

CASE REPORT

Open Access



Clinical characteristics and genetic analysis of a case of a patient with familial hereditary breast cancer: a case report

Yuan Liu¹, Jinglin Mao², Longquan Xiang², Xiangyu Zhang² and Zhen Qu^{2,3*}

Abstract

Background Breast cancer has emerged as the foremost cause of female mortality worldwide, with triple negative breast cancer accounting for approximately 10–15% of all breast cancer cases. The triple negative breast cancer family has obvious familial heritability, but no potential pathogenic variation was found in *BRCA1/2*.

Case presentation The patient was a 56-year-old woman of Han ethnicity. The clinical characteristics of this patient with breast cancer were summarized, peripheral blood of one normal female and two patients with breast cancer in this family was collected, DNA was extracted, and the potential pathogenic variation was analyzed by whole exome sequencing. The normal female and two patients with breast cancer in this family shared a maternal grandmother. The proband's right breast mass was punctured, and the biopsy showed invasive carcinoma of the right breast, grade II–III, with necrosis. No mutation was found in *BRCA1/2* gene test; immunohistochemical of surgical specimens showed triple negative breast cancer. Three mutation types and 17 gene mutation sites were detected through bioinformatics prediction analysis on the basis of co-segregation of genotype and phenotype within the family and whole exome sequencing results. Combined with the Cancer Genome Atlas database comprehensive analysis, the *MT1E* c.G107A (p.C36Y) mutation may be a potential pathogenic site.

Conclusions Through whole exome sequencing, we identified a total of 17 potential pathogenic mutation loci, none of which have been reported thus far. Therefore, our work expanded the gene mutation spectrum of familial hereditary triple negative breast cancer, which can provide more basis for family genetic counseling.

Keywords Hereditary triple negative breast cancer, Whole-exome sequencing, *MT1E*

Background

Breast cancer has emerged as the foremost cause of female mortality worldwide, with the highest incidence and mortality rates among malignancies affecting women [1]. At present, approximately 5–10% of all patients with breast cancer are caused by germline mutations, and these patients generally show obvious familial heritability. More than 20 breast cancer susceptibility genes have been reported, including *BRCA1*, *BRCA2*, *ATM*, *RAD51*, *CHEK2*, and *PALB2*, which are involved in DNA repair. Triple negative breast cancer (TNBC) has its name due to its negative expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth

*Correspondence:

Zhen Qu

quzhen66@126.com

¹ Department of Surgical Oncology, First Affiliated Hospital, Bengbu Medical College, Bengbu, Anhui, China

² Department of Pathology, Jining No. 1 People's Hospital, Jining 272000, Shandong, China

³ Department of Hepatobiliary and Pancreas, The Affiliated Hospital of Qingdao University, Qingdao University, Qingdao, Shandong, China



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

factor receptor 2 (HER2). TNBC accounts for approximately 10–15% of all breast cancer cases and exhibits a poor prognosis, with significantly lower 5-year survival rates compared with other breast cancer subtypes. Pathogenic variants involved in the homologous recombination repair (HRR) pathway, especially *BRCA1/2*, are predominantly implicated in hereditary TNBC cases. Patients carrying *BRCA1/2* pathogenic variants can benefit from poly(ADP-ribose) polymerase inhibitors (PARPi) treatment. We collected a case of familial triple negative breast cancer without *BRCA1/2* pathogenic variation. Whole exome sequencing (WES) showed that there were some potential pathogenic variation sites in this family, which could expand the spectrum of mutations in familial TNBC.

Case presentation

The proband was a 56-year-old Chinese Han female patient who presented to the First Affiliated Hospital of Bengbu Medical College in March 2020 with a breast mass. Clinical palpation revealed a poorly defined, immobile, hard mass measuring approximately 2 × 2 cm in the outer quadrant of the right breast. There was no tenderness upon compression, and no discharge or abnormalities were observed in the bilateral breasts or nipples.

