ORIGINAL ARTICLE

*HLA-B*13:01* and the Dapsone Hypersensitivity Syndrome

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ABSTRACT

BACKGROUND

Dapsone is used in the treatment of infections and inflammatory diseases. The dapsone hypersensitivity syndrome, which is associated with a reported mortality of 9.9%, develops in about 0.5 to 3.6% of persons treated with the drug. Currently, no tests are available to predict the risk of the dapsone hypersensitivity syndrome.

METHODS

We performed a genomewide association study involving 872 participants who had received dapsone as part of multidrug therapy for leprosy (39 participants with the dapsone hypersensitivity syndrome and 833 controls), using log-additive tests of single-nucleotide polymorphisms (SNPs) and imputed HLA molecules. For a replication analysis, we genotyped 24 SNPs in an additional 31 participants with the dapsone hypersensitivity syndrome and 1089 controls and performed next-generation sequencing for *HLA-B* and *HLA-C* typing at four-digit resolution in an independent series of 37 participants with the dapsone hypersensitivity syndrome and 201 controls.

RESULTS

Genomewide association analysis showed that SNP rs2844573, located between the *HLA-B* and *MICA* loci, was significantly associated with the dapsone hypersensitivity syndrome among patients with leprosy (odds ratio, 6.18; $P=3.84\times10^{-13}$). *HLA-B*13:01* was confirmed to be a risk factor for the dapsone hypersensitivity syndrome (odds ratio, 20.53; $P=6.84\times10^{-25}$). The presence of *HLA-B*13:01* had a sensitivity of 85.5% and a specificity of 85.7% as a predictor of the dapsone hypersensitivity syndrome, and its absence was associated with a reduction in risk by a factor of 7 (from 1.4% to 0.2%). *HLA-B*13:01* is present in about 2 to 20% of Chinese persons, 1.5% of Japanese persons, 1 to 12% of Indians, and 2 to 4% of Southeast Asians but is largely absent in Europeans and Africans.

CONCLUSIONS

*HLA-B*13:01* was associated with the development of the dapsone hypersensitivity syndrome among patients with leprosy. (Funded by the National Natural Science Foundation of China and others.)

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Dapsone (4-4′-sulfonyldianiline), which was first synthesized in 1908,[1] is both an antibiotic and an antiinflammatory agent. Dapsone alone or in combination with other drugs has been used for the prevention and treatment of infectious diseases (e.g., leprosy, malaria, and actinomycetoma, as well as *Pneumocystis jirovecii* pneumonia in persons with human immunodeficiency virus [HIV] infection) and chronic inflammatory diseases characterized by the infiltration of neutrophils or eosinophils (e.g., dermatitis herpetiformis, linear IgA dermatosis, subcorneal pustular dermatosis, and erythema elevatum diutinum).[2,3] About 0.5 to 3.6% of persons treated with dapsone have a drug hypersensitivity syndrome,[3-5] which was first described by Lowe and Smith[6] in 1949 and termed "dapsone hypersensitivity syndrome"[7] in 1951. The syndrome is a severe idiosyncratic drug reaction characterized by the clinical triad of fever, rash, and systemic involvement (most commonly of the liver and the hematologic system), which can cause severe organ dysfunction. The dapsone hypersensitivity syndrome is usually manifested 4 to 6 weeks after the initiation of therapy.

With the introduction of multidrug therapy for leprosy worldwide and with the use of dapsone in chemoprophylaxis for *P. jirovecii* pneumonia in patients with HIV infection, the incidence of the dapsone hypersensitivity syndrome may have increased. On the basis of a recent systematic review of the published epidemiologic studies, the estimated prevalence of the dapsone hypersensitivity syndrome is 1.4%, and the associated mortality is 9.9%.[8] According to the most recent study in the Chinese population, the incidence rate and mortality are 1.0% and 11.1%, respectively.[9] However, to date, there are no tests to predict the risk of the dapsone hypersensitivity syndrome.

