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Comparison of Lactase Variant MCM6 – 13910 C>T Testing and Self-Report of Dairy Sensitivity in Patients with Irritable Bowel Syndrome

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Abstract

Goals—To evaluate agreement of LCT-13910 with self-report of dairy sensitivity (DS) and lactose hydrogen methane breath test (LHMBT) results in subjects with IBS.

Background—Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder with symptoms including abdominal pain, variable bowel habits and bloating. Adult patients with lactose malabsorption may present with similar symptoms. Patients with lactose malabsorption have a lactase non-persistent (LNP) phenotype. Recent studies found two single nucleotide polymorphisms associated with LNP: G/A₋₂₂₀₁₈ and C/T₋₁₃₉₁₀.

Study—Genotyping the LCT-13910 variant of LNP in 538 IBS patients and 317 controls (without IBS). Subjects completed questionnaires pertaining to gastrointestinal problems and dietary consumption, with charts abstracted.

Results—Self-reported DS was higher in IBS (45%) than controls (9.8%, OR = 6.46, p<0.001). The C/C₋₁₃₉₁₀ genotype was similar in IBS cases and controls, 81 (15.1%) and 47 (14.8%). Among subjects reporting DS, 49 (18.0%) had the C/C genotype. Overall agreement between genotype and self-reported DS was 0.06 in IBS and 0.07 in controls. There were 20 subjects with LHMBT results; three had positive results, 17 were negative. Lactase non-persistence genotypes were found in all three of positive LHMBT results; 16 had negative LHMBT among the 17 who were lactase persistent. Agreement between C/C₋₁₃₉₁₀ genotype and LHMBT was excellent with κ -statistic of 0.83 [0.50–1.00].

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Conclusions—In IBS patients, self-report of lactose intolerance are highly prevalent but are a poor indicator of underlying C/C₋₁₃₉₁₀ genotype. LHMBT had excellent agreement with C/C₋₁₃₉₁₀ genotype.

Keywords

irritable bowel syndrome; lactase; dairy sensitivity

INTRODUCTION

Lactase is a disaccharidase enzyme crucial to hydrolysis of lactose to form galactose and glucose. During infancy, lactase activity is high, allowing for milk ingestion without complication; lactase concentrations decline with age and have been known to decline significantly after weaning.^{1, 2} The prevalence of lactase non-persistence (LNP) varies by geographic location, ranging from 3% in northwestern Europe to almost 100% in Asian and African countries,^{3–5} making it the most common enzyme deficiency in humans. LNP is an autosomal recessive trait that leads to down-regulation of intestinal lactase expression.⁶ LNP may then result in abdominal symptoms including abdominal pain, diarrhea, bloating, and flatulence after sufficient lactose ingestion due to lactose maldigestion.^{2, 7}

Symptoms of LNP are similar to those of irritable bowel syndrome (IBS), a functional bowel disorder characterized by symptoms of chronic, recurrent abdominal pain, and often bloating and diarrhea. Approximately 10–22% of the US population is affected by IBS. This represents one of the most common gastrointestinal diagnoses seen by primary care providers and gastroenterologists.^{8, 9} Research has shown the prevalence of lactose intolerance in IBS ranges from 17–86% depending on ethnicity and diagnostic modality used.^{10, 11}

Traditional testing includes the lactose hydrogen breath test (LHMBT) and methane breath test. However, both typically require an outpatient visit as well as laboratory facilities. Alternatively, upper intestinal biopsies may be taken to determine actual lactase activity, but is invasive, expensive, and not suitable for screening.^{11, 12}

Recently, a single nucleotide polymorphism (SNP) –13910 C/T on the *MCM6* gene 14kb upstream from the lactase gene (LCT) has been found to be associated with lactase persistence and LNP.^{13, 14} Variant C/C is associated with LNP while C/T and T/T are associated with lactase persistence.¹⁵ These three genotypes (C/C, C/T, T/T) correlate with levels of lactase activity from intestinal biopsies; C/C₋₁₃₉₁₀ was associated with very low lactase activity (<10 U/g protein) while C/T₋₁₃₉₁₀ and T/T₋₁₃₉₁₀ was associated with higher levels of lactase activity.¹⁵ Epidemiological studies have shown the prevalence of C/T₋₁₃₉₁₀ genotype is consistent with previously published reports of LNP in several populations.¹³ Yang et al. found the association between subjective and objective lactose tolerance to be similar, although a higher proportion of IBS-D patients reported DS compared to controls.¹⁶ This paper was from a Chinese population with a high prevalence of lactase deficiency.

