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Research Article

The Association of *GPR30/GPER-1* Polymorphisms with Breast Cancer Risk

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Abstract

Breast cancer is the second most common cancer worldwide and the most prevalent cancer among women, causing a large number of deaths annually. This fact underscores the importance of studying the risk factors, diagnostic methods, and treatments for this disease. Single-nucleotide polymorphisms are the most common type of genetic variation in eukaryotic genomes and are found in many genes associated with various cancers. Depending on their location within different regions of a gene, these genetic variants can differently affect gene expression and cancer susceptibility. In this case-control study, we investigated the single-nucleotide polymorphisms of the *GPR30/GPER-1* gene, including rs3808350, rs3808351, and rs11544331, and their association with breast cancer risk. The study was conducted on 70 breast cancer patients and 70 healthy women from the female population of Markazi Province, Iran. Blood samples were collected from all participants, and DNA was extracted. The target polymorphisms were genotyped using the tetra-primer amplification refractory mutation system PCR (tetra-ARMS PCR) method. Data analysis was performed using SPSS Statistics 26 and SNP Analyzer 2 software. The results showed a significant association between the AG genotype (co-dominant model) and the combined GG and AG genotypes (dominant model) of rs3808350, indicating an increased risk of breast cancer. For rs11544331, the TT genotype (recessive model) and the combined TT and CT genotypes (dominant model) were also significantly associated with higher risk. No significant association was observed for rs3808351. In conclusion, rs3808350 and rs11544331 polymorphisms may serve as potential biomarkers for early detection and risk assessment of breast cancer. Identifying such genetic markers could enhance diagnostic accuracy and support the development of personalized prevention and treatment strategies.

Keywords: GPER, rs3808350, rs3808351, rs11544331, SNP

Introduction

Cancer is a disease characterized by pathophysiological changes in the intrinsic process of cell division, causing approximately 9 million deaths annually, primarily among adults (Chhikara and Parang, 2023; Sarthy et al., 2019). It results from genetic alterations that lead to uncontrolled and sometimes invasive growth of abnormal cells. These cells bypass regulatory mechanisms, alter signaling pathways, and adapt metabolically, giving them the ability to survive and proliferate in adverse conditions. Environmental factors, lifestyle, and immune system dysfunction also contribute to the increased risk of cancer. Metastasis is considered the primary cause of cancer-related mortality (Chhikara and Parang, 2023; Jelonek et al., 2010; Saravana, 2023).

According to the latest data from the World Health Organization (WHO), breast cancer is the second most common cancer worldwide and the most frequent cancer in women as of 2022. Mortality from breast cancer ranks fourth, following lung, colorectal, and liver cancers. In Iran, breast cancer is also the most common cancer among women. A 2016 study identified Markazi Province as a high-risk area for breast cancer in Iran (Cheshmeh et al., 2024; Ferlay et al., 2020). Approximately 99% of cases occur in women, with only 0.6 to 1% affecting men (Wang et al.).

Breast cancer refers to malignant tumors originating from breast tissue (Sharma et al., 2010). Major risk factors include genetic and epigenetic abnormalities that affect critical events in the cell cycle and signaling pathways, leading to DNA damage (Jones and Baylin, 2007; Mehmood et al., 2020; You and Jones, 2012). No single gene or environmental factor is solely responsible for cancer; rather, mutations in multiple high-penetrance genes significantly increase individual risk. Furthermore, not only mutations but also polymorphic variations in such genes can contribute to cancer development (Jelonek et al., 2010). Single-nucleotide polymorphisms (SNPs) are the most abundant form of genetic variation in eukaryotic genomes, arising from mutations (Giess et al., 2010;

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McCouch et al., 2010; Shastry, 2002). For any given SNP, alleles are classified as 'major' or 'minor' based on population frequency. Humans, being diploid, can exhibit one of three genotypes per SNP: homozygous major, heterozygous, or homozygous minor (Crawford and Nickerson, 2005). Many cancer-related genes contain SNPs (You and Jones, 2012), which may be located in promoters, exons, introns, and untranslated regions (5'-UTR and 3'-UTR), affecting gene expression and cancer susceptibility depending on their location (Deng et al., 2017; Mammadov et al., 2012).

