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Toward an Improved Definition of the Tumor Spectrum Associated With *BAP1* Germline Mutations

Introduction

BAP1 is a tumor suppressor gene that is located on chromosome 3p21, a region which is deleted in several cancers, including mesothelioma, cutaneous and uveal melanoma, and cancers of the lung and breast. Somatic *BAP1* mutations are common in uveal melanoma[1] and mesothelioma.[2] We recently reported that germline mutations in *BAP1* predispose to multiple distinctive epithelioid melanocytic tumors and to uveal and cutaneous melanomas.[3] Independently, two other studies showed that *BAP1* germline mutations predispose to other types of cancer: Testa et al[4] reported that *BAP1* germline mutations predispose to malignant mesothelioma and uveal melanoma, whereas Abdel-Rahman et al[5] suggested that *BAP1* germline mutations may be also associated with lung adenocarcinoma, meningioma, and other cancers.

BAP1 is involved in various biologic processes, including chromatin dynamics,[6] DNA damage response,[7,8] and regulation of the cell cycle and cell growth.[9] This functional complexity and the distinct sets of tumors in patients in the aforementioned reports[3-5] raised the question as to whether different germline mutations in *BAP1* may predispose to distinct syndromes or to a single syndrome with a wide phenotypic range.[10] To clarify the *BAP1*-related tumor spectrum, we describe here a unique family with a *BAP1* germline mutation, and we provide a brief update on the occurrence of *BAP1*-associated tumors in families reported in our previous article (families 1 and 2[3]). With these case reports, we provide evidence that the *BAP1*-associated tumor spectrum shows significant overlap and that *BAP1* germline mutation carriers are predisposed to the development of melanocytic skin lesions, uveal and cutaneous melanoma, and mesothelioma with varying degrees of penetrance.

Case Report

Novel family with *BAP1* germline mutation. We identified a family in which mesotheliomas were inherited in an autosomal-dominant pattern over three generations (family 3; Fig 1A; age in years [y] at diagnosis is indicated below the symbols). The family was of European descent, and none of the family members had a history of exposure to asbestos or erionite. Three of four affected family members with mesothelioma were long-term survivors. Patient II-2 was in complete remission after resection of a peritoneal mesothelioma 6 years before, patient III-1 was in complete remission after resection of a pleural mesothelioma 2 years before, and patient III-2 had a slowly progressing malignant peritoneal effusion 8 years after resection and chemotherapy of pleural and peritoneal mesothelioma. Only patient I-1 died as a result of a pleural

