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Structure of tumor necrosis factor-alpha haploblocks in European populations

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Abstract

DNA variants in the tumor necrosis factor-α (*TNF*) and linked lymphotoxin-α genes, and specific alleles of the highly polymorphic human leukocyte antigen B (*HLA-B*) gene have been implicated in a plethora of immune and infectious diseases. However, the tight linkage disequilibrium characterizing the central region of the human major histocompatibility complex (MHC) containing these gene loci has made difficult the unequivocal interpretation of genetic association data.

To alleviate these difficulties and facilitate the design of more focused follow-up studies, we investigated the structure and distribution of *HLA-B*-specific MHC haplotypes reconstructed in a European population from unphased genotypes at a set of 25 single nucleotide polymorphism sites spanning a 66 kilobase-long region across *TNF*.

Consistent with the published data, we found limited genetic diversity across the so-called *TNF* block, with the emergence of seven common MHC haplotypes, termed TNF block super-haplotypes. We also found that the ancestral haplotype 8.1 shares a *TNF* block haplotype with HLA-B*4402. HLA-B*5701, a known protective allele in HIV-1 pathogenesis, occurred in a unique *TNF* block haplotype.

Keywords

SNPs; *TNF*; *LTA*; *HLA-B*

Allelic diversity at the HLA genes on chromosome 6p21.3 has been associated with a myriad of disease mechanisms underlying autoimmunity, infection and malignancy. Current data indicate that single nucleotide polymorphisms (SNPs) in immunoregulatory genes such as *TNF* and lymphotoxin A (*LTA*) are associated with the development of chronic diseases, cancer, and autoimmune conditions (Allcock et al. 1999; Cheong et al. 2001). For example, the ‘G’ allele at nucleotide position +252 (rs909253 A>G) of *LTA* alone or in combination with the ‘A’ allele at position −308 (rs1800629 G>A) of *TNF* have been repeatedly associated with increased risk for both classical and HIV-related non-Hodgkin’s lymphoma (NHL) (Juszczynski et al. 2002; Nowak et al. 2007; Nowak et al. 2008; Aissani et al. 2009) however, it remains uncertain whether variants in *LTA* and *TNF* or markers in adjacent loci represent true causal variants.

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While the −308A variant has been associated with high levels of TNF production, attempts to relate sequence variation in this gene to functional variation as measured by biologic activity of the molecules have been controversial (Bouma et al. 1996; He et al. 1995; Huizinga et al. 1997; Louis et al. 1998; Turner et al. 1995; Wilson et al. 1997). Finally, the SNPs in the two genes repeatedly associated with NHL most often occur on one of the most conserved extended haplotypes found in the human genome—the Caucasian HLA-B*0801-containing ancestral haplotype (8.1AH) (Degli-Esposti et al. 1992; Price et al. 1999) that spans more than 2 Mb across MHC. Understanding the structure of the joint HLA and MHC SNP haplotypes across the *TNF* locus is important for the correct interpretation of association data because the pattern of linkage disequilibrium (LD) across the MHC is HLA-specific (de Bakker et al. 2006).

In the present study, we have analyzed the genetic diversity across the *TNF* block in a collection of 660 participants enrolled in the Multicenter AIDS Cohort Study (MACS), a prospective study of HIV infection and AIDS (Kaslow et al. 1987). To validate our observations, two study groups from published studies of MHC haplotypes served as reference healthy populations. These were the CEU population (n=92) from the International HapMap project (de Bakker et al., 2006) and a study group (n=398) from the populations of Busselton and Perth, Australia (Valente et al. 2009).

Informed consent was obtained and the Institutional Review Board at each center approved the MACS study. We restricted the analysis to subjects of non-Hispanic European ancestry because of insufficient numbers of subjects from other ethnic groups. All of the 660 sampled individuals were HIV seropositive and half of them (n=330) had Kaposi's sarcoma; these two groups were cases (henceforth group #1) and matched controls (group # 2) selected from ongoing studies of HIV-related Kaposi's sarcoma. To prevent possible distortions of our estimate of population distribution of MHC haplotypes, we conducted separate analyses of these two study groups.

