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Original Article

The Effect of SNP rs6543115 in Gene IL1RL1 on Gastric cancer by gender

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ABSTRACT

Introduction: Gastric cancer is the uncontrolled growth of malignant cells in the stomach which is one of the most common causes of cancer mortalities worldwide. The prevalence of this cancer is owing to the process of formation of cancerous texture in the stomach in several stages. It is classified as a multifactorial disease, as it forms due to the presence of infectious, environmental and genetic factors in individuals. The main genetic factors are mutations and polymorphisms. **Materials and Methods**: Information on SNP rs6543115 of IL1RL1 gene was analyzed in 300 subjects (150 patients and 150 healthy individuals). the samples were subjected to sequencing by Sanger method after DNA extraction and PCR to find the effect of this single-nucleotide polymorphism (SNP), and the statistical analysis of genotypes and alleles of individuals was performed by using SPSS. **Results**: The findings of this study indicated a significant relationship between CC genotype of SNP rs6543115 in IL1RL1 gene and gastric cancer ($p < 0.03$, OR: 2.41, 95% CI: 1.03-5.61) at the molecular level. The percentages of CC, GC and GG genotypes in the patient group were 18, 40 and 42%, respectively, and the corresponding values in the control group were 8, 40 and 52%, respectively. **Conclusion**: the findings of this study indicated that there is a statistically significant relationship between the CC homozygous genotype of SNP rs6543115 of IL1RL1 gene and the pathogenesis of gastric cancer in the study population.

Keywords: Gastric cancer, IL1RL1, Polymorphism.

Introduction

Cancer is one of the most prevalent and severe diseases witnessed in medical science. Statistics show that cancer affects more than a third of the population and is responsible for more than 20% of mortalities. Overall, about two-thirds of cancers are reported in developing countries, i.e. where there is only 5 percent of all cancer control instruments worldwide [1].

Despite some achievements in the prevention of contagious diseases in recent decades, the incidence of chronic diseases is still on the rise [2]. Regardless of whether it occurs sporadically in one person, frequently in many family members, or is inherited, cancer is considered a genetically related disease.

Owing to their unique anatomical condition in terms of volume and surrounding large lymph nodes, upper gastrointestinal cancers not only lag in exhibiting symptoms but also rapidly disturb nearby and distant organs, two important feature that have caused patients to be admitted for treatment at advanced stages, which are mostly not treatable at this time due to the high involvement of the lymphatic system [3]. Gastric cancer is among the most prevalent malignancies worldwide. The prevalence of this type of cancer resulting from the process of formation of cancerous tumor in the stomach includes several stages. It is considered a multifactorial disease, as it forms under the influence of genetic and acquired infectious agents [4].

Every year in Iran, more than 5,000 new cases of cancer are reported. According to the latest statistics from the National Cancer Research Center, gastric cancer is the most prevalent cancer among men and the third most prevalent cancer among women. it mostly appears during the fourth decade of life and its prevalence increases with age, so that the maximum prevalence

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is observed in the seventh decade of life in men and especially women. The mean age of incidence in Iran in some studies is reported in the age of 50 to 60 years and about 75% of patients are admitted to hospitals in advanced metastatic stages [5].

Classifying gastric cancers based on anatomical features is quite the challenge, as the histological features of gastric cardia inflammation caused by Helicobacter pylori (H. pylori) infection and metaplasia caused by reflux are highly similar [6]. Cancer can occur sporadically in a single person or be of hereditary origin. Approximately 10% of cases of this cancer are classified as inherited, but only 1 to 3% of gastric carcinomas are caused by known inherited syndromes such as HDGC, FAP and Lynch. Gastric cancer of HDGC origin is an autosomal dominant disease, in which approximately 30% of patients have a mutation in one of the tumor inhibitory genes of Cadherin-E or CDH1. Adenocarcinoma is the most prevalent type of gastric cancer. About 85% of gastric cancers cases are adenocarcinomas, while the other 15% are due to non-Hodgkin's lymphoma (NHL) and leiomyosarcoma.

The relation between dietary patterns and the incidence of gastric cancer has been extensively examined. Continued consumption of high concentrations of nitrates in dry, smoked and salt-cured foods appears to be associated with a higher risk of incidence. Genetic predisposition is among the parameters of incidence of cancer in individuals, which is attributed to a set of features of the individual at the genome level. The main factors of genetic predisposition are mutations and polymorphisms that exercise their influence by varying the expression level or altering the function of proteins [7]. Several major groups of genes are linked to the development and progression of various types of cancers, notably including oncogenes, DNA tumor suppressors [8] and genes mediating in programmed cellular death.

