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Frequency of *MYO9B* polymorphisms in celiac patients and controls

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ABSTRACT

Introduction: the *MYO9B* gene contributes to the maintenance of the intestinal barrier and it has been postulated as a risk factor of celiac disease (CD). The objective of this study was to compare the frequency and association rs2305764, rs2305767and rs1457092 *MYO09B* polymorphisms in pediatric CD patients from and.

Patients and methods: the study was made in 104 CD pediatric patients (Chilean and Argentineans) and 104 controls subjects. *MYO9B* gene polymorphisms were analyzed by Taqman allelic probes. We evaluated the Hardy-Weinberg equilibrium by means of Chi-square and compared the haplotypes distribution using Fisher test.

Results: SNPs rs2305767 and rs1457092 were associated with celiac disease (CD); TT genotype in rs2305767 would be a protective factor ($p < 0.000$, OR = 0.19 CI 0.1-0.4) and the CT genotype would be a risk factor ($p < 0.0001$, OR = 4.9 CI 2.2 to 11.3). CC genotype in rs1457092 also showed a protective effect for celiac ($p < 0.000$, OR = 0.07 CI 0.0 to 0.3).

Conclusion: our findings suggest that genetic variation *MYO9B* gene is associated with CD, as a protective or a risk factor depending on the polymorphism studied.

Key words: *MYO9B* gene. Celiac disease. Haplotypes.

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ABBREVIATIONS

MYO9B: Myosin IX B.
SNP: Single nucleotide polymorphism.
CD: Celiac disease.
HLA: Human lymphocyte antigen.
ELISA: Enzyme-Linked ImmunoSorbent Assay.
DNA: Deoxi ribonucleic acid.
PCR-RT: “real time quantitative polymerase reaction”.
χ^2:Chi square.
OR: Odds ratio.

INTRODUCTION

Celiac disease (CD) is a chronic autoimmune disorder resulting from the interaction of susceptibility genes, gluten proteins provided by the environment (diet) and the immune system, which acts as an effector system. After passing through the small intestine epithelium, gluten proteins induce a chronic inflammatory process that results in various degrees of damage in the intestinal mucosa (1). Globally, prevalence of CD is about 1%, without significant differences regarding geographic, ethnic or racial characteristics (2). In recent years, frequency of diagnosis has substantially increased due to the generalized medical use of antiendomysial and anti transglutaminase antibodies as screening tools, both highly sensitive and specific (3), efficient in helping decide the need of the small intestinal biopsy, which remains as the confirmatory test for diagnosis.

CD is a polygenic condition that mainly involves histocompatibility class II genes; the *HLA DQ2* and *HLA DQ8* conformations explain about 50% of the disease (4), while a series of candidate non-HLA genes and epigenetic phenomena would explain the rest (3,5). It is well known that clinical manifestations of CD may appear at any time in life in HLA DQ2/DQ8 individuals; it has been postu-

lated that these genes would be responsible for the great variability in the time of appearance of symptoms. Homozygote HLA DQ2/DQ8 individuals have at least 5 times more risk of developing CD than those heterozygote for these haplotypes (6). However, between 30 and 40% of the general population carry these genes and do not develop the disease, making it clear that their presence is necessary but not sufficient to develop the condition. CD related non-HLA genes and the mechanisms they use to influence the appearance of the condition are not clear. Genic regions associated with CD have been described in chromosomes 2, 5, 6, 15, and 19. Four susceptibility regions are described, including CELIAC1 (6p 21.3) that contains the *HLA DQ2-8* genes; CELIAC2, containing a relevant locus that confers risk for CD (5q 31-q33); this latter region has been associated with other inflammatory disorders and its relation with CD is not clear yet. CELIAC3 (2q33) contains the *CTL4* gene and CELIAC4 (19p 13.1) the MYO9B gene (7). Although there is some evidence that specific polymorphisms in these genes play a role in the pathogenesis of CD, it is uncertain how each of them would participate. *CD28-CTLA4-ICOS* is localized in chromosome 2q33 and the available evidence relates it to cytotoxic lymphocytes, which would participate in maintaining the immunological tolerance to self-antigens (8). Antigen cytotoxic lymphocytes would provide the co-stimulatory signal essential for the initiation and progress of T cell responses. It is currently hypothesized that their function is to down regulate these cells, when activated in response to other stimuli. CTLA4 would block activated T cells and thus stop further reactions associated with them; the polymorphisms would be functional and would abort the negative T cell regulation (9).