Extended MHC haplotypes were reconstructed for a set of 25 SNPs spanning a 66 Kb interval across the *TNF* locus and including 12 SNPs shared with the CEU and Australian population studies. This genomic interval is flanked by telomeric *HLA-B* and encompasses seven other genes in the following telomere-to-centromere order; mitochondrial coiled coil domain 1 *(MCCD1)*, HLA-B associated transcript 1 (*BAT1*), ATPase G2 isoform (*ATP6V1G2*), nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor-like 1 (*NFKBIL1), LTA*, *TNF*, and leukocyte specific transcript 1 (*LST1*). We reconstructed haplotypes formed by these 25 tagging SNPs alone and jointly with *HLA-B.* With the joint haplotypes of *HLA-B* and MHC SNP being available only from the study of the HapMap sample, we compared our estimates of the joint *HLA-B* and SNP haplotype (henceforth joint MHC haplotypes) frequencies to those of the HapMap sample and of the SNP only haplotypes to both reference samples (Table 1).

SNPs were chosen by a systematic search of populations of Western European ancestry in public databases (HapMap I and SNP500 cancer database) and private databases (Illumina Technologies, San Diego, CA and Applied Biosystems Inc., Foster City, CA). The primary criteria for SNP selection included an aggressive ($r^2 > 0.80$) haplotype tagging potential (htSNP) across gene loci, minor allele frequency (MAF) > 5%, and predicted functionality (identified in PupaSuite (Conde et al. 2006)) Additionally we selected two-hit SNPs (or Illumina-validated) with a "designability" score of 1 (anticipated success rate > 80%).

HLA-B typing was performed to four-digit resolution by reference-strand conformation polymorphism and DNA sequencing-based typing methods. SNP typing was performed on a commercially available genotyping platform (BeadArray®, Illumina Inc., San Diego, CA).

Reliability in SNP typing was assessed by duplicate typing of a random set of 44 samples. SNP markers were examined separately in the two study groups for adherence to HWE using Pearson's chi-squared test

The expectation-maximization based haplotype inference program HAPLORE (Zhang et al. 2005) was used to estimate haplotype frequencies separately in the two study groups. All of the typed SNPs were in HWE ($p>0.05$) and were included in the reconstruction of haplotypes from the unphased genotype data. Comparison of genotype frequencies showed no significant difference ($p>0.05$) between the two study groups, indicating that disease status introduced no significant bias in our estimate of haplotype frequencies (data not shown).

We identified a total of 38 joint haplotypes, with 24 of them present in group 1 and 22 present in group 2 at a frequency ≥1% (Table 1). The cumulative frequencies of the joint haplotypes present at a frequency greater than 0.5% were 69.0% and 69.8% in study groups 1 and 2, respectively. The frequency of joint haplotypes did not differ significantly ($\alpha=5\%$) between group 1, group 2, and the CEU population of HapMap. Of the haplotypes found at ≥0.5% in group 1 or group 2, 18 of them were not found in the HapMap sample likely due to the smaller number of subjects.

Approximately 30% of the joint haplotypes in the study population were rare (<0.5%), with several private haplotypes (not shown). A higher number of rare haplotypes (approximately 40%) were seen in the HapMap sample because of the small size of this sample. Another non-exclusive explanation is a lower genetic diversity in the CEU population compared to that in the multicenter MACS population, The large proportion of rare and private haplotypes is undoubtedly due to the high heterozygosity at HLA-B; indeed, compared to the joint haplotypes, only 14–18% of the SNP-only haplotypes (henceforth SNP haplotypes) were rare or private.

