Frequency of SNP -336A/G in the promoter region of *CD209* in a population from northeastern Brazil

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ABSTRACT. Dendritic cells (DCs) mediate the initiation of the immune response against a variety of pathogens. The DC-SIGN receptor is encoded by the gene *CD209* and is expressed on the surface of DCs. It binds to mannose-rich carbohydrates and enables the recognition of bacteria, fungi, parasites, and viruses. SNP -336A/G in the promoter region of *CD209* influences the expression of the DC-SIGN receptor. Several studies have associated this SNP with an increased susceptibility to infectious diseases and the development of more severe forms of disease. Therefore, the aim of this study was to determine the prevalence of SNP -336A/G in a population from northeastern Brazil. We analyzed 181 individuals from the general

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population of Parnaíba, Piauí, Brazil, of which 37% were men and 63% were women. SNP -336A/G was detected by polymerase chain reaction and treatment with the restriction enzyme *Msc*I and visualized by electrophoresis on an 8% polyacrylamide gel stained with silver nitrate. Of the individuals analyzed, 116 (64.1%) were homozygous AA, 57 (31.5%) were heterozygous (AG), and 8 (4.4%) were homozygous GG. The allele frequency of -336G was 20.2%. Genotype frequencies were in Hardy-Weinberg equilibrium. To the best of our knowledge, this is the first report to describe the frequency of the *CD209* SNP -336A/G in a population in the State of Piauí. Further studies are needed to determine the relationship between this SNP and the vulnerability of this population to major infectious diseases.

Key words: DC-SIGN; CD209 gene; SNP-336A/G; Piauí State

INTRODUCTION

The human immune system attempts to control infection as soon as a pathogen begins to disrupt the physical and chemical barriers of innate immunity. This initial response is mediated by specialized cells that capture, process, and present microbial antigens to the effector cells of adaptive immunity. Dendritic cells (DCs) capture antigens in peripheral tissues and direct them to the lymph nodes. They are therefore essential for the initiation of the immune response against a variety of microorganisms (Merad et al., 2013). To carry out this important function, DCs constitutively express on their surfaces a variety of receptors known as pathogen recognition receptors (PRRs). PRRs recognize conserved structural components that are essential to pathogen survival (Sukhithasri et al., 2013).

A receptor known as DC-specific ICAM-3-grabbing non-integrin (DC-SIGN) recognizes and binds carbohydrates with a high mannose content. Such carbohydrates are present in the external structure of certain pathogens, where they promote pathogen internalization and subsequent antigen presentation. DC-SIGN is a member of the C-type lectin receptor family and is normally expressed in immature DCs of the skin or mucosal tissues. In addition to its role in pathogen capture, DC-SIGN is involved in the migration of DCs and activation of T lymphocytes (Geijtenbeek et al., 2002; Svajger et al., 2010). In recent years, studies have shown that the receptor participates in the initial contact between DCs and a variety of pathogens, including bacteria (*Mycobacterium tuberculosis*), parasites (*Schistosoma mansoni* and *Leishmania pifanoi*), fungi (*Candida albicans*), and especially HIV-1, HIV-2, *Ebolavirus*, hepatitis C virus, *Cytomegalovirus*, and dengue virus (Van Kooyk and Geijtenbeek, 2003).

The gene encoding DC-SIGN is known as *CD209* and is located at 19p13.2 (Soilleux et al., 2000). The gene contains seven exons distributed over 13 kb. The high density of genomic variations in the structure of *CD209* has prompted researchers to investigate the role of *CD209* single nucleotide polymorphisms (SNPs) in susceptibility to infectious diseases (Goméz et al., 2006; Selvaraj et al., 2009; Da Silva et al., 2012). Among the SNPs of interest are those located in the promoter region of *CD209*. These SNPs can influence the affinity of transcription factors and thus affect the expression of the DC-SIGN receptor (Barreiro et al., 2006; Barkhash et al., 2012; Alagarasu et al., 2013). One of the most well-studied SNPs is a

