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RESEARCH ARTICLE

Distribution of Her2 Single Nucleotide Polymorphism in Different Geographical location in Sulaimani Province, Iraq

Israa Saadaldin Shmasaldin, Muhammed Babakir-Mina, Taib Ahmed Hama Soor

Medical Laboratory Department, College of Health and Medical Technology, Sulaimani Polytechnic University, Sulaimani, Iraq

Corresponding author: Israa Saadaldin Shmasaldin
Email: israa.saadaldin@gmail.com

ABSTRACT Her2 single nucleotide polymorphism is known to be associated with the risk of breast cancer in women. The distribution of mutations in the Her2 gene differs from one geographic location to another. This study aimed to find two risky genotypes of Her2, Ile/Val Val/Val, in different geographical regions of Sulaimani province. For this purpose, 272 blood samples were collected from healthy women and women who have breast cancer for genetic analysis. The detecting alleles were performed by PCR amplification of the her2 gene and then digestion of the DNA by enzyme *BsmA*I to find different fragments of DNA representing different genotypes of Ile/Val, Val/Val. Among 272 cases, it was found that the highest rate of single nucleotide polymorphism was in Sulaimani City, 38.9% and the lowest rate of mutation of Her2gene was found in Raparin, 1.8%. The distribution of Ile/Val and Val/Val in other regions was as follows: Garmyan, 6.6% and Halabja, 2.2%. At the same time, the correlation between chronic diseases with breast cancer and with her2 single nucleotide polymorphism was studied. It was found that there were no significant relationships between chronic diseases and Her2 mutation. It concluded that risky genotypes, Ile/Val Val/Val, exist in Sulaimani province, and the highest rate was detected in Sulaimani city.

Keywords: Her2, Single Nucleotide Polymorphism, Geographical Distribution, Breast Cancer.

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INTRODUCTION

Breast cancer is known as the most prevalent cancer type among women. The occurrence of breast cancer is continuously rocketing in some countries, which creates a public health problem (Zahmatkesh et al., 2016; Momenimovahed, Salehiniya, 2019). Breast cancer is the highest cause of death globally among women (Bray et al. 2018). The data released in 2000 showed that breast cancer was the most common malignancy among women, with a rate of 35.7 per 100,000 (Maxwell 2001). Genetic mutation in the genes is one of the risk factors for breast cancer. Her2 gene diversity is known to have a role in developing breast cancer, and this is well-studied in many countries. It has been shown in several articles in China, Australia, and Taiwan that there is an association between HER2Ile655Val single nucleotide polymorphism and the risk of breast cancer in women (Siegel 2020, Xie et al. 2000; Montgomery et al. 2003). HER2 (Human epidermal growth factor receptor 2) is an integrated plasma-membrane glycoprotein receptor with 185 KDa and its gene located on the 17q21 chromosome in humans. HER2 has an intrinsic tyrosine kinase activity which belongs to the growth factor family, epidermal growth factor receptor (ErbB); the ErbB family of proteins contains four receptor tyrosine kinases (Lee et al. 2008, Friedländer 2008). A single nucleotide polymorphism (SNP) was identified for the first time by Papewalis and his colleagues at the codon number 655 of the gene HER2. This mutation is a missense mutation that changes

isoleucine (ATC) to valine (GTC) (Yarden 2011). This mutation and polymorphism create three genotypes: Ile/Ile, Ile/Val, and Val/Val. The first genotype, Ile/Ile, is a wild type and found in healthy women, but the other two genotypes that contain Val, Ile/Val, and Val/Val, are associated with developing breast cancer in women who carry the mutation. There are different records regarding the rate and incidence of breast cancer linked to HER2 single nucleoid polymorphism in different geographical regions and among different ethnicities (Papewalis 1991, Hishida 2009, Lee et al. 2008). However, the role of SNP in the susceptibility to breast cancer has not yet been identified in the Kurdish population of Iraq. In Asia, Europe and the Middle east, the distribution of HER2 SNP is well-studied, and it's also been found that there is a link between polymorphism and breast cancer. Therefore, it's important to know its role in developing breast cancer in every nation and geographical area among women. In addition, there are some studies in countries near Iraq, such as Iran and Turkey, but there is no study on the Kurdish population in the Kurdistan region of Iraq. Therefore, the aim of this research was to find the distribution of Her2 single nucleotide polymorphism ($HER2^{Ile655Val}$ gene) in different geographical locations in Sulaimani province in both breast cancer patients and healthy women.