Given the overlap between LNP and IBS, the aim of the present study was to evaluate the agreement of the LCT SNP C/C₋₁₃₉₁₀ genotype (rs4988235) with self-report of dairy sensitivity in patients with IBS from a US cohort.

MATERIALS AND METHODS

Study Design

This case-control study is part of an ongoing family study conducted at Mayo Clinic, Rochester. The methods of this multi-aim IBS study have been previously reported.¹⁷ All subjects completed one baseline symptom questionnaire, provided 10ml EDTA blood, and underwent a chart abstraction. The symptom questionnaire included the Talley Bowel Disease Questionnaire (BDQ), medical history, and dietary history per self-report. The BDQ is a self-report instrument, measuring symptoms experienced over the past year.¹⁸ The BDQ has adequate validity and contains a valid measure of non-gastrointestinal somatic complaints; the Somatic Symptom Checklist (SSC).¹⁹ Self-report of dietary history was in the form of 13 non-validated questions, inquiring about food allergies or sensitivities, average servings of dairy consumption per day and if the subject ever felt they needed to cut down on the amount of dairy products they consumed (yes/no) due to gut symptoms. All subjects underwent a standardized medical chart review. Information about other gastrointestinal diagnoses and tests was recorded. This study was approved by the Mayo Clinic Institutional Review Board (IRB) and informed consent was obtained from all subjects prior to participation.

Irritable bowel syndrome cases and controls

Cases were required to have a formal diagnosis of IBS and were subsequently defined according to the Rome II criteria²⁰ and be free of gastrointestinal diagnoses that could mimic IBS symptoms (i.e. celiac sprue, inflammatory bowel disease, or major abdominal surgery). Constipation-predominant IBS (IBS-C) was defined by meeting either Rome I or II criteria, but endorsing one or more constipation symptoms (less than 3 bowel movements per week, hard stools, straining) and no diarrhea symptoms (greater than 3 bowel movements per day, loose stools, urgent stools). Diarrhea-predominant IBS (IBS-D) was defined by meeting either Rome I or II criteria, and endorsing one or more diarrhea symptoms but no constipation symptoms while mixed-IBS (IBS-M) was defined as meeting either Rome I or II criteria for IBS-C or IBS-D.²⁰ Unclassified-IBS did not meet Rome I or II criteria for IBS-C/D/M but had a formal medical diagnosis of IBS. Irritable bowel syndrome cases were matched with controls with a similar age, gender, and region of residency. Controls were excluded if they met Rome I or II criteria for IBS, a concurrent cancer diagnosis, or other gastrointestinal diagnoses similar to cases.

Genotyping

Blood samples from IBS subjects and controls were collected and DNA was then extracted by polymerase chain reaction. Genotyping of the -13910 C/C variant for MCM6 was performed by the Mayo Clinic Genotyping Shared Resource core lab that was blinded to the samples using the Illumina Golden Gate custom SNP panel. All samples were de-identified and plated in a random order.

Genotyping of LCT C/T-13910 was determined as part of a custom GoldenGate panel.²¹ These assays encompass primer extension, ligation and universal PCR in very highly-plexed reactions (384–1536plex). Oligonucleotide tagged 3 micron beads, each type bearing hundreds of thousands of copies of a single stranded nucleotide sequence, are arrayed in wells etched into the ends of fibre optic strands. Each bead type is represented ~30 times in each single fibre optic strand.

