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Case Control Study

Polymorphisms of microRNA target genes *IL12B*, *INSR*, *CCND1* and *IL10* in gastric cancer

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Abstract

AIM

To evaluate associations between miRNA target genes *IL12B*, *INSR*, *CCND1* and *IL10* polymorphisms and gastric cancer (GC) in European population.

METHODS

Gene polymorphisms were analyzed in 508 controls and 474 GC patients from 3 tertiary centers in Germany, Lithuania and Latvia. Controls were patients from the out-patient departments, who were referred for upper endoscopy because of dyspeptic symptoms and had no history of previous malignancy. Gastric cancer (GC) patients had histopathological verification of gastric adenocarcinoma. Genomic DNA was extracted using salting out method from peripheral blood mononuclear cells. *IL12B* T>G (rs1368439), *INSR* T>C (rs1051690), *CCND1* A>C (rs7177) and *IL10* T>C (rs3024498) SNPs were genotyped by the real-time polymerase chain reaction. Associations between gene polymorphism and GC were evaluated using multiple logistic regression analysis with adjustment for sex, age and country of birth.

RESULTS

We observed similar distribution of genotypes and allelic frequencies of all polymorphisms between GC patients and controls except of *INSR* rs1051690. The frequency of the T allele of *INSR* gene was significantly higher in GC patients than in controls (23.26% and 19.19% respectively, $P = 0.028$). CT genotype was also more prevalent in patients compared to control group (38.48% and 30.12% respectively, $P < 0.021$). Logistic regression analysis revealed that only one polymorphism (rs1051690 in *INSR* gene) was associated with increased risk of GC. Carriers of CT genotype had higher odds of GC when compared to CC genotype (OR = 1.45, 95%PI: 1.08-1.95, $P = 0.01$). Similar association was observed in a dominant model for *INSR* gene, where comparison of TT+CT vs CC genotypes showed an increased risk of GC (OR = 1.44, 95%PI: 1.08-1.90, $P = 0.01$). Other analyzed SNPs were not associated with the presence of GC.

CONCLUSION

INSR rs1051690 SNP is associated with increased risk of GC, while polymorphisms in *IL12B*, *CCND1* and *IL10* genes are not linked with the presence of GC.

Key words: Gastric cancer; miRNA; Target genes; Single-nucleotide polymorphisms

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Core tip: Several studies have evaluated an association between single-nucleotide polymorphisms (SNPs) and gastric cancer (GC) risk. Here we used novel approach. Using bioinformatical analysis tools, several SNPs were identified as potential target sites of microRNAs that

previously have been linked with gastric carcinogenesis. This study evaluated an association between SNPs in the *INSR* (rs1051690), *IL12B* (rs1368439), *CCND1* (rs7177), and *IL10* (rs3024498) genes and risk of GC in subjects of European descent. The study found that *INSR* rs1051690 SNP was associated with increased risk of GC, while polymorphisms in *IL12B*, *CCND1* and *IL10* genes showed no association with GC.

Petkevicius V, Salteniene V, Juzenas S, Wex T, Link A, Leja M, Steponaitiene R, Skieceviciene J, Kupcinskas L, Jonaitis L, Kiudelis G, Malfertheiner P, Kupcinskas J. Polymorphisms of microRNA target genes *IL12B*, *INSR*, *CCND1* and *IL10* in gastric cancer. *World J Gastroenterol* 2017; 23(19): 3480-3487 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i19/3480.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i19.3480>

INTRODUCTION

Gastric cancer (GC) is one of the most prevalent cancers across the globe. Despite decline in the incidence over the last century, GC remains the third leading cause of cancer-related mortality worldwide^[1,2]. Furthermore, an upward trend of GC incidence was observed in young patients in recent years^[3]. The incidence and mortality of GC vary widely across different countries. Based on the GLOBOCAN 2012 estimates, the highest incidence is in East Asia. High rates are also observed in Central and Eastern Europe, where age-standardized GC mortality rates per 100000 are 16.8 in men and 7.1 in women^[1] and prevalence of *H. pylori* infection remains burdensome^[4].

