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Hereditary Breast and Ovarian Cancer Syndrome Associated with a Pathogenic BRCA1 Variant: A Familial Case Series of Six Sisters

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A B S T R A C T

Background: Hereditary Breast and Ovarian Cancer (HBOC) syndrome is most commonly associated with pathogenic variants in the BRCA1 gene and characterized by an increased lifetime risk of breast and ovarian cancers with variable penetrance. Familial case series provide valuable insights into genotype–phenotype correlations and the impact of preventive strategies.

Case Presentation: We report a family consisting of six sisters, four of whom were confirmed carriers of a pathogenic BRCA1 frameshift mutation (c.68_69del; p.Glu23ValfsTer17). Among the mutation carriers, two developed breast cancer, one developed ovarian cancer, and one developed both breast and ovarian cancer. The proband, a 44-year-old woman, was initially diagnosed with ductal carcinoma in situ of the breast, followed by high-grade serous ovarian carcinoma two years later. She underwent partial mastectomy, total abdominal hysterectomy with bilateral salpingo-oophorectomy, platinum-based chemotherapy, and is currently receiving maintenance therapy with olaparib. One BRCA1-positive sister underwent prophylactic gynecologic surgery and remains disease-free, while two sisters tested negative for the mutation and have no evidence of malignancy. A significant family history noted in a paternal aunt with early-onset breast cancer followed by ovarian cancer.

Discussion: This case series demonstrates the heterogeneous clinical expression of a single pathogenic BRCA1 mutation within one family, ranging from prophylactic surgery without malignancy to metachronous breast and ovarian cancers. The findings highlight the importance of cascade genetic testing, adherence to guideline-recommended surveillance, and timely risk-reducing interventions. Socioeconomic factors may influence access to preventive surgeries and considered in clinical decision-making.

Conclusion: This familial case series highlights the marked clinical heterogeneity of BRCA1-associated malignancies, even among individuals carrying the same pathogenic variant. The findings underscore the critical role of early genetic testing, cascade screening, and adherence to guideline-recommended surveillance and risk-reducing strategies.

Introduction

Hereditary Breast and Ovarian Cancer (HBOC) syndrome, most commonly due to pathogenic variants in the BRCA1 and BRCA2 genes, accounts for a significant proportion of familial breast and ovarian cancers. Carriers of BRCA1 mutations have lifetime risks of up to 72% for breast cancer and 44% for ovarian cancer by age 80. Early identification of mutation carriers allows implementation of surveillance strategies, risk-reducing surgeries, and targeted therapies, such as PARP inhibitors. Familial case

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series provide insight into clinical heterogeneity, variable penetrance, and challenges in adherence to preventive recommendations. Here, we present a case series of six sisters from a single family with BRCA1-associated cancers, illustrating the spectrum of disease expression and management strategies.

Case Presentation

Patient Cohort

The family consists of six sisters aged 34–52 years. Four sisters were found to carry a pathogenic BRCA1 frameshift mutation (c.68_69del; p. Glu23ValfsTer17), and two sisters tested negative.

Table 1. Clinical and Genetic Characteristics of the Six Sisters

Current Status	Systemic Treatment	Surgical Interventions	Ovarian Cancer	Breast Cancer	BRCA Status	Age (y)	Sister
Disease-free; planning risk-reducing mastectomy	6 cycles chemotherapy	TAH + BSO + staging	Yes (2011)	No	BRCA1 positive	52	Sister 1 (Parvaneh)
Alive, disease-free	None	TAH (ovaries preserved)	No	No	BRCA negative	49	Sister 2 (Maryam)
No evidence of disease	RT (25 sessions), Tamoxifen, 6 cycles Paclitaxel + Carboplatin ± Bevacizumab; maintenance Olaparib	Partial mastectomy; TAH + BSO + staging	Yes (HGSC, 2024)	Yes (DCIS, 2022)	BRCA1 positive	44	Sister 3 (Asieh – Proband)
Disease-free; under breast surveillance	None	Prophylactic TAH + BSO	No	No	BRCA1 positive	41	Sister 4 (Atefeh)
Alive, disease-free	None	None	No	No	BRCA negative	37	Sister 5 (Zahra)
Alive; gynecologic evaluation pending	8 cycles chemotherapy	Mastectomy with reconstruction	Not evaluated	Yes	BRCA positive	34	Sister 6 (Elham)

