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Association of XRCC6 C1310G and LIG4 T9I polymorphisms of NHEJ DNA repair pathway with the risk of colorectal cancer in the Polish population

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ABSTRACT:

Introduction: Colorectal cancer is the second most common cancer worldwide. DNA double strand breaks (DSBs) are the most dangerous lesions which can lead to carcinogenesis. Nonhomologous end joining (NHEJ) is an important pathway that allows for recovering DNA by direct end joining. The XRCC6 and LIG4 genes encode respectively Ku70 protein and human ATP-dependent DNA ligase, which are the components of the NHEJ repair pathway. The aim of our study was to evaluate the influence of XRCC6 C1310G and LIG4 T9I gene polymorphisms on colorectal cancer risk in the Polish population.

Materials and method: Genotyping was performed using TaqMan probes based on the analysis of PCR products amplified in Real Time PCR. The research was carried out on the material obtained from 100 patients with colorectal cancer and 100 cancer-free individuals who were age- and sex-matched as a control group. The results were developed using the chi-square test and odds ratio (OR).

Results: Odd ratio analysis indicates reduced risk of colorectal cancer for LIG4 T9I polymorphism in heterozygous model C/T (OR = 0.2717 95% CI = 0.1247–0,5918) and homozygous model T/T (OR= 0.3593 95% CI = 0.1394–0.9266). A similar situation was observed for XRCC6 C1310G gene polymorphism - a heterozygous variant C/G (OR = 0.1181 95% CI = 0.0145–0.964) and homozygous variant G/G (OR = 0.0972 95% CI = 0.0097–0.9713) were connected with a decreased risk of colorectal cancer.

Conclusions: Our research revealed that XRCC6 C1310G and LIG4 T9I polymorphisms are associated with diminished risk of colorectal cancer. However, to confirm the obtained results, further investigations should be carried out.

KEYWORDS: Colorectal Neoplasms/genetics, DNA-Binding Proteins/genetics, Genetic Predisposition to Disease/genetics, Genotype, Polymorphism, Single Nucleotide

INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of cancer-related death in both men and women in Europe [1–3]. Furthermore, incidence and mortality rates show an increasing trend [4].

Approximately 80% of CRC are non-heritable sporadic cases that occur as a result of cell exposure to certain environmental conditions [5]. Several risk factors were found to have major impact on colorectal cancer development, namely: a diet low in fruit and vegetables, excessive consumption of red meat and saturated fat, alcohol abuse, sedentary lifestyle, tobacco smoking and obesity [5, 6].

At the molecular level, there are three main phenotypes of sporadic CRC: chromosomal instability (CIN); microsatellite instability (MSI) and CpG island methylator phenotype (CIMP) pathways [7]. The dominant phenotype is CIN (65–70% of all sporadic CRCs) which is characterized by different types of chromosomal aberrations (i.a. aneuploidy), sub-chromosomal genomic amplifications, and frequent loss of heterozygosity (LOH) [7, 8]. Genome stability is continuously disturbed due to DNA damage induced by environmental factors. DNA double-strand breaks (DSBs) are the most genotoxic form of DNA damage that contribute to the loss of genetic information through fragmentation, loss and/or rearrangement of chromosomes [9]. If cells accumulate critic amounts of DNA and the damage and repair pathways are unable to restore genome integrity, control mechanisms ensure induction of apoptosis in order to prevent passing genetic errors. In sporadic unfortunate events, the mechanism of program cell death activation fails which triggers tumorigenesis [10, 11]. The survival ability during DSB stress is maintained by two major mechanisms: homologous recombination repair (HRR) and nonhomologous end joining (NHEJ) [12]. HRR requires the presence of a region of homology as a template for re-synthesis of lost sequence, thus its activity is limited to the S-phase but the outcome is error-free. Since NHEJ allows for recovering DNA by direct end joining, it is more flexible and therefore dominant over HRR in adult mammalian cells, nonetheless it provides low-fidelity repair. Briefly, at the initial stage of NHEJ, heterodimer consists of two proteins, Ku70 and Ku80, stabilizes free ends of DSBs and allows for recruitment of another NHEJ components. Herein, DNA-dependent protein kinase (DNA-PKcs) is activated which stimulates, in phosphorylation-dependent manner, the Artemis protein to perform nucleolytic processing of DSB ends. In the final reaction Ligase IV–XRCC4 complex restores DNA continuity by direct ligation of both ends [13, 14]. Mutagenic character of NHEJ suggests its vital role in carcinogenesis. Sporadic cancer susceptibility is the resultant of an interplay between environmental factor and protective

mechanism such as NHEJ. Low penetrance genetic variation like single nucleotide polymorphism (SNP) is the major modulator of response efficacy. We address the question whether SNPs within crucial HNEJ players my affect colorectal cancer risk. The present paper aims to validate the role of two polymorphisms; (1) C1310G (rs2267437) of XRCC6 gene and (2) T9I (rs1805388) of LIG4 gene.

