Single nucleotide polymorphisms associated with gastric cancer in Iranian patients

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Abstract

Gastric cancer is one of the leading worldwide cancers formed in the lining of the stomach, and is the most prevalent cancer in northern Iran. Recent interventions for the early diagnosis of gastric cancer are based on genetic susceptibility parameters and the interactions between genes and the environment. Accordingly, this narrative review was designed to summarize the genetic markers involved in Iranian patients with gastric cancer, classified by cellular function. There was a significant relationship between single nucleotide polymorphisms (SNPs) in rs1051208 C allele (RAF1), rs531564 (pri-miR-124-1), rs1053023 (STAT3), rs8193 C allele (CD44), rs3130932G allele (OCT4), rs283821943, rs2032586 (ABCB1), codons 72,248 (p53), -137 G/C (IL-18), Pro12Ala (PPARγ), rs1053023 (STAT3), rs4647603 (caspase 3), -712C>T (caspase 9), -1263 A> (caspase 9) and gastric cancer. Increased risk was observed in C677T (MTHFR). Finally, decreased risk of gastric cancer was explored in -938 C>A (bcl2). Asp299Gly (TLR-4), rs1028181-513T/C (IL-19) Pro12Ala (PPARγ) may play a crucial role in susceptibility of *Helicobacter pylori* and gastric pathogenesis. According to the findings, the genetic polymorphisms in the immune-associated genes were related to the gastric cancer among the Iranian patients. Therefore, further large-scale functional investigations are needed to draw definite conclusions.

Introduction

Cancer is one of the leading causes of death around the world. Gastric cancer, also known as stomach cancer, is one of the most prevalent cancers diagnosed in advanced stages due to poor prognosis (1). Most patients have a low five-year survival rate, even after surgery, and die due to inefficiency of conventional therapies. The gastric cancer is the second leading cause of cancer deaths worldwide. Previous studies have shown that the five-year survival rate in Iran has increased by 5% over the past few years, but is still lower than in countries such as China, the United States, Switzerland, France and Japan. About 798 000 patients are diagnosed with gastric cancer each year, with 628 000 people dying from the disease. In East Asian countries, such as China, mortality due to gastric cancer has been ranked first among all other cancers, and this trend has grown rapidly over the past two decades (2). In general, the cancer incidence is dramatically affected by various factors, such as bacterial infection (*Helicobacter pylori*

Key point

Genetic diversity studies illuminate many of the determinants of cancer incidence and propose strategies for the accelerated prevention and detection of cancers. The single nucleotide polymorphism (SNP) is the most common sequence variation in the human genome. Gastric cancer is one of the leading worldwide cancers formed in the lining of the stomach, and is the most prevalent malignancy in northern Iran. The genetic polymorphisms in the immune-associated genes were related to the gastric cancer among the Iranian patients.

infection), environmental factors (such as diet and climatic conditions), gender, age, and genetic factors such as mutations in genes associated with tumor suppression, apoptosis and proto-oncogenes (3,4). H. pylorus (*Helicobacter pylori*) is one of the most common infections in humans and affects almost half of the world's population. The prevalence of this bacterium varies in different regions according to public health and socioeconomic status (5). The mechanism of *H. pylori* pathogenesis is

