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2022-03

Repo , P , Staskiewicz , A , Sutinen , E , Rönty , M , Kivelä , T T , Myllärniemi , M & Turunen , J A 2022 , ' BAP1 germline variants in Finnish patients with malignant mesothelioma ' , Lung Cancer , vol. 165 , pp. 102-107 . https://doi.org/10.1016/j.lungcan.2022.01.017

http://hdl.handle.net/10138/346499
https://doi.org/10.1016/j.lungcan.2022.01.017

Lung Cancer 165 (2022) 102–107

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

BAP1 germline variants in Finnish patients with malignant mesothelioma

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ARTICLE INFO

Keywords:
Malignant mesothelioma
BAP1
Tumor predisposition
BAP1-TPDS
BAP1-inactivated nevus

ABSTRACT

Objectives: Although asbestos exposure is the most common cause of malignant mesothelioma (MM), an aggressive cancer of the pleura or peritoneum, up to 7% of patients harbor a genetic predisposition to MM. Pathogenic germline variants in the *BRCA1-associated protein 1* (*BAP1*) gene cause a dominantly inherited tumor predisposition syndrome, BAP1-TPDS, in which MM is the second most common associated cancer. Other frequent cancers in BAP1-TPDS are uveal melanoma (UM), cutaneous melanoma and renal cell carcinoma. Additionally patients can exhibit benign skin lesions, *BAP1*-inactivated nevi (BIN). Most BINs arise sporadically, but patients with BAP1-TPDS may harbor multiple BINs before other tumors or as the only indication of the syndrome. Our objective was to establish the frequency of pathogenic germline *BAP1* variants in Finnish patients with MM.

Materials and methods: 56 DNA samples archived in the Helsinki Biobank from Finnish patients with MM were sequenced for germline *BAP1* variations. Formalin fixed paraffin embedded nevi from a pathogenic variant carrier were subjected to immunohistochemistry and exome sequencing.

Results: Sanger sequencing identified one patient with Finnish founder mutation c.1780_1781insT, p.(G549Vfs*49) in *BAP1*. The carrier was diagnosed with MM over fifteen years before the cohorts mean onset age (mean 68, range 27 to 82) although the patient had no asbestos exposure or family history of BAP1-TPDS. However, the patient had three BINs removed prior to the MM. The c.1780_1781insT is now found from five Finnish BAP1-TPDS families with unknown common ancestor.

Conclusion: The frequency of pathogenic germline *BAP1* variants in Finnish patients with MM is 1.8 % (95 % CI, 0.04 to 9.2), comparable to the frequency in Finnish patients with UM (1.9 %). The frequency of recurring BINs in patients with BAP1-TPDS should be studied further and genetic testing for *BAP1* variants considered if the patient has $\geq$ 2 BAP1-TPDS core tumors, including BINs.

1. Introduction

Malignant mesothelioma (MM) is an aggressive cancer of the pleura or peritoneum with the annual incidence of 14.7/million in Finland [1]. Prolonged occupational or other exposure to asbestos is the most common cause of MM. The risk depends on age, gender, and geographical location because of differences in the use of asbestos [1]. Additionally, 12 % of the patients with MM are identified with a pathogenic germline variant in *BAP1*, *BLM*, BRCA1-2, *CDKN2A*, CHEK2, MLH1-2, MRE11A, PALB2, POT1 or TP53 [2,3]. Variants in the BRCA1-associated protein 1 (*BAP1*) tumor suppressor gene are the most frequent and found in up to 7 % of patients with MM [2]. In *Bap1* mutant mice, minimal exposure to asbestos is enough to promote the development of MM [4], but germline *BAP1* mutation prompts the MM formation independently of asbestos [5]. Almost one-half of patients with MM die within one year from diagnosis despite of treatment, and about 80 % die in three years [1]. Loss of BAP1 has adverse effects on patient prognosis as it can prolong survival for up to 5 years [6].

MM is the second most common cancer in the dominantly inherited BAP1-tumor predisposition syndrome (BAP1-TPDS; OMIM 614327)

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https://doi.org/10.1016/j.lungcan.2022.01.017
Received 30 November 2021; Received in revised form 17 January 2022; Accepted 20 January 2022
Available online 24 January 2022

arising in 17 % of non-probands and 25 % of probands with *BAP1* null variant [7]. Uveal melanoma (UM) is considered the most common BAP1-TPDS related tumor and observed in 16 % of non-proband and 36 % of proband variant carriers [7]. Other frequent cancers occurring in this syndrome are cutaneous melanoma and clear cell renal cell carcinoma, accounting for 12 %, and 5 %, respectively, of the tumors observed in non-proband null variant carriers [7]. The spectrum of cancers is expected to expand as more pathogenic variants carriers are identified [7].

