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Polymorphic genetic variation in immune system genes: a study of two populations of Espirito Santo, Brazil

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Abstract Mapping single nucleotide polymorphisms (SNPs) in genes potentially involved in immune responses may help understand the pathophysiology of infectious diseases in specific geographical regions. In this context, we have aimed to analyze the frequency of immunogenetic markers, focusing on genes CD209 (SNP -336A/G), FCγRIIa (SNP -131H/R), TNF-α (SNP -308A/G) and VDR (SNP Taq I) in two populations of the Espirito Santo State (ES), Brazil: general and Pomeranian populations. Peripheral blood genomic DNA was extracted from one hundred healthy individuals of the general population and from 59 Pomeranians. Polymorphic variant identification was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP). SNP genotype frequencies were in Hardy–Weinberg Equilibrium. There was no statistically significant difference in allelic and genotypic distributions between the two populations studied. Statistically significant differences were observed for SNP genotype distribution in genes CD209, TNF-α and VDR when comparing the ES populations with other Brazilian populations. This is the first report of CD209, FcγRIIa, TNF-α and VDR allelic frequencies for the general and Pomeranian populations of ES.

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Introduction

Small genetic variations such as SNPs can influence gene expression and change protein structure or function. SNPs located in the promoter or other regulatory regions may affect gene transcription and alter variability in the immune response. The presence of certain alleles may contribute to the susceptibility or host resistance for different infectious diseases caused by viruses [1], bacteria [2] and protozoa [3–5].

SNPs in genes CD209, FcγRIIa, TNF-α and VDR affect the immune response for various infections [1, 6–8]. Gene and protein nomenclature are shown in Table 1.

Dendritic cell-specific ICAM-3 grabbing non-integrin (DC-SING, encoded by CD209) is mainly expressed in dendritic cells (DC) and plays an important role in some infectious diseases [9–11]. DCs can be targets for pathogens, in an attempt to impair the initial immune response in early infection [12]. Among SNPs in the CD209, the guanine (G) to adenine (A) transition at position 2336 within the CD209 gene promoter (SNP -336 A/G) has been suggested to affect transcriptional activity of DC-SIGN [8]. Association studies have been performed between CD209 gene polymorphisms and pathogens: viruses such as human immunodeficiency virus-1 (HIV-1), hepatitis C virus (HCV), cytomegalovirus, Ebola virus and SARS-coV; bacteria such as *Mycobacterium tuberculosis* and parasites such as *Leishmania* and *Schistosoma mansoni* [13–17]. SNP -336A/G has been associated with the susceptibility to HIV [18], *M. tuberculosis* [19], HCV [20], and dengue [8].

Fcγ leukocyte receptors are essential for the immune defense against pathogens. Antibody binding to the Fc-receptors causes

Table 1 SNPs associated with response to infectious diseases

Gene	Protein	SNP	rs number	Reference allele	Variant allele
CD209	Dendritic cell-specific	−336 A/G	4804803	A	G
FcγRIIa	Fc gama	−131 H/R	1801274	A	G
TNF-α	Tumor necrosis factor	−308 A/G	1800629	G	A
VDR	Vitamin D receptor	Taq I	731236	T	C

Table 2 Primer sequences and RFLP conditions

Gene	SNP	Primer sequence	Product size	Restriction enzyme	Digestion pattern	Reference
CD209	−336 A/G (rs4804803)	5′-CAGAGCATG GACAGG GAGCAAG-3′	150 bp	MscI	Allele G—19 bp + 131pb	[8]
		5′- GGATGTACGTCTGCAGTGTG-3′			Allele A—150 bp	
FcγRIIa	−131 H/R (rs1801274)	5′- GGAAAATCCAGAAATTCTCGC-3′	366 bp	BstUI	Allele H—343 bp	[39]
		5′- CAACAGCCTGACTACCTATTACGCGGG-3′			Allele R—322 bp	
TNF-α	−308 A/G (rs1800629)	5′- AGGCAATAGGTTTTGAGGGCCAT-3′	107 bp	NcoI	Allele A—107 bp	[40]
		5′- TCCTCCCTGCTCCGATTCCG-3′			Allele G—87 bp + 20 bp	
VDR	Taq I (rs731236)	5′-CAGAGCATGGACAGGGAGCAAG-3′	340 bp	TaqI	Allele T—340 bp	[41]
		5′-GGATGTACGTCTGCAGTGTG-3′			Allele C—293 bp + 47pb	