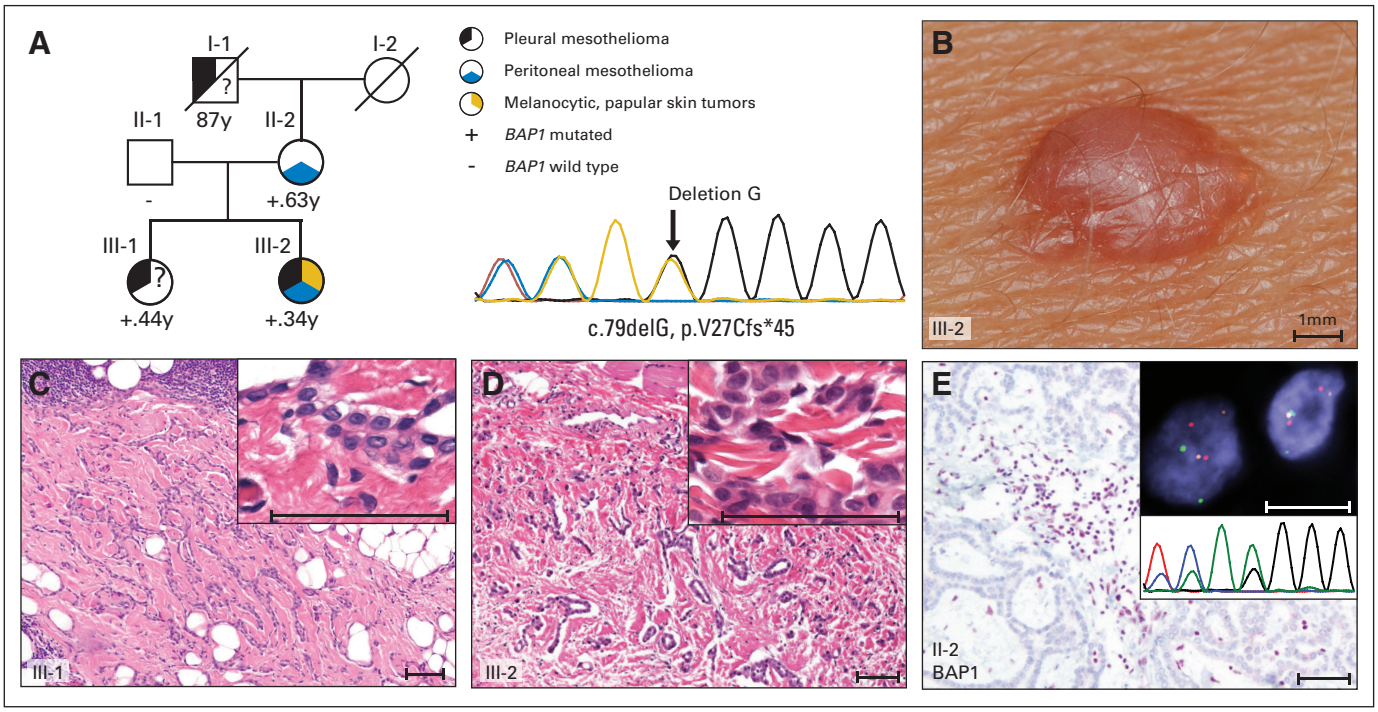

Fig 1.

mesothelioma within 2 years. The indolent clinical course contrasted with the comparatively rapid progression of sporadic and asbestos-associated mesotheliomas, which are characterized by a median survival of less than 18 months from diagnosis.[11]

We were able to examine the skin of two family members (ie, patients II-2 and III-2) for the presence of the typical *BAP1*-associated melanocytic skin tumors, as described previously.[3] Patient III-2 exhibited the characteristic melanocytic tumors, which presented clinically as inconspicuous, skin-colored to reddish-brown, dome-shaped papules (Fig 1B). Patient II-2 lacked cutaneous melanocytic tumors.

Prompted by the high incidence of mesothelioma and the characteristic skin lesion in this family, we sequenced three affected (patients II-2, III-1, and III-2) and one unaffected (patients II-1) family members for *BAP1* germline mutations using the previously described primers and polymerase chain reaction conditions for Sanger sequencing.[3] We identified a *BAP1* germline mutation (c.79delG, p.V27Cfs*45) in all affected family members, but not in the unaffected individual.

We also investigated the *BAP1* status in mesotheliomas from patients II-2, III-1, and III-2. Histologically, the malignant mesotheliomas were composed of cords and tubules of malignant cells (Figs 1C and 1D; hematoxylin and eosin staining). In all three mesotheliomas, interphase fluorescence in situ hybridization did not show loss of the *BAP1* region, but in two of the three mesotheliomas, the sequencing electropherogram showed reduced intensity of the wild-type sequence, which suggested that the neoplastic cells had lost the wild-type *BAP1* allele through copy number–neutral mechanisms. Immunohistochemistry showed loss of nuclear BAP1 staining in all three patients with mesothelioma but positive staining in intermingled lymphocytes (Fig 1E).

Update on the tumor spectrum in the previously described families. Additional evidence of phenotypic overlap that may be seen in *BAP1* mutation carriers is provided by the recent diagnosis of peritoneal mesothelioma in a member of one of our two previously reported families (patient II-6 of family 2 in Fig 1A of our previous article[3]) with multiple melanocytic tumors, including epithelioid nevi, cutaneous melanoma, and uveal melanoma. This patient harbored the previously described *BAP1* germline mutation (c.1305delG) and had no known history of occupational or environmental exposure to asbestos or erionite.

