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# Two unique *BAP1* pathogenic variants identified in the same family by panel cascade testing

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## Abstract

Germline pathogenic variants in the tumor suppressor gene *BAP1* are associated with the hereditary tumor predisposition syndrome with susceptibility to uveal melanoma, mesothelioma, cutaneous melanoma, renal cell carcinoma, and other cancers. Germline *BAP1* pathogenic variants are rare in the non-cancer general population with an estimated carrier frequency of 1:19,898 but more common in cancer patients with a carrier frequency of 1:1299. In the following we present the first report of a family with two unique *BAP1* pathogenic variants. Retrospective case report of a family with two unique pathogenic variants in *BAP1*. A male (proband) was referred to our ocular oncology clinic for second opinion for his multiple independent uveal melanomas at ages 65, 68 and 71. Given his personal history of squamous cell carcinoma at age 61, renal cell carcinoma at age 63, and family history of atypical meningioma, basal cell carcinoma, pancreatic and prostate cancers he was assessed for germline pathogenic variants in *BAP1* through our ongoing research study. Sanger sequencing identified the American founder pathogenic variant, c.1717delC, pL573Wfs*3, that was confirmed in a clinical laboratory. Both the proband's brother and nephew tested negative for the familial variant through single site cascade genetic testing.

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**Conflict of interest** The authors have no conflicts of interest to declare.

**Ethical approval** This work was done under a research protocol approved by the Institutional Review Board of The Ohio State University.

**Consent to participate** Signed informed consent to participate was obtained from the patient.

**Consent for publication** The participant has consented to publication of the case report.

However, based on the personal history of multiple basal cell carcinoma in the nephew and family history of pancreatic and laryngeal cancers (both not known to be associated with *BAP1*-TPDS), a large cancer panel testing was recommended for the nephew. His panel testing revealed a different *BAP1* pathogenic variant, c.605G>A, p. Trp202*. This variant was not detected in the proband or the proband's brother. Based on the frequency of germline *BAP1* variants in the cancer population, the chance of occurrence of two different *BAP1* variants in a family with cancer history is $5.9 \times 10^{-7}$. This case report provides support for the importance of offering large panel cascade genetic testing, rather than single site testing for only the family pathogenic variant, for all at risk family members especially when the family variant cannot explain all the cancers in the family.

**Keywords**

Panel cascade genetic testing; Case report; BAP1; Familial cancer

## Introduction

Germline pathogenic variants in the tumor suppressor gene *BAP1* are associated with the hereditary tumor predisposition syndrome, *BAP1*-TPDS (OMIM 614327). *BAP1*-TPDS is an autosomal dominant condition with parents, children, and siblings having a 50% chance of inheriting a familial variant. The syndrome is associated with susceptibility to uveal melanoma, mesothelioma, cutaneous melanoma, renal cell carcinoma, and other cancers including meningioma, basal cell carcinoma, bile duct and liver cancers [1]. This syndrome was first reported in 2011 so our knowledge is still evolving [2–4]. Germline *BAP1* pathogenic variants are rare in the non-cancer general population with an estimated carrier frequency of 1:19,898. In cancer patients it is the 12th most common germline mutated cancer gene with a carrier frequency of 1:1299 [5].

Cascade genetic testing (CGT) is the sequential genetic testing recommended for blood relatives of an individual with germline pathogenic variant [6]. For genes associated with cancer predisposition, cascade testing benefits the carriers of the disease variants, with early diagnosis through regular screening and/or preventive interventions and can also benefit individuals who lack the familial variant by preventing unnecessary screenings or procedures [7]. CGT can also promote a longer, potentially cancer free life by implementing cancer screenings, surgical and non-surgical interventions. Screening recommendations exist for carriers of pathogenic *BAP1* variants that includes annual clinical, ophthalmological and dermatological examinations as well as abdominal MRI every 2 years [1, 8, 9]. Other screenings and imaging are being considered.

The value of CGT can be measured by the number of lives saved from decreasing cancer mortality and early-stage identification of cancer. It also leads to reduction in financial cost by preventing cancer as a result of following screening recommendations, compared to the cost of treating cancer.

Traditionally, CGT only evaluates a single site location for family variants. This is currently the National Comprehensive Cancer Network guidelines for management of patients with hereditary cancers. However, panel cascade testing is becoming more utilized as the cost of

genetic testing decreases, and as patients gain increasing access to genetic services. It has been identified that up to 5% of first-degree relatives carry an unexpected pathogenic variant not found in the proband [10]. The application of large-panel cascade testing in families who had previously undergone single site or disease-specific panels can observe an increased rate of detection of actionable findings [11].

Herein, we report a family with two different pathogenic variants in *BAP1*. The second alteration was missed on single site cascade testing but identified through panel testing.

