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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-phlorizin 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 then 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.

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-phlorizin 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	
Gender n (%)	
Female	82 (50.93)
Male	79 (49.07)
Ethnicity n (%)	
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 n (%)	
≤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).

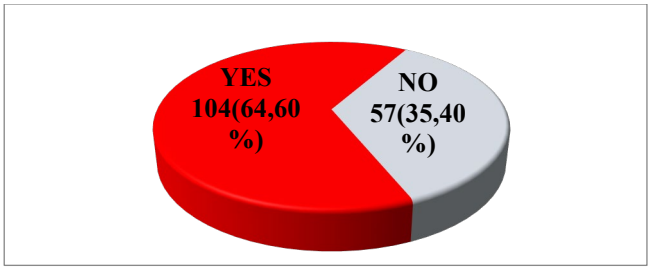

Figure 1: % of CC genotype which is associated with primary hypolactasia

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
	Male	79	53 (67.09)	26 (32.91)	p=0.52
Ethnicity	Macedonian	70	52 (74.29)	18 (25.71)	X^2=5.1
	Albanian	91	52 (57.14)	39 (42.86)	*p=0.024
Age groups	≤12	108	69 (63.89)	39 (36.11)	X^2=2.15
	13 – 20	12	7 (58.33)	5 (41.67)	p=0.54
	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
	No	57	11.0 ± 13.0	5(1 – 19)	p=0.32
≤12	Yes	69	3.7± 3.0	1 – 11	t=0.4
	No	39	3.5 ± 3.2	1 – 11	p=0.7
13 – 20	Yes	7	16.1 ± 2.1	13 – 19	t=0.18
	No	5	16.4 ± 2.9	14 – 20	p=0.86
21 – 35	Yes	11	28.2 ± 5.2	21 – 35	t=1.5
	No	8	25.0 ± 3.3	21 – 32	p=0.15
>35	Yes	17	49.2 ± 8.9	35 – 67	t=1.6
	No	5	42.20 ± 6.8	35 – 51	p=0.12

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

patients with CC genotype				
Age groups	Gender			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.

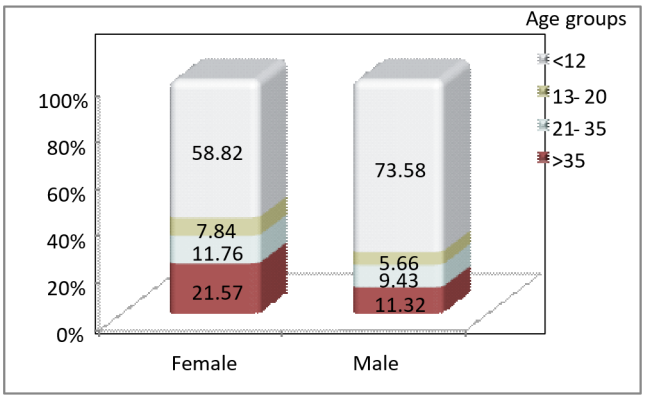

Figure 2: Male and female patients with C/T-13910 CC genotype

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

Group with C/T-13910 CC genotype					
Variable	Gender	Statistical parameters			p-level
		n	mean ± 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. Lapides 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.

References

1. Gallo A, Pellegrino S, Lipari A, Pero E, Ibba F, Cacciatore S, Marzetti E, Landi F, Montalto M. Lactose malabsorption and intolerance: What is the correct management in older adults? Clinical Nutrition. 2023 Dec 1;42(12):2540-5. https://doi.org/10.1016/j.clnu.2023.10.014 PMid:37931373

2. Ponte PR, de Medeiros PH, Havt A, Caetano JA, Cid DA, de Moura Gondim Prata M, Soares AM, Guerrant RL, Mychaleckyj J, Lima AÂ. Clinical evaluation, biochemistry and genetic polymorphism analysis for the diagnosis of lactose intolerance in a population from northeastern Brazil. Clinics. 2016 Feb;71(2):82-9. https://doi.org/10.6061/clinics/2016(02)06 PMid:26934237

3. Mattar R, do Socorro Monteiro M, Villares CA, dos Santos AF, Carrilho FJ. Single nucleotide polymorphism C/T-13910, located upstream of the lactase gene, associated with adult-type hypolactasia: validation for clinical practice. Clinical biochemistry. 2008 May 1;41(7-8):628-30. https://doi.org/10.1016/j.clinbiochem.2008.01.006 PMid:18237552