Cutaneous melanoma had been diagnosed in three individuals in only one (ie, family 2) of our two initially published families.[3] Subsequently, however, a member of the other family (subject II-1 of family 1, who also had a *BAP1* germline mutation, c.2057-2A>G, in Fig 1A of our previous article[3]) was also diagnosed with cutaneous melanoma. There was residual epithelioid nevus that was intimately associated with the base of the melanoma (Fig 2A). The nevus component was composed of epithelioid cells and moderate nuclear pleomorphism, which was typical of the melanocytic skin tumors seen in patients with *BAP1* germline mutations (Fig 2B). The melanoma component (Fig 2C) comprised large, pleomorphic melanocytes displaying vesicular nuclei, prominent nucleoli, and several mitotic figures (arrows). The histologic appearances strongly suggested that the melanoma arose from the nevus. Both melanoma and nevus showed loss of BAP1 expression by immunohistochemistry (data not shown).

Discussion

BAP1 is a tumor susceptibility gene, but the complete phenotypic spectrum of tumors in *BAP1* mutation carriers remains to be accurately defined. Our novel data provide strong evidence that the tumor

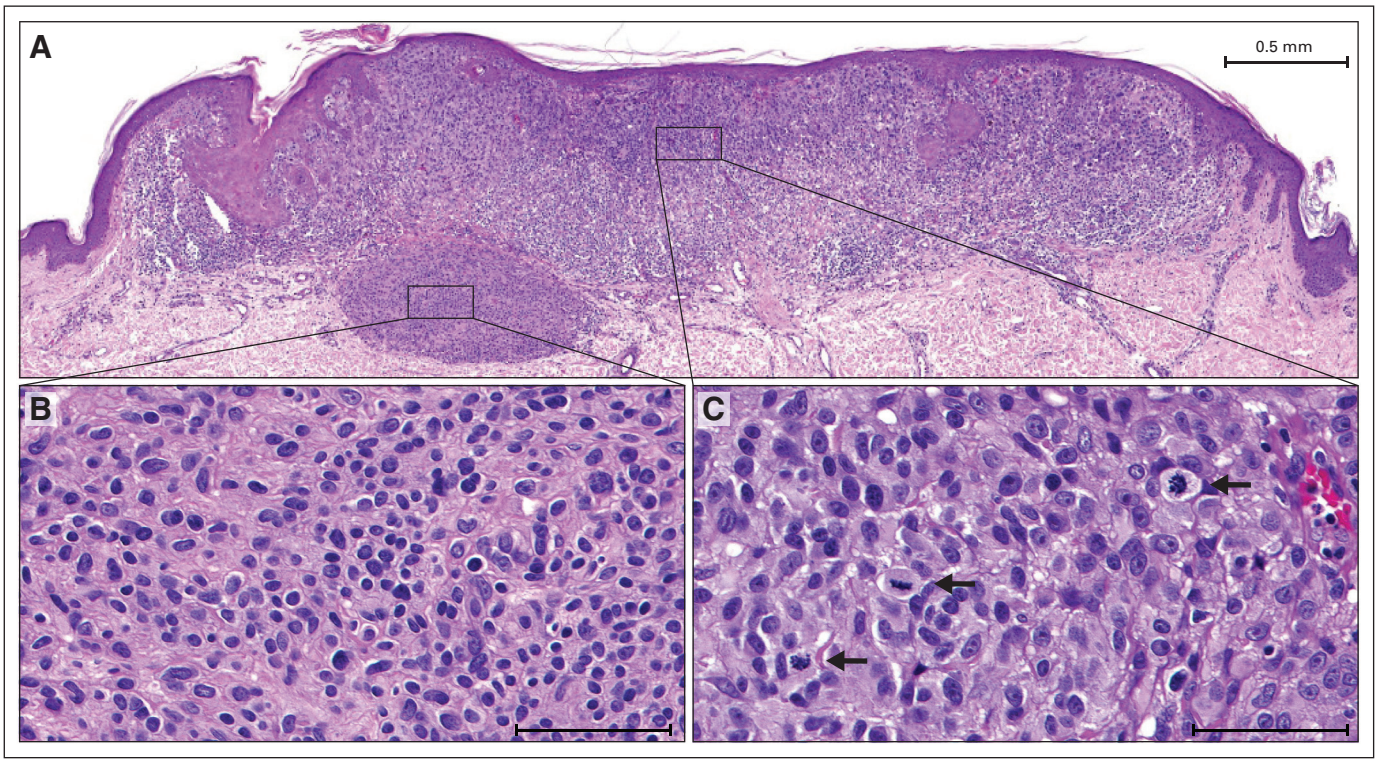

Fig 2.

spectrum associated with *BAP1* germline mutations shows significant overlap, and that melanocytic tumors and mesotheliomas may co-occur in patients with *BAP-1* germline mutations.