Mechanisms of cell signaling are crucial in functionally coordinating the different cell types. The different pathways are interconnected and form complex nets. During the last decades, Rho GTPase proteins have been described as forming part of these signaling nets.

Rho proteins form part of a subfamily of the superfamily of Ras GTPases. In mammals, the subfamily is formed by several members, one of them being RhoA. One of their main characteristics is that, as all G proteins, they bind guanine nucleotides and cycle between an inactive state bound to GDP and an active state bound to GTP. They have endogenous GTPase activity, being able to hydrolyze GTP to GDP in a Mg^{2+} dependent way. It is postulated that when bound to GTP, the Ras superfamily is activated to interact with effectors, which in turn will interact with other proteins inducing the signal cascade that allows for the response to continue. The great variety of biological functions exhibited by the different members of the Rho GTPase family is given by the different cell effectors they are able to bind. When they bind to the effector ROCK protein, they regulate myosin in the actin cytoskeleton (10).

MYO9B, the myosin gene recently described in chromosome 19 (intron 28) (11-13), encodes a non conventional myosin molecule that helps in remodeling actin in the epithelial enterocytes. It is a motor gene with a unique head containing an actin domain that enables it to bind to actin filaments and thus move along the cells. *MYO9B* would be able to activate the GTPase domain (Rho-GAP), which regulates the family of Rho GTPases. A relevant function of this family is to regulate the tight junctions and maintain the selective para-cellular pathway of enterocytes. A more active RhoA negatively regulates tight junctions, increasing the epithelial para-cellular permeability; in this way, RhoA appears to be a relevant participant in protecting the intestinal barrier (14). By modifying the intestinal barrier, gluten peptides would be able to access the sub-epithelial area, where the binding to HLA DQ2/DQ8 would initiate the inflammatory response.

It has been described that the presence of polymorphisms in the MYO9B gene results in an OR for CD of heterozygote and homozygote individuals (11). This gene has also been associated with some intestinal inflammatory conditions, such as ulcerative colitis, where it would also participate by altering the intestinal barrier (14). The objective of this study was to estimate the frequency and association of MYO9B gene polymorphisms (rs2305764, rs2305767 and rs1457092) in celiac patients (cases) and asymptomatic healthy controls.

MATERIALS AND METHODS

Subjects

This was a case-control study conducted in a total of 208 individuals, 104 celiac patients and 104 controls. 50 out of the 104 cases were Chileans (mean age 14 ± 15.4 years) and 54 were Argentinians (mean age 7.5 ± 7.1 years). All controls were Chileans. Chilean cases were recruited from San Juan de Dios, Exequiel González Cortés, Militar and Pontificia Universidad Católica hospitals in Santiago; Argentinean cases came from Resistencia city, Chaco (province). Inclusion of cases from both countries was based on previous studies that showed that HLA risk haplotypes for CD and frequency of native genes in patients from Chaco, Argentine were not different from those found in patients from Santiago, Chile (15) (for details see below). Diagnosis of CD included having EMA and/or tTG positive antibodies plus a concurrent small intestinal biopsy and subsequent clear clinical response to gluten free diet (16,17). Inclusion criteria for controls included attending a school/college in Santiago, being apparently healthy/asymptomatic, having no personal or family history of clinical CD or other immune conditions, having normal values of serum IgA and negative EMA and tTG antibodies. The protocol was approved by the IRB of the Institute of Nutrition and Food Technology (INTA), University of Chile. Prior to incorporation into the study, parents signed a written consent for children younger than 10 years. As for those 10 years or older, children provided written consent in addition to that signed by their parents.