Considering the multifactorial nature of cancer, genetic polymorphisms concurrent with other environmental and genetic parameters potentially affect individuals' susceptibility to its occurrence. On average, one polymorphism is witnessed in every 1000 to 1500 nucleotides of the genome. Polymorphisms are also the origin of individual differences in susceptibility to the incidence of disease and response to drug stimuli, and hence they are considered as important factors in personalized medicine which will be the foundation of medicine in the near future. Today, extensive and numerous studies are conducted on the relationship between genetic variations such as polymorphisms and the incidence risk of various types of cancers [9].

The correlation of polymorphisms in genes associated with cell proliferation and gastric cancer has also been examined in a plethora of studies. In a meta-analysis, it has been suggested that these polymorphisms are capable of being used as biomarkers for prognosis of gastric cancer [10].

Nowadays, the potential effect of polymorphisms on the increased or reduced risk of diseases is examined by the highly efficient method of polymorphic arrays. In this method, an average of 10,000 polymorphisms are studied simultaneously in the genome of a person, and thus polymorphisms associated with the incidence of the particular disease are identified as molecular markers [11]. In spite of its many advantages, the use of microarrays is expensive and requires advanced equipment, and hence now other methods such as polymerase chain reaction (PCR) array, which is based on real-time PCR, and in each experiment, about 100 polymorphs or mutations can be examined.

On the other hand, IL1RL1 (Interleukin 1 Receptor Like 1) is a Protein-Coding gene in organisms of Domain Eukarya such as mammals and primates. IL1RL1 binds to interleukin-33 (IL-33) and exert its function through the toll-like receptor (TLR) pathway. There are various forms of IL1RL1 that can both stimulate and suppress Th2 responses [12]. Full-length interleukin 33 is expressed by epithelial and endothelial cells and is then stored within chromatin in the nucleus. Interleukin-33 can have two functions, namely either as a molecular pattern dependent on degradation and cytokine, or as a nuclear factor modulating gene expression. Mature forms of interleukin 33 function as an alarmin during cellular stress processes and cell damage in the event of extracellular secretion. The interleukin-33 solution binds to its receptor and forms a heterodimer complex consisting of IL1RL1/ST2 (encoded by IL1RL1) and the IL-1 receptor protein (encoded by IL1RAP). IL-33 / ST2 signaling is mediated by the use of MyD88 and IL-1 receptor-associated kinase-4 (IRAK-4). Recent studies have shown that interleukin-33 is heavily involved in many cancerous conditions

rs6543115 is a Single-nucleotide polymorphism located on chromosome 2 and upstream of the IL1RL1 gene (chr2:102311181 (GRCh38.p12)), which is 2 kilo base pairs (kbp) in size. Genetic disposition is one of the causes of cancers in humans, which refers to a set of characteristics of an individual at the genome level. The main components of the genetic disposition are mutations and polymorphisms that exert their influence by altering the expression or function of proteins [13].

Moreover, owing to the multifactorial nature of cancer, genetic polymorphisms along with other environmental and genetic parameters potentially affect individuals' susceptibility to its occurrence. On average, one polymorphism is witnessed in every 1000 to 1500 nucleotides of the genome; However, studies reveal that a small fraction of polymorphisms are located in exon sequences (encoding proteins), and a plethora of these genetic alterations are in regulatory sequences of genes such as promoters and microRNA binding sites that affect individuals' susceptibility to disease by mechanisms of altering gene expression [14].

