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Research Article

A Computational Analysis of Four *RETN* SNPs in Iraqi Women with Breast cancer: A Cross-Sectional Study

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Abstract:

Background: Breast cancer is a leading malignancy in women, shaped by genetic and environmental factors. Resistin, a potential chemotherapy target, may contribute to chemoresistance when mutated. This study applies computational methods to analyze how single-nucleotide polymorphisms alter resistin's structure and function, potentially reducing its chemotherapy sensitivity.

Methods: A total of 105 fresh blood samples were collected from patients recruited from the Oncology Teaching Hospital, Medical City, Baghdad, Iraq. between March-2020 and September-2023. Samples were classified into 3 groups of 35 samples each: control, benign and patients. DNA extraction, PCR, Sanger sequencing and computational approaches were used to analyze four resistins' polymorphisms, namely rs1862513, rs3219175, rs34788323, and rs3745367. Functional impacts were predicted using HaploReg (regulatory effects), Regulome DB (regulatory annotations), PolyPhen-2 (pathogenicity), ProtParam (protein stability), and SWISS-MODEL (3d structural modelling). Data entry, descriptive statistics, and statistical analyses were performed using IBM SPSS Statistics version 20. The chi-squared test was applied, and a p-value <0.05 was considered statistically significant.

Results: Four Single-nucleotide polymorphisms in resistin showed notable associations with breast cancer. rs1862513: GG genotype was more frequent in malignant (40%) and benign (26%) cases versus controls (0%), indicating a strong link to disease presence. rs3219175: AA genotype showed a significant difference, while GA was non-significant. rs3745367 (phenylalanine-41-proline) (AA): identified as a risk factor (OR = 1.44) with a PolyPhen-2 score of 0.999, suggesting structural alterations in resistin. rs34788323 (arginine-65-lysine) (TT): acted as a protective factor (OR = 2.07) and was predicted benign (score = 0.015; sensitivity = 0.96; specificity = 0.79). Additionally, rs1862513 and rs3219175 may affect transcription factor binding sites.

Conclusion: *In silico* analysis predicts that specific resistins' polymorphisms may impair protein function and alter its structure and reduce chemotherapy sensitivity in Iraqi breast cancer patients. These variants could serve as biomarkers for personalized therapy but need experimental validation.

Keyword: Breast cancer; Haploreg; Protparam; Polyphen-2; Resistin.

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Introduction

Breast cancer (BC) is the most diagnosed tumor in women, and the second leading cause of mortality after lung cancer. Risk factors include: age, gynecological and reproductive characteristics, smoking and physical activities and a positive family history (1,2). Resistin is a cysteine-rich adipokine encoded by the resistin gene (HGNC Approved Gene Symbol: *RETN*; OMIM ID (605565); cytogenetic location: 19p13.2; Genomic coordinates (GRCh38) is secreted by adipose tissue and by macrophages. Several studies have reported its upregulation in BC and Polycystic Ovary Syndrome (PCOS). The length of the resistin peptide in human is 108 amino acid residues with molecular weight ~12.5 kDa (3,4). Recent studies have located several single nucleotide polymorphisms (SNPs) located at the promoter and 3'-untranslated regions of this gene. These SNPs are related to several disorders including BC. A previous study in Mexico concluded that the (rs1862513) SNP in *RETN* gene may increase BC risk (5). The promoter SNPs: rs1862513 (-420C→G; promoter region of *RETN*) and the other one rs3745367 (+ 299G→A) were studied and analyzed for their involvement in the progression of some diseases including BC and some other multifactorial disorders. The rs3219175 (G→A) represents another promoter variant with potential effects on transcriptional activity and rs34788323 (C→T), is a missense SNP leading to a coding change (6,7). Resistin plays multifunctional roles in the body, including potential involvement in therapeutic response to chemotherapy. Emerging evidence suggests that resistin may contribute to resistance against certain anticancer agents and immunomodulatory drugs. In particular, elevated resistin levels have been associated with reduced sensitivity to chemotherapy

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in breast cancer, including reduced sensitivity to doxorubicin. These findings indicate that resistin could be a key mediator of treatment resistance in cancer (8). The present study aimed to demonstrate the role of a computational methodology to analyze the structural and functional effect of SNPs on resistin protein and how can these SNPs alter the structure and function of resistin protein which make it less sensitive to chemotherapy.

