

The Lactase -13910C>T Polymorphism (rs4988235) in Macedonian Individuals with Abdominal Symptoms

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Abstract

INTRODUCTION: Primary hypolactasia is one of the main causes of lactose intolerance. Genetic tests are used in primary lactose intolerance. It is associated with two polymorphisms: C/T-13910 and G/A-22018 located upstream of the LCT gene which encodes for lactase-pherlorizin hydrolase.

AIM: The aim of this study was to determine the presence of C/T-13910 polymorphism in individuals with abdominal symptoms from North Macedonia.

METHOD: Realtime PCR (FLASH technique) for the C/T-13910 polymorphism was performed. A total of 161 patients from N. Macedonia (82 females, 79 males; from 1-67 years, mean age 11.2±14.9) were tested for the most common mutation C/T-13910 in the promoter of the LCT gene. Two groups were formed according to ethnicity: 70 subjects Macedonian and 91 Albanian subjects.

RESULTS: CC-13910 genotype was found in 64.6 % of total subjects, with higher prevalence in Macedonian than in Albanian subjects (74.29% vs 57.14%).

CONCLUSION: The results obtained show that N. Macedonia belongs to the group of European countries with low lactose tolerance.

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Introduction

Lactose is the main sugar in milk and dairy products and it is hydrolysed by lactase in the small intestine. People with lactose intolerance are unable to fully digest lactose. As a result of lactase deficiency, they have symptoms like diarrhea, gas and bloating after eating or drinking dairy products [1], [2]. There are four main types of lactase deficiency: primary, secondary, congenital and developmental lactose intolerance. In primary lactase deficiency, the activity of lactase decreases with age. This condition called adult type is a genetically determined type of reduced lactase. Biochemical methods such as the lactose hydrogen breath test and the direct lactase enzyme activity in small-bowel biopsy samples being a part of

approved procedure for clinical diagnosis of lactose intolerance have been discussed in literature before [3], [4], [5].

Along or separately with biochemical tests, genetic analysis of lactase gene [6], [7] is today also used to establish genetic susceptibility to hypolactasia. Lactase is encoded by a gene located on chromosome 2. Numerous polymorphisms of this gene have been sequenced where Enattah et al., in 2002, found that reduced lactase activity is related with C/T-13910 and G/A-22018 DNA variants, located upstream the gene encoding the lactase-pherlorizin hydrolase (LPH) [7], [8]. Positive correlation between genetic test and lactase activity detected by breath test reported by several groups, pointed that genetic testing is useful diagnostic tool for primary lactase deficiency [9], [10], [11]. A lot of publications have suggested that C/T-13910 is the

dominant polymorphism and that the C allele is linked to a decline in lactase mRNA expression. There is a large volume of published studies describing that the presence of CC genotype is associated with primary hypolactasia (gradual decrease in lactase activity which progresses with age), whereas the presence of CT and TT genotypes with intermediate and high lactase activity (lactase persistence) [7], [10], [11], [12].

Lactase persistence contrasts among different human populations, fluctuating from 95% in White northern Europeans and North Americans, to closely 0% in certain Asian countries, together with China [2], [8]. In European population this condition differs between Northern countries with tolerance level above 70% and the others European parts mostly in South Europe where N. Macedonia geographically belongs, as well as Turkey, Greece, and Italy where higher percent of people are affected.

In this study, we evaluated a frequency of C/T-13910 variants in $n = 161$ individuals with abdominal symptoms from North Macedonia.

Material and Methods

Study type

A cross-sectional study was conducted. All individuals provided written informed consent.

Subjects screening and enrollment

Patients ranged at age from 1 to 67, with an average age of 11.2 ± 14.9 and a median of 4 years; patients up to 12 years of age predominated. Individuals of both genders with abdominal pain, flatulence, borborygmus and osmotic diarrhea suspected for lactose intolerance by medical physicians or self-diagnosed, have been included as a main criteria in the study. Blood samples were collected for genotyping. Ultimately, a total of 161 subjects were enrolled in the study.

Genotyping

For each subject, a total of 3 mL of whole blood was collected in ethylenediaminetetraacetic acid (EDTA) tubes. The test was performed using real-time PCR (FLASH technique). The primary lactase deficiency is associated with single nucleotide variants in a regulatory region of LCT gene which is located in MCM6 gene on the chromosome 2 (2q21).

DNA was isolated from white blood cells using DNA isolation commercial kit (PREP-RAPID Genetics DNA Extraction Kit -DNA-Technology Research &

Production", LLC), according to the manufacturer's recommendations.