Patients affected by BAP1-TPDS exhibit often multiple benign skin lesions, *BAP1*-inactivated nevi (BIN) [7,8]. BINs may occur even before cancer or as the only associated tumor [9]. Variably referred to as a *BAP1*-inactivated melanocytic tumor, atypical Spitz tumor, or BAPoma, BIN is generally a small dome-shaped melanocytic lesion of the skin that can be pinkish in color [8]. By immunohistochemistry (IHC), BIN show at least partial loss of nuclear BAP1 staining. Because the skin has not been systematically screened, the true frequency of BINs in carriers of deleterious *BAP1* variants is not known [7]. Most BINs have underwent a somatic BAP1 inactivation, but 12–20 % of patients with BINs harbor a pathogenic *BAP1* variant in the germline and 75 % of variant carriers have at least one BIN [9].

The frequency of pathogenic germline *BAP1* variants in Finland has so far been systematically studied in patients with UM, where their frequency is 1.9% [10]. Two Finnish founder mutations have been identified in four (c.1780_1781insT) and two (c.67 + 1G > T) families [10]. Here we report germline variant analysis of *BAP1* in Finnish patients with MM collected from the biobank.

2. Materials and methods

2.1. Patient selection

All Finnish patients diagnosed with MM between 2010 and 2019 with relevant material donated to the Helsinki Biobank were eligible to participate in the study. The project was approved by the institutional review board of the Hospital Region of Helsinki and Uusimaa and was conducted following the tenets of the Declaration of Helsinki. All patients gave informed written Biobank consent.

2.2. DNA samples and mutation analysis

Germline DNA was isolated at the Helsinki Biobank from frozen peripheral blood buffy coats using QIASymphony DSP DNA Midi Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Germline *BAP1* variant analysis was done using Sanger sequencing as described earlier [10]. More on variant interpretation can be found in Supplementary Methods.

For mutation analyses on nevi, 1–3 punches (1 mm diameter) from formalin-fixed, paraffin-embedded (FFPE) blocks were subjected to QS GeneRead DNA FFPE Treatment followed by DNA extraction with QS DSP DNA mini kit using automated QIAsymphony SP (all from Qiagen) procedure at the Helsinki Biobank. Exome sequencing was done at the Institute for Molecular Medicine Finland (FIMM) Technology Centre, University of Helsinki (detailed description of exome sequencing and bioinformatics analysis are presented in Supplementary Methods). The panel of analyzed genes included those found often mutated in nevi and are listed in Supplementary Table S1.

2.3. Immunohistochemistry

The calretinin and BAP1 immunohistochemistry stainings for diagnostic purposes were obtained from the pathology department and detailed information is available upon request. Briefly, sections were stained for calretinin (Abcam, Cambridge, UK) and BAP1 (Santa Cruz Biotechnology, Dallas, TX) with Ventana Benchmark XT using Optiview detection kit (760–700, Roche, Ventana, Tucson, AZ). The stainings

Table 1
Rare germline *BAP1* variants identified in 56 Finnish patients with malignant mesothelioma (gnomAD minor-allele-frequency < 0.1 % in Finns).

Chromosomal location (GRCh37)	CDS position (NM_004656)	Region	Protein	rs number	gnomAD FIN	gnomAD ALL	CADD	SpliceAI Δ score	ClinVar	ACMG	
chr3:52437263_52437264	c.1780_1781insT	ex14	G594Vfs*49	-	n/a	n/a	n/a	–	NA	Pathogenic	PVS1, PM2, PP1, PS3
chr3:52 437 205	c.1839G > A	ex14	T613T	rs756450018	0.0002790	0.00004243	0.326	DG 0.11 (AG/AL/DL 0.0)	Likely benign	Benign	BS1, BS2, BP6, BP4

n/a = not available; CADD = Combined Annotation Dependent Depletion; DG = donor gain; AG = acceptor gain; AL = acceptor loss; DL = donor loss; ACMG = American College of Medical Genetics
PVS1 = null variant in a gene where LOF is a known mechanism of disease, PM2 = absent from controls in gnomAD, PP1 = cosegregation with disease in affected family members in a gene definitively known to cause the disease, PS3 = functional studies supportive of damaging effect on the gene, BS1 = allele frequency is greater than expected for disorder, BS2 = observed in healthy individual for a dominant disorder with full penetrance, BP6 = reputable source reports variant as benign, but the evidence is not available for independent evaluation, BP4 = multiple lines of computational evidence suggest no impact on the gene