Both environmental and genetic factors play a role in etiology of GC; however, as in most cancers, pathogenetic mechanisms in GC are still not fully understood. Demographic and environmental risk factors for GC include older age, male sex, family history, tobacco smoking, *H. pylori* infection and obesity^[5]. In recent years, different studies, including genome-wide association studies, examined genetic risk factors for GC. A number of gene polymorphisms have been shown to be related to gastric carcinogenesis, but this field mandates further research^[6,7].

The discovery of microRNAs (miRNAs) has opened new opportunities for understanding of pathophysiology and molecular biology of GC^[8]. Small non-coding miRNAs molecules (approximately 18-25 nucleotides) regulate gene expression through sequence-specific pairing with the target mRNA and inhibition of its translation^[9]. Previous studies have revealed that certain single-nucleotide polymorphisms (SNPs) of miRNA encoding genes may alter miRNA expression and influence cancer development^[10,11]. Moreover, genetic variations within miRNA binding sites affect the miRNA-mRNA interaction. SNPs within a miRNA target can

reinforce, weaken or disrupt the binding with miRNAs and change the expression of mRNA targets^[12-14].

Target gene identification may help to reveal specific functions of individual miRNAs. This process is challenging because miRNAs may bind to multiple target mRNAs. In order to identify potential miRNA targets computational modeling and experimental approaches are applied^[15]. In this study, selection of SNPs was carried out using freely available online database for miRNA target gene prediction^[16]. Using this bioinformatical approach we selected four SNPs: *IL12B* (rs1368439), *INSR* (rs1051690), *CCND1* (rs7177) and *IL10* (rs3024498) as putative miRNA-binding sites. Selected SNPs within the above mentioned genes are potential target sites of miR-27, miR-146a, miR-223 and miR-107, that have been linked with gastric carcinogenesis in different studies^[8,17].

The aim of this study was to evaluate potential associations between gene polymorphisms of predicted miRNA target genes *IL12B* (rs1368439), *INSR* (rs1051690), *CCND1* (rs7177) and *IL10* (rs3024498) and the presence of GC in European population. To date, these genetic variations have not been evaluated in case-control studies of GC.

MATERIALS AND METHODS

Study subjects

Patients and controls were recruited during the years 2005-2013 at three gastroenterology centers in Germany (Department of Gastroenterology, Hepatology and Infectious Diseases, Otto-von-Guericke University, Magdeburg), Lithuania (Department of Gastroenterology, Lithuanian University of Health Sciences, Kaunas) and Latvia (Riga East University Hospital and Digestive Diseases Centre GASTRO, Riga). Controls were patients from the out-patient departments, who were referred for upper endoscopy because of dyspeptic symptoms and had no history of previous malignancy. GC patients had histopathological verification of gastric adenocarcinoma and were recruited from out-patient and stationary departments. The data from the most of the patients were in focus of our previous studies to genetic predisposition of GC^[18-20].

In total, 982 individuals were included in this study (508 controls and 474 GC). There were 206 subjects from Germany (104 controls and 102 GC), 285 subjects from Latvia (146 controls and 139 GC) and 491 subjects from Lithuania (258 controls and 233 GC). All patients were of European descent.

DNA extraction and genotyping

Genomic DNA from samples was extracted using salting out method from peripheral blood mononuclear cells and stored at -20 °C until analysis. *IL12B* T>G (rs1368439), *INSR* T>C (rs1051690), *CCND1* A>C (rs7177) and *IL10* T>C (rs3024498) SNPs were

genotyped by real time PCR (RT-PCR), using TaqMan® assays with a 7500 TM real-time cycler, in accordance with the manufacturer's instructions (Life Technologies, CA, United States). Dubious samples had repetitive genotyping analysis. Duplicate genotyping was performed in 5% of all samples with one hundred percent concordance rates.

