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Genotype frequency and F_{ST} analysis of polymorphisms in immunoregulatory genes in Chinese and Caucasian populations

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Abstract Selection and genetic drift can create genetic differences between populations. Cytokines and chemokines play an important role in both hematopoietic development and the inflammatory response. We compared the genotype frequencies of 45 SNPs in 30 cytokine and chemokine genes in two healthy Chinese populations and one Caucasian population. Several SNPs in *IL4* had substantial genetic differentiation between the Chinese and Caucasian populations (F_{ST} ~0.40), and displayed a strikingly different haplotype distribution. To further characterize common genetic variation in worldwide populations at the *IL4* locus, we genotyped 9 SNPs at the *IL4* gene in the Human Diversity Panel's (N=1056) individuals from 52 world geographic regions. We observed low haplotype diversity, yet strikingly different haplotype frequencies between non-African populations, which may indicate different selective pressures on the *IL4* gene in different parts of the world. SNPs in *CSF2*, *IL6*, *IL10*, *CTLA4*, and *CX3CR1* showed moderate genetic differentiation between the Chinese and Caucasian populations ($0.15<F_{ST}<0.25$). These results suggest that there is substantial genetic diversity in immune genes and exploration of SNP associations with immune-related diseases that vary in incidence across these two populations may be warranted.

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Introduction

There is increasing evidence that cytokines, chemokines, and other immunomodulatory genes play an important role in hematopoietic development and in the inflammatory response (Farrar et al. 1989; O'Shea et al. 2002). Multiple studies have reported associations between single nucleotide polymorphisms (SNPs) in cytokine and chemokine genes and a wide range of diseases, such as asthma, atopy, progression of HIV infection, inflammatory bowel disease, lupus erythematosus, Alzheimer's disease, and cancer risk even though most still require replication. (Burchard et al. 1999; Lio et al. 2006; Qi et al. 2007; Reiche et al. 2007; Rothman et al. 2006; Thompson and Humphries 2007). The incident rates for some of these diseases vary substantially between different ethnic groups. For example, the incident rate of non-Hodgkin lymphoma (NHL) is relatively low among Asians and considerably higher among Caucasians (Hartge et al. 1994). Furthermore, there are marked ethnic differences in the incidence rates of particular NHL histologic subtypes, such as follicular lymphoma (Biagi and Seymour 2002; Hartge et al. 1994). As such, it is plausible that differences in disease rates across ethnic groups might be explained, at least in part, by differences in allele frequencies for disease-associated SNPs.

Human allele frequencies for many genetic variants differ by geographical regions (Ma et al. 2005; Nakajima et al. 2006; Sivakova et al. 2006). These geographic differences of allele frequency among various populations are considered to be the result of several factors including

Table 1 Cytokine and chemokine genes and single nucleotide polymorphisms evaluated in three populations

Gene	Name	Location	SNP rs number
CCR5	Chemokine, CC motif, receptor 5	3p21	rs2734648
CSF2	Colony stimulating factor 2 (granulocyte-macrophage)	5q31.1	rs1469149, rs25882
CX3CR1	Chemokine, CXC motif	3p21	rs3732379
CXCL12	Chemokine, CXC motif, ligand 12	10q11.1	rs1801157
FCGR2A	Receptor for Fc fragment of IgG, low affinity IIa (CD32)	1q21-q23	rs1801274
ICAM1	Intercellular adhesion molecule 1 (CD54)	19p13.3-p13.2	rs5491
IFNG	Interferon, gamma	21q14	rs1861494
IFNGR2	Interferon, gamma, receptor 2	21q22,10q22.2	rs9808753
IL1A	Interleukin 1-alpha	2q13	rs17561, rs1800587
IL1B	Interleukin 1-beta	2q14	rs1143627
IL1RN	Interleukin 1 receptor antagonist	2q14.2	rs454078
IL2	Interleukin 2	4q26–q27	rs2069762
IL4	Interleukin 4	5q31.1	rs2243250, rs2243248; rs2070874, rs2243290, rs2243268, rs2243247[a], rs2243251 [a], rs2243267 [a], rs2243270 [a], rs2243289[a],
IL4R	Interleukin 4 receptor	16p12.1–p11.2	rs2107356
IL5	Interleukin 5	5q31.1	rs2069812
IL6	Interleukin 6	7p15.3	rs1800795
IL8	Interleukin 8	4q12-q13	rs4073, rs2227307, rs2227306
IL8RA	Interleukin 8 receptor, alpha	2q35	rs2234671
IL8RB	Interleukin 8 receptor, beta	2q35	rs1126580
IL10	Interleukin 10	1q31–q32	rs1800871, rs3024509, rs3024496, rs3024491, rs1800890
IL12A	Interleukin 12, alpha	3q25.33	rs568408
IL12B	Interleukin 12B	5q33.3	rs3212227
IL13	Interleukin 13	5q23.3	rs20541, rs1800925, rs1295686
IL15RA	Interleukin 15 receptor, alpha	10p15.1	rs2296135
LTA	Lymphotoxin-alpha	6p21.3	rs909253
MIF	Macrophage migration inhibitory factor	22q11.23	rs755622
TGFB1	Transforming growth factor, beta 1	19q13.1–13.2	rs1800469
TLR4	Toll-like receptor 4	9q32-q33	rs4986790
TNF	Tumor necrosis factor	6p21.3	rs1800629, rs1799724
VCAM1	Vascular cell adhesion molecule 1	1p32-p31	rs3176879

[a] Additional *IL4* SNPs genotyped in the Human Diversity Panel.

natural selection and neutral genetic drift. In some instances, the functional consequences of specific genetic variants can lead to a more favorable response to environmental factors such as infectious organisms and environmental toxins. As a result, a subset of genetic variants could be under differential selective pressure. The selective pressures exerted by these environmental factors may lead to differences in allele frequencies between populations, particularly populations in which the environmental pressures differ, resulting in significantly higher frequencies among some populations and more than what would be expected from neutral drift. We hypothesized that the frequency of SNPs in key cytokine, chemokine, and other immunoregulatory genes that have been associated with a spectrum of immune-mediated diseases could vary across different continental populations. To test this hypothesis, we compared the genotype frequencies of 45 SNPs in 30 cytokine and chemokine genes from two healthy Chinese populations and one Caucasian population, and 9 SNPs spanning the *IL4* gene in the Human Diversity Panel. The SNPs analyzed in this study were selected on the basis of prior functional data in previous association studies or to help characterize the haplotype structure of the gene of interest and the availability of the assay for the previous studies.