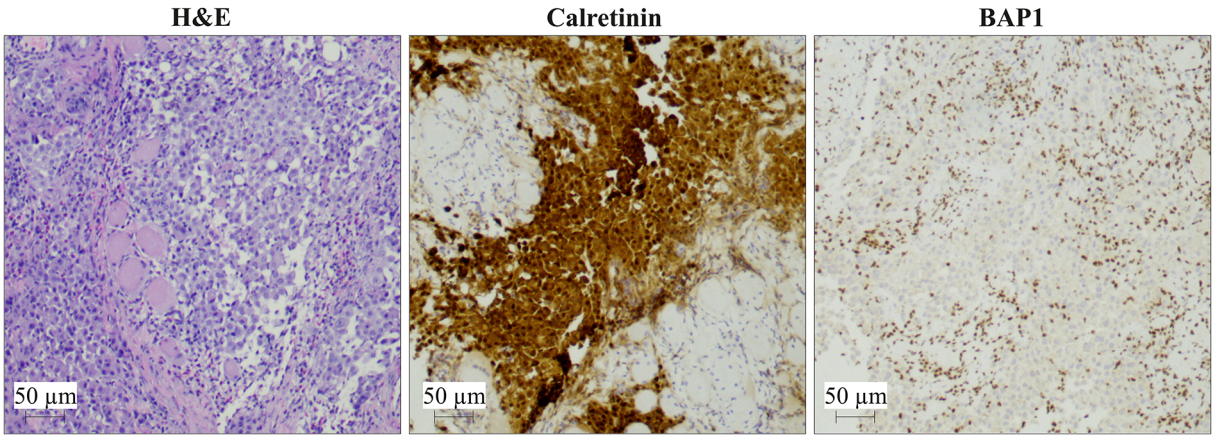

Fig. 1. Immunohistochemical stainings of the primary malignant mesothelioma. The biopsy (A) was stained for calretinin (B) and BAP1 (C). The tumor cells are calretinin positive and BAP1 negative.

were scanned using Pannoramic 250 FLSH III digital scanner (3DHistech, Budapest, Hungary) and analyzed using CaseViewer viewing application (3Dhistech).

3. Results

3.1. Study cohort

The 56 enrolled patients were mostly male (82 %) (Supplementary Table S2). 53 (95 %) of the patients exhibited pleural mesothelioma, one had peritoneal and one pericardial mesothelioma. Additionally, one patient was diagnosed with well-differentiated papillary mesothelioma of the peritoneum. The mean age at diagnosis was 68 years (range, 27 to 82); two patients (4 %) were younger than 50 years. Asbestos exposure was reported by 29 (52 %) patients, all male, 9 (16 %) patients were unaware of possible exposure, and exposure history was not available for a single patient. One patient, diagnosed with MM at the age of 58 years without any history of asbestos exposure, had 3 of 4 siblings diagnosed with MM. One of them reported asbestos exposure. The mean survival of 46 (82 %) deceased patients was 2.2 years. Ten patients were alive at the time of the study with a mean survival of 3.3 years after diagnosis. Patient demography can be found in Supplementary Table S2.

3.2. One patient with MM is heterozygous for a pathogenic Finnish founder mutation

Two patients, who reported no family history of BAP1-TPDS related cancers, were heterozygous for two different rare variants in exon 14 of *BAP1* (Table 1). However, the cohorts' only patient with several first-degree relatives affected by MM was not identified with a germline *BAP1* variant.

The first patient harbored a synonymous variant c.1839G > A (p.Thr613Thr, rs756450018), and the computational algorithm predicts no probable effect on splicing (Table 1). Following the classification of American College of Medical Genetics guidelines (ACMG), we interpret it as benign.

