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# Two new studies report germline mutations in *BAP1*

**Alisa M. Goldstein**
Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, MD 20892-7236

## Abstract

Two new studies describe germline mutations in *BAP1* in putatively dissimilar cancer-related syndromes. Although the predominant neoplasms – melanocytic tumors with distinct clinical and histopathological features versus mesothelioma – differ, uveal melanoma occurs, albeit infrequently, in both disorders.

*BAP1* is a tumor suppressor gene located on chromosome 3p21 in a region that shows loss or deletions in numerous cancers, including lung and breast cancer, as well as uveal melanoma and mesothelioma. Two recent studies reported high frequencies of somatic mutations in *BAP1* in uveal melanoma[1] and mesothelioma[2]. Harbour *et al*[1] found inactivating somatic mutations of *BAP1* in 47% (28/60) (Table 1) of uveal melanoma with a much higher frequency of somatic mutations (27/34, 79%) in metastasizing uveal melanoma. In addition, one tumor had a germline frameshift mutation, suggesting that this variant was a susceptibility allele. Bott *et al*[2] identified somatic inactivating mutations in *BAP1* in 23% (12/53) of a discovery set of malignant pleural mesotheliomas (MPM), half from patients who reported asbestos exposure, and in 18% (12/68) of an independent set of MPM [total: 20% (24/121)]. In this issue, Wiesner, Bastian, Speicher and colleagues[3] and Testa, Carbone, and colleagues[4] provide further links between *BAP1*, uveal melanoma and mesothelioma by reporting on germline mutations of *BAP1* in two putatively distinct cancer-related syndromes characterized predominantly by melanocytic tumors or mesothelioma, respectively, plus uveal melanoma in both disorders.

## Two new cancer-related syndromes?

Wiesner *et al*[3] identified co-segregating germline mutations of *BAP1* in two families (1 and 2) with multiple members with melanocytic tumors that ranged histopathologically from epithelioid nevi to atypical melanocytic proliferations that had features that overlapped with cutaneous melanoma. Both families had one member with uveal melanoma and family 2 had multiple members with cutaneous melanoma. Affected family members had many (5 to >50) of the clinically and histopathologically distinct melanocytic tumors, whereas few melanomas developed suggesting that the risk of malignant potential in individual tumors

Contact info: Genetic Epidemiology Branch, DCEG, NCI, NIH, 6120 Executive Blvd, MSC 7236, Bethesda, MD 20892-7236, Tele: 301-496-4375, FAX: 301-402-4489, goldstea@mail.nih.gov.

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was low. Examination of a subset of the familial melanocytic tumors revealed that the majority of tumors showed biallelic inactivation of *BAP1* by various somatic alterations.

Testa *et al*[4] discovered co-segregating germline mutations in *BAP1* in two families (L and W) with 5 or more members with mesothelioma. The families had modest levels of asbestos exposure from having lived in asbestos-containing houses but did not have occupational asbestos exposure. The families also had multiple members with various malignancies including two members with uveal melanoma in family L. Somatic alterations of the familial mesothelioma tumors indicated biallelic inactivation of *BAP1*. Testa *et al*[4] also sequenced *BAP1* in germline DNAs from 26 sporadic mesothelioma cases and uncovered two inactivating frameshift mutations in patients subsequently found to have had uveal melanoma. Given the rarity of both uveal melanoma and mesothelioma in the United States, the authors concluded that it was extremely unlikely for these two malignancies to have occurred in the same individuals by chance.

## Cancers and *BAP1* mutations

Besides uveal melanoma, mesothelioma, and the distinct melanocytic tumors, numerous additional tumors were observed in the families[3,4]. Several cancers including cutaneous melanoma (n=3), non-melanoma skin (n=2), ovarian (n=1), breast (n=1), renal (n=1), and pancreatic (n=1) cancer occurred in family members who inherited their family's inactivating *BAP1* mutation. Whether these cancers are part of the spectrum of tumors related to germline *BAP1* mutations requires additional study.