Haplotypes are combinations of alleles across multiple loci on a chromosome that are inherited together. Unlike individual SNPs, haplotypes assign alleles to specific chromosomes (Crawford and Nickerson, 2005). Recent studies on the extent of linkage disequilibrium in human populations have shown that haplotype analysis of SNPs, rather than individual SNPs, provides a more effective approach for associating alleles with traits (Rafalski, 2002). Once the haplotypes of each individual are identified, they can be considered as alleles of a multi-allelic marker (Liu et al., 2008).

Estrogens, particularly estradiol, play essential roles in reproduction, mammary gland development, metabolism, bone health, and cardiovascular function, mediated through both genomic and non-genomic pathways (Langer et al., 2010). These effects are carried out via hormone receptors, including GPER-1, a G protein-coupled receptor (GPCR) capable of mediating rapid signaling and genomic responses to estrogen alongside classical receptors ERα and ERβ. GPER is expressed in various hormone-related cancers, including breast cancer, and is associated with unfavorable clinical outcomes (Ghaderi Zefrhei M, 2017; Hernández-Silva et al., 2020; Kasap et al., 2016; Prossnitz et al., 2008; Tutzauer et al., 2020; Ulhaq et al., 2021). The *GPER-1* gene is located on chromosomal locus 7p22.3 and consists of three exons, including exon 3, which corresponds to the amino acid coding region (Aihara et al., 2012; Prossnitz and Barton, 2023). According to NCBI, this gene is also known as *GPR30* or *GPER* (Sayers et al., 2022). Its mRNA expression level may be influenced by SNPs. Among several SNPs identified in *GPER*, three—rs3808350 (located in the 5' regulatory region, A>G), rs3808351 (in the 5'-UTR, G>A), and rs11544331 (in exon 3, causing Pro16Leu substitution, C>T)—are biologically relevant to human neoplasms (Giess et al., 2010; Harrison et al., 2023; Korkmaz et al., 2014; Sayers et al., 2022; Ulhaq et al., 2021).

Breast cancer incidence and mortality have risen in *Iran* and worldwide, emphasizing the need to explore genetic risk factors. This study investigates *GPR30/GPER-1* gene polymorphisms and their association with breast cancer, aiming to aid early diagnosis and prevention.

Materials and Methods

Study Participants and Procedure

This study was designed as a case-control investigation. A total of 70 healthy women (controls) and 70 patients diagnosed with breast cancer (cases) from Arak, Markazi Province, were randomly selected. Ethical approval was obtained from Arak University of Medical Sciences (Code: IR.ARAKMU.REC.1399.294). Genomic DNA was extracted from whole blood using the Parstous extraction kit (Iran). The extraction process involved combining blood samples with binding buffer and proteinase K, vortexing, and incubating at 57°C, followed by ethanol addition. The mixture was transferred to a silica column, washed with buffers (Washing Buffer 1,2), centrifuged (13,000 rpm, 1 minute), and eluted with elution buffer. The quantity of extracted DNA was determined using spectrophotometry, while its quality was assessed by electrophoresis.

Tetra-ARMS PCR was used to genotype the selected SNPs. Four primers per SNP were designed (Table 1) and synthesized by Metabion (Germany). Each PCR reaction included 10 µL of Ampliqon 2x Master Mix RED, 4 µL DNA template, 0.5 µL of each primer (diluted 1:10), and 4 µL nuclease-free water. The PCR cycling protocol involved initial denaturation at 95°C for 5 minutes, followed by 40 cycles of denaturation (95°C, 45 s), annealing (59°C for rs3808350, 66°C for rs3808351, and 64°C for rs11544331, 45 s), and extension (72°C, 45 s), with a final extension at 72°C for 10 minutes. PCR products were analyzed using 2.5% agarose gel electrophoresis (see Figure 1). Product lengths are listed in Table 1.

