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Distribution of killer cell immunoglobulin-like receptor genes in the mestizo population from Venezuela

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Abstract

This study represents the first report on the distribution of *KIR* genes in 205 unrelated healthy mestizo Venezuelan individuals. Genotyping analysis showed that all *KIR* genes are present in this population. Frequency of inhibitory killer cell immunoglobulin-like receptors (KIRs) exceeded 0.69, except for *KIR2DL2* (0.29) and *2DL5* (0.37). Activating KIRs showed low frequencies (0.11–0.29), except for *KIR2DS4* (0.68). Forty-five different *KIR* genotypes were identified, with a predominance of three genotypes found in 50.7% of the population of which 25.9% were individuals homozygous for haplotype A. The frequencies of *KIR* genes reflect the ethnic admixture existing in the mestizo Venezuelan population.

Keywords

KIR; mestizo Venezuelan population; natural killer cells; polymerase chain reaction-sequence-specific primers

Killer cell immunoglobulin-like receptors (KIR) are glycoproteins and members of the immunoglobulin superfamily that are expressed on natural killer (NK) cells and some T lymphocytes (1, 2). They are named according to the structural characteristics of their extracellular immunoglobulin-like (Ig-like) domains (2D or 3D reflecting the number of Ig-like domains) and intracytoplasmic tail (S or L for short or long, respectively). These structural characteristics are correlated with their function (3–5). KIRs are encoded by a compact cluster of genes located on human chromosome 19ql3.4 (6). The *KIR* locus is

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highly diverse at both haplotype and allele levels. At least 14 functional genes and two pseudogenes have been identified (7, 8); 10 of these genes encode receptors with two Ig-like domains and four genes encode KIRs with three Ig-like domains. The *KIR* gene cluster shows extensive variability in terms of gene content across haplotypes, probably because of nonallelic homologous recombination (9) occurring between pairs of homologous *KIR* genes. More than 100 different *KIR* profiles based on presence/absence of *KIR* genes have been described (http://www.allelefrequencies.net/kir6001a.asp), and multiple studies have shown distinct *KIR* profiles across various populations. Two major haplotypes are distinguished based on their gene content: haplotypes *A* and *B*(10). The most common, haplotype *A,* is uniform in terms of gene content with five inhibitory *KIR* genes (*2DL1, 2DL3, 3DL1, 3DL2*, and *3DL3*), one activating gene (*KIR2DS4*), *KIR2DL4*, which may have both inhibitory and activating capacity, and the two pseudogenes (*2DP1* and *3DPI*). Haplotype *B* exhibits diversity in gene content particularly with respect to the number of activating *KIR* (10).

The specificity of the majority of inhibitory KIRs for their human leukocyte antigen (HLA) class I ligands has been clearly defined. KIR2DL2/3 and KIR2DL1 recognize two mutually exclusive groups of HLA-C allotypes, group 1 (HLA-C1 group) and group 2 (HLA-C2 group), which are distinguished by a dimorphism in the HLA-Cw α1 domain, HLA-C1 group is characterized by the amino acid serine at position 77 and asparagine at position 80 (Ser77/Asn80), and HLA-C2 group is characterized by asparagine at position 77 and lysine at position 80 (Asn77/Lys80) (11, 12). KIR3DL1 interacts with HLA-B allotypes having the serologically defined Bw4 motif (HLA-Bw4), which is based on the amino acid sequence at positions 77–83 (13). KIR3DL2 interacts with HLA-A3 and -All allotypes (14), whereas KIR2DL4 binds the non-classical class I molecule HLA-G (15). The ligands for the activating KIR have been difficult to define; KIR2DS2 and KIR2DS1 are thought to exhibit ligand specificity similar to their corresponding inhibitory counterparts (KIR2DL2/L3 and KIR2DL1, respectively), although their interactions are much weaker (16, 17). A single study showed an interaction of KIR2DS4 with HLA-Cw4, but not with HLA-Cw6, both of which belong to the HLA-C2 group of allotypes (18). More recently, however, it was shown that KIR2DS4 binds to subsets of HLA-C group 1 and group 2 as well as HLA-A*11 (19). Indirect evidence suggests that like KIR3DL1, KIR3DS1 might also interact with HLA-Bw4 (20, 21) although no direct interaction has been reported.

