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Influence of single nucleotide polymorphisms in *pri-miR-124-1* and *STAT3* genes on gastric cancer susceptibility

SM Mirnoori[a], SS Shahangian[a], Zivar Salehi[a], F Mashayekhi[a], S Talesh Sasani[a] and HS Saedi[b]

[a]Department of Biology, Faculty of Sciences, University of Guilan, Rasht, Iran; [b]Department of Radiation Oncology, Cancer Research Center, Guilan University of Medical Sciences (GUMS), Rasht, Iran

ABSTRACT

Introduction: MicroRNAs (miRNAs) are small ribonucleic acids that modulate the expression of downstream target genes. There is considerable evidence of their involvement in many malignancies, such as oesophageal and gastric. We hypothesised altered expressions of *pri-miR-124-1* rs531564 and *STAT3* rs1053023 polymorphisms in gastric cancer.

Materials and methods: Genomic DNA was extracted from peripheral blood of 250 patients with gastric cancer and 310 healthy individuals. The RFLP method was applied for determination of *pri-miR-124* polymorphism and the AS-PCR method for *STAT3* polymorphism.

Results: The distribution of rs531564 genotypes in cases and controls was different: the G allele carriers had a reduced gastric cancer risk (OR = 0.62; 95%CI = 0.49–0.80, $P = 0.0002$). Presence of the minor allele of *STAT3* (rs1053023) was linked with higher risk of gastric cancer (OR = 2.29; 95% CI = 1.79–2.93, $P < 0.0001$). Compared with the most frequent haplotype C-G [the SNP order was *pri-miR-124-1* (rs531564) and *STAT3* (rs1053023)] in controls, C-A haplotype was associated with a significantly increased risk of gastric cancer (OR = 2.28; 95%CI = 1.64–3.09, $P < 0.0001$).

Conclusion: There is a strong link between *pri-miR-124-1* rs531564 and *STAT3* rs1053023 and gastric cancer that may be pathogenic, and so worthy of further investigation.

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Introduction

Gastric cancer (GC) has the third highest mortality rates worldwide in both sexes, generally due to the poor understanding of its pathogenic mechanism and late diagnosis [1–4]. The intestinal-type gastric cancer is closely associated with certain environmental factors, including infection by *H. pylori*, lifestyle, and diet, whereas the diffuse type is predominantly related to genetic abnormalities [5]. Among genes involved in cancer initiation and progression, *STAT3* plays a key oncogenic role: STAT family members are involved in development, differentiation, proliferation, and cell homeostasis [6,7]. While cytoplasmic STATs are inactive under basal conditions, they can be activated by phosphorylation, inducing translocation to the nucleus, binding to DNA and regulation of target gene transcription [8,9]. In contrast with the transient activity of STAT3 in physiological conditions, it is constitutively active in a variety of cancers [10]. Moreover, STAT3 activation, as a consequence of *H. pylori* infection, leads to deregulation of tumorigenic genes in gastric carcinogenesis [11]. The initiation and progression of many cancers can be promoted by abnormal STAT3 signalling because it suppresses apoptosis or induces cell proliferation, angiogenesis, invasion and metastasis [12]. A high level of the active form of STAT3 is a hallmark of gastric cancer and is linked with adverse outcomes [13].

MicroRNAs (miRNAs) are small (~22 bp) nucleic acids that modulate the expression of downstream target genes, thereby regulating translation, and links between miRNA expression and multitude of human diseases have been reported [14]. *Pri-miR-124-1* binds to 3′UTR of STAT3 mRNA, and overexpression of results in suppression of STAT3 mRNA level and a decline in phosphorylated STAT3 [15]. Single nucleotide polymorphisms (SNPs) or mutations in miRNA gene sequences or their target genes may affect cancer risk and susceptibility [16,17]. Links between *pri-miR-124-1* rs531564 polymorphisms and the risk of malignancy, including oesophageal, colorectal and cervical cancer have been reported [18–22]. An rs1053023 SNP in the miR recognition element site of *STAT3* can modulate the risk of lymphoma and lung cancer [23–25]. We hypothesized that genetic variants in *pri-miR-124-1* (rs531564) and *STAT3* (rs1053023) are linked to gastric cancer.

Materials and methods

We recruited 250 unrelated individuals who underwent surgery for gastric cancer from the Razi Hospital, Rasht, Iran, from November 2014 to July 2017. Eligible cases were all newly diagnosed and histopathologically confirmed gastric adenocarcinoma

CONTACT Zivar Salehi geneticzs@yahoo.co.uk Department of Biology, Faculty of Sciences, University of Guilan, Rasht, Iran

and no prior history of the disease. Exclusion criteria were other cancer, secondary or recurrent gastric cancer, or radiotherapy, chemotherapy or immunotherapy prior to surgery. Patients' clinicopathological information such as tumour size, location and staging type was obtained. Blood samples were collected at diagnosis, before starting therapy. A total of 310 controls were frequency-matched for age with the patients and area of residence. Exclusion criteria for controls were history of personal or familial malignancy and other serious diseases. Informed consent was obtained from all participants. This study was approved by the local Research Ethics committee and performed in accordance with the declaration of Helsinki (1989).

