AHOT Acta Haematologica Oncologica Turcica

Acta Haematol Oncol Turc 2025;58(3):232-239

Original Article

DOI: 10.4274/ahot.galenos.2025.2025-10-6

Broadening the Clinical and Molecular Spectrum of *BAP1* Tumor Predisposition Syndrome: Findings from the First Reported Turkish Cohort

Ceren Damla Durmaz[1], Elifcan Taşdelen[2], Erdem Kındış[1], Hande Nur Cesur Baltacı[3], İrem Koç[4], Nesibe Saliha Bulut[1], Eren Kılınç[5], Özge Özalp[3], Munis Dündar[5], Naz Güleray Lafcı[1], Hayyam Kıratlı[4]

[1]*Hacettepe University Faculty of Medicine, Department of Medical Genetics, Ankara, Türkiye*

[2]*University of Health Sciences Türkiye, Ankara Etlik City Hospital, Clinic of Medical Genetics, Ankara, Türkiye*

[3]*University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Clinic of Medical Genetics Türkiye, Ankara, Türkiye*

[4]*Hacettepe University Faculty of Medicine, Department of Ophthalmology, Ankara, Türkiye*

[5]*Erciyes University Faculty of Medicine Hospitals, Department of Medical Genetics, Kayseri, Türkiye*

ABSTRACT

Aim: *BAP1*-tumor predisposition syndrome (*BAP1*-TPDS) is a rare autosomal dominant condition predisposing to multiple malignancies, most notably uveal melanoma and mesothelioma. The full phenotypic and genotypic spectrum remains incompletely defined, particularly in underrepresented populations.

Methods: Six unrelated Turkish probands carrying germline pathogenic or likely pathogenic *BAP1* variants were identified through multigene hereditary cancer panel testing. Clinical data, family histories, and segregation analyses were evaluated, and variant classification followed American College of Medical Genetics and Genomics guidelines.

Results: All six affected individuals were female, with cancer onset between 38 and 57 years of age. Breast carcinoma was the most common diagnosis (n=4), followed by uveal melanoma (n=2). Three novel *BAP1* variants were identified, expanding the mutational landscape of *BAP1*-TPDS. Pedigree analysis revealed extensive familial clustering of malignancies, including uveal melanoma, colon carcinoma, hepatocellular carcinoma, and mesothelioma. None of the breast cancer patients carried additional pathogenic variants in known susceptibility genes.

Conclusion: This study describes the first Turkish cohort of germline *BAP1* carriers and broadens the clinical and genetic spectrum of *BAP1*-TPDS. The predominance of breast carcinoma highlights the need to consider *BAP1* testing in patients with early-onset or familial breast cancer. Integrating *BAP1* analysis into hereditary cancer panels will enhance recognition, risk stratification, and surveillance across diverse populations.

Keywords: *BAP1*, uveal melanoma, *BAP1*-tumor predisposition syndrome, breast cancer, hereditary cancer syndromes

Introduction

BAP1-tumor predisposition syndrome (*BAP1*-TPDS) is a rare autosomal dominant hereditary cancer syndrome caused by heterozygous germline pathogenic or likely pathogenic variants in the BRCA1-associated protein 1 (*BAP1*) gene [1,2]. *BAP1*-TPDS was first reported in 2011 in families with uveal melanoma and mesothelioma. Since then, it has been recognized as involving a broader spectrum of cancers, most commonly uveal melanoma, malignant mesothelioma, cutaneous melanoma, and renal cell carcinoma, which are regarded as the core tumors of the syndrome [1-3]. These cancers often arise at younger ages than their sporadic counterparts, and multiple tumor types may develop within the same individual or within a family [4,5].

Address for Correspondence: Ceren Damla Durmaz MD, Hacettepe University Faculty of Medicine, Department of Medical Genetics, Ankara, Türkiye
E-mail: ceren.damla.durmaz@hacettepe.edu.tr **ORCID ID:** orcid.org/0000-0002-6054-0709

Received: 27.10.2025 **Accepted:** 02.12.2025 **Publication Date:** 12.12.2025

Cite this article as: Durmaz CD, Taşdelen E, Kındış E, Cesur Baltacı HN, Koç İ, Bulut NS, Kılınç E, Özalp Ö, Dündar M, Lafcı NG, Kıratlı H. Broadening the clinical and molecular spectrum of *BAP1* tumor predisposition syndrome: findings from the first reported Turkish cohort. Acta Haematol Oncol Turc. 2025;58(3):232-239

In addition to malignant tumors, *BAP1* mutation carriers frequently develop *BAP1*-inactivated melanocytic tumors (MBAITs). These are benign dermal lesions with distinctive histopathologic and immunohistochemical features, including loss of nuclear *BAP1* expression [6]. Although they are non-malignant, MBAITs are increasingly regarded as cutaneous indicators of germline *BAP1* mutations and may precede malignant transformation [2]. Over the past decade, additional tumor types, including meningioma, cholangiocarcinoma, hepatocellular carcinoma, basal cell carcinoma, and breast carcinoma, have been proposed as part of the *BAP1*-TPDS spectrum, although the strength of these associations remains under investigation [5,7,8]. Louie and Kurzrock [9] summarized over 200 germline carriers, highlighting this heterogeneity and underscoring the growing relevance of *BAP1* in diverse cancer contexts.