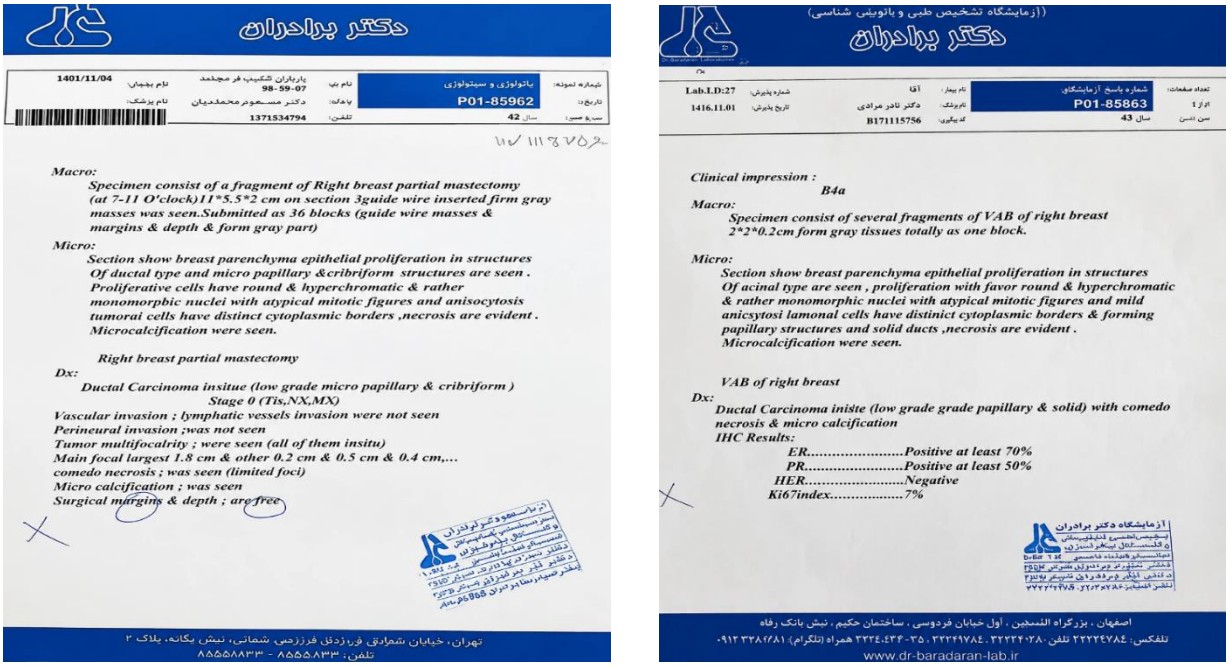

Figure 1. Pathology of breast cancer in the proband's sister

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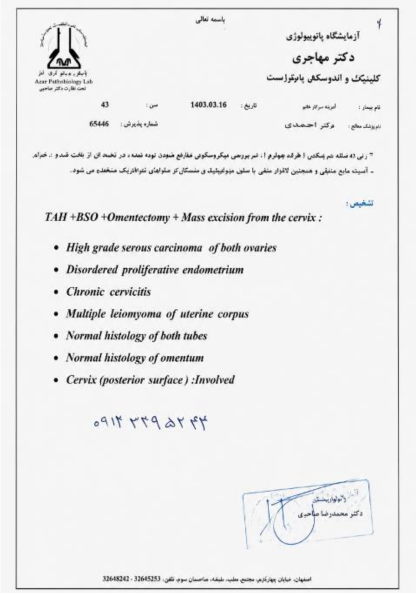
باسمه تعالی

آزمایشگاه پاتوبیولوژی

دکتر مهاجری

کلینیک و اندوسکپی پاتولوژیست

Azar Pathobiology Lab

سن : 43 تاریخ : 1403.03.16

شماره پذیرش : 65446

تشخیص :

TAH +BSO +Omentectomy + Mass excision from the cervix :

- *High grade serous carcinoma of both ovaries*
- *Disordered proliferative endometrium*
- *Chronic cervicitis*
- *Multiple leiomyoma of uterine corpus*
- *Normal histology of both tubes*
- *Normal histology of omentum*
- *Cervix (posterior surface) :Involved*

۰۹۱۴ ۳۳۹ ۵۲ ۴۴

دکتر محمدرضا صاحبی

32648242 - 32645253

Figure 2. Pathology of ovarian cancer in the proband's sister


باسمه تعالی

پاتولوژی

بیمارستان

آزمایشگاه پاتولوژیست

سن 41 تاریخ : 1403-11-30 شماره پرونده

شماره بایگانی 66248 نام و نام خانوادگی بیمار

تشخیص:

TAH + BSO Specimen :

1) Secretory endometrium
2) Endometrial polyp
3)Chronic cervicitis
4) Two leiomyoma of uterine corpus
5)Hemorrhagic corpus luteum cyst of right ovary
5) Normal histology of right tube
7) Normal histology of left ovary
8) Hydrosalpinx of left tube

پاتولوژیست

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Figure 3. Pathology of Atefeh, the fourth sister who BRCA-positive and has undergone prophylactic TAH-BSO.