Material and Methods

Study Design and Setting: A cross-sectional study was conducted between March-2020 and September-2023 at Oncology Teaching Hospital, Medical City, Baghdad, Iraq. Breast cancer was diagnosed by the oncologist in the hospital based on mammography, cytologic and serologic tests. The study recruited 3 groups of adult women: breast cancer group, group with fibroadenoma as a benign breast tumor, and healthy controls, 35 women were included for each group. Breast cancer group included any type of breast cancer, diagnosed by the oncologist irrespective of age, cancer subtype, clinical stage, or histologic grade.
Pregnant patients and those with coexisting chronic illnesses were excluded from the study. Following study ethical approval and patients' consents, a 3-5 mL peripheral blood sample was aspirated from each woman for DNA extraction (FavorPrep™ Blood / Cultured Cell Genomic DNA Extraction Mini Kit/ Favorgen/ Canada) and genetic analysis by sequencing.
Specifically designed primers for rs3745367 and rs34788323:
F: 5'-ATCAATGAGAGGATCCAGGAG-3', R: 5'AAGATCCTAGGGGAGTAGAGG-3'.
Specifically designed primers for rs1862513 and rs3219175:
F: 5'- TTTGTCATGTTTGCATCAGC-3', R: 5'-ATGGAGGGAGTAGGATCTGC-3'.
PCR: The PCR amplicon was checked by agarose gel electrophoresis (1.5%) with EtBr in tris borate EDTA buffer.
Sanger sequencing: All samples were analyzed by Sanger sequencing (Macrogen, Seoul, South Korea) and the data were analyzed by Geneious R11.0 and Molecular Evolutionary Genetics Analysis Version 11 (Mega 11) including sequence alignment and Sanger analysis.
***In Silico* Analysis:** To estimate the functional effects of SNPs:(rs1862513, rs3219175, rs34788323, rs3745367), a number of distinct bioinformatics methods were used. PolyPhen-2 (9), Haploreg (10), FuncPred program (SNPinfo) (11), Regulome DB (12), ExPasy (13), and SWISS-MODEL (14) which were among the algorithmic tools used.
Statistical Analysis: Data entries, descriptive, and statistical analysis were performed by the IBM-SPSS ver. 20. Chi-squared test was used. A p-value less than 0.05 was considered statistically significant.
Ethical Approval: Ethical approval was obtained from the ethical committee in University of Baghdad (Ref: 8021; 3-March-2021). Verbal consent was obtained from each participant before sample collection.

Result:

This genetic association study conducted on an Iraqi population identified several significant polymorphisms linked to breast cancer (BC) susceptibility. The analysis of the rs1862513 genotype in (Table 1) revealed a pronounced elevation in the frequency of the GG variant within both malignant (40%) and benign (26%) groups, in contrast to its complete absence (0%) in the control cohort, suggesting a potential association with disease development.

Table (1): Genotype of *RETN* gene for SNP (rs1862513) in three groups

Genotype *retn*	Control (35)	Benign (35)	Malignant (35)	χ2	OR	CI
CC	26(74%)	16(46%)	9(26%)	13.84 **	Reference	--
CG	9(26%)	10(28%)	12(34%)	1.772 NS	0.337	0.08-0.79
GG	0(0%)	9(26%)	14(40%)	12.75 **	1.78	1.02-3.67
Allele						
C	0.87	0.60	0.43	--	--	--
G	0.13	0.40	0.57	--	--	--

** (P<0.01).
* significant /** highly significant

For the rs3219175 locus, a significant disparity was observed in the distribution of the AA genotype in (Table 2). It was present at a considerably higher frequency in the malignant (40%) and benign (22.8%) groups compared to the control group (2.8%). While this indicates a strong association, the specific role (risk or protective) of this genotype remains to be definitively elucidated. The heterozygous GA genotype demonstrated no significant association.

Table (2): Genotype of the *RETN* gene for SNP (rs3219175) in three groups

Genotype *retn*	Control (35)	Benign (35)	Malignant (35)	χ2	OR	CI
GG	25(71.4%)	14(40%)	5(14.2%)	11.45 **	--	--
GA	9(25.7%)	13(37.1%)	16(45.7%)	3.77 NS	1.83	1.02-4.2
AA	1(2.8%)	8(22.8%)	14(40%)	4.71 *	0.523	0.22-0.71
Allele						
G	0.84	0.59	0.37	--	--	--
A	0.16	0.41	0.63	--	--	--

** (P<0.01).
* significant /** highly significant

The rs3745367 was identified as a risk factor for breast cancer as shown in (Table 3). The AA genotype was associated with an elevated risk, confirmed by an odds ratio (OR) of 1.44.