Preoperative examinations, including chest computed tomography (CT) scan and electrocardiogram, showed no significant abnormalities. Color Doppler ultrasound revealed a hypochoic lesion measuring 17 × 19 × 21 mm in the 9 o'clock position of the right breast. The lesion appeared irregular in shape with indistinct borders and exhibited lobulated margins. No apparent abnormal lymph nodes were detected in the right axilla. Molybdenum target imaging confirmed the presence of a nodule in the outer quadrant of the right breast, classified as BI-RADS 4c. Fine-needle aspiration biopsy of the right breast mass revealed invasive carcinoma, grade II–III, with necrosis (Fig. 1A). *BRCA1/2* genetic testing did not identify any pathogenic variants.

On 3 April 2020, the patient underwent breast-conserving surgery + sentinel lymph node biopsy (SLNB) under general anesthesia. Intraoperative frozen section analysis of the margins (upper, lower, inner, outer, and basal) was negative. Postoperative pathology confirmed invasive carcinoma of the right breast (Fig. 1B), grade 3, measuring 2.5 × 2.3 × 1.5 cm. Immunohistochemistry analysis revealed the following results: estrogen receptor (ER) negative, progesterone receptor (PR) negative, human epidermal growth factor receptor 2 (HER2) 1+, and high Ki-67 proliferation index (+, 80%) (Fig. 1C–F).

According to the patient's account, there is a clear familial predisposition to breast cancer. Therefore, information regarding the patient's pedigree was collected (Fig. 2). As depicted in Fig. 2, all female individuals within the family, with the exception of III:3, were affected by breast cancer. Unfortunately, detailed information regarding I:1, II:1, and II:3 is not available due to their demise. Both III:2 and the proband III:1 were diagnosed with TNBC. As indicated by the family pedigree, the inheritance pattern of this disease is dominant.

According to the predetermined criteria, WES-identified a total of 17 candidate variants (Table 1), including frameshift mutations, missense mutations, and splice site mutations. In addition, WES showed that the TNBC susceptibility genes *BRCA2* and *ATM* carry likely benign variations (Supplementary Material, Table S2). Metallothionein 1E (*MT1E*) harbored a c.G107A (p.C36Y) mutation. This mutation has been found to be absent or extremely rare in databases such as 1000 Genomes, ESP6500si_all, and gnomAD_ALL (Table 2). Furthermore, on the basis of the bioinformatics predictions from dbSNV and Spidex analysis software (Table 2), it is suggested that this mutation does not affect the splicing of *MT1E*. Multiple online prediction software tools, including SIFT, PolyPhen-2, MutationTaster, and CADD, indicate that *MT1E* c.G107A (p.C36Y) is a pathogenic variant.

Initially, we amplified a 156 bp polymerase chain reaction (PCR) fragment (Supplementary Material, Table S1) containing the *MT1E* c.G107A mutation (Fig. 3A, Supplementary Material, Fig. S1) and performed Sanger sequencing. The results confirmed the presence of the c.G107A mutation in both III:1 and III:2, while III:3 did not carry this mutation (Fig. 3B), consistent with the WES results. Furthermore, we used CLC Sequence Viewer8 software to analyze the conservation of the cysteine residue at position 36 of the *MT1E* protein across different species, including humans, macaques, chimpanzees, dogs, and mice. The results indicated a high level of conservation for p.C36 among these species (Fig. 3C).

To investigate the expression of *MT1E* in breast cancer compared with normal tissues, we utilized an online bioinformatics analysis system (GEPIA2, <http://gepia2.cancer-pku.cn/#general>) to analyze the expression of *MT1E* in cancer and para-cancer tissues in the Cancer Genome Atlas (TCGA) database. The analysis revealed a significant downregulation of *MT1E* in breast cancer tissues (Fig. 3D).