The second patient was heterozygous for the pathogenic Finnish founder variant c.1780_1781insT described previously from four different Finnish families with UM [10]. This thymine insertion causes a frameshift leading to premature termination of protein translation p.(Gly594Valfs*49). The patient developed MM more than 15 years before the cohort mean age at diagnosis (68 years, Supplementary Table S2), did not smoke, and had no asbestos exposure. Instead of the frequently longer survival observed in *BAP1* mutation carriers with MM [6], the patient died within a year after diagnosis. Immunohistochemical staining of the mesothelioma was positive for calretinin and negative for BAP1 (Fig. 1).

3.3. BAP1 c.1780_1781insT variant carrier with recurring BINs

The patient with the c.1780_1781insT variant had eight nevi removed before the diagnosis of MM. Three of the nevi (#2, 4, and 5) were BINs characterized by loss of nuclear BAP1 staining in immunohistochemistry (Fig. 2).

DNA extracted from five nevi, including the three BINs, was analyzed for somatic variations commonly observed in nevi using exome sequencing (Table 2, Fig. 2). Genes subjected for analysis are listed in Supplementary Table S1. Nevi #1 and 3 retained BAP1 and had somatic *BRAF* c.1799 T > A, p.(Val600Glu) and *NRAS* c.181C > A, p.(Gln61Lys) mutations. All three BINs harbored the *BRAF* p.(Val600Glu) variant, and nevus #4 additionally had a second *BRAF* variant c.1825C > G, p.(Gln609Glu) in the same allele. Nevus #2, a BIN with low-grade dysplasia, harbored a second truncating *BAP1* variant c.178C > T, p.(Arg60Ter) leading to biallelic loss of BAP1 and negative IHC staining. This BIN harbored an additional *PLCB4* variant c.1181A > T, p.(Glu394Val) with inconsistent *in silico* predictions about pathogenicity (Table 2, Supplementary Table S3). In the two other BINs, nevus #4 and 5, a somatic *BAP1* variant was not identified. The c.1780_1781insT VAF in nevus #4 and 5 were 55 % and 86 %, respectively, however, a copy number variation analysis was unsuccessful and the cause for nuclear BAP1 loss of the immunostaining remains undetermined. Details of the discovered variants are listed in Supplementary Table S3.

4. Discussion

Our search for pathogenic germline *BAP1* variants in Finnish patients with MM identified one patient (1/56) with c.1780_1781insT, p.(Gly594Valfs*49), a Finnish founder mutation previously published in five patients with UM from four families [10]. Based on the extended family history of these families (unpublished data) the frequencies of UM and MM in carriers of c.1780_1781insT are 47 % (7/15) and 20 % (3/15). Regardless of our efforts, the presumed common ancestor of these families has not been identified and the age of the mutation is unknown. This founder mutation is not recognized in any of the 141,456 individuals, of which 12, 562 are Finnish, represented in the gnomAD database. Nuclear localization and deubiquitinating activity are needed for the BAP1 protein to function as a tumor suppressor. The identified thymine insertion causes a frameshift that leads to a premature stop codon in protein translation and loss of the C-terminal nuclear localization signals of BAP1 [10]. The truncated p.Glu594Valfs*49 mutant protein is sequestered in the cytoplasm but preserves the enzymatic activity *in vitro* [10].