The implemented PCR method was based on amplification of a target DNA sequence. The detection was based on melting curve analysis. The Lactose Intolerance REAL-TIME PCR Genotyping Kit employs fluorescent probes each of one specific to one of two alleles of a gene. The PCR-mix contains two distinguishably labelled allele-specific probes bearing reporter fluorescent dyes (Fam and Hex) for each variant of polymorphism. After amplification melting of amplicon-signal probe complexes was performed. It results in changing fluorescence level and is detected by the real-time thermal cycler and is represented by the software as a graph. If the signal probe is partially complementary to the DNA-target the melting temperature will be less than in case when signal probe is absolute complementary to the DNA-target. The interpretation of results is made based on melting temperatures with integrated software. Each run was amplifying the sample but also internal control. It allows to control quantity of human DNA in amplification tube to exclude mistakes in genotyping and to assure successful amplification. The analysis was performed on automatic "DNA-Technology" RealTime PCR instrument.

Statistical analysis

Data statistical analysis obtained by the research was conducted in the statistical program SPSS for Window 23-0. Shapiro Wilk's test was used to test the normality of data distribution.

Categorical (attributive) variables are presented in absolute and relative numbers. Numerical (quantitative) variables are presented with mean, standard deviation, minimum and maximum values, median and interquartile range.

Chi-square test and Fisher's exact test were used to compare qualitative variables, quantitative variables were compared with Student's t-test for independent samples and Mann-Whitney test. Statistical significance was defined at the $p < 0.05$ level.

Results

The research included 161 respondents, patients with abdominal symptoms, of which 82 (50.93%) were female and 79 (49.07%) were male patients. In the structure according to ethnicity, Macedonians were represented by 70 (43.485%), and Albanians by 91 (56.52%) patients. Patients ranged from 1 to 67 years, with average age of 11.2 ± 14.9 years and a median of 4 years; patients under the age of 12 dominated 108 (67.08%) (Table 1).

Table 1: Characteristics of the respondents

Variable	n (%)
Gender	
Female	82 (50.93)
Male	79 (49.07)
Ethnicity	
Macedonian	70 (43.48)
Albanian	91 (56.52)
Age	
(mean ± SD)(min- max)[median (IQR)]	(11.2 ± 14.9) (1-67) [4(1 – 14)]
Age groups	
≤12	108 (67.08)
13 – 20	12 (7.45)
21 – 35	19 (11.8)
>35	22 (13.66)

C/T-13910 LCT polymorphism was analyzed in all respondents. The results presented 104 (64.6%) subjects with CC genotype, 51 (31.7%) subjects with CT genotype and 6 (3.7%) subjects with TT genotype (Table 2).

Table 2: Frequency of the C/T-13910 LCT genotypes

Genotype	n (%)
CC	104 (64.6)
CT	51 (31.68)
TT	6 (3.73)

CC genotype which is associated with primary hypolactasia was found in 104 respondents. The prevalence of the LCT-C/T-13910 gene mutation in this group of patients with abdominal symptoms was 64.6% (Figure 1).

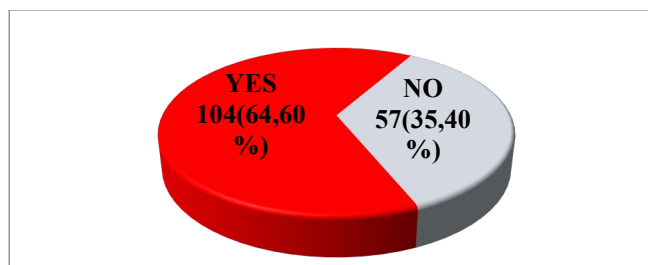


Figure 1: % of CC genotype which is associated with primary hypolactasia

Additionally, CC genotype which is associated with hypolactasia was not associated with patients' gender ($p = 0.52$); it was found in 62.2% female and 67.09% male patients.

Table 3: Patients with CC genotype in different gender, ethnicity and age groups

Variable	patients with CC genotype			p-level	
	n	yes n (%)	no n (%)		
Gender	Female	82	51 (62.2)	31 (37.8)	$X^2=0.4$ $p=0.52$
	Male	79	53 (67.09)	26 (32.91)	
Ethnicity	Macedonian	70	52 (74.29)	18 (25.71)	$X^2=5.1$ $*p=0.024$
	Albanian	91	52 (57.14)	39 (42.86)	
Age groups	≤12	108	69 (63.89)	39 (36.11)	$X^2=2.15$ $p=0.54$
	13 – 20	12	7 (58.33)	5 (41.67)	
	21 – 35	19	11 (57.89)	8 (42.11)	
	>35	22	17 (77.27)	5 (22.73)	

X^2 (Chi-square test); *sig $p < 0.05$.