Materials and methods

Data for the primary analyses were drawn from three different studies: (1) $n=113$ controls of a case-control study of lung cancer (southern Chinese) (Lan et al. 2004a), (2) $n=390$ subjects of a cross-sectional study of occupational benzene exposure (northern Chinese) (Lan et al. 2004b, 2005), and 3) $n=547$ controls of a case-control study of NHL (non-Hispanic Caucasian women living in Connecticut, USA) (Lan et al. 2006).

The southern Chinese population was derived from a population-based case-control study (Lan et al. 2000). In brief, this study was conducted between March 1995 and March 1996 in Xuan Wei, China. A control was selected for each lung cancer case matching on sex, age (±2 years), village, and type of fuel used currently for cooking and heating at home by a stratified random sampling scheme. A total of 122 controls were enrolled in this study. The participation rate of the controls was 100%. Each subject provided a sample of buccal cells and sputum for genotyping. DNA was extracted from sputum samples using phenol–chloroform extraction (Lan et al. 2000). DNA was available from 113 controls for the analyses presented here. Quality control duplicate samples had concordance rates >99% for all assays.

The northern Chinese population was drawn from a cross-sectional study of 250 workers exposed to benzene in two shoe manufacturing factories and 140 unexposed controls from three clothes-manufacturing factories in the same region of Tianjin, China (Lan et al. 2004b). Briefly, the unexposed workers were frequency-matched by sex and age to exposed workers. The participation rate was approximately 95%. This was a relatively young, working population. Although this sample set does not represent a random sample of the population, genotype frequencies in this group should approximate genotype frequencies in this region of China because workers were drawn from a broad area across this region. Blood samples were collected from 88 workers in June, 2000 during the first phase of the study and from the remaining workers (28 subjects enrolled in the first phase) in May and June, 2001. Blind replicate samples randomly interspersed throughout the study sample plates had concordance rates >98% for all assays.

The Caucasian population was drawn from a population-based case-control study conducted among women in Connecticut from 1995 to 2001 (Lan et al. 2006; Morton et al. 2003; Zhang et al. 2004). The controls were enrolled from one of two populations: (1) Women who were less than 65 years old were enrolled by random digit dialing; or (2) Women who were 65 years or older were randomly recruited based on Health Care Financing Administration files. Controls were frequency matched on age (±5years) to cases with a participation rate of 69% for women less than 65 years old and 47% for women 65 years or older. About 75% (535/717) of interviewed controls provided blood samples. The data presented in this paper were genotyped from blood-derived DNA only. Quality control samples had concordance rates at or above 97% for all assays.

For follow-up studies at the *IL4* locus, DNA from the Human Diversity Panel (HDP) comprised of $N=1{,}056$ individuals (CEPH; Paris, France) (Cann et al. 2002). The HDP can be divided into seven general geographic regions: Africans, Europeans, Western Asians, Central and Southern Asians, Eastern Asians, Oceanians, and Native Americans, with each group containing 7, 8, 3, 9, 18, 2, and 5 representative groups, respectively. For comparative purposes,

Table 2 Characteristics of study participants

Parameter	Northern Chinese n=390 (%)	Southern Chinese *n*=113 (%)	Caucasians *n*=547 (%)
Sex			
Male	138 (35)	73 (65)	0
Female	252 (65)	40 (35)	547 (100)
Ethnicity			
Han Chinese	390 (100)	113 (100)	
Caucasians			547 (100)
Age (Mean±SD)	30±9	55±12	62±14

Table 3 Genotype frequencies Cytokine and chemokine genes in Chinese and Caucasian populations

Genotypes	Southern Chinese	Northern Chinese	S. vs N. Chinese *P* value	Chinese	Caucasians	Chinese vs. Caucasian *P* value
CCR5 rs2734648 IVS1+151G>T						
GG	27 (25)	95 (24)	1.0	122 (25)	198 (41)	<0.0001
TG	53 (49)	190 (49)		243 (49)	218 (45)	
TT	29 (27)	104 (27)		133 (27)	65 (14)	
CSF2 rs1469149 −674A>C						
AA	92 (95)	340 (95)	0.87	432 (95)	159 (38)	<0.0001
AC	5 (5)	17 (5)		22 (5)	194 (46)	
CC	–	–		–	66 (16)	
CSF2 rs25882 Ex4+23T>C						
CC	42 (38)	135 (35)	0.76	177 (36)	22 (5)	<0.0001
TC	53 (48)	192 (49)		245 (49)	165 (34)	
TT	15 (14)	61 (16)		76 (15)	296 (61)	
CX3CR1 rs3732379 Ex2+754G>A						
AA	–	–	0.77	–	48 (10)	<0.0001
GA	7 (6)	27 (7)		34 (7)	193 (40)	
GG	106 (94)	360 (93)		466 (93)	246 (51)	
CXCL12 rs1801157 Ex4+535C>T						
AA	9 (8)	14 (4)	0.1	23 (5)	25 (5)	0.073
GA	46 (41)	144 (38)		190 (38)	152 (31)	
GG	58 (51)	225 (59)		283 (57)	308 (64)	
FCGR2A rs1801274 Ex4−120A>G						
AA	54 (49)	156 (41)	0.35	210 (43)	225 (47)	0.47
GA	47 (42)	186 (49)		233 (47)	212 (44)	
GG	10 (9)	39 (10)		49 (10)	46 (10)	
ICAM1 rs5491 Ex2+100A>T						
AA	92 (81)	333 (86)	0.13	424 (85)	486 (100)	<0.0001
TA	19 (17)	54 (14)		73 (15)	1 (0)	
TT	2 (2)	1 (0)		3 (1)		
IFNG rs1861494 IVS3+284G>A						
AA	50 (44)	143 (38)	0.38	193 (40)	248 (9)	<0.0001
AG	49 (43)	189 (51)		238 (49)	199 (41)	
GG	14 (12)	40 (11)		54 (11)	44 (51)	
IFNGR2 rs9808753 Ex2−16A>G						
AA	36 (33)	117 (30)	0.75	153 (31)	377 (78)	<0.0001
GA	56 (51)	200 (52)		256 (52)	100 (21)	
GG	18 (16)	71 (18)		88 (18)	6 (1)	
IL1A rs17561 Ex5+21G>T						
GG	93 (84)	323 (83)	0.42	416 (83)	244 (50)	<0.0001
TG	18 (16)	60 (15)		78 (16)	204 (42)	
TT	–	6 (2)		6 (1)	37 (8)	
IL1A rs1800587 Ex1+12C>T						
CC	94 (84)	324 (84)	0.47	417 (84)	247 (53)	<0.0001
TC	18 (16)	58 (15)		76 (15)	179 (38)	
TT	–	5 (1)		5 (1)	42 (9)	
IL1B rs1143627 −580C>T						
CC	21 (19)	85 (22)	0.69	106 (21)	60 (12)	<0.0001
TC	50 (45)	177 (46)		227 (46)	204 (42)	
TT	40 (36)	125 (32)		165 (33)	220 (45)	
IL1RN rs454078 IVS6+59A>T						
AA	95 (86)	322 (83)	0.28	417 (84)	272 (59)	<0.0001
TA	14 (13)	63 (16)		77 (15)	151 (33)	
TT	2 (2)	2 (1)		4 (1)	36 (8)	
IL2 rs2069762 Ex2T>G						
GG	7 (6)	47 (12)	0.078	54 (11)	44 (9)	0.12
TG	45 (40)	174 (45)		219 (44)	183 (39)	
TT	60 (54)	166 (43)		225 (45)	244 (52)	

