Distribution of the *IL-1RN*, *IL-6*, *IL-10*, *INF- γ* , and *TNF- α* Gene Polymorphisms in the Mexican Population

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Background: Cytokines are a group of polypeptides with an important role in the inflammatory response. It has been suggested that certain polymorphisms located in several cytokine genes are associated with different diseases. The aim of the present study was to establish the gene frequency of 13 polymorphisms of the *IL-1RN*, *IL-6*, *IL-10*, *INF- γ* , and *TNF- α* genes in a Mexican population. These polymorphisms have been reported in several populations, with important variation in frequency according to the studied population. **Methods:** Thirteen polymorphisms (rs419598, rs315951, rs2234663, rs3811058, rs1800796, rs2069827, rs1800896, rs1800871, rs1800872, rs1800629, rs2069709, rs2069710, and rs361525) were analyzed by 5' exonuclease TaqMan genotyping assays in a group of 248 healthy unrelated Mexican individuals. **Results:** The results obtained showed that the studied Mexican population presents significant differences ($p < 0.05$) in the distribution of the *IL1RN* (rs419598, rs315951, and rs2234663), *IL1F10* (rs3811058), *IL6* (rs1800796, rs2069827), *IL10* (rs1800896, rs1800871, and rs1800872), and *TNF- α* (rs1800629) polymorphisms when compared to Caucasian, Asian, and African populations. **Conclusions:** In summary, the distribution of the *IL-1RN*, *IL-6*, *IL-10*, and *TNF- α* cytokine gene polymorphisms distinguishes the studied Mexican population from other groups. Since the alleles of these cytokines are associated with the development of several inflammatory diseases, knowledge of the distribution of these alleles in the studied Mexican population could be helpful to understand their true role as a genetic susceptibility marker in this population.

Introduction

THE INFLAMMATORY PROCESS is divided into acute phase and chronic phase. Both phases are characterized by increased blood flow and vascular permeability along with the accumulation of fluid, leukocytes, and inflammatory mediators, such as cytokines (Tedgui and Mallat, 2006; Shantsila and Lip, 2009). Cytokines are a group of cell-derived polypeptides that, to a large extent, orchestrate the inflammatory response. In addition, they are pleiotropic molecules that elicit their effects locally or systemically in an autocrine or paracrine manner (Tedgui and Mallat, 2006). On the other hand, cytokines are involved in extensive networks that involve synergistic as well as antagonistic interactions and exhibit both negative and positive regulation effects on various target cells (Feghali and Wright, 1997; Tedgui and Mallat, 2006; Shantsila and Lip, 2009). Data from several studies support the role of cytokines, such as the antagonist receptor of interleukin 1 (IL-1ra), interleukin-6 (IL-6), interleukin-10 (IL-10), interferon-gamma (INF- γ), tumor necrosis factor-alpha (TNF- α), and transforming growth factor, in the acute inflammatory

process (Feghali and Wright, 1997; Tedgui and Mallat, 2006; Shantsila and Lip, 2009). IL-1 β is a proinflammatory molecule that participates in the regulation of endothelial and smooth muscle cell mitogenesis, thrombogenic response of endothelial cells, extracellular matrix production, and vascular permeability (Iacoviello *et al.*, 2005). Nonetheless, the proinflammatory effects of IL-1 can be inhibited by IL-1ra originally referred to as IL-1 inhibitor. This receptor is an anti-inflammatory nonsignaling molecule that competes for receptor binding with IL-1 α and IL-1 β (Maksymowych *et al.*, 2003; Timms *et al.*, 2004). TNF- α is a potent immunomediator and proinflammatory cytokine that has been implicated in activation of growth factors, cytokines, and chemoattractants, and by affecting the synthesis and stimulation of adhesion molecules (Azmy *et al.*, 2004; Sharma *et al.*, 2010). INF- γ plays a central role in the immune and inflammatory response to a wide range of stimuli. Also, it is a cytokine essential in the development and propagation of T helper 1 type immune response and is an important mediator of innate immunity (Qi *et al.*, 2005). IL-6 is a pleiotropic cytokine with a broad range of humoral and cellular immune effects relating

