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Detection of the C/C_{-13910} genotype associated with primary adult-type hypolactasia

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We detected the genotypes of C/T_{-13910} single nucleotide polymorphism by PCR-SNaPIT™ technology and determined intestinal lactase activity by the lactose tolerance test in 120 apparently healthy young persons to compare the results of genotyping with lactose tolerance testing in ethnically defined groups of the investigative subjects. The lactose tolerance test identified 38 subjects with intestinal lactase deficiency (31.7%) in the total study sample. The frequency of primary adult-type hypolactasia was found to be different in ethnically defined subgroups: 27.8% in the Lithuanian, 57.1% in the Russian and 54.5% in the Polish subgroups. The prevalence of the genotype C/C_{-13910}, associated with primary adult-type hypolactasia, has been estimated to be 42.5% in the total study sample. The rate of the C/C_{-13910} genotype varied in ethnically defined groups: 44.3 % in Lithuanians, 42.9% in Russians and 27.3% in Poles. The C/C_{-13910} genotype has been detected in 27 subjects (71.1%) with a low intestinal lactase activity and in 24 subjects (29.3%) with a high lactase activity evaluated by the lactose tolerance test. Results obtained by two adult-type hypolactasia diagnostic methods, molecular genotyping and lactose tolerance test, were in good agreement.

Key words: primary adult-type hypolactasia, single nucleotide polymorphism, genotyping, lactose tolerance test

INTRODUCTION

Lactase or lactase-phlorizin hydrolase (LPH, EC: 3.2.1.108, 3.2.1.2, 3.2.1.62.) is an integral glycoprotein of *microvillus* of small intestinal epithelial cells [1–4]. It is located on the apical surface of brush border enterocytes where it is anchored into the membrane by its C-terminal end, with the bulk of the molecule projecting into the lumen of the gut [3, 4]. Lactose, a disaccharide, is the principal calorific component of milk. To be absorbed, it must be hydrolyzed into glucose and galactose, a reaction mediated by LPH hydrolyzes lactose. LPH is a unique enzyme in its formation, location and enzymatic activity [1–5]. It is highly unusual, having two active sites within one polypeptide chain, one hydrolyzing lactose, the other aryl and aliphatic glycosides [6]. Lactase is encoded by a single human lactase gene (*LCT* [MIM 603202]), about 50 kb in size, composed of 17 exons located in 2q21–22 chromosome [3, 7].

Primary adult-type hypolactasia (PATH) or lactase deficiency is a genetically determined age-related condition resulting from the physiological decline in activity of LPH in intestinal cells after weaning [3, 8, 9]. Family studies have shown that adult lactase deficiency is an autosomal recessive trait [3, 8]. Secondary lactase deficiency is caused by other reasons than genetically determined adult type hypolactasia, such as microbial infections or coeliac disease that damage the intestinal *villi* [9–11]. There is a direct association between the severity of mucosal damage and the decrease of disaccharidase activity [12–17].

Epidemiological data indicate that the frequency of primary intestinal lactase deficiency varies widely depending on geography, age, race and ethnicity. The prevalence of adult-type hypolactasia varies from less than 5% to almost 100% among different populations in the world. Low prevalence has been found in populations living in northwestern Europe, the highest being found in Far East Asia countries [2, 18–20]. The prevalence of primary adult-type hypolactasia in the whole adult Lithuanian population was found to be 34% [21, 22].

A variety of methods has been used for diagnosing intestinal lactase deficiency [10, 13, 14, 23, 24]. Precise standards do not exist. A small intestinal biopsy is the only direct diagnostic procedure of measuring lactase activity. The other way to determine primary adult-type hypolactasia is indirect lactase activity evaluation by lactose load tests based either on serial blood glucose determinations (lactose tolerance test, LTT) or on the measurement of excreted hydrogen concentration in the exhaled air (breath hydrogen test) [23–26].