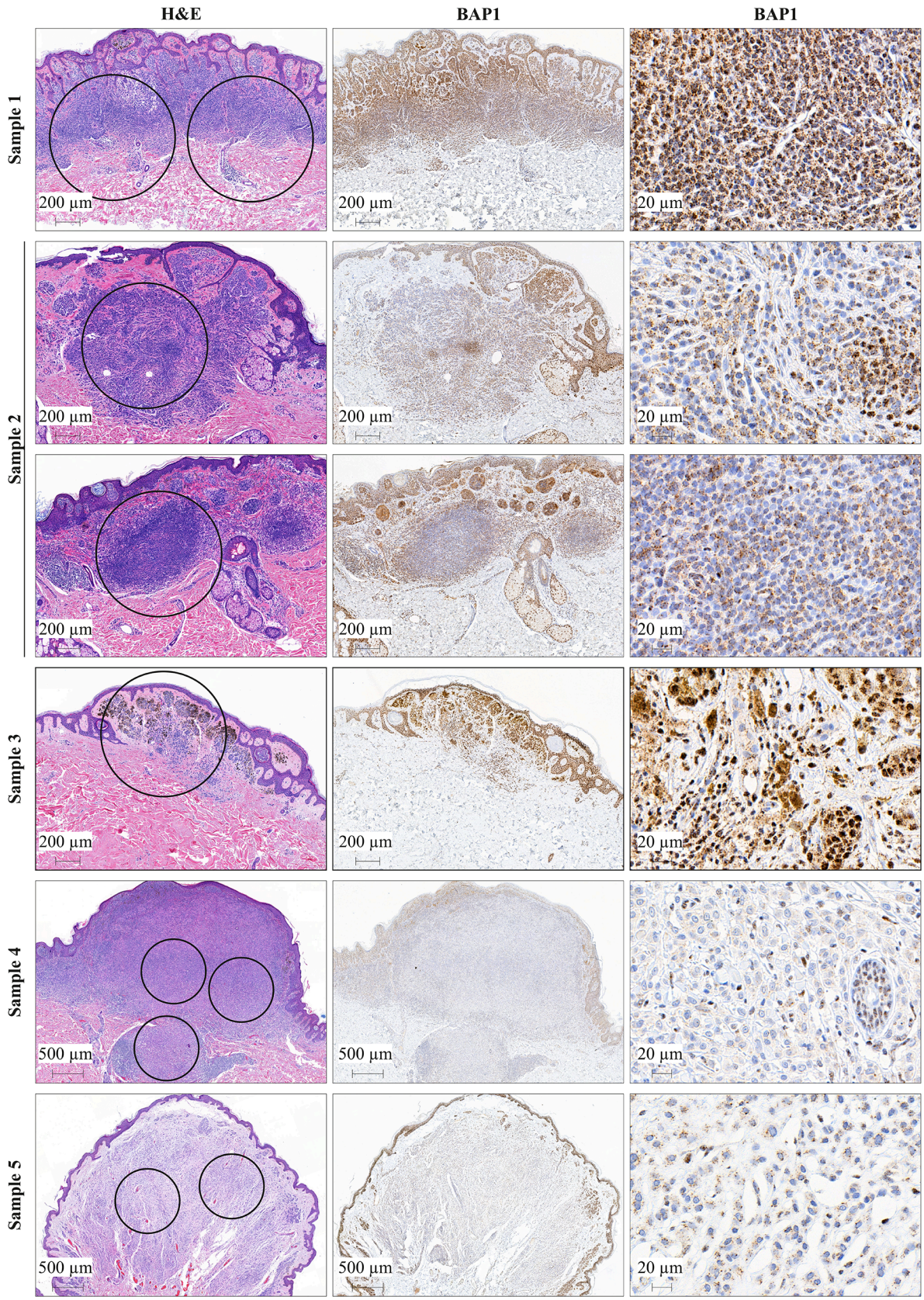

Fig. 2. Hematoxylin and eosin (H&E; left column) and BAP1 immunohistochemical staining (middle and right columns) of the five nevi that were analyzed for somatic variations. Areas used for DNA isolation (diameter of 1.0–1.2 mm) are indicated in the H&E staining. A higher magnification image from the BAP1 staining (middle column) was taken to show either the presence or absence of nuclear BAP1 staining (right column). The location of magnification is marked with a square in the middle column. Note granular immunoreaction displaced to the cytoplasm in nevi #2, 4, and 5.

Table 2
Somatic driver mutations identified in five nevi of a patient with malignant mesothelioma and germline pathogenic *BAP1* variant c.1780_1781insT p.(G594fs). Histological classification, status of nuclear BAP1 in IHC, and somatic variants of interest identified in nevi of pathogenic germline *BAP1* variant carrier.

Nevus	BAP1* IHC	Histological classification	*BAP1* c.1780_1781insT p.(G594fs)	*BAP1* c.178C > T p.(R60X)	*BRAF* c.1825C > G p.(Q609E)	*BRAF* c.1799 T > A p.(V600E)	*NRAS* c.181C > A p.(Q61K)	*PLCB4* c.1181A > T (p.E394V)
Nevus #1	+	compound nevus	DP 220 VAF 50 %			DP 120 VAF 33 %		
Nevus #2	–	combined BAP1- inactivated nevus, low-grade dysplasia	DP 172 VAF 48 %	DP 175 VAF 12 %		DP 145 VAF 23 %		DP 92 VAF 20 %
Nevus #3	+	intradermal nevus	DP 236 VAF 44 %				DP 244 VAF 30 %	
Nevus #4	–	combined BAP1- inactivated nevus, epithelioid Spitz type	DP 214 VAF 55 %		DP 124 VAF 25 %	DP 126 VAF 29 %		
Nevus #5	–	combined BAP1- inactivated nevus	DP 138 VAF 86 %			DP 123 VAF 39 %		