Selection of putative miRNA target gene SNPs

In order to select the candidate SNPs falling within 3'-UTR of genes which are putative targets of frequently deregulated miRNAs in GC, the mirsnpscore database was used (<http://www.bigr.medisin.ntnu.no/mirsnpscore>). The database contains *in silico* predictions of SNP effects on miRNA-target gene regulation, which are measured by ΔS score. The higher the ΔS score, the higher the possibility that the miRNA-mRNA interaction is disrupted^[16]. The candidate SNPs had to meet the following criteria: a minor allele frequency (MAF) > 0.2, the ΔS value > 0.25 and the target gene had to be previously reported as associated with GC. The MAFs and positions of SNPs for Central European population (CEU) were retrieved from 1000 Genomes Browser [phase 3, dbSNP build 149 (Homo sapiens Annotation Release 105)]^[21]. The list of selected miRNA target gene polymorphisms is presented in Table 1.

Statistical analysis

Age is shown as means \pm SD. Mean values of age was compared using Student's *t*-test. Categorical data are presented as frequencies and comparisons were performed using the χ^2 test. Each polymorphism was tested to ensure the fitting with Hardy-Weinberg equilibrium with alpha threshold of 0.05. Associations between GC and gene polymorphisms were calculated using multiple logistic regression analysis and expressed as OR with 95%CI. The ORs were adjusted for sex, age and country of birth. The ORs and 95%CI were calculated for each genotype compared with the wild-type allele homozygous group. Recessive (variant homozygous genotypes vs heterozygotes for the variant and homozygotes for the wild-type allele) and dominant (homozygotes variant + heterozygotes versus homozygotes for the wild-type allele) models were also evaluated. The Bonferroni-corrected alpha level was set at 0.013 (0.05/4 SNPs).

The analysis was performed using freely available statistical program PLINK v.1.9 available at pngu.mgh.harvard.edu/~purcell/plink.

RESULTS

Characteristics of the study group

The characteristics of control ($n = 508$) and GC ($n = 474$) groups are presented in Table 2. Control subjects were significantly younger than GC patients ($P < 0.001$). Proportion of men was considerably higher in

Table 1 Selected target genes and their corresponding single-nucleotide polymorphisms

Chromosome	Target gene	miRNA	Delta S	SNP ID	Position	MAF
5	<i>IL12B</i>	miR-27	0.3249	rs1368439	15874204	0.202
19	<i>INSR</i>	miR-146a	0.2591	rs1051690	7116963	0.242
11	<i>CCND1</i>	miR-223	0.4614	rs7177	69466115	0.419
1	<i>IL10</i>	miR-107	0.7057	rs3024498	206941529	0.267

SNP ID: Single-nucleotide polymorphisms number; MAF: Minor allele frequency.

Table 2 Characteristics of gastric cancer patients and control subjects *n* (%)

	Controls (<i>n</i> = 508)	Gastric cancer patients (<i>n</i> = 474)	<i>P</i> value
Age (mean ± SD)	58.1 ± 17.4	62.5 ± 18.4	< 0.001 ¹
Gender			
Male	139 (27.4)	288 (60.8)	< 0.001 ²
Female	366 (72.0)	178 (37.5)	
Unknown	3 (0.6)	8 (1.7)	
Country of birth			
Latvia	146 (28.7)	139 (29.3)	0.866 ²
Lithuania	258 (50.8)	233 (49.2)	
Germany	104 (20.5)	102 (21.5)	

¹Student *t*-test; ²χ² test.

GC group than in control group, 60.8% and 27.4% respectively ($P < 0.001$). Individuals in both groups did not differ significantly by country of birth. In order to avoid the potential influence of gender, age and country of birth, these variables were included in further logistic regression analysis.

Hardy-Weinberg equilibrium

The distributions of all analyzed genotypes in the control group did not differ from those predicted by a Hardy-Weinberg equilibrium: $P = 0.013$ for *IL12B* (rs1368439), $P = 0.819$ for *INSR* (rs1051690), $P = 0.856$ for *CCND1* (rs7177) and $P = 0.412$ for *IL10* (rs3024498).