The XRCC6 gene is coding Ku70 protein that, as mentioned above, is responsible for recruitment and activation of DNA-protein kinase in the NHEJ pathway. The XRCC6 polymorphisms were shown before to modulate the risk of cancer development [15]. Some of these studies included rs2267437 [16] which revealed that certain rs2267437 genotypes increased the risk of breast cancer [17], gastric cancer [18] and lung cancer [19].

The LIG4 gene, located at 13q33.3, encodes human ATP-dependent DNA ligase necessary to reconstitute the integrity of DNA. Single nucleotide polymorphism (SNP) within the LIG4 gene resides in the coding region which results in threonine-to-isoleucine change at codon 9 (rs1805388) after replacement of one nucleotide with another. Available reports on XRCC6 and LIG4 polymorphisms are limited to screening of mostly Asian populations. Importantly, a significant correlation between our polymorphisms of interest and cancer susceptibility has been demonstrated, hence there is a need to investigate whether the same relations occur in the European population.

MATERIAL AND METHODS

Patients

The peripheral blood samples were obtained from 100 patients: 49 women and 51 men with colorectal cancer, confirmed by histopathological examination, hospitalized in Department of General and Colorectal Surgery WAM, Medical University of Lodz, Poland. The major inclusion criterion was the lack of cancer family history. The average age of patients was 65(±11.2) years . The TNM scale was applied to determine the tumor stage. The following results were obtained: 18 cases (18%) of stage I, 33 cases (33%) of stage II and 49 cases (49%) of stage III (Tab. I.). The control group included 100 cancer-free, age- and sex-matched controls. The controls included 62 women and 38 men, with an average age of 59(± 9.6) years (Tab. II.). The samples were collected at the Department of Clinical Chemistry and Biochemistry, Medical University of Lodz. The study was approved by the Bioethics Committee of the Medical University of Lodz and each patient gave his/her written consent. Tab. I. summarizes the structure of the CRC group.

Genotyping

Genomic DNA was isolated from blood samples with the use of QIAamp DNA Blood Mini Kit for isolation of high-molecular-weight DNA (Qiagen, Chatsworth, CA, USA).

Genotyping was performed using TaqMan probes based on the analysis of PCR products amplified in Real Time PCR. The reaction was set up according to the TaqMan technology manual. In general, 100 ng genomic DNA, TaqMan ® Genotyping Master Mix (Applied Biosystems™), and TaqMan probes (catalog no. 4351379) were mixed and subjected to PCR reaction performed in Agilent Stratagene device (model Mx3005P) under the following conditions: 95°C for 10 min of initial denaturation, followed by 55 cycles inlcuding 92°C for 15 s and 60°C for 1 min.

Statistical analysis

The Chi-square tests were employed to assessed whether the observed genotype distribution is in accordance with the Hardy-Weinberg equilibrium. For comparison of genotype/allele frequencies in both groups, odds ratio (OR) with 95 % confidence interval was calculated.

The research was carried out with the consent of the Bioethical Commission of the Medical University of Lodz, consent No. RNN / 113/18 / EC.

RESULTS

The genotype distribution and allelic frequency of the evaluated polymorphisms are listed in Tab. II. and Tab. III.

The Hardy-Weinberg (HW) chi-square analysis revealed that in the study group ($X2 = 65.87$; $P < 0.05$) and in the control group ($X2 = 49.02$; $P < 0.05$) genotype distribution of XRCC6 (rs2267437) gene polymorphism is not in the Hardy-Weinberg equilibrium. Genotype distribution of LIG4 (rs1805388 polymorphism showed no deviation from the Hardy-Weinberg equilibrium in the control group ($X2 = 0.53$; $P = 0.47$) as opposed to the CRC group ($X2 = 16.73$; $P = 0.000043$).

Association between XRCC6 (rs2267437) gene polymorphism and colorectal cancer

As Tab. II. summarizes, a strong relation between certain genotypes and CRC was found. In accordance with the calculated odd ratio values, the heterozygous variant C/G (OR = 0.1181 95% CI = 0.0145-0.964) and the homozygous variant G/G (OR = 0.0972 95% CI = 0.0097-0.9713) decrease the risk of CRC. Surprisingly, screening of rs2267437 revealed no major differences in allele frequencies between the CRC and control group.