varied and can occur in a variety of routes, such as reducing gastric acid secretion, cell proliferation caused by infection, elongation of epithelial cells, destruction of cell-to-cell junctions, and production of systemic and mucosal antibodies of IgA and IgG (5). There is evidence that cytokines produced by both innate and adaptive immune systems can develop gastric ulcer, gastric cancer, and mucosa-associated lymphoid tissue (MALT) lymphoma. Anti-*H. pylori* treatment may be an effective way to prevent the gastric cancer. MicroRNAs are non-coding ribonucleic acids with18-25 nucleotides in length, which play an important role in regulating gene expression. They can act as oncogenes or tumor suppressors. A variety of these molecules are involved in various stages of cancer including tumorigenesis, metastasis and angiogenesis. The single nucleotide polymorphisms (SNPs) play a role in micro-RNAs and their binding site to mRNA is susceptible to gastric cancer. One of the most important factors that make people of each population susceptible to various diseases such as malignancy is the genetic differences of individuals. Genetic diversity studies illuminate many of the determinants of cancer incidence and propose strategies for the accelerated prevention and detection of cancer. The SNP is the most common sequence variation in the human genome (6). Concerning the gastric malignancy, it has been clearly demonstrated that the development and progression of this cancer are multi-factorial processes dependent on gene polymorphisms and environmental factors (7). Cancer-related SNPs have been studied for two aspects; the impact of individuals' susceptibility to and outcome of cancer (survival or response to treatment) (6). Since more than 50% of cancers diagnosed in the early stages are curable, identifying biomarkers and molecular alterations in gastric cancer can play an effective role in prevention, early detection and rapid treatment of the disease. Accordingly, the purpose of this article was to review the SNPs studied in gastric cancer in Iran.

Literature review
Genetic polymorphisms in the immune-associated genes
Type 17 helper T cells (Th17 cells), a new lineage of CD4+ T lymphocytes and the boundary between innate and adaptive immune responses, play a key role in the development of inflammation through the production of proinflammatory cytokines such as interleukin-22 (IL-22), IL-17A, IL-17F and IL-26, and are effective in the pathogenesis of many autoimmune diseases and inflammatory bowel diseases and malignancies. Some studies have shown that the Th17 cells enhance antitumor immune responses (8), while others have reported the association of Th17 cells, especially IL-17, with the angiogenesis process in tumors and the number of blood vessels in cancer tissues (9). The Th17 cells can be linked to the onset and progression of cancer due to their role in the emergence of inflammation, especially chronic inflammation. The IL-17F induces the production of many inflammatory cytokines such as IL-6

and GM-CSF, and the chemokines such as CxCL1, CxCL2 and CxCL5, and enhances granuloma formation, and plays a critical role in neutrophil recruitment (10). IL-27 serves as a bridge between innate and adaptive immune systems and contains regulatory and proinflammatory functions. Like IL-12, IL-27 also enhances differentiation of Th0 to Th1 and production of IFN-γ by T cells. The IL-27 is produced by macrophages and dendritic cells (DCs) in response to pathogens. The IL-27 is effective in proliferating CD4+ T cells and stimulating IFN production in these cells and thus the Th1-related immune response. In addition to the effect of IL-27 on naive CD4+ T-cells and the inhibitory role of lymphocyte activity by this cytokine, there is a report on the ability of IL-27 to stimulate CD8+ T cells and increase the lethal activity of these cells in infectious diseases and cancers (11). There is increasing evidence that failure to regulate cytokine production may lead to the development of infection and the inflammatory responses. Given the role of IL-27 in the inflammatory pathways and cell cycle, this cytokine may play a role in the incidence of gastritis following infection with *H. pylori* and even more severe inflammation leading to gastric ulcer. The aberrant and consecutive expression of STAT3 plays a critical role in carcinogenesis and accelerates the onset of malignant phenotype. The findings suggest a fundamental role of STAT3 activity in a wide range of tumors from blood malignancies (leukemia, lymphoma, and myeloma) to a variety of solid tumors (breast, lung, stomach, colorectal, prostate, liver and head and neck (12). Evidence suggests that the aberrant STAT3 expression signals the initiation and progression of cancers by inhibiting apoptosis or inducing phenomena such as cell proliferation, angiogenesis, and tumor invasion and metastasis (12). Continued activation of STAT3 in cancer stimulates expression of specific target genes, which induce cell proliferation. Previously, STAT3 had only been proposed as an oncogene in the past, but two roles for tumor inhibition or induction have been considered recently. Toll-like receptors (TLRs) are a class of membrane receptors that participate in the innate immune system and their 11 members have been identified so far. The TLRs expressed on the surface of gastric epithelial cells and infiltrated immune cells in the gastric mucosa were identified as the first line of host defense against *H. pylori* (13). Several studies have reported contradictory effects of TLR-4 on activation of innate immune responses against *H. pylori*. TLR-4 mutations reduce the identification of *H. pylori* LPS as well as reduce intracellular nuclear factor kappa B (*NF-κB*) activation and further reduce the secretion of various inflammatory cytokines, predisposing the individual to specific forms of the disease (14). The IL-19 has been investigated as an anti-inflammatory cytokine in a variety of diseases, including skin diseases of the liver, autoimmune diseases and microbial diseases. The gene of this molecule at the position (rs1028181, TC 0513) has a polymorphism that affects the expression