DP = read depth VAF = variant allele frequency (the percentage of sequence reads with the variant in question)
* Normal nuclear immunostaining

The estimated frequency of disease-causing germline *BAP1* variants is 1.8 % (95 % confidence interval, 0.05 % - 9.6 %) in Finnish patients with MM and thus similar to the frequency of pathogenic *BAP1* variant carriers in Finnish patients with UM (1.9 %) [10]. The mean survival of the cohort was 2.2 years as compared to less than a year in patients with pleural MM in a large study from Finland [1]. The median survival of patients with BAP1 loss is longer than that of patients with normal BAP1 expression [6]. Although the longer than average survival of our cohort might have favored the inclusion of patients with pathogenic *BAP1* germline variants, the majority of *BAP1* variants in MM are somatic. The findings of our study need to be validated in a larger population-based cohort to define the exact frequency of deleterious germline *BAP1* variants in Finnish patients with MM.

Here we report the fifth unrelated BAP1-TPDS family with the Finnish founder mutation c.1780_1781insT. Although BAP1-TPDS is inherited dominantly with at least 85 % penetrance [7], probands from two families have reported no family history of the four core cancers. The variant carrier identified here had three BINs removed before the MM. Generally, BINs are benign and frequent, and sometimes the only tumor type observed in patients with BAP1-TPDS [9]. The patient was relatively young at the time of MM diagnosis, a feature observed in germline *BAP1* null variant carriers [2,7]. Even when the family history is not suggestive of BAP1-TPDS, genetic testing for *BAP1* variants could be considered if the patient has $\geq$ 2 BAP1-TPDS core tumors, including BINs [8,9], and the patient is considerably young at the time of diagnosis [2,7]. As other MM predisposition genes have been described [2,3], further testing in other genes could be considered if inherited predisposition is suspected.

In conclusion, we found a comparable frequency of pathogenic *BAP1* germline variants (about 2 %) in patients with MM as we have previously reported in UM. The role of recurring BINs in BAP1-TPDS patients should be studied further. The frequency of disease-causing germline *BAP1* variants in Finnish patients with other BAP1-TPDS index tumors, cutaneous melanoma, and renal cell carcinoma should be studied.

CRediT authorship contribution statement

Pauliina Repo: Investigation, Formal analysis, Visualization, Validation, Writing – original draft, Writing – review & editing. **Aleksandra Staskiewicz:** Investigation. **Eva Sutinen:** Conceptualization, Data curation, Resources, Writing – original draft. **Mikko Rönty:** Investigation, Visualization, Validation. **Tero T. Kivelä:** Validation, Funding acquisition, Writing – original draft, Writing – review & editing. **Marjukka Myllärniemi:** Conceptualization, Resources. **Joni A. Turunen:** Project administration, Supervision, Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Validation, Funding acquisition, Resources.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: T. T.K. reports personal fees from Santen Finland and J.A.T. reports personal fees from Thea Finland and Blueprint Genetics Finland; all received outside this work. Other authors report no conflicts of interest.

Acknowledgements

This work was supported by the Eye Foundation (Helsinki, Finland) and the Finnish Cultural Foundation (Helsinki, Finland).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2022.01.017.

