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TaqI polymorphism of *VDR* gene in colorectal cancer and Crohn's disease patients

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To study the relation of TaqI polymorphism of VDR gene with age, sex and the disease phenotype in patients with colorectal cancer (CRC) and Crohn's disease (CD) from western regions of Ukraine. Fifty six patients with CRC, 46 patients with CD and 65 control individuals were included in this research. Assessment of TaqI polymorphism was performed using PCR-RFLP method. The genotype-phenotype association for this polymorphism was analyzed. The frequency of tt genotype in patients with CRC is 0.107 and among the control group is 0.138, OR (95% CI 0.248-2.246). The ratio of genotypes TT:Tt:tt in patients with CRC and in control was 37.5%:51.8%:10.7% and 44.6%:41.6%:13.8%. In men with Tt genotype the average age of CRC onset was 57.6 ± 3.6 years, in women with TT genotypethe mean age of the disease onset was 54.5 ± 4.5 years. The frequency of tt genotype in the patients with CD is 0.217 and among the control group is 0.138, OR (95% CI 0.640–4.666). The Tt genotype was detected in a half of patients with CD and TT genotype was found more frequently in control.The ratio of genotypes in men and women with CD was 38.0%:38.0%:24.0% and 20.0%:60.0%:20.0%. Among patients with CD, who underwent surgery, 33.3% individuals were carriers of tt genotype. It was confirmed no statistically significant difference in the allele frequencies and genotype distributions of Taq1 mutation in patients with CRC and CD in comparison to control group. The ratio of men and women with Tt genotype by groups of B1-B3 forms of CD behaviour according to the Montreal classification is differs, in particular, women with Tt genotype are four times more likely to have the B1 form. A study of Taq1 mutation might contribute to the identification of the groups that are at the greatest risk of severe form of CD.
Key words: VDR gene TaqI polymorphism; genotypes distribution; colorectal cancer; Crohn`s disease; sex; age at the diseases onset; disease phenotype.

INTRODUCTION

The third most common cancer worldwide, with an estimated incidence of more than 1.2 million cases globally, is colorectal cancer (CRC) represent one of the most frequent malignancies within the gastrointestinal tract [1]. CRC remains a major cause of cancer mortality at an estimated 1.2 million new cancer cases and 608,700 deaths worldwide each year [2]. The highest rates of CRC have been reported in Southern Europe (25.4% for males and 15.9% for females) whereas the lowest rates are in South-Central Asia (3% for males and 2% for females) [3]. According to the data of National Cancer Registry in Ukraine (2022-2023) the crude incidence rate of colon/rectum, anus cancer was is 25.1/24.3 in men and 22.7/17.3 in women and crude mortality rate was 12.5/12.7 among men and 11/8.1 among women per 100000 individuals, accordingly [4]. Progress in reducing CRC death rates can be accelerated by improving access to screening and early diagnosis in all populations. CRC is a multifactorial disease, involving the complex interactions between genetic and environmental factors. However, the underlying pathogenesis of CRC remains poorly understood. A large

number of candidate genes responsible for the genesis of CRC have been identified [5, 6].

Recent studies have reported an association between CRC risk and vitamin D receptor (VDR) TaqI polymorphism however, the results are controversial. The VDR gene has several polymorphic sites, and 4 polymorphisms recognized by restriction enzymes are reported: ApaI, BsmI and TaqI, which are found at the 3' end of the VDR gene, exon 8, and FokI, which is found at the 5' end of the VDR gene, exon 2 [7]. Significant associations with VDR polymorphisms have been reported for prostate (Fok1, Bsm1, Taq1), colon-rectum (Fok1, Bsm1, Taq1) and skin cancer (Fok1, Bsm1, Taq1) up to June 2012 on the basis of 79 independent studies for a total of 52427 cases and 62225 controls [8]. Vitamin D status is negatively associated with the CRC incidence and recurrence, and lower serum vitamin D levels increased CRC risk [9, 10]. VDR, an intracellular hormone receptor, is expressed in normal colon epithelial cells and other colon cells at various levels [11]. Vitamin D has a protective effect against several cancers, including CRC. This effect is modulated by the vitamin D receptor (VDR) and its ligand. The VDR ligand (1,25 $(OH)_2D_3$) inhibits proliferation and maintain the differentiation of colon carcinoma cell [12]. Some studies have shown that the VDR gene is markedly downregulated in the CRC progression, suggesting that the VDR expression is negatively correlated with the cancer progression and it has been proposed that high VDR expression could be a good prognostic marker for CRC [11-13]. The data of 5 studies on TaqI polymorphism confirmed the deviation from Hardy-Weinberg equilibrium (HWE) [14-17]. In meta-analysis a total of 47 reports predicted a possible genetic association, and 45 of which were used to comprehensively estimate the relationship between VDR polymorphisms (FokI, BsmI, TaqI, ApaI, Cdx-2, and Tru9I) and CRC risk [13]. VDR polymorphisms may influence both the risk of cancer occurrence and prognosis. Polymorphisms in VDR have been studied extensively in studies of CRC.