Recent consensus guidelines recommend annual dermatologic and ophthalmologic surveillance, periodic imaging for mesothelioma and renal cancer, and cascade testing in families with confirmed pathogenic variants [10]. However, surveillance strategies for other, less established tumor types are not yet defined because their associations remain uncertain. Therefore, the publication of new clinical and genotypic data from diverse cohorts is essential to refine management recommendations and delineate the full phenotypic spectrum of the syndrome.

BAP1 is a tumor suppressor gene located on chromosome 3p21.1 that encodes a ubiquitin carboxyl-terminal hydrolase involved in chromatin remodeling, histone modification, the deoxyribonucleic acid (DNA) damage response, cell-cycle regulation, and apoptosis [11]. As the catalytic subunit of the polycomb repressive deubiquitinase complex, *BAP1* removes monoubiquitin from histone H2A (H2AK119ub) and thereby helps maintain transcriptional control and genomic integrity [12]. Similar to many hereditary cancer syndromes, tumor development in *BAP1*-TPDS is thought to follow a two-hit mechanism involving germline loss of one allele and somatic inactivation of the other [13].

Despite growing awareness of *BAP1*-TPDS, its true prevalence and associated cancer risks remain uncertain. Current estimates suggest lifetime risks of approximately 20-25% for uveal melanoma, mesothelioma, and cutaneous melanoma, with an overall risk of any *BAP1*-associated malignancy approaching 80-85% [5]. However, these figures are likely influenced by ascertainment bias, as most published series focus on index cases with multiple tumors or strong family histories, while unaffected carriers are underrepresented. In several studies, only probands underwent genetic testing, further limiting accurate penetrance estimates [7].

Most germline *BAP1* carriers reported to date are of European ancestry, while considerably fewer cases have been described in other ethnic groups, resulting in the underrepresentation of some populations in current knowledge of the syndrome. To date, no germline *BAP1*-positive families have been reported in Türkiye, highlighting a major gap in global data.

In this context, the present study reports the first Turkish cohort of individuals carrying germline *BAP1* variants, including those with uveal melanoma and breast carcinoma. The series also expands the genotypic landscape by identifying novel *BAP1* variants and integrates clinical and molecular data, enhancing understanding of *BAP1*-TPDS across populations.

Methods

This multicenter study included six unrelated probands from different families who were found to carry germline *BAP1* pathogenic or likely pathogenic variants. These variants were detected among individuals undergoing multigene hereditary cancer panel testing for various clinical indications. All participants were evaluated at the Department of Medical Genetics because of a clinical suspicion of hereditary cancer predisposition.

Clinical information, including tumor type, age at diagnosis, histopathologic findings, and family history of malignancy, was obtained through review of medical records and patient interviews.

The study was approved by the University of Health Sciences Türkiye, Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee (approval number: AEŞH-BADEK-2024-845, date: 25.09.2024) and conducted in accordance with the ethical standards of the Declaration of Helsinki. Written informed consent for genetic testing and publication of anonymized results was obtained from all participants before inclusion.

Peripheral blood samples were collected in ethylenediaminetetraacetic acid tubes, and genomic DNA was extracted using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. Next-generation sequencing was performed with a custom hereditary cancer panel targeting the coding exons and exon-intron boundaries of at least forty tumor-predisposition genes, including *APC, ATM, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, FANCC, FLCN, GALNT12, HOXB13, MEN1, MET, MLH1, MSH2, MSH6, MUTYH, NBN, NTHL1, PALB2, PMS2, POLD1, POLE, PTCH1, PTEN, RAD51C, RAD51D, RB1, RET, SMAD4, STK11, TP53,* and *VHL*.

Variant filtering and interpretation were conducted using the Seq Genomize Variant Analysis Platform and, in some cases, the Sophia DDM software, in accordance with each laboratory's standard workflow, following the recommendations of the American College of Medical Genetics and Genomics (ACMG) [14]. Only variants classified as pathogenic or likely pathogenic were reported. Each variant was manually reviewed in the Integrative Genomics Viewer (IGV) to confirm accuracy. Segregation analysis by Sanger sequencing was performed in available relatives who provided informed consent; this was feasible in only one family, in which the *BAP1* variant was tested in three unaffected daughters of the proband (P6).

Statistical Analysis

Descriptive statistics were applied to summarize demographic and clinical variables. Categorical data were expressed as frequencies and percentages, and continuous variables as medians with corresponding ranges. Owing to the descriptive nature of this cohort, no comparative or inferential statistical analyses were conducted. All calculations were performed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA; accessed October 2025).