Genetic factors have been shown to play an important role in drug-induced hypersensitivity reactions. For example, the *HLA-B*15:02* allele was identified as an important predictor of the risks of carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis in the population of Southeast Asia.[10] Clinical testing for this allele led to decreases in the incidence of each of these disorders in the Taiwanese population.[11] Recently, a genomewide association study linked the *HLA-A*31:01* allele with carbamazepine-induced hypersensitivity reactions in the European population.[12] This finding highlighted the genetic heterogeneity of drug-induced hypersensitivity among ethnic populations and may facilitate the development of a diagnostic test for this potentially life-threatening condition in the European population.

To identify the genetic risk factors for the dapsone hypersensitivity syndrome, we performed a genomewide association study in the Chinese population, comparing patients with leprosy in whom the dapsone hypersensitivity syndrome developed after the initiation of treatment (case patients) with those in whom the syndrome did not develop (controls).

Methods

Study Participants

A total of 77 case patients (39 patients in the discovery analysis and 38 in the replication analysis) participated in this study, all of whom were patients with leprosy who had survived the dapsone hypersensitivity syndrome and were of Chinese descent. All received dapsone as part of multidrug therapy, and the dapsone hypersensitivity syndrome was diagnosed on the basis of the criteria proposed by Richardus and Smith.[13] Controls included 2064 patients (955 patients in the discovery analysis and 1109 in the replication analysis) who had been cured of leprosy after treatment with dapsone as part of multidrug therapy for at least 6 months but whose status with respect to the dapsone hypersensitivity syndrome could not be determined owing to insufficient medical information. The case patients and controls in both the discovery and replication analyses were matched for geographic origin and ethnic group. The demographic and clinical characteristics of the two groups are provided in Table 1. Healthy persons of Chinese descent were assessed in order to estimate the allele frequency of *HLA-B*13:01* in the Chinese population, including 951 persons from Guangdong Province, 523 from Shandong Province, and 470 from Yunnan Province. The study was approved by the institutional review board at the Shandong Provincial Institute of Dermatology and Venereology. Written informed consent was obtained from all participants. All the authors vouch for the accuracy and completeness of the data.

Genotyping of Single-Nucleotide Polymorphisms and Association Analysis

The case patients and controls of the discovery analysis and healthy persons from Shandong and Yunnan were genotyped with the use of Illumina

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Table 1. Baseline Characteristics of Patients with the Dapsone Hypersensitivity Syndrome (Case Patients) and Control Patients.

Characteristic	Discovery Data Set		Replication Data Set		Total	
	Case Patients (N=39)	Controls (N=833)	Case Patients (N=38)	Controls (N=206)	Case Patients (N=77)	Controls (N=1039)
Sex — no. (%)						
Male	24 (62)	626 (75)	23 (61)	136 (66)	47 (61)	762 (73)
Female	15 (38)	207 (25)	15 (39)	70 (34)	30 (39)	277 (27)
Median age — yr	34	24	42	24	38	24
Ethnic group — no. (%)*						
Han	28 (72)	644 (77)	29 (76)	176 (85)	57 (74)	820 (79)
Chuang	4 (10)	182 (22)	2 (5)	5 (2)	6 (8)	187 (18)
Other	7 (18)	7 (1)	7 (18)	25 (12)	14 (18)	32 (3)
Indication for dapsone therapy for leprosy						
Onset of symptoms — days	34.1		31.5		32.8	
Fever — no. (%)	34 (87)		30 (79)		64 (83)	
Mean temperature —°C	39.2		39.0		39.1	
Skin lesions — no. (%)	35 (90)		35 (92)		70 (91)	
Lymphadenopathy — no. (%)	18 (46)		24 (63)		42 (55)	
Elevated aminotransferases — no. (%)	31 (79)		27 (71)		58 (75)	

* All ethnic groups are from the Chinese population.

Human660W-Quad BeadChips, and the healthy persons from Guangdong were genotyped with the use of Illumina Human610-Quad BeadChips.[14] After quality-control measures were implemented, a total of 430,276 single-nucleotide polymorphisms (SNPs) in 39 case patients and 833 controls were used in the genomewide discovery analysis of association. For the test of replication, 24 selected non–major histocompatibility complex (MHC) SNPs were successfully genotyped in an additional 31 case patients and 1089 controls with the use of the Sequenom MassARRAY platform.