Given that genes that encode KIR and HLA molecules are located on different chromosomes and that both of them are polymorphic, the independent segregation of these unlinked highly polymorphic gene loci produces an additional level of diversity with respect to the number and type of KIR+HLA receptor-ligand pairs present in a given individual. Variation of *KIR-HLA* compound genotypes has been implicated in disease pathogenesis of viral infections, autoimmune diseases, inflammatory disorders, and cancer (22).

Genetic characterization of *KIR* has been performed in Caucasian populations from Europe and North America, certain groups from Asia and Africa (23–27), and a few populations from Central and South America (Amerindians and mestizos) (28–32). Although *KIR* gene profiles have been determined in three Amerindian Venezuelan tribes: Yucpa, Bari, and Warao (30), there is no study focused on the mestizo Venezuelan population, which is the

product of Native American, African, and European admixture. Here, we present the distribution of 14 *KIR* genes and 2 *KIR* pseudogenes in a representative Venezuelan mestizo population group. We define the mestizo population as descendants with different degrees of admixture between European migrants, local Amerindians, and African slaves (33, 34).

A total of 205 unrelated healthy Venezuelan mestizo individuals were analyzed by two immunogenetics laboratories. Genomic DNA was extracted from peripheral blood leucocytes as previously described (35) or using a commercial DNA extraction kit (QLAamp DNA Blood Mini kit; Qiagen GmbH, Hilden, Germany) as specified by the manufacturer. *KIR* genotyping was performed using polymerase chain reaction-sequence-specific primers (PCR-SSP), with different sets of specific primers to detect 14 *KIR* genes (*2DL1*-5, *2DS1*-5, *3DL1–3,* and *3DS1*) and two pseudogenes (*2DPI* and *3DP1*). *KIR* genotyping was determined in 99 samples according to the protocol developed by Gomez-Lozano et al. (36) with some modifications. Briefly, PCR was carried out using 100 ng of DNA in 5 μl of 10× PCR buffer (200 mM Tris-HCl, 500 mM KCl), 3.3 mM $MgCl_2$, 2.5 mM KCl, 0.2 mM Tris-HCl, 0.2 mM dNTPs, 1U Taq polymerase (Platinum; Invitrogen, Sao Paulo, Brazil), 1 μl of each forward and reverse primer specific for *KIR* genes, at different final concentration as reported by Gomez-Lozano et al. (36). *Growth hormone-1* gene (*GH1*) was used as internal control. PCR products were electrophoresed in a 2% agarose gel containing ethidium bromide and visualized under ultraviolet light. The rest of the samples (106 samples) were tested using the PCR-SSP protocol standardized and described by Martin et al. (37). Each PCR reaction consisted of approximately 5 ng of DNA, l× PCR Buffer (200 mM Tris-HCl, 500 mM KC1), 500 nM primer, 1.5 mM $MgCl_2$,0.2 μM dNTP mix, and 1U Taq polymerase (Platinum; Invitrogen). The third intron of DRB1 was used as an internal control. The PCR products were loaded in a 3% agarose gel. *KIR3DP1* was not genotyped by this method. No differences between the two methods used for KIR genotyping were observed. Genotyping of *HLAA,-B,* and -*C* alleles was accomplished by sequence-specific oligonucleotide probe (PCR-SSOP) typing, using commercial kits (RELI SSO™; Dynal Biotech, Wirral, UK).

Data from both laboratories were grouped and analyzed. Frequencies of each *KIR* gene were determined by direct counting. Observed carrier frequencies (F) were calculated by the ratio of frequency of the presence of each gene within the population to the total population number. Estimated gene frequencies (f) were calculated using Bernstein's formula as $f = 1 - \sqrt{(1 - F)}$ (38). Genetic distances between populations were calculated by Phylogeny Inference Package (PHYLIP) version 3.6.

All 14 *KIR* genes and pseudogenes were present in the population studied. Table 1 shows the carrier frequencies (F) and estimated gene frequencies (*f*) for each *KIR* in the population studied. The framework genes *KIR2DL4, KIR3DL2,* and *KIR3DL3* and the pseudogene KIR3DP1 were present in all individuals. Inhibitory *KIR* gene frequencies exceeded 0.69, except for *KIR2DL2* (0.29) and *KIR2DL5* (0.37). However, the activating *KIRs 2DS1, 2DS2,2DS5*, and *3DS1* showed low frequencies ranging from 0.23 to 0.29. *KIR2DS3* showed the lowest gene frequency (0.11), whereas *KIR2DS4* was the only activating *KIR* gene with a high frequency (0.68), which is similar to that observed in the Venezuelan Amerindian Warao population (*KIR2DS3* and *KIR2DS4* gene frequency 0.1 and 0.57, respectively) (30).