The overall distributions of SNP haplotypes in the two study groups were not statistically different from one another, and are comparable to those obtained in the HapMap and Australian general populations. Haplotype 148 was seen in our samples and the Australians but not in the HapMap sample, probably due to the small number of subjects in that group. The remarkable similarity of the distributions between these three groups indicates that our results are generalizable to healthy populations of European descent. Reconstruction of SNP haplotypes identified 15 haplotypes in group 1 and 13 in group 2, present at frequencies greater than ≥0.5%. The number of reconstructed haplotypes was similar in groups 1 and 2 (11 and 14 haplotypes respectively) as well as to the smaller population from the HapMap project (12 haplotypes) (de Bakker et al.). In the Australian subjects from Busselton and Perth, there were 18 and 15 haplotypes respectively, possibly due to the inclusion of a larger number of test SNPs (n=38) in that study (Valente et al. 2009).

The present study identified several HLA-specific patterns of haplotype sequences across the TNF block in the European populations. First, consistent with the published data [(Belfer et al. 2004; Valente et al. 2009), we show that genetic diversity across *TNF* is very limited across the TNF block, which appears to span at least a 66 Kb-long region flanked by *MMCD1* and *LST1*, the telomeric and centromeric gene loci, respectively. Second and for the first time, we show that haplotype sequence diversity across the TNF block differentiates in seven common haplotypes (frequency greater than 2%) defined by a small number of SNP sites. We propose to name these common joint haplotypes "TNF block super-haplotype" (highlighted as alternate gray and white bands in column 1 of Table 1). Third, about one third of the joint haplotypes occurs at a frequency of less than 0.5%, reflecting the remarkable genetic diversity at the *HLA-B* locus.

The first TNF block super-haplotype accounts for 12.4–14.8% of the total haplotypes and is essentially made up of two HLA-B*0702-containing haplotypes differing by a unique tagging SNP (rs3130062) A>G in *NFKBIL1*, and a single haplotype carrying HLA-B*4001.

The second TNF block super-haplotype, is defined by 4 SNP sites; rs2071594 (*ATP6V1G2*), rs2071592 (*NFKBIL1)*, rs1800683 (*LTA*) and *TNF* −308 SNP rs1800629. Super-haplotype II, accounts for 12.3–12.5% and comprises the known 8.1AH, which invariably carries the A allele at TNF −308 (G>A) (Aissani et al. 2009). The other member of super-haplotype II carries HLA-B*4402, accounting for about 2% and carrying also TNF −308A; this study is the first to show that this allele also occurs on a HLA background other than 8.1AH. The implication of this finding for association studies of 8.1AH- and TNF −308A-associated diseases is important. In effect, when both B*4402 and B*0801 alleles are associated with the outcome under study; this would exclude HLA-B and provide a means to focus the follow-up study on the carriers of B*4402 because the extent of the B*4402 haplotype is much limited compared to 8.1AH. Inversely, if B*4402 is not associated in the presence of an association with B*0801, then *HLA-B* or a gene outside the TNF block carried on 8.1AH is the most likely causal gene. Accounting for this observation in planning follow-up association studies of 8.1AH-associated diseases such as type 1 diabetes (T1D) may speed and lower the cost of follow-up studies.

The third TNF block super-haplotype occurs at a frequency of 8.7–11.8% and is defined by 3 SNP sites; rs2071594 (*ATP6V1G2*), rs2071592 (*NFKBIL1*), and rs1800683 (*LTA*). SNP haplotype 31 containing B*4001, does not carry the minor allele at rs2071592, but is more closely related to super-haplotype III than any of the other super-haplotypes.

The fourth super-haplotype is the least common (2.0–3.9%) and comprises one HLA-B*5701, and another putative B*5701 haplotype (highlighted by a question mark) that has emerged in the reconstruction of SNP haplotypes and not in that of the joint haplotypes at our cut-off frequency of 0.5%. It appears to be most closely related to the B*5701-bearing haplotype, differing only in a C>G transversion in *TNF* (rs3093668) and an A>C in the intergenic region between *MICB* and *MCCD1*. Although rare, if confirmed, the second putative B*5701 haplotype is of great interest in HIV association studies as it may help clarify the causal relationship of this allele to HIV infection and progression as discussed above for B*4402 and B*0801 alleles. An observation that deserves a comment is the lower estimates of the joint B*5701 haplotype frequency in our HIV study population compared to that of the general European population, which is about 5%. This clear difference is expected because B*5701 has consistently been shown to be protective for HIV infection and progression (Fellay et al. 2009; Fellay et al. 2007; Goulder et al. 1996; Liu et al. 2003).