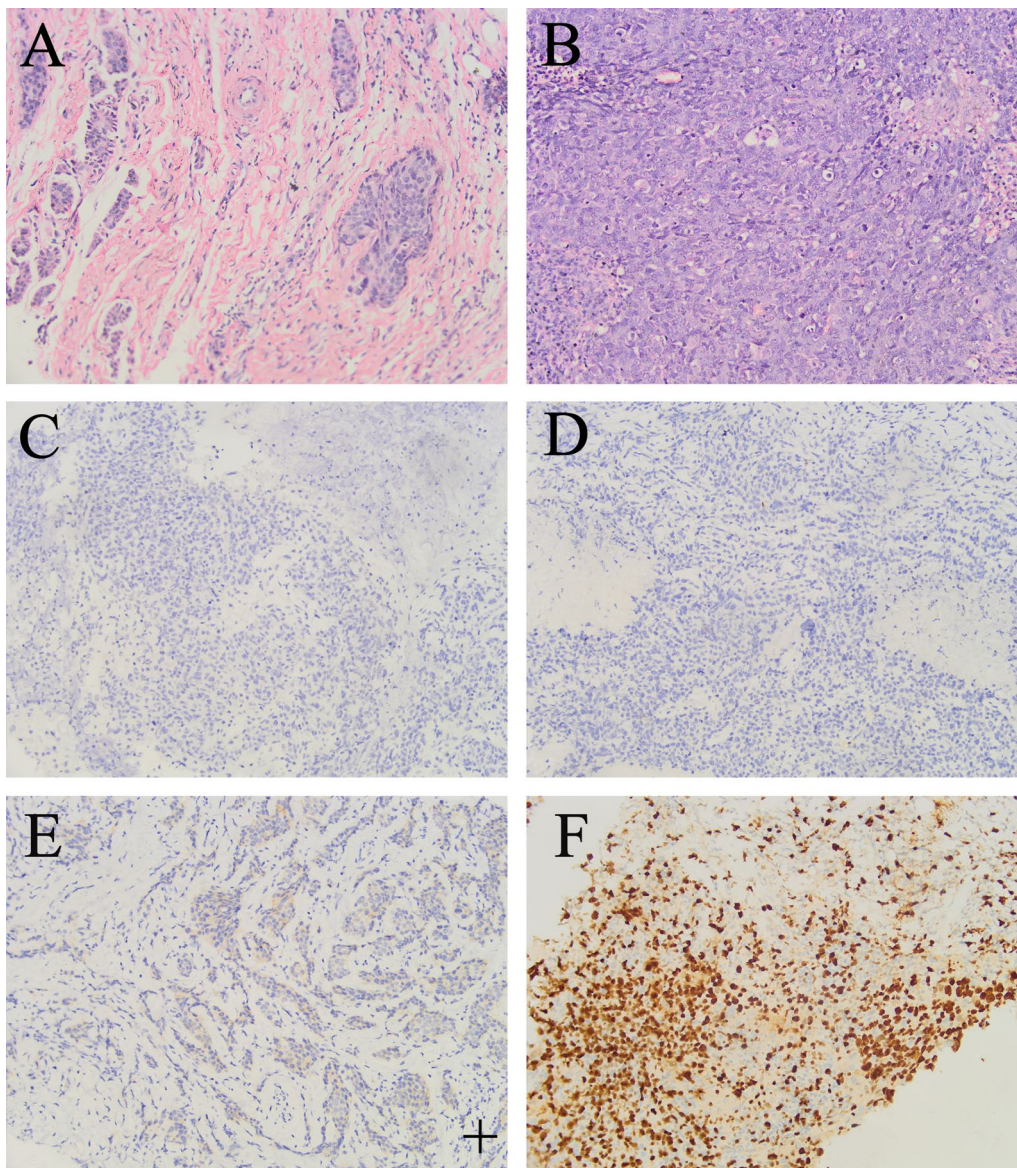


Fig. 1 Pathological diagnosis results of the proband. **A** Pathological puncture results of the right breast of the proband shows invasive cancer. **B** Proband's postoperative pathological diagnosis is invasive carcinoma of the right breast. **C** Estrogen receptor is negative. **D** Progesterone receptor is negative. **E** Human epidermal growth factor receptor 2 is one "+". **F** Ki67 is positive, approximately 80%. Original magnification, 200x

The conservation analysis demonstrated the high conservation of *MT1E* p.C36 across different species. Bioinformatics analysis indicated that the *MT1E* c.G107A mutation (p.C36Y) has an extremely low frequency and is highly pathogenic in the population. Additionally, compared with breast cancer tissues, the expression of *MT1E*

is higher in the para-cancer tissues, which indicates that *MT1E* may play an important role as a tumor suppressor gene. Further, the *MT1E* c.G107A mutation may down-regulate the expression of *MT1E*, potentially contributing to the development of breast cancer.