Current evidence indicates that IL1RL1 can function as a potential inducer and prognostic markers of cancer progression. In a sample of cancerous mice, IL1RL was induced in adenomatous cells and ST2L-derived cells and subepithelial myofibroblasts were activated. These activated cells in turn release growth hormones, resulting in tumor progression and polyposis. Recent studies suggest that IL1RL imprinting leads to the development of myeloproliferative neoplasms. In this experiment, stromal cells were distributed into the bone marrow by IL1RL, increasing the level of IL-33-expressing cell levels in

bone marrow samples of MPN patients. Consistent with these findings, it also has been suggested that promoting stimulation of human epithelial cells in vitro reduces the degradation of IL-33 or ST2L in cancer cells. In another sample of cancerous mice, IL-33 injection led to increased survival of cancer cell and metastasis. Furthermore, laboratory studies show IL1RL in human gastric cancer cells increases invasive capacity and migration after treatment. In overall, these studies prove that the IL-33 / ST2L pathway may lead to cancer and metastasis. Latest evidence from the literature suggests that IL1RL may act as a prognostic marker during ovarian and lung cancer as well as squamous-cell carcinoma (SqCC). It is notable however that tumor-resulting IL1RL is able to stabilize tumor growth by increasing the number of invasive natural killer (NK) cells and CD8 + T cells, while more activated NK cells contribute to anti-tumor immunity IL1RL. Further experiments are needed to determine the function of IL-33 from IL1RL1 gene during cancer growth and whether tumorigenesis may be influenced by other cytokines, and thus suppress IL-33. In this case, IL-33 activates NF-κB, itself leading to neoplasms. furthermore, IL-33 is exploited by basal tumor cells to shape a desired anti-inflammatory Th2 environment through induction [15]. The aim of this purpose was to investigate the effect of SNP rs6543115 in IL1RL1 on susceptibility to gastric cancer as well as polymorphisms given the influence of genes as well as polymorphisms in the incidence of various diseases including cancer.

Materials and Methods

Sampling

The statistical population of the study was consisted of two treatment and control groups, namely 100 patients with gastric cancer in the age range of 17-60, whose disease was confirmed by an oncologist and using existing techniques, and 100 healthy individuals with no prior history of cancer in the age range of 16-70. Blood samples of patients were collected from Hospitals affiliated to the University of Medical Sciences during the study. Sampling from the control group was performed after collecting patient samples, while the control subjects matched the demographic sub-categories of age group and gender of patients. All participants in this study offered their written consent for performing various steps. Then 5 ml of venous blood was taken from healthy and patients with gastric cancer in a standard sample tube containing EDTAK3. After blood sampling, the samples were transferred to the laboratory and stored at -20 ° C.

DNA extraction was performed using GeNet Bio kit. Electrophoresis device was used to assess the quality of the extracted DNA. In this method, the amount of fragmented DNA purified is determined based on the residual range on the gel after DNA electrophoresis. Base substitution polymerase chain reaction (PCR) was also used for cloning with the purpose of generating unlimited values of a desired sequence.

The first and most basic step in amplifying a specific block of DNA and performing PCR is primer design. The notes discussed were used to design the primer

Determining the primer for amplification of fragments of IL1RL1 gene

After achieving equal concentration, PCR method was employed on DNA of all samples to determine the existing polymorphism in IL1RL1 gene. For this purpose, two primers of (F) and (R) were used to amplify the desired fragment. The primers used in this design and its features and quality were determined from www.ncbi.nlm.nich.gov.com and the Blast. The specifications of these primers are given in Table 1. The PCR product length of this primer is 372 bp.

Table 1: Sequence of primers in PCR technique

No.	Name of Site	Sequence of primers 3′→ 5’	Length of primer
1	*IL1RL1* rs6543115	P F: ACATACCAAATTACTGCACAC	21
		P R: GTCTTAACTATATTTTGCCTTCTTC	25

Dilution of primers and preparation of working solutions was requested from Iranian Novin Gene Company. The primers were experimented in lyophilized forms. After adding water to the vials, the primers were transferred to freezers of -20°C. To prepare the working solution, 10 µl of each of the main primers was extracted and diluted to a volume of 100 µl with 90 µl distilled water (10 µM concentration) and were then stored in a 1.5 ml microtube at -20°C.

Preparation of PCR mixture

Materials and concentrations required for conducting PCR are presented in Tables 3 and 3. The volume needed for each component of PCR was brought up to the number of samples considered for the operation. For each sample, a PCR mixture containing the specific primers studied was prepared. The reaction components were transferred into a 1.5 ml microtubule (excluding DNA), and then they were pipetted to achieve uniformity. The mixture was consequently added to PCR microtubes, after which, DNA of each individual was added to microtubes containing PCR components. Lastly, the microtubes were subjected to spin and placed inside the block of the thermocycler device, which was then turned on.