## Case study

A 71-year-old Caucasian male (proband, patient III, 3) was referred to our uveal melanoma group for second opinion upon his third diagnosis of an independent uveal melanoma (UM). The patient was diagnosed with an inferotemporal cilio-choroidal melanoma in the left eye at 65 years old and he was treated with brachytherapy. He was diagnosed with a supernasal choroidal melanoma in the left eye 3 years later. Fine needle aspiration biopsy was performed, which confirmed the diagnosis of UM, and he was treated with diode laser. Three years later he was diagnosed with a third choroidal melanoma lesion nasally, also in the left eye, that was separate from the other lesion and was treated with diode laser ablation. Given the separate locations of the multiple UM tumors it has been concluded that these UM are likely separate primaries rather than recurrence from the original tumor.

His past medical history was significant for squamous cell carcinoma (SCC) at age 61 and renal cell carcinoma at 63. The histological type of renal cell carcinoma was not available from his medical chart. His renal cell carcinoma was treated with neoadjuvant therapy with temsirolimus, cytoreductive nephrectomy and adrenalectomy with IVC thrombectomy, and retroperitoneal lymphadenectomy. His family history was significant for a reported pancreatic cancer at age 64 in his mother (II, 3), late onset prostate cancer in his father (II, 2), an atypical meningioma in his sister at age 52 (III, 4), and a nephew (IV, 3) with three occurrences of basal cell carcinoma at age 47 (Fig. 1).

Due to the proband's extensive family and personal cancer history, he was referred to our research study for evaluation for *BAP1*-TPDS. Germline Sanger sequencing of *BAP1* was carried out according to our published protocol [2]. A pathogenic germline *BAP1* variant was identified c.1717delC, pL573Wfs*3 in our research lab, and was confirmed in a CLIA certified clinical laboratory [12–14]. The proband was also found to have a benign *BAP1* variant (c.1026C>T, p.SYN, rs71651686) that is known to segregate with this pathogenic variant [12–14].

Following identification of the *BAP1* c.1717delC, pL573Wfs*3 pathogenic variant, we encouraged the proband to invite members of his family to join our research study. The proband's nephew from his deceased sister, as well as his remaining brother, consented and underwent single site cascade genetic testing and both were negative for the family variant. However, the nephew (IV, 3) was referred for genetic counseling and large panel testing to rule out genetic alterations based on the family history of pancreatic cancer, which is not part of the *BAP1*-TPDS as well as, his personal history of multiple basal cell carcinomas.

He underwent testing in a clinical laboratory with a commercial thirty-three cancer gene panel that identified another pathogenic truncating variant in *BAP1* c.605G>A (p. Trp202*). Further evaluation showed that neither the proband (III, 3), the proband's brother (III, 2), nor the father of his nephew (III, 5) had this variant.

## Discussion

Herein we report two unique *BAP1* pathogenic variants identified within the same family. Both variants have been previously reported [12–14]. The c.1717delC, pL573Wfs*3 in our research lab, and was confirmed in a CLIA certified clinical laboratory. This variant is an American founder mutation previously reported in several families with different *BAP1* associated cancers [12–14]. The c.605G>A variant has been reported in a family from France with the proband presenting with UM and renal cell carcinoma [14].

BAP1 pathogenic/likely pathogenic (P/LP) variants in non-cancer general population as reported in the genome aggregate consortium (gnomAD) is rare with a carrier frequency of 1:19,898 [15]. However, the carrier frequency in unselected cancer patients is much higher 1:1299 with a frequency ranging from 0.5 to 3% in patients with hepatocellular carcinoma, renal cell carcinoma, uveal melanoma and mesothelioma. Based on the observed frequency of ~ 1:1299 germline *BAP1* pathogenic variants in cancer patients [5], the probability of incidentally identifying two separate *BAP1* variants in the same family is $5.9 \times 10^{-7}$. Panel testing may be warranted based on the combined personal and family history. In this case, it was obtained mainly due to the family history of pancreatic cancer which has not been associated with *BAP1*-TPDS, to rule out other genetic predisposition in the proband's nephew especially with his personal history of multiple basal cell carcinoma. In families where the familial variant cannot explain all the cancers in the family, panel testing is warranted to rule out additional genetic risk factors.

Individuals with a pathogenic variant in *BAP1* have up to 15%, 16.9%, 12%, and 7% risk for the development of uveal melanoma, mesothelioma, skin melanoma, and renal cancer, respectively [14]. In this case, the large-panel cascade genetic testing and diagnosis of *BAP1*-TPDS enabled the nephew to start surveillance for cancers associated with *BAP1*-TPDS, which identified multiple uveal nevi that are now being monitored.

This case demonstrates an example of a potential actionable genetic diagnosis that would have been missed without the use of panel cascade testing. Based on published costs of different clinical laboratories, panel cascade genetic testing is becoming increasingly more cost-effective [10]. The clinical cancer panels cost currently ranges from $250 to $500 while single site variant testing cost ranges from $150 to $250. Logistical barriers faced when obtaining family history can be overcomed by panel CGT, as this type of genetic testing serves to identify any variant important for cancer management [7].