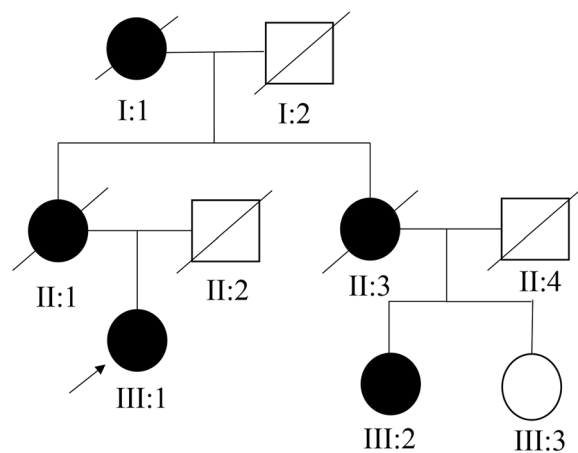


Fig. 2 Pedigree structure of the patients with breast cancer. The circle represents female, the square represents male, black represents patient, white represents normal person, “fullwidth solidus” represents deceased, and the proband (III:1) is indicated with an arrow

Discussion and conclusions

On the basis of the pedigree analysis, we could confirm the familial inheritance of TNBC as dominant but could not further determine whether it follows an autosomal or X-linked pattern [2]. Additionally, due to the majority of

family members being deceased, further investigation of potential pathogenic genes and variant sites through co-segregation analysis was not feasible.

Through WES analysis of two patients and one normal individual within the pedigree, we filtered the mutation sites and performed bioinformatics analysis, resulting in a total of 17 variant sites. Our study provides evidence that the *MT1E* c.G107A (p.C36Y) mutation has a very low frequency in the general population and is predicted to be pathogenic by multiple bioinformatics tools. Moreover, the high conservation of *MT1E* throughout evolution and the conservation of the p.C36 residue across species further support the potential significance of this mutation in relation to breast cancer. However, further functional studies are needed to gain a deeper understanding of the molecular mechanisms underlying the role of this mutation in breast cancer pathogenesis.

MT1E is a member of the metallothionein family, which generally exhibits high affinity for heavy metal ions such as zinc and mercury [3]. Previous studies have shown that in human glioma cell lines, *MT1T* can promote tumor cell migration and invasion through the regulation of the *MT1E*-NF- κ B p50-MMP-9 signaling pathway [4]. However, in studies on prostate cancer and hepatocellular carcinoma, *MT1E* has been found to act

Table 1 Summary of deleterious mutations from whole exome sequencing

Gene	Mutation type	Transcript	Site	AA change	Pathogenicity prediction
<i>TOP1MT</i>	Frameshift	NM_052963	c.765delC	p.S255Rfs*9	Deleterious
<i>LAMC2</i>	Missense	NM_005562	c.T3142C	p.S1048P	Deleterious
<i>RPS6KC1</i>	Missense	NM_001349663	c.A1483C	p.S495R	Deleterious
<i>SLCO2A1</i>	Missense	NM_005630	c.G1136A	p.G379E	Deleterious
<i>LSG1</i>	Missense	NM_018385	c.C1039T	p.R347W	Deleterious
<i>FYB</i>	Missense	NM_001465	c.A995G	p.K332R	Deleterious
<i>BEND3</i>	Missense	NM_001080450	c.C2041T	p.R681W	Deleterious
<i>AUTS2</i>	Missense	NM_015570	c.G2461A	p.A821T	Deleterious
<i>ZCWPW1</i>	Missense	NM_017984	c.C1064T	p.P355L	Deleterious
<i>CEL</i>	Missense	NM_001807	c.T2068G	p.S690A	Deleterious
<i>NCAPD2</i>	Missense	NM_014865	c.C2548T	p.R850W	Deleterious
<i>IGDCC3</i>	Missense	NM_004884	c.C2435A	p.S812X	Deleterious
<i>CALML4</i>	Missense	NM_033429	c.G442A	p.D148N	Deleterious
<i>MT1E</i>	Missense	NM_175617	c.G107A	p.C36Y	Deleterious
<i>PODNL1</i>	Missense	NM_024825	c.T1016G	p.L339R	Deleterious
<i>GFY</i>	Missense	NM_001195256	c.C67T	p.P23S	Deleterious
<i>LYL1</i>	Splice site	NM_005583	c.427+5G>A	unknown	Deleterious