Association analysis of rs1368439, rs1051690, rs7177 and rs3024498 SNPs with gastric cancer

Genotype and allele distributions for analyzed gene polymorphisms are shown in Table 3. No significant differences in the frequencies of the *IL12B*, *CCND1* and *IL10* genotypes or alleles between control and GC groups were found. The rare G allele of *IL12B* gene had the lowest frequency (14.47% in controls and 15.30% in patients). C allele of *CCND1* gene was found in 44.18% of controls and 43.13% of GC patients, while C allele of *IL10* gene - in 28.04% and 25.53% respectively. Distribution of *INSR* genotypes and alleles differed between control and GC patients groups. The frequency of T allele was 19.19% in controls and 23.26% in GC patients ($P = 0.028$). Distribution of TT genotypes was similar in both groups, while CT genotype was more prevalent in patients than in controls (38.48% and 30.12% respectively, $P =$

0.021). Logistic regression analysis revealed that only one polymorphism (rs1051690 in *INSR* gene) was associated with increased risk of GC. Carriers of CT genotype had higher odds of GC when compared to CC genotype (OR = 1.45, 95%PI: 1.08-1.95, $P = 0.01$). A similar association was observed in a dominant model for *INSR* (rs1051690), where comparison of TT + CT vs CC genotypes showed an increased risk of GC ($P = 0.01$). A tendency for T allele vs C allele to be associated with higher risk of GC was observed; however, the difference did not reach the adjusted significance threshold (OR = 1.32, 95%PI: 1.04-1.67, $P = 0.02$). No associations with GC risk was found for other analyzed SNPs (Table 3).

DISCUSSION

This study evaluated the association between SNPs in the *INSR* (rs1051690), *IL12B* (rs1368439), *CCND1* (rs7177), and *IL10* (rs3024498) genes and risk of GC in subjects of European descent. These SNPs were selected as candidate miRNA-related genetic alterations that may change the expression of miRNAs linked to GC and potentially mediate carcinogenesis. The study found that *INSR* rs1051690 SNP was associated with increased risk of GC, while no link has been found for the polymorphisms in *IL12B*, *CCND1* and *IL10* genes and GC risks. To our best knowledge this is the first study which evaluated the effect of these SNPs for the development of GC.

The biological actions of insulin are mediated by *INSR* gene. de-Freitas-Junior *et al.*^[22] demonstrated that changes in the *INSR* gene can affect the insulin signaling pathway by modulating E-cadherin glycosylation and destabilization of cellular membranes that may have detrimental effects in gastric carcinogenesis. A recent study also identified *INSR* as new candidate gene for diffuse gastric cancer susceptibility^[23]. Landi *et al.*^[13] showed that alleles regulate differentially the amount of a reporter gene (luciferase) in an *in vitro* assay and may have a functional role in regulating the expression of *INSR* proteins. Several studies have described the role of miRNAs in the regulation of *INSR* gene in different cancers^[24,25]. In our study we selected rs1051690 of *INSR* gene which is a potential binding site for miR-146a^[16]. Previous case-control studies carried out in Czech Republic, Spain and Israel revealed an association between rs1051690 and colorectal cancer^[13,26,27]. The findings of our study are partly in line with the latter

Table 3 Genotype and allele frequencies in control and gastric cancer patients and odds ratio of gastric cancer by genotypes *n* (%)