of the molecule. One of the other pro-inflammatory cytokines is IL-18 found in the inactive precursor in healthy intestinal mucosa, which can be immediately transformed to bioactive molecule using IL-1β-converting enzyme (caspase-1) (15), and can be important in the inflammation and immune responses in many disorders. The tumorigenesis can be associated with some products of pro-inflammatory gene, including IL-18, highlighting the role of inflammation as a risk factor for cancer (16). Thus, the IL-18 may act as pro-inflammatory cytokine in the process of gastrointestinal inflammation to progress the gastrointestinal cancers. Tumor necrosis factor (TNF) as a key agent to develop the gastric cancer can impede the production of gastric acid. The patients with advanced gastric cancer show a significant elevation in the expression of serum TNF-α. In a study, the male patients infected with *H. pylori* exhibited an increase in the level of TNF-α (17). The SNPs can control the TNF-α expression. The main cancer-associated genes are tumor suppressor and oncogenes genes that are involved in the DNA repair and apoptosis, more importantly including CD44, Myc and K-Ras that are associated with gastrointestinal cancers. According to cytogenetic findings, the CD44 gene is positioned on the short arm (p13) of chromosome 11, responsible for encoding different isoforms of protein through alternative processing and post-translation modifications (18). CD44 and related isoforms mediate various cellular functions, including cell growth, mobility and survival. CXCL12 (SDF-1) is a chemokine binding to CXCR4 and CXCR7 receptors, involved in maturation and homing of T and B lymphocytes (19), angiogenesis, immune system regulation and stem cell trafficking (20). There is evidence on the over-expression of CXCR4 in various human cancers (23 variants), such as prostate, ovarian and breast cancers as well as the expression of CXCR7 in many tumor cells and tumor-associated endothelial cells (21) (Figure 1).