Table 1. The sequence and product length of the primers for rs3808350, rs3808351, and rs11544331

SNP	Primer Information	Primer Sequence (5' → 3')	Product Size (bp)		
			450	**294**	**205**
rs3808350	Outer Forward	CAGTACAAGTTACTTACCCGCC	*	*	
	Outer Reverse	ATATGTACCTTTTTGTATTTGGATGATA	*		*
	Inner Forward (A)	CTATTTTTAAGTGACATGTCGCA			*
	Inner Reverse (G)	ATAAAAATTCAAACCTTGAAATATCC		*	
			385	**231**	**196**
rs3808351	Outer Forward	CTCATACTCAGCGGACAAAGGATCACTCAGC	*	*	
	Outer Reverse	CTGCTCATGGTTGCGGATTTCACAGTCT	*		*
	Inner Forward (G)	GGCTTGGGGGGCCTCGCTATG			*
	Inner Reverse (A)	CGATGGCCGCCCCATGAGTGT		*	
			391	**237**	**198**
rs11544331	Outer Forward	AACAAACCCAACCCAAACCACCACAGGT	*	*	
	Outer Reverse	AGCCGATGGGGAAGAGGAAGATGGTGTA	*		*
	Inner Forward (C)	GGGCGTGGGCCTGGAGATGTAACC			*
	Inner Reverse (T)	CGCAGGCTGCGCGGTGCATA		*	

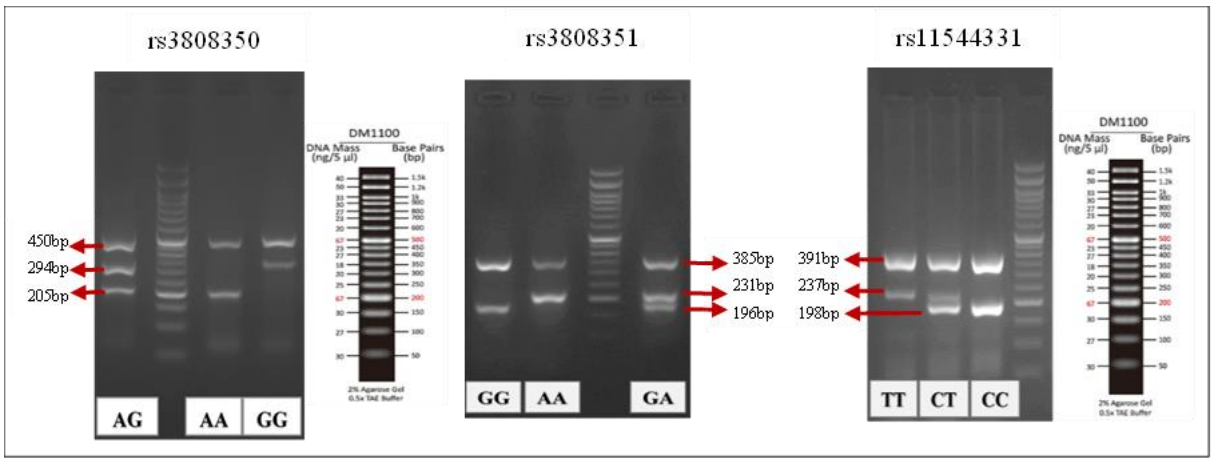


Figure 1. The electrophoresis results of the PCR products corresponding to the three genotypes rs3808350, rs3808351, and rs11544331.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics 26. Genotype and allele distributions for each SNP were compared between the cases and controls using the chi-square (χ^2) test. Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) for the association between genotypes and breast cancer risk. SNP Analyzer 2 was also used for mutation and haplotype analyses. A P-value (P) less than 0.05 was considered statistically significant.

Results

Statistical analysis revealed a significant association between the genotype and allele frequencies of rs3808350 and rs11544331 with breast cancer, while no such association was observed for rs3808351. Specifically, rs11544331 was associated with increased breast cancer risk in both the dominant and recessive models, and rs3808350 was associated with increased risk in the dominant and co-dominant models.