Table 2. Final concentration of PCR components for amplifying the rs6543115 polymorphism in IL1RL1 gene

Reaction components	Volume (µl) in 25 µl of PCR mixture	Basal concentration
PCR master mix	16	X2
F primer	0.8	10
R primer	0.8	
DNA	1.5	
DDW	5.9	_

Table 3: PCR schedule for amplification of SNP rs6543115 in IL1RL1 gene

Stage	Temp (°C)	Time	Number of cycles
Initial denaturation	95	5 min	1
Denaturation	95	30 s	
Binding	56.2	30 s	35
Amplification	72	35 s	
Final amplification	72	5 min	1

Gel staining: After heating the agarose and dissolving it in the buffer, 1 to 3 microliters of DNA safe stain solution was dissolved in the agarose gel to directly observe very small amounts of DNA.

Agarose gel electrophoresis of PCR by-products

To perform electrophoresis on PCR products in this study, 3% agarose gel was prepared using the following method; First, the casting plate was placed on a perfectly level surface, such that all the indentations are fixed with same distance from the surface. Employing a sloped surface at this stage causes a difference of elevation in different parts of the gel and hence the electric force therein loses uniform distribution. The analysis of results from such a scenario is error-prone and hence is not reliable. In the next step, 9 g of agarose is mixed with 30 cc of TBE buffer (0.5 X) and heated with an alcohol lamp to dissolve all the existing agarose crystals in the buffer. The resulting uniform, transparent and bubble-free solution is kept at room temperature for a while until the temperature drops to about 45-55 °C. The resulting agarose is gently poured from one corner into the casting plate such that not even the smallest of bubbles is formed on its surface. The solution is then kept at room temperature until the gel is completely polymerized. The comb is prudently and slowly removed from the hardened gel. The gel is transferred with the casting place to an electrophoresis tank containing a sufficient amount of clean TBE buffer (0.5 X). Then 8 microliters of PCR product is poured into the wells. The DNA ladder is poured in the first well and finally the tank is connected to the power supply so that the current is maintained from the negative pole to the positive. Thus, PCR products were electrophoresed for 45 minutes at a voltage of 125 volts.

Gel imaging: After completion of the aforementioned steps, the gel is captured directly using a UV transilluminator, after which the condition of the transferred DNA fragments on the gel is examined.

Statistical analysis of data: Finally, the demographic information of the patients and PCR results were inputted to SPSS V.18 and descriptive analysis was performed on the data. Data were also analyzed using Exact Test Fishers and Chi-Square statistical tests. $p < 0.05$ was considered as the significance level.

Results and Findings

Demographics of the statistical population

In this study, a sample of two groups, namely a group of 100 patient with gastric cancer and a control group of 100 healthy individuals, who were homogenized in terms of age (±5) and gender were examined. The mean age of the patients' group was 55.59 ± 10.30 with an age range of 28-85, while the mean age of healthy individuals in the control group was 56.30 ± 10.60 with an age range of 32-87. The study had a case-control design in which the subjects of the statistical population were compared for genotypes of SNP rs6543115 in IL1RL1 gene. The ratio of men to women in the study population was approximately 2:1. The abovementioned information is presented in full details in Table 4.

Table 4: Demographics of the study population

Characteristics	Control Groups	Patients' Group
Frequency of sample	100	100
Gender		
Male	66	66
Female	34	34
Age (years)		
Age range	32-87	28-85
Mean ± SD	56.30 ± 10.60	55.59 ± 10.30
Male	55.68 ± 12.61	56.87 ± 11.42
Female	56.23 ± 10.66	53.04 ± 12.33
Subjects with H. pylori	0	28
Type of gastric cancer		
Intestinal	0	35
Diffuse	0	17
Subjects with gastric ulcer	0	35

Molecular analysis

Conventional PCR and consequently Sangar Sequencing were eventually used to examine SNP rs6543115 of IL1RL1 gene. The product resulting from the amplification of primers used in this area leads to the generation of a product with a length of 372 bp (Figure 1). The presence of two overlapping graphs as a result of sequencing (at the polymorph position) indicates the genotype of the heterozygous individual, while the presence of only one graph

points to the homozygosity of the subject. 2% agarose gel was used to examine the genotypes in this study.