SNPs in cell signaling, apoptotic and cell cycle genes
The eNOS gene encoding an endothelial nitric oxide synthase (23.5 kb) with two exons is located on the long arm of chromosome 7. The mRNA transcript (4052 nucleotides) of this gene encodes a 135-kDa protein with 1203 amino acids (22). Endothelial NOS (eNOS) and its potential role in gastric cancer have not been fully understood. The aberrant expression of eNOS has been observed in specific tumor cells, such as colorectal adenocarcinoma. However, the mechanisms involved in the aberrant expression of eNOS in cancer cells and tumor-associated endothelial cells are largely unknown. Evidence suggests that the eNOS expression can be regulated by various hormones, cytokines, growth factors and genetic alterations such as oncogene activation and tumor suppressor inactivation. Many tumors often show aberrant expression of these factors and genetic alterations (22). Screening for eNOS gene polymorphisms with the extent of gastric cancer development may be useful to identify individuals at high risk for gastric cancer. Peroxisome proliferator-activated receptor-γ (PPAR-γ) is a member of the super-family of hormone receptors in the cell nucleus that plays an important role in cell differentiation and metabolism regulation. It is highly expressed in tissues with high levels of adipose or epithelial cells. PPAR-γ is effective in regulating the expression of other genes by forming a heterodimer with the retinoid X receptor. This gene inhibits cancer cell growth and induces apoptosis in cancer cells (23) and is considered as one of the host factors in the inhibition of some cancers, such as colorectal cancer. PPAR-γ is a ligand-dependent transcription factor that is involved in various disease processes, including inflammatory processes and cancer. It is important to evaluate the PPAR-γ gene polymorphism and its association with *H. pylori* infection and gastrointestinal diseases in patients. NAD (P) H quinone dehydrogenase 1 (NQO1) is an oxidoreductase enzyme that plays an important role in the detoxification and damage caused by quinone radicals and their derivatives. The function of this enzyme is to reduce quinone and nitro-quinone and azoquinone compounds and to produce non-oxidant forms of vitamin E and ubiquinone (24). This enzyme is found largely in kidneys, stomach, respiratory epithelial cells, and in vessel endothelial cells, as well as
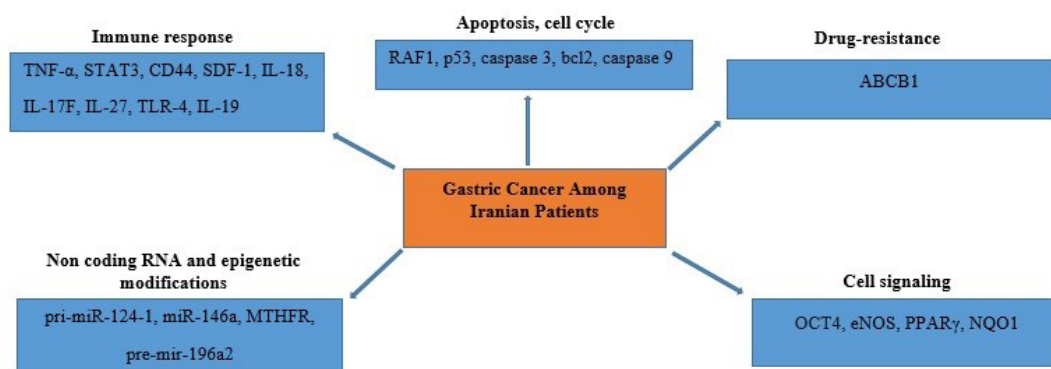

Figure1. All the cellular processes which are study in gastric cancer progression among Iranian patients.

in small amounts in the liver, colon and breast. Defects in the apoptotic pathway may cause the accumulation of immortal cells, which eventually leads to several disorders, including cancer. Several studies have suggested that some differences in apoptotic pathway genes are associated with susceptibility to several different cancers. Caspase-1 plays a key role in both the extrinsic and intrinsic pathways of apoptosis as the executive caspase. Therefore, the caspase-3 gene polymorphism can affect the activity of this gene and thus its susceptibility to gastric cancer. Many studies have found that polymorphisms in the caspases can alter function and result in different cancers. The BCL2 family has an important role in the regulation of apoptosis, and the impact of bcl2 gene SNPs has been shown to be involved in gastric cancer. Caspase 9 is the initiator caspase involved in the intrinsic pathway of apoptosis and plays an important role in the development and progression of cancer. Polymorphisms in the promoter region of the caspase 9 gene can affect the activity of this gene and thus the susceptibility to gastric cancer. The caspase 9 is a member of the intrinsic pathway that is activated as a result of mitochondrial damage and cytochrome c release. Studies show that the caspases, including caspase 9, play an important role in cancer development. It seems that the mechanism of induction of apoptosis in cancers, including lung cancer, is altered by the tumor and causes the cells to become cancerous. The role of this caspase in gastric cancer is not fully understood. Human Oct4 gene located on chromosome 6 contains three spliced variants of Oct4A, Oct4B, and Oct4B1. OCT4A serves as a central component in the regulatory network of pluripotent stem cells (25). Evidence shows the function of OCT4B in the development of self-renewal and embryonic stem cell (ESCs). Human ESCs predominantly produce the OCT4B1 that is involved in embryonic carcinomas and cancer stem cells in various malignancies, which acts as a marker for carcinogenesis. DNA-binding protein of p53 has role in the regulation of transcription. It is a tumor suppressor gene (TSG) to conserve genome integrity and impede aberrant cell proliferation due to genotoxic and non-genotoxic stresses (26). During the immune response, the p53 helps to arrest G1 /S cycle by triggering p21 cip1/kip1 protein, which links to and impedes CDK2 from attachment with cyclin E. P53 dysfunction, which acts as a blocking factor for cell cycle progression, affects genome integrity and is associated with a selective advantage for tumor cells (27). The estimated mutation in the p53 gene involved in human cancers is approximately 40%, so that the p53 is the most prevalent inactivated TSG present in human cancers. The abnormalities of p53 gene have major role to form the gastric cancer, which are associated with early stages of gastric carcinogenesis like dysplasia, intestinal metaplasia (IM) and gastritis. Neoplasms and eventually gastric cancer are likely to develop from these precancerous lesions following subsequent genetic abnormalities (27).

