ORIGINAL ARTICLE

Genetic Variation of the BCL-2 Gene and its Relation to Breast Cancer in Iraqi Women

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ABSTRACT

INTRODUCTION: B-cell lymphoma-2 (BCL-2) is a key regulator of apoptosis, and its dysregulated expression contributes to cancer cell survival in several malignancies, including breast cancer. The BCL-2 gene, specifically rs2279115, has been found to significantly modulate transcriptional activity and affect BCL-2 protein expression in various tissues and diseases. Genetic differences affecting apoptotic pathways may therefore contribute to the susceptibility and progression of breast cancer. The present study aims to investigate variation in the BCL-2 genotype in humans, determine the nucleotide sequence of the gene, and determine whether this correlates with the incidence of breast cancer in 45 women. **MATERIALS AND METHODS:** This case–control study included 30 women with breast cancer and 15 an age-matched group of healthy women controls. The genetic polymorphism of the BCL-2 gene in situ (rs2279115) was determined using the tetra-primer amplification refractory mutation system-polymerase chain reaction technique. Nucleotide sequencing of the amplified fragments was performed using DNA sequencing technology. Fisher's exact test was used to compare the genotype and allele frequencies between patients and controls. **RESULTS:** There is genetic variation of the BCL-2 gene in patients with breast cancer, with three genotypes, CC, CT, and TT, in comparison with one genotype in healthy controls. The percentage of incidence of the T allele was 25% in breast cancer patients compared to 0% in controls. The sequencing test for the amplified BCL-2 gene reported multiple nucleotide variations in the breast cancer samples compared with controls. **CONCLUSION:** The present study showed a possible genetic variation with multiple mutations in the BCL-2 gene in patients with breast cancer, which needs to be confirmed by further larger cohorts.

Keywords:
BCL-2 Gene; breast cancer; genetic variation; mutation; nucleotide sequencing

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INTRODUCTION

Breast cancer is a malignant tumour in which mammary gland epithelial cells proliferate out of control due to different carcinogenic factors. The incidence of this cancer has increased and is considered a threat to women's lives and health. For instance, in the USA, breast cancer accounts for approximately 30% of women's malignant tumours. It has been approved that breast cancer is a heterogeneous tumour and, multiple genes have been confirmed to affect the course of disease progression.[1] In addition to the important role of mutation, deletion, or activation of several key oncogene and tumour suppressor genes in the development of the tumour, the inhibition of apoptosis has been implicated in breast cancer progression.[2]

The *BCL*-2 gene (rs2279115) is responsible for the expression of the antiapoptotic *BCL*-2 protein family. In addition, *BCL*-2 has a significant role in ensuring normal tissue development and function by maintaining the balance between cellular survival and death. It plays a role in preventing high cellular death in different physiological conditions.[3] Normal breast epithelial cells are tightly modulated by balanced pro-apoptotic and anti-apoptotic signals, while disturbance of this balance can play a crucial

role in tumorigenesis and anticancer treatment resistance.[4] Additionally, mutation of the genes has an important impact on health because a devastating genetic disorder or a beneficial adaptation can occur due to a single base change.[5,6]

The rs2279115 variation in the promoter region has garnered interest for its possible impact on transcriptional activity among its regulatory polymorphisms. A case-control study of women from England revealed no association between the rs2279115 polymorphism and breast cancer risk or overall survival, indicating its minor role in Caucasian populations.[7] A thorough meta-analysis of several studies indicated that the C allele of rs2279115 may be linked to an elevated risk of several types of cancer, including breast, lung, and prostate malignancies.[8] However, the same study reported that rs2279115 could be correlated with a significantly higher risk of malignancy in Asia but not for Caucasians, which potentially supports the use of rs2279115 as a tumour marker for cancer therapy in Asia. Given these population-dependent and inconsistent findings, it is necessary to perform sequencing of the amplified BCL-2 gene region in addition to genotyping to identify potential additional nucleotide variations that may coexist with rs2279115 and contribute to altered gene regulation and breast cancer incidence. This study aimed to investigate the hypothesis that the genetic variation of the BCL-2 gene, particularly the rs2279115 polymorphism, is attributed to the incidence of breast cancer and to determine the nucleotide sequencing of this gene.