METHOD

Sampling

A total of 272 women participated in this study, including women who have breast cancer and healthy women. The study was carried out between September 2021 and November 2022 At Hiwa Hospital's Medical Oncology Unit. The number of samples was as follows: breast cancer patients, 151 cases, and control healthy cases, 121. Healthy women are those women who have never before been diagnosed with cancer. Participants were chosen randomly, and it included people who come from different geographical areas. A questionnaire was given to all women who agreed to participate in the study, asking them to answer questions about a wide range of known risk factors for breast cancer development, including their hormone profile, family history of the disease, number of cigarettes smoked per day, number of pack-years, and lifetime alcohol consumption. The participants were asked to think about their lifestyles over a long period of time, not just the period leading up to their enrolment. In order to distinguish between familial and non-familial forms of Breast Cancer, the questionnaire gathered all of the necessary data. After participants signed the consent form, an enveloped questionnaire was distributed to them. For participating adolescents under 18 years, parents were requested to sign the consent form and to fill in the questionnaire. The questionnaire and consent forms were written in the English language. The questionnaire consisted of five main sections. The first section consists of demographic and socioeconomic data, which includes gender, age, nationality, profession, education level, and Occupation. The second section consisted of the Present Medical History. The third section included the Family History. The fourth section included Daily habits, and the fifth section included Information about the area of the patient. An informed written consent was obtained from each patient included in the study prior to sample collection. The study was approved by the Ethics Committee of the College of Health of Medical Technology /Sulaimani Polytechnic University prior to initiation of the work and was carried out according to the guidelines of the Committee.

Blood collection and DNA extraction

The (2ml) blood was collected from every person in the tube containing coagulant (EDTA tube) from the patient with breast cancer in the Hiwa hospital and from healthy persons. The blood was then kept cold until it arrived at the laboratories for DNA extraction. The patient group included patients with breast cancer

(n=151), and the control group was people that are negative for malignancy; this group included (n=121).

Determination of genotypes:

To find mutation and Her2 polymorphism, we depended on PCR amplification of Her2 and then enzymatic digestion (*BsmA*I) of the DNA to analyze different fragments of DNA after cutting to find three genotypes. The protocols were performed according to Xie et al. (2000).

Primers used in this study, HER2 primers:

Forward:
AGAGCGCCAGCCCTCTGACGTCCA

Reverse
TCCGTTTCCTGCAGCAGTCTCCGC.

In the final steps, the DNA fragments that represent different genotypes were analyzed through DNA agarose gel electrophoresis.

Statistical Analysis

All statistical computation is enhanced using the statistical method Statistical Package for Social Sciences (SPSS 24) (SPSS Inc. IBM, Chicago, USA). The data had been coded, tabulated, and presented in a descriptive form. The statistical procedure that was applied to determine the results of the present study included:

1- Descriptive statistical data analysis (Frequency, Percentage, Mean, Stander deviation)

2-Inferential data analysis: Chi-square & Independent sample T-test

The significance level of all statistical procedures was determined at the parametric test (F test), $P<0.000$. There are criteria of the probability level of determining the significance of the test: P value as:

Ethical approval

All procedures in this study were performed according to the ethical committee of the College of Health and Medical Technology/ Sulaimani Polytechnic University. The participants of this study who donated blood samples were informed about the research and asked to share information for research purposes. Oral consent was obtained about the nature of the study, including the objectives and laboratory procedures that would be performed.

RESULTS

HER2 gene mutations increase breast cancer risk. This gene mutation causes 10–40% of female breast cancer. Considering that breast cancer is a multifactorial disease with genetic and environmental factors involved in its aetiology and that the influence of some factors may differ according to race and geographic localization. In this study, HER2 genotypes in Kurdistan breast cancer cases and controls were determined, thereby focusing on a north of Iraq population. In this study, allele-specific PCR was used to identify the genotype in the HER2 gene quickly and cheaply. This method also identified breast cancer patients' allelic types better than Sanger sequencing. Blood samples from 272 participants (151 cancer cases and 121 healthy control women) were used in the research. The three genotypes were indicated with their rates and distribution according to the geographical location, and the demographic characterization of risky genotype carriers was analyzed.

Distribution of genotypes Ile/Val, Val/Val among Kurdish women in different geographical locations.