IHC04-111

Immunohistochemical study result

Breast cancer IHC results:

Institution initially processing the core specimen: Sajadieh lab, Esfahan

Paraffin block number: 04-258/1

4 Processing Date: 1404/04/22 Fixation time:1404 /04/23 Fixation: formalin

Specimen(s) origin:	Left(7 o clock) breast mass CNB, paraffin block:04-258/1		
Pathologic diagnosis	Invasive breast carcinoma with ductal /Nos		
IHC result (According to ASCO/CAP guideline):	ER	**Positive** Nuclear staining: 80% Stain of intensity:+3	Positive test is defined as positive staining of greater than or equal to 1% of tumor cell nuclei Stain intensity as weak(+1) moderate(+2) strong(+3)
	PR	**Negative** Nuclear staining:0	Positive test is defined as positive staining of greater than or equal to 1% of tumor cell nuclei Stain intensity as weak(+1) moderate(+2) strong(+3)
	Her2/ neu	**Negative (0)**	No observable staining or membrane staining that is incomplete and is faint / barely perceptible in <10% of invasive tumor cells.
	Ki67	**30%**	mitotic score (Proliferative nuclear index)
Sign out			

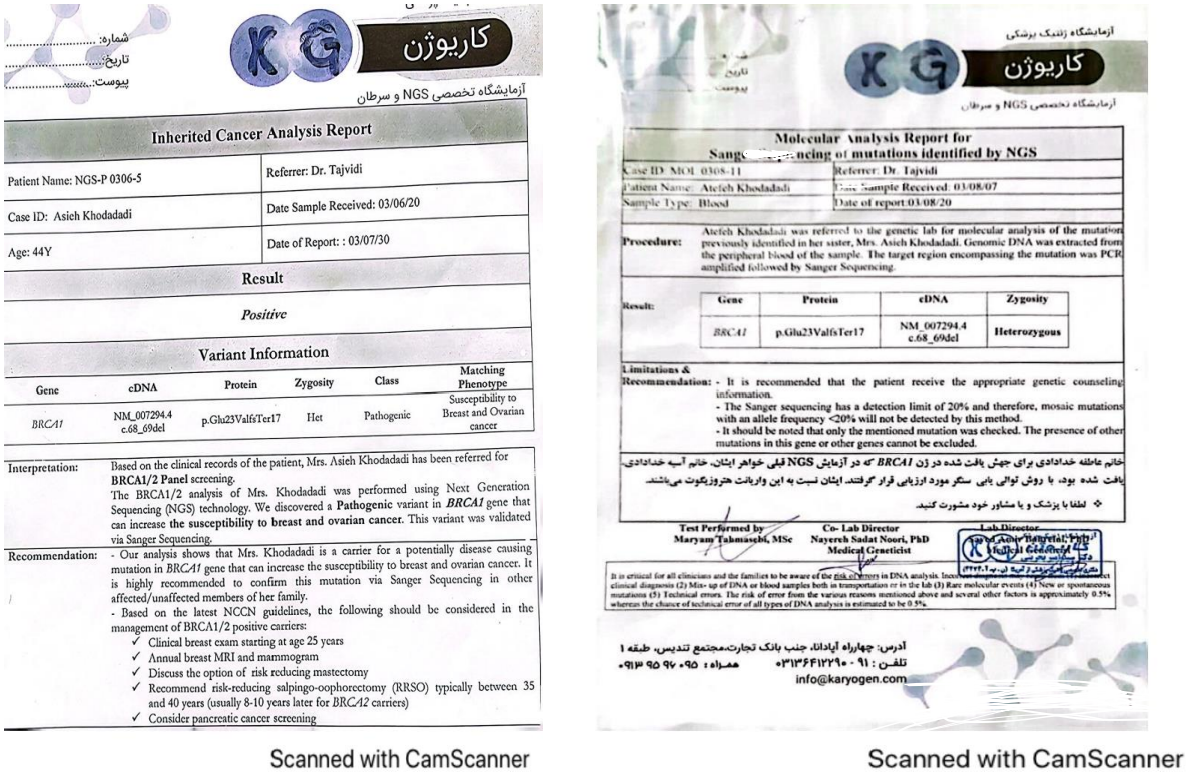
Figure 4. Pathology of the sixth sister with breast cancer and a positive BRCA mutation.