MATERIALS AND METHODS

Study Design

The study design is a case-control study. The study has been conducted on 45 women of different ages, ranging from 39 to 76 years. The participants are categorized into two groups: 15 individuals who are healthy and considered as a control group, and 30 women with diagnosed breast cancer upon visiting the Hospital of Nuclear Medicine Oncology in the city of Mosul/Iraq, during the period from December 2023 to February 2024. The participants are identified as having breast cancer at stages (I to IV) by histopathology, following clinical evaluation and imaging. They are then managed by an oncologist at the aforementioned hospital. The control participants were selected to match the cases in terms of age and were further screened to exclude individuals with a family history of cancer or any major chronic diseases to minimize potential confounding bias. This study has been performed according to formal approval from the Ethics Committee of the University of Mosul

Sample Size Calculation

The sample size was computed under the assumption of a case-control study to determine the significant relationship between the polymorphism of the BCL-2 gene and the occurrence of breast cancer. In the computation of the sample size, it is assumed to have a confidence level of 95%, 80% statistical power, and an effect size based on prior similar studies. However, the final sample size used in the study consists of 30 breast cancer-affected individuals and 15 control subjects, since the study faced constraints in the selection of the participants.

Collection of Blood Samples and DNA Extraction

Blood samples were collected from all participants using EDTA tubes. DNA has been extracted from the whole blood samples using a Whole Blood Genomic DNA Extraction Kit (ADD BIO, Korea) in accordance with the manufacturer's guidelines. The quality of the extracted DNA was evaluated by measuring absorbance at two wavelengths (260 and 280) using a nanodrop spectrophotometer. DNA was isolated from the blood of all 45 samples included in the study, and, then all extracted DNA samples were stored at −20°C for future experiments.

The tetra-primer amplification refractory mutation system-polymerase chain (Tetra–ARMS-PCR) Reactions
The DNA concentration in each sample was adjusted with TE buffer solution (10mM Tris-HCl containing 1mM EDTA•Na_2) to 25 ng/µl for PCR amplification. For primer reactions, four primers were used, including F-outer and R-outer throughout the gene. For the mutant allele, the forward outer-reverse inner primers are

used, instead of those for the normal allele. Nucleic acid from each sample was mixed with appropriate primers for the targeted mutations and the master mix components to form the PCR reaction blend in 0.2-ml PCR tubes. This mixture was quickly centrifuged to achieve optimal components. Then, the PCR tubes were cycled in a thermocycler using customized procedures for particular mutations. The reaction product (at 2% concentration) was loaded into the wells of a prepared agarose gel after a DNA ladder from BIOLAB Company was injected into specified wells. After 40 minutes of electrophoresis used to migrate the samples, the bands were imaged using a gel-electrophoresis apparatus. Tetra-ARMS-PCR was used to assess the genetic variation of the *BCL*-2 gene at locus (rs2279115).

Determination of genetic variation of the *BCL-2* gene in situ (rs2279115) using Tetra–ARMS-PCR technique

Tetra–ARMS-PCR technique was performed to detect any mutation in the *BCL*-2 gene. Template DNA (4 µl = 100 nanogram) and each mutation-specific primer for the *BCL2* gene (1 µl = 10 picomol), supplied by Macrogen (Korea), have been added to the contents of the master mix.[9] The primers used to determine genetic mutation at the locus (rs2279115) are shown in Table 1. Then, to conduct the multiplication reaction, the reaction tubes were inserted into the thermocycler. The amplification refractory mutation system ARMS-PCR technique was used to identify the mutation (rs2279115) (Table 2).

Table 1: The primers which are used to deduce the genetic mutation at the locus (rs2279115) via PCR technology.

Locus	primer	Sequence	Band size	annealing
rs2279115 for *BCL2*	F-outer	5- CCGGCTCCTTCATCGTCTCC-3	300 bp	58°C
	R-outer	5- CCCAGGAGAGAGACAGGGGAAA-3		
	F-inner	5- AATAAAACCCTCCCCCACCACCT-3	220bp	
	R-inner	5- CCCTTCTCGGCAATTTACACGC-3	121 bp	

In this reaction, 58C° was considered an optimal temperature for the primer bonding, depending on the Gradient program in the thermocycler device. Then, 2% agarose gel was used to separate the products resulting from the PCR reaction.