Super-haplotype V is defined by variant A at SNP rs2256965 (*LST1*). B*3501, an allele consistently associated with a rapid progression of HIV infection, occurs on 4 MHC haplotypes, three of which are members of super-haplotype V and one of super-haplotype VI.

Super-haplotype VI is defined by 2 SNPs; one in *LTA* (rs2009658) and the other in *NFKBIL1* (rs2255798). It occurs at a frequency of 11.2–12.8%. One of the B*3501 carrying haplotypes occurs in this group. Two of the haplotypes in this group contain B*1501 but differ in two SNPs in *NFKBIL1* (rs2239707 and rs2230365).

The seventh super-haplotype is defined by two SNPs, one occurring in *BAT1* (rs2239528) and the other in *LTA* (rs928815). Only three haplotypes fall into this group, occurring at 1.8–2.9%. HLA-B*4901 occurs in both super-haplotype VII and III. Our categorization of *TNF*

block haplotypes into super-haplotypes allows convenient grouping of similar haplotypes by tag SNPs for analysis in association studies.

Several tag SNPs used here to reconstruct haplotypes have been reported in association studies. For example, the minor allele (C allele) of the intergenic polymorphism rs3093993, occuring between *MICB* and *MCCD1*, was shown to be associated with decreased HIV-1 cellular DNA and viral control in HIV infected individuals through genome wide association (GWA) studies (Dalmasso et al. 2008). Our data shows that that the minor allele of rs3093993 occurs on the haplotype carrying the HIV-protective allele B*5701 (SNP haplotype 79), in addition to haplotypes with B*0702, *4001, *5701, and *4901. HLA-B*57 molecules have been shown in numerous studies to be protective in HIV infection (Fellay et al. 2009; Fellay et al. 2007; Goulder et al. 1996; Liu et al. 2003) and also to be associated with lower viral load (Kloverpris et al. 2012). Whether the protection seen in these studies is due to the sole effect of *HLA-B* or to its joint effect with the gene tagged by rs3093993 or by another polymorphism in LD with these polymorphisms is difficult to ascertain. However, comparisons of haplotype sequence conservation and divergence across super-haplotypes of interest may be informative for the delineation of the most likely candidate region.

The minor alleles of SNPs rs2857605, rs2239707, and rs2230365; all intronic in *NFKBIL1*, comprise a haplotype that has been associated with increased risk of NHL (Wang et al. 2009). SNPs rs2857605 and rs2239707 occurred in super-haplotype I and SNPs rs2239707 and rs2230365 occurred in super-haplotype VI. All three SNPs were found in super-haplotype VII except with B*4901.

SNPs rs2071592 and rs2071594, located in *NFKBIL1* and the 3’ flanking region of *ATP6V1G2* respectively, are associated with an increased incidence of rheumatoid arthritis (RA) (Okamoto et al. 2003). Most commonly (>50% of haplotypes) the minor alleles of these two SNPs occurred on HLA-B*0801, *4402, or *2705; all of which have been associated with adult or juvenile RA in previous studies (Avila-Portillo et al. 1994; Berntson et al. 2008; Raychaudhuri et al. 2012). These haplotypes are of super-haplotype II and III. Another *NFKBIL1* SNP (rs4947324) associated with RA (Jung et al. 2009) occurs in both super-haplotype IV and two B*3501-carrying members of super-haplotype V.

The minor allele of rs2009658 has been associated with an increased risk of breast cancer (Madeleine et al. 2011). This SNP only occurred in super-haplotype VI and frequently (>30% of the time) was found with either HLA-B* 1501 or *1402, both of which have been associated with an increased incidence of breast cancer (Biswal et al. 1998; Cantu de Leon et al. 2009). B*1501 alleles from super-haplotype III lack the C>G transversion, allowing for discrimination between these polymorphisms in association studies.