All association analyses were performed with the use of logistic regression with an additive model of inheritance (log-additive test) by means of PLINK software,[15] version 1.07. Because the case patients and controls were well matched genetically (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), the association analysis was performed without controlling for population stratification. The discovery and replication samples were treated as independent samples in the combined analysis. Heterogeneity was assessed with the use of Cochran's Q statistic and quantified by calculating the I^2 statistic.

HLA ALLELE IMPUTATION, SEQUENCING, AND ASSOCIATION ANALYSIS

Imputation of classical HLA alleles and amino acid variants of HLA (whose haplotypes defined the classical alleles) was performed with the use of Beagle software[16] and the reference panel from the HapMap dataset of Han Chinese in Beijing (CHB) and Japanese in Tokyo (JPT).[17,18] Association was tested with the use of both the imputed classical alleles (at two-digit or four-digit resolution) of HLA class I molecules (*A*, *B*, and *C*) and class II molecules (*DQA1*, *DQB1*, and *DRB1*) and the amino acid variants. The sequencing analysis of *HLA-B* and *HLA-C* molecules was performed with the use of the Roche 454 GS FLX platform. HLA alleles were identified at a four-digit resolution by means of HLA Caller,[19] as implemented in the Genome Analysis Toolkit.

Additional information regarding the diagnostic criteria for the dapsone hypersensitivity syndrome; genotyping, quality control, and analysis of population structure in the genomewide discovery analysis; the selection of SNPs for the replication test; and the imputation, sequencing, and association analysis of HLA alleles is provided in the Supplementary Appendix.

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RESULTS

GENOMEWIDE ASSOCIATION ANALYSIS

Summary statistics for the complete data set of 430,276 SNPs examined in the genomewide association analysis are available at the database of Genotypes and Phenotypes (dbGaP) (www.ncbi.nlm.nih.gov/gap); accession number, phs000217.v2.p1. Smaller P values than would be expected by chance were observed at the tail of the quantile–quantile distribution (Fig. S2A in the Supplementary Appendix), whereas the overall distribution did not show any indication of inflation due to population stratification, as indicated by the value for genetic control (λ_{GC}=1.012). Significant associations were observed for 91 SNPs within the MHC region on chromosome 6 ($P<1\times10^{-4}$ for all comparisons) (Fig. S2B in the Supplementary Appendix), with the strongest association at rs2844573, located between the *HLA-B* and *MICA* loci (odds ratio, 6.18; $P=3.84\times10^{-13}$).

We imputed classical HLA alleles and amino acid positions as well as untyped SNPs within the MHC region in the discovery samples. A total of 66 classical HLA alleles imputed at two-digit resolution, 118 classical HLA alleles imputed at four-digit resolution, 309 amino acid substitution variants of HLA, and 4206 untyped SNPs, together with the 4636 genotyped SNPs, were tested for association with the dapsone hypersensitivity syndrome. Of the 309 amino acid variants, 238 were biallelic and 71 were multiallelic. For each multiallelic variant, association was analyzed with the use of a biallelic test of every possible grouping of amino acids, for a total of 497 tests across the 309 amino acid variants.

Of the imputed SNPs, only rs2844586 showed a stronger association (odds ratio, 14.77; $P=2.50\times10^{-15}$) than did rs2844573, but the two SNPs were correlated ($D'=0.764$, $r^2=0.26$). Much stronger associations were discovered at *HLA-B*13:01* (odds ratio, 21.67; $P=2.04\times10^{-16}$) and *HLA-C*03:04* (odds ratio, 13.43; $P=1.84\times10^{-14}$) (Fig. 1A and Table 2). These two HLA alleles were in linkage disequilibrium ($D'=0.93$, $r^2=0.74$). Controlling for *HLA-B*13:01* eliminated the effect of *HLA-C*03:04* (adjusted P=0.76), but controlling for *HLA-C*03:04* did not fully eliminate the effect of *HLA-B*13:01* (adjusted $P=5.16\times10^{-5}$; adjusted odds ratio, 17.92). The two-digit classical *HLA-B*13* allele also showed an association, but it was much weaker than the association at *HLA-B*13:01* (Table S1 in the Supplementary Appendix).