Pedigree Description

The family pedigree revealed an autosomal dominant inheritance pattern consistent with HBOC. The paternal aunt had early-onset breast cancer at age 30 during pregnancy, followed by ovarian cancer 3-4 years later, and was BRCA-positive. Among the sisters, the proband developed sequential breast and ovarian cancers; one BRCA-positive sister underwent prophylactic TAH-BSO and remains disease-free; two sisters are BRCA-negative and have no malignancy. Pedigree illustrates variable penetrance and expressivity of the BRCA1 mutation.

Genetic Analysis

NGS testing confirmed a heterozygous pathogenic BRCA1 frameshift mutation (NM_007294.4: c.68_69del; p. Glu23ValfsTer17) in four sisters. The mutation was validated via Sanger sequencing. This variant is known to significantly increase susceptibility to breast and ovarian cancers. Cascade genetic testing was performed in available family members to guide surveillance and preventive strategies.



کاریوژن

آزمایشگاه تخصصی NGS و سرطان

Inherited Cancer Analysis Report

Patient Name: NGS-P 0306-5	Referrer: Dr. Tajvidi
Case ID: Asieh Khodadadi	Date Sample Received: 03/06/20
Age: 44Y	Date of Report: : 03/07/30

Result

Positive

Variant Information

Gene	cDNA	Protein	Zygosity	Class	Matching Phenotype
BRCA1	NM_007294.4 c.68_69del	p.Glu23ValfsTer17	Het	Pathogenic	Susceptibility to Breast and Ovarian cancer

Interpretation: Based on the clinical records of the patient, Mrs. Asieh Khodadadi has been referred for **BRCA1/2 Panel** screening.
The BRCA1/2 analysis of Mrs. Khodadadi was performed using Next Generation Sequencing (NGS) technology. We discovered a **Pathogenic** variant in ***BRCA1*** gene that can increase **the susceptibility to breast and ovarian cancer.** This variant was validated via Sanger Sequencing.

Recommendation:
- Our analysis shows that Mrs. Khodadadi is a carrier for a potentially disease causing mutation in *BRCA1* gene that can increase the susceptibility to breast and ovarian cancer. It is highly recommended to confirm this mutation via Sanger Sequencing in other affected/unaffected members of her family.
- Based on the latest NCCN guidelines, the following should be considered in the management of BRCA1/2 positive carriers:
  - ✓ Clinical breast exam starting at age 25 years
  - ✓ Annual breast MRI and mammogram
  - ✓ Discuss the option of risk reducing mastectomy
  - ✓ Recommend risk-reducing salpingo-oophorectomy (RRSO) typically between 35 and 40 years (usually 8-10 years later for *BRCA2* carriers)
  - ✓ Consider pancreatic cancer screening

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کاریوژن

آزمایشگاه ژنتیک پزشکی

آزمایشگاه تخصصی NGS و سرطان

Molecular Analysis Report for
Sanger [illegible]ncing of mutations identified by NGS

Case ID: MOL 0308-11	Referrer: Dr. Tajvidi
Patient Name: Atefeh Khodadadi	Date Sample Received: 03/08/07
Sample Type: Blood	Date of report:03/08/20

Procedure: Atefeh Khodadadi was referred to the genetic lab for molecular analysis of the mutation previously identified in her sister, Mrs. Asieh Khodadadi. Genomic DNA was extracted from the peripheral blood of the sample. The target region encompassing the mutation was PCR amplified followed by Sanger Sequencing.

Result:

Gene	Protein	cDNA	Zygosity
BRCA1	p.Glu23ValfsTer17	NM_007294.4 c.68_69del	**Heterozygous**

Limitations & Recommendation:
- It is recommended that the patient receive the appropriate genetic counseling information.
- The Sanger sequencing has a detection limit of 20% and therefore, mosaic mutations with an allele frequency <20% will not be detected by this method.
- It should be noted that only the mentioned mutation was checked. The presence of other mutations in this gene or other genes cannot be excluded.