Table (3): Genotype of *RETN* gene for SNP (rs3745367) in three groups

Genotype *retn*	Control (35)	Benign (35)	Malignant (35)	χ^2	OR	CI
GG	24 (68.57%)	7 (20.00%)	7 (20.00%)	11.57 **	Reference	--
GA	9 (25.71%)	19 (54.29%)	18 (51.43%)	8.63 **	1.37	0.72-2.36
AA	2 (5.71%)	9 (25.71%)	10 (28.57%)	8.92 **	1.44	0.89-1.92
Allele						
G	0.81	0.47	0.46	--	--	--
A	0.19	0.53	0.54	--	--	--
			** (*P*<0.01).			

* significant /** highly significant

Conversely, the rs34788323 demonstrated a protective effect in (Table 4). The TT genotype was significantly more prevalent in the control (48.57%) and benign (25.71%) groups than in the malignant group (2.86%). This protective role was further supported by an odds ratio (OR) of 2.07.

Table (4): Genotype of the *RETN* gene for SNP (rs34788323) in three groups

Genotype *retn*	Control (35)	Benign (35)	Malignant (35)	χ^2	OR	CI
CC	5 (14.29%)	16 (45.71%)	21 (60.00%)	12.57 **	Reference	--
CT	13 (37.14%)	10 (28.57%)	13 (37.14%)	0.092 NS	0.552	0.26-1.31
TT	17 (48.57%)	9 (25.71%)	1 (2.86%)	12.30 **	2.07	1.25-4.07
Allele						
C	0.66	0.60	0.79	--	--	--
T	0.34	0.40	0.21	--	--	--
			** (P<0.01)			

* significant /** highly significant

***In silico* analysis:** *In silico* analysis of *RETN* in Homo sapiens was used to predict the probable functional effect of SNPs located in the promoter region. PolyPhen-2 (Polymorphism Phenotyping v2) (http://genetics.bwh.harvard.edu/pph2): The PolyPhen-2 score of the SNP arginine-65-lysine (rs34788323) of the *RETN gene* was 0.015; therefore, this SNP is predicted to be benign, with a score of about 0.015 (sensitivity: 0.96; specificity: 0.79). The PolyPhen-2 score of the SNP phenylalanine-41-proline (rs3745367) of the *RETN* gene was 0.999. Therefore, this SNP is predicted to be harmful, as shown in Figure 1, with a score of 0.999 (sensitivity: 0.14; specificity: 0.99).

Figure 1: Prediction of the possible impact of the SNP (rs3745367) phenylalanine-41-proline of RETN gene on the structure and function of resistin using PolyPhen-2. The red color suggests possible structural and functional disruption of the resistin protein.

(a)HaploReg v4.1 software represented the polymorphism frequencies in African 0.43, American 0.23, Asian 0.34 and European population 0.28, dbSNP functional annotation, motifs altered, promoter histone marks and enhancer histone marks. These altered motifs directly affect transcription factor binding sites, leading to the upregulation of the resistin gene. HaploReg v4.1 software predicted an alteration on 4 regulatory motifs; B. double prime 1. Subunit of RNA polymerase III transcription initiation factor IIIB (BDP1), DNA-binding nuclear protein (transcription factor) (PU.1), Rad 21 and transcription factor II (TFII) caused by polymorphism (rs1862513) in *RETN* gene (Table 5).

Table (5): Results from SNP (rs1862513) in *RETN* gene. HaploReg v4.1 software predicted an alteration on 4 regulatory motifs; B double prime 1. Subunit of RNA polymerase III transcription initiation factor IIIB (BDP1), DNA-binding nuclear protein (transcription factor) (PU.1), Rad 21 and Transcription Factor II (TFII); potentially influencing transcriptional regulation of resistin.