Table 2 Pathogenicity prediction of *MT1E* c.G107A (p.C36Y) mutation

Number	Analysis tool	Mutation rate	Risk prediction	Score
1	1000g_ALL	0	-	-
2	esp6500si_all	0	-	-
3	GnomAD_ALL_AF	0.00004690	-	-
4	dbscSNV_SCORE	-	-	None
5	Spidex	-	-	None
6	SIFT	-	Deleterious	0
7	Polyphen2_HVAR	-	Deleterious	0.998
8	Polyphen2_HDIV	-	Deleterious	0.997
9	MutationTaster	-	Deleterious	1
10	CADD	-	Deleterious	27.3

as a tumor suppressor gene, promoting cancer cell apoptosis and inhibiting cell proliferation and metastasis [5, 6]. In breast cancer research, elevated methylation levels of *MT1E* have been observed in patients with triple negative breast cancer with positive KI-67 expression [7]. Higher methylation levels of *MT1E* indicate lower gene expression levels, which is consistent with our experimental results. Currently, research on *MT1E* remains limited, and its specific molecular mechanisms have yet to be elucidated.

In summary, our study suggests that the *MT1E* c.G107A (p.C36Y) variant may be an important mutation associated with the development of TNBC. In addition, this work may expand the spectrum of mutations in familial TNBC, and also provide more clues for subsequent triple negative breast cancer research.