Results

Clinical Characteristics of Affected Individuals

This study included six affected individuals from six unrelated families, each carrying germline *BAP1* variants. Detailed demographic, clinical, and molecular characteristics are summarized in Table 1. All patients were female and had a confirmed diagnosis of cancer. The ages at diagnosis ranged from 38 to 57 years, with a median of 47.5 years.

Breast carcinoma was the most frequent malignancy, occurring in four patients (66.7%). All tumors were unilateral; three were diagnosed as invasive ductal carcinoma and one as an invasive pleomorphic lobular carcinoma. Uveal melanoma was identified in the remaining two patients (33.3%), both of whom had unilateral involvement. One of these patients underwent enucleation and later developed distant metastases to the liver and iliac bone, while the other remained disease-free under regular ophthalmologic surveillance.

Pedigree analysis showed that four of the six families had at least two relatives affected by cancer, whereas the remaining families had only one or no additional affected individuals. In Family 6, the proband's brother was diagnosed with uveal melanoma and died of the disease; one of his sons developed a central nervous system tumor. Segregation analysis confirmed the presence of the familial *BAP1* variant in three unaffected daughters of the proband (P6). They are currently under follow-up in the dermatology, ophthalmology, and urology departments for surveillance of potential *BAP1*-associated manifestations. Family 5 also exhibited a substantial cancer burden, with close relatives diagnosed with colon carcinoma, mesothelioma, hepatocellular carcinoma, and primary brain tumors. Several other families had recurrent gastrointestinal or breast cancers across generations.

Genetic Findings

Six distinct *BAP1* variants, classified as pathogenic or likely pathogenic, were identified in the six affected individuals (NM_004656.4). These included three splice-site variants, two frameshift variants, and one non-sense variant (Figure 1). Three of these alterations [c.659+1G>A, c.784-2A>G, and c.1294_1295insGAA (p.Ser432Ter)] were novel and not previously reported in population or disease databases.

All affected individuals were heterozygous for their respective *BAP1* variants. The splice-site variant c.659+1G>A is located within the ubiquitin carboxy-terminal hydrolase (UCH) domain, which mediates the deubiquitinase activity of the *BAP1* protein [9]. The other two splice-site variants (c.783+1G>A and c.784-2A>G) are located in the *BARD1*-binding region, which interacts with the *BRCA1/BARD1* E3 ubiquitin ligase complex and participates in homologous recombination-mediated DNA repair (Figure 1) [9].

The frameshift variant c.1766_1770del (p.Ile589ArgfsTer52) and the nonsense variant c.1294_1295insGAA (p.Ser432Ter)

Table 1. Clinical and molecular characteristics of six affected individuals with germline *BAP1* variants

ID	Gender	Diagnosis	Age at cancer diagnosis (y)	Family history	*BAP1* (NM_004656.4) variant	Concurrent variant
P1	F	Breast cancer	38	-	c.1934del (p.Asn645Thr*fs*Ter10)	*BRCA2* (NM_000059.4) c.8524C>T p.(Arg2842Cys)
P2	F	Breast cancer	49	Father pancreas ca	c.659+1G>A	-
P3	F	Breast cancer	55	Father gastric ca, sister breast cancer, maternal cousin gastric ca	c.783+1G>A	-
P4	F	Breast cancer	42	Father prostate and lung ca, maternal uncle colon ca, maternal cousin leukemia, another maternal cousin breast ca	c.784-2A>G	-
P5	F	Uveal melanoma	44	Sister colon ca, another sister mesothelioma, maternal uncle HCC; one of his daughter CNS tumor, another maternal uncle dermatological ca, maternal cousin CNS tumor, paternal cousin colon ca	c.1766_1770del (p.Ile589Arg*fs*Ter52)	-
P6	F	Uveal melanoma	57	Brother uveal melanoma, one of his son CNS	c.1294_1295insGAA (p.Ser432Ter)	-

F: Female, HCC: Hepatocellular carcinoma, CNS: Central nervous system, ca: Carcinoma, –: not detected