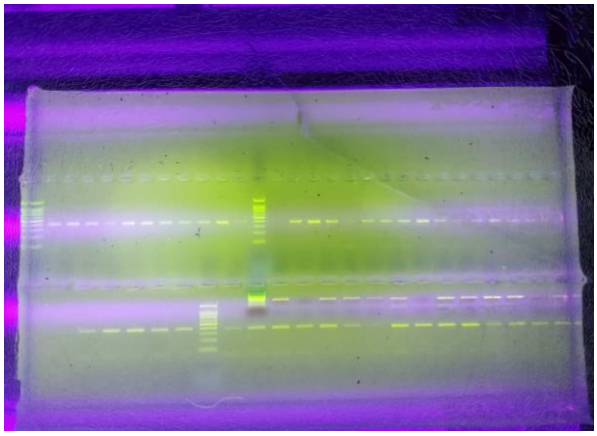

Figure 1: Electrophoresis of PCR product associated with SNP rs6543115 in IL1RL1 gene on 3% agarose gel.

Hardy–Weinberg equilibrium: According to results from Chi-square test, the control group ($P < 0.05$, $df = 1$) and patient group ($P < 0.05$, $df = 1$) satisfied Hardy-Weinberg equilibrium.
Relationship between SNP rs6543115 polymorphism of IL1RL1 gene with gastric cancer by sex
The relationship between SNP rs6543115 of IL1RL1 gene was studied using logistic regression test separately in both male and female populations. To investigate the relationship between different genotypes of this polymorphic locus and the risk of gastric cancer based on gender, GG genotype was considered as the reference genotype, with which other genotypes were compared. The results are presented in Tables 5 and 6. $P < 0.05$ was considered as the statistically significance level.

Table 5: Relationship between SNP and gastric cancer risk in females

Genotype	Control Group	Patient Group	OR (95% CI)	P
GG	29	17	1	-
GC	4	13	3.66 (0.1-23.92)	0.45
CC	8	25	3.33 (0.10-51.66)	0.04

Table 6: Relationship between SNP and gastric cancer risk in males

Genotype	Control Group	Patient Group	OR (95% CI)	P
GG	23	14	1	-
GC	36	27	1.72 (0.3-81.63)	0.15
CC	8	25	2.54 (0.7-91.09)	0.07

Sangar Sequencing

The results of Sangar sequencing in a homozygous mutated sample, a homozygous non-mutated sample and a heterozygous sample are shown respectively in Figures 2, 3 and 4.

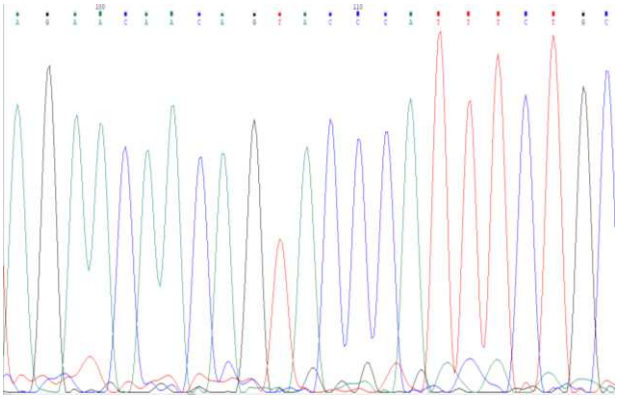

Figure 2: Confirmation of the presence of G> C mutation in IL1RL1 gene using Sangar sequencing in a proband with CC genotype at position 104.

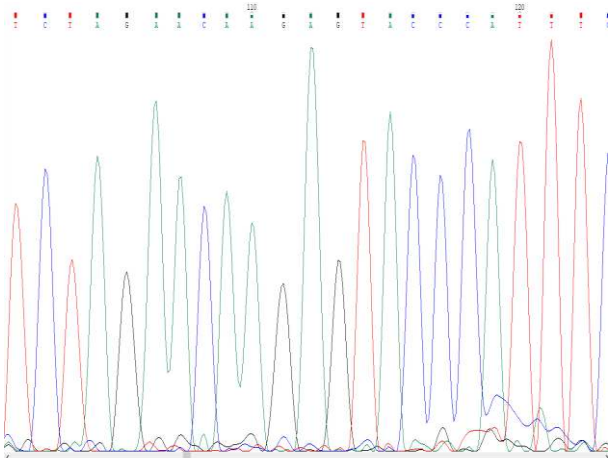

Figure 3: Confirmation of the presence of G> C mutation in IL1RL1 gene using Sangar sequencing in a proband with healthy homozygous genotype of GG at position 104.