Several gastrointestinal cancers, especially of CRC, are strongly linked to chronic inflammatory conditions. The risk for CRC may even increase according to the degree of underlying inflammation as is the case of long-standing inflammatory bowel diseases (IBD) [18]. Pro-inflammatory stimulus may lead to continuous cell proliferation, angiogenesis and eventually DNA damage. Vitamin D is a hormone is responsible for the balance of calcium between mineralized bone and the blood. It inhibits pro-inflammatory factors, and the production of cytokines [19]. Vitamin D plays a role in the development of IBD – ulcerative colitis and Crohn's disease (CD) because its effects are mediated by steroid receptors regulating the transcription of multiple cellular genes [20]. The vitamin D receptor (VDR) gene is expressed by macrophages, monocytes, B and T cells, and dendritic cells. Vitamin D can play a role in the CD pathogenesis, binding to VDR triggers a cascade of intracellular molecular signaling that regulates the transcription of multiple genes [21]. There are numerous evidences regarding the relationship between gut dysbiosis and vitamin D metabolism, while suboptimal levels of this vitamin have been linked to increased clinical disease relapse rates, inadequate response to drugs, as well as decreased quality of life in patients with CD [22].

To study the relation of TaqI polymorphism of VDR gene with age, sex characteristics and the disease phenotype in the patients with CD, CRC, control group from the western regions of Ukraine.

METHODS

A molecular genetic study of the polymorphic TaqI locus of the vitamin D3 – VDR receptor gene was carried out in the patients with CRC, CD and in the control group, residents of the western regions of Ukraine. Fifty six patients with CRC, 46 patients with CD, and 65 age and sex matched healthy controls were enrolled. These patients were referred to a

Proctology Department of Lviv Regional Hospital during eight-year period (2015-2022). Written informed consent was obtained from all patients. All patients included in the study are Caucasian, and we collected demographic and clinical data from them, including age, sex and disease behavior. Genomic DNA samples were extracted from the peripheral blood cells and amplified with polymerase chain reaction (PCR). TaqI polymorphism (rs721236) was genotyped (rs721236) using the PCR restriction on fragment length polymorphism (PCR-RFLP) based analysis. The primers were used shown on Table 1.

Table 1. Primers sequence of TaqI SNP

SNP	Primers (5'-3')	Bases variation	Annealing temperature (°C)
rs731236	Sense: CAG AGC ATF FAC AGG GAG CAA		
(TaqI)	Antisense: GCA ACT CCT CAT GGC TGA GGT CT	T > C	58

Amplification was performed using the following thermocycling conditions: 95°C for 5 min (initial denaturation), followed by 35 cycles of denaturation at 94°C for 30 sec, then by 65°C for 30 sec, and succeeded by 72°C for 30 sec for oligonucleotide annealing. The final extension occurred at 72°C for 10 min. Following amplification, PCR products were digested with Taq I (2 U at 65°C) and electrophoresed on 2% agarose gels stained with ethidium bromide; giving rise to TT (490, 245 bp), Tt (490, 290, 245, 205 bp) or tt (290, 245, 205 bp) for Taq I polymorphism (dominant alleles denoting absence of restriction site). Electrophoresis was performed for 20-40 min at a voltage of 100 V and the electrophoresis was scanned on an ultraviolet transilluminator. The received signals were compared with length markers and control samples, and based on this, the sizes of the received fragments were determined.

Case–control studies were designed to investigate the association between VDR gene TaqI polymorphism at codon 352 at codon 352 of exon 8 and diseases. Sufficient data were available to calculate the odds ratio (OR) and 95% confidence interval (CI). HWE adherence to the genotypic frequency in controls was analyzed by the chi-square (χ^2) test with a degree of freedom. The strength of the associations between the VDR polymorphism and CRC and CD risk was appraised by the OR and relevant 95% CI under genetic models. Statistical significance was at $P < 0.05$.