				Regulatory Motifs Altered
Position Weight Matrix ID (Library from Kheradpour and Kellis, 2013)	Strand	Ref	Alt	Match on: Ref: ACCTCCTGACCATGCTCTGACCATGAAGAGAGGCCTCTGTGAGATGGGAAGGTCC Alt: ACCTCCTGACCATGCTCTGACCATGAAGAGAGGCCTCTGTGAGATGGGAAGGTCC
BDP1_disc1	+	0.6	-0.1	CMNGGMGRGRTKCCTGGAGGAGG
PU.1_disc3	+	10.7	11.2	RGVVVNDGSVDSDS
Rad21_disc6	+	1.8	13	SNSHNSNNSNKSSHRSB
TFII-I	+	13	14.6	DGRBKKAGG

This software predicted a possible alteration on 2 regulatory motifs; erythroblast transformation specific) family, which is one of the largest families of transcription factors (Ets), resulted from polymorphism (rs3219175) in the *RETN* gene (Table 6).

Table (6): Results from SNP (rs3219175) in *RETN* gene. HaploReg v4.1 software predicted an alteration on 2 regulatory motifs; (Erythroblast transformation specific) family which is one of the largest families of transcription factors (Ets); potentially influencing transcriptional regulation of resistin.

				Regulatory Motifs Altered
Position Weight Matrix ID (Library from Kheradpour and Kellis, 2013)	Strand	Ref	Alt	Ref: CCTCTCCCTCAGGCCTTTACTGTTGGTGAGGGCTTCTCTTGGCCCGAATGTGGACCG Alt: CCTCTCCCTCAGGCCTTTACTGTTGGTGAGGGCTTCTCTTGGCCCGAATGTGGACCG
Ets_known1	-	12	12	BBMVBYAYWTCCTSB
Ets_known9	-	14	4.1	WVDBRYTTCCTSYH

The software predicted a possible alteration on 2 regulatory motifs: max interactor 1 protein (Mxi1) and regulatory element of sterol binding proteins (SREBPs), which are the membrane-bound TFs and activate some genes, caused by polymorphism (rs34788323) in the *RETN* gene (Table 7).

Table (7): Results from SNP (rs34788323) in the *RETN* gene. HaploReg v4.1 software predicted an alteration on 2 regulatory motifs: Max interactor 1 protein (Mxi1) and regulatory element of Sterol binding proteins (SREBPs) which are the membrane bound TFs and activate some genes, potentially influencing transcriptional regulation of resistin.

				Regulatory Motifs Altered
Position Weight Matrix ID (Library from Kheradpour and Kellis, 2013)	Strand	Ref	Alt	Ref: GTGAGTGGCAGGAGACTGTTGTTCGCAGGGCGCCATTTCTGTTCCTCAAGTCCCCTGGGAATGC Alt: GTGAGTGGCAGGAGACTGTTGTTCGCAGGGCGCCATTTCTGTTCCTCAAGTCCCCTGGGAATGC
Mxi1_disc1	-	10.1	5.6	GTTGCYAKGGMRACVR
SREBP_disc1	+	11.1	7.4	GTTGCYAKGGCRACS

HaploReg software predicted an alteration on 2 regulatory motifs (erythroblast transformation specific) family, which is one of the largest families of transcription factors (Ets) and SIN3 transcription regulator family member A (SIN3AK-20), resulting from polymorphism (rs3745367) in the *RETN* gene (Table 8).

Table (8): Results from SNP (rs3745367) in *RETN* gene. HaploReg v4.1 software predicted an alteration on 2 regulatory motifs; Erythroblast transformation specific) family which is one of the largest families of transcription factors (Ets) and SIN3 transcription regulator family member A (SIN3AK-20); potentially modulating resistin gene regulation.

Query SNP: rs3745367											
Chr pos	Variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	Promoter histon marks	Motifs Changed	GENCODE genes	dsSNP func annot
19 7669625	rs3745367	G	A	0.75	0.25	0.34	0.24	ESC IPSC BLD	Ets.Sin3AK-20	RETN	Intronic

(b) FuncPred program (https://snpinfo.niehs.nih.gov/): The funcPred program predicted the allele frequency for *RETN* gene polymorphisms in different populations, none of the SNPs affects the miRNA binding site. The highest allele frequency was recorded in Europeans and Hispanics for rs3219175.

(c) Regulome DB program: Shows the effect of physicochemical properties on Resistin (15, 16). The gene is consisting of exons: 4, coding exons: 3, transcript length: 516 bps, translation length (number of amino acids): 108 residues. molecular weight: 11419.34 KDa, the value of pI evaluated by the Protparam program showed the pI of RETN was (Theoretical pI: 6.52), indicating that RETN is acidic in nature (pH<7). Isoelectric point (pI) is the pH value when the protein carries no net charge and is said to be neutral (17, 18). The total number of residues with negative charge (Asp + Glu) are nine. Total number of residues with positive charge (Arg + Lys) are also nine.