خانم عاطفه خدادادی برای جهش یافت شده در ژن ***BRCA1*** که در آزمایش **NGS** قبلی خواهر ایشان، خانم آسیه خدادادی، یافت شده بود، با روش توالی یابی سنگر مورد ارزیابی قرار گرفتند. ایشان نسبت به این واریانت هتروزیگوت می‌باشند.

❖ لطفا با پزشک و یا مشاور خود مشورت کنید.

Test Performed by Maryam Tahmasebi, MSc
Co- Lab Director Nayereh Sadat Noori, PhD Medical Geneticist
Lab Director [illegible] Medical Geneticist

It is critical for all clinicians and the families to be aware of the risk of errors in DNA analysis. Incorrect [illegible] clinical diagnosis (2) Mix- up of DNA or blood samples both in transportation or in the lab (3) Rare molecular events (4) New or spontaneous mutations (5) Technical errors. The risk of error from the various reasons mentioned above and several other factors is approximately 0.5% whereas the chance of technical error of all types of DNA analysis is estimated to be 0.5%.

آدرس: چهارراه آبادانا، جنب بانک تجارت،مجتمع تندیس، طبقه ۱
تلفن : ۹۱ - ۰۳۱۳۶۶۱۲۲۹۰ همراه : ۰۹۱۳ ۹۶ ۰۹۵ ۹۵
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Figure 5. Summary of germline BRCA genetic testing results in two sisters from the same family. FIGURE5

Discussion

Hereditary Breast and Ovarian Cancer (HBOC) syndrome, most commonly caused by BRCA1 mutations, is associated with variable expressivity and incomplete penetrance. This case series demonstrates heterogeneous clinical manifestations, ranging from prophylactic surgery without malignancy to metachronous breast and ovarian cancers. Early identification of mutation carriers allowed targeted interventions, including surveillance, risk-reducing surgery, and PARP inhibitor therapy, which have shown to improve outcomes. Socioeconomic barriers delayed preventive interventions in some carriers, highlighting the importance of multidisciplinary support. The proband exemplifies dual primary malignancies, emphasizing adherence to NCCN guidelines for risk-reducing strategies and timely genetic counseling.

Patient Perspective

The sisters shared their perspectives regarding genetic testing, cancer diagnosis, and preventive strategies. The proband, Asieh, emphasized her commitment to completing surveillance and maintenance therapy with olaparib after dual breast and ovarian cancers. Parvaneh expressed her intention to undergo a risk-reducing mastectomy. Atefeh highlighted financial constraints delaying her prophylactic breast surgery, while she maintains regular breast surveillance. Elham reported relief after completing breast surgery and chemotherapy but expressed concern regarding the evaluation and management of her ovaries. Maryam and Zahra, both BRCA-negative, valued genetic testing and continued regular monitoring. Collectively, the sisters underscored the importance of early genetic counseling, informed decision-making, and family support in managing hereditary cancer risk.

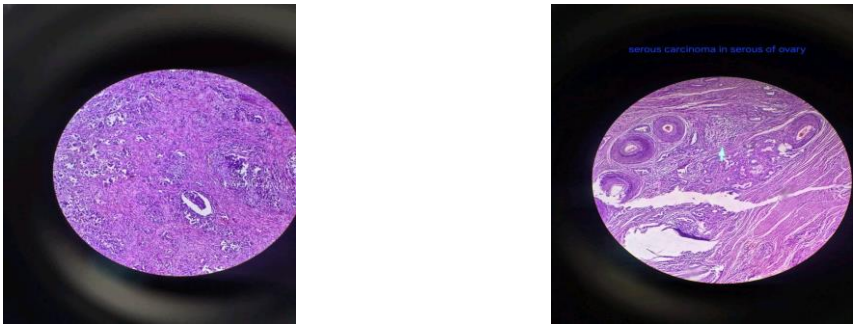

Figure 6. Histopathologic section of ovarian serous carcinoma (proband sister) showing complex papillary architecture with marked nuclear atypia and high mitotic activity (Hematoxylin and Eosin stain).

Conclusion

This familial case series highlights the marked clinical heterogeneity of BRCA1-associated malignancies, even among individuals carrying the same pathogenic variant. The findings underscore the critical role of early genetic testing, cascade screening, and adherence to guideline-recommended surveillance and risk-reducing strategies. Timely prophylactic interventions and personalized treatment approaches, including PARP inhibitor therapy, can significantly improve outcomes in high-risk families. Increased awareness and equitable access to preventive care remain essential components in the management of hereditary cancer syndromes.

Disclosure Statement

No potential conflict of interest reported by the authors.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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