Genotype Frequency

The relative frequencies of the genotypes for all three SNPs are presented in Table 2 and Figure 2. For rs3808350, the AG genotype compared to the combined genotypes AA and GG (co-dominant model) is significantly associated with breast cancer risk and increases that risk (OR=7.071, 95% CI: 2.281–21.920, P=0.000). The combined genotypes AG and GG versus genotype AA (dominant model) also show a significant association with increased breast cancer risk (OR=13.600, 95% CI: 3.038–60.872, P=0.000). The GG genotype compared to

the combined genotypes AG and AA does not show a significant association with breast cancer risk (P=0.559). For rs3808351, no significant difference was found (P=0.179). Regarding rs11544331, the TT genotype was significantly associated with increased risk in the recessive model (OR=37.458, 95% CI: 14.291–98.181, P=0.000), and TT and CT versus CC (dominant model) also showed a significant risk (OR=28.097, 95% CI: 8.057–97.979, P=0.000). Interestingly, the CT genotype was associated with a reduced risk in the codominant model (OR=0.301, 95% CI: 0.128–0.712, P=0.005). The results of this analysis for rs3808350 and rs11544331 are detailed in Table 3 and Figure 3.

Table 2. Genotype and allele distribution of rs3808350, rs3808351, and rs11544331

SNP	Number		Genotype Frequency (%)						Allele Frequency (%)			
	Cases	Controls	Cases			Controls			Cases		Controls	
rs3808350	70	70	AA	GG	AG	AA	GG	AG	A	G	A	G
			2.9%	2.9%	94.2 %	28.6 %	1.4%	70.0 %	50.0 %	50.0 %	63.6 %	36.4 %
rs3808351	70	70	GG	AA	GA	GG	AA	GA	G	A	G	A
			15.7 %	11.4 %	72.9 %	27.1 %	14.3 %	58.6 %	52.1 %	47.9 %	56.4 %	43.6 %
rs11544331	70	70	CC	TT	CT	CC	TT	CT	C	T	C	T
			4.3%	82.8 %	12.9 %	55.7 %	11.4 %	32.9 %	10.7 %	89.3 %	72.1 %	27.9 %

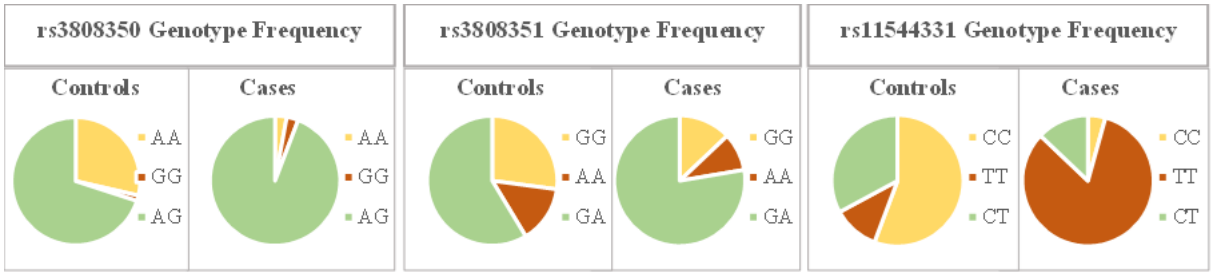


Figure 2. The genotype distribution of rs3808350, rs3808351, and rs11544331 was compared between cases and controls

Table 3. Analysis of the significance of dominant, recessive, and co-dominant models for rs3808350 and rs11544331

SNP	Model	Test Genotype vs. Reference Genotype	χ^2	Df	P	OR	95% Confidence Interval	
							Lower Bound	Upper Bound
rs3808350	Recessive	GG/AA+AG	0.341	1	0.559	2.029	0.180	22.907
	Dominant	GG+AG/AA	17.473	1	0.000	13.600	3.038	60.872
	Codominant	AG/AA+GG	14.073	1	0.000	7.071	2.281	21.920
rs11544331	Recessive	TT/CC+CT	71.663	1	0.000	37.458	14.291	98.181
	Dominant	TT+CT/CC	44.082	1	0.000	28.097	8.057	97.979
	Codominant	CT/TT+CC	7.940	1	0.005	0.301	0.128	0.712