Table 3 (continued)

Genotypes	Southern Chinese	Northern Chinese	S. vs N. Chinese *P* value	Chinese	Caucasians	Chinese vs. Caucasian *P* value
IL4 rs2243250 −588C>T						
CC	2 (2)	17 (4)	0.24	19 (4)	353 (73)	<0.0001
TC	36 (32)	142 (37)		177 (36)	115 (24)	
TT	73 (66)	228 (59)		301 (61)	18 (4)	
IL4 rs2243248 Ex2T>G						
GG	–	–	0.058	–	2 (0)	0.34
GT	7 (6)	50 (13)		57 (11)	52 (11)	
TT	103 (94)	338 (87)		441 (89)	432 (89)	
IL4 rs2070874 Ex1−168C>T						
CC	5 (4)	23 (6)	0.057	28 (6)	356 (74)	<0.0001
TC	53 (47)	134 (35)		187 (37)	107 (22)	
TT	55 (49)	231 (60)		286 (57)	20 (4)	
IL4 rs2243290 IVS3−9A>C						
AA	80 (71)	224 (58)	0.02	304 (61)	16 (3)	<0.0001
AC	31 (28)	142 (37)		173 (35)	115 (23)	
CC	1 (1)	18 (5)		19 (4)	359 (73)	
IL4 rs2243268 IVS2−1443A>C						
AA	1 (1)	17 (4)	0.064	18 (4)	358 (73)	<0.0001
CA	33 (30)	142 (37)		175 (35)	116 (24)	
CC	77 (69)	230 (59)		307 (61)	16 (3)	
IL4R rs2107356 −28120T>C						
CC	41 (37)	166 (43)	0.21	207 (41)	162 (34)	0.048
TC	57 (51)	161 (41)		218 (44)	228 (48)	
TT	14 (13)	61 (16)		75 (15)	87 (18)	
IL5 rs2069812 −745C>T						
CC	9 (8)	47 (12)	0.45	56 (11)	245 (50)	<0.0001
TC	46 (41)	146 (38)		192 (38)	211 (43)	
TT	58 (51)	194 (50)		252 (54)	30 (6)	
IL6 rs1800795 −236C>G						
CC	–	–	0.17	–	69 (14)	<0.0001
CG	1 (1)	13 (3)		14 (3)	233 (48)	
GG	110 (99)	377 (97)		486 (97)	183 (38)	
IL8 rs4073 −351A>T						
AA	15 (13)	61 (16)	0.31	76 (15)	83 (17)	0.43
AT	49 (44)	194 (50)		243 (49)	245 (50)	
TT	48 (43)	134 (34)		181 (36)	158 (33)	
IL8 rs2227307 IVS1+230G>T						
GG	16 (14)	60 (15)	0.4	76 (15)	89 (19)	0.29
TG	49 (44)	194 (50)		243 (49)	232 (49)	
TT	47 (42)	134 (35)		180 (36)	156 (33)	
IL8 rs2227306 IVS1−204C>T						
CC	47 (43)	159 (42)	0.95	205 (42)	174 (36)	0.17
TC	48 (43)	174 (46)		222 (45)	232 (48)	
TT	15 (14)	49 (13)		64 (13)	75 (16)	
IL8 RA rs2234671 Ex2+860C>G						
CC	–	5 (1)	0.34	5 (1)	2 (0)	<0.0001
CG	20 (18)	82 (21)		102 (20)	49 (10)	
GG	92 (82)	301 (78)		393 (79)	440 (90)	
IL8RB rs1126580 Ex3−1010G>A						
AA	4 (4)	27 (7)	0.055	31 (6)	106 (22)	<0.0001
GA	34 (31)	157 (40)		191 (38)	248 (51)	
GG	71 (65)	204 (53)		275 (55)	132 (27)	
IL10 rs1800871 −7334T>C						
CC	9 (8)	49 (13)	0.43	58 (12)	284 (58)	<0.0001
TC	50 (45)	170 (44)		219 (44)	176 (36)	
TT	51 (47)	167 (43)		218 (44)	26 (5)	

Table 3 (continued)