RESULTS AND DISSCUSION

There are numerous evidences regarding the association between CRC risk, CD and TaqI polymorphism however, the results are controversial. In the present study the genotypes distribution and alleles frequency analysis of TaqI polymorphism was carried out in patients with CRC, CD and healthy controls. The results of the analysis of the genotypes and alleles frequency of the TaqI polymorphic locus in the patients with CRC and in the control group individuals without oncologic diseases in anamnesis are shown in Table 2.

The ratio of genotypes TT:Tt:tt in patients with CRC and in control group is as follows: 37.5%:51.8%:10,7% and 44.6%:41.6%:13.8%, accordingly ($P > 0.05$). In the patients with CRC Tt genotype was detected in 29/56 (51.8%) patients, and in the control group the TT genotype was occured in 29/65(44.6%) individuals. The ratio of genotypes in the controls depending of sex is as follows: in men – 35.5%:54.7%:9.8%, in women – 52.9%:29.5%:17.6% ($P < 0.001$) and in the patients with CRC is 34.5%:55.1%:10.3% in man and 40.7%:48.1%:11.1% in women ($P > 0.05$). The mean age of CRC onset depending of genotypes of Taq I locus was investigated. The results of the study are shown in Table 3.

In men with Tt genotype the average age of CRC onset was 57.6 ± 3.6 years, in women with TT genotype the mean age of the disease

Table 2. The genotypes distribution and alleles frequency of the TaqI locus of the VDR gene in patients with CRC and individuals of the control group

Taq I locus	Patients with CRC (56 individuals, 112 alleles)			Control group (65 individuals, 130 alleles)			χ^2	P	OR (95% CI)
	N	%	HWE	n	%	HWE			
Alleles									
T	71	0.634	–	85	0.654	–	0.002	> 0.05	[0.541; 1.554]
t	41	0.366	–	45	0.346	–			[0.644; 1.849]
Genotypes									
TT	21	0.375	0.400	29	0.446	0.428	0.011	> 0.05	[0.359; 1.544]
Tt	29	0.518	0.464	27	0.416	0.452	0.025	> 0.05	[0.736; 3.105]
tt	6	0.107	0.134	9	0.138	0.120	0.007	>0.05	[0.248; 2.246]

onset was 54.5 ± 4.5 years. The proportion of patients with CRC with positive/negative familial anamnesis depending on genotypes of Taq I locus was investigated. The ratio of genotypes in patients with positive CRC anamnesis and without familial anamnesis of cancer is as follows: (22.2%:66.6%:11.1%):(44.7%:44.7%:10.5%), accordingly (P > 0.05).

The analysis of genotypes and alleles frequency of polymorphic TaqI locus in patients with CD was carried out. The results of this study are shown in Table 4.

Thus, statistically significant differences in the frequencies of genotypes and alleles in the experimental and control groups were not confirmed. The Tt genotype is detected in a half of the patients with CD and TT genotype was found more frequently in the control group. The tt genotype was found in 10/46(21.7%) patients and only in 9/65 (13.8%) individuals of the control. The ratio of genotypes in the patients with CD and in the control group is following: 28.3%:50.0%:21.7% and 44.6%:41.6%:13.8% (P > 0.05).

The ratio of patients with CD with different genotypes of Taq I locus depending on sex is shown in Table 5.

The ratio of genotypes in men and women with CD is following: 38.0%:38.0%:24.0% and 20.0%:60.0%:20.0%, P<0.001. It was found that the distribution series of men and women with CD have a statistically significant difference. In some literature data, the relation of the tt genotype was noted in patients with the disease only among men from Asian countries [21], while other authors found an association only among male Europeans [23].

The average age of CD onset in patients with different genotypes is presented in Table 6.

The youngest average age of CD diagnosis

Table 3. The mean age of patients with CRC depending of genotypes of Taq I locus

Gender	Mean age (years)			
	TT	Tt	tt	total
Male	55.5 ± 2.8 (n = 10)	57.6 ± 3.6 (n = 16)	52.0 ± 12.5 (n=3)	56.3 ± 2.4 (n1 = 29)
Female	54.5 ± 4.5 (n = 11)	49.2 ± 3.8 (n = 13)	50.3 ± 6.2 (n = 3)	51.5 ± 2.6 (n1 = 27)
Total	55.0 ± 2.6 (n = 21)	53.8 ± 2.6 (n = 29)	51.2 ± 6.3 (n = 6)	54.0 ± 1.8 (n = 56)