SNPs rs531564 within the *pri-miR-124-1* and rs1053023 within 3′UTR of *STAT3* were selected based on their functionality using databases of the National Center of Biotechnology Information (http://www.ncbi.nlm.nih.gov/), the International Hap Map Project database (http://www.hapmap.org) and the Target Scan Human (http://www.targetscan.org). rs531564 and rs1053023 have a minor allele frequency (MAF) of 0.13 and 0.31, respectively.

Genomic DNA was extracted from peripheral blood into K_2EDTA using a Gpp extraction kit (Gene Pajohan, Iran). DNA was assessed for purity and concentration using absorbance via Nanodrop (Thermo Scientific, CA, USA), aiming for an A260/A280 ratio ≥ 1.8. The samples < 1.8 were purified using an ethanol precipitation protocol to guarantee DNA sample purity, and samples were stored at −20 °C.

The *pri-miR-124* rs531564 genotyping was performed by PCR-RFLP. The sequences of specific primers were designed based on relevant DNA sequences available in the NCBI GenBank database (http://www.ncbi.nlm.nih.gov/genbank) using Oligo-primer analysis software (Version 7.54, Molecular Biology Insights, USA). The primer sequences were 5′-ACACACAAGCACTCCGCAAT-3′ (Forward) and 5′-ATCCCTCTCCCCGCTGTCA-3′ (Reverse). Primers were synthesized by MWG-Biotech (Ebersberg, Germany). All PCR reactions were carried out by a 96-well mini PCR System Thermal cycler (BioRad, USA) in a final volume of 25 µl containing 200 ng of each primer, 5 ng genomic DNA, 1.5 mM $MgCl_2$, 200 µl dNTPs and 1.0 unit of Taq DNA Polymerase in the buffer provided by the manufacturer. The PCR reaction for *pri-miR-124* rs531564 was conducted at 94 °C for 5 min, and then in 35 cycles: 94 °C for 45 s, 59 °C for 40 s, 72 °C for 45 s and final incubation at 72 °C for 5 min. The PCR amplicon generated for *pri-miR-124* (543-bp) was digested by *BsmAI*, resulting in 425 and 118-bp products for homozygous major type, 543, 425, 118-bp for heterozygous (GC) and 543-bp for the homozygous minor type.

A polymorphism-spanning fragment of *STAT3* (rs1053023) was analysed by tetra-primers amplification refractory mutation system PCR (ARMS-PCR). Primer sequences were 5′-CTGAGCCCTGTTGTGGTCCA-3′ and 5′-CTGCCATGCTATCAGACGGTT-3′ for A allele; 5′-CTGAGCCCTGTTGTGGTCCG-3′ and 5′-TCCAGGCACCCCTTACCTCC-3′ for G allele. Two amplification reactions were necessary for each one of the subjects analysed one with the A allele primers and another with the G allele primers. The PCR cycling conditions were an initial denaturation at 94 °C for 5 min; 35 cycles of denaturation at 94 °C for 30 s, annealing at 59 °C for 30 s, and extension at 72 °C for 45 s; and a final extension at 72 °C for 2 min. All samples were genotyped successfully. To provide quality control, genotyping was performed without knowledge of the subjects' case/control status and a 20% random sample of gastric cancer and healthy control subjects were genotyped twice by different researchers and the results of the retesting were 100% concordant.

The OpenEpi software (www.OpenEpi.com) was used to calculate a required sample size. Our study had 80% power to detect the associations of *pri-miR-124*and *STAT3* variants with the risk of gastric cancer. Hardy-Weinberg equilibrium probability was determined by the chi-square test. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated to determine links between alleles or genotypes in cases and controls. We tested four genetic models including codominant, dominant, recessive and overdominant. Results were considered significant when $P < 0.05$. Analyses were conducted using the SPSS v.19.0 statistical software (SPSS, Chicago, IL, USA).

Results

Among the patients, 187 were male and 63 were female, whilst in the control group 236 were male and 74 were female ($P = 0.71$). Patient's mean (standard deviation) age was 62 (18.3) years, and controls were aged 60 (10.8) ($P = 0.21$). At diagnosis, 178 patients had stage III–IV disease, and 72 had stage I–II. A total of 185 patients had intestinal type and 66 had the diffuse type of tumour. Seventy-one tumours were in the cardiac region, 185 were the intestinal type of gastric cancer [26].