The minor allele of rs1800683, found in *LTA*, has been associated with protection from myocardial infarction (Koch et al. 2007) and decreased antibody response to measles (Dhiman et al. 2008) as part of an extended haplotype with other SNPs in *TNF* and *LTA*. Allele A of this SNP occurred in super-haplotype II and III. Another SNP located in *LTA*, rs2229094 (previously known as rs2857713) encodes a missense mutation (Cys13Arg) in the encoded peptide. This polymorphism has been associated with several disparate conditions including gastric cancer in Japanese men (Takei et al. 2008), preeclampsia in pregnant women (Parimi et al. 2008), proliferative vitreoretinopathy (Rojas et al. 2010), and cancer-related mortality (Gallicchio et al. 2008). In a study of an Indian population, the minor allele of rs2229094 was found to be negatively associated with Type 2 diabetes mellitus (Mahajan et al. 2010). SNP rs2229094 occurred on super-haplotype IV, the B*3501-containing super-haplotype V, and super-haplotype VI.

SNP rs1799964 is located at position T-1031C of *TNF*. Modeling with MFOLD indicates that the C allele of this polymorphism prevents the binding of several transcription factors by altering the accessibility of the DNA (Basu et al. 2012). In studies of malaria, this SNP has been associated with increased parasitemia, heightened severity of disease, and incidence of cerebral involvement (Basu et al. 2012; Hananantachai et al. 2007; Sinha et al. 2008). Case studies have found the minor allele G of this SNP to be associated with Crohn's disease, asthma, decreased immunity after natural infection or vaccination against measles, and cancer-associated mortality (Dhiman et al. 2008; Gallicchio et al. 2008; Puthothu et al. 2009; Sanchez et al. 2009). Interestingly, this is the only allele shared by all members of super-haplotypes IV and VI, suggesting that within the TNF block, *TNF* is the sole candidate gene for these diseases.

Experimental evidence suggests that haplotypic differences in the promoter region of *TNF* alter the transcription level of this important cytokine (Basu et al. 2012). Occurring with rs1799964 in this study was rs3093668, a SNP in the 3' UTR of *TNF*. A family-based study identified this SNP with type 1 diabetes mellitus (Boraska et al. 2009). Both of these *TNF* SNPs occurred on super-haplotype IV and rs1799964 also occurred on super-haplotype VI.

The most studied *TNF* promoter −308 (G>A) SNP, rs1800629, has been implicated in the development of multiple diseases. The minor allele (A) has been associated with cerebral malaria (McGuire et al. 1994) and susceptibility to septic shock (Mira et al. 1999). Case studies have found an increased frequency of the A allele in lung (Shih et al. 2006) and hepatocellular cancers (Akkiz et al. 2009) but the G allele has been found with increased frequency in basal cell carcinoma (Rizzato et al. 2011) and renal cell cancer (Basturk et al. 2005). The differential findings related to this potent cytokine in malignancy may highlight the delicate balance between immune surveillance and inflammation in cancer development. Other diseases that have been associated with the A allele include type 1 diabetes mellitus (Noble et al. 2006), type 2 diabetes mellitus (Kubaszek et al. 2003), and asthma (Wang et al. 2004; Witte et al. 2002). Amongst healthy volunteers, individuals homozygous for AA at −308 exhibited decreased gray matter in the hippocampus (Baune et al. 2012), possibly indicating that this polymorphism plays a role in neurodegenerative disease. This SNP was only found on super-haplotype II, with the ancestral HLA-B*0801 and also B*4402. Because the B*0801 haplotype is so common, the minor allele frequency (MAF) of rs1800629 was 12.3–12.5%.