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to inflammation, host defense, and tissue injury (Tanaka *et al.*, 2005; Morgan *et al.*, 2006). On the other hand, IL-10 plays a crucial role in the regulation of inflammation. Moreover, this cytokine inhibits the proinflammatory cytokines synthesis, suppresses macrophages function, and inhibits the activation of Th1 cells and adhesion molecules (Koch *et al.*, 2001). Polymorphisms of these genes have been reported in several populations with important variation in frequency according to the studied population. Moreover, numerous investigators have reported correlations between the specific polymorphic variants of these cytokines with several diseases (Koch *et al.*, 2001; Maksymowych *et al.*, 2003; Azmy *et al.*, 2004; Timms *et al.*, 2004; Iacoviello *et al.*, 2005; Qi *et al.*, 2005; Tanaka *et al.*, 2005; Morgan *et al.*, 2006; Fragoso *et al.*, 2010a, 2010b, 2011; Sharma *et al.*, 2010). Thus, the aim of the present study was to establish the gene frequency of 13 polymorphisms of the *IL-1RN*, *IL-6*, *IL-10*, *INF- γ* , and *TNF- α* genes in a Mexican population.

Materials and Methods

The study included a group of 248 healthy unrelated individuals (196 men and 52 woman, mean age 56.0 ± 4.12) who met the following criteria: no history or symptoms of bronchial diseases, allergy, dermatitis, hypertension, diabetes, infections, cardiovascular diseases, and systemic diseases. All subjects included in the study were Mexican Mestizos. We considered as Mexican Mestizos only those individuals who had been born in Mexico for three generations, including their own. A Mexican Mestizo is defined as someone born in Mexico, who is a descendant of the original autochthonous inhabitants of the region and of individuals, mainly Spaniards, of Caucasian and/or African origin, who came to America during the 16th century. The Institutional Ethics and Research Committees approved the study, and all subjects provided written informed consent.

DNA extraction

Genomic DNA from whole blood containing ethylenediaminetetraacetic acid was isolated by a standard technique (Lahiri and Numberger, 1991).

Determination of the polymorphisms

Twelve of the thirteen studied single nucleotide polymorphisms were genotyped using 5' exonuclease TaqMan genotyping assays on an 7900HT Fast Real-Time PCR system according to manufacturer's instructions (Applied Biosystems, Foster City, CA). The *IL-1RN* variable number tandem repeat (VNTR) polymorphism was determined by polymerase chain reaction using the forward primer 5'-CTCAGCAACACTCCTAT-3' and the reverse primer 5'-TCCTGGTCTGCAGGTAA-3'. The products were analyzed by phototyping in 2% agarose gels, stained with ethidium bromide (Lai *et al.*, 2006) (Table 1).

Statistical analysis

Allele and genotype frequencies of the *IL-1RN*, *IL-6*, *IL-10*, *INF- γ* , and *TNF- α* gene polymorphisms were obtained by direct counting. Also, Hardy-Weinberg equilibrium (HWE) was calculated using the chi-square test. Allele frequencies obtained in the studied Mexican population were compared among them and with those reported in other populations using Mantel-Haenszel's chi-square. Fisher's exact test was used if the number in any cell of the 2×2 contingency table was less than 5. The *p*-values were corrected multiplying by the number of comparisons. Pairwise linkage disequilibrium estimations between polymorphisms and haplotype reconstruction were performed with Haploview version 4:1 (Broad Institute of Massachusetts Institute of Technology and Harvard University, Cambridge, MA). The groups used for comparison included Caucasian, Asian, and African populations.

