Associations between single-nucleotide polymorphisms of the interleukin-18 gene and breast cancer in Iraqi women

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Introduction

Breast cancer (BC) is the most common cancer in females worldwide, with nearly 2.3 million new cases diagnosed in 2020. It accounts for approximately 11.7% of all cancer cases and 24.5% of all cancer cases in females [1]. Since 2008, the global incidence of BC has increased by more than 20%, and the death rate has risen by 14% [2]. As a result, research on relevant tumor indicators for early diagnosis and monitoring is required, and recent studies have concentrated on the role of the immune system in cancer progres-
After the ethical committee of the Medical City directorate approved this study, 100 women who visited the oncology teaching hospital’s breast clinic were recruited from January 28, 2020 to August 11, 2022. Group 1 included 60 women who had recently been histopathologically diagnosed with BC and provided written informed consent for participation in the study. Group 2 included 40 healthy women who served as controls. Patients with other systemic diseases and those taking any hormone-modifying drug were excluded from the study.

DNA extraction and genotyping

Each patient and control had 8–10 mL of blood taken. Blood samples were taken from the cubital vein and placed directly into an anticoagulant tube containing EDTA. Genomic DNA extraction was performed using a Norgen Biotek kit (Thorld, ON, Canada). The optical density ratio at 260/280 nm was used to assess the quantity and quality of isolated DNA Using a Nano-Drop device (Qubit 4, Invitrogen, Waltham, MA, USA). It was preferable to have a balance of 1.7–1.9. Electrophoresis on a 1% agarose gel was performed to corroborate the findings. Until the genotyping analysis, the DNA samples were stored at –20°C.

Polymerase chain reaction

Polymorphisms were investigated by utilizing sequence-specific amplification–polymerase chain reaction (SSP-PCR) at locations –607C/A rs1946518 and –137G/C rs187238 within the promoter region of IL18. For the targeted location –607C/A, a common reverse primer and two specific forward primers were utilized, with an amplified product size of 196 bp, and a forward control primer was used to amplify a 301-bp fragment covering the polymorphism region as an internal control (Table 1).

In the location –137G/C, a common reverse primer and two specific forward primers were also utilized, with an amplified product size of 261 bp, and a forward control primer was used to amplify a 446-bp fragment covering the polymorphism region as an internal control (Table 2). The polymerase chain reaction (PCR) reactions were carried out in a volume of 25 μL, including 12.5 μL of 2 × Go-Taq Green Master mix (Promega, Madison, WI, USA), 3 μL of genomic DNA, and 6.5 μL of nuclease-free water. All reaction mixtures contained one sequence-specific primer, one internal positive control and polymerase chain reaction (PCR) reactions were carried out in a volume of 25 μL, including 12.5 μL of 2 × Go-Taq Green Master mix (Promega, Madison, WI, USA), 3 μL of genomic DNA, and 6.5 μL of nuclease-free water. All reaction mixtures contained one sequence-specific primer, one internal positive control, and a forward control primer was used to amplify a 446-bp fragment covering the polymorphism region as an internal control (Table 2). The polymerase chain reaction (PCR) reactions were carried out in a volume of 25 μL, including 12.5 μL of 2 × Go-Taq Green Master mix (Promega, Madison, WI, USA), 3 μL of genomic DNA, and 6.5 μL of nuclease-free water. All reaction mixtures contained one sequence-specific primer, one internal positive control, and a forward control primer was used to amplify a 446-bp fragment covering the polymorphism region as an internal control (Table 2).