Recent reports have identified single nucleotide polymorphism (SNP) which is closely associated with lactase persistence and non-persistence phenotypes [11, 27–34]. Enattah et al. [29] identified two single nucleotide polymorphisms (SNPs) cytosine (C) to thymidine (T), residing 13,910 base pairs, and guanine (G) to adenine (A) change, residing 22,018 base pairs upstream of exon 1 of the *LCT* locus. The finding was based on linkage disequilibrium and haplotype analysis of the region associated with

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lactase persistence of the 47 kb region outside of the *LCT* gene and successive sequence comparison in family members carrying haplotypes with lactase persistence and/or nonpersistence. In accordance with results of subsequent studies, the second SNP G/A_{-22018} is thought to be only in linkage disequilibrium. Both DNA variants, C/T_{-13910} and G/A_{-22018}, are located in introns 9 and 13 of the minichromosome maintenance gene (*MCM6*) [35].

Further analysis of lactase activity lactase / sucrase ratio from more than 200 intestinal biopsy specimens from ethnically different populations showed that only the DNA variant C/T_{-13910} completely associates with biochemically verified lactase non-persistence. The C/C_{-13910} genotype, matched with a low LPH-specific mRNA expression and low lactase activity in intestinal biopsies (10 u/g per protein), suggests primary adult-type hypolactasia, whereas the genotypes C/T_{-13910} and T/T_{-13910}, matched with high LPH-specific mRNA expression and high lactase activity (over 10 U/g per protein), strongly suggest lactase persistence [29, 32, 33, 36, 37]. The SNP C/T_{-13910} was reported to perfectly match with phenotypic hypolactasia and lactose malabsorption for the C/C_{-13910} genotype. Therefore, the SNP C/T_{-13910} was identified as a genetic marker for adult-type hypolactasia [38]. Using this SNP, hypolactasia can be diagnosed more easily and accurately.

The aim of the present study was to detect the C/C_{-13910} genotype, associated with primary adult-type hypolactasia, in ethnically defined groups of apparently healthy young persons, to determine the relationship between the DNA C/T_{-13910} variant genotyping and intestinal lactase activity evaluated by LTT, and to compare the results of genotyping with lactose tolerance testing in study sample.

MATERIALS AND METHODS

Study subjects

The study cohort comprised 120 healthy young adults, students, 19–28 years old (age average in years ± standard deviation 20.68 ± 1.053), 94 women and 26 men. Inclusion criteria: individuals of both genders over 18 years of age; exclusion criteria: diseases and treatment methods which could cause secondary lactase deficiency. Participants of the study were requested to provide information on any known diagnosis of disease or health problem. The ethnic dependence of each participant of the study was revealed by means of a questionnaire including the birthplace and the mother tongue of the parents and grandparents. Only the reports in which at least three of the four grandparents belonged to the same ethnic group were considered as belonging genetically to the corresponding ethnic group. Written informed consent was obtained from all participants. The Lithuanian Bioethics Committee approved the protocol of the study. The study was carried out at Vilnius University Faculty of Medicine and at Research Center of Fermentas UAB.

All participants underwent clinical investigation and the lactose tolerance test for the assessment of the intestinal enzyme lactase activity. The genotyping of the SNP C/T_{-13910} was performed.

Lactose tolerance test

Lactose tolerance test (LTT) was employed for assessment of activity of the intestinal enzyme lactase due to its high specificity (up to 96%) and sensitivity (up to 94%) [23] as well as the relatively simple procedure. The study persons were administered 50 g lactose dissolved in 300 ml water for drinking. Capillary blood samples to test plasma glucose concentration were taken before the lactose load and at 20, 40 and 60 min of the test. An acutrend GCT (Roche Centralized Diagnostics, Germany) glucometer was used for glucose concentration measurements. Intestinal lactase deficiency was considered if glucose levels failed to rise >1.1 mmol/l compared to baseline [23, 25, 26]. The participants of the study registered lactose intolerance symptoms after LTT in the questionnaire.