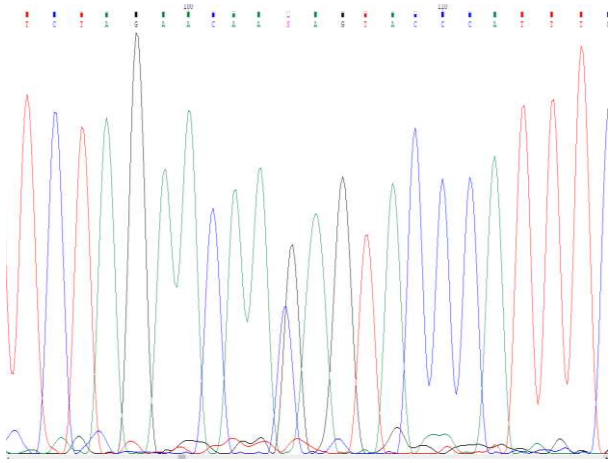

Figure 4: Confirmation of the presence of G> C mutation in IL1RL1 gene using Sangar sequencing in a proband with heterozygous GC genotype at position 104

Discussion

Gastric cancer is the second most common prevalent and the second cause of cancer mortalities worldwide. In Iran, Gastric adenocarcinoma is the most fatal type of gastric cancer and

people with this type of cancer have a shorter lifespan compared to others.

Different parts of the world report varying rate of incidence for this type of cancer, which in Iran, is diagnosed in 26.1 per 100,000 men and 11.1 per 100,000 women [16]. In many developed countries, this incidence of this cancer is decreasing, yet, due to high population growth in developing countries which also have a high prevalence of gastric cancer, the rate of this cancer has not decreased cumulatively in the last 30 years. With recent breakthroughs in medical and surgical treatments, the survival rate of these patients has improved as well. About two-thirds of patients are admitted for treatment in the advanced stages of the disease, further challenging therapeutic interventions, for whom surgery is considered as the most important method of treatment

Metastasis is a complex process in which cancerous cells are spread from the primary site, enter the arteries by destroying the surrounding tissue and form secondary tumors in distant location. In recent years, in spite of recent advances in the treatment of patients with gastric cancer and employment of novel interventions, it is still among the cancer that have not experienced promising results in treatment [17].

Poor prognosis of this cancer is attributed to complex biological features and high degree of malignancy of this type of cancer, which is often diagnosed along with metastasis in advanced stages. metastasis is not only a sign of severity but also the main cause of failure of treatment and subsequent death. Therefore, new studies are aimed at identifying markers related to tumor invasion and its role in gastric cancer pathology for offering scientific principles in their early diagnosis and treatment [18].

The most common age of this malignancy is the sixth decade of life, but its occurrence is also highly reported at younger ages. it is completely curable if diagnosed early, and contrarywise, it may spread beyond the stomach and invade other parts of the body if diagnosed late on. Therefore, being vigilante towards the clinical signs of this disease can help detect the disease earlier. Signs and symptoms of this disease include: unexplainable weight loss, anorexia, vague symptoms of indigestion such as a sense of fullness in the upper abdomen after eating a small meal, premature satiety, nausea and vomiting. The main treatment for gastric cancer in the early stages is surgery, while radiotherapy and chemotherapy are supplemented if needed. In the advanced stages of the disease, surgery, radiotherapy, and therapeutic chemotherapy are also used to treat the disease, but it is usually not associated with promising results. The most important measure for improving the success rate of treatment for this type of cancer is early diagnosis [19].

Risk factors for gastric cancer include gastric infection with Helicobacter pylori, chronic gastritis, being older than 50 years and male, diet high in salt while low in fruits and vegetables, anemia, smoking, intestinal metaplasia, familial adenomatous polyposis with gastric polyposis, and consumption of nitrate-containing foods.

