Clinicopathologic and Molecular Characteristics of Middle-Eastern Breast Cancer Patients with Pathogenic or Likely Pathogenic ATM Variants: A Comprehensive Cohort Analysis

Hikmat Abdel-Razeq, Lulwa El Saket, Hira Bani Hani, Sarah Abdel-Razeq, Faris Tamimi, Baha Sharaf, Yazan Talab, Areej Al-Atary, Maryam El-Atrash, Tamer Al-Batsh, Malek Horani, Omar Othman, Yosra Al-Masri, Osama El Khatib, Mahmoud Abu-Nasser
King Hussein Cancer Center, Amman, Jordan

Abstract

Background
ATM is a moderate-risk DNA-repair gene associated with increased breast cancer susceptibility. Data from Middle Eastern populations are limited. This study describes the clinicopathologic and genetic features of ATM-mutant breast cancer in Jordan.

Methods
Retrospective review of 52 female breast cancer patients (2010–2025) with P/LP ATM variants identified through multigene panel testing. Clinical, pathologic, and genetic variables—including tumor subtype, grade, HR/HER2 status, variant type, co-mutations, and treatment—were collected and analyzed descriptively.

Results
Median age was 48 years; 61.5% diagnosed <50. Most tumors were IDC (78.8%), HR-positive, and HER2-negative. High-grade disease occurred in 39.2%, and lymph-node involvement occurred in 51.9%. Frameshift variants were most common (46.2%), with hotspots c.2284_2285del and c.5755C>T. Co-mutations were found in 11.5% and VUS in 30.8%. Neoadjuvant therapy produced a 12.2% pCR. 9.6% of patients would not have met NCCN/ASCO testing criteria.

Conclusion
ATM-mutant breast cancers in this cohort were predominantly HR-positive with frequent high-grade and node-positive disease. The variant diversity and co-mutations highlight clinical complexity. A portion of patients would be missed by guideline-based testing, supporting broader germline screening in this region.

Methods and Materials

Study Design: Retrospective cohort study of 52 female breast cancer patients treated in Jordan between 2010–2025, all carrying pathogenic or likely pathogenic (P/LP) ATM germline variants.

Genetic Testing: Variants were identified using multigene panel testing (20- or 84-gene panels) performed at accredited international laboratories.

Data Collection: Patient clinical characteristics, tumor pathologic characteristics, genetic variables (ATM variant type, hotspot mutations, and co-occurring germline variants) and systemic treatments were extracted from institutional records

Statistical Approach: Descriptive analyses were used to characterize clinicopathologic features, mutation patterns, and treatment outcomes.

Introduction

ATM is a key DNA-damage response gene, and germline pathogenic or likely pathogenic (P/LP) variants are increasingly recognized as contributors to hereditary breast cancer susceptibility.
Carriers of ATM mutations face an approximately 25% lifetime risk of developing breast cancer, with emerging evidence suggesting associations with specific tumor phenotypes and potential therapeutic relevance, particularly regarding radiation sensitivity and targeted therapy.[1,2]
Despite growing global interest, the clinical and molecular landscape of ATM-mutant breast cancer remains under-reported in Middle Eastern and Arab populations, where genetic testing uptake has historically been limited and variant patterns may differ from Western cohorts. Understanding these differences is essential for refining cancer-risk assessment, surveillance strategies, and precision oncology approaches in the region.[3,4]
This study provides a comprehensive evaluation of Jordanian breast cancer patients with germline P/LP ATM variants, examining demographic profiles, tumor characteristics, variant spectrum, co-mutations, and treatment patterns. Additionally, we assess whether current NCCN/ASCO genetic-testing criteria adequately capture ATM-positive patients, given the increasing movement toward universal testing in hereditary cancer programs.

Results

Cohort Characteristics
Median age: 48 years (27–79); 61.5% diagnosed <50.
Family history: Breast/ovarian cancer (40.4%); colon cancer (9.6%).
Histology: Invasive ductal carcinoma (78.8%) most common; ILC and rare subtypes less frequent.
Receptor status: ER+ 92.3%, PR+ 90.4%, HER2– 70.6%.
Tumor grade & proliferation: High-grade (GIII 39.2%); Ki-67 ≥20% in ~50%.
Stage & nodal status: Stage I–II (75%); lymph-node involvement 51.9%.

Genetic Findings: ATM variant types: Frameshift (46.2%), nonsense (17.3%), missense (15.4%), splice-site (11.5%).
Recurrent hotspot variants: *c.2284_2285del* and *c.5755C>T*.
Co-mutations (11.5%): BRCA2 ×3, RAD50 ×1, MUTYH ×1, second ATM variant ×1.
Variants of uncertain significance (VUS): 30.8%.
Outside NCCN/ASCO genetic-testing criteria: 9.6%, despite harboring P/LP ATM variants.
Treatment Outcomes
Neoadjuvant chemotherapy: 32.7%.
Pathologic complete response (pCR): 12.2%.
Endocrine therapy: Widely used due to high HR positivity.