Two risky genotypes, Ile/Val Val/Val, are associated with breast cancer and the rate of those two genotypes was analyzed among Kurdish women. In general, the larger number of women who have breast cancer comes from the city of Sulaimani, 80.8%. Among them, 38.8% were carriers of unhealthy genotypes, Ile/Val and Val/Val, which was the highest rate in the current study in comparison to

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other regions of Sulaimani province (Table 1).

After Sulaimani City, the Garmyan region recorded the second-highest rate with 6.6%. The rate of Ile/Val, Val/Val, 6.6%. Was higher than healthy genotypes among women who have breast cancer, 4.4%. Halabja and Raparin recorded the lowest rate in comparison to previous regions. The rate of the Her2 polymorphism of Ile/Val Val/Val genotypes was 2.2% in Halabja and 1.8% in Raparin (Figure 1).

Association of women who carry Her2 single nucleotide polymorphism (the case & the control groups) with Chronic Disease

In Cases with high blood pressure, the frequency of the participants lowered moderately (112) of the participants were not diagnosed with high blood pressure, while the frequency of (39) of the participants were diagnosed with high blood pressure. (1.99%) of the participants had pain in the chest or heart, while most of them did not have pain, which is (98.01%). For noticing any extra heartbeat only, the frequency of (1) participant had this condition while the frequency of (150) participants did not. In cases of having an abnormal electrocardiogram (ECG or EKG), heart attack or coronary (1.99%) of the participants answered YES. On the other hand, (98.01%) of the participants answered NO for the condition. Only (5.30%) of the participants had difficulty breathing, whereas most of the participants who are (94.70%) did not have this condition. Most of the participants did not have high levels of cholesterol or glucose in their blood. To illustrate, only (11.26%) had high cholesterol levels and (16.56%) had high glucose levels. None of the participants had significant childbirth-related problems. The majority of the participants did not have urination problems; only (2.65%) had this condition, (95.36%) were negative. In control, the majority of the participants had an answer (NO) for having conditions such as high blood pressure, pain in the chest or heart, and noticing extra heartbeats, which are (86.78%, 94.87%, and 100.00%), respectively. In case of any abnormal electrocardiogram (ECG or EKG), heart attack or coronary, (96.69% answered (NO), and only a few had this condition which is (3.31%). The frequency of (1) had the condition of having difficulty breathing; on the other hand, the majority, which has a frequency of (120), did not have this condition. Similar to the case group, most of the participants do not have high cholesterol or high glucose levels in their blood, which are (95.04% and 80.99%), respectively. Fortunately, there is zero condition related to urination problems.

Table 1: The distribution of risky genotypes, Ile/Val, and Val/Val among Kurdish ethnicity in different geographical areas.

Address	Genotype	Total N0. (272)	Percentage
Slemani Governorate	Ile/Ile	114	41.9%
Slemani Governoarte	Ile/Val	64	38.9%
Slemani Governoarte	Val/Val	42	
Raparin	Ile/Ile	5	1.8%
Raparin	Ile/Val	3	1.8%
Raparin	Val/Val	2	
Halabja Governorate	Ile/Ile	6	2.2%
Halabja Governorate	Ile/Val	5	2.2%
Halabja Governorate	Val/Val	1	
Garmyan District	Ile/Ile	12	4.4%
Garmyan District	Ile/Val	12	6.6%
Garmyan District	Val/Val	6	

Figure 1: The distribution of risky genotypes, Ile/Val and Val/Val, among Kurdish ethnicity in different geographical areas.