Table 1. Primers for the IL18 –607C/A rs1946518 polymorphism

| Primer sequence | Primer sequence |
|-----------------|-----------------|
| Forward primer 1 | 5′-GTGCAGAAGTGTTAATAATTTAC-3′ |
| Forward primer 2 | 5′-GTGCAGAAGTGTTAATAATTTAA-3′ |
| Reverse primer | 5′-TACCTCATTCAAGACTTCC-3′ |
| Internal positive control | 5′-CTTTCATATTTCCAGGAA-3′ |

Methods

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IL18, interleukin-18.
common reverse primer, and one internal position control primer, each at a concentration of 1 μL. As a result, each piece of DNA was subjected to two PCR tests: one for the F1 wild-type allele and one for the F2 mutant allele [8]. The assays were carried out in a thermocycler (Applied Biosystems, Waltham, MA, USA). Denaturation was carried out at 95°C for 5 min, followed by 30 cycles at 94°C for 30 s, 57°C for 30 s, 72°C for 40 s, and 72°C for 10 min. Then, the PCR results were visualized using electrophoresis on 2% agarose gel, and the molecular weight was calculated using a 100-bp DNA ladder.

### Statistical analysis

The genotype of cytokines was statistically analyzed using the SPSS version 25 (IBM Corp., Armonk, NY, USA). The allele frequencies of the cytokine genes were calculated by the direct gene counting method. A freely available online calculator was used to calculate whether there was a significant departure from Hardy-Weinberg (H-W) equilibrium for two alleles (http://www.h2know.com/academics/Hardy-Weinberg_equilibrium-calculator-3-alleles.html). H-W equilibrium is the expected frequency of genotypes if mating is non-assortative and there are no mutations from one allele to another. When there are two alleles for a particular gene, A and B, and their respective population frequencies are p and q, the expected frequencies of the genotypes AA, AB, and BB are p², 2pq, and q², respectively. The Pearson chi-square test was used to assess whether there were significant differences between the observed and expected frequencies. The alleles and genotypes of cytokines were presented as percentages and frequencies, and the two-tailed Fisher exact test was calculated to assess the significance of differences between their distributions in BC patients and controls. Odds ratios (ORs) were also estimated to define the association between cytokine alleles and genotypes with BC. OR values can range from between 0 and 1 (for a negative association) to more than 1 (for a positive association).

### Results

#### IL18 –607C/A (rs1946518) SSP-PCR

This study analyzed the distribution of the genotype and allele frequencies of the rs1946518 polymorphism (at the –607C/A position) in patients and controls (Fig. 1). This polymorphism presented three genotypes (CC, CA, and AA) that corresponded to two alleles (T and A) in BC patients and controls. The genotype frequencies in both groups were not in agreement with H-W equilibrium, and there were highly significant differences between the observed and expected frequencies in both patients and controls (χ² = 3.16 and χ² = 16.5), respectively (Table 3).

Fig. 1. Agarose gel electrophoresis image that shows the sequence-specific amplification-polymerase chain reaction product analysis of interleukin-18 (IL18) –607 (rs1946518) (C/A) gene polymorphism. Where M, marker (100–1,200 bp), the presence of C or A allele were observed at 196-bp product size. The (CC) wild type homozygote were showed in C allele only, the (AA) mutant type homozygote were showed in A allele only, whereas the (C/A) heterozygote were showed in both C and A allele, internal control at 301-bp product size.
than in controls (15.0% vs. 65.5%, p < 0.001), and the magnitude of this negative association was 0.11. However, the AA genotype frequency was higher in patients (51.7%) than in controls (22.5%); this difference was significant (OR, 2.83; p = 0.004). The CA genotype frequency was also significantly higher in patients than in controls (33.3% vs. 15.0%; OR, 3.68; p = 0.04). The C allele frequency was lower in patients than in controls (25.0% vs. 38.7%), while the A allele frequency was higher (75.0% vs. 61.3%, respectively). A negative association was found for the C allele (OR, 0.19) and a positive association for the A allele (OR, 5.03) (p < 0.001 for both) (Table 4).

**Table 3.** Hardy–Weinberg equilibrium–expected genotype frequencies in *IL18* rs1946518

| Groups | CC | CA | AA | C  | A  | χ² |
|--------|----|----|----|----|----|----|
| Patient genotypes | | | | | | |
| Observed | 9 | 20 | 31 | 0.68 | 0.32 | 3.16* |
| Expected | 6.0 | 26.0 | 28.0 | Not detected | - | |
| Control genotypes | | | | | | |
| Observed | 25 | 6 | 9 | 0.30 | 0.70 | 16.5* |
| Expected | 19.6 | 16.8 | 3.6 | Not detected | - | |

*IL18*, interleukin–18.