Results

Distributions of the studied polymorphisms are shown in Table 2. The observed and expected frequencies in all polymorphic sites were in HWE in our studied population. Allele and genotype frequencies of these polymorphisms in Mexicans were compared to those reported in other populations as Caucasian, Asian, and African. Distribution of *INF- γ -179 T > G* (rs2069709), *INF- γ -155G > A* (rs2069710),

TABLE 1. POLYMORPHISMS STUDIED IN A MEXICAN POPULATION

Gene	Chromosomal location ^a	Gene name ^a	Total SNPs studied ^a	Marker (dbSNPID) ^a	Site polymorphic ^a
<i>IL1RN</i>	2q13	Antagonist receptor of the IL-1	3	rs419598 rs315951 rs2234663	<i>IL1RN</i> 4 T/C <i>IL1RN</i> 6.2 C/G <i>IL1RN</i> -VNTR
<i>IL1F10</i>	7p21	Structural homologue gene to IL-1A/B	1	rs3811058	<i>IL1F10.3</i> C/T
<i>IL6</i>		Interleukin-6	2	rs1800796 rs2069827	<i>IL6</i> -572 G/C <i>IL6</i> -1426 T/G
<i>INF-γ</i>	12q15	Interferon-gamma	2	rs2069709 rs2069710	<i>INF-γ-179</i> G/T <i>INF-γ-155</i> G/A
<i>IL10</i>	1q31	Interleukin-10	3	rs1800896 rs1800871 rs1800872	<i>IL10</i> -1082 A/G <i>IL10</i> -819 C/T <i>IL10</i> -592 A/C
<i>TNF-α</i>	6p21	Tumor necrosis factor-alpha	2	rs361525 rs1800629	<i>TNF-α-238</i> A/G <i>TNF-α-308</i> A/G

^aAs defined by Entrez gene (www.ncbi.nlm.nih.gov/sites/entrez?db=gene). SNP, single nucleotide polymorphism.

TABLE 2. ALLELE (AF) AND GENOTYPE (GF) FREQUENCIES OF THE IL-1 β , IL-1RN, IL-6, IL-10, INF- γ , AND TNF- α POLYMORPHISMS IN MEXICANS AND OTHER POPULATIONS