Genotyping

Genomic DNA extraction was performed from frozen venous blood samples taken from all the participants and collected in EDTA tubes, using a Genomic DNA Purification Kit (#K0512, Fermentas UAB, Lithuania) under the experimental protocol. The PCR primer was designed to amplify the region containing C/T_{-13910} polymorphism [29]. Diagnostic (s., forward) primer: C/T – MCM6-C/T(3) 5`FAM(6–FAM) 5'-GCT-GGC-AAT-ACA-GAT-AAG-ATA-ATG-T-3 (MWG Biotech AG, Germany). Non-diagnostic (s., reverse) primer: C/T – MCM6 rev-C/T (6) CGT-TAA-TAC-CCA-CTG-ACC-TAT-CC. The genotyping of the SNP C/T_{-13910} was performed by using the PCR-SNaPIT™ technology [39, 40]. PCR reactions were performed in a total volume of 20 µl containing 2 µl 10X *Taq* buffer, 2 µl of each primer, 2 µl dNTP mix, 1.6 µl $MgCl_2$, 0.1 µl Taq DNA polymerase (Fermentas UAB, Lithuania), 2 µl template DNA. Thermal cycling conditions were: the initial denaturation stage at 95 °C for 2 min, followed by 35 cycles of denaturation at 95 °C for 30 s, annealing at 62 °C for 15 s, extension at 72 °C for 20 s and final extension at 72 °C for 5 min. Then digestion and purification of the PCR product were performed under the experimental protocol with a genotyping kit (#K2001CodeRed™, Fermentas UAB, Lithuania). Aliquots from 1 µl diagnostic fragment (digested and purified PCR product) and ROX mix (#K2001CodeRed™, Fermentas UAB, Lithuania) solution were prepared. The ROX mix is an internal size standard for sizing DNA fragments for fluorescence-based electrophoresis systems. The analysis was performed by capillary electrophoresis on an ABI Prism 310 genetic analyzer (Applied Biosystems, USA). Each allele of the SNP resulting in a diagnostic fragment is of pretermined size. The presence of C allele resulted in the appearance of a diagnostic fragment 26 nucleotides in length, and the presence of the T allele gave the appearance of the diagnostic fragment of 24 nucleotides in length. A heterozygote sample generated both diagnostic fragments of both 26 and 24 nucleotides in size.

Statistical analysis

A 2 × 2 table was used to evaluate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), positive and negative likelihood ratios of the two DNA variants in comparison to LTT results. The ROC (receiver operating characteristic) curve was used for a comparison, too. The association of the prevalence rate of hypolactasia with gender was assessed using the χ^2 test of independence, and for ethnical dependency Fischer's exact test was employed. The variables were significantly related to each other when p was less than 0.05. All statisti-

cal data analysis was performed using SPSS 14.0 for Windows (SPSS, Inc., USA).

RESULTS

According to the questionnaire, 97 of the 120 study subjects considered themselves Lithuanians (80.8%), 11 were Poles (9.2%), 7 Russians (5.8%) and 5 of other nationalities (4.2%).

Lactose tolerance test results

Lactose tolerance test (LTT) showed that from the total study population of 120, 82 subjects (68.3%) had no decrease in activity of the small intestine enzyme lactase. Low intestinal lactase activity, or hypolactasia, was diagnosed in 38 individuals (31.7%). The female hypolactasia rate (34%) was higher than male (23.1%), but the difference was not statistically significant ($\chi^2 = 1.132$; df = 1; p = 0.287).

The frequency of hypolactasia in ethnically defined subgroups varied: it was found in Lithuanians 27 (27.8%), 4 (57.1%) Russians, 6 (54.5%) Poles and (20%) in 1 from the subgroup of other nationalities. The rate of hypolactasia was approximately twice lower in Lithuanians than in Poles (54.5%) and Russians (57.1%). However, the rate in Lithuanians didn't differ significantly from that in Poles and Russians (p = 0.068 and p = 0.102, respectively).