In addition to this family, we have observed several other families where the segregation of the family variant doesn't explain different cancers in the family. To ensure that we do not miss additional pathogenic variants in family members, panel cascade testing will now be our standard for patient testing especially in those where the family variant cannot fully

explain the phenotype. We are reviewing families studied previously to assess if panel CGT can provide these families a clearer estimate of their cancer risk.

In conclusion, we report a two separate *BAP1* pathogenic variants in a family presenting with multiple different cancers because of panel CGT. This case report provides additional support for the importance of offering large panel cascade genetic testing, rather than testing for only the family pathogenic variant, for at risk family members especially in families where the family variant cannot fully explain all the cancers in the family.

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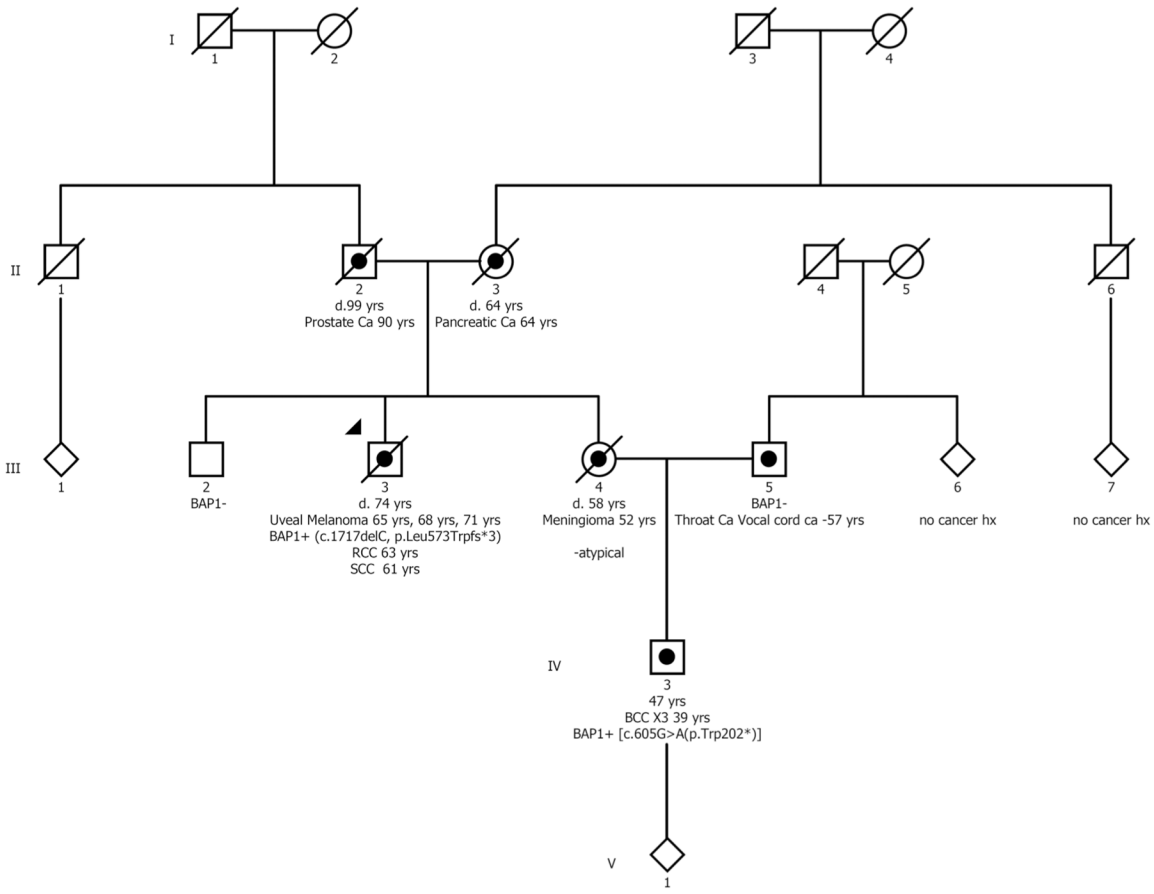


**Fig. 1.**

Pedigree of a family with two unique *BAP1* pathogenic variants. The proband (III.3) presented with recurrent uveal melanoma with personal history of renal cell and squamous cell carcinomas. Sanger sequencing identified a pathogenic variant c.1717delC. His nephew (IV.3) presented with personal history of recurrent basal cell carcinoma. He tested negative for the c.1717delC variant but has a different *BAP1* pathogenic variant c.605G>A. The brother of the proband (III.2) was negative for the two variants and the father of the nephew was negative for the c.605G>A variant. Other family members were not tested