nucleotide transition from adenine (A) to guanine (G) at position -336 (-336A/G, rs4804803) in the promoter region of *CD209* (Barreiro et al., 2006). *In vitro* studies have demonstrated that this substitution modulates the expression of *CD209* by affecting the binding of transcription factor Sp1 (Sakuntabhai et al., 2005; Chan et al., 2010). Recently, Wang et al. (2011) reported that *CD209* expression in individuals with the AG genotype was higher than in individuals with the AA genotype, leading to higher expression of DC-SIGN on the surface of DCs in subjects harboring allele -366G. Thus, *CD209* has been extensively studied for its influence on the susceptibility to various infectious diseases (Olesen et al., 2007; Kashima et al., 2009; Chan et al., 2010; Barkhash et al., 2012; Xavier-Carvalho et al., 2013). The first evidence of a relationship between the *CD209* SNP -336A/G and disease susceptibility was documented in a study by Martin et al. (2004), which showed that the risk of parenteral HIV infection was higher in subjects with allele -336G. Subsequently, Barreiro et al. (2006) examined *CD209* SNPs in 351 tuberculosis patients and 360 healthy controls in an African population and reported that SNP -336A/G was associated with an increased risk of developing tuberculosis. Additionally, Sakuntabhai et al. (2005) found initial evidence for the association of this SNP with the pathogenesis of dengue virus infection. These authors found that allele -336G was associated with disease severity, a finding corroborated by a more recent case-control study, in which Wang et al. (2011) demonstrated that the GG and AG genotypes were associated with increased susceptibility to dengue hemorrhagic fever, the most severe form of the disease.

Given the documented association of SNP -336A/G with disease susceptibility and the severity of clinical manifestations, studies on the molecular epidemiology of this variant in different populations are needed. Thus, the aim of this study was to analyze the prevalence of *CD209* SNP -336A/G in a population from northeastern Brazil.

MATERIAL AND METHODS

Study population

This study included 181 individuals from the general population of the city of Parnaíba, Piauí, in northeastern Brazil. They were volunteers from a large project to study frailty in the elderly, already developed in Brazil, the FIBER Network (Network of Research on Frailty in Elderly Brazilians). All volunteers were informed about the purpose of the research and the experimental procedures, and they signed consent forms. For analysis, 4 mL peripheral blood was collected from each volunteer. The study protocol was approved by Universidade Federal do Piauí Ethics Committee in Research.

DNA extraction and genotyping

Genomic DNA was extracted from peripheral blood leukocytes using the Wizard® Genomic DNA Purification kit (Promega Inc., Madison, WI, USA) according to the manufacturer specifications.

To analyze SNP -336A/G in *CD209*, we used polymerase chain reaction, followed by treatment with a restriction endonuclease (PCR-RFLP). The region containing SNP -336A/G was amplified with the forward primer 5'-GAA CTG GGG GTG CTA CTC GGC-3' and the reverse primer 5'-CAG TGG TTC TCT GGA CTT GTC AC 3', generating a product of 384

bp. In a total reaction volume of 25 µL, the following reagents were used: 50 ng DNA, 1X buffer (100 mM Tris-HCl, pH 8.5, 500 mM KCl), 1.5 mM $MgCl_2$, 0.4 mM of each primer, 0.2 mM dNTP, 1.5 U Taq DNA polymerase, and Milli-Q H_2O. The reaction parameters used were: initial denaturation at 95°C for 5 min; 35 cycles of 45 s at 95°C, 30 s at 57°C, and 45 s at 72°C; and a final extension at 72°C for 7 min. After amplification, the reaction products were incubated in the presence of the enzyme *Msc*I (New England BioLabs, Ipswich, MA, USA) for RFLP analysis, according to the manufacturer instructions. After digestion, RFLP products were electrophoresed on an 8% polyacrylamide gel and stained with silver nitrate to visualize the band patterns. In the -336G allele, *Msc*I recognizes a restriction site that, after enzymatic digestion, generates two fragments of different sizes (363 and 21 bp). Allele -336A is not cleaved. Therefore, individuals with the AA genotype have a single band of 384 bp, whereas individuals with the GG genotype have two bands, of 363 and 21 bp. Heterozygous individuals have all three bands.