Genotyping results

The C/C_{-13910} genotype, suggesting the genetic disposition for lactase non-persistence of SNP C/T_{-13910}, was detected in 51 (42.5%) persons of the total study cohort. DNA analysis estimated lactase persistence in 69 subjects (57.5%): 57 persons (47.5%) were found to have a C/T_{-13910} genotype and 12 (10%) a T/T_{-13910} genotype. Both the female and male participants had the same C/C_{-13910} genotype frequencies – 42.6% and 42.3% ($\chi^2 = 0.001$; df = 1; p = 0.982).

The ratio of the C/C_{-13910} genotype associated with primary adult-type hypolactasia was examined in ethnically defined subgroups of the study population (Table 1). Analysis of the distribution of the DNA variant $C/T_{-131910}$ genotypes in ethnically defined groups revealed that the ratio of the C/C_{-13910} genotype associated with a low intestinal lactase activity was the highest in the Lithuanian group (44.3%) and the lowest in the Polish group (27.3%).

We have correlated SNP C/T_{-13910} genotyping with LTT results (Table 2). C/C_{-13910} genotype, associated with low lactase activity or non-persistence (deficiency), was detected in 27 subjects (71.1%) with a low and in 24 subjects (29.3%) with a high intestinal lactase activity estimated by LTT. The C/T_{-13910} and T/T_{-13910} genotypes, associated with lactase activity persistence (sufficient activity), were detected in 58 subjects (70.7%) with a high intestine lactase activity and in 11 subjects (28.6%) with low lactase activity, estimated by the lactose tolerance test ($\chi^2 = 18.552$; df = 1; p = 0.000).

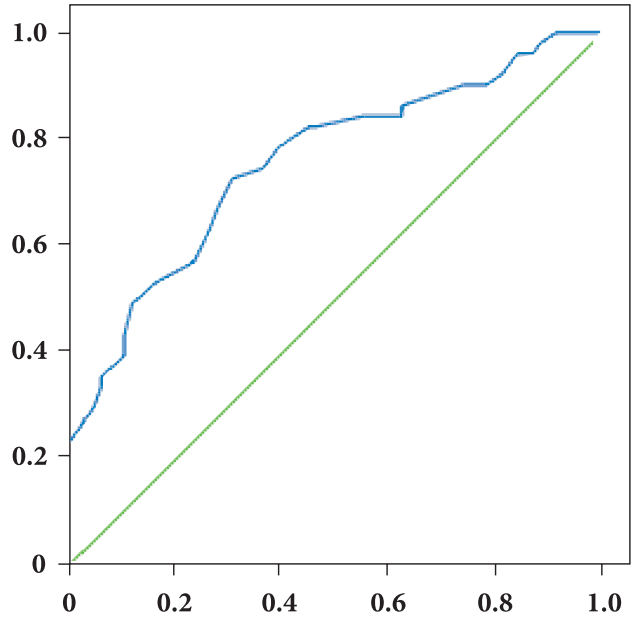

Figure. Comparative curve of lactose tolerance test and C/T_{-13910} SNP genotyping. Cut-off point 1.45 (maximal values: specificity 70%, sensitivity 73%)

Table 1. **Distribution of the single nucleotide polymorphism C/T_{-13910} in ethnically defined subgroups**

Number of subjects in ethnic sugroup	C/T_{-13910} genotypes			Allele frequency	
	C/C	C/T	T/T	C	T
Lithuanians (n = 97)	43 (44.3%)	46 (47.4%)	8 (8.3%)	0.68	0.32
Russians (n = 7)	3 (42.9%)	4 (57.1%)	–	0.71	0.29
Poles (n = 11)	3 (27.3%)	5 (45.4%)	3 (27.3%)	0.5	0.5
Others (n = 5)	2 (40.0%)	2 (40.0%)	1 (20.0%)	0.7	0.33
Total (n - 120)	51 (42.5%)	57 (47.5%)	12 (10.0%)	0.68	0.32