*a* χ² > 3.84, significant.

**Table 4.** Genotype distribution and allele frequency of *IL18* rs1946518 (–607C/A) in breast cancer patients and controls with risk estimation

| Study group | Genotype groups | OR (95% CI) | Fisher’s exact probability* | p-value |
|-------------|-----------------|-------------|----------------------------|---------|
| | C/C | 9 (15.0) | 25 (62.5) | 0.11 (0.04–0.28) | 0.000 | 0.0001*** |
| | C/A | 20 (33.3) | 6 (15.0) | 2.83 (1.02–7.86) | 0.061 | 0.040* |
| | A/A | 31 (51.7) | 9 (22.5) | 3.68 (1.49–9.04) | 0.003 | 0.004** |
| Allele distribution | | | | | | |
| | C | 38 (31.7) | 56 (70.0) | 0.19 (0.11–0.36) | 0.000 | 0.0001*** |
| | A | 82 (68.3) | 24 (30.0) | 5.03 (2.72–9.30) | 0.000 | |

*IL18*, interleukin–18; OR, odds ratio; CI, confidence interval.

Significant, *p < 0.05, **p < 0.01, ***p < 0.001.

**Fig. 2.** Agarose gel electrophoresis image that shows the sequence-specific amplification–polymerase chain reaction product analysis of interleukin-18 (IL18) –137 (rs187238) (G/C) gene polymorphism. Where M, marker (100–1,200 bp), The presence of G or C allele were observed at 261-bp product size, the (GG) wild type homozygote were showed in G allele only, the (CC) mutant type homozygote were showed in C allele only, whereas the (G/C) heterozygote were showed in both G and C allele. Internal control at 446-bp product size.
there was a highly significant difference between the observed and expected frequencies ($\chi^2 = 5.74$) (Table 5).

At the position –137G/C in IL18, patients had a significantly higher frequency of the GC genotype than controls (43.3% vs. 22.5%; OR, 2.63; p = 0.04). In contrast, the frequency of the CC genotype was significantly higher in patients than in controls (23.3% and 12.5%; OR, 2.13). Therefore, the G allele frequency was significantly lower in patients than in controls (55.0% vs. 76.2%, respectively), with a highly significant difference (p = 0.002). A negative association was found for the G allele (OR, 0.38) and a positive association for the C allele (OR, 2.36) (Table 6).

**Discussion**

The present study investigated the two most commonly studied SNPs of the IL18 gene (–607C/A and –137G/C). The patients and controls both showed deviation from H-W equilibrium for the –607C/A genotype, which may have been related to BC or intermarriage in Arab Iraqi society between relatives. This result aligns with that of a previous study on BC [14]. Although the distribution of the –137G/C genotype in the patient group was consistent with H-W equilibrium, this was not the case for the control group, which showed a highly significant difference between the observed and expected frequencies ($\chi^2 = 5.74$). This SNP may be considered a common genotype in the Iraqi population, with the wild-type G allele having a protective function, reducing susceptibility, and the mutant C allele having an environmental effect.

These SNPs’ genotypes and alleles showed significant differences between BC patients and controls. The present study observed that the IL18 –607 CA and AA genotypes were present in about 85% of BC cases. The wild-type CC genotype had a low frequency (about 15%) in BC patients, which may highlight the role of the IL18 –607 polymorphism in the pathogenesis of disease. The A allele was an environmental effect allele, while the C allele had a preventive fraction because the CC genotype showed the highest frequency in the control group (70%). These highly significant findings for the AA and CA genotypes at position IL18 –607 suggest that this polymorphism may play a role in cancer progression.