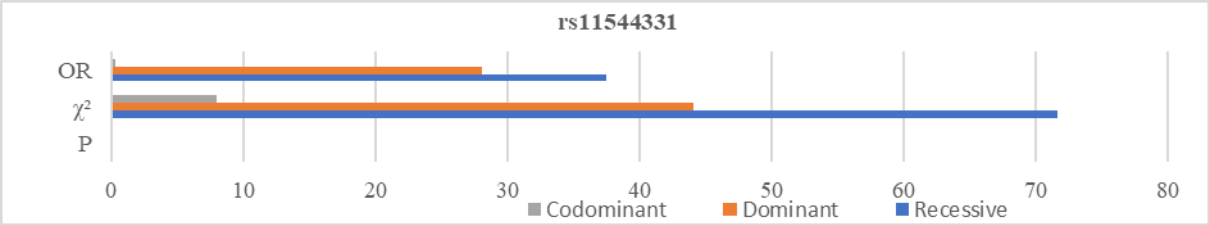


Figure 3. The P-value (P), odds ratio (OR), and chi-square (χ^2) statistics were evaluated for the dominant, recessive, and co-dominant inheritance models of rs3808350 and rs11544331

Haplotype analysis indicated that certain combinations—such as AAGACC, AAGGCC, AGAACC, AGAATT, AGGACC, and AGGATT—were associated with increased breast cancer risk ($P < 0.05$ and $OR > 1$), as shown in Table 4 and Figure 4. According to the data analysis results from the SNP Analyzer 2 software, presented in Table 5, rs3808350 and rs11544331 showed statistically significant linkage in this study (Figure 5).

Allele Frequency

The analysis of rs3808350 showed that the relative frequency of allele A was 63.6% in the controls and 50.0% in cases, while allele G was present in 50.0% of cases and 36.4% of the controls. The relative allele frequencies of this SNP are shown in Table 1. According to the chi-square test, there was a significant association between the G/A alleles in the cases and controls ($P = 0.022$). Logistic regression analysis indicated that an A to G substitution reduces the risk of breast cancer ($OR = 1.745$).

For rs3808351, the relative frequency of allele A was 47.9% in cases and 43.6% in the controls, while allele G had a frequency of 56.4% in the controls and 52.1% in cases. The chi-square test showed no statistically significant association between the A/G alleles in the two groups ($P = 0.472$).

In contrast, for rs11544331, allele T had a frequency of 89.3% in cases and 27.9% in controls, while allele C was found in 72.1% of the controls and only 10.7% of cases. The chi-square test revealed a highly significant association between T/C alleles in cases and controls ($P = 0.000$). According to logistic regression analysis, a substitution from C to T increases the risk of breast cancer ($OR = 21.581$).

The relative frequencies of all three SNP alleles are presented in Figure 6 and Table 2, and the results of the corresponding analyses are available in Table 6.

Table 4. The association between the combined genotypes of the three investigated SNPs and breast cancer risk was analyzed in both cases and controls

Genotype	OR	95% Confidence Interval		χ^2	Df	P
		Lower Bound	Upper Bound			
AAGACC	2.077	1.743	2.474	5.185	1	0.023
AAGGCC	2.129	1.776	2.552	8.485	1	0.004
AGAACC	2.061	1.733	2.450	4.118	1	0.042
AGAATT	2.111	1.765	2.525	7.368	1	0.007
AGGACC	2.321	1.894	2.843	19.350	1	0.000
AGGACT	0.364	0.108	1.221	2.857	1	0.091
AGGATT	14.333	5.728	35.868	40.320	1	0.000
AGGGCT	1.000	0.240	4.167	0.000	1	1.000
AGGGTT	4.182	0.455	38.393	1.867	1	0.172

