Germline Mutation Landscape in Patients with Breast Ductal Carcinoma In-Situ (DCIS): Impact of Age and Family History in a Middle Eastern Cohort

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Background

- Ductal carcinoma in situ (DCIS) represents a heterogeneous pre-invasive breast cancer entity, with genetic predisposition playing a potential role in disease development.
- Current NCCN guidelines recommend considering germline testing for patients with DCIS if they fulfill certain criteria, such as diagnosis at a young age, triple-negative receptor status (for invasive disease), or family history of breast, ovarian, or other associated cancers.
- The actual prevalence of pathogenic or likely pathogenic (P/LP) germline variants in patients with DCIS remains underexplored compared to invasive breast cancer. Reported rates vary, with some studies noting prevalence approaching 10% in selected populations, though most large-scale data derive from North American and European cohorts.
- Most of the existing evidence on germline mutations in DCIS comes from Western cohorts, while data from the Middle East remain scarce.
- The Middle Eastern and North African (MENA) region is characterized by distinct demographic and epidemiologic patterns, including a younger median age at breast cancer diagnosis compared with Western populations.
- This study aims to evaluate the frequency and spectrum of pathogenic germline variants among Jordanian patients with DCIS who underwent genetic testing.

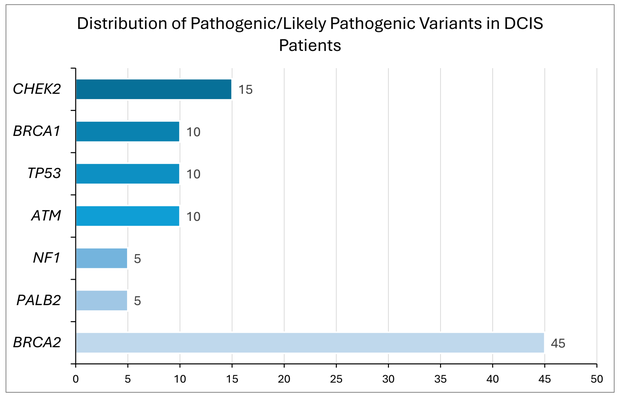
Methods and Materials

- A retrospective review was conducted on clinical and genetic data on patients diagnosed with DCIS.
- Variables included age at diagnosis, hormonal receptor status (ER/PR/HER2), family history of cancer, and results of germline genetic testing.
- Variant classification was harmonized according to the American College of Medical Genetics and Genomics (ACMG) guidelines. Eligible patients, as per the National Comprehensive Cancer Network (NCCN) guidelines, underwent germline genetic testing (GGT) using an NGS-based multi-gene panel.
- Rates of GGT was stratified against known variables including age, family history and hormonal status.

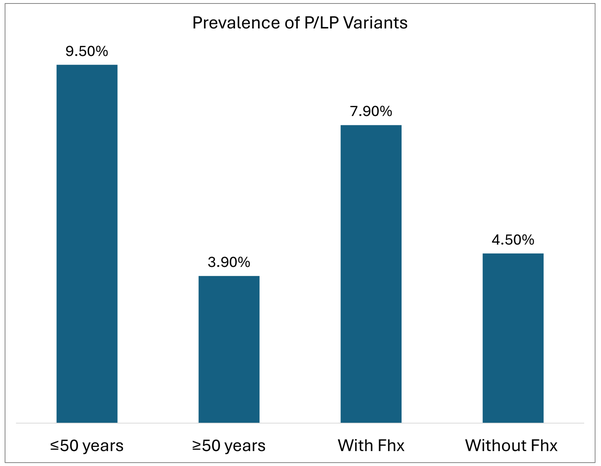
Results

- Between July 2006 and September 2024, a total of 622 patients with DCIS were treated and followed at our institution.
- Germline genetic testing was performed on 271 (43.6%) patients.
  - Except for one, all were female
  - Median age (range) was 47 (20-90) years.
- Twenty patients (7.4%) were identified as harboring pathogenic or likely pathogenic (P/LP) variants.
- The most frequently mutated genes are illustrated in Figure-1.
- Additionally, 4 (1.5%) patients carried variants classified as "Increased Risk Allele"; all were in the *APC* gene and were considered separately.
- A significant proportion of patients (n=94, 34.7%) had variants of uncertain significance (VUS).
- Patients with P/LP variants tended to be diagnosed about 5 years younger:
  - Mean age: 43.7 years compared to 48.9 years for those without.
- The prevalence was notably higher in patients aged ≤50 years (n=16, 9.5%) compared to those over 50 (n=4, 3.9%), though the difference did not reach statistical significance (p = 0.078), Figure-2.
- While there's a clear numerical difference in rates among 229 patients with family history of cancer (n=18, 7.9%) versus (n=2, 4.8%) in 42 patients without, it didn't reach statistical significance (p = 0.52), Figure-2.
- Hormone receptors (HR) positivity was high in both groups and did not significantly distinguish carriers from non-carriers.

Characteristics		Number (%)
Age at diagnosis (years)	Median (Range)	47 (20-90)
	≤50	168 (62%)
	>50	103 (38%)
Sex	Female	270 (99.6%)
	Male	1 (0.4%)
Hormonal Receptors	ER	217 (48.7%)
	PR	202 (45.3%)
	HER2	27 (6%)
Nationality	Jordanian	271 (100%)
Family History of Malignancies	Positive	229 (84.5%)
Genetic Testing	Carrier	2 (0.7%)
	Increased Risk Allele	4 (1.5%)
	Pathogenic	20 (7.4%)
	Negative	151 (55.7%)
	Uncertain Significance	94 (34.7%)



Results



Conclusions

- P/LP rate in DCIS: 7.4%
  - *Lower than invasive breast cancer*
- *BRCA2* predominance
  - *Possible regional founder effect*
- High VUS rates
  - *Need for regional interpretation resources*
- Routine testing warranted for younger patients & family history cases

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