Table 4. The genotypes distribution and alleles frequency of the Taq I locus of VDR gene in patients with CD and in the control group

Taq I locus	Patients with CD (46 individuals, 92 alleles)			Control group (65 individuals, 130 alleles)			χ^2	P	OR (95% CI)
	n	%	HWE	n	%	HWE			
Alleles									
T	49	0.533	–	85	0.654	–	0.06	>0.05	[0.349; 1.042]
t	43	0.467	–	45	0.346	–			[0.96; 2.862]
Genotypes									
TT	13	0.283	0.284	29	0.446	0.428	0.06	>0.05	[0.218;1.096]
Tt	23	0.500	0.496	27	0.416	0.452	0.02	>0.05	[0.658;3.009]
tt	10	0.217	0.220	9	0.138	0.120	0.05	>0.05	[0.64; 4.666]

was found in women and men with tt genotype, and the highest age was identified in men with TT genotype.

Surgical interventions caused of CD required 27/46 (58.7%) of all the CD patients. Among those who underwent surgery 9/27 (33.3%) patients were carriers tt genotype. The proportion of patients requiring surgical interventions for CD with different genotypes of Taq I locus is shown in the Figure.

Table 5. The ratio of male and female patients with CD depending of genotypes of Taq I locus

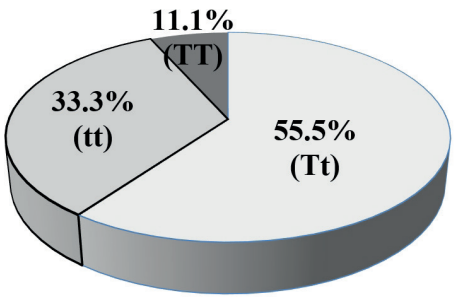
Sex	Genotypes		
	TT	Tt	tt
Male (n1 = 21)	8/21(38.0%)	8/21(38.0%)	5/21(24.0%)
Female (n1 = 25)	5/20(20.0%)	15/20(60.0%)	5/20(20.0%)

CRC developed in six patients (5 males:1 female) with CD. Half of these patients had TT genotype and 1/6 (16.7%) had tt genotype. The mean age of CRC onset was 66.2 ± 2.6 years in these patients.

The Montreal classification organizes CD into following subtypes of disease behavior: non-stricturing – B1 and non-penetrating, stricturing – B2, penetrating – B3, and peri-anal disease – B3P [24]. Among the subtypes of CD, age at onset and pathological behaviour (including development of penetrating or stricturing lesions) have recently been considered as the most relevant and potentially genetically

Table 6. The mean age of patients with CD depending of genotypes of Taq I locus and gender

Gender	Mean age (in years)			
	TT	Tt	tt	total
Male (n1 = 21)	42.0±4.7 n=8	39.9±5.7 n=8	23.4±6.1 n=5	36.8±3.4 n=21
Female (n1 = 25)	35.4±9.4 n=5	33.3±8.6 n=15	22.8±3.2 n=5	31.6±3.1 n=25
Total (n = 46)	40.1 ±4.5 (n1=13)	38.0± 3.2 (n2=23)	23.1 ±3.1 (n3=10)	34.0±2.3 (n4=46)



The proportion of the patients requiring surgical interventions for CD with different genotypes of Taq I locus

determined. The development of penetrating lesions could be a consequence of the severity of the inflammatory reaction at the mucosal level [25]. The proportion of patients with different behavior of clinical course of CD according to the Montreal classification depending on genotypes of Taq I locus is shown in Table 7.

The ratio of men and women with Tt genotype by groups of B1-B3 forms of CD behaviour according to the Montreal classification is differs (P = 0.01), in particular, women with Tt genotype are four times more likely to have the (B1) form (P = 0.057). The penetrating form (B3) was detected in 37.0% patients among them 70% were carriers of tt genotype. The data of some authors confirmed that the tt genotype was more often detected in patients with CD with fistulas or with a stenotic form of the disease [26]. Disease phenotypes carry important prognostic information, such as risk for surgery and other complications, and are used to guide treatment for patients with CD.