Dissection

- Breast cancers arising in carriers of germline ATM pathogenic variants in this Jordanian cohort demonstrated a predominance of hormone-receptor–positive, HER2-negative, and invasive ductal phenotypes, consistent with international reports. However, the relatively high proportion of high-grade tumors (39.2%) and lymph-node involvement (51.9%) suggests a more aggressive clinical profile than typically expected for moderate-risk hereditary genes.
- The diversity of ATM variant types, with frameshift mutations representing nearly half of all alterations, reflects the molecular heterogeneity of ATM-associated cancers. The recurrence of hotspot variants (c.2284_2285del and c.5755C>T) may indicate regional enrichment patterns within Middle Eastern populations, emphasizing the importance of establishing population-specific variant databases and improved annotation for underrepresented groups.
- The identification of additional pathogenic variants (11.5%) in genes such as BRCA2, RAD50, and MUTYH further highlights the clinical value of multigene panel testing. These findings reinforce that reliance on BRCA-only testing would miss clinically actionable information and underestimate hereditary cancer risk. The relatively high rate of VUS (30.8%) also illustrates the diagnostic challenges faced in populations with limited representation in global genomic datasets.
- Treatment outcomes revealed a modest pCR rate (12.2%) following neoadjuvant chemotherapy, which aligns with published literature suggesting that ATM-mutant tumors may respond differently to cytotoxic therapy. The high prevalence of HR-positive disease supported widespread use of endocrine therapy, reflecting expected therapeutic patterns for this gene.
- Importantly, 9.6% of patients in this study would not have met NCCN/ASCO genetic-testing criteria, despite harbouring pathogenic germline ATM variants. This finding reinforces international calls for broader or universal germline testing, especially in regions with understudied variant distributions. Early identification of ATM carriers has implications not only for cancer management but also for family cascade testing, surveillance planning, and risk-reduction strategies.
- Collectively, these data deepen our understanding of ATM-associated breast cancer in Middle Eastern populations, demonstrate the value of comprehensive genomic testing, and highlight the need for region-tailored guidelines, variant curation, and improved access to germline testing to support precision oncology strategies.

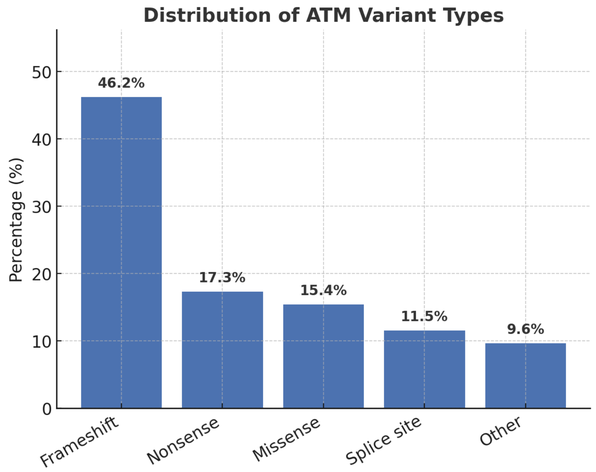


Figure 1: Distribution of ATM Variant Types

Conclusions

Breast cancers associated with germline ATM mutations in this Jordanian cohort were predominantly hormone receptor–positive and HER2-negative, but notable for a high frequency of high-grade tumors and lymph-node involvement, suggesting a more aggressive phenotype than typically expected for moderate-risk genes. The mutation spectrum demonstrated considerable heterogeneity, including recurrent hotspot variants and a meaningful rate of co-occurring pathogenic alterations in other cancer predisposition genes, emphasizing the complexity of ATM-related cancer genetics. Despite most patients presenting with early-stage disease, responses to neoadjuvant chemotherapy were modest. Importantly, nearly 10% of mutation carriers would not have met current NCCN/ASCO testing criteria, highlighting limitations of guideline-based selection in Middle Eastern populations. These findings collectively support the implementation of broader or universal germline testing for breast cancer patients in the region to improve risk detection, guide management, enable family cascade testing, and strengthen precision-oncology approaches.

Contact

Hikmat Abdel-Razeq, MD
King Hussein Cancer Centre
Email: habdelrazeq@KHCC.JO
Tel: +962 6 5300460, Ext: 1000
Mobile: + 962 79 643 3993

References

1. Seca M, et al. Breast cancer and ATM mutations: treatment implications. Hereditary Cancer in Clinical Practice. 2024;22:6.
2. Hu C, et al. "A Population-Based Study of Genes Previously Implicated in Breast Cancer." N Engl J Med. 2021;384:440-451.
3. Moslemi, M., Moradi, Y., Dehghanbanadaki, H. et al. The association between ATM variants and risk of breast cancer: a systematic review and meta-analysis. BMC Cancer 21, 27 (2021). https://doi.org/10.1186/s12885-020-07749-6
4. Bu, R., Siraj, A.K., Al-Rasheed, M. et al. Identification and characterization of ATM founder mutation in BRCA-negative breast cancer patients of Arab ethnicity. Sci Rep 13, 20924 (2023). https://doi.org/10.1038/s41598-023-48231-0

PS3-05-03

This presentation is the intellectual property of the author/presenter. Contact them at <<your email address>> for permission to reprint and/or distribute.

© Poster Template by Genigraphics® 1.800.790.4001 www.genigraphics.com