Three oligonucleotides were designed for each SNP locus. Two ASOs (allele-specific oligonucleotides) are specific for one of each allele of the SNP site; the other, an LSO (locus specific oligonucleotide) hybridizes several bases downstream of the SNP site. All three oligonucleotides contain universal primer sites and the LSO also contains a unique sequence address. The amount of DNA required per SNP assay panel is 250ng, at 50ng/ul. DNA was first activated using streptavidin-biotin then incubated with assay oligonucleotides, hybridization buffer and paramagnetic particles. Extension of the appropriate ASO/query oligo and ligation of the extended product to the LSO provided a template for PCR using Cy3 and Cy5 labeled universal PCR primers. The PCR products were bound and the dye-labeled strand was eluted and hybridized to the bead array matrices. The single stranded, dye-labeled DNAs were hybridized to their complement bead type through their unique address sequences. The BeadArrays were scanned using an Illumina iScan reader and the fluorescent signals were analyzed using software, GenomeStudio, for automated genotype clustering and calling.

Lactose Hydrogen Methane Breath Test (LHMBT)

During the medical chart review, IBS cases that were clinically referred for a LHMBT were reviewed. The LHMBT was performed clinically and patients were instructed not to eat whole grains or bran, dairy, fruit or drink fruit concentrates 24 hours prior to testing. Additionally, they underwent a 12 hour fast prior to the LHMBT. After a baseline measurement, an oral load of lactose of 0.5 g/kg of body weight was administered per standardized protocol and breath samples were collected every 15–30 minutes for at least two hours. Lactose malabsorption was classified as a change in H₂ concentration by at least 20 ppm or a change of at least 12 ppm for H₂/CH₄ combined.

Statistical Analysis

Demographic characteristics were analyzed with Kruskal-Wallis test for continuous variables and Chi-square (or Fischer's exact tests) for categorical variables. Genotype comparisons between cases and controls were analyzed with logistic regression assuming a recessive genetic model. The analysis was run unadjusted and adjusted for age, sex, somatization score, and BMI. To make genotype comparisons between IBS sub-types, generalized logit models were fit both unadjusted and adjusted for age, sex, and somatization score. The agreements of genotype with self-report of dairy sensitivity and LHMBT results was a % agreement using a kappa statistic (95% CI). A p-value of <0.05 was considered to be statistically significant.

RESULTS

Subject Characteristics

A total of 855 individuals, 538 IBS patients (25.7% IBS-D, 10.8% IBS-C, 30.3% IBS-M, and 33.3% Other) and 317 controls were used for this study. Characteristics of IBS subjects and of healthy matched controls are provided in Table 1.

Allele, Genotype, and Dairy Sensitivity Distributions

Among the IBS and control subjects, the frequency of the CC genotype was similar between cases and controls (14.8% v. 15.1%) (Table 2). Self-reported dairy sensitivity was significantly higher in IBS subjects than controls (45.0% vs. 9.8%, OR = 6.46, $p < 0.001$, adjusted for age at recruitment, gender, BMI, and somatization score) (Table 2). Among IBS patients who tested positive for the CC genotype, the frequency was not significantly different ($p = 0.152$) between the IBS subtypes (13.1% IBS-D, 22.4% IBS-C, 11.7% IBS-M and 17.3% IBS-Other); LNP was not associated with IBS (Table 3). Those with IBS-D had a higher self-report of dairy sensitivity (57.7%) compared with IBS-C (36.2%, $p = 0.007$), IBS-M (46.3%, $p = 0.037$), and IBS-Other (37.4%, $p < 0.001$) after adjusting for age, gender, and somatization score.

Self-Reported Dairy Sensitivity, LHMBT and –13910 C>T Polymorphism

Of subjects who reported a dairy sensitivity, the C/C₋₁₃₉₁₀ polymorphism (LNP) was detected in 49 (18.0%), while the presence of the C/T and T/T₋₁₃₉₁₀ polymorphism (lactase persistence) was detected in 223 (82.0%). The agreement between genotype and dairy sensitivity was 55.9% in cases and 80.1% in controls. K-values (95% CI) which are corrected for chance were calculated for agreement between self-reported dairy sensitivity and genotype were 0.06 (–0.01, 0.12) for cases and 0.07 (–0.05, 0.20) for controls, which indicates no agreement for both groups.

The kappa value, reflecting agreement between genotype and self-reported dairy sensitivity ranged from 0.03 (IBS-D) to 0.19 (IBS-C) among the IBS subgroups, a slight agreement at most.