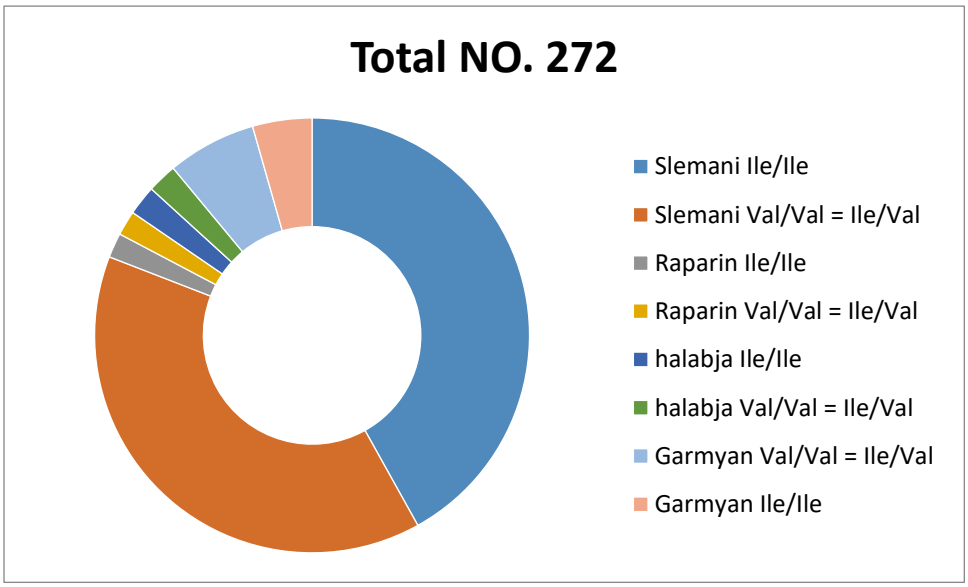

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Table (2): Association between Her2 polymorphism with the Medical History

Variables	Items	Case group (N=151)		Control Group (N=121)		Total (N=272)		Significance test
		Fr.	%	Fr.	%	Fr.	%	
Hypertension High blood pressure	No	112	74.17	105	86.78	217	79.78	χ^2 =6.616 p= 0.01
	Yes	39	25.83	16	13.22	55	20.22	
Heart Disease pain in your chest or heart	No	148	98.01	116	95.87	264	97.06	χ^2 =1.083 p= 0.298
	Yes	3	1.99	5	4.13	8	2.94	
Notice extra heartbeats	No	150	99.34	121	100.00	271	99.63	χ^2 =0.804 p= 0.37
	Yes	1	0.66	0	0.00	1	0.37	
an abnormal electrocardiogram (ECG or EKG), heart attack or coronary	No	148	98.01	117	96.69	265	97.43	χ^2 =0.466 p= 0.495
	Yes	3	1.99	4	3.31	7	2.57	
often have difficulty breathing	No	143	94.70	120	99.17	263	96.69	χ^2 =4.198 p= 0.04
	Yes	8	5.30	1	0.83	9	3.31	
Hyperlipidaemia cholesterol level is high	No	134	88.74	115	95.04	249	91.54	χ^2 =3.444 p= 0.063
	Yes	17	11.26	6	4.96	23	8.46	
Diabetes Glucose level is high	No	126	83.44	98	80.99	224	82.35	χ^2 =0.278 p= 0.598
	Yes	25	16.56	23	19.01	48	17.65	
Total		151	100.00	121	100.00	272	100.0	

DISCUSSION

Globally, breast cancer among women is a serious public health problem. According to the data released by the International Agency for Cancer Research (IARC) (Suelmann, van Dooijeweert 2021), breast cancer is the most common cancer among females, and its occurrence is increasing in the majority of nations, creating a concern to public health (Jian et al. 2020, Ingelman, sim 2010). The causes of breast cancer, a multifactorial disease, including genetics and the influence of certain factors, may vary by race and geographic location; we determined HER2 genotypes in Portuguese breast cancer cases and controls, focusing on a population in southern Europe (Ferlay 2001).

Her2 gene single nucleotide polymorphism is known as one of the genetic factors causing breast cancer. In Asia, Europe and the Middle East, there are several studies on HER2 SNP and its role in developing breast cancer among women. In addition, there are studies conducted in countries that are near to Iraq, such as Iran, Turkey, and the Arab ethnicity of Iraq, but there is no study in the Kurdistan region of Iraq according to the final distribution. Therefore, the main goal of the current study was to find the rate and distribution of polymorphism in different geographical locations in Sulaimani province. Furthermore, the link between HER2^{Ile655Val} gene single nucleotide polymorphism and chronic diseases was investigated to determine whether to have the risk of breast cancer among Kurdish women.

There is variation in rates among those patients who carry Her2 gene polymorphism according to the geographical area in Sulaimani province. In the study, we realized that the incidence of genetic alteration in the city of Sulaymaniyah and its surrounding areas is as follows: Sulaymaniyah city recorded the highest percentage of the carriers, 40 % (the samples either having double allelic mutation or they are carriers). The lowest rate was found in Rania, 1.83 %. The rate of polymorphism among breast cancer cases in the other regions of Sulaymaniyah was: Halabja, 2.20%, and Garmian, 2.28%. The rate of spreading diseases and infection theoretically in any environment is a reflection of a number of facts related to the environment of that location as well as natural and human factors such as social behaviour, standard of living, cultural level, level of urbanization, as well as housing pattern and level of nutrition. In addition, previous research on the subjects suggested that there are three geographical factors that have an effect on human health. These factors are as follows: (place, climate, and work) (Montgomery et al. 2003).