Of the 497 tests for association across all 309 amino acid variants, 18 showed an association ($P<1\times10^{-4}$ for all comparisons), with the strongest association at a variant encoding leucine residue at position 145 (Leu145) of *HLA-B*13:01* (odds ratio, 8.41; $P=5.11\times10^{-13}$), but all these associations were weaker than the association at *HLA-B*13:01* (Table S1 in the Supplementary Appendix). Adjustment for *HLA-B*13:01* eliminated the extensive associations observed within the whole MHC region, including the strong associations at rs2844573, rs2844586, and Leu145

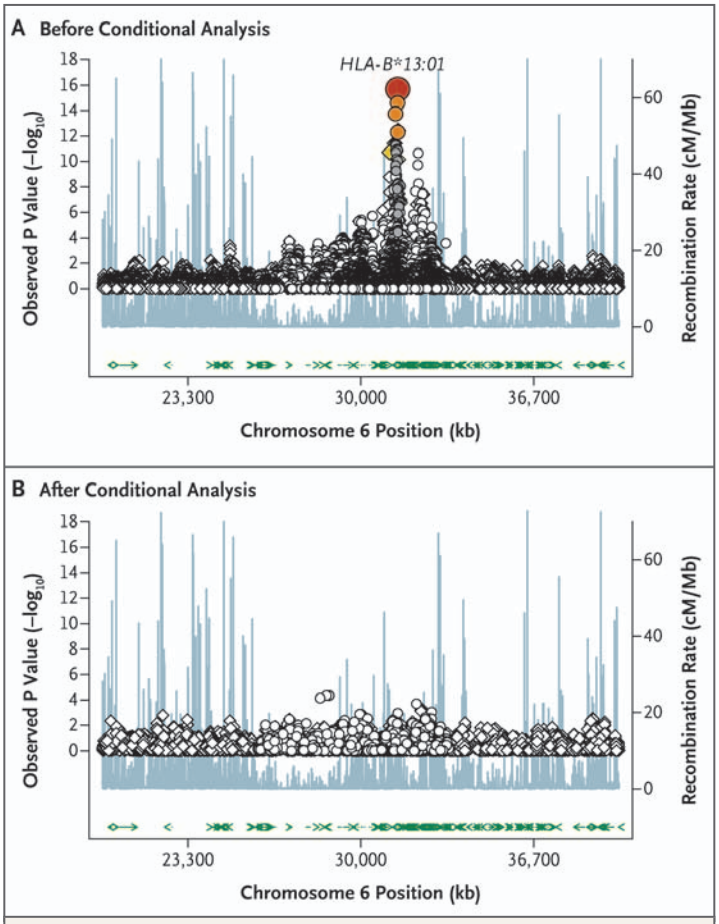

Figure 1. Regional Association Plots of the HLA Region.

Panel A shows *HLA-B*13:01* as the allele within the MHC region that has the strongest association with the dapsone hypersensitivity syndrome. Recombination rates are superimposed on light-blue peaks. Circles represent imputed single-nucleotide polymorphisms (SNPs), alleles, and amino acids, and diamonds represent genotyped SNPs. Colors denote the strength of the linkage disequilibrium of the SNPs, HLA alleles, and amino acids to *HLA-B*13:01*. Red denotes an r^2 value of 0.8 or more, orange 0.5 to less than 0.8, yellow 0.2 to less than 0.5, gray less than 0.2, and white 0. Panel B shows the regional association plot after conditional analysis was performed to control for the association at *HLA-B*13:01*.