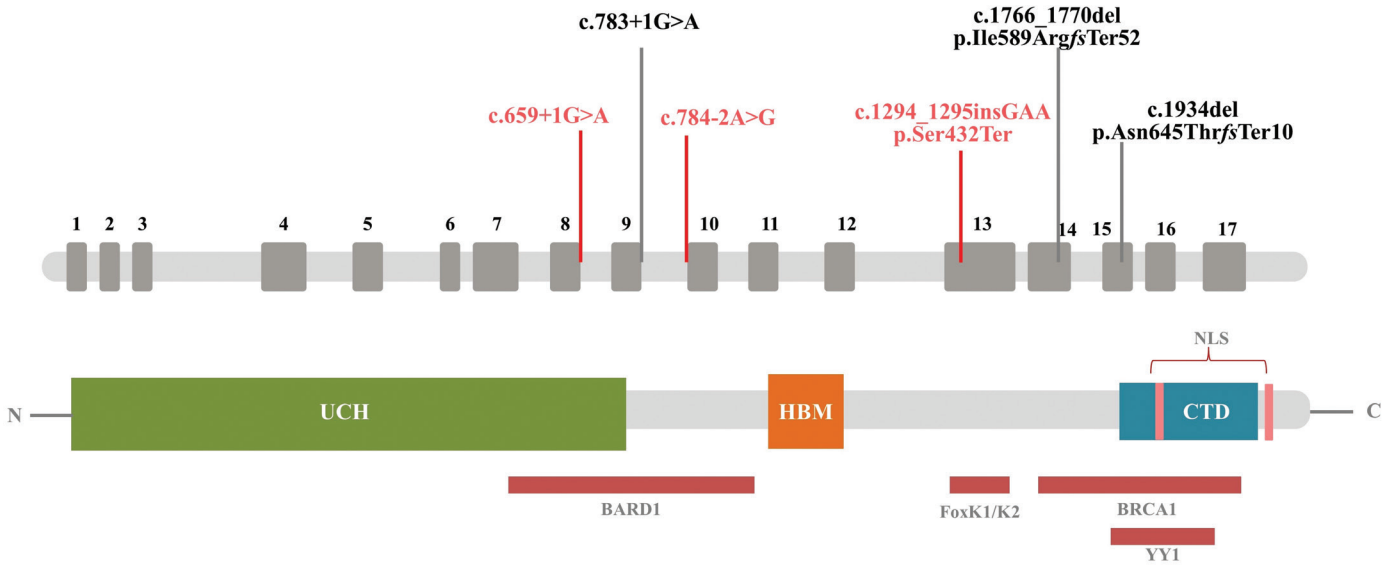


Figure 1. Schematic representation of *BAP1* protein domains and distribution of germline mutations
The upper bar represents the exons of the *BAP1* gene, while the lower bar depicts the corresponding functional protein domains. Intermittent red bars indicate known binding regions. Pathogenic variants identified in our cohort are mapped along the *BAP1* gene with the corresponding functional domains; novel variants are highlighted in red

UCH: Ubiquitin carboxyl hydrolase domain, *BARD1*: *BRCA1*-associated RING domain protein 1 (*BARD1*) binding region, HBM: host cell factor 1 (HCF1) binding domain, FoxK1/K2: Forkhead Box Protein K1/2 binding region, *BRCA1*: Breast cancer type 1 (*BRCA1*)-binding region, CTD: C-terminal domain, YY1: Yin Yang 1 (YY1) binding domain, NLS: Nuclear localization signals

both affect the C-terminal region of the protein, which is predicted to be intrinsically flexible and involved in dynamic interactions with chromatin-associated and transcriptional regulators [15,16]. The remaining frameshift variant c.1934del (p.Asn645ThrfsTer10) is located in the BRCA1-binding region, which is essential for the tumor-suppressive cooperation between *BAP1* and *BRCA1* in maintaining genomic stability [9]. Read-level IGV and Sanger views for all six germline *BAP1* variants are presented in Figure 2. In patients with breast cancer, no pathogenic or likely pathogenic variants were detected in other well-established breast cancer susceptibility genes. A heterozygous *BRCA1* variant (NM_000059.4: c.8524C>T, p.Arg2842Cys) identified in one patient was classified as a variant of uncertain significance according to ACMG guidelines [14].

Discussion

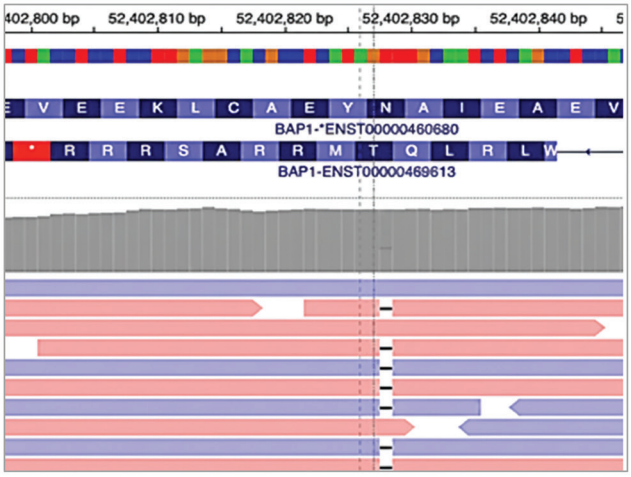
This study is the first report from Türkiye of a small cohort of six unrelated probands with germline *BAP1*-related cancers. The cohort included two patients with uveal melanoma and four with breast cancer, highlighting both classical and non-classical manifestations of *BAP1*-TPDS.