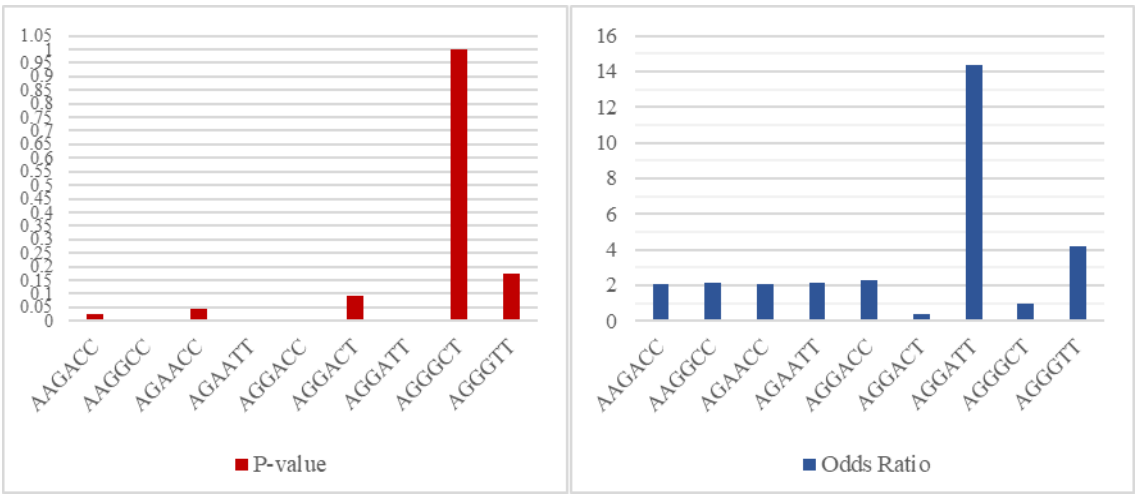


Figure 4. The P-value (P) and odds ratio (OR) were assessed for the combined genotype profiles of the three investigated SNPs in case and control groups.

Table 5. The combined genotype patterns of the three investigated single-nucleotide polymorphisms (SNPs) were analyzed in both case and control groups to assess their association with breast cancer risk.

Tetra-ARMS	SNP	χ^2	P	OR	Lower Bound	Upper Bound
1	rs3808350	5.254	0.022	0.573	0.355	0.924
2	rs3808351	0.518	0.472	0.841	0.525	1.347
3	rs11544331	108.856	0.000	21.581	11.259	41.368

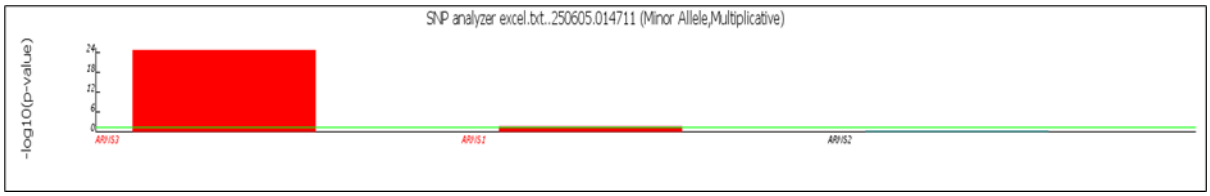


Figure 5. The significance levels of mutations rs3808350, rs3808351, and rs11544331 were analyzed using SNP Analyzer 2 software.

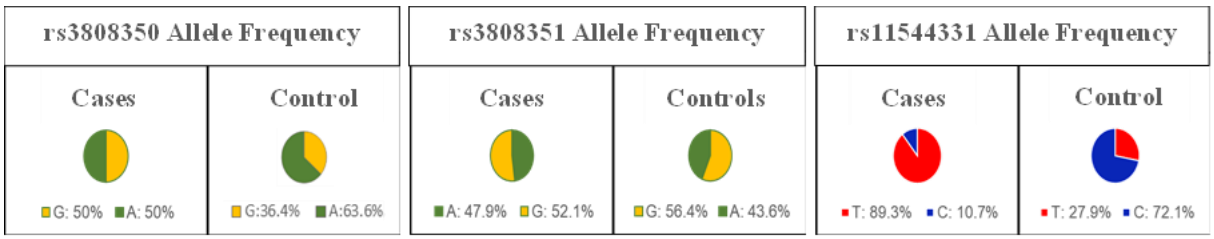


Figure 6. Allele frequencies of rs3808350, rs3808351, and rs11544331 in the case and control groups

Table 6. Breast cancer risk was evaluated based on the allele frequencies of the rs3808350, rs3808351, and rs11544331 SNPs.