Mexican			Caucasian			Asian			African			References
IL1 RN4T/C	n	(n=248)	n	(n=490)	af	n	(n=193)	af	n	(n=100)	af	
Allele	335	af	668	68.2	af	342	af	89.0	187	af	94.0	Maksymowych <i>et al.</i> (2003) Lubbe <i>et al.</i> (2008) Chou <i>et al.</i> (2006)
T	161	32.5 ^a	312	31.8	31.8	44		11.0	13	7.0	7.0	
Genotype	n	gf	n	gf	gf	n	gf	gf	n	gf	gf	
TT	113	45.6	230	46.9	46.9	152	46.9	79.0	87	87.0	87.0	
TC	109	43.9	208	42.4	42.4	38	42.4	20.0	13	13.0	13.0	
CC	26	10.4 ^b	52	10.6	10.6	3		2.0	0	0.0	0.0	
IL1 RN6/2C>G		(n=248)		(n=488)			(n=196)					Chou <i>et al.</i> (2006) Maksymowych <i>et al.</i> (2003)
Allele	n	af	n	af	af	n	af	af	—	—	—	
C	323	65.1	700	71.7	71.7	221	57.0	57.0	—	—	—	
G	173	34.9 ^c	276	28.3	28.3	171	43.0 ^e	43.0 ^e	—	—	—	
Genotype	n	gf	n	gf	gf	n	gf	gf	—	—	—	
CC	108	43.5	248	50.8	50.8	66	34.0	34.0	—	—	—	Timms <i>et al.</i> (2004) Chou <i>et al.</i> (2006)
GC	107	43.1	204	41.8	41.8	89	45.0	45.0	—	—	—	
GG	33	13.3 ^d	36	7.4	7.4	41	21.0 ^f	21.0 ^f	—	—	—	
IL1 F10.3C/T		(n=248)		(n=188)			(n=191)					
Allele	n	af	n	af	af	n	af	af	—	—	—	
T	395	79.6	358	95.2	95.2	148	38.0	38.0	—	—	—	Lai <i>et al.</i> (2006) Lubbe <i>et al.</i> (2008) Vijgen <i>et al.</i> (2002) Chou <i>et al.</i> (2005)
C	101	20.4 ^g	18	4.8	4.8	238	62.0 ⁱ	62.0 ⁱ	—	—	—	
Genotype	n	gf	n	gf	gf	n	gf	gf	—	—	—	
TT	158	63.7	170	90.4	90.4	39	20.0	20.0	—	—	—	
TC	79	31.9	18	9.6	9.6	102	53.0	53.0	—	—	—	
CC	11	4.4 ^h	0	0.0	0.0	50	26.0 ^j	26.0 ^j	—	—	—	Timms <i>et al.</i> (2004) Chou <i>et al.</i> (2006)
IL1 RN-VNTR		(n=248)		(n=401)			(n=163)			(n=98)		
Allele	n	af	n	af	af	n	af	af	n	af	af	
1	312	62.9	596	74.3	74.3	307	94.2	94.2	178	91.0	91.0	
2	173	34.8 ^k	191	23.3	23.3	17	5.2	5.2	14	7.0	7.0	
3	6	1.2	15	1.9	1.9	2	0.6	0.6	2	1.0	1.0	Lai <i>et al.</i> (2006) Lubbe <i>et al.</i> (2008) Vijgen <i>et al.</i> (2002) Chou <i>et al.</i> (2005)
4	5	1.0	0	0.0	0.0	0	0.0	0.0	2	1.0	1.0	
Genotype	n	gf	n	gf	gf	n	gf	gf	n	gf	gf	
1, 1	104	41.9	233	58.1	58.1	146	89.0	89.0	80	0.82	0.82	
1, 2	96	38.7	122	30.4	30.4	15	9.0	9.0	14	0.14	0.14	
1, 3	6	2.4	8	2.0	2.0	0	0.0	0.0	2	0.2	0.2	Lai <i>et al.</i> (2006) Lubbe <i>et al.</i> (2008) Vijgen <i>et al.</i> (2002) Chou <i>et al.</i> (2005)
1, 4	2	0.8	0	0.0	0.0	0	0.0	0.0	2	0.2	0.2	
2, 2	38	15.3 ⁱ	32	8.0	8.0	1	1	1	0	0.0	0.0	
2, 3	0	0.0	5	1.2	1.2	0	0.0	0.0	0	0.0	0.0	
2, 4	0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	
3, 3	0	0.0	1	0.3	0.3	0	0.0	0.0	0	0.0	0.0	Lai <i>et al.</i> (2006) Lubbe <i>et al.</i> (2008) Vijgen <i>et al.</i> (2002) Chou <i>et al.</i> (2005)
4, 2	1	0.4	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	
4, 4	1	0.4	0	0.0	0.0	1	1.0	1.0	0	0.0	0.0	
TNF -238 G/A		(n=248)		(n=495)			(n=155)			(n=120)		
Allele	n	af	n	af	af	n	af	af	n	af	af	Lai <i>et al.</i> (2006) Lubbe <i>et al.</i> (2008) Vijgen <i>et al.</i> (2002) Chou <i>et al.</i> (2005)
G	477	96.1	927	93.6	93.6	296	95.5	95.5	231	96.3	96.3	
A	19	3.8	63	6.4	6.4	14	4.5	4.5	9	3.7	3.7	

(continued)

TABLE 2. (CONTINUED)