All six probands in our study carried heterozygous loss-of-function *BAP1* variants, comprising three splice-site and three frameshift mutations. Three of the six variants were novel, thus contributing to the expanding genotypic spectrum of *BAP1*-TPDS. All identified alterations are predicted to result in premature truncation or aberrant splicing, leading to complete loss of functional *BAP1* protein. Saturation genome-editing data from Waters et al. [17] show that variants impacting the catalytic and UCH domains, as identified in our patients, are strongly depleted, which is consistent with a loss of deubiquitinase function and supports their pathogenic role. These findings reinforce the concept that pathogenic *BAP1* variants act as tumor suppressors, with tumorigenesis following biallelic inactivation via a somatic second hit.

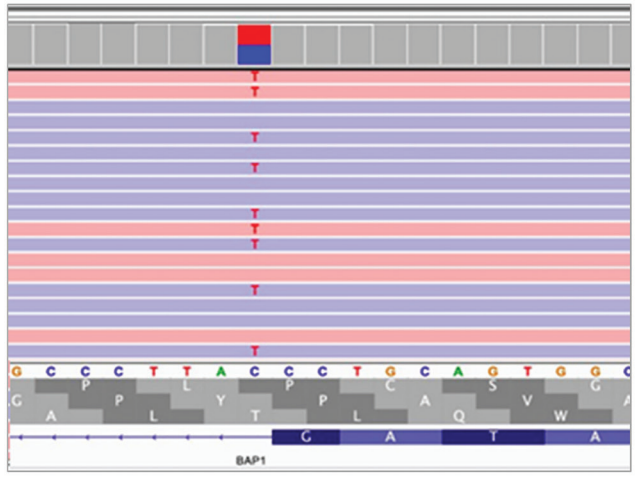
The clinical characteristics of our cohort illustrate the diversity of tumor presentation in *BAP1*-TPDS. All six probands were female, with cancer onset between 38 and 57 years of age. Four patients presented with breast carcinoma, three of whom were diagnosed before the age of 50, supporting the trend toward early tumor onset in *BAP1*-associated cancers, which is consistent with prior studies. The breast tumors were mainly invasive ductal carcinomas; one was of the lobular subtype, and several showed hormone receptor positivity and a high proliferative index.

The predominance of breast carcinoma in our cohort adds to the growing discussion about the potential inclusion of breast carcinoma within the *BAP1*-associated tumor spectrum. While these tumors have not yet been incorporated into formal diagnostic criteria, several case reports and small series have described this association [5,8]. Non-etheless, the predominance of breast cancer in our series may partly reflect selection bias, as individuals with suspected hereditary breast cancer represent the largest group referred for multigene panel testing in our clinical practice. Functionally, the link is biologically plausible: *BAP1* interacts with BRCA1 and other homologous recombination (HR) repair proteins, and its loss impairs double-strand break repair, resulting

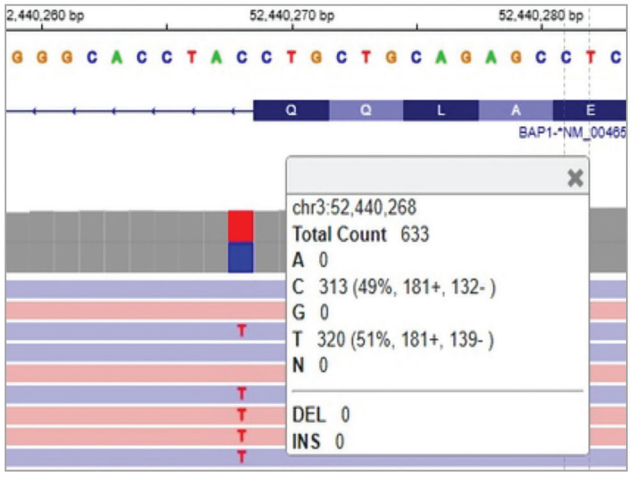
P1 *BAP1*: c.1934del (p.Asn645Thr*fs*Ter10)