Procedures

A 12 ml venous blood sample was obtained from the antecubital vein to determine EMA and tTG antibodies and for DNA extraction. Clinical history was obtained from clinical charts, and from the study subjects and their parents. Because clinical history data was not complete in all cases, it was not possible to analyze the relationships between the clinical presentations and the presence of MYO9B polymorphisms and HLA.

Genetic studies

DNA was extracted from frozen total blood by routine techniques. DNA integrity was measured by agarose gel electrophoresis stained with 1% ethidium bromide. DNA concentration was determined with the quantification NANODROP equipment (Thermo Fisher Scientific, USA). Determination of rs2305767 C/T, rs1457092 A/C and rs2305764 A/G (11, 18-21) in MYO9B was performed using Taqman probes.

Polymorphisms were determined by means of quantitative qPCR (Agilent Technologies Stratagene Mx 3000p). Briefly, we amplified the polymorphic region of the *MYO9B* gene using TaqMan analysis for the alleles: C_1654927_20, C_1654895_10, and C_1654873_1 (Applied Biosystems, Foster City, CA). The standard protocol used was: initial denaturation during 10 minutes at 95 °C followed by 40 cycles consisting of 15 seconds of denaturation at 92 ° C and annealing/ extension at 60 °C during 1 minute (22). The TaqMan probes used corresponded to the following sequences:

- rs2305764: ACACGTGTGAGTGTGTTTTTCCCCC [A/G] GCATATACGGAGCCGTAGTCTTGAA.
- rs2305767: GTCAGTTCCTCCATAGCAAGCCCCG [C/T] TGGATGCACGTCCCACCCTGTAGAT.
- rs1457092: GCATCCACCGGGCACAGAGAAGCCC [A/C] CAGGAGGATATCAGCAGCTCCCGTC.

Sample size and statistical analysis

Sample size was calculated for 80% potency and 5% significance level, considering the maximum differences found between allelic frequencies. The highest frequency among controls (0.5) and the lowest frequency among cases (0.3) were used following Wolters et al. (18), yielding a sample size of 104.

Data analysis included percent distribution of frequencies of the rs2305767, rs1457092 and rs2305764 polymorphisms in the *MYO9B* gene. χ^2 was used to compare proportions and determine associations of allelic and genotypic frequencies in cases and controls, and also to assess potential associations between polymorphisms and clinical and immunological characteristics (not shown). The risk of the assessed polymorphisms (rs2305767, rs1457092 and rs2305764) was expressed as odds ratio. Logistic regression was chosen to evaluate the association between polymorphisms and CD. p values < 0.05 were considered significant.

Data were analyzed by STATA 10.0 (Stata Statistical Software 1984-2009), StataCorp LP, Texas, USA. Comparisons of haplotypes were performed by χ^2 and Fisher's exact test, using Shesis (URL:http://202.120.7.14/Analysis.php). Assessment of genotypic frequencies in the Hardy-Weinberg equilibrium was performed by means of χ^2.

RESULTS

Data were first analyzed by country of origin. No differences were found in the clinical and genetic variables analyzed; for this reason, results are presented as one group. Comparison of HLAs considered of risk for CD (HLA alleles and *DQ2/DQ8*) showed no differences between celiac patients coming from Chile and Argentine (Table I). At the time of this study, mean age ± SD in the celiac group was 11.1 ± 12.7 years. Age at diagnosis ranged between 7.5 and 14 years. Distribution by sex was similar in cases and controls, with 65 and 66 women, respectively.

No differences were observed in the frequency of the rs23305764 polymorphism in cases and controls ($p > 0.05$). TT and CT genotypes in rs2305767 were less frequent among celiacs; OR in TT was 0.19 [IC 0.1-0.4] suggesting that this genotype may protect from CD; instead, OR for CT was 4.9 [IC 2.2-11.3], suggesting that this latter may act as a susceptibility factor. Analysis of the rs1457092 polymorphism showed that only the CC genotype was associated with CD, with an OR of 0.7 [IC 0.0-0.3], which suggests that this polymorphism would also act as a protective factor for CD. Only the rs1457092 polymorphism showed the Hardy Weinberg equilibrium in controls (Table II).