bp base pairs

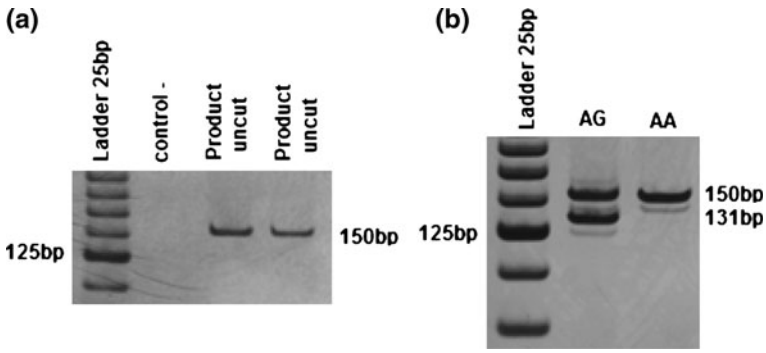

Fig. 1 CD209 genotypes. **a** amplified DNA products. **b** MscI digestion of PCR products. *bp* base pairs; Ladder: 25 bp molecular weight marker

important biological consequences, e.g. antibody dependent cell-mediated cytotoxicity or inhibition and phagocytosis [21]. FcγRIIa has two co-dominantly expressed alleles, R131 (G at position 494) and H131 (A at position 494), which differ in their ability to bind immunoglobulin G (IgG) subclasses. Cells expressing H131 bind more efficiently to IgG2 and IgG3 than those expressing the R131 variant [22]. This SNP has been associated with susceptibility and severity of some infectious disease such as meningococcal disease, *Streptococcus pneumoniae* infections, dengue fever and HIV infection [1, 23–25]. RR genotype seems to be associated with protection against intracellular pathogen infections [2, 26, 27].

TNF-α is a pleiotropic pro-inflammatory cytokine, with effects on apoptosis and activation of target cells involved in the amplification of immunological cellular processes [28]. Among several TNF-α gene polymorphisms, the SNP located at nucleotide position 308 (G or A) has been shown to directly affect TNF-α expression [29]. The AA genotype has been significantly associated with higher TNF-α production and in some cases with increased morbidity and mortality in sepsis, malaria, chronic obstructive pulmonary disease (COPD), leishmaniosis, systemic lupus erythematosus (SLE), type 1 autoimmune hepatitis and other immune mediated disorders (asthma and contact dermatitis) [30–34].

The vitamin D receptor (VDR) mediates the immunoregulatory effects of the hormonal form of vitamin D, which includes activating monocytes, stimulating cellular immune responses, suppressing immunoglobulin production and lymphocyte proliferation [35]. The TT genotype of VDR Taq I SNP (substitution of a thymine (T) for a cytosine (C) at position 352) [36] has been recently associated with tuberculoid leprosy, enhanced clearance of hepatitis B infection and resistance to pulmonary tuberculosis [37, 38].