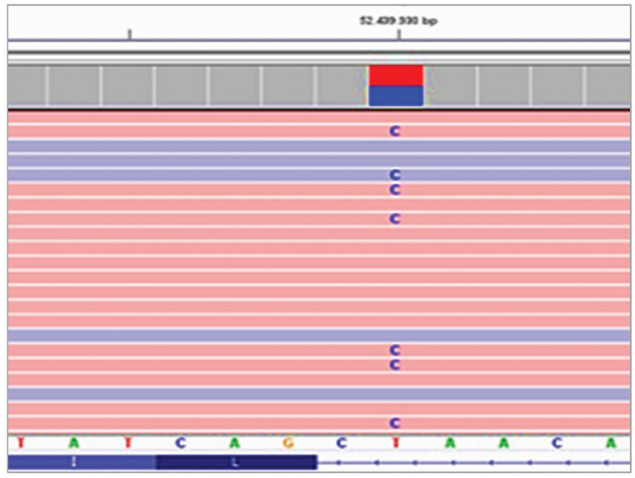
P2 *BAP1*: c.659+1G>A



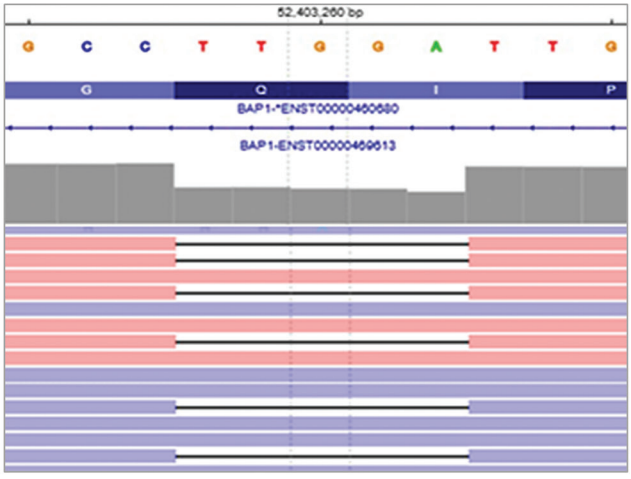
P3 *BAP1*: c.783+1G>A



P4 *BAP1*: c.784-2A>G



P5 *BAP1*: c.1766_1770del (p.Ile589ArgfsTer52)



P6 *BAP1*: c.1294_1295insGAA (p.Ser432Ter)

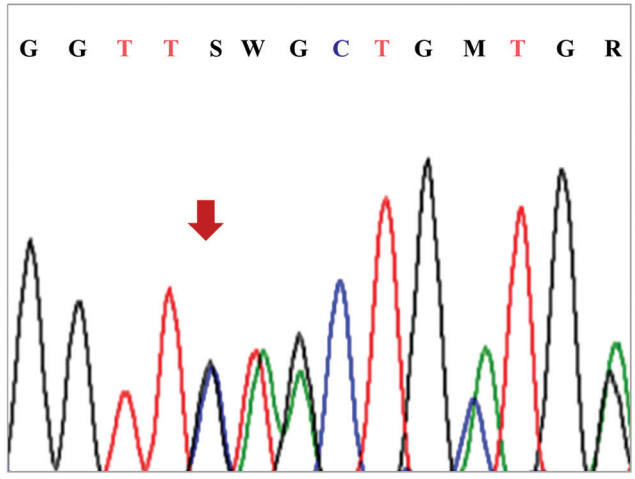


Figure 2. IGV and Sanger representations of the germline *BAP1* variants in probands P1-P6
Integrative genomics viewer (IGV) screenshots and Sanger sequencing chromatograms demonstrating the six germline *BAP1* variants detected in probands P1-P6

in genomic instability [18]. This HR-deficient phenotype resembles that seen in *BRCA1/2*-mutated tumors, suggesting potential therapeutic overlap. As such, confirming the role of *BAP1* in breast cancer predisposition could have clinical implications, including the application of poly (adenosine diphosphateribose) polymerase inhibitors in selected patients. Evaluating homologous recombination deficiency (HRD) in *BAP1*-mutant breast cancers may help identify those who could benefit from such therapies, representing an important direction for future studies.

The two probands with uveal melanoma were diagnosed at ages 44 and 57, respectively, consistent with the typical tumor spectrum of *BAP1*-TPDS. Their family histories were remarkable for additional malignancies: the 44-year-old proband had a sister with malignant mesothelioma, and the 57-year-old proband had a brother who died from uveal melanoma. In our cohort, family histories also included a wide range of other cancers—such as breast, colorectal, bladder, pancreatic, and hematologic malignancies—among relatives who were not genetically tested. The occurrence of these diverse tumors within *BAP1*-positive families may indicate that the phenotypic spectrum of *BAP1*-TPDS is broader than currently appreciated.

Beyond its role in inherited cancer risk, *BAP1* status influences tumor aggressiveness and treatment response, making it a potential biomarker for prognosis and therapy selection. *BAP1*-mutant uveal melanoma is associated with aggressive clinical behavior and early metastasis [19], whereas *BAP1*-deficient mesothelioma paradoxically exhibits improved outcomes and longer survival compared with sporadic forms of mesothelioma, likely due to increased sensitivity to platinum-based chemotherapy [20]. Thus, *BAP1* testing can inform both prognosis and therapy, identifying patients who may benefit from DNA-damaging agents or, conversely, those who require intensified surveillance.

Clinicians should maintain a high level of suspicion for *BAP1*-TPDS in specific clinical contexts. Testing should be considered in patients with (i) early-onset or multifocal uveal melanoma, (ii) patients with malignant mesothelioma diagnosed before age 50 or in the absence of significant asbestos exposure, (iii) patients with atypical melanocytic lesions with *BAP1* loss on immunohistochemistry, and (iv) individuals or families with multiple primary cancers, including uveal melanoma, mesothelioma, renal cancer, or early-onset breast carcinoma [7,10] (Table 2). From a clinical management perspective, our findings emphasize the importance of including *BAP1* in hereditary cancer panels. Several of our patients were identified through broad multigene testing rather than clinical suspicion alone, demonstrating that single-gene approaches may overlook this syndrome. The recognition of *BAP1*-TPDS in patients with early-onset or multiple primary cancers is crucial, especially when *BRCA1/2* testing is negative. Panel inclusion not only improves detection but also enables family-based risk assessment and cascade testing.