SNPs in microRNA target sites
The miRNA polymorphism may alter the cancer- associated genes, including RAF-1, affecting possible susceptibility to cancer. There is association between RAF-1 and various cancers, in particular colorectal cancer. The miR-146a by linking to mRNAs of IRAK1 and TRAF6 can regulate the NF-κB pathway (28). The cancer-related miR-146a reportedly exhibited expression alters in prostate, colorectal and breast cancers (29,30). The premir-196a2 mediates various bioprocesses, such as tumorigenesis, immune response and cell proliferation, differentiation and death, (31). In the folate metabolism, the methylenetetrahydrofolate reductase (*MTHFR)* is responsible to reduce 5, 10-methylene-tetrahydrofolate to 5-methyltetrahydrofolate as the most prevalent circulatory folate, donating the methyl group for remethylation of homocysteine to methionine and then to s-adenosyl-L-methionine. Any deficiency or decrease in the activity of this enzyme can decline s-adenosyl-L-methionine levels and enhance cancer risk because of gene hypomethylation (32). This enzyme can enhance cancer development through an elevation in the deoxy uridylate monophosphate/deoxythymidylate monophosphate ratio, thus can elevate the uracil incorporation into DNA rather than thymine, and can result in DNA/chromosome damage and point mutations (33).

SNP in the ABCB1 gene
The alteration of anticancer drug transport is among the strategies for drug resistance, which can be attributed to the superfamily of ABC transporter proteins such as ABCB1 gene. Among these, various tissues can express the ABCB1 to protect against adverse effects of toxins (34). The subjects with high level of ABCB1 expression are at risk of mutation and drug resistance over time. The activated ABCB1 can be a key biomarker for prognosis and a major target for drug manipulation (34). There are various pathways for the overexpression of ABCB1, such as SNPs (such as promoter SNPs and structural RNA SNPs), aneuploidy (gene amplification and rearrangements) and mutations (Table 1).

Conclusion
According to Table1, the presence of SNP rs2910164 (miR-146a), C3435T (ABCB1), G801A(SDF-1), Glu298Asp (eNOS), rs11614913 T/C (pre-mir-196a2 T/C), A7488G (IL-17F), -609C>T(NQO1) genes have no significant relationship with GC, while there is a significant relationship between SNP in rs1051208 C allele (RAF1), rs531564 (pri-miR-124-1), rs1053023 (STAT3), rs8193 C Allele (CD44), rs3130932G allele (OCT4), rs283821943, rs2032586 (ABCB1), codons 72,248 (p53), -137 G/C (IL-18), Pro12Ala (PPARγ), rs1053023(STAT3), rs4647603 (caspase 3), -712C>T (caspase 9), -1263 A> (caspase 9) and GC. Asp299Gly (TLR-4) rs1028181-513T/C (IL-19) Pro12Ala (PPARγ) may play crucial roles in helicobacter pylori susceptibility and gastric pathogenesis. According