Genotypes	Southern Chinese	Northern Chinese	S. vs N. Chinese *P* value	Chinese	Caucasians	Chinese vs. Caucasian *P* value
IL10 rs3024509 IVS3−58C>T						
CC	–	–	0.59	–	3 (1)	<0.0001
TC	–	1 (0)		1 (0)	69 (14)	
TT	112 (100)	382 (100)		494 (100)	418 (85)	
IL10 rs3024496 Ex5+210C>T						
CC	–	–	0.69	–	82 (17)	<0.0001
TC	8 (7)	32 (8)		40 (8)	254 (52)	
TT	105 (93)	356 (92)		461 (92)	150 (31)	
IL10 rs3024491 IVS1−286G>T						
GG	105 (93)	354 (91)	0.62	459 (92)	155 (32)	<0.0001
TG	8 (7)	33 (9)		41 (8)	252 (52)	
TT	–	–		–	82 (17)	
IL10 rs1800890 −3584T>A						
AA	–	–		–	44 (9)	<0.0001
TA	–	22 (6)		22 (6)	235 (48)	
TT	–	347 (94)		347 (94)	212 (43)	
IL12A rs568408 Ex7+277A>G						
AA	1 (1)	6 (2)	0.19	7 (1)	13 (3)	0.25
AG	31 (27)	73 (19)		103 (21)	111 (23)	
GG	81 (72)	305 (79)		386 (78)	362 (74)	
IL12B rs3212227 Ex8+159A>C						
AA	40 (36)	133 (35)	0.83	173 (35)	318 (65)	<0.0001
CA	53 (47)	193 (50)		246 (50)	155 (32)	
CC	19 (17)	58 (15)		77 (16)	16 (3)	
IL13 rs20541 Ex4+98A>G						
AA	8 (7)	40 (10)	0.61	48 (10)	17 (4)	<0.0001
AG	46 (42)	166 (43)		211 (43)	158 (33)	
GG	54 (50)	180 (47)		234 (47)	304 (63)	
IL13 rs1800925 −1069C>T						
CC	86 (77)	287 (74)	0.4	373 (75)	302 (62)	0.0002
TC	25 (22)	90 (23)		114 (23)	165 (34)	
TT	1 (1)	12 (3)		13 (3)	17 (4)	
IL13 rs1295686 IVS3−24T>C						
CC	56 (50)	178 (46)	0.54	234 (47)	304 (62)	<0.0001
TC	48 (43)	170 (44)		218 (44)	166 (34)	
TT	8 (7)	40 (10)		48 (10)	19 (4)	
IL15RA rs2296135 Ex8−361A>C						
GG	17 (15)	66 (17)	0.89	83 (17)	135 (28)	<0.0001
TG	57 (51)	191 (49)		248 (50)	232 (48)	
TT	38 (34)	132 (34)		170 (34)	120 (25)	
LTA rs909253 IVS1+90G>A						
AA	31 (30)	151 (39)	0.008	182 (37)	238 (49)	0.0005
GA	53 (50)	200 (52)		253 (51)	195 (40)	
GG	22 (20)	37 (10)		58 (12)	55 (11)	
MIF rs755622 −269G>C						
CC	5 (5)	16 (4)	0.86	21 (4)	17 (3)	0.003
GC	37 (34)	142 (37)		179 (36)	130 (27)	
GG	67 (61)	229 (59)		296 (60)	343 (70)	
TGFB1 rs1800469 −509C>T						
CC	29 (27)	109 (29)	0.76	138 (29)	225 (46)	<0.0001
TC	48 (45)	174 (46)		222 (46)	217 (44)	
TT	30 (28)	92 (25)		122 (25)	48 (10)	
TLR4 rs4986790 Ex4+636A>G						
AA	112 (100)	385 (99)	0.45	497 (100)	416 (91)	<0.0001
GA	–	2 (1)		2 (0)	38 (8)	
GG	–	–		–	2 (0)	

Table 3 (continued)

Genotypes	Southern Chinese	Northern Chinese	S. vs N. Chinese *P* value	Chinese	Caucasians	Chinese vs. Caucasian *P* value
TNF rs1800629 −487A>G						
AA	–	–	0.55	–	15 (3)	<0.0001
GA	12 (11)	34 (9)		46 (9)	121 (25)	
GG	101 (89)	353 (91)		454 (91)	353 (72)	
TNF rs1799724 −1036C>T						
CC	80 (73)	288 (74)	0.93	368 (74)	379 (79)	0.22
TC	28 (25)	93 (24)		121 (24)	98 (20)	
TT	2 (2)	6 (2)		8 (2)	5 (1)	
VCAM1 rs3176879 Ex9+149G>A						
AA	78 (69)	264 (68)	0.98	342 (69)	460 (95)	<0.0001
GA	31 (27)	107 (28)		138 (28)	23 (5)	
GG	5 (4)	15 (4)		19 (4)	1 (0)	

the chimpanzee sequence (NW_107077) was obtained from GenBank (http://www.ncbi.nlm.nih.gov/entrez/).

Genotyping of DNA samples from all four studies was carried out at the National Cancer Institute Core Genotyping Facility (CGF, Advanced Technology Corporation, Gaithersburg, MD) by endpoint-read TaqMan assays on an ABI 7900HT sequence detection system as described on the SNP500 website (Packer et al. 2006b).

For the primary analyses, genotype frequencies were analyzed only for SNPs genotyped in the Caucasian population and at least one of the Chinese studies. A χ^2 test was used to test the comparisons between groups. A Pearson χ^2 test with 1 *df* was used to test for Hardy–Weinberg equilibrium (HWE) based on observed genotype frequencies. Genetic diversity at each SNP was measured using two different measures: F_{ST} and *d*. F_{ST} measures the reduction in pooled heterozygosity due to population subdivision and was calculated using the formula, $F_{ST} = \frac{H_T - H_S}{H_T}$, where H_T is the expected heterozygosity in the total population, and H_S is the observed heterozygosity (Lewontin and Krakauer 1973). All F_{ST} values less than 0 were set equal to 0. The second measure, *d*, measures the genetic divergence between subpopulations and was calculated using the formula, $d = 1 - \left[(p_1 p_2)^{1/2} + (q_1 q_2)^{1/2}\right]$, where p_1 and p_2 are the frequencies for the first allele of a biallelic SNP in the two subpopulations, respectively, and q_1 and q_2 are the frequencies for the second allele in the two subpopulations, respectively (Nei and Chakravarti 1977). Further analysis restricted to females yield similar results. We present data here that include all study subjects.