Mexican			Caucasian			Asian			African			References
Genotype	n	gf	n	gf	n	n	gf	n	n	gf	n	
GG	229	92.3	434	87.7	141	113	91.0	113	113	94	113	Azmy <i>et al.</i> (2004)
GA	19	7.7	59	11.9	14	5	9.0	5	5	4	5	Sharma <i>et al.</i> (2010)
AA	0	0.0	2	0.4	0	2	0	2	2	1.7	2	Corbett <i>et al.</i> (2002)
TNF - 308 G/A	(n = 248)								(n = 325)			
Allele	n	af	n	af	n	n	af	n	n	af	n	
G	460	92.7	900	84.3	527	545	87.8	545	545	83.8	545	
A	36	7.3 ^m	168	15.7	73	105	12.2	105	105	16.2	105	
Genotype	n	gf	n	gf	n	n	gf	n	n	Gf	n	
GG	214	86.2	376	70.0	231	224	77.0	224	224	69.0	224	Herrmann <i>et al.</i> (1998)
GA	32	12.9 ⁿ	148	28.0	65	97	22.0	97	97	30.0	97	Park <i>et al.</i> (1997)
AA	2	0.8	10	2.0	4	4	1.0	4	4	1.0	4	McGuire <i>et al.</i> (1994)
IL10 - 592 A/C	(n = 248)								(n = 86)			
Allele	n	af	n	af	n	n	af	n	n	Af	n	
C	301	60.7	1679	74.2	166	114	30.7	114	114	66.3	114	
A	195	39.3	583	25.8	374	58	69.3 [#]	58	58	33.7	58	
Genotype	n	gf	n	gf	n	n	gf	n	n	gf	n	
CC	94	37.9	615	54.4	28	33	10.4	33	33	38.4	33	Scarpelli <i>et al.</i> (2006)
CA	113	45.5	449	39.7	110	48	40.8	48	48	55.8	48	Liu <i>et al.</i> (2010)
AA	41	16.5 ^t	67	5.9	132	5	48.8 ^a	5	5	5.8	5	Meenagh <i>et al.</i> (2002)
IL10 - 819 T/C	(n = 248)								(n = 86)			
Allele	n	af	n	af	n	n	af	n	n	af	n	
C	289	0.582	488	71.7	166	114	30.7	114	114	66.3	114	
T	207	0.417 [†]	192	28.2	374	58	69.3 [§]	58	58	33.7	58	
Genotype	n	gf	n	gf	n	n	gf	n	n	gf	n	
CC	85	0.342	175	51.5	28	33	10.4	33	33	38.4	33	Koch <i>et al.</i> (2001)
CT	119	0.479	138	40.6	110	48	40.7	48	48	55.8	48	Liu <i>et al.</i> (2010)
TT	44	0.177 [‡]	27	7.9	132	5	48.8 ^p	5	5	5.8	5	Nakajima <i>et al.</i> (1999)
IL10 - 1082 A/G	(n = 248)								(n = 86)			
Allele	n	af	n	af	n	n	af	n	n	af	n	
A	356	71.8	1486	65.7	507	107	93.9	107	107	62.2	107	
G	140	28.2 ^r	776	34.3 ^s	33	65	6.1	65	65	37.8 ^w	65	
Genotype	n	gf	n	gf	n	n	gf	n	n	gf	n	
AA	125	50.4	485	42.9	240	29	88.9	29	29	33.7	29	Scarpelli <i>et al.</i> (2006)
AG	106	42.7	516	45.6	27	49	10.0	49	49	57.0	49	Liu <i>et al.</i> (2010)
GG	17	6.9 ^q	130	11.5 ^t	3	8	1.1	8	8	9.3 ^h	8	Meenagh <i>et al.</i> (2002)
IL6 - 572 G/C	(n = 248)								(n = 63)			
Allele	n	af	n	af	n	n	af	n	n	af	n	
G	321	64.7	4962	95.0	50	114	17.6	114	114	90.5	114	
C	175	35.2 ^x	262	5.0	234	12	82.3 ^z	12	12	9.5	12	
Genotype	n	gf	n	gf	n	n	gf	n	n	gf	n	
GG	109	43.9	2359	90.4	4	54	2.8	54	54	85.7	54	Morgan <i>et al.</i> (2006)
GC	103	41.5	244	9.3	42	6	29.6	6	6	9.5	6	Nakajima <i>et al.</i> (1999)
CC	36	14.5 ^y	9	0.3	96	3	67.6 [†]	3	3	4.8	3	Osiri <i>et al.</i> (1999)
IL6 - 1426 T/G	(n = 248)								(n = 644)			
Allele	n	af	n	af	n	n	af	n	n	af	n	

(continued)

TABLE 2. (CONTINUED)