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Table 2. Odds Ratios for *HLA-B*13:01* and *HLA-C*03:04* in the Discovery, Replication, and Combined Samples.*

Allele	Discovery Sample				Replication Sample				Combined Sample			
	Minor Allele Frequency		Odds Ratio (95% CI)	P Value	Minor Allele Frequency		Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value	P Value by Cochran's Q Test	Heterogeneity Index
	case patients (N=39)	*controls (N=833)*			*case patients (N=37)*	*controls (N=201)*						
*HLA-B*13:01*	0.47	0.07	21.67 (10.41–45.12)	2.04×10^{-16}	0.46	0.16	23.54 (8.71–63.62)	4.74×10^{-10}	20.53 (11.55–36.48)	6.84×10^{-25}	0.74	0
*HLA-C*03:04*	0.46	0.09	13.43 (6.91–26.11)	1.84×10^{-14}	0.42	0.16	5.90 (2.90–11.97)	9.15×10^{-7}	9.00 (5.87–15.50)	2.23×10^{-19}	0.14	53.5

* Odds ratios are per allele. Unless otherwise indicated, P values were calculated with the use of logistic-regression analysis. The odds ratios and P values for the combined samples were adjusted for study variable. Scores on the heterogeneity index range from 0 to 100, with higher scores indicating greater heterogeneity. CI denotes confidence interval.

(Fig. 1B). Taken together, these results indicate that *HLA-B*13:01* is the primary risk variant for the dapsone hypersensitivity syndrome within the MHC region.

REPLICATION ANALYSIS

None of the 24 non-MHC SNPs selected for the replication analysis showed a significant genomewide association with the dapsone hypersensitivity syndrome when the discovery and replication samples were analyzed together, although a consistent association was observed at 3 SNPs (rs991773, rs2280899, and rs13187034) with nominal significance ($P<0.05$) when the replication sample alone was analyzed (Table S2 in the Supplementary Appendix).

To directly test for an association between *HLA-B*13:01* and the dapsone hypersensitivity syndrome as well as to assess the accuracy of the HLA imputation, we determined the *HLA-B* and *HLA-C* alleles in the 39 case patients and 78 controls included in the discovery analysis and an additional 38 case patients and 206 controls, using Roche 454 GS FLX sequencing. Both sets of controls were randomly selected from the discovery and replication samples. Of the 361 samples, 354 were successfully sequenced for *HLA-B* (98.1%) and 359 were successfully sequenced for *HLA-C* (99.4%), with coverage of at least 10 reads per exon per sample.

Although the sample from one control could not be sequenced, the concordance between the imputed and sequencing-determined genotypes of the *HLA-B*13:01* allele in the 116 samples from the discovery analysis was 99%; there was only one discrepancy, in which a case patient was found to carry one copy of this allele by imputation but was not found to carry this allele on sequencing. For *HLA-C*03:04*, the concordance was 99%, with one discrepancy, in which a case patient was found to be a heterozygous carrier by imputation but a homozygous carrier by sequencing. Our sequencing analysis confirmed the high accuracy of the HLA imputation, particularly for *HLA-B* and *HLA-C* alleles (additional concordance data are shown in Table S3 in the Supplementary Appendix).

The replication analysis involving 37 case patients and 201 controls showed a significant genomewide association of *HLA-B*13:01* with the dapsone hypersensitivity syndrome (odds ratio, 23.54; $P=4.74\times10^{-10}$) and *HLA-C*03:04* (odds ra-

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tio, 5.90; $P=9.15\times10^{-7}$). We also observed that controlling for *HLA-B*13:01* fully eliminated the effect of *HLA-C*03:04* (adjusted P=0.46) but not vice versa (adjusted $P=4.74\times10^{-7}$). The combined analysis of the discovery and replication samples resulted in a very strong association of *HLA-B*13:01* with the dapsone hypersensitivity syndrome (odds ratio, 20.53; $P=6.84\times10^{-25}$), with no evidence of genetic heterogeneity between the discovery and replication samples (P=0.74 by Cochran's Q test; $I^2=0$) (Table 2). A severe deviation of *HLA-B*13:01* genotype frequency from Hardy–Weinberg equilibrium was observed in the samples from the case patients ($P=2.69\times10^{-7}$) (Table 3).