Genotype analysis using a recessive distribution model showed that only rs2305767 would be associated with CD (Table III). OR for this genotype was 0.19 [IC 0.07-0.4], suggesting that it may protect from developing CD. Finally, assessment of the most frequent haplotypes for the three polymorphisms evaluated showed that ATA (39%) and CGG (25%) haplotypes were more frequent in cases than

Table I. Frequency distribution of risk HLA *(DQ2/DQ8)* haplotypes in Chilean and Argentinean celiac patients

	Cases (Chileans) (n = 52)		*Cases (Argentineans) (n = 52)*		*Controls (n = 104)*	
	n	*Frec.*	*n*	*Frec.*	*n*	*Frec.*
DQ2-DQ8 homozygote	18	0.346	16	0.308	10	0.096
DQ2-DQ8 heterozygote	32	0.615	30	0.577	41	0.394
noDQ2-noDQ8	2	0.039	6	0.115	53	0.510

Comparison between Chilean and Argentinean cases p = 0.192.

Table II. Genotypic and allelic frequency distribution of rs2305764, rs2305767 and rs1457092 polymorphisms in cases and controls (n = 104)

MYO9B	*Cases n (%)*	*Controls n (%)*	*p value*	*OR IC [95%]*
rs2305764				
AA	18 (17)	20 (19)	0.7	0.87 [0.4-1.9]
AG	70 (68)	66 (64)	0.6	1.2 [0.6-2.2]
GG	16 (15)	18 (17)	0.7	0.87 [0.4-1.9]
A	106 (51)	106 (51)	1	1 [0.7-1.5]
G	102 (49)	102 (49)	1	1 [0.7-1.5]
H-W p value	$4* 10^{-4}$	$4.5*10^{-3}$		
rs2305767				
CC	2 (2)	3 (3)	0.7	0.7 [0.05-5.9]
CT	93 (89)	66 (63)	0.0001	4.9 [2.2-11.3]
TT	9 (9)	35 (34)	0.0001	0.19 [0.1-0.4]
C	97 (47)	72 (35)	0.01	1.7 [1.1-2.5]
T	111 (53)	136 (65)	0.01	0.6 [0.4-0.9]
H-W p value	0.0000	$1.4*10^{-4}$		
rs1457092				
AA	40 (38)	29 (28)	0.1	1.6 [0.9-3.0]
AC	62 (60)	51 (49)	0.1	1.5 [0.9-2.8]
CC	2 (2)	24 (23)	0,001	0.07 [0.0- 0.3]
A	142 (68)	109 (52)	$9*10^{-4}$	1.9 [1.3-3.0]
C	66 (32)	99 (48)	$9*10^{-4}$	0.5 [0.3-0.8]
H-W p value	1*10-4	0.978		

in controls (p = 0.006, OR = 1.78 [IC 1.2-2.7] and OR = 2.01[IC 1.2-3.3], respectively). In contrast, GCA (17%) and GTC (12%) haplotypes were more frequently present among controls (p = 0.033, OR = 0.53 [IC 0.3-0.9] and p = 0.02, OR = 0.44 [IC 0.2-0.9], respectively) (Table IV).

DISCUSSION

In the conditions of this study, rs2305767 and rs1457092 polymorphisms were associated with CD while rs2305764 was not. In the former, the TT genotype of the rs2305767 polymorphism acted as a protective factor and the CT genotype of the rs1457092 polymorphism, as a risk factor. These results support the idea that polymorphisms in MYO9B associate with CD, either protecting or conferring susceptibility depending on the SNPs present.

In Chile, the second National Health Survey showed that the frequency of tTG positive population is about 1% (23). Sub diagnosis is very high, estimations being that less than 10% of celiac individuals are diagnosed (6). Unfortunately, there are no data in the country or the Latin American region that would help in understanding the role of the polymorphisms assessed in this protocol, which would indeed contribute to a better knowledge of CD in this population.