Statistical analysis

Genotypic and allelic frequencies were determined by simple counting. To test whether the population was in Hardy-Weinberg equilibrium for the locus in question, genotype frequencies were first calculated from the allele frequencies. Their deviation from the number of observed genotypes was then determined using the chi-square test. We adopted a significance level of 5% and used the Fisher exact test to compare the allele frequencies in this study with those of other populations. The BioEstat 5.0 program was used for the statistical evaluation of data.

RESULTS

Of the 181 elderly subjects analyzed, 67 (37%) were male and 114 (63%) were female, with a mean age of 73 years (ages 65 to 93 years). As shown in Table 1, 116 individuals had the AA genotype (64.1%), 57 had the AG genotype (31.5%), and 8 had the GG phenotype (4.4%). The allele frequency of -336G was 20.2%.

Table 1. Distribution of the genotype and allele frequencies of the *CD209* SNP -336A/G in the population of Parnaíba, Piauí, in northeastern Brazil.

	Genotypic frequency [N (%)]			P	Allelic frequency (%)		P
	AA	AG	GG		A	G	
Total (N = 181)	116 (64.1)	57 (31.5)	8 (4.4)		79.8	20.2	
Gender							
M (N = 67)	41 (61.2)	25 (37.3)	1 (1.5)	0.119	79.9	20.1	0.570
F (N = 114)	75 (65.8)	32 (28.1)	7 (6.1)		79.8	20.2	
Age							
≤73 (N = 108)	66 (61.1)	35 (32.4)	7 (6.5)	0.149	77.3	22.7	0.142
>73 (N = 73)	50 (68.5)	22 (30.1)	1 (1.4)		83.6	16.4	

The distribution of SNP -336A/G was within Hardy-Weinberg equilibrium ($\chi^2 = 0.041$, P = 0.979). The frequency of allele -336G was similar between genders: 20.2% in women and 20.1% in men. Furthermore, there was no statistically significant difference between the frequencies of the SNP in individuals over 73 years (22.7%) and under 73 years (16.4%; P > 0.05).

DISCUSSION

Molecular epidemiology studies aim to characterize the distribution of genetic variants, especially those of medical importance, in different ethnic populations around the world. Despite its limited practical applicability, this area of research provides a basis for the development of personalized medicine, and it will have a great impact on public health by allowing researchers to track populations at higher risk of developing certain diseases or those more susceptible to disease worsening. In this study, we described the frequency of *CD209* SNP -336A/G in a population from Piauí State, located in northeastern Brazil. This SNP has been associated with infectious diseases of different etiologies, notably those of viral origin (Kashima et al., 2009; Chan et al., 2010; Ryan et al., 2010; Wang et al., 2011; Barkhash et al., 2012).

SNP -336A/G is heterogeneously distributed among different regions of the world (Table 2). In the population analyzed in this study, the observed allele frequency was 20.2%, which is similar to the frequency observed in European countries ($P > 0.05$). In an Irish population, for example, the frequency of allele -336G is 19% (Ryan et al., 2010). In Spain, the frequency varies between 20.8% in the north to 22% in the south (Núñez et al., 2006; Dieguez-Gonzalez et al., 2009). The frequency of SNP -336A/G in some African regions, such as in South Africa (40.3%) and Guinea-Bissau (49.9%), is considerably higher than the frequency found in this study ($P < 0.05$) (Barreiro et al., 2006; Olesen et al., 2007). However, in some northern African countries, such as Tunisia and Morocco, the frequency of this polymorphism is not statistically different from that of European countries (Ben-Ali et al., 2007; Sadki et al., 2009). Moreover, the frequency of allele -336G observed in this study was significantly higher than the frequency observed in Asian populations, such as those of eastern China (7.3%) (Zheng et al., 2011), northern Thailand (9.5%) (Wichukchinda et al., 2007), and different regions of Taiwan (Table 2). However, the frequency did not differ from that found in Indonesia (12.7%) (Kobayashi et al., 2011), western and south India (15.9 and 22.3%, respectively) (Selvaraj et al., 2009; Alagarasu et al., 2013), or the Asian portion of Russia (18.4%) (Barkhash et al., 2012). There was no statistically significant difference between the frequencies of allele -336G observed in the present study population and a population from Australia (16%) (Clifford et al., 2011).