Table 2. **Single nucleotide polymorphism C/T_{-13910} genotyping and lactose tolerance test results**

SNP C/T_{-13910}	DNA specimens		Lactose tolerance test			
	Absolute number	Percent	Subjects with low lactase activity		Subjects wit high lactase activity	
			Absolute number	Percent	Absolute number	Percent
C/C_{-13910}	51	42.5	27	71.1	24	29.3
C/T_{-13910}	57	47.5	10	26.3	47	57.3
T/T_{-13910}	12	10.0	1	2.3	11	13.4
Total	120	100	38	100	82	100

The sensitivity and specificity values of the molecular genetic method was 71% in the case of the genotyping C/T_{-13910} variant versus lactose tolerance test results. After comparing the two diagnostic methods we determined that for subjects with hypolactasia evaluated by LTT the probability to have genetic adult-type hypolactasia markers was higher approximately 2.5 times (positive likelihood ratio (PLR) 2.43). We extended the test out to more than two possible results. The genotyping and LTT correlation was growing: in case of maximum glucose concentration in blood serum after oral lactose challenge up to 0.1 mmol/l the PLR was 10.81 and at the maximum glucose concentration 0.9 mmol/l PLR – 3.69 versus 2.43 in case of 1.1 mmol/l (the usually used cutoff value of glucose concentration elevation). For clinical prognosis we used the ROC curve (Figure). The area under the curve was 0.76 in case of C/T_{-13910} genotyping, indicating the molecular genetic diagnostic method as good with regard to LTT results.

DISCUSSION

The prevalence of hypolactasia in our study on LTT data basis was 31.7%. Hypolactasia frequency in native Lithuanians was 27.8%, in the Russian ethnic subgroup 57.1% and in Poles 54.5%. These findings demonstrated a good agreement with the earlier published epidemiologic study results when the prevalence of hypolactasia was 34% [21, 22]. In our study, the frequency of hypolactasia in native Lithuanians was similar to the earlier published 32%, too [21, 22], but the prevalence of hypolactasia in the Russian ethnic subgroup was twice higher as compared with the earlier detected 21% [21, 22]. These discrepancies could be explained by a rather small number of participants in our study or imprecisely referred ethnical dependency. The rate of hypolactasia detected in the Polish subgroup was approximately one quarter higher as compared with the rate 42.5% earlier detected in Lithuanians [21, 22]. In Poland, the average hypolactasia rate reported in earlier studies was 37.5% [19]. The probable reasons of this data discrepancy could be the same – the small number of participants or incorrectly referred ethnical dependency.

We compared the frequency of the detected C/C_{-13910} genotype (42.5%), suggesting lactase non-persistence, with data from other studies carried out in a few different countries. In Finnish population, the prevalence of the C/C_{-13910} genotype was 18.1%, which is in accordance with the earlier published data [29, 41]. In Austrian studies, the C/C_{-13910} genotype frequency varied from 21.4% to 31%. Generally, these data were in good concordance with the frequency of lactose intolerance diagnosed by breath hydrogen test [30, 42, 43]. In a study from Germany there was detected a C/C_{-13910} genotype associated with adult-type hypolactasia, its rate being 21.4%. The genotyping data, slightly dissociating with the reported 15 % of hypolactasia frequency in Germany, were based on the breath hydrogen test [28]. In a study on British subjects, the frequency of C/C_{-13910} genotype was 9% [41]. This value was higher than the earlier reported frequencies of lactose malabsorption (5%) in the United Kingdom [20]. In the same study, C/C_{-13910} genotype frequency in Spanish subjects was 34.6% [41]. This rate was higher than the earlier determined hypolactasia prevalence in Spain, which ranged from 19% in Southern Spain to 28% in Valencia [41].