SNP rs3093662 is located in an intron of *TNF*. Previously this SNP was shown to be overrepresented in HIV controllers, individuals with low viral load and no disease symptoms after ten years of treatment-naïve HIV infection (Dalmasso et al. 2008; Kloverpris et al. 2012). Occurring on super-haplotype IV and one B*3501-containing super-haplotype V, rs3093662 was most commonly (>70% of extended haplotypes) found in LD with HLA-B*5701. This particular B allele is strongly protective in HIV infection (Kamya et al. 2011; Kloverpris et al. 2012; Miura et al. 2009; Nou et al. 2009) whereas B*3501 is rather at risk; in the light of our data, this observation indicated that *HLA-B* and not *TNF* is the most likely causally-related gene.

The distribution patterns of the TNF block super-haplotypes revealed in the present study will likely undergo refinements and updates in future studies of larger samples, higher SNP coverage and diverse European and other Caucasian populations. However, it is quite possible that the TNF block super-haplotypes are the local structure of much longer MHC haplotypes, plausibly the conserved extended haplotypes or ancestral haplotypes (Dawkins et al. 1999).

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Table 1

Distribution of joint HLA-B and MHC SNP Haplotypes in European populations

Hap #	*MCCD1*	*BAT1*	*ATP6V1G2*	*NFKBIL1*							*LTA*						*TNF*					*LST1*		*NCR3*	HLA-B	Joint HLA-B and SNP haplotype frequency			SNP only haplotype frequency				
																										North America		HapMap	North America		HapMap	Australia	
	rs3093993 A>C	**rs2239528 G>A**	**rs2071594 G>C**	**rs2071592 T>A**	rs2255798 C>G	rs6929796 G>A	**rs2857605 A>G**	rs2239707 A>G	**rs2230365 G>A**	**rs3130062 A>G**	**rs4947324 G>A**	rs928815 C>A	rs2009658 A>G	rs4647191 G>A	rs1800683 G>A	rs2229094 A>G	rs3093542 C>G	**rs1799964 A>G**	**rs1800629 G>A**	**rs3093662 A>G**	**rs3093665 A>C**	**rs3093668 C>G**	rs769177 G>A	rs2256965 G>A	rs986475 A>G		Group 1 N=330	Group 2 N=330	N=92	Group 1	Group 2	N=92	Busselton N=193	Perth N=205
4	C	A	.	.	.	.	G	G	.	G	.	A	.	.	.	.	.	.	.	.	.	.	.	A	.	0702	0.067	0.059	0.053	0.069	0.076	0.087	0.060	0.076
8	C	A	.	.	.	.	G	G	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	A	.	0702	0.043	0.073	0.095	0.070	0.100	0.130	0.089	0.076
83	C	A	.	.	.	.	G	G	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	A	.	4001	0.014	0.016	0.031					
3	.	.	C	A	.	.	.	.	.	.	.	.	.	.	A	.	.	.	A	.	.	.	.	.	.	0801	0.104	0.103	0.138	0.149	0.145	0.178	0.142	0.124
28	.	.	C	A	.	.	.	.	.	.	.	.	.	.	A	.	.	.	A	.	.	.	.	.	.	4402	0.019	0.022	0.007					
34	.	.	C	A	.	A	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	4402	0.036	0.025	0.007	0.164	0.109	0.142	0.116	0.133
97	.	.	C	A	.	A	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	3502	0.014	0.014	NA					
14	.	.	C	A	.	A	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	1801	0.006	NA	NA					
19	.	.	C	A	.	A	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	2705	0.018	0.014	0.006					
67	.	.	C	A	.	A	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	1501	0.016	0.015	0.019					
44	.	.	C	A	.	A	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	4001	0.008	0.013	0.010					
136	.	.	C	A	.	A	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	3906	0.008	NA	NA					