For the *IL4* follow-up analysis, haplotypes were estimated separately for each of the 52 groups using PHASE (Stephens et al. 2001). The phylogeny of the common observed haplotypes and the chimpanzee sequence was reconstructed using MEGA3.1 (Kumar et al. 2004).

Results

A total of 45 SNPs in 30 genes that have been related to immune responses were analyzed (Table 1) according to the genotype frequency distribution and genetic diversity across three populations. Table 2 shows the distribution of characteristics for all study subjects from the three populations: northern Chinese (Han), southern Chinese (Han), and Caucasians. Han Chinese have traditionally been geographically divided by the Yangtze River into two parts, northern Han Chinese and southern Han Chinese. In our study, there were more females in the northern Chinese group compared to the southern Chinese group because of the study designs from which these subjects came. There was no correlation between sex and genotype frequency in the Chinese population except *LTA* IVS1+90G>A (P=0.01). All loci were nominally in HW equilibrium, except for two SNPs (*IL4R* rs2107356 -28120T>C and *LTA* rs909253 IVS1+90G>A) for the northern Chinese population and two SNPs (*IL4* rs2243250 -588C>T and rs2070874 Ex1-168C>T) for the Caucasian population showed small departures from Hardy–Weinberg equilibrium (HWE) ($0.05>p>0.01$). Quality control data were rechecked, and the accuracy was confirmed for each assay that was not in HWE. The concordance rates for the QC samples for all SNPs in the three studies are >99%. Therefore, it is likely that these deviations from Hardy–Weinberg proportions occurred by chance.

As expected, the genotype frequencies between northern and southern Chinese for most of the SNPs were similar, with the exception of *IL4* rs2243290 IVS3–9A>C and *LTA* rs909253 IVS1+90G>A (Table 3), which are probably due to chance (p values were between 0.05 and 0.01). Therefore, we combined the northern and southern Chinese subjects together. The genotype frequencies between the Chinese and Caucasians for the majority of the SNPs were

Table 4 SNPs genotyped in the control samples from the Xuan Wei, Tianjin, and Connecticut population-based studies and estimates of genetic diversity, Chinese vs Caucasian, sorted by F_{ST} high to low

Gene	dbSNP IDs	Location and notes	*d*	F_{ST}
IL4	Rs2243290	IVS3−9A>C	0.231	0.414
IL4	rs2243268	IVS2−1443A>C	0.232	0.410
IL4	rs2243250	−588C>T, aka −524	0.224	0.404
IL4	rs2070874	Ex1−168C>T, 5′UTR	0.207	0.399
CSF2	rs1469149	−674A>C	0.131	0.225
IL6	rs1800795	−236C>G, aka −174	0.147	0.203
IL10	rs1800871	−853C>T, aka −819	0.097	0.187
IL5	rs2069812	−745C>T	0.091	0.182
IL10	rs3024491	IVS1−286G>T	0.126	0.166
IL10	rs3024496	Ex5+210C>T, 3′UTR	0.129	0.164
CX3CR1	rs3732379	V249I	0.075	0.160
CSF2	rs25882	I117T	0.080	0.137
IL1RN	rs454078	IVS6+59A>T, aka A9589T	0.024	0.118
IL1A	rs1800587	Ex1+12G>A, aka −889, 5′UTR	0.034	0.108
VCAM1	rs3176879	K644K	0.037	0.108
IFNGR2	rs9808753	Q64R	0.069	0.094
IL1B	rs1143627	−580C>T, aka −31	0.006	0.076
TLR4	rs4986790	D299G	0.015	0.069
IL10	rs1800890	−3584A>T	0.094	0.068
TGFB1	rs1800469	−1346C>T, aka −509	0.014	0.060
TNF	rs1800629	−487A>G, aka −308	0.018	0.059
IL1A	rs17561	A114S	0.034	0.058
IL4R	rs2107356	−28120T>C	0.001	0.044
CCR5	rs2734648	IVS1+151G>T	0.011	0.043
IL10	rs3024509	IVS3−58C>T	0.031	0.042
ICAM1	rs5491	K56M	0.032	0.036
IL8RB	rs1126580	Ex3−1010G>A, 3′UTR	0.026	0.034
IL12A	rs568408	Ex7+277A>G, 3′UTR; aka 8685G>A	0.001	0.032
IL2	rs2069762	IVS1−100G>T	0.001	0.028
IL12B	rs3212227	Ex8+159A>C, 3′UTR	0.028	0.027
IL15RA	rs2296135	Ex8−361A>C, 3′UTR	0.005	0.023
IL13	rs1800925	−1069C>T	0.004	0.006
IL8	rs2227306	IVS1-204C>T	0.001	0.005
IL13	rs20541	Q144R	0.008	0.005
MIF	rs755622	−269G>C, aka −173	0.002	0.003
IL8RA	rs2234671	S276T	0.006	0.002
IL13	rs1295686	IVS324T>C	0.007	0
IFNG	rs1861494	IVS3+284G>A	0.002	0
LTA	rs909253	IVS1+90G>A, aka NcoI, aka A252G	0.002	0
TNF	rs1799724	−1,036C>T, aka −857	0.001	0
CXCL12	rs1801157	Ex4+535C>T, 3′UTR	0.001	0
IL8	rs2227307	IVS1+230G>T	0.001	0
IL8	rs4073	−351A>T, aka −251	0.000	0
FCGR2A	rs1801274	H165R	0.000	0
IL4	rs2243248	−1,098G>T	0.000	0

statistically different ($P<0.01$) (Table 3). For several SNPs, the most common allele was different between the populations. For example, the C allele at *IL4* IVS2–1443 (rs2243268) was found to be common among Chinese (79%), but uncommon among Caucasians (15%). As the southern Chinese subjects were more comparable to the Caucasian subjects in terms of age than the younger northern Chinese subjects, we compared genotype frequencies of the former directly with the Caucasian population, and the results are very similar to the comparison of the combined Chinese population and Caucasians using likelihood ratio test, adjusting for age (data not shown). However, as data were available for *IL10* rs1800890 -3584T>A only in the Northern Chinese population, we explored age effects in that group and among the Caucasian group. After adjusting for age, the results remained similar. As such, the striking difference in genotype frequencies (Table 3) could not have been due to the difference in age