The ethnicity of the patients with CC genotype was statistically significant ($p = 0.024$). More often CC genotype which indicates primary hypolactasia was proven in Macedonian than in Albanian subjects

(74.29% vs 57.14%), with higher prevalence in group of patients older than 35 years (77.27%), followed by patients under 12 years (63.89%), patients in group from 13 to 20 (58.33%) and aged from 21 to 35 years (57.89%) (Table 3).

Patients with CC genotype were insignificant older than patients without this condition ($p = 0.32$). The mean age of patients with and without LCT-C/T-13910 gene mutation was 14.6 ± 17.8 and 11.0 ± 13.0 years, respectively, and a median of 5 years in both groups (Table 4).

Table 4: CC genotype associated with primary hypolactasia in different age groups

Age	CC genotype	Statistical analysis			p-level
		n	mean ± SD	min- max/ median (IQR)	
All	Yes	104	14.6 ± 17.8	5(2 – 23)	Z=1.0 $p=0.32$
	No	57	11.0 ± 13.0	5(1 – 19)	
≤12	Yes	69	3.7 ± 3.0	1 – 11	t=0.4 $p=0.7$
	No	39	3.5 ± 3.2	1 – 11	
13 – 20	Yes	7	16.1 ± 2.1	13 – 19	t=0.18 $p=0.86$
	No	5	16.4 ± 2.9	14 – 20	
21 – 35	Yes	11	28.2 ± 5.2	21 – 35	t=1.5 $p=0.15$
	No	8	25.0 ± 3.3	21 – 32	
>35	Yes	17	49.2 ± 8.9	35 – 67	t=1.6 $p=0.12$
	No	5	42.20 ± 6.8	35 – 51	

Z (Mann-Whitney test); t (Student t-test).

Male and female patients with C/T-13910 CC genotype most often were 12 years or younger – 58.82% vs 73.58%), followed by male and female patients older than 35 years – 21.57% vs 11.32% (Table 5, Figure 2).

Table 5: C/T-13910 CC genotype prevalence in male and female patients

Age groups	patients with CC genotype			p-level
	N	female n (%)	Male n (%)	
≤12	69	30 (58.82)	39 (73.58)	p=0.4
13 – 20	7	4 (7.84)	3 (5.66)	
21 – 35	11	6 (11.76)	5 (9.43)	
>35	17	11 (21.57)	6 (11.32)	

P (Fisher's exact test).

Female patients with C/T-13910 CC genotype were insignificant older than male patients ($p=0.21$); average age of the patients of both genders were 17.2 ± 18.8 и 12.1 ± 16.6 years, respectively, and median from 8 and 4 years respectively.

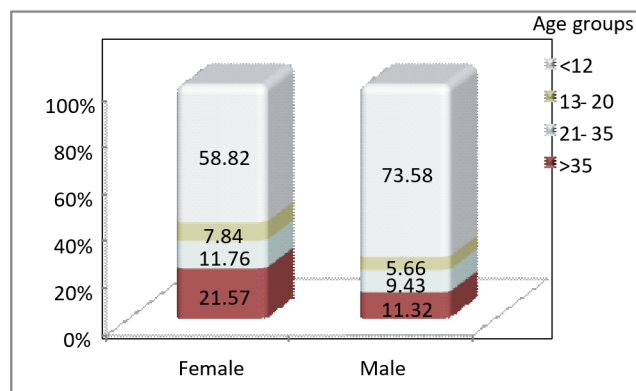


Figure 2: Male and female patients with C/T-13910 CC genotype

In separate age groups, female and male patients did not differ significantly in terms of age ($p>0.05$). In the age group 12 years and younger, average age of both genders with C/T-13910 CC genotype was 3.7 ± 3.1 and 3.7 ± 3.0 years and median of 2 and 3 years, respectively, female and male patients in age group from 13 to 20 were with average age from 16.5 ± 2.1 to 15.7 ± 2.5 years, in age group from 21 to 35 years, 29.7 ± 5.5 and 26.4 ± 4.7 years and in age group older than 35 years 47.4 ± 9.4 and 52.5 ± 7.7 years, respectively (Table 6).