Table 2: The program adopted in the amplification refractory mutation system ARMS-PCR technique to identify the mutation (rs2279115)

No.	Stage	Locus	Temperature	Time	Cycle number
1	Initial denaturation	for all sites	95°C	6 min.	1
2	Denaturation	for all sites	95°C	45 sec.	35
3	Annealing	(rs2279115)	58°C	1 min.	
4	Extension	for all sites	72°C	1 min.	
5	Final extension	for all sites	72°C	5 min.	1
6	Stop reaction	for all sites	4°C	5 min.	1

Measurement of nucleotide sequencing for the amplified fragments via DNA sequencing technology

The PCR products, which are amplified using specific primers (initiators) targeted to the BCL-2 genes, were analysed to determine the sequence of the nitrogenous bases of the gene. The resulting DNA fragments were sequenced to identify the mutations. The 3130 Genetic Analyzer instrument (Hitachi, Japan) was used to read the sequence of the genes. Then, matching of the reported gene sequences in this study with the gene sequences documented in the National Centre for Biotechnology Information (NCBI) was performed, and the findings were analysed using the Basic Local Alignment Search Tool (BLAST) program.

Statistical analyses

P-values, confidence intervals (CIs) value, and odds ratios (ORs) were calculated using MedCalc statistical software, version 20.009 https://www.medcalc.org . Fisher's exact test was utilised to evaluate the association between genotypes or alleles and breast cancer. The value of a statistically significant difference was $P<0.05$. The following frequencies were calculated based on the following dependency: Allelic frequency of the normal allele=2 (number of homozygous individuals) + (number of heterozygous individuals)/2 (total number). The allelic frequency of the mutant allele=2 (number of heterozygotes) + (number of heterozygotes)/2(total number).

RESULTS

Extraction of DNA from blood samples

The results showed the genome packages that were extracted from blood samples (Figure 1). The purity of

the DNA sample ranged between (1.5-1.7), and the concentration ranged from (50-125 ng/µl).

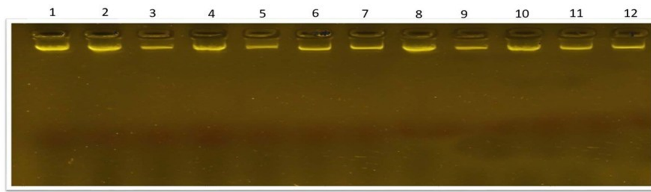

Figure 1: Genomes extracted from blood samples and separated by agarose gel at a concentration of 1%.

Determination of genetic variation of the *BCL*-2 gene in situ (rs2279115) using Tetra–ARMS-PCR technique

The results showed that there is a relationship between women who suffer from breast cancer and the genetic variation in the *BCL*-2 gene at the site (rs2279115) on chromosome 18 (Figure 2). It has been found from the PCR reaction that the genetic variation of the gene appears in the three genotypes CC, CT, and TT, whereas in control samples, there was no genetic variation in the *BCL*-2 because only one main gene has been found, as shown in Table 3.

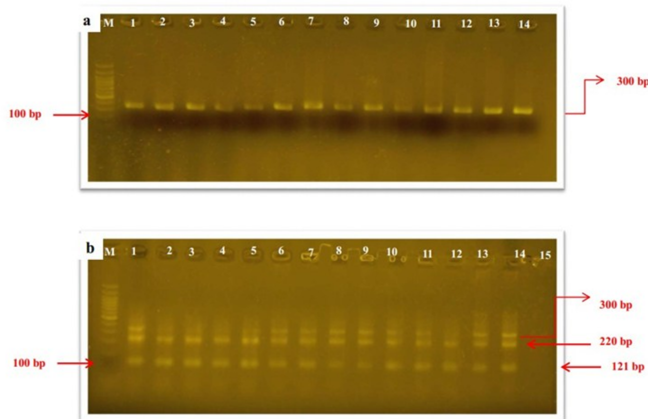

Figure 2: The product of the PCR reaction of the genetic variation (rs2279115) of the *BCL2* gene. M denotes to the Ladder which was prepared by Biolabs with a size of 100 bp, and separated by 2% agarose gel. A: The control samples showed only one band of 300 bp size for the main gene. B: The samples from patients of breast cancer showed 3 bundles, the first with a size of 300 bp for the main gene, the second with a size of 121 bp for the natural allele, and the third bundle with a size of 220 bp for the mutant allele.