Surveillance and prevention remain the cornerstones of managing *BAP1* carriers. Current consensus guidelines recommend initiating follow-up in late adolescence, with annual dermatologic and ophthalmologic examinations, periodic chest and abdominal imaging, and avoidance of exposure to ultraviolet radiation and asbestos [7,10]. Predictive genetic testing should be offered once a familial pathogenic variant is confirmed. Identifying carriers before tumor onset enables early intervention and risk-adapted monitoring.

Although our study includes a small number of cases, it provides valuable insight from an underrepresented population. The predominance of breast carcinoma, a history of multifocal tumors, and strong familial clustering observed in our cohort highlight the importance of considering *BAP1* alterations in patients with suggestive clinical features. Further functional and clinical studies are needed to better define the prevalence and biological behavior of *BAP1*-mutant breast cancers and to identify potential therapeutic vulnerabilities related to HRD.

While *BAP1* loss impairs several DNA damage-response pathways and contributes to genomic instability, environmental factors may further modify cancer risk and phenotype in certain populations. Cappadocia, in central Türkiye, has a high incidence of mesothelioma owing to long-standing environmental exposure to erionite and asbestos [21]. Previous investigations in these villages did not identify germline *BAP1* mutations, suggesting that environmental carcinogenesis alone was sufficient to explain the observed clustering of cases [22]. Nevertheless, given the established synergistic effect of *BAP1* deficiency and mineral fiber exposure in experimental models, continued genetic surveillance in this region remains warranted. Identifying potential germline carriers among individuals with early-onset or familial mesothelioma could provide valuable insight into the interplay between environmental and hereditary risk factors.

Study Limitations

The main limitation of this study is the small cohort size, which restricts the generalizability of the findings. A second limitation is the inability to perform functional assays to validate the pathogenicity of the novel *BAP1* variants. In addition, segregation analysis in cancer-affected relatives could not be completed, as several affected family members were not available for testing. Despite these constraints, the study provides valuable insight into the clinical and genetic features of *BAP1*-TPDS in an underrepresented population.

Conclusion

In conclusion, our findings demonstrate that *BAP1*-TPDS is a clinically actionable hereditary cancer syndrome. It should be considered in patients with early-onset cancers or multiple primary malignancies, particularly when the family history includes diverse cancer types. Recognizing and testing for *BAP1* is crucial for accurate risk assessment, prognostic evaluation, and treatment planning. Incorporating *BAP1* analysis into hereditary cancer panels will facilitate the timely identification of carriers, the implementation of structured surveillance, and

Table 2. Clinical situations in which germline *BAP1* testing may be considered

Clinical context	Rationale
Early-onset uveal melanoma (<50 years) or multifocal uveal melanoma	Classical *BAP1*-associated tumor; early onset increases suspicion
Malignant mesothelioma <50 years or without significant asbestos exposure	Suggests hereditary etiology rather than environmental cause
Atypical melanocytic lesions with loss of *BAP1* expression on IHC (MBAITs)	Recognized dermatological marker of germline *BAP1* variants
Individuals with multiple primary tumors, including any core *BAP1*-associated tumors	Fits the typical pattern of *BAP1*-TPDS
Families with ≥2 relatives affected by uveal melanoma, mesothelioma, renal cell carcinoma, or related malignancies	Suggestive familial clustering
Early-onset or familial breast cancer with additional diverse tumors in the family	Emerging association; not a formal criterion, but may raise suspicion

Core *BAP1*-associated tumors: uveal melanoma, malignant mesothelioma, cutaneous melanoma, and renal cell carcinoma. IHC: Immunohistochemistry, MBAITs: BAP1-inactivated melanocytic tumors, BAP1-TPDS: *BAP1*-tumor predisposition syndrome

the consideration of targeted therapeutic strategies, such as platinum-based therapies. Altogether, this study reinforces that *BAP1* predisposition extends beyond its classical tumor spectrum and carries significant implications for precision oncology and the prevention of familial cancer.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee (approval number: AEŞH-BADEK-2024-845, date: 25.09.2024) and conducted in accordance with the ethical standards of the Declaration of Helsinki.

Informed Consent: Written informed consent for genetic testing and publication of anonymized results was obtained from all participants before inclusion.