Data from COSMIC (Catalogue Of Somatic Mutations In Cancer)[5,6] showed low frequencies of somatic *BAP1* mutations in several of the observed tumors including breast (0.4%), ovarian (3.4%), and pancreatic (0.0%) cancer (table 1). In addition, Wiesner *et al*[3] showed that five percent (3/60) of primary melanomas originating from acral skin (n=15), mucosa (n=15), or skin with (n=15) or without chronic sun damage had somatic *BAP1* mutations. Finally, lung cancer, which was one of the first cancers originally reported to have *BAP1* somatic mutations[7], also had very few somatic mutations (0.6%)[5,6] suggesting that another gene in the 3p21 region may be implicated in some of the cancers that show loss/deletion in this region[8–10]. Alternatively, a different mechanism of inactivation of *BAP1* may be involved. In contrast to the low frequency of somatic mutations for the tumor types described above, 44% (41/93) of uveal melanoma and 20% (28/139) of sporadic mesotheliomas had somatic mutations of *BAP1*[1–4] (table 1). For most of the tumors evaluated, *BAP1* showed biallelic loss. Harbour *et al*[1] hypothesized that biallelic loss of *BAP1* was a key event in uveal melanoma metastasis. The current studies suggest a potentially more complex scenario that may depend on various combinations of the tissue of origin, environmental exposures, functional consequences of the *BAP1* mutations, and mechanisms of inactivation of the second *BAP1* allele.

BAP1 (ubiquitin carboxy-terminal hydrolase/BRCA1-associated protein 1), a 729 amino acid nuclear-localized deubiquitinating enzyme, was originally identified as an ubiquitin hydrolase that binds to the RING finger domain of BRCA1[7,11]. BAP1 contains numerous functional domains including the ubiquitin carboxy-terminal hydrolase (UCH) domain, a

host cell factor-1 (HCF-1) binding domain, and binding domains for BRCA1 and BARD1. BAP1 has been functionally implicated in numerous biologic processes including chromatin, DNA damage response, and regulation of the cell cycle and cell growth[1,2,7,11–15]. Given its complexity, different germline mutations in *BAP1* may predispose to divergent tumor types.

## Future Directions

These studies raise several provocative questions. Are these disorders two distinct syndromes or a single syndrome with a wide phenotypic range? For what tumor types do germline mutations of *BAP1* increase susceptibility? What role do exposures (e.g. asbestos, ultraviolet radiation) have on the tumor types that develop? Are there genotype-phenotype correlations between specific germline (or somatic) mutations and the resultant tumors? Answers to these questions will require extensive additional clinical, molecular genetic, genetic epidemiologic and functional studies. Since its original discovery in 1998[7], *BAP1* has captivated and beguiled scientists. The studies by Wiesner, Bastian, Speicher and colleagues[3] and Testa, Carbone, and colleagues[4] continue this trend.

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## Table 1

Tumors with somatic mutations in *BAP1*

| Tumor Type | No. Tumors | Somatic Mutations | | Reference |
|---|---|---|---|---|
| | | No. | % | |
| *Melanocytic* | | | | |
| Common nevi | 29 | 0 | 0.0 | Wiesner *et al*[3] |
| Spitz nevi | 17 | 0 | 0.0 | Wiesner *et al*[3] |
| Atypical Spitz nevi | 18 | 2* | 11.1 | Wiesner *et al*[3] |
| Cutaneous melanoma | 60 | 3 | 5.0 | Wiesner *et al*[3] |
| *Uveal melanoma, total* | 93 | 41 | 44.1 | Wiesner *et al*[3]; Harbour *et al*[1] |
| Wiesner *et al*[3] study | 33 | 13 | 39.4 | Wiesner *et al*[3] |
| Harbour *et al*[1] study | 60 | 28 | 46.7 | Harbour *et al*[1] |
| Low metastatic risk | 26 | 1 | 3.8 | Harbour *et al*[1] |
| High metastatic risk | 31 | 25 | 80.6 | Harbour *et al*[1] |
| Metastatic | 3 | 2 | 66.7 | Harbour *et al*[1] |
| *Mesothelioma, total* | 139 | 28 | 20.1 | Testa *et al*; Bott *et al*[2] |
| Testa *et al* study[4] | 18 | 4 | 22.2 | Testa *et al*[4] |
| Bott *et al* study[2] | 121 | 24 | 19.8 | Bott *et al*[2] |
| *Breast* | 251 | 1 | 0.6 | Forbes *et al*, 2008 & 2011[5,6] |
| *Lung* | 322 | 2 | 0.4 | Forbes *et al*, 2008 & 2011[5,6] |
| *Ovary* | 59 | 2 | 3.4 | Forbes *et al*, 2008 & 2011[5,6] |
| *Pancreas* | 30 | 0 | 0.0 | Forbes *et al*, 2008 & 2011[5,6] |

* These tumors had morphologic features similar to the melanocytic tumors observed in families 1 and 2 (Wiesner *et al*[3])