	Mexican			Caucasian			Asian			African			References
G	487	0.981	623	90.6	1288	100	—	—	—	—	—	—	
T	9	0.018	†	65	9.4	0	—	—	—	—	—	—	
Genotype	<i>n</i>	gf	<i>n</i>	gf	<i>n</i>	gf	—	—	—	—	—	—	Cussigh <i>et al.</i> (2011)
GG	239	96.4	285	82.8	644	100	—	—	—	—	—	—	Shin <i>et al.</i> (2007)
GT	9	3.6	*	53	15.4	0	—	—	—	—	—	—	
TT	0	0.0	6	1.8	0	0	—	—	—	—	—	—	
INF- γ - 155 A/G*	(<i>n</i> = 248)						(<i>n</i> = 210)			(<i>n</i> = 104)			
Allele	<i>n</i>	af	—	—	<i>n</i>	af	—	<i>n</i>	—	—	af	—	
A	493	99.4	—	—	420	100	—	207	99.5	—	99.5	—	
G	3	0.6	—	—	0	0	—	1	0.5	—	0.5	—	
Genotype	<i>n</i>	gf	—	—	<i>n</i>	gf	—	<i>n</i>	gf	—	gf	—	
AA	245	98.8	—	—	210	100	—	103	99.0	—	99.0	—	
AG	3	1.2	—	—	0	0	—	1	1.0	—	1.0	—	Qi <i>et al.</i> (2005)
GG	0	0.0	—	—	0	0	—	0	0.0	—	0.0	—	Chevillard <i>et al.</i> (2003)
INF- γ - 179 G/T**	(<i>n</i> = 248)					(<i>n</i> = 1451)				(<i>n</i> = 104)			
Allele	<i>n</i>	af	<i>n</i>	af	—	—	—	<i>n</i>	—	—	af	—	
G	494	99.6	2899	99.9	—	—	—	203	97.6	—	97.6	—	
T	2	0.4	3	0.1	—	—	—	5	2.4	—	2.4	—	
Genotype	<i>n</i>	gf	<i>n</i>	gf	—	—	—	<i>n</i>	gf	—	gf	—	
GG	246	99.2	1448	99.8	—	—	—	99	95.2	—	95.2	—	
GT	2	0.8	3	0.2	—	—	—	5	4.8	—	4.8	—	
TT	0	0.0	0	0	—	—	—	0	0	—	0	—	

ab; Significantly increased frequencies of the C allele and CC genotype in Mexicans when compared to Asian ($pC=4 \times 10^{-6}$ and $pC=0.0004$, respectively) and African ($pC=4 \times 10^{-6}$ and $pC=0.03$, respectively) populations.
c; Significantly increased frequencies of the G allele and GG genotype in Mexican ($pC=0.036$ and $pC=0.036$, respectively) and Asian ($pC=4 \times 10^{-6}$ and $pC=1.6 \times 10^{-5}$, respectively) populations when compared to Caucasians.

g; Significantly increased frequencies of the C allele and CC genotype in Mexican population when compared to Caucasians ($pC=4 \times 10^{-6}$ and $pC=0.012$, respectively).
i; Significantly increased frequencies of the C allele and CC genotype in Asian population when compared to Caucasians ($pC=4 \times 10^{-6}$ and $pC=4 \times 10^{-6}$, respectively).
k; Significantly increased frequencies of the 2 allele and 2,2 genotype in Mexicans when compared to Caucasian ($pC=4 \times 10^{-4}$ and $pC=0.012$, respectively), Asian ($pC=4 \times 10^{-6}$ and 2×10^{-5} , respectively) and African ($pC=4 \times 10^{-5}$ and $pC=0.0002$, respectively) populations.

m; Significantly decreased frequencies of the A allele and AG genotype in the Mexicans when compared to Caucasian ($pC=0.00012$ and $pC=0.00016$, respectively), Asian ($pC=0.022$ and $pC=0.028$, respectively) and African ($pC=0.0002$ and $pC=4 \times 10^{-5}$, respectively) populations.
r; Significantly increased frequencies of the A allele and AA genotype in Mexicans when compared to Caucasian population ($pC=0.04$).
s; Significantly increased frequency of the AA genotype in Mexicans when compared to African population ($pC=0.04$).
t; Significantly increased frequencies of the A allele and AA genotype in Asian population when compared to Caucasian ($pC=4 \times 10^{-6}$ and $pC=4 \times 10^{-6}$, respectively) and African ($pC=4 \times 10^{-6}$ and $pC=4 \times 10^{-6}$, respectively) populations.