Several studies on IL18 polymorphisms have been conducted in various populations in multiple countries; one of them has found a link between IL18 polymorphisms and the risk of BC [15]. The IL18 –607C/A polymorphism may be linked to an increased risk of BC in Asian and mixed populations [16]. Furthermore, the present results showed that the IL18 rs1946518 SNP might play a role in BC because the wild-type allele C of the –607 SNP had a protective effect against BC (OR, 0.19). In contrast, the mutant allele A had a positive association (OR, 5.03) suggesting an etiological impact; therefore, women who carry allele A of –607 may be more susceptible to BC than women who have allele C. However, the results of some studies were mixed; in a study involving 72 BC patients and 93 control women, Fathi Maroufi et al. [17] discove-

### Table 5. Hardy-Weinberg equilibrium–expected genotype frequencies in IL18 rs187238

| Groups | CC  | CA  | AA  | C   | A   | $\chi^2$ |
|--------|-----|-----|-----|-----|-----|---------|
| Patients' |     |     |     |     |     |         |
| genotypes |     |     |     |     |     |         |
| Observed | 20  | 26  | 14  | 0.45| 0.55| 0.93 NS |
| Expected | 18.2| 29.7| 12.2| Not detected | - |
| Control  |     |     |     |     |     |         |
| genotypes |     |     |     |     |     |         |
| Observed | 26  | 9   | 5   | 0.24| 0.76| 5.74*   |
| Expected | 23.3| 14.5| 2.30| Not detected | - |

*IL18, interleukin–18; NS, not significant.

$\chi^2 > 3.84$, significant.

### Table 6. Genotype distribution and allele frequency of IL18 rs187238 (–137G/C) in breast cancer patients and controls with risk estimation

| Genotype groups | Study group | OR (95% CI) | Fisher’s exact probability* | p-value |
|-----------------|-------------|-------------|----------------------------|---------|
|                 | Patient (n = 60) | Control (n = 40) |                             |         |
| G/G             | 20 (33.3) | 26 (65.0) | 0.27 (0.12–0.62) | 0.002 | 0.002** |
| G/C             | 26 (43.3) | 9 (22.5) | 2.63 (1.07–6.48) | 0.035 | 0.04* |
| C/C             | 14 (23.3) | 5 (12.5) | 2.13 (0.70–6.47) | 0.203 | 0.180 NS |

| Alleles distribution | Study group | OR (95% CI) | Fisher’s exact probability* | p-value |
|----------------------|-------------|-------------|----------------------------|---------|
| G                    | 66 (65.0) | 61 (76.2) | 0.38 (0.20–0.71) | 0.002 | 0.002** |
| C                    | 54 (45.0) | 19 (23.8) | 2.63 (1.40–4.92) | 0.03 |

*IL18, interleukin–18; OR, odds ratio; CI, confidence interval; NS, not significant.

Significant, *p < 0.05, **p < 0.01.

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erred that the *IL18* –607A/C polymorphism was not linked to BC in an Iranian population sample. The *IL18* rs187238 polymorphism results showed no significant differences according to the CC genotype frequencies between BC patients and controls.

Nonetheless, it was interesting to note in the present study that the heterozygous GC genotype had an OR of 2.63 for the patient group, implying that the mutant allele C may have had an environmental effect on the Iraqi population, conferring susceptibility to BC, while the wild-type allele G had a preventive effect against BC (OR, 0.38). Our findings show that the *IL18* –137G/C polymorphism is associated with the development of BC. The conversion of G (guanine) to C (cytosine) at position –137G/C of the *IL18* gene removes a nuclear factor binding site for histone-4 transcriptional factor-1 [18]. Genetic variants have been considered the most critical cancer risk factors. Although high-penetrant capability genes (e.g., *BRCA1* and *BRCA2*) have strong links to BC, low-penetrant susceptibility genes that predispose individuals to the disease have yet to be identified; nonetheless, immune responses and surveillance may be affected by genetic variability in a sequence of immune regulatory genes [19]. The *IL18* promoter polymorphism –137G/C has previously been linked to various cancers in different populations, including esophageal squamous cell malignant tumors, prostate cancer in the Chinese population [20], colorectal cancer in Greek people [21], and ovarian cancer in native Hawaiians [22]. Additional case-control studies on BC and gastric cancer progression have been published [23, 24]. However, there is no link between type 2 diabetes mellitus development and the *IL18* –137G/C gene polymorphism [25].

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