Based on the *KIR* profile numbering system of Yawata et al. (39), 45 different *KIR* genotype profiles were identified in our population (Figure 1). Genotype 1 was the most frequently observed (25.9%), followed by genotype 4 (13.7%) and genotype 2 (11.2%). Fifty-one per cent of our mestizo population showed one of these three genotype profiles. Of the 45 profiles, 26 were restricted to a single individual and 6 were possibly new profiles. Genotype 1, which represents individuals homozygous for the *A* haplotype, showed a frequency of 25,9%, which is similar to that observed in Caucasians (31.2%) and two Amerindian tribes from Venezuela: Yucpa (24.59%) and Warao (30.34%), but a lower frequency than that reported in African populations (35.5%) (30, 39). Individual genotypes corresponding definitively to homozygosity for haplotype *B* (based on the absence of one or more of the following genes that are characteristic of haplotype A: *KIR2DL1, KIR2DL3, KIR3DL1, KIR2DS4*) were of relatively low frequency ranging from 0.49%-2.93%. However, the total frequency of all confirmed homozygous haplotype B genotypes was 15.16%. Thirty-four profiles carried all four classical class I HLA-specific inhibitory *KIR* genes (*2DL1, 2DL2/3, 3DL1* and *3DL2*) and represent 88.29% of our population. The other 11.71% correspond to 11 profiles that lack *KIR2DL1* and/or *KIR3DL1* genes.

Because numerous population studies indicate the relevance of KIR with their HLA ligands in disease pathogenesis and resistance to viral infections among populations (22), we evaluated the *KIR-HLA* class I ligand combinations (*KIR/HLA* pair) in our population. Results showed that most of the individuals with *KIR2DL2* and/or *2DL3* also have *HLA-C1* group (79.5%), followed by the combination *KIR2DL1* with *HLA-C2* group (75%). However, *KIR3DL1* with *HLA-Bw4* and *KIR3DL2* with *HLA-A3/11* showed the lowest percentage, 48.8% and 21.1%, respectively (Table 2). These findings are comparable with those reported by Du et al. in Caucasian and Hispanic populations (24) except for *KIR2DL1+HLA-C2* group, which showed a higher frequency.

We also determined the frequency of *KIR* genes with their *HLA* class I ligand present in the same individual (Table 3). All individuals carried at least one inhibitory KIR/HLA pair. Individuals with a single inhibitory *KIR/HLA* pair (23.4%) showed one of the two combinations: 2DL2/3+C1 group (58.6%) and 2DL1+C2 group (41.4%). Most individuals carried two *KIR/HLA* pairs (45.2%) distributed in five combinations with 2DL1+C2 group, and 2DL2/3+C1 group being the most frequent (44.6%). Twenty-eight per cent of individuals carried three pairs, distributed in four combinations, with the combination of 2DL1+C2 group, 2DL2/3+C1 group and 3DL1+Bw4 being the most frequent (67.6%). Finally, only 4% of individuals carried all four inhibitory KIR/HLA pairs. These findings are comparable with those reported by Du et al. in Hispanics (24) and by Rudnick et al. in Brazilians (32).

Differences between the Venezuelan populations and other populations as measured by genetic distances based on *KIR* gene frequencies are shown in Figure 2. The native populations, Warao, Yucpa, and Bari, are equally distant from other native populations from Mexico (Huicholes, Purepechas, and Tarahumaras), but the genetic distances of Bari and Warao are closer to one Amerindian population from Argentina (Chiriguanos). In the mestizo population cluster, the distance between Argentineans and Venezuelans is small and very proximate to Caucasians, indicating a high degree of relatedness, which may be

because of European immigration flow (mostly Spanish, Italian, and Portuguese). A small genetic distance was also found between Venezuelan Amerindians and Asiatic populations, the likely origin of Amerindian populations.