Table 6: Female and male patients with C/T -13910 CC genotype in separate age groups

Variable	Gender	Group with C/T-13910 CC genotype			p-level
		n	mean \pm SD	min- max/ median (IQR)	
Age	Female	51	17.2 ± 18.8	8(2 – 35)	Z=1.25
	Male	53	12.1 ± 16.6	4(2 – 13)	p=0.21
≤12	Female	30	3.7 ± 3.1	2(1 – 5)	Z=0.2
	Male	39	3.7 ± 3.0	3(1 – 5)	p=0.84
13 – 20	Female	4	16.5 ± 2.1	14 – 19	t=0.48
	Male	3	15.7 ± 2.5	13 – 18	p=0.65
21 – 35	Female	6	29.7 ± 5.5	22 – 35	t=1.0
	Male	5	26.4 ± 4.7	21 – 33	p=0.32
>35	Female	11	47.4 ± 9.4	35 – 67	t=1.1
	Male	6	52.5 ± 7.7	39 – 60	p=0.27

Discussion

Lactose intolerance is generally most common in Asian countries, specifically in East Asian, with more than 70 % frequency; it is least prevalent in Northern and Central Europe, where only about 5% of the population has lactose intolerance [9], [13]. The reason for the variation is that selective (primary) hypolactasia is genetically determined by an autosomal recessive single gene. According to World Population Review in South Europe where N. Macedonia geographically belongs, higher percent of people are affected, with 30% in Spain, 40% in Portugal 55% in Greece, and more than 70% in Italy. In this study we analyzed polymorphic variants of the LCT gene associated with different lactase activity in patients with abdominal symptoms in N. Macedonia. In analyzed study group, we estimated 64.6% with CC genotype 31.7% of the subjects with CT genotype and 3.7% of the subjects with TT genotype which according to literature are associated with hypolactasia, intermediate activity and lactase persistence, respectively. According to available literature data, comparisons among genotype and phenotype frequency have shown that the -13910*T allele cannot always be related to lactase persistence (LP) frequencies especially in the most African and Middle Eastern populations where absence of 13910T allele showed high rates of lactase persistence [14], [15]. Instead, different LP-associated alleles occurring in the same genomic region have been reported, indicating convergent evolution [13], [16], [17], [18]. However, the -13910*T allele frequency ranges from 6%–36% in eastern and southern Europe, 56%–67% in Central and Western Europe, to 73%–

95% in the British Isles and Scandinavia while LP ranges in frequency from 15%–54% in Eastern and Southern Europe, 62%–86% in Central and Western Europe, to 89%–96% in the British Isles and Scandinavia [13]. Shown results indicate that the -13910*T allele is a good candidate for predicting LP in Europe where N. Macedonia as a multiethnic country geographically belong. In our study group we found very low rate of -13910*T allele, which according literature data is associated with hypolactasia. Lapidus at all. in their review article reported that there are no differences in the C/T-13910 polymorphism between two genders. Additionally, Baadkar at all. reported that females had significantly higher incidence of lactose intolerance. In our research group CC genotype, which is associated with hypolactasia was also not related with patients' gender ($p=0.52$); it was found in 62.2% female and 67.09% male patients. This was also confirmed from other authors in different geographical parts as well as another ethnicity [19], [20], [21], [22].

Raz at all. reported significant association between ethnicity and genotype in polymorphic LCT SNPs -13910C/T among Bedouin-Arabs and Iraqi, Ashkenazi and Moroccan Jews in Israeli study group [23]. Ethnicity-related frequency of this polymorphism was also studied in Brazilians, where prevalence of the CC genotype associated with hypolactasia was similar among White and Brown groups; followed by higher prevalence among Blacks (80%) and those of Japanese descent (100%)[24], [25]. Correspondingly, difference in the genotype was also confirmed in another Brazilian research group among the Mennonites (a group with European ancestry and a long history of endogamy) and the Euro-Brazilians [26].

In our study group, we found significant association between ethnicity and genotype. The ethnicity of the patients with CC genotype was statistically significant ($p=0.024$). More often CC genotype which indicates primary hypolactasia (lactase non-persistence) was proven in Macedonian than in Albanian subjects (74.29% vs 57.14%), with higher prevalence in group of patients older than 35 years (77.27%), followed by patients under 12 years (63.89%), patients in group from 13 to 20 (58.33%) and patient aged from 21 to 35 years (57.89%).

Conclusion

Our study contributes to understanding the prevalence of genetic variants related to lactase non-persistence in patient with different abdominal symptoms. The obtained results confirm the high prevalence of C/T-13910 CC genotype in the Republic of North Macedonia, which indicates a high percentage of lactose intolerance in this region.

Further large studies (for exp. G/A-22018 testing) should scan the situation in the country. Genetic consulting measures must follow up and

recommendations for transformation of dairy industry should be given publicly.

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