Table 3 shows the frequency of the different genotypes of the *BCL2* gene with the percentage of allelic observations at the site (rs2279115). The present study found that the women with breast cancer had the highest frequency of the mutant genotype (TT) (16.7%) in comparison with the same mutant genotype in the healthy control group (0%).

Table 3: Distribution of allelic viewing and genotype of the *BCL-2* gene at the locus (rs2279115) among the healthy women group and women with breast cancer group, where the C allele is the normal allele and the T allele is the mutant allele.

Comparison	Patients (n=30)	Controls (n=15)	OR	95% CI	P-value*
CC vs. (CT+TT)	20 (66.6%)	15 (100.0%)	3.75	0.40 – 35.54	0.249
CT vs. (CC+TT)	5 (16.7%)	0 (0.0%)	-	-	0.3
TT vs. (CC+CT)	5 (16.7%)	0 (0.0%)	-	-	0.3
C vs. T	C = 45 (75%) T = 15 (25%)	C = 30 (100%) T = 0 (0.0%)	3.17	0.97 – 10.35	0.056

*Fisher's exact test was used to compute the p-value.

In contrast, the women with breast cancer had the lowest percentage of the normal genotype (CC) (66.6%) in comparison with the healthy control group, which showed a 100% for the normal genotype. However, the percentage of the variant genotype (CT) was high in the experimental group (16.7%) compared to the control group (0%).

In addition to that, the present study showed that the percentage of the presence of the mutant T allele was higher in the women with breast cancer (25%) in comparison with the healthy control group (0%). In contrast, the percentage of presence of the normal allele in patients was only 75% versus 100% in the control group.

The results of the study also showed that there are suggestive trends of association between breast cancer and the mutations of the *BCL*-2 gene because the value of odds ratio (OR) for the mutant genotype TT was 3.75, and for the mutant allele OR was 3.17.

Measurement of the nucleotide sequencing for the amplified fragments via DNA sequencing technology for the *BCL*-2 gene

The sequencing test for the amplified *BCL*-2 gene reported differences in some nucleotides in the studied gene in comparison with the original gene documented in NCBI (the accession number is LC802665.1). In addition, different types of genetic variations were reported for the *BCL*-2 gene in breast cancer patients after comparing them with the gene sequences at the NCBI site using a sequencing test.

DISCUSSION

BCL-2 Genetic Variants and Breast Cancer Susceptibility
A link has been established between gene variants and different diseases.[10–13] Additionally, the *BCL-2* gene and its variants have relationships with some diseases and syndromes such as Alzheimer's disease, schizophrenia, and depression.[14–16] However, the direct association between rs2279115 and other known variants with breast cancer remains unclear. In the current study, it is hypothesized that genetic variation in BCL-2, which is a key regulator of apoptosis, could affect susceptibility to breast cancer, considering its role in tumour progression and therapy resistance. So, the study selected BCL-2 (rs2279115) and focused on the potential functional significance in breast cancer pathogenesis.

The present study is the first to investigate the link between the *BCL-2* gene polymorphism (rs2279115) and breast cancer risk in women from Mosul and the northern Iraq region. This novel localized genetic study is critical because allele frequencies and genotype distributions are different between populations due to ethnic, environmental, and lifestyle factors. The present genetic findings may clinically lead to the development of personalized screening strategies, especially if future studies confirm that certain alleles are associated with a higher risk in this population. The present findings underscore the significance of regional genetic research as a foundation for accurate oncology initiatives in underrepresented populations. These findings are fundamental in understanding the relationship between the transformation of some genes, the incidence of specific pathological conditions, and the development of future therapeutic strategies.

BCL-2 Polymorphism, Expression, and Prognostic Implications

The role of *BCL*-2 gene in breast cancer is still controversial. Some reports found that *BCL*-2 gene expression can reduce breast cancer incidence via blocking apoptosis, prolonging the cell cycle, and delaying tumour cell growth.[17] In addition, good pathophysiological behaviour in breast cancer patients was linked to increased expression of the *BCL*-2 gene, which makes the gene a promising indicator to predict the progression of lymph node metastasis.[18] In addition, reports are showing that there is no correlation between the BCL-2 promoter polymorphism and the prognosis of breast cancer.[8] Population-specific differences may be the reason for these discrepancies. It is important to note that genetic diversity, environmental influences, and lifestyle differences can vary across different populations. The present study focuses on Iraqi women, a population that may have distinct genetic and environmental backgrounds compared to those examined in other studies. It is highly recommended to further research in different populations to confirm the impact of BCL-2 promoter polymorphisms on breast cancer prognosis.