In summary, the frequency distribution of *KIR* genotypes in the Venezuelan population reflects the ethnic admixture existing in our mestizo population. Our data will contribute to the analysis of the genetic diversity of *KIR* genes across populations and its significance in the outcome of diseases associated with distinct *KIR* gene profiles.

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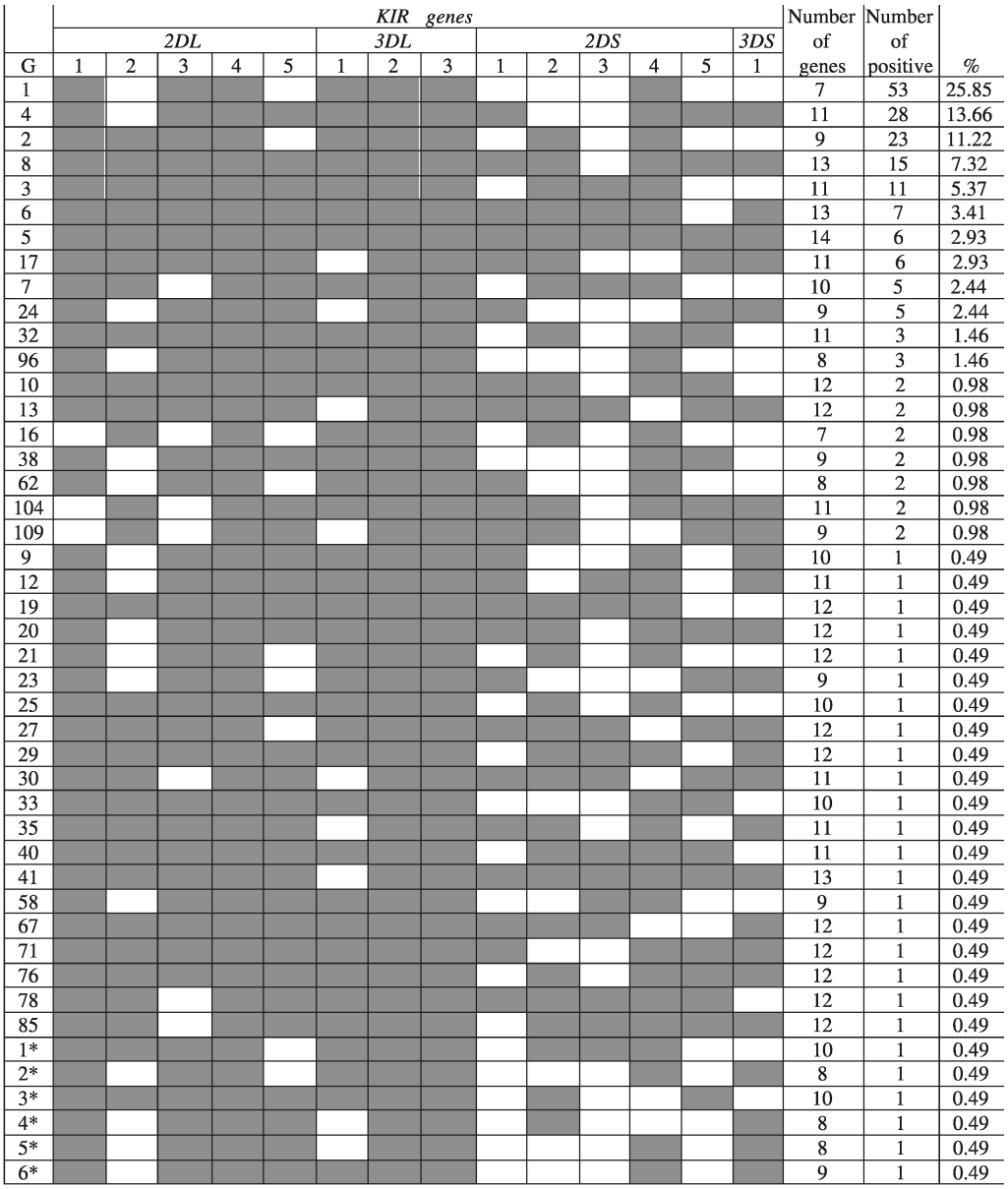