Of the 49 C/C₋₁₃₉₁₀ subjects who reported a dairy sensitivity, 28 (57.1%) consumed a minimum of 1–2 servings of dairy per day. The number of cases who reported dairy sensitivity and were lactase persistent ($n = 199$) far exceeded those with the LNP genotype ($n = 42$).

There were a total of 20 patients who underwent a clinical LHMBT; three were positive (15%) while 17 were negative (85%) (Table 4). There were no significant differences between gender and age. All three patients who had a positive LHMBT result had the LCT-13910 C/C genotype, while one patient had a negative LHMBT test result and the C/C genotype; the remaining 16 patients who had a negative LHMBT result had the C/T or T/T genotype. The agreement between genotype and LHMBT was 95.0%. K-values (95% CI) for agreement between LHMBT and genotype were 0.83 (0.50–1.00), which indicates excellent

agreement. Among the IBS subgroups, k-values for agreement was 0.18 (−0.7, 0.44) in IBS-C, 0.03 (−0.06, 0.13) in IBS-D, and 0.05 (−0.06, 0.15) in IBS-M.

DISCUSSION

This study comprehensively assessed the lactase variant *MCM6*–13910 C/T testing and self-report of dairy sensitivity among a large cohort of IBS patients. We identified self-report symptoms of dairy sensitivity does not accurately indicate LNP genotype status but a positive LHMBT does display a very good level of agreement.

The inability to hydrolyze lactose is commonly associated with gastrointestinal symptoms when dairy products are consumed. In this study, we demonstrated patient self-report of dairy sensitivity does not help in identifying LNP in IBS patients as the number of cases who reported a dairy sensitivity and were lactase persistent far exceeded those with LNP genotype. The discrepancy may be explained as these patients may avoid dairy products based on their own assessment of their sensitivity to milk.

Previous studies of subjects have shown up to 57–63% who report dairy sensitivity do not have LNP,^{22,23} while 82% of our study population reported dairy sensitivity but did not have LNP. In another study, it was found self-report dairy sensitivity to be unpredictable when determining lactase persistence status by hydrogen breath testing.²⁴ Yang et al. found patients with IBS-D were more intolerant to lactose at various doses when compared to controls while reporting LNP more frequently.¹⁶ This study found the prevalence of the LNP genotype was similar to ours for cases and controls at 14–15%.

In our study of IBS patients, we found a 95% agreement between genotype and LHMBT. Previous studies found similar results of a 97–100% agreement.^{25, 26} The advantage of genetic analysis aside from excellent sensitivity is breath test results can produce false-positive findings. Pimentel et al.²⁷ has reported an abnormal breath test could be the result of small intestinal bacterial overgrowth or rapid intestinal transit while other researchers reported older patients have higher hydrogen breath concentrations which may impact breath test results.²⁶ However our data suggest close agreement between breath testing and genotype data at least in the populations tested.

Performing a lactose intolerance test by PCR is a lower-cost option compared to breath testing and/or EGD with small bowel biopsies, according to the CMS website a blood test would cost approximately \$58.23 (CPT [current procedural terminology] codes 81400 and 36415) while the cost of LMHBT is \$75.73 (CPT code 91065) followed by an EGD with biopsies (CPT codes 43239 and 88305 and facility fee) costing \$565.25. Furthermore, lactose intolerance test by PCR would be further presumed to be cost-effective due to less time spent in a clinic, facility fees and personnel time.

Many IBS patients state their gastrointestinal symptoms are intensified when consuming a trigger meal and as a result avoid these meals.^{28, 29} Avoidance of milk and dairy products in many IBS patients may be unwarranted as they are lactase persistent. As a result, IBS patients who believe they are lactose intolerant may consume less amounts of calcium which may lead to reduced bone mineral density, placing them at possible risk for osteoporosis,³⁰

although this has not been formally studied. Despite reporting a dairy sensitivity, many people with LNP are able to consume a small amount of milk (approximately 1 cup) with minimal problems and milk products should not discontinued arbitrarily.^{31,32}

Limitations of this study include the predominant Caucasian population which has the lowest prevalence of lactase persistence, ranging from nearly non-existent to 30%.³³ European populations, particularly those around the North Sea, have the highest reported prevalence rates of lactase persistence, ranging from 80–90% of adults³⁴ while Asian populations can have lactase persistence prevalence rates as low as 0–10%.^{5, 33} This study recruited a relatively small number of subjects who had a LHMBT performed clinically; however, the agreement was excellent between LHMBT results and genotype. Additionally, self-report of dairy sensitivity may not be able to adequately capture the patient's experience.