Instability index: is computed to be 37.53 which classify the protein as "Stable". Depending on amino acids sequence, the stability of the protein in vivo can be predicted by using the instability index. When the instability index of protein <40, this protein is considered stable.

Aliphatic index: 89.44. Grand average of hydropathicity (GRAVY): 0.381 (Hydrophobic). (GRAVY) was used to calculate the hydrophilic and hydrophobic property of a peptide depending on hydropathy of amino acids divided by sequence length. If the GRAVITY value was positive, the protein is hydrophobic while negative GRAVITY means hydrophilic protein. All these physicochemical values could be calculated on ExPASy website. (http://www.expasy.org (http://www.expasy.org/).

SWISS-MODEL (https://swissmodel.expasy.org/): This server was used to study the three-dimensional (3D) resistin structure for mutant sample protein [(arginine-65-lysine; rs34788323), (phenylalanine-41-proline; rs3745367)] and comparative protein structure study (19,20). The variation between protein structures was present within samples as shown in Figures (2, and 3).

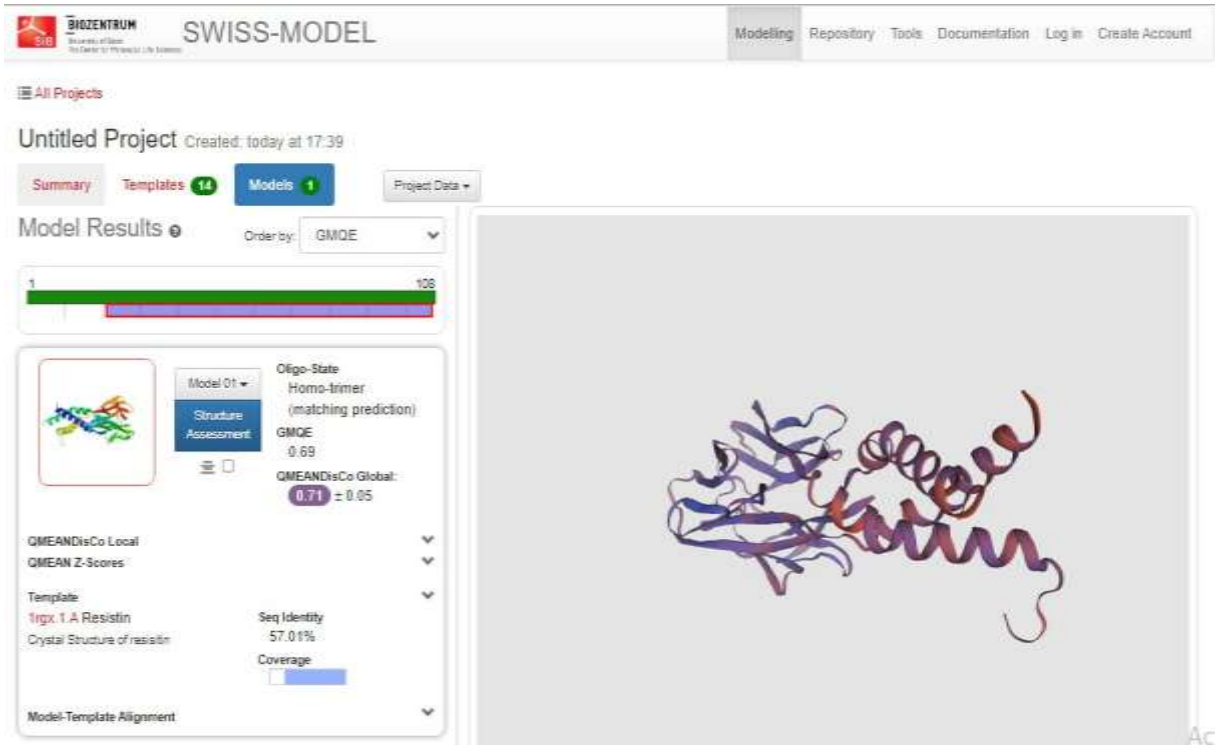

Figure 2: Three-dimensional (3D) resistin structure as a reference protein by SWISS-MODEL. This server was used to study the 3D structure of resistin protein which is an automated modeling for comparative protein structure study. Resistin length: 108 amino acid residues, molecular weight ~12.5 kDa.