Furthermore, the type of breast cancer may be responsible for the variation in the findings. Breast cancer could be hormone receptor-positive or hormone receptor -negative. Hormone receptor-positive tumours are dependent in their growth on estrogen or progesterone because they have estrogen or progesterone receptors on the breast cancerous cells. In contrast, hormone receptor-negative tumours have no estrogen and progesterone receptors, so their proliferation does not depend on hormones.[19] *BCL*-2 has been reported as a significant prognostic marker for breast cancer because it is overexpressed in approximately 75% of this malignant tumour.[20] However, a better prognosis in patients with luminal breast cancer has been linked to high expression of the *BCL*-2 gene in hormone receptor-positive tumors.[21] In contrast, in hormone receptor-negative or triple-negative tumours showed that overexpression of the *BCL*-2 gene could be regarded as an independent poor prognostic marker.

Genotyping, Sequencing Findings, and Methodological Considerations

The present study showed genetic variations in the *BCL*-2 gene in patients with breast cancer, while in healthy women, there was only one gene without variation. The present study found that the women with breast cancer had the highest frequency of the mutant genotype (TT) in comparison with the absence of the same mutant genotype in the healthy control group, who had only the

normal genotype (CC). In addition, the variant genotype (CT) has present only in breast cancer patients. It has been proved by RNA-seq data that *BCL*-2 gene is the most frequently mutated gene in germinal center B-cell (GCB). Schuetz and co-authors found that there is a high level of *BCL*-2 mutations in follicular lymphoma and GCB, whereas in activated B-cell diffuse large B-cell lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma and small lymphocytic leukaemia, the *BCL*-2 mutations were low. Moreover, no *BCL*-2 mutations have been found in GC centroblasts in the same study.[22] T-ARMS-PCR was selected as the primary method for genotyping in this current study due to its high specificity, well-established reliability, and accuracy in detecting targeted SNPs. This technique is suitable for resource-limited settings and population-specific studies because it is cost-effective and requires relatively simple laboratory infrastructure. However, the use of more advanced methods of multi-omics approaches or high-throughput technologies, such as next-generation sequencing, could provide a broader genomic context and enhance the overall depth of analysis.

Mutation Patterns and Comparative Evidence

Identifying the genomic sites that undergo frequent mutation in human tumours is considered an efficient way to discover the causative genes in oncogenesis. So then, DNA is isolated from samples of both controls and patients with breast cancer, and analysed using a polymerase chain reaction (PCR)-mismatch technique for rapid identification of potential point mutations in the *BCL*-2 gene. Interestingly, multiple point mutations have been reported in the *BCL*-2 gene of patients with breast cancer. In line with the present finding, DNA sequencing in a previous study has confirmed the high incidence of a total of six mutations in the *BCL*-2 gene in 3 out of 5 patients with lymphoma or leukemia tumors.[23] It is noteworthy that the multiple mutations in this gene were reported for the first time in this sample population, Iraqi women.

Previous studies have shown controversial findings about the relationship between *BCL-2* polymorphism (rs2279115) and breast cancer. Several studies on different populations worldwide have focused on investigating various polymorphisms within the *BCL-2* gene and their association with breast cancer, resulting in inconsistent outcomes on a global scale. Some studies on different populations, including Asians, Middle Eastern, and European populations, have shown that different populations exhibit different allele and genotype distributions for various *BCL-2* gene polymorphisms, including rs2279115, which may play an important role in Breast cancer risk and prognosis.[8] A recent study on 175 Turkish population showed no relationship between (rs2279115) gene polymorphisms and breast cancer.[24] In contrast, another study on 110 breast cancer patients identified that the AA genotype of *BCL-2* is associated with advanced tumor stage, lymph node metastasis, and elevated Ki67 index, indicating its involvement in tumor growth.[25] In Africa, specifically in Egypt, there was a relationship between genetic polymorphism of *BCL-2* (rs2279115) and increased susceptibility to cancer.[26] These inconsistent outcomes which may occurred probably due to ethnic, and environmental factors highlight that investigations on different populations worldwide need to be carried out to understand the role of *BCL-2* gene mutation in breast cancer development and progression.