The Brazilian population is characterized by high genetic diversity, a result of the intense mixing of people of different ethnicities, which began shortly after the arrival of the Portuguese in Brazil in the 15th century and intensified with the arrival of Africans. Moreover, as a country with great territorial extension associated with some historical aspects of colonization, the pattern of miscegenation between people is different in regions that today comprise the states. It is therefore reasonable to infer that the distribution pattern of genetic variants, such as SNP -336A/G in *CD209*, varies among the different geographical areas of the country (Table 3). A study by Kashima et al. (2009) highlights the effect of ethnicity on the frequency of allele -336G in Brazil. In this research, the frequency of allele -336G observed in Brazilians of European descent was 26.7%, whereas it was 42% in those of African descent and was 5.4% in individuals of Asian descent. The allele was not observed in Native American Indians. In the study, the frequency of allele -336G was 29.7% in a naturally mixed population, a frequency that does not differ statistically from the frequency we observed (20.2% in a mixed population in northeastern Brazil).

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Table 2. Comparison of the allele frequencies of the *CD209* SNP -366A/G in other populations worldwide.

Population	N	Allelic frequency		P	Ref.
		A	G		
Brazil, Piauí	181	79.8	20.2		This study
Europe					
Western Ireland	79	81.0	19.0	0.500	Ryan et al. (2010)
Northern Spain	1570	79.2	20.8	0.500	Dieguez-Gonzalez et al. (2009)
Southern Spain	312	78.0	22.0	0.431	Núñez et al. (2006)
Africa					
South Africa (South Africa)	360	59.7	40.3	0.001	Barreiro et al. (2006)
Guinea-Bissau (West Africa)	347	50.1	49.9	<0.001	Olesen et al. (2007)
Tunisia (North Africa)	140	72.7	27.3	0.158	Ben-Ali et al. (2007)
Morocco (North Africa)	151	71.2	28.8	0.094	Sadki et al. (2009)
Asia					
South India	157	77.7	22.3	0.431	Selvaraj et al. (2009)
Western India	104	84.1	15.9	0.290	Alagarasu et al. (2013)
Southern Taiwan	120	96.2	3.8	0.0004	Wang et al. (2011)
Southwestern Taiwan	243	96.5	3.5	0.0004	Yu et al. (2012)
Northern Thailand	290	90.5	9.5	0.036	Wichukchinda et al. (2007)
Indonesia, Java provinces	564	87.3	12.7	0.126	Kobayashi et al. (2011)
Eastern China	244	92.6	7.3	0.006	Zheng et al. (2011)
Russia, Siberia	263	81.6	18.4	0.428	Barkhash et al. (2012)
Oceania					
Western Australia	150	84.0	16.0	0.290	Clifford et al. (2011)

Table 3. Comparison of the allelic frequencies of the *CD209* SNP -366A/G in this study and other regions of Brazil.