4. Bernardes-Silva CF, Pereira AC, da Mota GD, Krieger JE, Laudanna AA. Lactase persistence/non-persistence variants, C/T_13910 and G/A_22018, as a diagnostic tool for lactose intolerance in IBS patients. Clinica chimica acta. 2007 Nov 1;386(1-2):7-11. https://doi.org/10.1016/j.cca.2007.07.012 PMid:17706627

5. Pimentel M, Kong Y, Park S. Breath testing to evaluate lactose intolerance in irritable bowel syndrome correlates with lactulose testing and may not reflect true lactose malabsorption. Official journal of the American College of Gastroenterology| ACG. 2003 Dec 1;98(12):2700-4. https://doi.org/10.1111/j.1572-0241.2003.08670.x PMid:14687820

6. Bond JH, Levitt MD. Quantitative measurement of lactose absorption. Gastroenterology. 1976 Jun 1;70(6):1058-62. https://doi.org/10.1016/S0016-5085(76)80311-3 PMid:1269865

7. Enattah NS, Sahi T, Savilahti E, Terwilliger JD, Peltonen L, Järvelä I. Identification of a variant associated with adult-type hypolactasia. Nature genetics. 2002 Feb;30(2):233-7. https://doi.org/10.1038/ng826 PMid:11788828

8. Pérez-Jeldres T, Bustamante ML, Segovia-Melero R, Aguilar N, Magne F, Ascui G, Uribe D, Azócar L, Hernández-Rocha C, Estela R, Silva V. Genotype Prevalence of Lactose Deficiency, Vitamin D Deficiency, and the Vitamin D Receptor in a Chilean Inflammatory Bowel Disease Cohort: Insights from an Observational Study. International Journal of Molecular Sciences. 2023 Oct 3;24(19):14866. https://doi.org/10.3390/ijms241914866 PMid:37834314 PMCid:PMC10573577

9. Santonocito C, Scapaticci M, Guarino D, Annicchiarico EB, Lisci R, Penitente R, Gasbarrini A, Zuppi C, Capoluongo E. Lactose intolerance genetic testing: Is it useful as routine screening? Results on 1426 south-central Italy patients. Clinica Chimica Acta. 2015 Jan 15;439:14-7. https://doi.org/10.1016/j.cca.2014.09.026 PMid:25281930

10. Mattar R, do Socorro Monteiro M, Villares CA, dos Santos AF, Carrilho FJ. Single nucleotide polymorphism C/T-13910, located upstream of the lactase gene, associated with adult-type hypolactasia: validation for clinical practice. Clinical biochemistry. 2008 May 1;41(7-8):628-30. https://doi.org/10.1016/j.clinbiochem.2008.01.006 PMid:18237552

11. Bodlaj G, Stocher M, Hufnagl P, Hubmann R, Biesenbach G, Stekel H, Berg J. Genotyping of the lactase-phlorizin hydrolase− 13910 polymorphism by LightCycler PCR and implications for the diagnosis of lactose intolerance. Clinical Chemistry. 2006 Jan 1;52(1):148-51. https://doi.org/10.1373/clinchem.2005.057240 PMid:16391332

12. Kuchay RA, Thapa BR, Mahmood A, Mahmood S. Effect of C/T− 13910 cis-acting regulatory variant on expression and activity of lactase in Indian children and its implication for early genetic screening of adult-type hypolactasia. Clinica Chimica Acta. 2011 Oct 9;412(21-22):1924-30. https://doi.org/10.1016/j.cca.2011.06.032 PMid:21763294

13. Itan Y, Powell A, Beaumont MA, Burger J, Thomas MG. The origins of lactase persistence in Europe. PLoS computational biology. 2009 Aug 28;5(8):e1000491. https://doi.org/10.1371/journal.pcbi.1000491 PMid:19714206 PMCid:PMC2722739

14. Mulcare CA, Weale ME, Jones AL, Connell B, Zeitlyn D, Tarekegn A, Swallow DM, Bradman N, Thomas MG. The T allele of a single-nucleotide polymorphism 13.9 kb upstream of the lactase gene (LCT)(C− 13.9 kbT) does not predict or cause the lactase-persistence phenotype in Africans. The American Journal of Human Genetics. 2004 Jun 1;74(6):1102-10. https://doi.org/10.1086/421050 PMid:15106124 PMCid:PMC1182074