Genotype	Controls (<i>n</i> = 508)	Gastric cancer patients (<i>n</i> = 474)	OR	95%CI	<i>P</i> value
<i>IL12B</i> (rs1368439)					
TT	366 (72.05)	338 (71.31)	1.00		
TG	137 (26.97)	127 (26.79)	0.87	0.63-1.18	0.39
GG	5 (0.98)	9 (1.90)	1.27	0.39-4.14	0.68
GG <i>vs</i> TG + TT			1.33	0.41-4.30	0.63
GG + TG <i>vs</i> TT			0.88	0.65-1.20	0.42
Allele T	869 (85.53)	803 (84.70)	1.00	0.83-1.45	0.63
Allele G	147 (14.47)	145 (15.30)	1.10		
<i>INSR</i> (1051690)					
CC	334 (65.75)	272 (57.51)	1.00		
CT	153 (30.12)	182 (38.48)	1.45	1.08-1.95	0.01
TT	21 (4.13)	19 (4.02)	1.30	0.66-2.60	0.44
TT <i>vs</i> CT + CC			1.15	0.58-2.30	0.70
TT + CT <i>vs</i> CC			1.44	1.08-1.90	0.01
Allele C	821 (80.81)	726 (76.74)	1.00		
Allele T	195 (19.19)	220 (23.26)	1.32	1.04-1.67	0.02
<i>CCND1</i> (rs7177)					
AA	160 (31.56)	159 (33.62)	1.00		
AC	245 (48.32)	220 (46.51)	0.92	0.68-1.26	0.63
CC	102 (20.12)	94 (19.87)	1.07	0.73-1.58	0.70
CC <i>vs</i> AC + AA			1.12	0.80-1.60	0.50
CC + AC <i>vs</i> AA			0.97	0.72-1.30	0.83
Allele A	565 (55.72)	538 (56.87)	1.00		
Allele C	449 (44.28)	408 (43.13)	1.02	0.84-1.24	0.81
<i>IL10</i> (rs3024498)					
TT	252 (50.30)	259 (54.87)	1.00		
TC	217 (43.31)	185 (39.19)	0.92	0.69-1.22	0.57
CC	32 (6.39)	28 (5.93)	1.05	0.58-1.87	0.88
CC <i>vs</i> TC + TT			1.08	0.29-1.61	0.78
CC + TC <i>vs</i> TT			0.94	0.71-1.23	0.64
Allele T	721 (71.96)	703 (74.47)	1.00		
Allele C	281 (28.04)	241 (25.53)	1.03	0.83-1.30	0.78

studies, suggesting that this SNP might mediate not only colorectal but also GC risks, pointing to a potential joint mechanism of gastrointestinal cancers. A study by Xiao *et al*^[28] showed that miR-146a was upregulated in 20 gastric cancer tissues compared with matched non-tumor adjacent tissues. Due to the design of the study we were not able to evaluate whether rs1051690 could mediate the expression of miR-146a and this remains to be evaluated in further studies.

Chronic inflammation plays a crucial role in GC development, thus multiple genes in inflammatory pathways may be associated with GC risk^[29]. To date, different gene polymorphism related to inflammatory pathways have been evaluated, with *IL-1B* and *IL-1RN* being the most widely studied ones^[18,30-34]. Computational analysis tools that we used in our study suggested two genes polymorphisms - *IL12B* (rs1368439) and *IL10* (rs3024498) - situated in inflammatory pathways, that might be the involved in miRNA-target gene interaction^[16]. The other studies evaluated some gene polymorphisms located in *IL12* and *IL10*; however, they were different from the ones selected for our study. *IL12B* encodes a subunit p40 of interleukin (IL) 12. Proinflammatory cytokine IL12 is expressed by activated macrophages and favors the differentiation of T helper 1 (Th1) cells^[35]. Th1 lymphocytes prevail over Th2 in *H. pylori* associated

chronic gastritis^[36]. *IL10* down-regulates the expression of Th1 cytokines and enhances B cell survival, proliferation, and antibody production^[37]. Our study did not find significant association between polymorphisms in *IL12B* or *IL10* genes with GC risk. Our results support the previous data to other populations, which analyzed associations between SNPs in genes regulating the inflammatory response and GC^[30-32,34].