Table 5 Common *IL10* and *IL4* haplotypes among the three populations

Genes	Haplotypes*	Southern Chinese	%†	Northern Chinese	%	Caucasians	%	P
IL10								*<0.0001*
	C-T-A-C-G					416	42.4	
	T-G-A-C-A					322	32.8	
	T-G-A-T-A	158	69.3	502	64.4	5	0.5	
	T-G-C-C-A	52	22.8	205	26.3	7	0.7	
	T-G-C-T-A			6	0.8	225	22.9	
IL4†								*<0.0001*
	T-T-C-C-A	50	22.1	164	21.0	3	0.3	
	T-T-T-C-A	137	60.6	430	55.1	143	14.6	
	T-C-T-A-C	15	6.6	117	15.0	1	0.1	
	T-C-C-A-C	13	5.8	8	1.0	770	78.4	
	G-C-C-A-C	0	0.0	6	0.8	55	5.6	
	G-C-T-A-C	5	2.2	42	5.4	0	0.0	
	Rare Haplotypes	6	2.7	13	1.7	10	1.0	

[a] Order of SNPs comprising *IL10* haplotypes: rs3024496, rs3024491, rs1800872, rs1800871, rs1800896. Order of SNPs comprising *IL4* haplotypes: rs2243248; rs2243250; rs2070874; rs2243268; rs2243290.
[b] Colors identify *IL4* haplotypes presented in Fig. 1.

of the two groups. Also, we note that the difference in genotype frequencies for this SNP are similarly apparent across Caucasians and Pacific Rim populations in the NCI SNP500Cancer database (Hughes et al. 2005;Packer et al. 2006a). Furthermore, results were similar when the analysis was restricted to females.

Estimates of genetic diversity (F_{ST} and d) are presented in Table 4. Several SNPs in *IL4* showed substantial genetic differentiation (F_{st}>0.25 and d>0.20), and one or more SNPs in *CSF2*, *IL6*, and *IL10,* and *CX3CR1* showed moderate genetic differentiation (0.15<F_{ST}<0.25). Table 5 shows estimated *IL10* and *IL4* haplotypes based on ten and five SNPs, respectively, and their frequencies in the three populations, which differed markedly between the Caucasian and Chinese groups (p<0.0001). The haplotype distribution of the five *IL4* SNPs is shown graphically in the three populations (Fig. 1).

We genotyped ten *IL4* SNPs in the (N=1056) Human Diversity panel (HDP) samples (five in primary analysis and five additional SNPs to provide more coverage of the locus) to characterize worldwide haplotype distributions at the *IL4* locus. Overall, a total of 18 haplotypes were observed at a frequency of >5% among the HDP groups. Figure 2 shows the distributions of common (>5%) haplotypes by location for the 52 HDP groups. For comparative purposes, haplotypes estimated to occur at <5% frequency were excluded from these plots; in non-African groups these rare haplotypes only account for between 0 and 6% of the total for each group. As expected, the African groups exhibited more (between four and ten common haplotypes) diversity than those of European, Asian, Oceania, or Native American origin. Figure 3 shows a phylogenetic tree, based on proportion of distance (p), which was reconstructed using the 18 observed haplotypes (numbered arbitrarily) and their average frequencies in the seven geographic groups and the sequence from the chimpanzee. A high degree of variability of haplotype frequencies was observed within the major geographic regions, particularly in the African group, which has the greatest haplotype diversity and

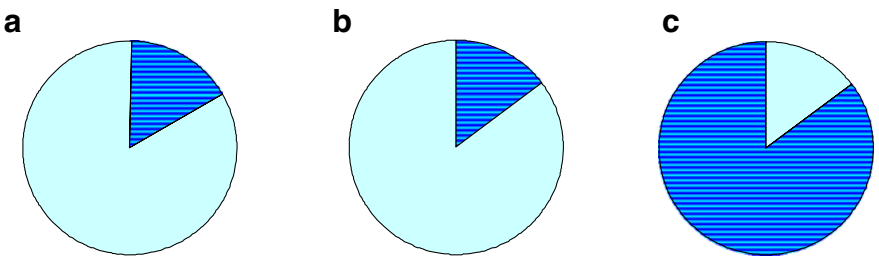

Fig. 1 Estimated haplotype distributions for 5 *IL4* SNPs (see Table 5 footnote for identification of haplotypes) for *A* N=390 individuals from Tianjin, China, *B* N=112 individuals from Xuan Wei County, *C* N=491 Caucasian individuals from Connecticut