Owing to the fact that genetic factors are among the most effective factors in the incidence of gastric cancer, in this study, the relationship between rs4365115 in the IL1RL1 gene and the risk of gastric cancer was examined for the first time. In this study, which had an observational control-case design with a population of 200 people including 100 patients and 100 healthy individuals, the frequency of GG, GC and CC genotype polymorphisms for SNP rs4365115 in IL1RL1 gene was studied. According to the experiments conducted in this study and subsequent statistical analyzes of IL1RL1 gene in gastric cancer, CC, CG and GG genotypes had a significant relationship with control group. In GG, the index is OR = 1 and is not associated with gastric cancer, but P in CC is less than 0.5 and equal to 0.2, hence being correlated to gastric cancer. The findings are consistent with previous studies on the effect of the IL1RL1 gene on a variety of cancers; Danny et al. (2018) conducted a study on the role of polymorphisms in the occurrence of diseases in USA, in which an integrated framework of functional genes was developed and the features of these polymorphic genes from were studied using four important gene databases of FANTM5, ENCODE and GTEX among others.

Jiang and et al. (2017) conducted a study to evaluate IL-33 in gastric cancer (GC) and its relationship with clinical features and prognosis. IL-33 protein was detected in tumor and surrounding tissue using immunohistochemistry in 179 GC patients, and its clinical features as well as prognostic value were analyzed using Pearson Chi-square test and Kaplan-Meier test in Cox finite risk model. IL-33 protein levels in tumor tissues were significantly lower than those of adjacent tissues (29.05% vs. 78.77%, $\chi 2 = 89.05$, $P < 0.001$). The positive level of IL-33 in the partially ulcered group was lower than all groups ($P < 0.05$). IL-33 levels were correlated with age ($P = 0.025$) and depth of invasion ($P = 0.030$) while they were not significantly correlated with overall survival of GC patients. IL-33 expression is also associated with the age and invasive type of cancer in patients with GC.

Matsumato and et al. (2017) examined the relationship between the IL1RL1 gene and asthma and the increase in the number of eosinophils in Japan, and proved that polymorphisms of IL1RL1 are correlated to the incidence of this disease. In this study, clinical measurements, including the permissible output volume of FEV1, FeNO and SST2, and differences in serum IGE levels were confirmed in 110 patients in Japan, and the relation of IL1RL1 gene and asthma and high eosinophil levels was thus confirmed.

Chang et al. (2017) studied association of 18 genes, including IL1RL1, with ovarian Endometriosis in Taiwan, the findings of which suggested the role of these genes in the molecular function of membrane inflammation in the stimulation of this cancer, moreover, there was a significant correlation between target genes and the progression level. High levels of ALM2 and ki 67 in clinical samples suggested its involvement in disease progression.

Diaz Gimenez et al. (2017) studied the relationship between IL33 and st2, and ulcerative colitis (UC) in the United States, the

results of which suggested that the ST2 receptor, encoded by the IL1RL1 gene, was associated with UC, for which glucocorticosteroids is prescribed for treatment.

Van Wark et al. (2017) reported an association between ST2 and heart attack in the Netherlands, which was conducted by cohort studies on patients.

Dannell et al. (2016), studied the role of ST2 and IL33 and their relationship with colorectal cancer (CRC), and their serum levels were measured using ELISA method. The relationship between their expression and immunohistochemistry was studied, the results of which indicate that degradation of ST2 in colorectal cancer cells increases tumor growth in mice in vivo, and that st2 can play a protective role in colon cancer.

Harigoshi et al. (2016) studied interleukin-33, a member of the IL1 family, and confirmed the role of IL-33 in inflammation and cancer. The authors assessed the intestinal epithelial cells of mice with colon cancer using PCR method. IL33 production was evaluated in culture medium and in epithelial cells and cytokine levels were determined using ELISA. The result indicated that EGF is reportedly a key growth factor that increases IL33 production and ST2 receptor expression during intestinal inflammation and carcinogenesis.

Due to the high mortality rate of gastric cancer and the complexity of early diagnosis, it is important to investigate the association of IL1RL1 polymorphism with cancer risk for prevention and early diagnosis.

Messenger RNAs (mRNAs) are a group of small RNAs with regulatory functions that, by binding to the three-primer untranslated (3'-UNT) region of each mRNA, are able increase or decrease the stability of mRNAs and hence affect the expression of different genes. Based on the type and activity of the protein, in which the microRNAs attach to its mRNA and alter its expression, they can be considered tumor inhibitors or oncogenes.

As future avenues of research, prospective researchers are recommended to examine these polymorphisms and other polymorphisms of the IL1RL1 gene in larger populations and different ethnicities to achieve more accurate results.

According to this study, IL1RL1 gene is significantly associated with gastric cancer. Further research is needed to express the process of expression and its relation with gastric cancer.

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