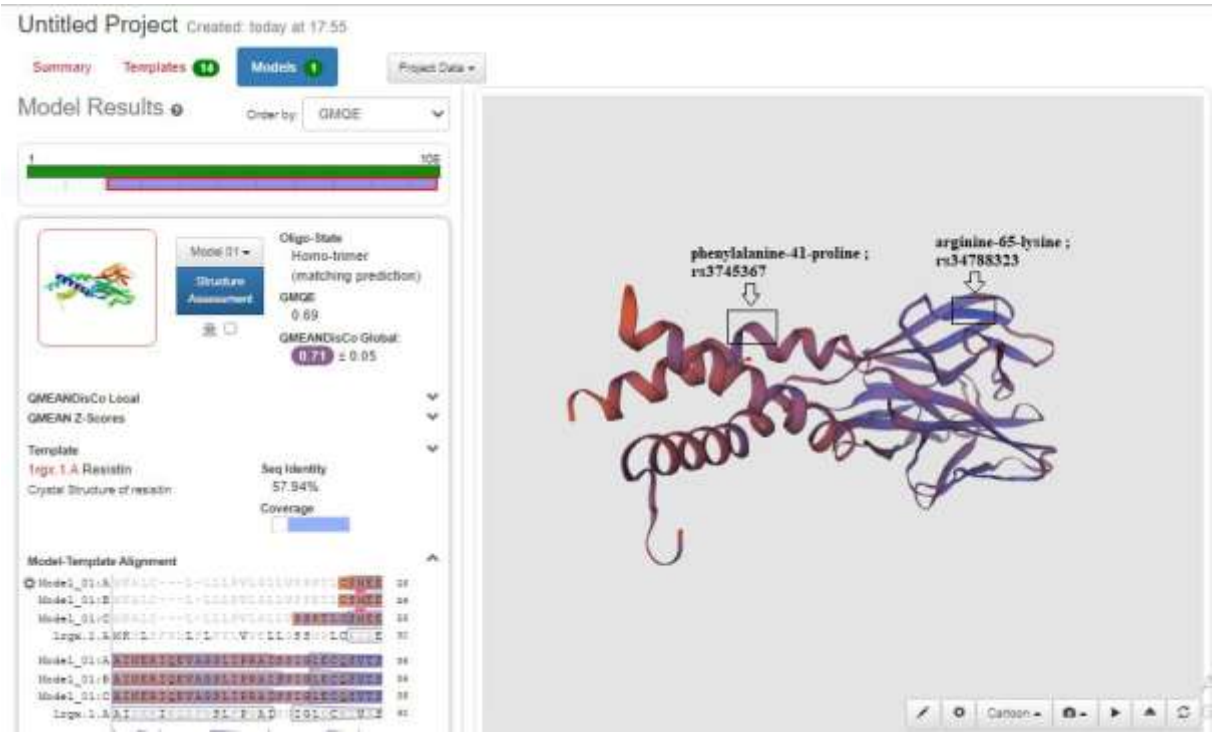

Figure 3: Three-dimensional (3D) resistin structure for the mutant sample protein by SWISS-MODEL [(arginine-65-lysine; rs34788323), (phenylalanine-41-proline; rs3745367)]. This server was used to study the 3d structure of resistin protein, which is an automated modelling for comparative protein structure study. Model-template alignment was used to compare models.

Discussion

Allelic discrimination analysis of the *RETN* promoter polymorphism (rs1862513) revealed a significant association with breast cancer susceptibility (Table 1). The GG genotype may be identified as a potential genetic risk factor. These findings highlight the potential role of *RETN* gene polymorphisms as genetic determinants of breast cancer susceptibility among Iraqi women (23). In contrast, the CC genotype showed a protective role. It was therefore concluded that carriers of the GG genotype have a higher likelihood of developing breast cancer. The genotype variation of (rs3219175) of *RETN* gene may be considered as a risk factor for a sample of Iraqi women suffering from BC. It could be concluded that women carrying the A allele were more likely to develop BC (Table 2). The genotype variation of (rs3745367) of *RETN* gene; AA genotype may be considered as a risk factor for BC Iraqi women (Table 3). According to (rs34788323) of *RETN* gene, TT genotype may be considered as a protective factor for BC Iraqi women (Table 4). This observation aligns with the hypothesis that variations in the *RETN* gene could influence disease susceptibility through modulation of inflammatory or metabolic pathways (24).