SNP	χ^2	Df	P	OR	Lower Bound	Upper Bound
rs3808350 alleles (allele G / allele A)	5.254	1	0.022	1.745	1.082	2.814
rs3808351 alleles (allele A/allele G)	0.518	1	0.472	1.189	0.742	1.903
rs11544331 alleles (allele T / allele C)	108.856	1	0.000	21.581	11.259	41.367

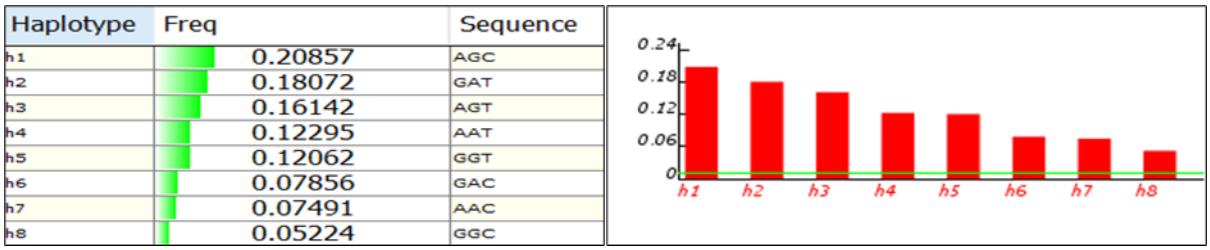
Haplotype Analysis

The analysis of the three studied SNP haplotypes in both the control group and cases revealed that the haplotypes h1, h2**,** and h3, with sequences AGC (20.8%), GAT (18%), and AGT (16.1%), respectively, had the highest frequencies among individuals (Figure 7).

The results of the case-control haplotype statistical analysis, performed using SNP Analyzer 2, are shown in Figure 8. In this figure, columns above the horizontal green line indicate statistically significant mutations, while columns below the green line represent non-significant mutations. According to these results, the haplotypes h1, h3, h2, h6, and h7 were statistically significant.

Discussion

Numerous studies have investigated the association between single-nucleotide polymorphisms (SNPs) of the *GPER* gene and various diseases, including breast cancer. The findings of several such studies are discussed below: The study by Pupo et al. (2017), which examined the rs11544331 (P16L) polymorphism among women with breast cancer in Tunisia, reported that the T allele and TT genotype were associated with an increased risk of cancer, metastasis, and more aggressive forms such as triple-negative tumors. These findings confirm the potential role of this SNP in breast cancer development and are consistent with the results of the present study regarding rs11544331 (Pupo et al., 2017). In a systematic review and meta-analysis by Ulhaq et al. (2021), the three *GPER* SNPs—rs3808350, rs3808351, and rs11544331—were analyzed. The results indicated that rs3808350 and rs3808351 were significantly associated with cancer risk in Asian populations, while rs11544331 showed no such association. These findings align with the current study's results for rs3808350, but the discrepancies regarding rs11544331 and rs3808351 could be due to the pooling of studies with diverse population characteristics. (Ulhaq et al., 2021). The study by Korkmaz et al. (2014) on Turkish adolescent boys with gynecomastia revealed a significant association between rs3808350 and rs3808351 with the disease, and the GAT haplotype was also associated with increased risk. Although the disease focus differs from the present study, the risk role of the G allele in rs3808350 and the high frequency of the GAT haplotype are consistent with our findings (Korkmaz et al., 2014). In a study by Park et al. (2020) involving Korean patients with ovarian cancer, no significant association was found between the three studied SNPs and the disease. The results for rs3808351 are consistent with our findings, whereas those for rs3808350 and rs11544331 differ. These discrepancies may be due to differences in the type of cancer studied or the genetic background of the population (Park et al., 2020). Feldman et al. (2014) investigated the biological function of the rs11544331 variant and found that it is associated with reduced GPER function and increased blood pressure in women. Although this study did not focus on cancer, its functional data biologically support the current findings, as impaired GPER function and reduced apoptosis may contribute to the proliferation of precancerous cells (Feldman et al., 2014). In their study on Turkish women, Kasap et al. (2016) found that the G allele of rs3808350 and rs3808351 was associated with increased risk of uterine fibroids, and the GGC haplotype also raised disease risk. The results for rs3808350 are consistent with our findings; however, rs3808351 did not show a significant association in our study, which could be due to differences in the type of cancer examined (Kasap et al., 2016).