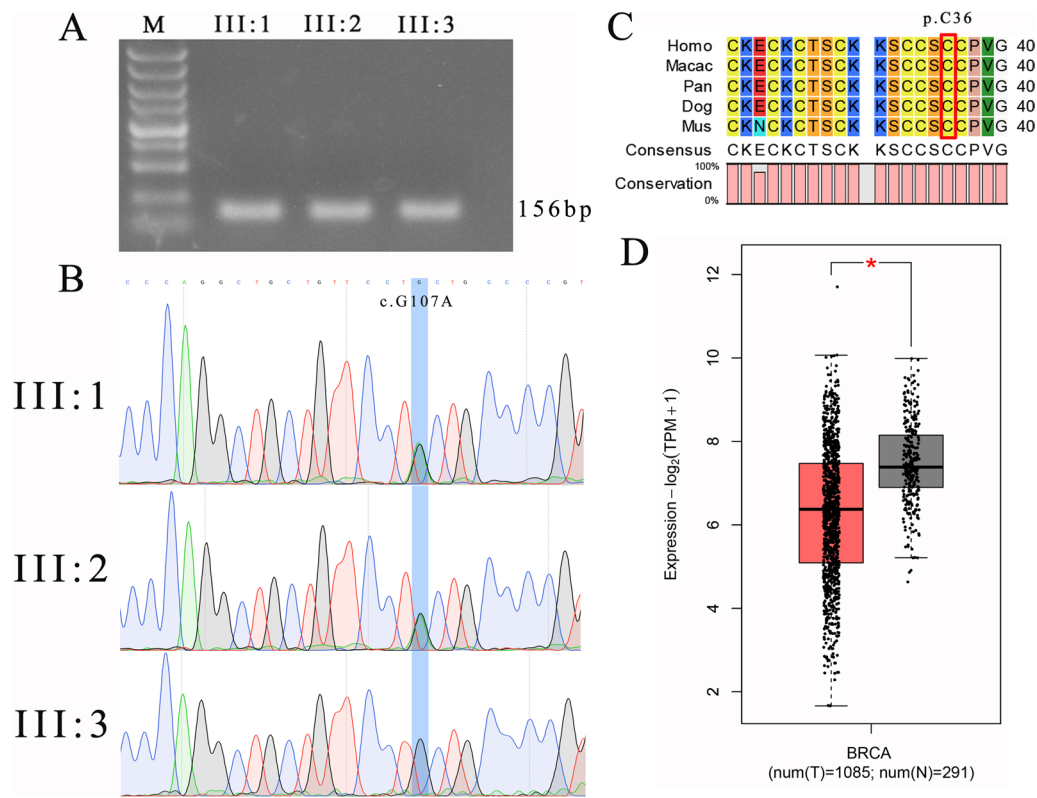


Fig. 3 Conservative and expression analysis of Metallothionein 1E. **A** Agarose gel electrophoresis of polymerase chain reaction amplification fragment. Polymerase chain reaction fragment is 156 bp and contains the Metallothionein 1E c.G107A mutation site. **B** Sanger sequencing confirms the mutation. Polymerase chain reaction fragments are sequenced by Sanger, and the mutation is consistent with whole exome sequencing. **C** Metallothionein 1E p.C36 is conserved in different species such as human, macaque, chimpanzee, dog, and mice. **D** Analysis of Metallothionein 1E expression in breast cancer and para-cancer tissues in the Cancer Genome Atlas database. Red represents breast cancer, gray represents normal tissue; *BRCA* breast cancer

Abbreviations

MT1E	Metallothionein 1E
TNBC	Triple negative breast cancer
WES	Whole-exome sequencing
ER	Estrogen receptor
PR	Progesterone receptor
HER2	Human epidermal growth factor receptor 2
HRR	Homologous recombination repair

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13256-024-04685-y>.

Supplementary Material 1.

Acknowledgements

We are very grateful to Dr. Shulong Jiang from Jining No. 1 People's Hospital for his support and help in this study.

Author contributions

Conception and design of the study: Zhen Qu, Yuan Liu, and Longquan Xiang; acquisitions of subject data: Yuan Liu and Xiangyu Zhang; analysis of the data: Zhen Qu, Yuan Liu, and Jinglin Mao; and original drafting of the paper: Zhen Qu, Yuan Liu, Jinglin Mao, and Xiangyu Zhang; All authors read and approved the final manuscript.

Funding

This work was supported by the Natural Science Foundation of Shandong Province (no. ZR2023QH483).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations**Ethics approval and consent to participate**

The study was approved by the ethics committee of Jining No. 1 People's Hospital. The research protocols were conformed to the tenets of the Declaration of Helsinki. Informed consent for the participation was obtained from each subject.

Consent for publication

Written informed consent was obtained from the patients for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare no conflict of interest.

Received: 4 March 2024 Accepted: 5 July 2024

Published online: 14 August 2024

References

- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71(3):209–49.
- Liu F, Huang Y, Liu L, Liang B, Qu Z, Huang G, Li C, Tian R, Jiang Z, Liu F, Yu X, Huang Y, Liu J, Tang Z. Identification of a novel NOG mutation in a Chinese family with proximal symphalangism. *Clin Chim Acta.* 2014;429:129–33.
- Coyle P, Philcox JC, Carey LC, Rofe AM. Metallothionein: the multipurpose protein. *Cell Mol Life Sci.* 2002;59(4):627–47.
- Ryu HH, Jung S, Jung TY, Moon KS, Kim IY, Jeong YI, Jin SG, Pei J, Wen M, Jang WY. Role of metallothionein 1E in the migration and invasion of human glioma cell lines. *Int J Oncol.* 2012;41(4):1305–13.
- Demidenko R, Daniunaite K, Bakavicius A, Sabaliauskaite R, Skeberdyte A, Petroska D, Laurinavicius A, Jankevicius F, Lazutka JR, Jarmalaite S. Decreased expression of MT1E is a potential biomarker of prostate cancer progression. *Oncotarget.* 2017;8(37):61709–18.
- Liu Q, Lu F, Chen Z. Identification of MT1E as a novel tumor suppressor in hepatocellular carcinoma. *Pathol Res Pract.* 2020;216(11): 153213.
- Sadzeviciene I, Snipaitiene K, Scesnaite-Jerdiakova A, Daniunaite K, Sabaliauskaite R, Laurinaviciene A, Drobnieni M, Ostapenko V, Jarmalaite S. Analysis of intrinsic breast cancer subtypes: the clinical utility of epigenetic biomarkers and TP53 mutation status in triple-negative cases. *Int J Mol Sci.* 2022;23(23):15429.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.