References

[1] S. Laaksonen, I. Ilonen, E. Kuosma, E. Sutinen, H. Wolff, T. Vehmas, K. Husgafvel-Pursiainen, J.A. Salo, K. Koli, J. Rasanen, M. Myllarniemi, Malignant pleural mesothelioma in Finland: regional and gender variation, Acta Oncol. 58 (1) (2019) 38–44.
[2] R. Hassan, B. Morrow, A. Thomas, T. Walsh, M.K. Lee, S. Gulsuner, M. Gadiraju, V. Panou, S. Gao, I. Mian, J. Khan, M. Raffeld, S. Patel, L. Xi, J.S. Wei, M. Hesdorffer, J. Zhang, K. Calzone, A. Desai, E. Padiernos, C. Alewine, D. S. Schrump, S.M. Steinberg, H.L. Kindler, M.-C. King, J.E. Churpek, Inherited predisposition to malignant mesothelioma and overall survival following platinum chemotherapy, Proc. Natl. Acad. Sci. U. S. A. 116 (18) (2019) 9008–9013.
[3] A. Bononi, K. Goto, G. Ak, Y. Yoshikawa, M. Emi, S. Pastorino, L. Carparelli, A. Ferro, M. Nasu, J.-H. Kim, J.S. Suarez, R. Xu, M. Tanji, Y. Takinishi, M. Minaai, F. Novelli, I. Pagano, G. Gaudino, H.I. Pass, J. Groden, J.J. Grzymski, M. Metintas, M. Akarsu, B. Morrow, R. Hassan, H. Yang, M. Carbone, Heterozygous germline BLM mutations increase susceptibility to asbestos and mesothelioma, Proc. Natl. Acad. Sci. U. S. A. 117 (52) (2020) 33466–33473.
[4] A. Napolitano, L. Pellegrini, A. Dey, D. Larson, M. Tanji, E.G. Flores, B. Kendrick, D. Lapid, A. Powers, S. Kanodia, S. Pastorino, H.I. Pass, V. Dixit, H. Yang, M. Carbone, Minimal asbestos exposure in germline BAP1 heterozygous mice is associated with deregulated inflammatory response and increased risk of mesothelioma, Oncogene 35 (15) (2016) 1996–2002.
[5] T. Wiesner, I. Fried, P. Ulz, E. Stacher, H. Popper, R. Murali, H. Kutzner, S. Lax, F. Smolle-Jüttner, J.B. Geigl, M.R. Speicher, Toward an improved definition of the tumor spectrum associated with BAP1 germline mutations, J. Clin. Oncol. 30 (32) (2012) e337–e340.
[6] F. Baumann, E. Flores, A. Napolitano, S. Kanodia, E. Taioli, H. Pass, H. Yang, M. Carbone, Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival, Carcinogenesis 36 (1) (2015) 76–81.
[7] S. Walpole, A.L. Pritchard, C.M. Cebulla, R. Pilarski, M. Stautberg, F.H. Davidorf, A. de la Fouchardière, O. Cabaret, L. Golmard, D. Stoppa-Lyonnet, E. Garfield, C.N. Njauw, M. Cheung, J.A. Turunen, P. Repo, R.S. Järvinen, R. van Doorn, M.J. Jager, G.P.M. Luyten, M. Marinkovic, C. Chau, M. Potrony, V. Höiom, H. Helgadottir, L. Pastorino, W. Bruno, V. Andreotti, B. Dalmasso, G. Ciccarese, P. Queirolo, L. Mastracci, K. Wadt, J.F. Kiilgaard, M.R. Speicher, N. van Poppelen, E. Kilic, R.T. Al-Jamal, I. Dianzani, M. Betti, C. Bergmann, S. Santagata, S. Dahiya, S. Taibjee, J. Burke, N. Poplawski, S.J. O'Shea, J. Newton-Bishop, J. Adlard, D.J. Adams, A.M. Lane, I. Kim, S. Klebe, H. Racher, J.W. Harbour, M.L. Nickerson, R. Murali, J.M. Palmer, M. Howlie, J. Symmons, H. Hamilton, S. Warrier, W. Glasson, P.

Johansson, C.D. Robles-Espinoza, R. Ossio, A. de Klein, S. Puig, P. Ghiorzo, M. Nielsen, T.T. Kivelä, H. Tsao, J.R. Testa, P. Gerami, M.H. Stern, B.B. Paillerets, M. H. Abdel-Rahman, N.K. Hayward, Comprehensive Study of the Clinical Phenotype of Germline BAP1 Variant-Carrying Families Worldwide, J. Natl. Cancer Inst. (2018).

[8] A.J. Zhang, P.S. Rush, H. Tsao, L.M. Duncan, BRCA1-associated protein (BAP1)-inactivated melanocytic tumors, J. Cutan. Pathol. 46 (12) (2019) 965–972.

[9] E.M. Garfield, K.E. Walton, V.L. Quan, T. VandenBoom, B. Zhang, B.Y. Kong, M. C. Isales, E. Panah, G. Kim, P. Gerami, Histomorphologic spectrum of germline-related and sporadic BAP1-inactivated melanocytic tumors, J. Am. Acad. Dermatol. 79 (3) (2018) 525–534.

[10] P. Repo, R.S. Järvinen, J.E. Jäntti, S. Markkinen, M. Täll, V. Raivio, J.A. Turunen, T.T. Kivelä, Population-based analysis of BAP1 germline variations in patients with uveal melanoma, Hum. Mol. Genet. 28 (14) (2019) 2415–2426.