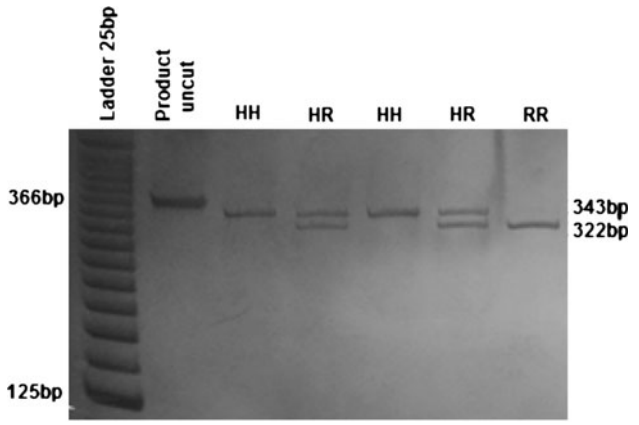

Fig. 2 FcγRIIa genotypes. **a** amplified DNA products and BstUI PCR product digestion. *bp* base pairs; Ladder: 25 bp molecular weight marker

SNP frequency characterization of genes encoding immune mediators may aid in the creation of alternative methods for diagnosis, vaccine development or more effective therapies according to the population genetic profile. SNP frequencies are population specific, reason because we decided to characterize the general population and the Pomeranian subpopulation of ES, Brazil, for 4 SNPs in immune system genes.

Materials and methods

This study was approved by the Research Ethics Committee of the Federal University of ES and all patients signed an informed consent (Protocol n°190/11).

Sample

Five milliliters (ml) of peripheral blood were collected from 100 healthy volunteers of the ES general population. As for the 59 healthy Pomeranian volunteers of Santa Maria de Jetibá, ES, 3–5 peripheral blood drops were collected on FTA® Elute Cards (Whatman, USA).

SNP genotyping

Genomic DNA was isolated using phenol/chloroform extraction or following FTA® Elute Card manufacturer's recommendations (Whatman, USA). CD209, FcγRIIa, TNF-α and VDR alleles were detected by PCR–RFLP.

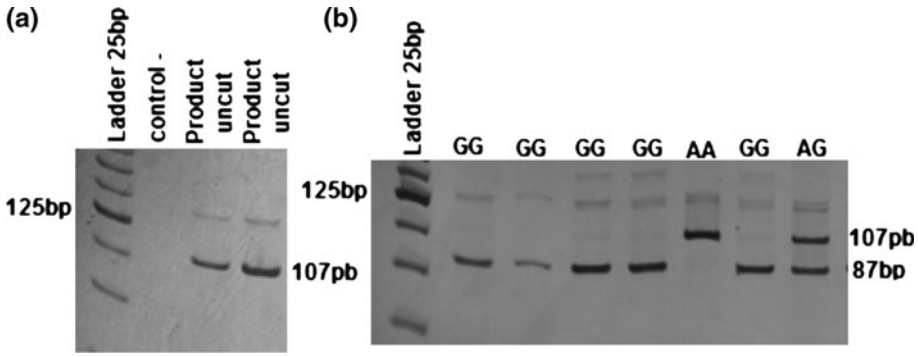

Fig. 3 TNF-α genotypes. **a** amplified DNA products. **b** NcoI digestion of PCR products. *bp* base pairs; Ladder: 25 bp molecular weight marker