Genotype frequencies of *pri-miR-124-1* (rs531564) and *STAT3* (rs1053023) polymorphisms did not deviate from Hardy-Weinberg equilibrium in both patients and controls ($P = 0.06$, $P = 0.11$, $P = 0.06$, $P = 0.06$, respectively). The genotype and allele distributions of the *pri-miR-124-1* (rs531564) and *STAT3* (rs1053023) polymorphisms in gastric cancer patients and controls are shown in Table 1. There were marked differences in the *pri-miR-124-1* (rs531564) genotype frequencies in the codominant ($P = 0.0003$), dominant ($P = 0.0001$)

Table 1. Genotypic distribution of rs531564 and rs1053023 in cases and controls.

Polymorphic Site	Inheritance Model	Genotype	Cases $N = 250$	Controls $N = 310$	OR (95% CI)	P
pri-miR-124 (rs531564)	Codominant	CC	97 (38.8)	81 (26.1)	Ref	–
		CG	128 (51.2)	168 (54.2)	0.63 (0.43–0.92)	0.01
		GG	25 (10)	61 (19.7)	0.34 (0.19–0.59)	0.0001
	Dominant	CC	97 (38.8)	81 (26.1)	Ref	
		CG+GG	153 (61.2)	229 (73.9)	0.55 (0.38–0.79)	0.001
	Recessive	CC+CG	225 (90)	249 (80.3)	Ref	
		GG	25 (10)	61 (19.7)	0.45 (0.27–0.74)	0.001
	Overdominant	CC+GG	122 (48.8)	142 (45.8)	Ref	
		CG	128 (51.2)	168 (54.2)	0.88 (0.63–1.23)	0.48
STAT3 (rs1053023)	Codominant	GG	30 (12)	71 (22.9)	Ref	
		GA	94 (37.6)	171 (55.2)	1.30 (0.79–2.13)	0.29
		AA	126 (50.4)	68 (21.9)	4.38 (2.61–7.36)	<0.0001
	Dominant	GG	30 (12)	71 (22.9)	Ref	
		GA+AA	220 (88)	239 (77.1)	2.17 (1.36–3.46)	0.001
	Recessive	GG+GA	124 (49.6)	242 (78.1)	Ref	
		AA	126 (50.4)	68 (21.9)	3.61 (2.50–5.21)	<0.0001
	Overdominant	GG+AA	156 (62.4)	139 (44.8)	Ref	
		GA	94 (37.6)	171 (55.2)	0.48 (0.34–0.68)	<0.0001

Table 2. Haplotype analysis of *pri-miR-124-1* and *STAT3* polymorphic sites in GC cases and controls.

Alleles *pri-miR-124-1*	*STAT3*	Cases *n* (%)	Controls *n* (%)	OR (95% CI)	*P*
C	G	119 (23.8)	188 (30.3)	Ref	–
G	G	35 (7)	125 (20.2)	0.44 (0.28–0.68)	0.0003
C	A	203 (40.6)	142 (22.9)	2.28 (1.64–3.09)	<0.0001
G	A	143 (28.6)	165 (26.6)	1.36 (0.99–1.88)	0.049

and recessive ($P = 0.002$) models, but not in the overdominant model ($P = 0.498$), leading to significant ORs for the former three models. The C allele was more frequent in patients than in controls (patients vs. controls, 0.64 vs. 0.53). Thus the G allele confers protective effects on gastric cancer risk (OR = 0.62; 95% CI = 0.49–0.80, $P = 0.0002$).

There were also marked differences in the *STAT3* (rs1053023) genotype frequencies in the codominant, dominant, recessive and overdominant models (all $p \leq 0.001$), leading to significant ORs. A significant difference was observed when comparing the A and G allele frequencies (A vs. G allele: OR = 2.29; 95% CI = 1.79–2.93; $P < 0.0001$). Haplotype analysis to evaluate the joint effect of the two SNPs on GC susceptibility is shown in Table 2. Compared with the most frequent haplotype C-G (the SNP order was *pri-miR-124-1* (rs531564) and *STAT3* (rs105302)) in controls, the frequency of haplotype C-A was significantly higher in gastric cancer patients. In addition, the G-G haplotype has a protective effect on gastric cancer risk.

Discussion

Altered levels of miRNAs are present in a large number of malignancies [18–22,27,28]. Against this background we hypothesised a link between *pri-miR-124-1* rs531564 and *STAT3* rs1053023 polymorphisms and gastric cancer susceptibility. Results reveal that rs1053023 A allele in *STAT3* is linked with a significantly higher risk, whilst the *pri-miR-124-1* G allele confers protective effects on gastric cancer risk. Subsequent haplotype analysis shows that the haplotype C-A confers increased risk of gastric cancer. These findings support our hypothesis that the *pri-miR-124-1* rs531564 and *STAT3* rs1053023 may contribute to susceptibility to gastric cancer.

