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Toxicogenomics of nevirapine-associated cutaneous and hepatic adverse events among populations of African, Asian, and European descent

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Abstract

Objective—Nevirapine is widely prescribed for HIV-1 infection. We characterized relationships between nevirapine-associated cutaneous and hepatic adverse events and genetic variants among HIV-infected adults.

Design—We retrospectively identified cases and controls. Cases experienced symptomatic nevirapine-associated severe (grade III/IV) cutaneous and/or hepatic adverse events within 8 weeks of initiating nevirapine. Controls did not experience adverse events during more than 18 weeks of nevirapine therapy.

Methods—Cases and controls were matched 1 : 2 on baseline CD4 T-cell count, sex, and race. Individuals with 150 or less CD4 T cells/μl at baseline were excluded. We characterized 123 human leukocyte antigen (HLA) alleles and 2744 single-nucleotide polymorphisms in major histocompatibility complex (MHC) and drug metabolism and transport genes.

Results—We studied 276 evaluable cases (175 cutaneous adverse events, 101 hepatic adverse events) and 587 controls. Cutaneous adverse events were associated with *CYP2B6* 516G→T (OR 1.66, all), *HLA-Cw*04* (OR 2.51, all), and *HLA-B*35* (OR 3.47, Asians; 5.65, Thais). Risk for cutaneous adverse events was particularly high among Blacks with CYP2B6 516TT and *HLA-Cw*04* (OR 18.90) and Asians with *HLA-B*35* and *HLA-Cw*04* (OR 18.34). Hepatic adverse events were associated with *HLA-DRB*01* (OR 3.02, Whites), but not *CYP2B6* genotypes. Associations differed by population, at least in part reflecting allele frequencies.

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Conclusion—Among patients with at least 150 CD4 T cells/μl, polymorphisms in drug metabolism and immune response pathways were associated with greater likelihood of risk for nevirapine-related adverse events. Results suggest fundamentally different mechanisms of adverse events: cutaneous, most likely MHC class I-mediated, influenced by nevirapine CYP2B6 metabolism; hepatic, most likely MHC class II-mediated and unaffected by such metabolism. These risk variants are insensitive for routine clinical screening.

Keywords

CYP2B6; HIV; human leukocyte antigen; nevirapine; pharmacogenomics; rash; toxicogenomics

Introduction

Nevirapine is widely prescribed for type 1 HIV (HIV-1) infection. Although generally well tolerated and effective, some individuals who receive multiple doses of nevirapine experience severe cutaneous and/or hepatic adverse events during the initial weeks of therapy, especially when initiated at higher CD4 T-cell counts [1]. It is therefore recommended that nevirapine therapy not be initiated in antiretroviral-naive women and men with greater than 250 and 400 CD4 T cells/μl, respectively [2].

Human genetic variants may affect risk for nevirapine-associated adverse events, but results of prior genetic association studies have been inconsistent [3]. A study from Australia implicated *HLA-DRB1*0101* as a risk for hepatic adverse events [4], whereas studies from Sardinia and Japan implicated *HLA-Cw*08* [5,6]. Studies from South Africa and Mozambique implicated a polymorphism in *ABCB1* (which encodes the multidrug efflux pump P-glycoprotein) with hepatic adverse events [7,8] but not *CYP2B6* 516G→T [7], which is known to increase nevirapine plasma exposure [9–15]. Studies from Thailand implicated *HLA-Cw*0401* and *HLA-B*3505* as being associated with nevirapine-associated cutaneous adverse events [16,17]. Such inconsistencies may reflect different adverse event phenotypes, patient ancestries, and/or genotyping strategies. False discovery is also possible even with seemingly well-designed studies [18].

To identify genetic variants associated with severe cutaneous rash and/or hepatic adverse events during the initial 8 weeks (the period of highest risk) of nevirapine-containing regimens we recruited cases and controls (matched on sex, race, and CD4 T-cell counts), and genotyped both human leukocyte antigen (HLA) and non-HLA genes among cohorts of African, Asian, and European descent (hereafter referred to as Black, Asian, and White, respectively).

Materials and methods

Study population

This was a retrospective, case-controlled study with prospective DNA collection. