study.

¶This patient had subtle hemihypertrophy and proteinuria.

Table 3. Comparison of Clinical Characteristics Between Germline Mutation Carriers and Nonmutation Carriers

Characteristic	Germline Mutation Carrier	No Germline Mutation	*P*
Total	23 (12)	175 (88)	
Sex			
Female	9 (39)	53 (30)	.47
Male	14 (61)	122 (70)	
Age at diagnosis, median (IQR)	61 (56-71)	67 (59-73)	.04
Site of origin			
Pleura	11 (48)	137 (78)	.01
Peritoneum	11 (48)	33 (18)	
Pleura and peritoneum	1 (4)	2 (1)	
Tunica vaginalis	0 (0)	3 (2)	
Histology*			
Epithelioid	21 (95)	136 (80)	.26
Sarcomatoid	0 (0)	13 (7)	
Biphasic	1 (5)	22 (13)	
Additional cancer primary†			
Yes	7 (30)	20 (11)	.02
No	16 (70)	155 (89)	
FDR with cancer†			
Yes	17 (74)	119 (69)	.81
No	6 (26)	54 (31)	
FDR or SDR with mesothelioma			
Yes	3 (13)	10 (6)	.18
No	20 (87)	165 (94)	
Asbestos exposure*			
Definite	7 (30)	97 (56)	.02
Probable	4 (17)	18 (10)	
Possible	3 (13)	32 (19)	
None	9 (39)	26 (15)	
Type of asbestos exposure (n = 161)			
Primary	7 (50)	91 (62)	.62
Secondary	4 (29)	28 (19)	
Primary and secondary	3 (21)	28 (19)	
Smoking status			
Current	0 (0)	1 (1)	.28
Former	7 (30)	82 (47)	
Never	16 (70)	90 (52)	

NOTE. Data are given as No. (%) unless otherwise noted.
Abbreviations: FDR, first-degree relative; IQR, interquartile range; SDR, second-degree relative.
*Patients with missing values excluded histology (n = 5), asbestos exposure (n = 2), type of asbestos exposure, and smoking.
†Excludes nonmelanoma skin cancer.

In univariable analysis, pleural site (odds ratio [OR], 0.23; 95% CI, 0.10 to 0.58; $P < .01$), asbestos exposure (OR, 0.28; 95% CI, 0.11 to 0.72; $P < .01$), and age (OR, 0.95; 95% CI, 0.92 to 0.99; $P = .01$) were associated with decreased odds of carrying a germline mutation, whereas having a second cancer diagnosis (OR, 3.33; 95% CI, 1.22 to 9.07; $P = .02$) significantly increased the odds (Data Supplement). In multivariable analysis, adjusting for age, asbestos exposure, and a second cancer diagnosis, all three remained significant predictors. The addition of the site of origin did not improve model fit (likelihood ratio test, $P = .13$), and OR estimates remained similar.

Of 23 patients with a germline mutation, seven (30%) had a personal and/or family history that met clinical genetic testing criteria for hereditary breast and ovarian cancer (n = 6) or colon cancer[23,24] (n = 1; Table 2). Of these, three patients had undergone prior clinical genetic testing that identified the germline mutation confirmed in this study in two patients. The third patient had prior negative clinical testing via a panel that did not include *SDHA* in which a mutation was identified in this study. Only one (10%) of 10 patients found to carry mutations in hereditary breast cancer genes met clinical genetic testing criteria.[23] Three (50%) of six patients who were found to carry a germline *BAP1* mutation met clinical recommendations for *BAP1* genetic testing[25,26] (Table 2 and Data Supplement). The familial *BAP1* mutation segregated with *BAP1* syndrome-related tumors in two of two families tested. Among 13 total families with more than one case of MM, three carried a germline mutation, all in *BAP1* (Data Supplement).

Germline Mutation Frequency in MM Cases Versus Controls

Compared with the noncancer ExAC population, the odds of carrying a mutation in *BAP1* (OR, 1,658; 95% CI, 199 to 76,224; $P < .001$), *BRCA2* (OR, 5; 95% CI, 1.0 to 14.7; $P = .03$), *CDKN2A* (OR, 53; 95% CI, 6 to 249; $P < .001$), *TMEM127* (OR, 88; 95% CI, 1.7 to 1,105; $P = .01$), *VHL* (OR, 51; 95% CI, 1.1 to 453; $P = .02$), and *WT1* (OR, 20; 95% CI, 0.5 to 135; $P = .049$) were significantly higher in our study population (Table 4).

Somatic Mutations

Fifty-four patients had adequate specimens available for tumor sequencing, including 37 MPM and 17 MPeM specimens. Thirty-two specimens were sequenced using UCM-OncoPlus and 22 had been sequenced as part of clinical care using Foundation Medicine (Fig 2 and Data Supplement). Acquired pathogenic mutations in *BAP1* were the most common, found in 13 MPM (43%) and 11 MPeM (65%) specimens. Only two (6%) of 31 *BAP1* mutations were germline. Rare *BAP1* variants of uncertain significance were common, found in six (22%) of 27 tumors with a known pathogenic *BAP1* variant and eight (30%) of 27 of those without a pathogenic *BAP1* variant. *CDKN2A* (n = 10 [19%] of 54), *NF2* (n = 10 [19%] of 54), *SETD2* (n = 6 [11%] of 54), *DDX3X* (n = 4 [7%] of 54), and *FBXW7* (n = 4 [7%] of 54) were also commonly mutated in both MPM and MPeM. *TP53* mutations were only found in MPM (n = 7 [19%] of 37). In total, 52% (29 of 54) of tumors tested had one or more germline or acquired mutation in a homologous recombination (HR) DNA repair pathway gene. Twelve (38%) of 32 MM tested on UCM-OncoPlus had 10 or more copy number changes.

Among the five patients with germline mutations whose tumor was also sequenced (Fig 2 and Table 2; UC016, 059, 041, 102, and 170), the tumors acquired zero to three additional pathogenic mutations. Both individuals with germline *BAP1* mutations (UPIN041 and 102) acquired a second pathogenic *BAP1* mutation in the tumor, with one confirmed in trans configuration (Data Supplement). Patient UPIN059, who developed MPeM in the radiation field post-treatment of Wilms tumor, had a germline *WT1* mutation and acquired a pathogenic *BAP1* mutation in the context of a complex karyotype that was detected by conventional karyotyping. Patient UPIN081 carried a germline *MSH6* mutation. His MPM, as well as a colon cancer sample from an unrelated patient with Lynch syndrome that carried the exact same germline *MSH6* mutation, were both microsatellite stable and demonstrated the presence of all four mismatch repair (MMR) proteins on IHC (Data Supplement), which suggests that this specific mutation may not cause the usual microsatellite instability (MSI) phenotype. An additional five MM specimens that were tested by polymerase

Table 4. Mutation Frequencies in Patients With Malignant Mesothelioma Versus a Noncancer Population Estimate

Gene	University of Chicago Patients with MM (n = 198)		ExAC Noncancer Population (n = 53,105)*			University of Chicago Versus ExAC Population, OR (95% CI)	P†
	No. of Mutated Alleles	Proportion of Individuals With a Mutation	No. of Mutated Alleles	No. of Individuals Sequenced, Mean*	Proportion of Individuals With a Mutation		
BAP1	6	0.0303	1	53,040	0.000019	1,657.5 (199.0 to 76,224.0)	< .001‡
BRCA2	3	0.0152	167	53,007	0.003151	4.9 (1.0 to 14.7)	.03
CDKN2A	2	0.0101	10	51,540	0.000194	52.6 (6.0 to 249.0)	< .001‡
TMEM127	1	0.0051	3	52,250	0.000057	88.4 (1.7 to 1,105.0)	.01
VHL	1	0.0051	5	49,703	0.000101	50.5 (1.1 to 453.0)	.02
WT1	1	0.0051	13	51,405	0.000253	20.1 (0.5 to 135.0)	.049
ATM	2	0.0101	155	52,921	0.002929	3.5 (0.4 to 12.9)	.12
CHEK2	3	0.0152	770	49,743	0.015480	0.98 (0.2 to 2.9)	1.00
BRCA1	1	0.0051	102	51,002	0.002000	2.5 (0.1 to 14.6)	.33
MRE11A	1	0.0051	33	52,827	0.000625	8.1 (0.2 to 49.0)	.12
TP53	1	0.0051	29	52,875	0.000548	9.3 (0.2 to 56.4)	.10
MSH6	1	0.0051	102	52,736	0.001934	2.6 (0.1 to 15.0)	.32
SDHA	1	0.0051	53	51,660	0.001026	4.9 (0.1 to 29.0)	.18

Abbreviations: ExAC, Exome Aggregation Consortium; MM, malignant mesothelioma; OR, odds ratio.
*The number of individuals sequenced varies by genomic position.
†Two-sided exact binomial tests without adjustment for multiple testing.
‡Remain significant at $\alpha < .004$ if Bonferroni correction is used.

chain reaction and IHC and 32 tested by UCM-OncoPlus were all microsatellite stable.

DISCUSSION

We found that 12% of patients with MM carry germline cancer susceptibility gene mutations. This prevalence is strikingly similar to the proportion found in other solid tumors, including ovarian, colon, metastatic prostate cancer, and diverse advanced solid tumors.[16,27-29] The recognized MM susceptibility gene, *BAP1*, accounted for only one quarter of mutations identified. This may help explain why many patients with MM who have a strong personal or family cancer history reported in the literature tested negative for germline mutations in *BAP1*.[8,30,31] We demonstrate that 13 genes, including genes that were previously identified in single MM cases,[11-16] as well as genes that have not been previously linked to MM, including *TMEM127, CHEK2, MRE11A, VHL, WT1*, and *SDHA*, contribute to MM and other cancer susceptibility in these patients and their families. Our finding that pathogenic mutations in *BAP1, CDKN2A, BRCA2, TMEM127, VHL*, and *WT1* are overrepresented in patients with MM compared with a control population provides additional evidence that supports the association of cancer susceptibility genes with MM carcinogenesis.

Specific clinical characteristics predict the presence of germline mutations and provide insight into differences in subset-specific MM etiology. First, we found that minimal-to-no asbestos exposure was the most significant predictor of the presence of a germline cancer susceptibility mutation, which confirmed an observation made for germline *BAP1* mutations[8] and similar observations in patients with MPM.[12] Two other important predictors—younger age and having had a second cancer—are not surprising given the known association of cancer susceptibility gene mutations and earlier onset and multiple cancers. Second, although the spectrum of mutations is similar across MPM and MPeM, the overall proportion of patients with mutations was significantly different (7% *v* 25%; $P < .01$, respectively), which implies that inherited susceptibility may play a larger role in MPeM than in MPM. This is an interesting observation given the overlap in site and cisplatin sensitivity of MPeM and ovarian cancer, a cancer for which 18% to 24%[27,32] of patients will carry a germline mutation in some of the same genes identified here. Furthermore, although MPeM is also associated with asbestos exposure, the strength of this association is weaker than for pleural site of origin.[33] Our data suggest that genetic susceptibility and/or a gene by environment interaction effect, as previously demonstrated for asbestos exposure in *Bap1*-deficient mouse models,[9,10] may contribute to these differences.

Our findings add to the accumulating evidence of the importance of deficits in DNA damage response pathways in MM.[12] Six of the genes with germline mutations in this series—*BAP1, BRCA1, BRCA2, CHEK2, ATM*, and *MRE11A*—have a well-established role in the HR DNA repair pathway.[34-38] *WT1* may also be involved in HR-mediated repair.[39,40] We found acquired mutations in additional HR pathway genes, including *FANCA* and *ATR*, in MM tumors. In total, 52% of MM tumors sequenced had an HR pathway defect either as a result of a germline or acquired event, and 12 (38%) of 32 tested had multiple copy number rearrangements. These observations are consistent with prior data that demonstrate multiple chromosomal rearrangements in the majority of MM cases,[41] with the genomic instability pattern observed in other tumors with HR defects, and with the observation of the loss of BRCA1 expression in 39% of MM tumors.[42]

These data are immediately relevant for potential prognostic biomarkers and chemotherapeutic targets for MM. In other cancers that are commonly caused by HR defects, such as ovarian cancer, the subset of patients who carry germline *BRCA1* or *BRCA2* mutations is more likely to respond to cisplatin and have a better prognosis.[43] Our study's findings may help explain the cisplatin sensitivity of a substantial subset of MM and the observed improvement in prognosis in patients with MM who carry a germline *BAP1* mutation.[44] Furthermore, poly (ADP-ribose) polymerase

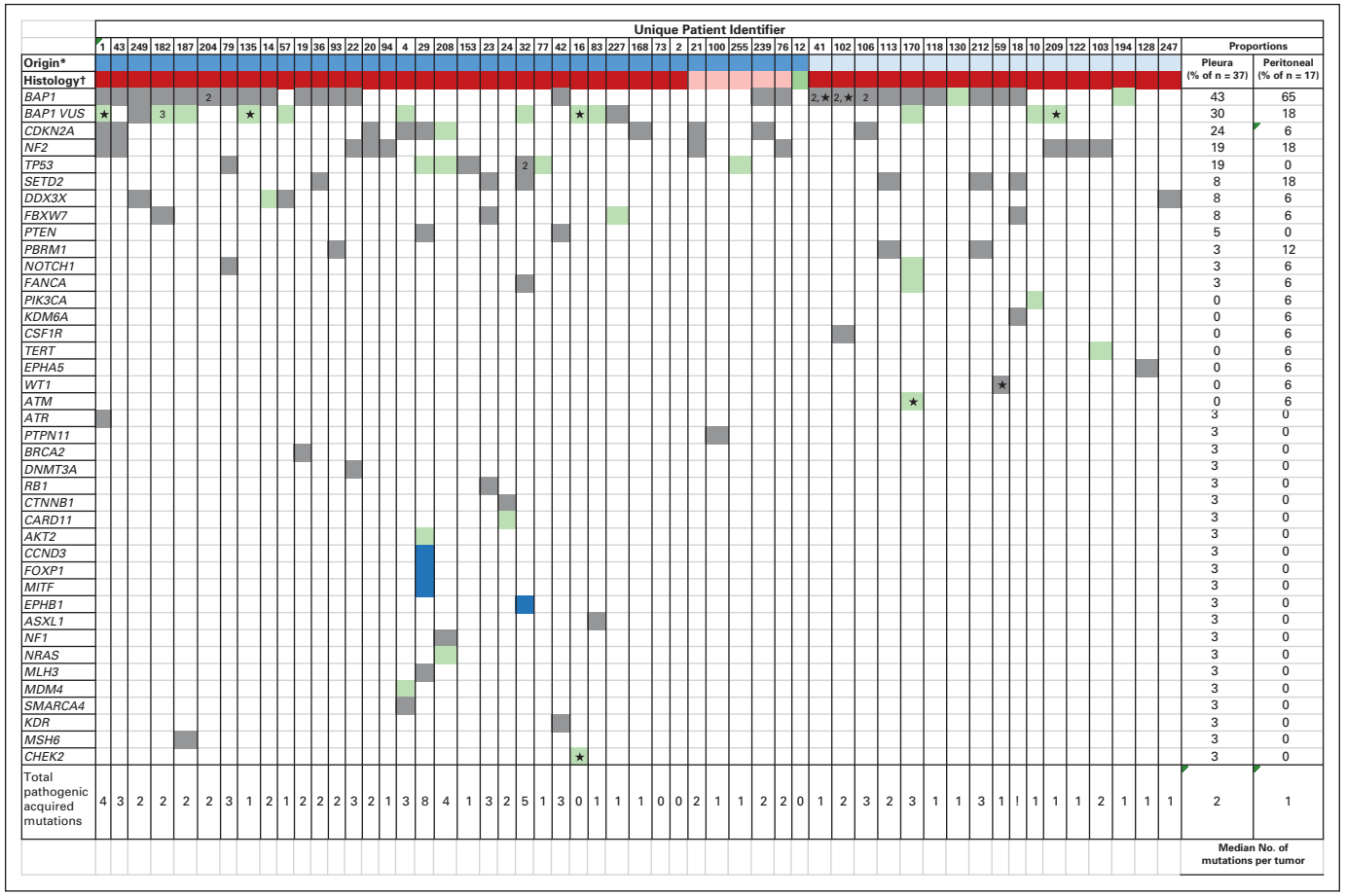

Fig 2. Genetic variants identified by site of origin and histology in 54 malignant mesothelioma specimens. Transcript numbers: ATM [NM_000051.3], AKT2 [NM_001626]; ASXL1 [NM_015338]; ATR [NM_001184.3]; BAP1 [NM_004656.3]; BRCA2 [NM_000059.3]; CARD11 [NM_032415]; CDKN2A [NM_000077]; CSF1R [NM_001288705.1]; CTNNB1 [NM_001904]; DDX3X [NM_001356.4]; DNMT3A [NM_022552]; EPHA5 [NM_004439]; EPHB1 [NM_004441]; FANCA [NM_000135]; FBXW7 [NM033632.3]; FOXP1 [NM_032682]; KDM6A [NM_021140]; KDR [NM_002253.2]; MDM4 [NM_002393]; MLH3 [NM_001040108.1]; MSH6 [NM_00179.2]; NF1 [NM_001042492]; NF2 [NM_000268]; NOTCH1 [NM_017617.4]; NRAS [NM_002524]; PIK3CA [NM_006218]; PTEN [NM_000314.6]; PTPN11 [NM_002834]; RB1 [NM_000321]; SETD2 [NM_014159]; SMARCA4 [NM_003072]; TERT [NM_198253.2]; TP53 [NM_000546.5]; WT1 [NM_24426.4]. Mutation types: loss, large deletion or duplication, nonsense, frameshift, splice site (dark gray); missense, in-frame deletion, promoter mutation (green); amplification (blue). VUS, variant of uncertain significance. (*) Origin: Dark blue, pleural; light blue, peritoneal. (†) Histology: Dark red, epithelioid; pink, biphasic; green, sarcomatoid. Germline variants are notated by ★. Tumors with multiple variants in the same gene are notated with the number of unique variants identified.

inhibitors (PARPi) have demonstrated improved efficacy in ovarian, breast, and prostate cancers with HR defects.[45-47] MM cells lines, regardless of *BAP1* status, have been demonstrated to be sensitive to PARPi,[38,48,49] which supports the hypothesis that PARPi could be effective in MM.[12,48,50] Taken together, PARPi trials in patients with MM, especially those not refractory to platinum-based chemotherapy, are justified and already in development. Active investigation of HR deficits in MM is warranted to identify biomarkers of prognosis and chemotherapy responsiveness as well as novel drug targets.

We also identified germline (*MSH6*) and acquired mutations (*MSH6, MLH3*) in the MMR pathway. Similar to two other germline MMR gene-mutated MPeM in the literature,[14,15] none of these tumors featured the MSI pattern typical of other cancers with MMR deficits.[51] We did not observe an MSI pattern in 32 total MM examined. The role of these genes and the MMR pathway in MM remains to be determined. Finally, the identification of germline mutations in *VHL* and *SDHA*, genes that induce tumorigenesis through impaired hypoxia-inducible factor expression,[52,53] and in *TMEM127*, which negatively regulates the mammalian target of rapamycin signaling pathway,[54] highlight additional pathways that warrant investigation.

Our data support clinical panel-based genetic testing for all patients with MM. Clinical genetic testing guidelines[23-26] would identify only 12 (52%) of 23 germline mutation carriers in this study, which suggests a need for a universal testing strategy. This testing would allow primary cancer prevention and early detection in at-risk close relatives and in patients with MM with disease features that portend extended survival. Lastly, *BRCA1* or *BRCA2* germline mutation status has been incorporated into US Food and Drug Administration approvals of specific PARPi for the treatment of advanced ovarian and breast cancer and is expected for prostate cancer. Whether a similar paradigm will hold in MM awaits investigations of the effect of germline mutation status on the response to established and novel therapies.

Our study has limitations. First, our germline genetic testing assay cannot detect copy number variants, and our variant interpretation approach was conservative, including only proven pathogenic or likely pathogenic mutations. Thus, the proportion of

patients with MM in our study who carried a pathogenic mutation may be underestimated. Similarly, the UCM-OncoPlus genes analyzed in tumors in this study did not include all HR pathway genes and, similar to other next-generation sequencing–based assays, may miss small copy number changes.[55] Second, UCM is a tertiary referral center, which makes our study population subject to referral bias. Third, insufficient tumor tissue for many of the patients who carried a germline mutation and the lack of germline mutations other than *BAP1* in families with more than one MM case to allow segregation with MM cases limited our ability to provide more direct evidence of causation. Finally, family history of malignancy and prior asbestos exposure were self-reported, which may limit accuracy; however, our observation that lower self-reported asbestos exposure is a significant predictor of carrying a germline mutation is concordant with prior work.[12] Furthermore, a strong family cancer signal has been previously reported in patients with MM.[8,31,56-61] Our data confirm these observations and provide a rationale for broader investigations of inherited genomics in patients with MM.

In conclusion, we found that 12% of patients with MM carry germline mutations in cancer susceptibility genes; especially those with peritoneal disease, a second cancer diagnosis, young age at onset, and minimal known asbestos exposure. These data support the inclusion of clinical germline genetic testing in the evaluation of all patients with MM. We found additional evidence of an HR pathway DNA repair defect in a substantial subset of patients with MM, providing a rationale for PARPi clinical trials and additional research into this pathway in MM etiology.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Support

Supported by a Pilot Research Grant, awarded by The University of Chicago Comprehensive Cancer Center and supported with funds from John D. Cooney and the firm of Cooney and Conway (J.E.C.), National Institute of Diabetes and Digestive and Kidney Diseases (Grant No. T35DK062719-29) (E.S.), and the Pritzker School of Medicine (S.R.Z.).

Prior Presentation

Presented at the Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 1-5, 2018.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Frequency of Germline Mutations in Cancer Susceptibility Genes in Malignant Mesothelioma

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No relationship to disclose

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Research Funding: Aduro Biotech, AstraZeneca, Bayer, GlaxoSmithKline, Merck, MedImmune, Verastem, Bristol-Myers Squibb, Eli Lilly, Polaris, Deciphera

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Acknowledgment

We thank all of the patients and their family members who participated in this study. At the time of publication, we are aware of data with similar findings presented by Dr. Raffit Hassan at the Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 1-5, 2018.