u; Significantly increased frequencies of the T allele and TT genotype in Mexican when compared to Caucasian population ($pC=4 \times 10^{-5}$ and $pC=0.0012$, respectively).
v; Significantly increased frequency of the TT genotype in Mexican when compared to African population ($pC=0.021$).
w; Significantly increased frequencies of the T allele and TT genotype in Asian population when compared to Caucasian ($pC=4 \times 10^{-6}$ and $pC=4 \times 10^{-6}$, respectively) and African ($pC=4 \times 10^{-6}$ and $pC=4 \times 10^{-6}$, respectively) populations.

x; Significantly decreased frequency of the G allele in Mexican population when compared to Caucasian ($pC=0.036$) and African ($pC=0.04$) populations.
y; Significantly increased frequencies of the G allele and GG genotype in Mexicans ($pC=4 \times 10^{-6}$ and $pC=0.0028$, respectively), Caucasians ($pC=4 \times 10^{-6}$ and $pC=8 \times 10^{-5}$, respectively) and Africans ($pC=4 \times 10^{-5}$ and $pC=0.0028$) when compared to Asian population.

z; Significantly increased frequencies of the C allele and CC genotype in Mexicans when compared to Caucasian ($pC=4 \times 10^{-6}$ and $pC=4 \times 10^{-6}$, respectively) and African ($pC=4 \times 10^{-6}$ and $pC=0.03$) populations.
aa; Significantly increased frequencies of the C allele and CC genotype in Asian population when compared to Mexican population ($pC=4 \times 10^{-6}$ and $pC=4 \times 10^{-6}$, respectively).
ab; Significantly decreased frequencies of the T allele and GT genotype in Mexican population when compared to Caucasians ($pC=4 \times 10^{-6}$ and $pC=1 \times 10^{-5}$, respectively).

**The distribution of the INF-155 G/A and INF-179G/T polymorphisms was similar in all the studied populations.
IL, interleukin; INF- γ , interferon-gamma; TNF- α , tumor necrosis factor-alpha.

TABLE 3. HAPLOTYPE DISTRIBUTION IN MEXICANS

(n = 248)		(n = 248)		(n = 248)	
(IL-1RN 4T/C, VNTR, 6.1G/C)		(TNF- α -238A/G, -308 A/G)		(IL-6 -572G/C, -1426G/T)	
Block	Hf	Block	Hf	Block	Hf
T1C	(34.9)	GG	(89)	GG	(62.9)
T1G	(21)	AG	(7.2)	GC	(35.3)
C2C	(16.3)	GA	(3.7)	TG	(1.8)
C2G	(8.7)				
C1C	(7.4)				
T2C	(7.2)				
T2G	(4)				
(IL-10 -592C/A, -819C/T, -1082G/A)		(INF- γ -155G/A, -179G/T)			
Block	Hf	Block	Hf		
ATA	(38.5)	AG	(99.4)		
CCA	(30.3)				
CCG	(27.2)				
CTA	(2.5)				

The order of the polymorphisms in the haplotypes is according to the positions in the chromosome. As defined by Entrez gene (<http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene>).

Hf, haplotype frequency.

and TNF- α -238 A>G (rs361525) polymorphisms was similar in the Mexican and the other populations. However, some differences were observed in the other polymorphisms.

The polymorphisms of the IL-10, IL-6, and INF- γ were in linkage disequilibrium with delta values of ≥ 0.95 . The distribution of these haplotypes is shown in Table 3. On the other hand, the polymorphisms in the IL-1RN and TNF- α genes were not in linkage disequilibrium.