	KIR genes														Number of genes	Number of positive	%
	2DL					*3DL*			*2DS*					*3DS*			
G	1	2	3	4	5	1	2	3	1	2	3	4	5	1			
1	■		■	■		■	■	■				■			7	53	25.85
4	■		■	■	■	■	■	■	■			■	■	■	11	28	13.66
2	■	■	■	■		■	■	■		■		■			9	23	11.22
8	■	■	■	■	■	■	■	■	■	■		■	■	■	13	15	7.32
3	■	■	■	■	■	■	■	■		■	■	■			11	11	5.37
6	■	■	■	■	■	■	■	■	■	■	■	■		■	13	7	3.41
5	■	■	■	■	■	■	■	■	■	■	■	■	■	■	14	6	2.93
17	■	■	■	■	■		■	■	■	■			■	■	11	6	2.93
7	■	■		■	■	■	■	■		■	■	■			10	5	2.44
24	■		■	■	■		■	■	■				■	■	9	5	2.44
32	■	■	■	■	■	■	■	■		■		■	■		11	3	1.46
96	■		■	■	■	■	■	■				■			8	3	1.46
10	■	■	■	■	■	■	■	■	■	■		■	■		12	2	0.98
13	■	■	■	■	■		■	■	■	■	■		■	■	12	2	0.98
16		■		■		■	■	■		■		■			7	2	0.98
38	■		■	■	■	■	■	■				■	■		9	2	0.98
62	■		■	■		■	■	■	■			■			8	2	0.98
104		■		■	■	■	■	■	■	■		■	■	■	11	2	0.98
109		■		■	■		■	■	■	■			■	■	9	2	0.98
9	■		■	■	■	■	■	■	■			■		■	10	1	0.49
12	■		■	■	■	■	■	■	■		■	■		■	11	1	0.49
19	■	■	■	■	■	■	■	■	■	■	■	■			12	1	0.49
20	■		■	■	■	■	■	■	■	■		■	■	■	12	1	0.49
21	■		■	■		■	■	■		■		■			12	1	0.49
23	■		■	■		■	■	■	■				■	■	9	1	0.49
25	■	■	■	■	■	■	■	■		■		■			10	1	0.49
27	■	■	■	■		■	■	■	■	■	■		■	■	12	1	0.49
29	■	■	■	■	■	■	■	■		■	■	■		■	12	1	0.49
30	■	■		■	■		■	■	■	■	■		■	■	11	1	0.49
33	■	■	■	■	■	■	■	■				■	■		10	1	0.49
35	■	■	■	■	■		■	■	■	■		■		■	11	1	0.49
40	■	■	■	■	■	■	■	■		■	■	■	■		11	1	0.49
41	■	■	■	■	■		■	■	■	■	■	■	■	■	13	1	0.49
58	■		■	■	■	■	■	■			■	■			9	1	0.49
67	■	■	■	■	■	■	■	■	■	■	■			■	12	1	0.49
71	■	■	■	■	■	■	■	■	■			■	■	■	12	1	0.49
76	■	■	■	■	■	■	■	■		■		■	■	■	12	1	0.49
78	■	■		■	■	■	■	■	■	■	■	■	■		12	1	0.49
85	■	■		■	■	■	■	■		■	■	■	■	■	12	1	0.49
1*	■	■	■	■		■	■	■		■	■	■			10	1	0.49
2*	■		■	■		■	■	■				■		■	8	1	0.49
3*	■	■	■	■	■	■	■	■		■			■		10	1	0.49
4*	■		■	■	■		■	■		■				■	8	1	0.49
5*	■		■	■	■		■	■				■		■	8	1	0.49
6*	■		■	■	■	■	■	■				■		■	9	1	0.49

Figure 1.

Killer cell immunoglobulin-like receptor (KIR) genotypes from mestizo Venezuelan population. Filled boxes indicate the presence of a *KIR* gene; open boxes its absence. In the study group, 45 genotypes are listed in order of frequency ($n = 205$). Thirty-nine genotypes (G) are designated according to the model of Yawata et al. (39). Six possible new genotypes are described (1*—6*).