The PolyPhen-2 score of the SNP arginine-65-lysine (rs34788323) scores probably damaging (0.999); replacing a bulky hydrophobic phenylalanine with proline could disrupt local secondary structure, folding, or receptor-interaction surfaces, consistent with the tool's very high specificity (0.99) but lower sensitivity (0.14).

These findings support previous reports linking *RETN* polymorphisms to disease progression. Notably, rs3745367 appears to significantly impact transcription factor binding, potentially altering gene regulation in breast cancer cells. Two SNPs (rs34788323 and rs3745367) are located in the intron of the *RETN* gene. Intronic variants can impact alternative splicing by interfering with splice site recognition (21). These SNPs have an impact on the neighboring exon and change two amino acids at two different locations.

SWISS-MODEL can predict the polymorphisms effects as the polymorphisms may not affects the site directly, but could change at the far site, and its effect doesn't change the form of structure (coil, turn, beta strand and alpha helix). Both structures have the same properties, including sequence identity: (57%), oligostate: homo-trimer, GMQE Score: (0.69). GMQE (global model quality estimation) which is a value ranged between 0 to 1, and a higher value means higher reliability (22, 23). The final conclusion of *in silico* analysis indicates that promoter SNPs (rs1862513 and rs3219175) directly change the *RETN* gene expression as well as risk of BC. The intron SNPs (rs34788323 and rs3745367) did not have a direct effect on resistin structure and their effect is limited to alternative splicing (25,26).

According to current results of *in silico* analysis, these SNPs may have an effect on the binding site of some transcription factors (TFs) as follow: HaploReg v4.1 software prediction; an alteration on 4 regulatory motifs; B. double prime 1, subunit of RNA

polymerase III- transcription initiation factor IIIB (BDP1), DNA-binding nuclear protein (transcription factor) (PU.1), Rad 21 and transcription factor II (TFII) due to polymorphism (rs1862513) in *RETN* gene.

An alteration in 2 regulatory motifs; erythroblast transformation specific family, which is one of the largest families of transcription factors (Ets), resulting from the polymorphism (rs3219175) in *RETN* gene.

An alteration in 2 regulatory motifs; max interactor 1 protein (Mxi1) and sterol-regulatory-element-binding-proteins (SREBPs), which are a group of membrane-bound transcription factors that activate some genes resulting from the polymorphism (rs34788323) in *RETN* gene.

An alteration on 2 regulatory motifs: erythroblast transformation specific family, which is one of the largest families of transcription factors (Ets) and SIN3 transcription regulator family member A (SIN3AK-20), resulting from the polymorphism (rs3745367) in the *RETN* gene. In contrast, none of the SNPs affects the miRNA binding site (24,25).

Limitations

1. small sample size and limited geographic/ethnic variations.
2. Data Interpretation; Limited local reference genomes may affect polymorphisms significance.

Conclusion

According to current results of *in silico* analysis, SNPs (rs1862513, rs3219175) may have an effect on the binding site of some transcription factors. SNP (rs34788323) arginine-65-lysine was predicted to be benign, while the SNP (rs3745367) phenylalanine-41-proline was predicted to induce subtle alterations in the structure of the resistin protein, potentially influencing the efficacy of targeted therapeutic responses in breast cancer patients

Authors' declaration

We confirm that all the Figures and Tables in the manuscript belong to the current study. Besides, the Figures and images, which do not belong to the current study, have been given permission for re-publication attached to the manuscript. Authors sign on ethical consideration's Approval-Ethical Clearance: The project was approved by the local ethical committee in (Place where the research was conducted or samples collected and treated) according to the code number (18295) on (01.06.2021).

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Data acquisition

Available upon reasonable request from the corresponding author.

Authors' contributions

Study conception & design: (*Khadija A. Sahan & Zahraa A. Sahan*). Literature search: (*Khadija A. Sahan & Zahraa A. Sahan*). Data acquisition: (*Khadija A. Sahan & Zahraa A. Sahan*). Data analysis & interpretation: (*Thualfiqar Gh. Turki & Zahraa A. Sahan*). Manuscript preparation: (author(s) name). Manuscript editing & review: (*Thualfiqar Gh. Turki*).