Haplotype	Freq	Sequence
h1	0.20857	AGC
h2	0.18072	GAT
h3	0.16142	AGT
h4	0.12295	AAT
h5	0.12062	GGT
h6	0.07856	GAC
h7	0.07491	AAC
h8	0.05224	GGC

Figure 7. Analysis of haplotypes of the three studied SNPs in controls and cases.

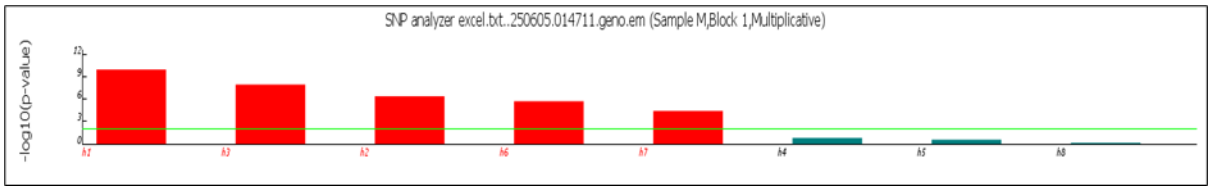


Figure 8. Statistical analysis results of haplotypes in case-control studies using SNP Analyzer 2 software

The study by Giess et al. (2010) on Caucasian women investigated the association of three *GPER* SNPs with pathological features of breast cancer, such as PR negativity, tumor size, and metastasis. Although no direct association with cancer risk was found, their results support the role of these SNPs in tumor aggressiveness, which aligns with our findings for rs3808350 and rs11544331 (Giess et al., 2010). In a study by Chevalier et al. (2014) conducted in France on patients with testicular seminoma, rs3808350 and rs3808351 were associated with increased disease risk, while rs11544331 showed no association. The findings regarding rs3808350 are consistent with our study, but the results for the other two SNPs differ, possibly due to differences in sex or cancer type (Chevalier et al., 2014). Using a bioinformatics approach, Zhang et al. (2014) evaluated the relationship between the three targeted polymorphisms and *GPER* gene expression and reported no significant findings. The differences in research approach (bioinformatics vs. clinical studies) and the use of various statistical models or software may have affected the outcomes (Zhang et al., 2014). In a study from Portugal, Alves et al. (2010) found no significant association between rs3808350 and breast cancer risk, a result that contrasts with our findings. This could be due to differences in population genetics or sample size (Alves et al., 2010).

Conclusion

A comparison of different studies suggests that rs3808350 and rs11544331 polymorphisms have been repeatedly associated with increased risk of breast cancer or related disorders, including in the current study. Thus, their role as potential genetic biomarkers is supported. In contrast, findings on rs3808351 remain inconsistent and may depend on ethnicity or disease type. Differences in study outcomes may stem from variations in the studied populations, disease types, sample sizes, or statistical methods. Nonetheless, our results are in agreement with strong evidence supporting the important role of GPER and its genetic variants in the development and progression of breast cancer, emphasizing the need for large-scale studies.

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Conflict of Interests

None.

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