Association between LIG4 (rs1805388) gene polymorphism and colorectal cancer

Tab. III. highlights rs1805388 genotyping results. We found the frequencies of the C and T alleles were respectively 46% and 54% in the study group and 56% and 44% in the control group whereas genotype distribution was 11% for CC, 70% for C/T and 19% for TT within the study group and 29% for CC, 53% for C/T and 18% for TT in the control group. The reduced CRC risk in LIG4 (rs1805388) polymorphism was demonstrated in the heterozygous model C/T (OR= 0.2717 95% CI= 0.1247-0,5918) and in the homozygous model T/T (OR= 0.3593 95% CI= 0.1394-0.9266).

Tab. IV. The effect of LIG4 polymorphism on progression of colorectal cancer. Comparison of noninvasive stage I cases with stages II and III.

Finally, we attempted to estimate the risk of cancer progression for particular genotypes/allele. For this purpose, we utilized the

Tab. I. Distribution of age, sex and clinical characteristics in the study group.

PATIENTS	AGE	GENDER		TNM CLASSIFICATION*									AJCC CLASSIFICATION		
No	Average	♀	♂	T				N			M		I° (T1-2N0)	II° (T3-4N0)	III° (T1-4N1-2)
				1	2	3	4	0	1	2	1	2			
100	65 ± 11.2	49	51	3	19	75	3	52	29	79	98	2	18	33	49

*T(1–4) size of tumor, N(0–2) degree of spread to regional lymph nodes, M(0–1) presence of metastasis.

Tab. II. Genotype and allelic frequency distribution of XRCC6 gene polymorphisms and the risk of CRC.

GENOTYPE/ALLELE	PATIENTS		CONTROL GROUP		OR (95% CI)	P
	N = 100		N = 100			
	number	frequency	number	frequency		
C/C	1	0,01	8	0,08	ref	
C/G	90	0,9	85	0,85	0.1181 (0.0145–0.964)	P = 0.02
G/G	9	0,09	7	0,07	0.0972 (0.0097–0.9713)	P = 0.03
allel C	92	0,46	101	0,51	ref	
allel G	108	0,54	99	0,49	0.835 (0.5638–1.2365)	P = 0.37

TNM cancer staging system to differentiate the group of patients in noninvasive first stage (I) and advanced second (II) and third stage (III) (Tab. I.). In computing strategy, we included stage I CRC subjects as control group to compare it statistically with stage II and III. For LIG4 (rs1805388) gene polymorphism comparison of I to II and III showed no statistical significance (Tab. IV.). The number of reference genotypes in the group with XRCC6 (rs2267437) gene polymorphism was insufficient to compare the data.

DISCUSSION

DNA double-strand breaks (DSBs) are rare but highly tumorigenic. One double-strand break of DNA is enough to change the structure of the entire chromosome and induce cell death [10, 9]. In our previous studies we found [20] the impact of HRR gene XRCC3 Thr241Met polymorphism on CRC risk and progression. In another two case-control studies we showed no CRC modulation for common RAD51 gene promoter 135 G/C polymorphism and elevated CRC risk for RAD51 heterozygous variant G/A at -4601 position [21, 22]. We also evaluated NHEJ gene polymorphism in patients with head and neck cancer. Walczak et al. observed a significant increase of DNA repair efficiency in cancer cells in comparison to lymphocytes. In the HTB-43 larynx cancer cell line, a 1.7-fold higher level of NHEJ was observed and in the SCC-25 tongue cancer cell line the level of NHEJ repair was 1.49-fold higher [23]. Since we explored the most common HRR gene SNPs in CRC subjects, we are now focused in our current research on NHEJ gene SNPs to learn more about their role in modulating CRC susceptibility.

XRCC6 (rs2267437) polymorphism has been investigated in various malignancies. Our study revealed an association between polymorphism of XRCC6 gene with a decreased probability of CRC occurrence in the Polish population. The Swedish population case-control study showed that XRCC6 (rs2267437) is not associated with CRC risk. Hernández et al. found a correlation between XRCC6 (rs2267437) polymorphism and a higher risk of prostate cancer in patients with the G/G genotype [24]. In their meta-analysis, Jia et al. found the rs2267437 polymorphism to be associated with a vital increase of breast cancer risk for homozygous G/G (OR = 1.79 95% CI = 1.26–2.56) and renal cancer for heterozygous C/G (OR = 1.36 95% CI = 1.10–1.68). It might also influence the increase of the cancer risk in the Asian population, especially in case of homozygotus variant G/G (OR = 1.38 95% CI = 1.10–1.73) [25]. Asian population-based studies conducted by Haito et al. reported that the homozygotus variant G/G is significantly associated with increased breast cancer risk (OR = 1.79 95% CI = 1.25–2.56). Hong et al. revealed that the XRCC6 (rs2267437) polymorphism was a risk factor of cancer among Asians, but not among Europeans [26]. Singh et al. indicate that small-cell lung carcinoma (SCLC) patients with XRCC6 61C>G polymorphism have a poor prognosis. Non-smokers with this polymorphism were protected against lung cancer [27]. The majority of publications confirm the connection between XRCC6 (rs2267437) polymorphism and increased risk of cancer development. However, the results of our studies showed a reduced risk of developing colorectal cancer in patients with this polymorphism.