Interestingly, three of the five patients with mesothelioma (two of four patients in family 3 and one patient in family 2) had peritoneal mesotheliomas. This contrasts with sporadic mesothelioma, which arises in the pleura in approximately 70% of cases.[12] This is in keeping with previous reports about mesothelioma villages, a term that describes autosomal dominant inheritance of mesothelioma in certain families in which the incidence of peritoneal mesothelioma to pleural mesothelioma is approximately 1:1.[13,14] Thus, the incidence of peritoneal mesotheliomas may be relatively increased in the setting of hereditary susceptibility.

The identification of cutaneous melanoma in three separate families (family 1 and 2 in our reports, and in the family described by Abdel-Rahman[5]) suggests that cutaneous melanoma is also a *BAP1*-associated tumor. Our findings indicate that some of the typical epithelioid melanocytic skin tumors in *BAP1* mutation carriers may progress to melanoma. Thus, in melanocytes of the skin, *BAP1* seems to play a role similar to that of *APC* in familial adenomatous polyposis. Biallelic inactivation of *APC* causes multiple colorectal adenomas (akin to multiple epithelioid melanocytic tumors in patients with biallelic loss of *BAP1*). The adenomas (like the epithelioid melanocytic tumors) undergo malignant transformation at a low frequency and usually require other mutations to do so. We previously provided evidence that such additional mutations in the melanocytic skin tumors is the $BRAF^{V600E}$ mutation, which are observed in approximately 90% of tumors.[3]

In total, we identified 19 *BAP1* germline mutation carriers in our three families. Sixteen (84.3%) carriers developed epithelioid melanocytic tumors; five (26.3%) patients were diagnosed with mesothelioma (two peritoneal and two pleural, and one with both pleural and peritoneal); and cutaneous and uveal melanoma occurred in four (21.1%) and two (10.5%) patients, respectively. Although we did not observe other cancers in our families, Testa et al[5] and Abdel-Rahman et al[5] reported occurrence in *BAP1* mutation carriers of other tumors, such as cancers of the ovary, breast, kidney, pancreas, prostate, lung, and meningioma.

According to the Catalogue of Somatic Mutations in Cancer (COSMIC) database,[15,16] somatic *BAP1* mutations occur in 5% (three of 60) of ovarian cancers, 1% (one of 353) of breast cancers, 1% (two of 322) of lung adenocarcinomas, 0% (zero of 30) of pancreatic cancers, and 0% (zero of 58) prostate cancers. The COSMIC database does not yet include *BAP1* mutation data on meningioma or renal cell cancer, but a recent report describes somatic *BAP1* mutations in approximately 8% (eight of 98) of clear cell/renal cell carcinomas.[17] However, the low frequency of somatic *BAP1* mutations does not necessarily reflect the cancer risk in individuals with germline mutations; eg, somatic *BRCA1* mutations occur only in 2% of breast cancer (25 of 1,012 cases in COSMIC), but women with *BRCA1* germline mutations have a 54% to 85% risk of developing breast cancer.[18,19] The tumor susceptibility spectrum in patients with *BAP1* germline mutations can therefore only be determined by extensive genetic-epidemiologic studies.

In summary, our data support the suggestion[10] that the initial studies on *BAP1* germline mutations[3-5] were reporting a single syndrome with a wide range of tumors. According to our data, *BAP1* germline mutation carriers are predisposed to the development of melanocytic skin lesions, uveal and cutaneous melanoma, and mesothelioma with varying degrees of penetrance. The variation in the number of melanocytic tumors and in the incidence of mesothelioma among *BAP1* mutation carriers may reflect differences in the genetic background of the individuals or differences in their exposure to external contributing factors such as solar ultraviolet radiation or asbestos. Whether *BAP1* germline mutations also predispose to other cancer types remains to be clarified.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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