Table 1. Polymorphisms in genes involved in gastric cancer among Iranian patients

SNP	Gene	Main Results
rs1051208, rs1799964	MicroRNA binding site of TNF-α and RAF1	Significant association between the rs1051208 C allele of RAF1 gene and GC.
rs531564 rs1053023	pri-miR-124-1, STAT3	Strong link between pri-miR-124-1 rs531564 and STAT3 rs1053023 polymorphisms and GC.
rs8193 C Allele	CD44 Gene	rs8193 is statistically associated with the risk of malignancy, lymph node spread and stage of GC.
rs3130932	OCT4	rs3130932G allele and odds of GC are related to each other.
rs2910164	miR-146a	No relationship between the rs2910164 polymorphism of miR-146a gene and risk of GC.
C677T	MTHFR	MTHFR C677T SNP seems to increase the risk of GC and the effect is significantly inflated by interactions with *H. pylori* infection, age and gender.
rs28381943, rs2032586, C3435T	ABCB1	rs283821943 and rs2032586 may elevate the expression of ABCB1 gene, while this was not the case for C3435T.
G801A	SDF-1	SDF-1 gene polymorphism at position 801 (G>A) was not associated with GC.
Exons 2–7. Microsatellite markers: NR-27, NR-21, NR-24, BAT-25, BAT-26	p53	The highest rate of alteration was seen in codons 72 (85.6%, SNP) and 248 (30.9%, mutation).
-607C/A -137G/C	IL-18	SNP at position -137 G/C and haplotype frequency may play a role in predisposition to GC.
Glu298Asp	eNOS	No association between the eNOS genotypes and GC risk was found.
rs11614913 T/C	pre-mir-196a2 T/C	Did not find any significant association between rs11614913 T/C polymorphism and GC risk
A7488G	IL-17F	IL-17F A7488G polymorphism of IL-17F gene is not directly assumed as a genetic risk factor in the predisposition to GC.
Pro12Ala	PPARγ	Pro12Ala PPARγ polymorphism is associated with GC and gastritis. Is a potential marker for genetic susceptibility to these two diseases in the presence of *H. pylori*
-964 A/G	IL-27	IL-27 (rs964 A/G) polymorphism gene is not directly involved as a genetic risk factor in the predisposition to *H. pylori*.
rs1053023	STAT3	STAT3 rs1053023 polymorphism is associated with the risk of GC.
G >A (rs4647603)	caspase 3	Results showed a relationship between increase in AG genotype and GC.
-609C >T	NQO1	NQO1 rs1800566 allelic and genotypic frequencies were not significantly different between the patients and controls.
-938 C >A	bcl2	Presence of AC genotype may decrease the risk of GC.
-712C >T	caspase 9	The results showed a relationship between increase in allele T and GC.
rs4647601: G> T 1263 A> G	caspase-3, caspase 9	It seems that screening of -1263 A> caspase 9 polymorphism could be a useful marker in personal sensitivity to GC
Asp299Gly	TLR-4	TLR-4 Asp299Gly SNP increases the expression levels of IL-6 and has an important role in development of pylori-associated gastritis.
rs1028181-513T/C	IL-19	It appears that a direct relationship exists between H. Pylori infection and C allele at rs1028181-513T/C position.

to the findings, the genetic polymorphisms in the immunity-associated genes related with the gastric cancer amongst the Iranian patients (Figure 1). Therefore, more large-scale functional investigations would be necessary for confirming the results.

Authors' contribution
AA, GF and MMS were the principal investigators of the study. ASB, AA, GF and MMS were included in preparing the concept and design. MMS, MB and AA revised the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. Authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest
The authors declare that they have no competing interests.

Ethical considerations
Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. This article does not contain any studies with human participants or animals performed by any of the authors.

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