To date, no research has been published on LIG 4 (rs1805388) gene polymorphism and its impact on the risk of CRC. We found the heterozygous variant 9C/T is prevalent in CRC cases, whereas the frequency of alleles remains comparable in CRC cases and in control subjects. Several studies have shown that certain variants of rs1805388 influence the risk of breast cancer, lung cancer, ovarian cancer and many others. Interestingly, they present conflicting results [28, 29]. Zhao et al. [30] presented research which revealed a significant association of heterozygous model C/T (OR=1.62 95% CI = 1.20–2.18) and homozygous model T/T (OR = 3.27 95% CI = 1.87– 3.27) with increased risk of glioma in the Chinese population.

The same trend has been noticed in two other studies where rs1805388 polymorphism appearance contributed to an increased incidence of glioma, non-small cell lung carcinoma (NSCLC) [31] and lung cancer [32].

No general statement can be made on the role of (rs1805388) in the context of cancer risk, as other publications present opposite results. The above mentioned studies concerning LIG4 (rs1805388) suggest that the investigated variant of this polymorphism may be population-specific. For instance, screening of the Caucasian

Tab. III. Genotype and allelic frequency distribution of LIG4 gene polymorphisms and the risk of CRC.

GENOTYPE/ALLELE	PATIENTS		CONTROL GROUP		OR (95% CI)	P
	N = 100		N = 100			
	number	frequency	number	frequency		
C/C	11	0,11	29	0,29	ref	
C/T	70	0,70	53	0,53	0.2717 (0.1247–0,5918)	P < 0.01
T/T	19	0,19	18	0,18	0.3593 (0.1394–0.9266)	P = 0.03
allel C	92	0,46	111	0,56	ref	
allel T	108	0,54	89	0,44	0.683 (0.4607–1.0127)	P = 0.06

Tab. IV. The effect of LIG4 polymorphism on progression of colorectal cancer. Comparison of noninvasive stage I cases with stages II and III.

GENOTYPE/ ALLELE	I° (T1-2N0)		II° (T3-4N0)		III° (T1-4N1-2)		II° VS I°		III° VS I°	
	number	frequency	number	frequency	number	frequency	OR (95% CI)	P	OR(95% CI)	p
C/C	2	0.11	3	0.09	6	0.12	ref	-	ref	-
C/T	10	0,56	24	0.73	36	0.73	1.6 (0.23 – 11.08)	0.49	1.2 (0.21 – 6.88)	0.58
T/T	6	0.33	6	0.18	7	0.14	0.67 (0.08 – 5.54)	0.56	0.39 (0.06 – 2.7)	0.31
allel C	14	0,39	30	0.45	48	0.49	ref	-	ref	-
allel T	22	0,61	36	0.54	50	0.51	0.76 (0.33 – 1.75)	0.52	0.66 (0.3 – 1.44)	0.3

population for LIG4 (rs1805388) polymorphism suggested an increased cancer risk [28], whereas another study provided evidence for reduced risk of multiple myeloma among Europeans with the studied polymorphism. [33] Shisc et al. [34] in their review pointed to miscellaneous possibilities of NHEJ activity, which can result in an increased or reduced cancer risk. The NHEJ activity may explain inconsistency in the results of the above mentioned studies.

CONCLUSIONS

Our study, being an analysis of 100 patients and 100 controls, revealed an association between the polymorphism of XRCC6 and LIG4 gene, and the decreased risk of CRC occurrence in the Polish population. Although the results are promising, our research has some limitations like a small number of patients or deviations from HW. Our research has not included studies of the exact biological mechanism of XRCC6 rs2267437 and LIG4 rs1805388 polymorphism influence on the development of CRC. Further investigations are essential to elucidate this process. The evaluation of the effectiveness of DNA repair with comet assay or cell culture models, in the context of the analyzed polymorphism is our goal in further research. The results of our research could have been affected by certain factors. First, it was a hospital-based case study, therefore obtaining samples from one center could significantly disrupt the randomization of groups. Additionally, polymorphisms not included in our study could have influenced the results. Therefore, our findings need to be extended by other independent studies with a larger group of respondents.

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