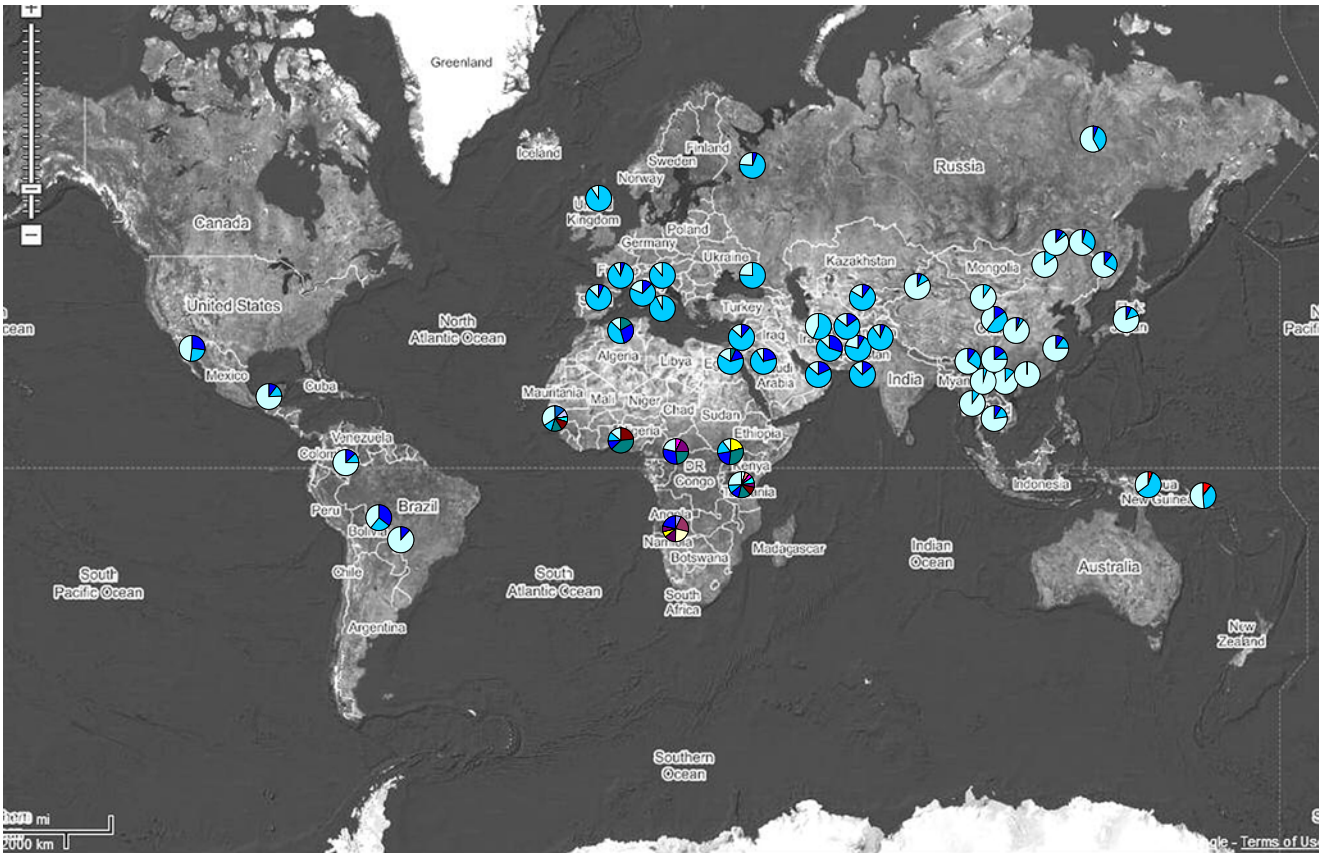

Fig. 2 *IL4* haplotype distribution graphs for the 52 populations in the Human Diversity Panel (HDP). Map used with permission from Google

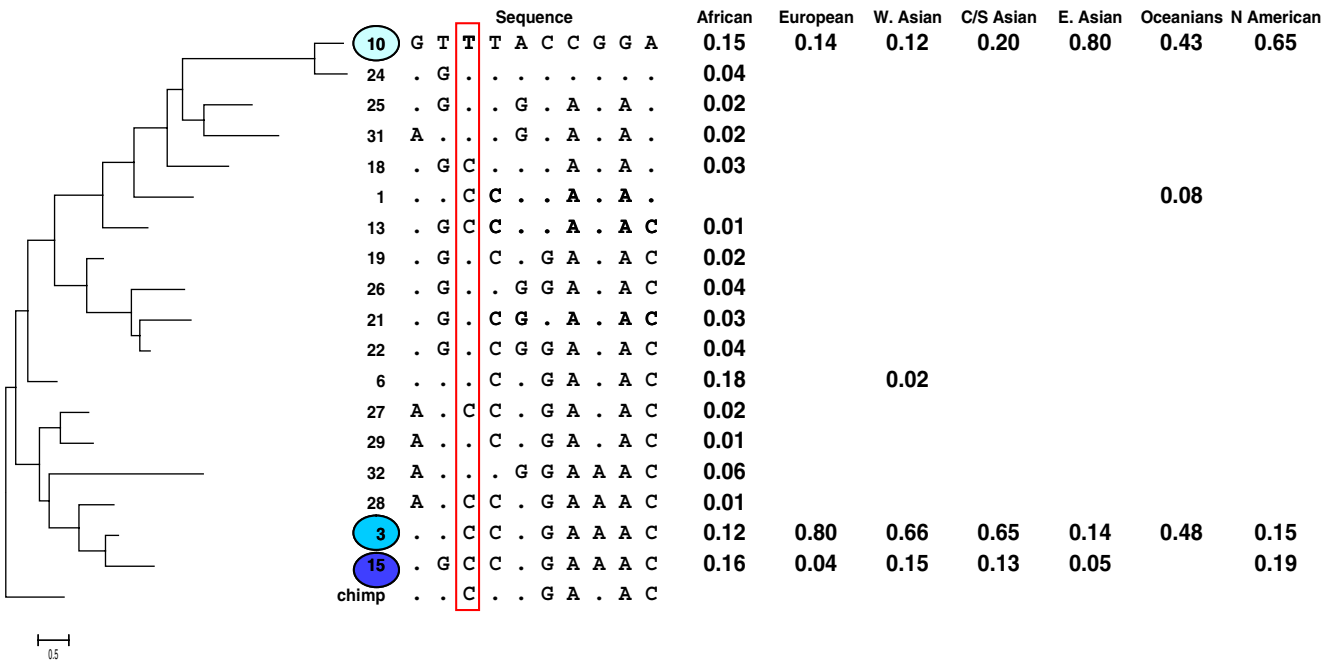

Fig. 3 Phylogenetic tree and average frequencies of *IL4* haplotypes. Order of *IL4* SNPs is as follows: rs2243247; rs2243248; rs2243250; rs2070874; rs2243251; rs2243267; rs2243268; rs2243270; rs2243289; rs2243290

lower frequency of the common haplotypes as shown in Fig. 3. Most of the observed haplotypes were present in the African groups, while in non-Africans, only one to three haplotypes were observed. Although the number of observed haplotypes was consistently low, and the haplotypes, themselves, were the same among these non-African groups, the frequencies of the haplotypes were remarkably different between groups from Europe and Western/Central/Southern Asia than those in Eastern Asia, Oceania, and Native Americans (Figs. 2 and 3). For example, haplotypes 10 and 3 (Fig. 3) occurred at a frequency of 80 and 14%, respectively, in Eastern Asians and at 14 and 80% in Europeans.