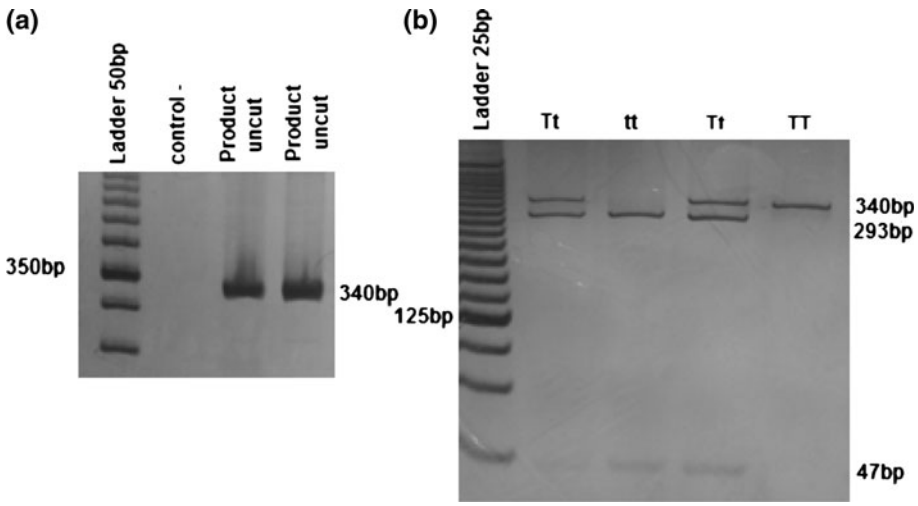

Fig. 4 VDR genotypes. **a** amplified DNA products. **b** Taq I digestion of PCR products. *bp* base pairs; Ladder: 25 bp molecular weight marker

Table 3 Allele and genotype SNP frequencies

Allele/genotype	General population (n = 100)	Pomeranian population (n = 59)
CD209: −336 A/G		
A	62.5 (125)	80.5 (95)
G	37.5 (75)	19.5 (23)
AA	61 (61)	66.1 (39)
AG	36 (36)	28.8 (17)
GG	3 (3)	5.1 (3)
FcγRIIa: −131 H/R		
H	48 (96)	50.8 (60)
R	52 (104)	49.2 (58)
HH	21 (21)	22 (13)
HR	54 (54)	57.6 (34)
RR	25 (25)	20.4 (12)
TNF-α: −308 A/G		
A	20 (40)	17.8 (21)
G	80 (160)	82.2 (97)
AA	5 (5)	3.4 (2)
AG	30 (30)	28.8 (17)
GG	65 (65)	67.8 (40)
VDR: Taq I		
T	63.5 (127)	66.1 (78)
C	36.5 (73)	33.9 (40)
TT	41 (41)	44.07 (26)
TC	45 (45)	44.07 (26)
CC	14 (14)	11.9 (7)

Numbers in parenthesis represents allele or genotype counts

Primer sequences, restriction enzymes and conditions are shown in Table 2.

Statistical analysis

SNP allele and genotype frequencies were determined by direct counting. *P* values <0.05 were considered statistically significant. Chi square test was used to determine whether a genotype was at HWE, using Chi square HWE equilibrium test calculator for biallelic markers (http://www.genes.org.uk/software/hardy-weinberg.shtml). Fisher's exact test was performed using *Graphpad Prism*® version 5.0 (www.graphpad.com).

Results

Representative genotyping results are shown in Figs. 1, 2, 3 and 4.

SNP allele and genotype frequencies for genes CD209, FcγRIIa, TNF-α and VDR in the Pomeranian and general populations of ES are given in Table 3. All polymorphisms were at HWE equilibrium among Pomeranian and non-Pomeranian individuals ($p > 0.05$, Table 4). Genotype and allele frequencies were not significantly different between the two populations ($p > 0.05$, Table 5).

Table 4 *p*- and x^2 values for HWE calculations in both populations was performed by x^2-test

Gene/SNP	X^2/p value (General population)	X^2/p value (pomeranian population)
CD209/−336 A/G	0.72/0.40	0.40/0.53
FcγRIIa/−131 H/R	0.67/0.41	1.38/0.24
TNF-α/−308 A/G	0.39/0.53	0.01/0.92
VDR/Taq I	0.09/0.76	0.02/0.89

Table 5 Allele and genotype frequencies, *p* value calculated by Fischer's exact test

Genotype/Allele	*p* value (General population vs. Pomeranians)
CD209: −336 A/G	
A and G	0.32
AA	0.61
AG	0.39
GG	0.67
FcγRIIa: −131 H/R	
H and R	0.64
HH	1.0
HR	0.74
RR	0.57
TNF-α: −308 A/G	
A and G	0.66
GG	0.86
AG	1.0
AA	1.0
VDR: Taq I	
T and C	0.72
TT	0.74
TC	1.0
CC	0.81

Discussion

This study aimed to characterize the general and Pomeranian populations of ES, Brazil as for 4 SNPs in genes important for the immune response to infections.