Discussion

The present study describes the allele and genotype frequencies of some IL-1RN, IL-6, IL-10, INF- γ , and TNF- α gene polymorphisms in a Mexican population. The cytokines coding for these genes are involved in extensive networks that involve synergistic as well as antagonistic interactions and exhibit both negative and positive regulation effects on various target cells (Feghali and Wright, 1997; Tedgui and Mallat, 2006; Shantsila and Lip, 2009). Data from several studies establish that cytokines have an important role in the acute inflammatory process (Feghali and Wright, 1997; Tedgui and Mallat, 2006; Shantsila and Lip, 2009). For this reason, polymorphisms in cytokine genes have been studied in many populations. In addition, numerous investigators have reported correlations between the specific polymorphic variants of these cytokines and several diseases (Koch *et al.*, 2001; Maksymowych *et al.*, 2003; Azmy *et al.*, 2004; Timms *et al.*, 2004; Iacoviello *et al.*, 2005; Qi *et al.*, 2005; Tanaka *et al.*, 2005; Morgan *et al.*, 2006; Fragosio *et al.*, 2010a, 2010b; 2011; Sharma *et al.*, 2010). The frequencies obtained in the present study were compared to those reported in other populations (Caucasian, African and Asian). Similar distribution of the INF- γ -179 T>G, INF- γ -155 G>A, and TNF- α -238 A>G gene polymorphisms was observed between Mexican, Caucasian, Asian and African populations (Bream *et al.*, 2002; Corbett *et al.*, 2002; Chevillard *et al.*, 2003; Azmy *et al.*,

2004; Qi *et al.*, 2005; Sharma *et al.*, 2010). In other polymorphisms, several differences were observed among Mexicans and other populations. Mexicans showed different distribution of some polymorphisms when compared to Caucasians (IL-1RN6/2, IL-1F10, IL-6-1426, IL-1RN VNTR, TNF-308, IL-10-592, IL-10-819, and IL6-572), to Asians (IL-1RN4, IL-1RN VNTR, TNF-308, and IL-10-1082), and to Africans (IL-1RN4, IL-1RN VNTR, TNF-308, IL-10-592, IL-10-819, and IL6-572). Only two polymorphisms (IL-1RN VNTR, and TNF-308) presented different distribution in Mexicans when compared to the other three populations (Caucasians, Asians, and Africans) (McGuire *et al.*, 1994; Park *et al.*, 1997; Herrmann *et al.*, 1998; Nakajima *et al.*, 1999; Osiri *et al.*, 1999; Koch *et al.*, 2001; Bream *et al.*, 2002; Corbett *et al.*, 2002; Meenagh *et al.*, 2002; Vijgen *et al.*, 2002; Chevillard *et al.*, 2003; Maksymowych *et al.*, 2003; Azmy *et al.*, 2004; Timms *et al.*, 2004; Chou *et al.*, 2005; Qi *et al.*, 2005; Chou *et al.*, 2006; Lai *et al.*, 2006; Morgan *et al.*, 2006; Scarpelli *et al.*, 2006; Shin *et al.*, 2007; Lubbe *et al.*, 2008; Liu *et al.*, 2010; Sharma *et al.*, 2010; Cussigh *et al.*, 2011).

On the other hand, after construction of haplotypes in the different genes in Mexicans, it was only possible to compare the distribution of the IL-10 and TNF- α haplotypes. Haplotypes of the studied polymorphisms in the IL-1RN, INF- γ , and IL-6 have not been reported in other populations. Considering the IL-10 haplotypes, we observed similitude between Asian and Mexican populations. The distribution of the "ATA" haplotype, conformed by the IL-10-592C/A, -819C/T, and -1082G/A polymorphisms, showed increases in Asian and Mexican populations (68.1% and 38.5%, respectively) when compared to a Caucasian population (28%) (Koch *et al.*, 2001; Liu *et al.*, 2010). On the other hand, the distribution of the "AG" haplotype, conformed by the TNF- α -238 A/G and TNF- α -308 A/G polymorphisms, showed a decrease in Mexican (7.2%) and Asian populations (Chinese and Korean) (8.8% and 8.2%, respectively) when compared with two European populations (Romanian and Macedonians), which present 13.2% and 14%, respectively (Trajkov *et al.*, 2005; Cao *et al.*, 2006; Park *et al.*, 2006; Popa *et al.*, 2011).

In summary, the distribution of the IL-1RN, IL-6, IL-10, INF- γ , and TNF- α cytokine polymorphisms distinguishes the studied Mexican population from other groups, including Caucasian, Asian, and African. Since the alleles of these cytokines are associated with the development of several inflammatory diseases, knowledge of the distribution of these alleles in a given Mexican population could be helpful to understand their true role as a genetic susceptibility marker in that population.

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Author Disclosure Statement

No competing financial interests exist.

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