Population	N	Allelic frequency		P	Ref.
		A	G		
Piauí, northeast	181	79.8	20.2		This study
Pernambuco, northeast	78	68.6	31.4	0.052	Da Silva et al. (2012)
Pará, north	72	82.6	17.4	0.358	Oliveira et al. (2014)
São Paulo, southeast					Kashima et al. (2009)
Caucasians	45	73.3	26.7	0.158	
African-Brazilian	25	58	42	<0.001	
Asian	28	94.6	5.4	0.001	
Mixed descent	32	70.3	29.7	0.070	
Espírito Santo, southeast					Dettogni et al. (2013)
General population	100	62.5	37.5	0.003	
Pomerana population	59	80.5	19.5	0.570	
Rio de Janeiro, southeast	332	72.0	28.0	0.123	Xavier-Carvalho et al. (2013)
Amerindians (Mato Grosso)	25	100	0	<0.001	Kashima et al. (2009)

Although the frequency of *CD209* SNP -336A/G found in this study was similar to the frequency found in other Brazilian regions (Xavier-Carvalho et al., 2013; Oliveira et al., 2014), it was significantly lower than that found in a population in the southeast, where the observed frequency was 37.5% ($P < 0.05$) (Dettogni et al., 2013). However, a higher frequency of allele -336G has been observed even in neighboring Piauí states such as Pernambuco; the allele frequency in the study performed by Silva et al. (2012) was 31.4% ($P = 0.052$). In that case, the high frequency of SNP -366A/G might reflect the greater African contribution to the genetic background of the population, which is estimated to be 34% (Alves-Silva et al., 2000). The degree of mixing in the Piauí population was documented in a recent study (Lopes et al., 2014), which showed that the genetic background of the population is predominantly European (60%), followed by African (21.5%) and Amerindian (18.5%). The participants involved in this study were residents of the city of Parnaíba, Piauí, which is racially mixed.

The DC-SIGN receptor is essential for the capture of a variety of pathogens by DCs. However, some pathogens exploit the natural function of these cells and evade detection by the immune system or use DCs to enhance transmission to other cells. In HIV-1 infection, viral particles captured by DC-SIGN are transported to regional lymph nodes, where they are transmitted to $CD4^+$ T cells (Van Kooyk and Geijtenbeek, 2003). SNP -336A/G in *CD209* influences the expression of the DC-SIGN receptor. One study found that allele -336G was associated with higher expression of DC-SIGN on the surface of DCs (Wang et al., 2011). In this context, SNP -336A/G in *CD209* could confer greater protection or increased susceptibility to certain infectious diseases (Barreiro et al., 2006; Kashima et al., 2009; Chan et al., 2010; Ryan et al., 2010). However, because some studies have reported contradictory results, the actual effect of SNP -336A/G remains inconclusive in some cases (Wang et al., 2011; Alagarasu et al., 2013; Oliveira et al., 2014), emphasizing the need for validation studies in different populations.

Our study population included 181 participants, all of them elderly individuals, aged between 65 and 93 years. This age group is most susceptible to infectious diseases because of a natural reduction in immunity (McElhaney and Effros, 2009). For example, according to Ministério da Saúde do Brasil (2013), in the state of Piauí, people over 60 years have a 12 times greater risk of dying from dengue than people in other age groups. Moreover, of the total deaths in the first quarter of 2013, 42% occurred in this age group. SNP -336A/G in *CD209* has been associated with an unfavorable prognosis for patients with dengue (Sakuntabhai et al., 2005; Wang et al., 2011). Therefore, it is reasonable to infer that this SNP might contribute to the occurrence of fatal dengue cases in the elderly population of Piauí, given that the SNP is common in this population, as observed in this study.

CONCLUSION

To our knowledge, this is the first report to describe the frequency of the *CD209* SNP -336A/G in a population in the State of Piauí. The frequency did not differ significantly from those reported in European countries and most Brazilian regions. Studies conducted in Brazilian and European populations have found an association between SNP -336A/G and susceptibility to a variety of diseases (Núñez et al., 2006; Kashima et al., 2009; Da Silva et al., 2012). Therefore, further studies are needed to investigate the relationship between this SNP and the vulnerability of the population of Piauí State to infectious diseases.

Conflicts of interest

The authors declare no conflict of interest.

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