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تحليل حاسوبي لأربعة طفرات جينية (SNPs) في جين RESISTIN لدى نساء عراقيات مصابات بسرطان الثدي: دراسة مقطعية

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الملخص:

خلفية البحث: يعد سرطان الثدي من أكثر الأورام الخبيثة شيوعا بين النساء، ويتأثر بعوامل وراثية وبيئية. تعتبر بروتين الريستين (Resistin)هدفا محتملا للعلاج الكيميائي، وقد تسهم الطفرات فيه في مقاومة العلاج. تهدف هذه الدراسة إلى توظيف المنهجيات الحاسوبية لتحليل التأثيرات البنيوية والوظيفية للطفرات الجينية أحادية النوكليوتيد (SNPs) في بروتين الريستين، وبيان كيف يمكن أن تحدث هذه الطفرات تغيرات في بنية البروتين ووظيفته، مما يجعله أقل استجابة للعلاج الكيميائي.

طرق العمل :تم جمع 105 عينة دم حديثة من مريضات من مستشفى الأورام التعليمي، مدينة الطب، بغداد – العراق، وذلك خلال الفترة من مارس 2020 إلى سبتمبر 2023. تم تقسيم العينات إلى ثلاث مجموعات (35 عينة لكل مجموعة): مجموعة الضبط (الأصحاء)، مجموعة الأورام الحميدة، ومجموعة المرضى المصابين بسرطان الثدي. تم إجراء استخلاص الحمض النووي(DNA) ، تفاعل البلمرة المتسلسل(PCR) ، التسلسل باستخدام تقنية سانجر، ومن ثم تحليل الطفرات الأربعة (rs1862513 ، rs3219175، rs34788323، rs3745367) باستخدام أدوات حاسوبية :HaploReg .لتحليل التأثيرات التنظيمية RegulomeDB للتعليقات التنظيمية و :PolyPhen-2 لتقييم التأثير المرضي للطفرات و ProtParam لتحليل استقرار البروتين و SWISS-MODELلنمذجة البنية ثلاثية الأبعاد للبروتين. تم إدخال البيانات وتحليلها إحصائيا باستخدام برنامج SPSS الإصدار 20، وتم استخدام اختبار مربع كاي ، مع اعتبار أن قيمة ($P<0.05$) دالة إحصائيا.

النتائج:أظهرت الطفرات الأربعة المدروسة في جين الريستين ارتباطا واضحا بسرطان الثدي: كان النمط الجيني rs1862513 GG أكثر شيوعا في حالات الأورام الخبيثة (40%) والحميدة (26%) مقارنة بمجموعة الضبط (0%)، مما يشير إلى ارتباط قوي بالمرض. النمط الجيني rs3219175 AAأظهر فرقا معنويا، في حين لم يكن النمط rs3745367 GA ذا دلالة إحصائية. تحويل الحمض الأميني فينيل ألانين إلى برولين في الموقع 41 :(AA – اعتبر عامل خطر) نسبة الأرجحية(OR = 1.44 ، مع نتيجة PolyPhen-2بلغت 0.999، مما يشير إلى تغيرات هيكلية كبيرة في البروتين.
rs34788323 تحويل الحمض الأميني أرجينين إلى لايسين في الموقع 65 :(TT – عمل كعامل وقائي(OR = 2.07) ، وتوقعت أداة PolyPhen-2أنه طفرة حميدة (الدرجة = 0.015؛ الحساسية = 0.96؛ النوعية = 0.79).
كما أظهرت النتائج أن الطفرتين rs1862513 و rs3219175 قد تؤثران على مواقع ارتباط عوامل النسخ.

الاستنتاج: تتنبأ التحليلات الحاسوبية بأن بعض الطفرات في جين الريستين قد تؤثر سلبا على وظيفة البروتين وتقلل من حساسيته للعلاج الكيميائي لدى مريضات سرطان الثدي العراقيات. كما كشفت نماذج البنية ثلاثية الأبعاد عن تغييرات في الشكل البنيوي للبروتين الطافر مقارنة بالبروتين الطبيعي، مما يشير إلى آليات محتملة لمقاومة العلاج. تبرز هذه النتائج أهمية هذه الطفرات كواسمات جينية محتملة للعلاج الشخصي، إلا أنها تتطلب المزيد من الدراسات التجريبية لتأكيدها.

مفتاح الكلمات: رسستين؛ سرطان الثدي؛ haploreg؛ بروتوباترم؛ بوليفن-2.