Future studies are warranted and should include a more diverse population, a larger cohort undergoing LHMBT recording their gastrointestinal symptoms, and detailed dairy sensitivity questions to understand what dairy sensitivity means to patients. Data on the impact of unnecessary dairy restriction in IBS should also be evaluated.

In summary, we found dairy sensitivity was reported significantly more often in those with IBS than controls while the prevalence of the LNP genotype was similar for both cases and controls while self-report of dairy sensitivity is a very weak indicator of underlying LNP genotype status in patients with IBS. Genotyping may be of interest in the management of IBS patients reporting a lactose intolerance and excluding milk products from their diet, by confirming they do not have LNP (for most of them).

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Table 1

Subject Characteristics

	IBS (n=538)	Controls (n=317)	p-value
Age, median (range)	49.3 (18.0–70.0)	50.4 (20.4–69.7)	0.372
Gender			
Female, n (%)	444 (82.5%)	261 (82.3%)	0.933
BMI, median (range)	25.1 (14.1–52.1)	26.6 (17.5–51.0)	0.002
Race			
Caucasian, n (%)	528 (98.1%)	317 (100.0%)	
Marital status			
Married, n (%)	395 (73.7%)	234 (74.1%)	0.825
Single, n (%)	78 (14.6%)	49 (15.5%)	
Other, n (%)	63 (11.8%)	33 (10.4%)	
Educational level			
College and/or beyond, n (%)	463 (86.2%)	289 (91.7%)	0.055
High school, n (%)	71 (13.2%)	25 (7.9%)	
Less than high school, n (%)	3 (0.6%)	1 (0.3%)	
Abuse history, n (%)	205 (38.2%)	69 (21.8%)	<0.001
SSC score, median (range)	1.1 (0.0–3.5)	0.5 (0.0–2.6)	<0.001
IBS Subtype			
IBS-C, n (%)	58 (10.8%)	-	N/A
IBS-D, n (%)	138 (25.7%)	-	
IBS-M, n (%)	163 (30.3%)	-	
Other	179 (33.3%)	-	

SSC—Somatic symptom checklist

Table 2Genotype –13910 C>T Polymorphism and Dairy Sensitivity Distributions

	IBS (n=538)	Controls (n=317)	OR[†] (95% CI)	P[‡]
Genotype, n (%)				
C/C (lactase non-persistent)	81 (15.1%)	47 (14.8%)	0.90 [±] (0.59–1.39)	0.644 [±]
C/T or T/T	457 (84.9%)	270 (85.2%)		
Self-reported dairy sensitivity, n (%)	241 (45.1%)	31 (9.8%)	6.46 (4.21–9.89)	<0.001

[†]From model adjusted for age, gender, somatization score, and BMI[±]Testing C/C vs. C/T or T/T

Table 3

Genotype – 13910 C>T Polymorphism and Dairy Sensitivity by IBS Sub-Type

	IBS-C (n=58)	IBS-D (n=138)	IBS-M (n=163)	Other (n=179)	p [‡]
Genotype, n (%)					
C/C (lactase non-persistent)	13 (22.4%)	18 (13%)	19 (11.7%)	31 (17.3%)	0.152 [‡]
C/T or T/T	45 (77.6%)	120 (87%)	144 (88.3%)	148 (82.7%)	
Self-reported dairy sensitivity, n (%)	27 / 58 (36.2%)	79 / 137 (57.7%)	75 / 162 (46.3%)	67 / 179 (37.4%)	0.003

[‡] From model adjusted for age, gender, and somatization score

[‡] Testing C/C vs. C/T or T/T

Table 4Lactose Hydrogen Breath Test (LHBT) and Genotype Results (−13910 C>T Polymorphism)

	C/C	C/T or T/T	Total
Positive LHMBT, n (%)	3 (100%)	0 (0%)	3
Negative LHMBT, n (%) (n=17)	1 (5.9%)	16 (94.1%)	17
Total	4	16	20