Study Limitations and Future Directions

The limitations of the study are the relatively small sample size. This was due to the expensive materials and techniques used in this self-funded study. Future studies with larger cohorts could provide a greater statistical power and generalizability, and a better understanding of genetic vulnerability to breast cancer. Despite the observed correlation between *BCL*-2 mutations and the incidence of breast cancer chromosomal mapping, it is unknown whether it would be possible to target this specific gene mutation with drugs and improve the pathological condition. Chromosomal mapping is recommended as a future study to confirm and further explore the correlation between the genetic variation and breast cancer. Additionally, the present study included cases of all cancer stages (I-IV). This may require future investigation to determine whether a specific stage show higher percentage of mutation. In addition, future studies

are required to address the functional consequences of these genetic variations, correlate genotypic data with some clinical indicators (e.g., BCL-2 expression, and tumour markers CA 15-3 and CA 27.29), protein function and apoptosis mechanism, and highlight the most effective treatment that regulates this gene and prevents or reduces the incidence and progression of the disease. The effect of different anticancer drugs on *BCL-2* gene should be addressed because these medications can adversely affect different biological parameters.[27,28] Finally, future study of the *BCL-2* allele polymorphism with other clinicopathological parameters and other tumours is recommended.

CONCLUSION

The current study demonstrated a possible association between genetic variation in the *BCL*-2 gene and patients with breast cancer. The mutations in the gene involved multiple mutations in nucleotides. These findings suggest that genetic variation in BCL-2 may contribute to breast cancer susceptibility; however, any potential stratification of breast cancer patients based on *BCL-2* mutational status requires further validation. The therapeutic response and prognosis of the disease in *BCL*-2 -mutant patients should be studied extensively and compared with *BCL*-2 -nonmutant patients.

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REFERENCES

1. Weitzel JN, Kidd J, Bernhisel R, et al. Multigene assessment of genetic risk for women for two or more breast cancers. Breast Cancer Res Treat 2021;188:759–768.
2. Yuan L, Cai Y, Zhang L, et al. Promoting Apoptosis, a Promising Way to Treat Breast Cancer With Natural Products: A Comprehensive Review. Frontiers in Pharmacology. 2022;12. doi:10.3389/fphar.2021.801662.
3. Hatok J, Racay P. Bcl-2 family proteins: Master regulators of cell survival. Biomolecular Concepts. 2016;7:259–270.
4. Iksen, Witayateeraporn W, Hardianti B, Pongrakhananon V. Comprehensive review of Bcl-2 family proteins in cancer apoptosis: Therapeutic strategies and promising updates of natural bioactive compounds and small molecules. Phytotherapy Research. 2024;38:2249–2275.
5. Hernandez LM, Blazer DG. *Genes, behavior, and the social environment: Moving beyond the nature/nurture debate.* 2006 doi:10.17226/11693.
6. Ismael SS, Al-Shamaa SD. Mutation in microtubule-associated protein tau mapt coding gene and its correlation with Alzheimer's disease. Int J Res Pharm Sci 2020;11:5150–5157.
7. Searle CJ, Brock IW, Cross SS, et al. A BCL2 promoter polymorphism rs2279115 is not associated with BCL2 protein expression or patient survival in breast cancer patients. Springerplus 2012;1:1–8.
8. Yao Z, Yang B, Liu Z, et al. Genetic polymorphisms of Bcl-2 promoter in cancer susceptibility and prognosis: A meta-analysis. Oncotarget 2017;8:25270–25278.
9. Haider Al-Mawlah Y, Fadhil Alasadi Y, Hadi AM, Sajed Abdul-Abbas H. Association Between Some Candidate Gene Variants And The Development Of Osteoporosis. nveo.orgYH Al-Mawlah, YF Alasadi, AM Hadi, HS Abdul-AbbasNVEO-NATURAL VOLATILES Essent OILS Journal| NVEO, 2021•nveo.org 2021;8:1125–1142.
10. Vucicevic K, Jakovljevic V, Sretenovic J, et al. Expression of the BCL2 gene in chronic lymphocytic leukaemia patients. Serbian J Exp Clin Res 2015;16:187–191.
11. Correia C, Schneider PA, Dai H, et al. BCL2 mutations are associated with increased risk of transformation and shortened survival in follicular lymphoma. Blood 2015;125:658–667.
12. Ahmad A, Barani S, Sultan S. Role of the IL-10 gene and its genetic variations in the development of diabetes mellitus in women . World Acad Sci J 2025;7:1–7.