15. Enattah NS, Jensen TG, Nielsen M, Lewinski R, Kuokkanen M, Rasinpera H, El-Shanti H, Seo JK, Alifrangis M, Khalil IF, Natah A. Independent introduction of two lactase-persistence alleles into human populations reflects different history of adaptation to milk culture. The American Journal of Human Genetics. 2008 Jan 10;82(1):57-72. https://doi.org/10.1016/j.ajhg.2007.09.012 PMid:18179885 PMCid:PMC2253962

16. Mulcare C. The evolution of the lactase persistence phenotype. University of London, University College London (United Kingdom); 2006.

17. Bersaglieri T, Sabeti PC, Patterson N, Vanderploeg T, Schaffner SF, Drake JA, Rhodes M, Reich DE, Hirschhorn JN. Genetic signatures of strong recent positive selection at the lactase gene. The American Journal of Human Genetics. 2004 Jun 1;74(6):1111-20. https://doi.org/10.1086/421051 PMid:15114531 PMCid:PMC1182075

18. Poulter M, Hollox E, Harvey CB, Mulcare C, Peuhkuri K, Kajander K, Sarner M, Korpela R, Swallow DM. The causal element for the lactase persistence/non-persistence polymorphism is located in a 1 Mb region of linkage disequilibrium in Europeans. Annals of Human Genetics. 2003 Jul;67(4):298-311. https://doi.org/10.1046/j.1469-1809.2003.00048.x PMid:12914565

19. Grand RJ, Montgomery RK, Chitkara DK, Hirschhorn JN. Changing genes; losing lactase. Gut. 2003 May 1;52(5):617-9. https://doi.org/10.1136/gut.52.5.617 PMid:12692040 PMCid:PMC1773627

20. Lapides RA, Savaiano DA. Gender, age, race and lactose intolerance: is there evidence to support a differential symptom response? A scoping review. Nutrients. 2018 Dec 11;10(12):1956. https://doi.org/10.3390/nu10121956 PMid:30544891 PMCid:PMC6316196

21. Santonocito C, Scapaticci M, Guarino D, Annicchiarico EB, Lisci R, Penitente R, Gasbarrini A, Zuppi C, Capoluongo E. Lactose intolerance genetic testing: Is it useful as routine screening? Results on 1426 south-central Italy patients. Clinica Chimica Acta. 2015 Jan 15;439:14-7. https://doi.org/10.1016/j.cca.2014.09.026 PMid:25281930

22. Baadkar SV, Mukherjee MS, Lele SS. Study on influence of age, gender and genetic variants on lactose intolerance and its impact on milk intake in adult Asian Indians. Annals of Human Biology. 2014 Nov 1;41(6):548-53. https://doi.org/10.3109/03014460.2014.902992 PMid:24734931

23. Raz M, Sharon Y, Yerushalmi B, Birk R. Frequency of LCT-13910C/T and LCT-22018G/A single nucleotide polymorphisms associated with adult-type hypolactasia/lactase persistence among Israelis of different ethnic groups. Gene. 2013 Apr 25;519(1):67-70. https://doi.org/10.1016/j.gene.2013.01.049 PMid:23415628

24. AS Arroyo M, P Lopes AC, B Piatto V, Victor Maniglia J. Perspectives for Early Genetic Screening of Lactose Intolerance:-13910C/T Polymorphism Tracking in the Gene. The Open Biology Journal. 2010 Jul 16;3(1). https://doi.org/10.2174/1874196701003010006 6

25. Mattar R, Monteiro MS, Villares CA, Santos AF, Silva JM, Carrilho FJ. Frequency of LCT-13910C> T single nucleotide polymorphism associated with adult-type hypolactasia/lactase persistence among Brazilians of different ethnic groups. Nutrition Journal. 2009 Dec;8:1-3. https://doi.org/10.1186/1475-2891-8-46 PMid:19799794 PMCid:PMC2761420

26. Boschmann SE, Boldt AB, De Souza IR, Petzl-Erler ML, Messias-Reason IJ. The frequency of the LCT*-13910C> T polymorphism associated with lactase persistence diverges among Euro-Descendant groups from Brazil. Medical Principles and Practice. 2015 Dec 1;25(1):18-20. https://doi.org/10.1159/000440807 PMid:26334798 PMCid:PMC5588315