Table III. Recessive model of genotypic frequencies for rs2305764, rs2305767 and rs1457092 polymorphisms in cases and controls (n = 104)

MYO9B	*Cases n (%)*	*Controls n (%)*	*p value*	*OR IC [95%]*
rs2305764				
AA	18 (17)	20 (19)	0.7	0.87 [0.4-1.9]
AG + GG	86 (83)	84 (81)		
rs2305767				
TT	9 (9)	35 (34)	0.001	0.19 [0.07-0.4]
TC + CC	95 (91)	69 (66)		
rs1457092				
AA	40 (38)	29 (28)	0.1	1.6 [0.9-3.0]
AC + CC	64 (62)	75 (72)		

MYO9B is one of the most recently described genes related to CD, which participates in maintaining the intestinal barrier. In preparation to this study, the literature was reviewed but no data was found about this gene in Latin American populations. Our results show some differences in comparison to some publications originated in Europe. That none of the genotypes of the rs2305764 polymorphism were associated with CD differs from data by Sanchez et al. (22), who found that the AA genotype was associated with CD, with OR 2.3 [IC 1.3- 4.2] p = 0.01. In the same line, Monsuur et al. found a similar association, with OR 1.66 [IC 1.23-2.13] p = 0.00053 in heterozygote and OR 2.27 [IC 1.56-3.30] p = 0.00155 in homozygote individuals (11). However, other recent publications found no association between this polymorphism and CD (12,20,21,24-27).

In the rs2305767 polymorphism, we found that the CT genotype was associated with CD with OR 4.9 [IC 2.2-11.3] p = 0.001, while the TT genotype appeared as a protective factor for CD with OR 0.19 [IC 0.1-0.4] p = 0.0001. Instead, in Sanchez's study this polymorphism was associated with CD with OR 1.5 [IC 1.0-2.0] p = 0.03. Monsuur et al. (10) also found that this polymorphism was associated with CD.

Table IV. Frequency distribution of main haplotypes in rs2305764, rs2305767 and rs1457092 polymorphisms in cases and controls

Haplotype	*Cases (%)*	*Controls (%)*	*p value*	*OR IC [95%]*
ATA	80.72 (0.39)	55.49 (0.27)	0.006	1.78 [1.2-2.7]
GCC	51.54 (0.25)	29.72 (0.14)	0.006	2.01 [1.2-3.3]
GCA	20.18 (0.09)	35.25 (0.17)	0.033	0.53 [0.3-0.9]
GTC	12.05 (0.06)	25.80 (0.12)	0.021	0.44 [0.2-0.9]

This table shows only the main haplotypes observed.

As for rs1457092 and concurring with Monsuur's data, we found that the CC genotype is a protective factor (OR 0.07 [0.0-0.3] p = 0.0001), however, this differs from data by Sanchez et al. (21). The similarities and differences described make evident the large generic variability present in the global population. There is a clear need for more data to help in understanding the relationship between these polymorphisms and CD. Hardy-Weinberg equilibrium was observed only in controls; however, we believe that the studied sample is representative and that there is no stratification bias; the sample size was accomplished. Authors estimate that it is possible that the sample size obtained was borderline because it was calculated using 80% potency. Other confusing factors, such as selection bias, would be controlled by the fact that patients and controls originated from different places. The rather large proportion of heterozygote individuals in rs2305764 and rs2305767 polymorphisms might be responsible for mistaken allele assignment, although the protocol used for allelic discrimination did not use a standard and all samples were considered as unknown samples.

Distribution of genotypes resulted in that only the rs2305767 polymorphism would be associated with CD (Table III). Presence of this trait would protect from developing CD. Analysis of haplotypes (Table IV) showed two possible risk combinations, ATA and GCC, which would cover 64% of the possible combinations with OR 1.78 and 2.01, respectively. In contrast, two other combinations (GCA and GTC) provided protection from CD, with OR 0.53 and 0.44, respectively.

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