There is considerable literature on miR-124 and cancer. For example, miR-124 is downregulated in colorectal adenoma: the ectopic expression of miR-124 induced apoptosis and autophagy by regulating the PKM1/PKM2 ratio through the targeting of *PTB1* in colon cancer cells [29], and miR-124 expression is significantly lower in gastric cancer tissue samples when compared to the adjacent normal tissues [30]. In addition, miR-124 inhibited the epithelial-mesenchymal transition process by repressing the Snail2 expression in gastric cancer cells, suggesting that miR-124 acts as a tumour suppressor and so may be a target for gastric cancer treatment [30]. SNPs are the most common genetic variations which influence inter-individual predisposition to gastric carcinogenesis and prognosis. Qi et al. suggested that the GG genotype changes the formation of a ring-shaped structure compared with the CC genotype on the secondary structure of *pri-miR-124-1*. They also found that mature miR-124 expression in the GG homozygosity is higher than that in the CC homozygosity [31].

There are few studies describing the effect of *pri-miR-124-1* rs531564 polymorphism on risk of different diseases [18,31,32], but none have investigated the effect of *pri-miR-124-1* rs531564 on

gastric cancer susceptibility. In a study conducted by Zhang et al., a link between GG genotype of *pri-miR-124-1* rs531564 and decreased risk of Oesophageal Squamous Cell Carcinoma comparing with the CC/CG genotypes was demonstrated (P = 0.005; OR = 0.61, 95% CI = 0.43–0.86)[18]. Chuanyin et al. reported that the frequency of the rs531564G allele was higher in the cervical intraepithelial neoplasia and control groups than in the cervical cancer group (P = 0.019 and 0.017, respectively) [32]. MiR-124 suppresses tumour growth through targeting STAT3 in colorectal cancer, CD151 in breast cancer [33] and ERK in cutaneous squamous cell carcinoma [34]. *STAT3* encodes a protein that is constitutively activated in a variety of cancers, including gastric, and plays crucial roles in cancer cell proliferation, survival, metastasis and angiogenesis [35,36].

Our results provide the first evidence that *STAT3* rs1053023 is associated with an increased risk of gastric cancer. A study conducted by Butterbach et al. found a risk reduction of 28% among AG carriers for lymphoma [24]. However, Wang et al. found a similar distribution of *STAT3* genotypes in anti-tuberculosis drug-induced hepatitis cases and controls [37]. In a study performed on recurrent spontaneous miscarriage, Massaoudi et al. demonstrated the positive effect of *STAT3* rs1053023 on risk [38]. Between racial and ethnic groups, the frequencies of genetic polymorphisms vary. Our data add to others of miRNAs in gastric cancer: Pirooz et al. [39] reported altered *miRNA-491-5p*, whilst Yedegari et al. failed to link *miR-146a* to this disease [40]. In our study, the allele frequency of *STAT3* rs1053023 was 0.49 in 310 control subjects, consistent with that in Japanese (0.43) and African-American (0.38) populations, but lower than that of South Africans (0.50) in the SNP Database (http://www.ncbi.nlm.nih.gov/SNP). The discrepancies of these results could be explained by differences in small sample size, race/ethnicity, study design, heterogeneity of the cancer subtype as well as environmental backgrounds.

We acknowledge several limitations in the current study: First, the results obtained in this study should be verified with more subjects and in additional populations. Second, the samples were collected at a single institution. Third, genetic factors involved in the development of gastric cancer differ by ethnic group; therefore, replication studies of different racial groups would be beneficial. Finally, gastric cancer is a multifactorial disease, so genetic variants may not only exert primary effects, but also interact with other genes or environmental factors to contribute to its development. However, larger multicentre collaborative groups are needed to achieve a clearer understanding of the molecular events leading to gastric cancer.

This work represents an advance in biomedical science because it demonstrates a link between *pri-miR-124-1* rs531564 and *STAT3* rs1053023 polymorphisms and gastric cancer susceptibility.

Summary table

What is known about this subject

- High level of active form of STAT3 is a hallmark of gastric cancer and correlated with adverse outcomes.
- STAT3 is a target of miR-124.
- The effect of common *pri-miR-124-1*rs531564 polymorphism on the risk of several types of cancer had been investigated.

What this paper adds

- The G allele of *pri-miR-124-1*(rs531564) is protective of the risk of gastric cancer.
- The minor allele of *STAT3* (rs1053023) is associated with higher risk of gastric cancer.

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Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

ORCID

SS Shahangian http://orcid.org/0000-0001-9861-4702

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