137	.	.	C	A	.	A	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	3901	0.006	NA	NA					
148	.	.	C	A	.	.	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	4901	NA	0.006	NA	0.007	0.006	NA	0.010	NA
31	.	.	C	.	.	A	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	4001	0.006	NA	0.009	0.014	0.022	0.010	0.023	0.017
79	C	.	.	.	.	.	.	.	.	.	A	.	.	.	.	G	.	G	.	G	.	G	.	.	.	5701	0.031	0.020	0.057	0.037	0.030	0.054	0.039	0.045
?	.	.	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	G	.	G	.	.	.	.	.	?	NA	NA	NA	0.008	0.009	NA	0.014	0.005
43	.	A	.	.	.	.	.	.	.	.	A	.	.	.	.	G	G	.	.	.	.	.	.	A	.	3501	0.020	0.019	NA	0.040	0.025	0.025	0.028	0.027
118	.	.	.	.	.	.	.	.	.	.	A	.	.	.	.	G	.	.	.	G	C	.	.	A	.	3501	0.006	0.008	NA	0.010	0.017	0.011	0.018	0.022
74	.	.	.	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	A	G	3501	NA	0.006	NA	0.115	0.097	0.056	0.142	0.124
15	.	.	.	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	A	G	3801	0.023	0.014	0.007					
77	.	.	.	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	A	G	3503	0.006	0.014	0.007					
36	.	.	.	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	A	G	1801	0.019	0.017	NA					
66	.	.	.	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	A	G	5101	NA	0.008	NA					
25	.	.	.	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	A	G	2705	0.011	0.005	NA					
77	.	.	.	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	A	G	5501	0.009	0.009	NA					
16	.	.	.	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	A	G	1501	0.009	NA	NA					
7	.	.	.	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	A	.	4403	0.040	0.052	0.023	0.025	0.020	0.056	0.057	0.076
125	.	.	.	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	A	.	1302	0.010	0.020	0.017					
9	.	.	.	.	G	.	.	.	.	.	.	.	G	.	.	G	.	G	.	.	.	.	.	.	.	1501	0.012	0.020	0.029	0.020	0.023	0.056	0.047	0.047
11	.	.	.	.	.	.	.	.	.	.	.	.	G	.	.	G	.	G	.	.	.	.	.	.	.	4002	0.019	0.006	NA	0.025	0.020	NA	0.018	0.015
69	.	.	.	.	G	.	.	G	A	.	.	.	G	.	.	G	.	G	.	.	.	.	.	.	.	1501	0.013	0.016	0.014	0.100	0.127	0.106	0.094	0.130
65	.	.	.	.	G	.	.	G	A	.	.	.	G	.	.	G	.	G	.	.	.	.	.	.	.	5101	0.020	0.022	0.021					
40	.	.	.	.	G	.	.	G	A	.	.	.	G	.	.	G	.	G	.	.	.	.	.	.	.	1402	0.017	0.030	NA					
64	.	.	.	.	G	.	.	G	A	.	.	.	G	.	.	G	.	G	.	.	.	.	.	.	.	4001	0.013	0.008	NA					
32	.	.	.	.	G	.	.	G	A	.	.	.	G	.	.	G	.	G	.	.	.	.	.	.	.	3501	0.018	0.026	0.028					
78	.	A	.	.	.	.	G	G	A	.	.	A	.	A	.	.	.	.	.	.	.	.	.	.	.	3701	0.014	0.006	0.013	0.016	0.007	0.005	0.057	0.023
85	.	A	.	.	.	.	G	G	A	.	.	A	.	.	.	.	.	.	.	.	.	.	A	.	.	5201	0.009	0.006	0.013					
70	C	A	.	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	A	.	4901	0.006	0.006	NA	0.010	0.009	0.015	0.022	0.007
																										Number of haplotypes ≥ 1%	24	22	15	15	13	13	17	15
																										Cumulative frequency	69.0%	69.8%	60.4%	85.7%	81.6%	92.0%	86.1%	86.2%

There were 24 subjects in group 1 and 22 in group 2 that were present in the population at ≥ 1.0 %. Frequencies were defined by the HAPLORE program (Zhang et al. 2005) using the expectation maximization algorithm. Only the minor allele is listed. NA represents 'not found' in the samples tested. (?) is a potentially distinct HLA-B*5701-containing haplotype. SNPs in bold were typed in all three study populations.