Allelic frequencies for all SNPs were in HWE equilibrium. There was no statistically significant difference in allelic and genotypic distributions between the two populations. This result confirms data of Stur et al. [42] which reported gene flow between the general and Pomeranian populations of ES.

Table 6 SNPs frequencies in association studies of various ethnic groups (healthy individuals). *P* values calculated by Fischer's exact test

SNP	Population	Sample size	Genotype	Frequency	*p* value (population of column 2 vs. general population of ES)	*p* value (population of column 2 vs. pomeranian population of ES)	Reference
CD209: −336 A/G	Taiwanese	120	AA	111	<0.0001*	<0.0001*	[43]
			AG	9	<0.0001*	0.0004*	
			GG	0	0.1	0.03*	
	South African	360	AA	137	<0.0001*	<0.0001*	[19]
			AG	156	0.21	0.04*	
			GG	67	<0.0001*	0.008*	
	Brazilian (Sao Paulo)	32	AA	18	0.68	0.37	[44]
			AG	9	0.52	1.0	
			GG	5	0.02*	0.12	
FcγRIIa: −131 H/R	African American	170	HH	44	0.38	0.6	[45]
			HR	73	0.1	0.07	
			RR	53	0.33	0.13	
	Caucasian	220	HH	69	0.06	0.15	
			HR	97	0.1	0.08	
			RR	54	1.0	0.6	
	Brazilian (Sao Paulo)	48	HH	13	0.41	0.65	[22]
			HR	25	0.2	0.7	
			RR	10	0.68	1.0	
TNF-α: −308 A/G	Italian	138	GG	109	0.02*	0.1	[6]
			GA	29	0.13	0.27	
			AA	0	0.01*	0.09	
	American (USA)	235	GG	164	0.44	0.75	[46]
			GA	67	0.79	1.0	
			AA	4	0.13	0.35	
	Brazilian (Minas Gerais)	43	GG	29	0.85	1.0	[47]
			GA	14	0.84	0.83	
			AA	0	0.32	0.51	
VDR: Taq I	Vietnamese	247	TT	231	<0.0001*	<0.0001*	[1]
			TC	15	<0.0001*	<0.0001*	
			CC	1	<0.0001*	<0.0001*	
	Indian	143	TT	70	0.24	0.54	[48]
			TC	62	0.89	1.0	
			CC	11	0.13	0.42	
	Brazilian (Rio de Janeiro)	40	TT	29	0.001*	0.007*	[49]
			TC	7	0.003*	0.009*	
			CC	4	0.78	1.0	

* Statistically significant values

For each SNP, we analyzed the difference in genotype distribution among ES populations and two other populations of different ethnic groups randomly selected and a population of southeast Brazil (Table 6).

CD209 gene SNP showed a significant difference in genotype distribution between the ES populations separately, as well as when they were compared with the population of Taiwan and South Africa. Moreover, the GG genotype had a significant difference in distribution between the general ES and Sao Paulo populations.

FcγRIIa SNP genotype distribution was not different among ES populations and other populations analyzed.

Comparing TNF-α SNP genotype frequencies among ES populations and other 3 populations, there was a statistically significant difference in homozygous genotypes distribution between the general ES population and Italians.

VDR SNPs showed a significant difference in genotype distribution among ES populations and populations of Rio de Janeiro and Vietnam.

These variations indicate the need to characterize specific populations for SNP composition in genes important for the immune system in various regions of the world.

The ES state, as well as the entire southeastern Brazil, presents high prevalence of many infectious diseases. Thus, assessing the genetic diversity of immune system components may generate knowledge relevant to the understanding of how the population responds to infectious diseases such as dengue, tuberculosis, hepatitis, malaria, HIV and others.

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