13. Ramadan ZJ, Hamed OM, Khalaf IH. Detection of Genetic Variation for Some Genes That Related With Recurrent Spontaneous Abortion in Nineveh Province. Biochem Cell Arch 2020;20:6407–6414.
14. Liu ME, Huang CC, Yang AC, et al. Effect of Bcl-2 rs956572 Polymorphism on Age-Related Gray Matter Volume Changes. PLoS One 2013;8. doi:10.1371/journal.pone.0056663.
15. Chang CC, Chang YT, Huang CW, et al. Associations of Bcl-2 rs956572 genotype groups in the structural covariance network in early-stage Alzheimer's disease. Alzheimer's Res Ther 2018;10. doi:10.1186/s13195-018-0344-4.
16. Zhang C, Wu Z, Hong W, et al. Influence of BCL2 gene in major depression susceptibility and antidepressant treatment outcome. J Affect Disord 2014;155:288–294.
17. Raha P, Thomas S, Thurn KT, Park J, Munster PN. Combined histone deacetylase inhibition and tamoxifen induces apoptosis in tamoxifen-resistant breast cancer models, by reversing Bcl-2 overexpression. Breast Cancer Res 2015;17. doi:10.1186/s13058-015-0533-z.
18. Sirotković-Skerlev M, Plavetić ND, Sedlić F, et al. Prognostic value of circulating Bcl-2 and anti-p53 antibodies in patients with breast cancer: A long term follow-up (17.5 years). Cancer Biomarkers 2021;30:95–104.
19. Lee HJ, Park IA, Park SY, et al. Two histopathologically different diseases: Hormone receptor-positive and hormone receptor-negative tumors in HER2-positive breast cancer. Breast Cancer Res Treat 2014;145:615–623.
20. Lindeman GJ, Visvader JE. Targeting BCL-2 in breast cancer: exploiting a tumor lifeline to deliver a mortal blow? Breast Cancer Manag 2013;2:1–4.
21. Dawson SJ, Makretsov N, Blows FM, et al. BCL2 in breast cancer: A favourable prognostic marker across molecular subtypes and independent of adjuvant therapy received. Br J Cancer 2010;103:668–675.
22. Schuetz JM, Johnson NA, Morin RD, et al. BCL2 mutations in diffuse large B-cell lymphoma. Leukemia 2012;26:1383–1390.
23. Tanaka S, Louie DC, Kant JA, Reed JC. Frequent incidence of somatic mutations in translocated BCL2 oncogenes of non-Hodgkin's lymphomas. Blood 1992;79:229–237.
24. Ozoran E, Trabulus FDC, Erhan D, Batar B, Guven M. Association of XRCC3, XRCC4, BAX, and BCL-2 Polymorphisms with the Risk of Breast Cancer. Int J Breast Cancer 2022;2022. doi:10.1155/2022/5817841.
25. bhushann Meka P, Jarjapu S, Vishwakarma SK, et al. Influence of BCL2-938 C>A promoter polymorphism and BCL2 gene expression on the progression of breast cancer. Tumor Biol 2016;37:6905–6912.
26. Ahmed HS, Wahab EA, Elhady HA, Elgerby MM. Association of genetic polymorphism of BCL-2 (rs2279115) with susceptibility to HCV-related hepatocellular carcinoma. Immunol Res 2020;68:189–197.
27. Hammo AA, Ahmad AA, Althanoon ZA. Role of Gender in the Protection Against Doxorubicin-Induced Oxidative Stress. Pharmacogn J 2022;14:782–788.
28. Ali AA, Khalaf MM, Ahmad AA. The potential cardioprotective effect of Ganoderma lucidum against 5-fluorouracil cardiotoxicity. Rev Clin Pharmacol Pharmacokinet Int Ed 2024;38:211–219.