CONCLUSIONS

Thus, the frequencies of alleles and genotypes in patients with CRC and control group are comparable. The ratio of genotypes TT:Tt:tt in patients with CRC and in control group is as follows: 37.5%:51.8%:10.7% and 44.6%:41.6%:13.8%, accordingly (P > 0.05). In men with Tt genotype the average age of CRC onset was 57.6 ± 3.6 years, in women with TT genotype the mean age of the disease onset was 54.5 ± 4.5 years. Statistically significant differences in the frequencies of genotypes and alleles in the CD patients and control groups were not confirmed. The Tt genotype is detected in a half of the patients with CD and TT genotype was found more frequently in the control group. The ratio of genotypes in men and women with CD is following: 38.0%:38.0%:24.0% and 20.0%:60.0%:20.0%, P < 0.001, consequently it was found that the distribution series of men and women with CD have a statistically significant difference. Surgical interventions caused of CD required 58.7% of all CD patients. Among those who underwent surgery 33.3% patients were carriers tt genotype. The ratio of men and women with Tt genotype by groups of B1-B3 forms of *CD* behaviour

Table 7. The proportion of patients with different behavior of clinical course of CD according to the Montreal classification depending on genotypes of Taq I locus and gender

Clinical course of CD according to the Monreal classification	Genotypes			
	TT males:females (%)	Tt males:females (%)	tt males:females (%)	Total (%)
B1	5/13 (38.5%) (3m:2f) 60.0%:40.2%	10/23 (43.5%) (2m:8f) 20.0%:80.0%	1/10 (10.0%) (0m:1f) 0 /100%	16/46(34.8%) (5m:11f) 31.3%:68.8%
B2	5/13 (38.5%) (2m:3f) 40.0%:60.0%	6/23 (26.1%) (4m:2f) 66.7.1%:33.3%	2/10 (20.0%) (1m:1f) 50.0%:50.0%	13/46 (28.2%) (7m:6f) 53.8%:46.2%
B3 (including B3p)	3/13 (23.0%) (3m:0f) 100%:0	7/23 (30.4%) (2m:5f) 28.6%:71.4%	7/10 (70.0%) (4m:3f) 57.1%:42.9%	17/46 (37.0%) (9m:8f) 52.9%:47.1%

according to the Montreal classification is differs (P = 0.01), in particular, women with Tt genotype are four times more likely to have the (B1) form (P = 0.057). The penetrating form (B3) was detected in 37.0% patients. A study of Taq1 polimorphism might contribute to the identification of the groups that are at the greatest risk of severe form of CD.

The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of co-authors of the article.

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ПОЛІМОРФІЗМ TAQI ГЕНА *VDR* У ПАЦІЄНТІВ ІЗ КОЛОРЕКТАЛЬНИМ РАКОМ ТА ХВОРОБОЮ КРОНА

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Мета дослідження – визначити зв'язок TaqI поліморфізму гена *VDR* зі статево-віковими ознаками і фенотипом захворювання в пацієнтів із хворобою Крона (ХК; n = 46), колоректальним раком (КРР; n = 56) та в осіб контрольної групи (n = 65) західних областей України. Оцінку поліморфізму TaqI проводили методом ПЛР-ПДРФ. Було проаналізовано асоціацію генотип-фенотип для цього поліморфізму. Частота генотипу tt у пацієнтів із КРР становила 0,107, а в контрольній групі – 0,138, ВШ (95% CI 0,248–2,246). Співвідношення генотипів TT:Tt:tt у хворих на КРР та у контрольній групі: 37,5%:51,8%:10,7% та 44,6%:41,6%:13,8%. У чоловіків з генотипом Tt середній вік початку захворювання становив 57,6 ± 3,6 року, у жінок з генотипом TT – 54,5±4,5 року. Генотип Tt виявляється у половини хворих на ХК, а генотип TT – був частішим у контрольній групі. Частота генотипу tt у пацієнтів із ХК становила is 0,217, а в контрольній групі – 0,138, ВШ (95%CI 0,640–4,666). Співвідношення генотипів у чоловіків і жінок із ХК: 38,0%:38,0%:24,0% та 20,0%:60,0%:20,0%. Серед оперованих хворих на ХК 33,3% осіб були носіями генотипу tt. Не було підтверджено достовірної різниці за частотою генотипів і алелів у пацієнтів із КРР і ХК порівняно з контрольгною групою. Співвідношення чоловіків і жінок з генотипом Tt за групами B1-B3 форм ХК за Монреальською класифікацією відрізняється, зокрема, у жінок із генотипом Tt у чотири рази частіше (B1) форма. Дослідження мутації Taq1 може сприяти ідентифікації груп, які мають найбільший ризик важкої форми ХК.

Ключові слова: поліморфізм TaqI гена *VDR;* розподіл генотипів; колоректальний рак; хвороба Крона; стать; вік початку захворювання; фенотип захворювання.

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