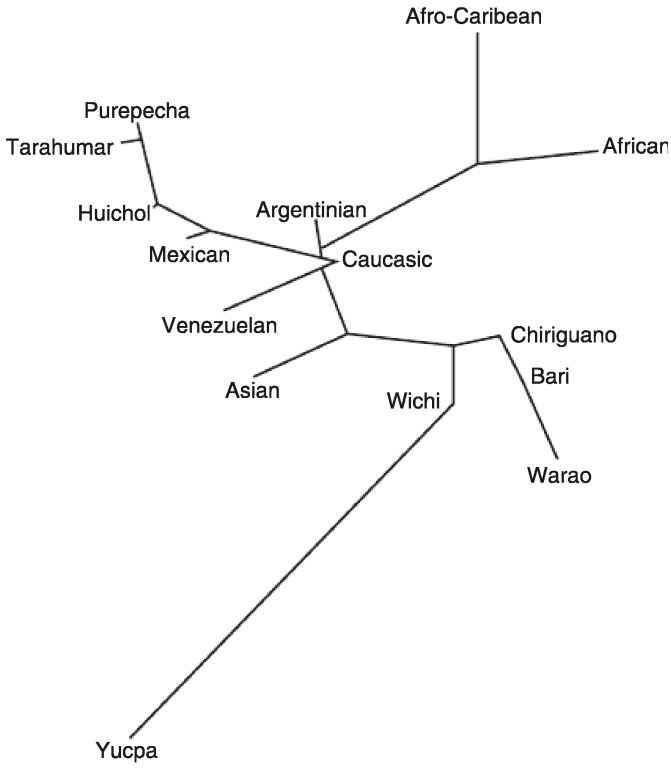

Figure 2.
Phylogenetic dendrogram. Neighbor-joining (NJ) tree from genetic distance based on *KIR* gene frequencies in mestizo Venezuelan population and previously published world populations.

Table 1

Distribution of *KIR* genes in the Venezuelan mestizo population[a]

KIR genes	*2DL1*	*2DL2*	*2DL3*	*2DL4*	*2DL5*	*2DS1*	*2DS2*	*2DS3*	*2DS4*	*2DS5*	*3DL1*	*3DL2*	*3DL3*	*3DS1*	*2DP1*	*3DP1*
n	199	101	191	205	123	88	102	43	184	84	185	205	205	90	199	96
F	97.1	49.3	93.2	100.0	60.0	42.9	49.8	21.0	89.8	41.0	90.2	100.0	100.0	43.9	97.1	100.0
f	0.83	0.29	0.74	1.00	0.37	0.25	0.29	0.11	0.68	0.23	0.69	1.00	1.00	0.25	0.83	1

F, carrier frequency; *f,* estimateci gene frequency; *n,* number of individuals positive for each gene.

[a]A total of 205 individuals were genotyped for each *KIR* gene, except for *KIR3DP1,* which was genotyped in 96 individuals.

Table 2

Frequency of the co-inheritance of KIR+HLA class I ligand combinations in the Venezuelan mestizo population

KIR+HLA class I	Frequency (%)
KIR2DL1+HLA-C2 group	75.4
KIR2DL2+HLA-C1 group	87.5
KIR2DL3+HLA-C1 group	79.8
KIR3DL1+HLA-Bw4	48.5
KIR3DL2+HLAA3/11	21.1

Table 3

Frequency of the number of co-in herited KIR+HLA class I ligand combinations in the Venezuelan mestizo population

Number KIR+HLA pairs	F (%)	KIR+HLA ligand combinations	F(%)
One pair	23.4	2DL2/3+C1	58.6
		2DL1+C2	41.4
Two pairs	45.2	2DL1+C2 and 2DL2/3+C1	44.6
		2DL2/3+C1 and 3DL1+Bw4	30.4
		2DL1+C2 and 3DL1+Bw4	12.5
		2DL2/3+C1 and 3DL2+A3/11	7.1
		2DL1+C2 and 3DL2+A3/11	5.4
Three pairs	27.4	2DL1+C2, 2DL2/3+C1, and 3DL1+Bw4	67.6
		2DL1+C2, 2DL2/3+C1, and 3DL2+A3/11	20.6
		2DL1+C2, 3DL1 +Bw4, and 3DL2+A3/11	5.9
		2DL2/3+C1, 3DL1+Bw4, and 3DL2+A3/11	5.9
Four pairs	4.0	2DL1+C2, 2DL2/3+C1, 3DL1+Bw4, and 3DL2+A3/11	

C1, HLArC group 1; C2, HLA-C group 2; F, frequency.