Declaration Regarding the Use of AI and AI-Assisted Technologies

During manuscript preparation, the authors used OpenAI's ChatGPT (GPT-5, San Francisco, CA, USA) as a language-support tool to improve the clarity, grammar, and fluency of the text. The tool was not used for data analysis, figure preparation, or the generation of scientific content. All outputs produced by the AI tool were carefully reviewed, edited, and verified by the authors. The authors take full responsibility for the integrity and accuracy of the entire manuscript.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.D.D., E.T., E.K., H.N.C.B., İ.K., Ö.Ö., M.D., N.G.L., H.K., Concept: C.D.D., H.K., Design: C.D.D., N.S.B., N.G.L., H.K., Data Collection or Processing: C.D.D., E.T., E.K., H.N.C.B., İ.K., Ö.Ö., M.D., N.G.L., H.K., Analysis or Interpretation: C.D.D., E.T., E.K., H.N.C.B., İ.K., Ö.Ö., N.G.L., Literature Search: C.D.D., N.G.L., Writing: C.D.D., E.T., E.K., H.N.C.B., İ.K., Ö.Ö., M.D., N.G.L., H.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Testa JR, Cheung M, Pei J, et al. Germline BAP1 mutations predispose to malignant mesothelioma. Nat Genet. 2011;43:1022-1025.
2. Wiesner T, Obenauf AC, Murali R, et al. Germline mutations in BAP1 predispose to melanocytic tumors. Nat Genet. 2011;43:1018-1021.
3. Popova T, Hebert L, Jacquemin V, et al. Germline BAP1 mutations predispose to renal cell carcinomas. Am J Hum Genet. 2013;92:974-980.
4. Rai K, Pilarski R, Cebulla CM, Abdel-Rahman MH. Comprehensive review of BAP1 tumor predisposition syndrome with report of two new cases. Clin Genet. 2016;89:285-294.
5. Walpole S, Pritchard AL, Cebulla CM, et al. Comprehensive study of the clinical phenotype of germline BAP1 variant-carrying families worldwide. J Natl Cancer Inst. 2018;110:1328-1341.
6. Carbone M, Ferris LK, Baumann F, et al. BAP1 cancer syndrome: malignant mesothelioma, uveal and cutaneous melanoma, and MBAITs. J Transl Med. 2012;10:179.
7. Pilarski R, Byrne L, Carlo MI, et al. BAP1 Tumor Predisposition Syndrome. 2016 Oct 13 [Updated 2024 Dec 5]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.
8. Abdel-Rahman MH, Pilarski R, Cebulla CM, al. Germline BAP1 mutation predisposes to uveal melanoma, lung adenocarcinoma, meningioma, and other cancers. J Med Genet. 2011;48:856-859.
9. Louie BH, Kurzrock R. BAP1: not just a BRCA1-associated protein. Cancer Treat Rev. 2020;90:102091.
10. Lalloo F, Kulkarni A, Chau C, et al. Clinical practice guidelines for the diagnosis and surveillance of BAP1 tumour predisposition syndrome. Eur J Hum Genet. 2023;31:1261-1269.
11. Wang A, Papneja A, Hyrcza M, Al-Habeeb A, Ghazarian D. Gene of the month: BAP1. J Clin Pathol. 2016;69:750-753.
12. Ventii KH, Devi NS, Friedrich KL, et al. BRCA1-associated protein-1 is a tumor suppressor that requires deubiquitinating activity and nuclear localization. Cancer Res. 2008;68:6953-6962.
13. Harbour JW, Onken MD, Roberson ED, et al Frequent mutation of BAP1 in metastasizing uveal melanomas. Science. 2010;330:1410-1413.
14. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-424.
15. Daou S, Hammond-Martel I, Mashtalir N, et al. The BAP1/ASXL2 histone H2A deubiquitinase complex regulates cell proliferation and is disrupted in cancer. J Biol Chem. 2015;290:28643-28663.

16. Sharma A, Biswas A, Liu H, et al. Mutational landscape of the BAP1 locus reveals an intrinsic control to regulate the miRNA network and the binding of protein complexes in uveal melanoma. Cancers (Basel). 2019;11:1600.
17. Waters AJ, Brendler-Spaeth T, Smith D, et al. Saturation genome editing of BAP1 functionally classifies somatic and germline variants. Nat Genet. 2024;56:1434-1445.
18. Ismail IH, Davidson R, Gagné JP, Xu ZZ, Poirier GG, Hendzel MJ. Germline mutations in BAP1 impair its function in DNA double-strand break repair. Cancer Res. 2014;74:4282-4294.
19. Robertson AG, Shih J, Yau C, et al. Integrative analysis identifies four molecular and clinical subsets in uveal melanoma. Cancer Cell. 2017;32:204-220.e15.
20. Baumann F, Flores E, Napolitano A, et al. Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival. Carcinogenesis. 2015;36:76-81.
21. Carbone M, Emri S, Dogan AU, et al. A mesothelioma epidemic in Cappadocia: scientific developments and unexpected social outcomes. Nat Rev Cancer. 2007;7:147-154.
22. Carbone M, Yang H, Pass HI, Krausz T, Testa JR, Gaudino G. BAP1 and cancer. Nat Rev Cancer. 2013;13:153-159.