The findings in the combined sample of 76 case patients and 1034 controls were consistent with those in the discovery sample. The variants at amino acid positions 94, 95, and 145 (whose haplotype Ile94–Ile95–Leu145 defines the *HLA-B*13:01* allele) were significantly associated with the dapsone hypersensitivity syndrome, but these associations were much weaker than that at *HLA-B*13:01* ($P=5.38\times10^{-15}$, $P=7.11\times10^{-15}$, and $P=2.43\times10^{-19}$, respectively, by an omnibus test) (Table S4 in the Supplementary Appendix). Controlling for *HLA-B*13:01* eliminated the associations of the three amino acid variants (Tables S1 and S4 in the Supplementary Appendix) but not vice versa. The variant encoding Leu145 was also carried by the *HLA-B*13:02* haplotype, which was present only in our controls (with a frequency of 6%). Similarly, the variants encoding Ile94 and Ile95 were also carried by another *HLA-B* haplotype that did not show any association with the dapsone hypersensitivity syndrome (Table S5 in the Supplementary Appendix). Taken together, these data indicate that the *HLA-B*13:01* haplotype, rather than any component variant, is likely to be a susceptibility risk variant.

*HLA-B*13:01* AS A RISK PREDICTOR FOR THE DAPSONE HYPERSENSITIVITY SYNDROME

Analysis of the pooled discovery and replication samples showed that the *HLA-B*13:01* allele was present in 86% of the case patients (65 of 76) but in only 14% of the controls (148 of 1034) (Table 3). These findings suggest that the presence of *HLA-B*13:01* had a sensitivity of 85.5% and a specificity of 85.7% as a risk predictor for the dapsone hypersensitivity syndrome, with an area under the curve of 0.89 (Fig. S3 in the Supplementary Appendix). According to these results, the risk among persons carrying one copy of the *HLA-B*13:01* allele is 33.6 times as high as the risk among those carrying no copies (heterozygous odds ratio) and the risk among persons carrying two copies is 100.7 times as high (homozygous odds ratio). On the basis of an estimated prevalence of the dapsone hypersensitivity syndrome of 1.4%,[8] we calculated that *HLA-B*13:01* would have a positive predictive value of 7.8% and a negative predictive value of 99.8%, and 84 patients would need to be screened in order to prevent one case of the syndrome. Clinical testing for *HLA-B*13:01*, with persons who had positive results receiving treatment that excluded dapsone, could theoretically reduce the risk of the dapsone hypersensitivity syndrome by a factor of 7 (from 1.4% to 0.2%).

We investigated the prevalence of the *HLA-B*13:01* allele in the Chinese population by evaluating 1944 healthy Chinese persons from Shandong, Yunnan, and Guangdong provinces through HLA imputation. The frequency of this allele was 3.3%, 7.1%, and 8.6% in the three provinces, respectively (Table 3), findings that are consistent with the reported frequency of *HLA-B*13:01* in northern China (2 to 5%) and southern China (5 to 20%).[20-22] The frequency of *HLA-B*13:01* varies greatly across ethnic populations, with rates of 0% in European and African populations, 1.5% in Japanese persons, 1 to 12% in Indians, 2 to 4% in Southeast Asians, about 2 to 20% in Chinese persons, and 28% in Papuans and Australian aborigines[20,23] (Fig. S4 in the Supplementary Appendix).

DISCUSSION

In this study, we found an association of *HLA-B*13:01* with the dapsone hypersensitivity syndrome. *HLA-B* belongs to HLA class I heavy-chain paralogues that play a central role in the immune system by presenting peptides derived from the lumen of the endoplasmic reticulum. A study of HLA-associated drug reactions to abacavir has shown that small-molecule drugs can alter the peptide repertoire by specifically and noncovalently interacting with HLA class I molecules.[24] Amino acid residues 94, 95, and 145, which are affected by the variants defining the *HLA-B*13:01* allele and distinguish it from other *HLA-B*13* alleles, are located at the binding groove and binding pocket, with residues 94 and 95 in peptide-binding pocket F

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Table 3. Allele and Genotype Frequencies of *HLA-B*13:01* and P Values for Hardy–Weinberg Equilibrium in Case Patients, Controls, and Healthy Persons.