The investigation of illness causes is one of the most difficult aspects of medical science and medical geography, particularly the aspects of disease origins that are associated with malignant or transitional disorders. It is normal for the infection to vary according to seasonal and seasonal differences. It is possible that the human body is affected by the

climate or by other environmental conditions before it receives the disease, preparing it to be infected with it. This can happen before the human body actually gets the disease (Montgomery et al. 2003).

The role of HER2 polymorphism in increasing the risk of breast cancer among women may depend on many factors in addition to the HER2 genotypes. One of the possibilities could be ethnicity. The rate is different in different ethnic groups; for example, the rate of polymorphism is higher in the Kurdish ethnic than in the Arab population of the same country. The second possibility may be related to the location and geographical region. In Iraq, in general, the rate is higher than in most countries worldwide (Shmasaldin et al., 2023). Another reason that may contribute to the geographical region is the diet, environment and style of life. Therefore, a detailed study is necessary to investigate the reasons for gene polymorphism among different populations on the molecular level and their link to cancer risk.

Chronic diseases have no significant effect on breast cancer and women who carry Her2 polymorphism. On the other hand, when our patients for the HER2 Ile655Val polymorphism were stratified according to clinic-pathological variables, such as employment and high blood pressure, urinary issues, oral contraceptive usage, and menopause, we did not find any significant differences between the groups. Clinico-pathological findings in Iranian breast cancer patients were found to be comparable to those seen elsewhere (Zu´bor et al. 2006).

Breast cancer with carrier polymorphism genes is more common among those persons who had surgery in both group cases and control (79.47%, 16.53%). This may be an indication that the breast cancer caused by Her2 polymorphism is more metastatic type and spreads or enlarges very quickly and requires surgery for removal. Previous research has shown conflicting findings when it comes to the survival benefit of surgical removal of the main tumour in stage IV breast cancer (Dominici 2011, Kamali 2004, Bafford 2009, Barbie, Golshan 2018, Mudgway et al. 2020).

Reluctance to remove the primary breast tumour in the face of metastatic disease has been based on (Dominici 2011) theories that primary tumour resection may stimulate disease progression at distant sites (Dominici 2011) due to tissue trauma causing dissemination and increased adhesion of circulating tumour cells to the vascular endothelium of target organs (Mudgway et al. 2020), and surgery-induced immunosuppression, or activation of the inflammatory cascade. Other ideas, however, exist that provide a probable physiologic explanation for the improvement in survival following surgery for individuals with metastatic breast cancer (Fisher et al. 1989).

CONCLUSIONS

In the current study, the correlation between HER2 codon 655 polymorphisms in healthy women and patients with breast cancer was investigated according to different geographical locations.

The distribution of Val/Val and Ile/Val was indicated. It's found that the highest rate of mutation is found in the city of Sulaimani. Therefore, people of Sulaimani are more vulnerable to breast cancer, especially those women who carry Her2 polymorphism. Additional research at the molecular level is required in order to gain a better understanding of the relationship that exists between different ethnic groups and geographical regions, gene polymorphism, and the likelihood of developing cancer. The second rate was found in Garmyan district, and the lowest distribution was in Raparin. There was no significant result between chronic diseases and Her2 polymorphism.

Ethical Approval Statement

This research study, titled " **Distribution of Her2 Single Nucleotide Polymorphism in Different Geographical location in Sulaimani Province, Iraq**" conducted by [**Israa Saadaldin Shmasaldin, Muhammed Babakir-Mina, Taib Ahmed Hama Soor**], has received ethical approval from the [ethical committee of the College of Health and Medical Technology] at [Sulaimani Polytechnic university].

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AUTHOR'S CONTRIBUTIONS

All authors contributed equally to the conception and design of the study, data collection, and analysis, and drafted the initial manuscript. All authors critically reviewed and edited the manuscript. All authors approved the final version of the manuscript for submission.

DISCLOSURE STATEMENT:

The authors report no conflict of interest.

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