The results from British laboratory showed a perfect association of the C/T_{-13910} genotypes with lactase persistence / non-persistence phenotypes in Northern European samples, but no association was observed in Southern European samples [2, 44]. The lactase persistence genotype was typed in individuals from 20 distinct cultural groups in seven African countries. The researchers found the T allele to be so rare that it could explain the frequency of the lactase persistence phenotype in Africa. They concluded that C/T_{-13910} polymorphism is not a predictor of lactase persistence in sub-Saharan Africans. The C/C_{-13910} genotype frequency in most study samples was 100% or close to that rate [45]. We observed a higher frequency of C/C_{-13910} genotype than the prevalence of hypolactasia diagnosed by the lactose tolerance test. This fact might indicate a higher sensitivity of genotyping compared to the lactose tolerance test which can be influenced by numerous factors.

In conclusion, analysis of the SNPs may assist in differentiating patients with primary adult-type hypolactasia and lactose intolerance. Attention should be paid to an appropriate interpretation of genetic findings in order to avoid a potentially harmful reduction in dairy intake or misdiagnosis of secondary lactase deficiency [31].

CONCLUSIONS

The lactose tolerance test revealed primary adult-type hypolactasia in approximately one third of healthy young adults (31.7%). The frequency of hypolactasia was found to be different in ethnical subgroups: 27.8% in Lithuanians, 57.1% in Russians and 54.5% in Poles.

A correlation of data obtained by such adult-type hypolactasia diagnostic methods as molecular genotyping and lactose tolerance test was close. The genotype C/C_{-13910}, which according to the literature data is strongly associated with adult-type hypolactasia, was detected in more than two thirds (71.1%) of subjects with a low lactase activity estimated by the lactose tolerance test, and in about one third (29.3%) of subjects with a normal lactase activity.

The sensitivity and specificity value of the molecular genetic method was 71% versus the lactose tolerance test results.

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Danutė Kalibatienė, Sonata Varvuolytė

C/C$_{-13910}$ GENOTIPO, SUSIJUSIO SU PIRMINE SUAUGUSIŲJŲ HIPOLAKTAZIJA, NUSTATYMAS

Santrauka

Ištyrėme vieno nukleotido polimorfizmo genotipus taikydami SNaPIT™ technologiją ir nustatėme laktazės fermentinį aktyvumą pagal laktozės toleravimo mėginio rezultatus 120 jaunų sveikų asmenų, taip pat palyginome dviejų laktazės aktyvumo diagnostikos metodų duomenis etniniuose tiriamųjų pogrupiuose. Bendroje tyrimo populiacijoje laktozės toleravimo mėginiu 38 asmenims (31,7%) nustatėme mažai aktyvią laktazę. Pirminės suaugusiųjų hipolaktazijos dažnis etniniuose pogrupiuose buvo nevienodas: lietuvių – 27,8% (31,4%), rusų – 57,1% ir lenkų – 54,5%. Bendroje tyrimo populiacijoje C/C$_{-13910}$ genotipo, susijusio su pirmine suaugusiųjų hipolaktazija, dažnis prilygo 42,5%, o etniniuose pogrupiuose pasiskirstė taip: 44,3% lietuvių, 42,9% rusų ir 27,3% lenkų turėjo šį genotipą. 27 (71%) asmenys, kuriems laktozės toleravimo mėginiu nustatytas mažas laktazės fermentinis aktyvumas, ir 24 (29,3%) asmenys, kuriems nustatytas didelis laktazės aktyvumas, turėjo C/C$_{-13910}$ genotipą. Pirminės suaugusiųjų hipolaktazijos diagnostinių metodų, molekulinio genotipavimo ir laktozės toleravimo mėginio rezultatai sutapo gerai.

Raktažodžiai: pirminė suaugusiųjų hipolaktazija, vieno nukleotido polimorfizmas, genotipavimas, laktozės toleravimo mėginys