Study Group	Genotype Frequency			Allele Frequency	P Value for Hardy–Weinberg Equilibrium
	Noncarrier	Heterozygous	Homozygous		
	number/total number (percent)			%	
Case patients	11/76 (14)	60/76 (79)	5/76 (7)	46.1	2.69×10^{-7}
Controls	886/1034 (86)	144/1034 (14)	4/1034 (>0.5)	5.8	0.65
Healthy persons					
Shandong Province	488/523 (93)	35/523 (7)	0/523	3.3	0.06
Yunnan Province	406/470 (86)	61/470 (13)	3/470 (1)	7.1	0.72
Guangdong Province	794/951 (83)	151/951 (16)	6/951 (1)	8.6	0.84

and residue 145 on the α-helix of the peptide-binding groove (Fig. S5 in the Supplementary Appendix). Residue 95 has been shown to be critical for the binding of the C-terminal of the peptide to *HLA-B*. Polymorphisms at this site can markedly alter the specificity of the peptide motif.[25] Because the side chains of the peptide anchor residues provide the molecular basis for allele-specific recognition of antigenic peptides, the amino acid combination of these three unique sites of *HLA-B*13:01* may play a role in the immunopathogenesis of the dapsone hypersensitivity syndrome.

The deviation of *HLA-B*13:01* genotype frequency from Hardy–Weinberg equilibrium for the case patients (but not the controls) is consistent with *HLA-B*13:01* as a susceptibility variant for the association with the syndrome. The strong genetic effect of *HLA-B*13:01* was expected to cause an oversampling of *HLA-B*13:01* in our case patients. Furthermore, only the surviving patients with the dapsone hypersensitivity syndrome were recruited in this study as the case patients; their symptoms are likely to have been relatively mild as compared with those of patients with the dapsone hypersensitivity syndrome who died before sample collection. Nonrandom sampling and the absence of patients with fatal dapsone hypersensitivity syndrome in our study may have contributed to the deviation of *HLA-B*13:01* genotype frequency from Hardy–Weinberg equilibrium in the case patients.

A limitation of our study is that we did not have clinical confirmation that all our controls were free of the dapsone hypersensitivity syndrome; only 6% of them were known, on the basis of medical records, to be free of the dapsone hypersensitivity syndrome after 6 to 24 months of treatment. It is therefore possible that some of the controls actually had the dapsone hypersensitivity syndrome, and if so, this might have caused an underestimation of the risk effect of *HLA-B*13:01*, but any effect should be minimal, because the prevalence of the syndrome is low, and all patients with leprosy who served as controls had been cured of the disease with multidrug therapy and were therefore likely to be free of the dapsone hypersensitivity syndrome.

*HLA-B*13:01* typing for dapsone-related treatments is clinically relevant. By identifying carriers of the *HLA-B*13:01* allele and modifying the therapeutic regimen they receive — for example, by substituting clofazimine for dapsone in multidrug therapy for paucibacillary disease or by eliminating dapsone from multidrug therapy for multibacillary disease — the risk of the dapsone hypersensitivity syndrome could be reduced by a factor of 7 (from 1.4% to 0.2%).

However, the clinical benefit of *HLA-B*13:01* typing is going to vary across populations owing to differences in the use of dapsone as treatment and in the prevalence of the dapsone hypersensitivity syndrome and *HLA-B*13:01*. *HLA-B*13:01* is one of the most frequent members of *HLA-B*13*, but it is present primarily in Asian populations. Current information indicates that *HLA-B*13:01* is absent in European and African populations. Among the nations with a high incidence rate of leprosy, India has the highest recorded prevalence of the *HLA-*

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*B*13:01* allele, although prevalence varies greatly among regions (0 to 12%).[20] India also has the highest incidence of leprosy in the world (134,752 new cases in 2012).[26]

In conclusion, we found that *HLA-B*13:01* is a strong risk factor for the dapsone hypersensitivity syndrome in the Chinese population; this finding sheds light on the pathogenesis of the syndrome. More important, our findings may facilitate the development of *HLA-B*13:01* tests for use in clinical practice to identify persons at risk for this potentially life-threatening condition and may thus improve the safety of dapsone therapy.

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