CCND1 is an important regulator of the cell cycle. It plays essential role in the activation of G1/S transition, which increases cell proliferation and growth. Mutations, amplification and overexpression of this gene are observed frequently in a variety of tumors and may contribute to tumorigenesis^[38]. The study by Ma *et al*^[39] confirmed that high *CCND1* expression was related with poor prognosis in patients with resected gastric adenocarcinoma. A meta-analysis of associations between the most extensively studied *CCND1* polymorphism rs9344 and GC demonstrated negative results^[40]. In our study we did not find an association between *CCND1* (rs7177) SNP and the risk of GC. One study found no association between rs7177 and risk of head and neck cancer in a case control study^[41], but no data is available until now for GC.

Target site polymorphisms in gene may strengthen or weaken the miRNA-mRNA interaction and change expression of gene^[42]. This field still remains poorly

explored in different cancers including GC. The importance of miRNA related SNPs in gene regulation and the mechanism by which these SNPs can induce alteration in molecular pathways is largely unknown. Wang *et al.*^[43] suggested that rs4901706 SNP of *C14orf101* gene in the microRNA binding site might be used as a valuable biomarker when predicting GC risk. One other study showed that polymorphisms of the microRNA-binding sites in the 3' UTR region of integrin are associated with GC susceptibility (rs2675), tumor stage (rs2675, rs17664, and rs3809865), and lymphatic metastasis (rs17664) in Chinese Han population^[44]. In our previous studies we could not determine the link between *miR-27a*, *miR-146a*, *miR-196a-2*, *miR-492* and *miR-608* gene polymorphisms and the risk of gastric^[45] or colorectal cancers^[46].

Our study carries certain limitations that have to be taken into account. First of all, the selection of putative miRNA target genes and corresponding gene polymorphism is based on bioinformatical databases that may over- or underestimate real interaction effects. Future studies are needed to validate our findings in other cohorts and to investigate whether the gene variant affecting the insulin receptor (*INSR* gene) leads to changes in the expression level of the receptor. Since this is the first study on these SNPs in GC, direct comparison with the results of other studies is not possible yet. Nevertheless, overall our data provide important novel aspects on genetic susceptibility for GC.

The study showed that *INSR* rs1051690 SNP is associated with increased risk of GC. We did not find the association between polymorphisms in *IL12B*, *CCND1* and *IL10* genes and GC risks.

COMMENTS

Background

The discovery of microRNAs (miRNAs) has opened new opportunities for understanding of pathophysiology and molecular biology of gastric cancer (GC). MiRNAs regulate gene expression through sequence-specific pairing with the target messenger RNA (mRNA) and inhibition of its translation. Genetic variations within miRNA binding sites can affect the miRNA-mRNA interaction and change expression of gene. This study evaluated an association between single-nucleotide polymorphisms (SNPs) in the *INSR* (rs1051690), *IL12B* (rs1368439), *CCND1* (rs7177), and *IL10* (rs3024498) genes and risk of GC in subjects of European descent.

Research frontiers

Target site polymorphisms in gene may strengthen or weaken the miRNA-mRNA interaction. This field still remains poorly explored in different cancers including GC. The importance of miRNA related SNPs in gene regulation and the mechanism by which these SNPs can induce alteration in molecular pathways is largely unknown. Studied SNPs were selected as candidate miRNA-related genetic alterations that may change the expression of miRNAs linked to GC and potentially mediate carcinogenesis.

Innovations and breakthroughs

In this study, novel approach was applied. Using bioinformatical analysis tools, several SNPs were identified as potential target sites of microRNAs that previously have been linked with gastric carcinogenesis. The study found that *INSR* rs1051690 SNP was associated with increased risk of GC, while

polymorphisms in *IL12B*, *CCND1* and *IL10* genes showed no association to GC. Our data provide important novel aspects on SNPs of miRNA and their target gene interaction sites in GC.

Applications

Polymorphisms in microRNA binding site might be used as a valuable biomarker when predicting GC risk.

Peer-review

The authors investigated the association of selected polymorphisms with the risk of developing gastric cancer in European population. Their analyses were performed on relatively large population of patients. Overall, the manuscript presents the hypothesis and results well.

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