Three of the most uniformly frequent haplotypes observed were 3, 10, and 15 (as shown in Fig. 3). Phylogenetically, haplotype 10 is distantly related haplotype to both 3 and 15, which are closely related to each other. Haplotypes 3 and 15 are also more closely related to the chimpanzee (ancestral) sequence. In Fig. 3, the 589 putatively functional SNP is outlined in red. While the chimpanzee and haplotypes 3 and 15 contain the C allele, haplotype 10 contains the T allele, which has been associated with increased levels of IL4. It is interesting to note that in the two populations from the Oceanic region, a novel haplotype (no. 1, Fig. 3) is observed that is unique to this region.

Discussion

We identified a subset of cytokine SNP genotypes that varied substantially between the Caucasians and Chinese populations. SNPs in the *IL4* gene showed the greatest genetic differentiation and SNPs in the *CSF2*, *IL6,* and *IL10*, and *CX3CR1* genes showed moderate differentiation. A previous report found evidence of genetic diversity for several of these same SNPs across a total of 102 DNA samples from a nonrandom sample of subjects in four ethnic groups (i.e., Caucasian; African-American; Pacific Region; Hispanic Caucasians) using the NCI SNP500 database (Hughes et al. 2005). Other reports have compared SNPs in one or more of the cytokine genes we studied between Asians and Caucasians (Hoffmann et al. 2002; Marron et al. 1997; Rockman et al. 2003). However, the study populations were smaller than ours.

We have extended observations from these previous reports in a relatively large series of almost 1,000 subjects, including two groups that represent a sample of their respective populations—Han Chinese from Southern and Northern China and Caucasians in the United States. Our findings are consistent with previous reports on genotype frequencies of the same *IL4* SNP -588C>T (rs2243250) in various populations, although those studies were substantially smaller than ours, and in many instances, did not define the extent to which the findings could be applied to the population at large. For example, the TT genotype frequency has been reported to be 1.8% in Caucasians in the UK (Heward et al. 2001), 2% in Caucasians in the US (Wang et al. 2006), 6% in Australians (Annells et al. 2004), 9% in Egyptians (Hegab et al. 2004), 47% in Japanese (Hegab et al. 2004), 49% in Filipinos (Bugawan et al. 2003), 63% in Chinese (Yang et al. 2005), and about 70% in Taiwan Chinese (Tsai et al. 2005; Wu et al. 2003).

The pattern of distribution of common haplotypes across *IL4* is striking in relation to geography. In Fig. 2, there is a clear divide between East Asia and Europe and Central Asia with respect to the frequency distribution of common haplotypes, suggesting that local selective pressure or assertive mating could be more recent for geographically distinct regions. It is also apparent that the haplotype frequencies for *IL4* display the 'ying–yang' phenomenon, namely, two haplotypes with near-mirror frequencies (Zhang et al. 2003). For *IL4*, a gene critical in immune regulation, it is plausible that recent natural selection could be driven by one or more discrete environmental challenges, such as infection, which could be unique to either side of this "genetic divide', or perhaps both. Further studies are required to determine whether population splitting with maintenance of lineage by selection or genetic drift is responsible for this finding.

The *IL4* gene mediates a number of key immune pathways. It plays an important role in the proliferation and differentiation of T cells, inhibits Th1-induced signals, influences Th1/Th2 balance, provokes B cells to undergo immunoglobulin type-switching, participates in IgE synthesis (Finkelman et al. 1986), and down-regulates expression of CCR5 (major coreceptors for HIV). In vitro data have shown that promoter SNPs in *IL4* -588C>T have increased reporter gene expression (Nakashima et al. 2002). Association studies of diseases suggest that SNPs in the *IL4* gene may now be associated with severity of infection in diseases that can be suitably supported or treated, such as respiratory syncytial virus (RSV) in young children, asthma, atopy, atopic dermatitis, fungal infection with *Candida albicans* in leukemia patients, inflammatory bowel disease, and altered HIV survivorship in an HIV + cohort (Beghe et al. 2003; Burchard et al. 1999; Choi et al. 2002, 2003; Hoebee et al. 2003; Kawashima et al. 1998; Noguchi et al. 2001; Pawlik et al. 2005; Rockman et al. 2003; Zhu et al. 2000). In addition, we have recently reported that SNPs in *IL4* were associated with increased risk of non-Hodgkin lymphoma (NHL) or for specific NHL subtypes (Lan et al. 2006; Purdue et al. 2006).

It is noteworthy that SNP genotype frequencies in three genes that exhibited moderate to substantial variation between our Chinese and Caucasian populations play important roles in the T helper 2 (Th2) pathway (i.e., *IL4*, *IL6*, and *IL10*). Th2

lymphocytes and other related cells produce IL-4, IL-6, and IL-10 that control humoral immunity by up-regulating antibody production to protect against extracellular pathogens. These cytokines play an important role in immunoglobulin production, lymphoid development, and balance immune function. Studies have reported that SNPs in these cytokines may be associated with a wide variety of diseases, including NHL (Akira and Kishimoto 1992; Brouet and Levy 1991; Deng et al. 2002; Gauldie et al. 1992; Lan et al. 2006; Powrie and Coffman 1993a,b; Schuitemaker 1994; Swain 1993; Tepper 1993). A large pooled analysis and a recent report found that the *IL10* -3584A variant was associated with an increased risk of NHL, particularly diffuse large B-cell lymphoma, among Caucasians (Purdue et al. 2006; Rothman et al. 2006). Interestingly, Chinese have a lower incidence of NHL and the *A* allele was found to be less in frequency in Chinese compared to Caucasians in our data (3 vs 33%, respectively, $p<0.0001$).

In conclusion, we have found that SNPs in several genes that play important roles in immune function vary substantially in genotype frequency across Chinese and Caucasians populations. It is interesting that SNPs with the highest F_{ST} values were in genes that regulate the Th2 pathway, which have pleiotropic functions including response to infectious agents and modulation of the inflammatory process. Further exploration of genetic diversity in these and other genes that influence immune function and the inflammatory response are likely to improve our understanding of potential divergent selection pressures on distinct populations, and ultimately, could provide insight into why the incidence of several immune-mediated diseases vary significantly between these two populations.

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