[Abstract:0247]

Clinicopathological Characteristics of Germline Pathogenic Variants in PALB2, RAD51C and RAD51D in Breast Cancer Patients: A Single-Center Experience

Oğuzhan Yılmaz, Ebru Erzurumluoğlu Gökalp, Sevilhan Artan
Department of Medical Genetics,Eskişehir Osmangazi University Faculty of Medicine,Eskişehir,Türkiye

Introduction and Objective: Hereditary factors account for approximately 8% of breast cancer cases. While *PALB2* germline pathogenic variants (GPV) are detected in roughly 1% of screened women—carrying a 7.2-fold relative risk and a 53% cumulative risk by age 80—prevalence data for *RAD51C* and *RAD51D* remain scarce. Although these genes are frequently linked to triple-negative breast cancer (TNBC), comprehensive data regarding other clinicopathological features like histological subtype and stage are limited. This study aims to characterize the clinicopathological profiles of patients with *PALB2*, *RAD51C*, or *RAD51D* GPVs identified via NGS at our center (2020–2025) and compare these findings with the current literature.
Results: Among 487 breast cancer patients screened, germline pathogenic variants (GPVs) were identified in *PALB2* (n=7; 1.4%), *RAD51C* (n=2), and *RAD51D* (n=2). The age at diagnosis for patients with PALB2 GPVs ranged from 35 to 67 years, with a median age of 51. Genotypically, the c.557dup (p.Asn186LysfsTer4) variant was identified in two unrelated patients, emerging as a recurrent mutation within this group. Analysis of histopathological data revealed a heterogeneous distribution; while the majority of patients presented with hormone receptor-positive (Luminal A and B) tumors, divergent phenotypes were observed among patients harboring the same genotypic alteration: one patient exhibited a HER2-positive phenotype, while the other presented with Triple-Negative Breast Cancer (TNBC). The most prominent shared clinical feature among *RAD51C* GPV carriers was an early age at diagnosis (41 and 45 years, respectively). Patients with *RAD51D* GPVs were of similar ages (54 and 52 years), and both were diagnosed with the Triple-Negative Breast Cancer (TNBC: ER-, PR-, HER2-) histological subtype.
Discussion: Despite our limited cohort (n=11), these findings provide critical clinical insights. While international data report a median diagnosis age of 60–71 for *RAD51C* carriers, local studies suggest a younger onset of 50–55 years in Türkiye. Our notably earlier median of 43 may stem from ascertainment bias in high-risk clinical referrals or the early penetrance of specific variants like c.706-2A>G. Regarding *RAD51D*, the 100% correlation with the TNBC phenotype aligns with its established risk profile. Conversely, the *PALB2* group exhibited significant phenotypic heterogeneity; although Luminal subtypes predominated, the presence of TNBC and HER2-positive cases reflects a broad spectrum similar to *BRCA2*. Finally, the recurrent c.557dup variant reinforces the likelihood of a population-specific founder mutation, highlighting the importance of geographic genetic signatures.
Conclusion: Current guidelines classify *PALB2, RAD51C*, and *RAD51D* as moderate-to-high penetrance genes. Despite our limited cohort, these findings align with existing literature. The identification of population-specific variants, such as *PALB2* c.557dup, underscores the clinical significance of geographic ancestry in genetic counseling. To establish the definitive prevalence of these genes in the Turkish population, larger multicenter studies are warranted.

Keywords: *PALB2, RAD51C, RAD51D*, Breast Cancer

Clinicopathological Characteristics of Germline Pathogenic Variants in PALB2, RAD51C, and RAD51D in Breast Cancer Patients: A Single-Center Experience Introduction Breast cancer is the most common malignancy among women worldwide, with hereditary predisposition playing a pivotal role in approximately 10-15% of cases. For decades, genetic testing was synonymous with BRCA1 and BRCA2 analysis. However, the advent of multigene

panel testing using Next-Generation Sequencing (NGS) has expanded the landscape of hereditary breast and ovarian cancer (HBOC) to include other high- and moderate-penetrance genes involved in the homologous recombination repair (HRR) pathway, specifically PALB2, RAD51C, and RAD51D. PALB2 (Partner and Localizer of BRCA2) is now recognized as a high-risk breast cancer gene. Germline pathogenic variants (GPVs) in PALB2 are detected in approximately 1% of screened women, conferring a 7.2-fold relative risk and a cumulative breast cancer risk of up to 53% by age 80, placing it in a risk category similar to BRCA2. Conversely, RAD51C and RAD51D were initially established as ovarian cancer susceptibility genes. Their association with breast cancer has been more recently solidified, particularly with the Triple-Negative Breast Cancer (TNBC) subtype. Despite establishing these associations, data regarding the specific clinicopathological features—such as histological subtype, hormone receptor status, and age of onset—remain limited, particularly in non-Western populations. Recent studies, such as Spijkervet et al. (2025), have provided data from Dutch cohorts, yet population-specific data for Türkiye is crucial for refining genetic counseling guidelines. This study aims to characterize the clinicopathological profiles of Turkish breast cancer patients harboring PALB2, RAD51C, or RAD51D GPVs identified at our center and to benchmark these findings against global data. Materials and Methods Study Design and Population This retrospective, single-center study included patients diagnosed with breast cancer who underwent multigene panel testing at our institution between 2020 and 2025.Genetic Analysis Genomic DNA was isolated from peripheral blood leukocytes. NGS was performed using a targeted panel covering HRR pathway genes. Variants were classified according to the American College of Medical Genetics and Genomics (ACMG) criteria. Only pathogenic or likely pathogenic variants in PALB2, RAD51C, and RAD51D were included in this analysis.Data Collection Clinicopathological data, including age at diagnosis, histological subtype and receptor status were retrieved from electronic medical records. Results Among 487 breast cancer patients screened, germline pathogenic variants(GPVs) were identified in PALB2 (n=7; 1.4%), RAD51C (n=2), and RAD51D (n=2). The age at diagnosis for patients with PALB2 GPVs ranged from 35 to 67 years, with a median age of 51.Genotypically, the c.557dup (p.Asn186LysfsTer4) variant was identified in two unrelated patients, emerging as a recurrent mutation within this group. Analysis of histopathological data revealed a heterogeneous distribution; while the majority of patients presented with hormone receptor-positive (Luminal A and B) tumors, divergent phenotypes were observed among patients harboring the same genotypic alteration: one patient exhibited a HER2-positive phenotype, while the other presented with Triple-Negative Breast Cancer (TNBC).The most prominent shared clinical feature among RAD51C GPV carriers was an early age at diagnosis (41 and 45 years, respectively). Patients with RAD51D GPVs were of similar ages (54 and 52 years), and both were diagnosed with the Triple-Negative Breast Cancer (TNBC:ER-, PR-, HER2-) histological subtype. Discussion Despite the limited cohort size (n=11), these findings provide clinical insights that contribute to the evolving understanding of non-BRCA hereditary breast cancer in the Turkish population.A significant observation in our study is the early onset of breast cancer among RAD51C carriers (median 43 years)(Table 1). This stands in contrast to recent international data, such as the Dutch cohort described by Spijkervet et al. (2025), which reported a median diagnosis age of 71 years, and general literature citing a median onset of approximately 60 years. While our findings align somewhat more closely with local Turkish studies suggesting a younger onset of 50–55 years, the notably earlier median in our cohort may stem from ascertainment bias in high-risk clinical referrals. Alternatively, this discrepancy suggests that specific variants, such as the c.706-2A>G splicing variant detected here, might exhibit higher penetrance or distinct clinical behaviors within the Turkish genetic background.Regarding RAD51D, the presentation of the Triple-Negative Breast Cancer (TNBC) phenotype observed in our cohort aligns with the gene's established risk profile. This mirrors findings from large case-control studies indicating that RAD51D loss-of-function mutations are significantly enriched in TNBC patients.PALB2 group exhibited significant phenotypic heterogeneity, similar to the spectrum seen in BRCA2-associated cancers. Although Luminal subtypes predominated, the presence of both TNBC and HER2-positive

cases reflects a diverse presentation. The identification of the recurrent c.557dup (p.Asn186Lysfs*4) variant in unrelated individuals reinforces the likelihood of a population-specific founder mutation. Furthermore, the observation of discordant tumor subtypes in patients carrying the identical mutation highlights that while germline variants confer susceptibility, somatic events likely play a decisive role in dictating the specific tumor phenotype. Conclusion Current guidelines classify PALB2, RAD51C, and RAD51D as moderate-to-high penetrance genes. Our single-center experience confirms the high risk associated with these genes but highlights population-specific nuances. Specifically, RAD51C carriers in Türkiye may present at a significantly younger age than Western guidelines suggest, necessitating earlier surveillance. The identification of population-specific recurrent variants, such as PALB2 c.557dup, underscores the clinical significance of incorporating geographic ancestry into genetic counseling and panel design. Larger multicenter studies are warranted to establish definitive prevalence rates and modify screening protocols for the Turkish population. TABLE 1 Gene Variant Protein change Rs ID Zygosity ACMG Criteria Mutation Type PATOLOJİ PALB2 c.1008_1010delinsA TA p.Asn336delinsLys * Novel Heterozygous Pathogenic NONSENSE 35 Unknown PALB2 c.172_175del p.Gln60ArgfsTer7 rs180177143 Heterozygous Pathogenic NONSENSE 51 IDC-ER:+ PR:+ HER2:- PALB2 c.2587-1G>C * rs761214886 Heterozygous Pathogenic SPLICE 54 IDC-ER:+ PR:+ HER2:- PALB2 c.3170_3175delCTT CAGinsAATCA p.A1057Efs*18 rs1597073266 Heterozygous Pathogenic NONSENSE 67 IDC-ER:+ PR:- HER2:+ PALB2 c.1647_1648del p.(His549GInfsTer 28) rs786201773 Heterozygous Pathogenic NONSENSE 46 IDC ER:+ PR:+ HER2:- PALB2 c.557dup p.(Asn186LysfsTer 4) rs1555461727 Heterozygous Pathogenic NONSENSE 47 IDC(Carcinoma with Apocrine Differentiation) ER:- PR:- HER2:+ PALB2 c.557_558insA p.Asn186Lysfs*4 rs1555461727 Heterozygous Pathogenic NONSENSE 58 IDC ER:- PR:- HER2:- RAD51 C c.706-2A>G * rs587780259 Heterozygous Pathogenic SPLICE 41 Unknown RAD51 C c.454_455insT p.(Leu152fs) Novel Heterozygous Pathogenic NONSENSE 45 Unknown RAD51 D c.293del p.(Asp98Valfs*25) rs750282687 Heterozygous Pathogenic NONSENSE 54 IDC ER:- PR:- HER2:- RAD51 D c.294del p.(Asp98Glufs*25) Novel Heterozygous Pathogenic NONSENSE 52 IDC ER:- PR:- HER2:-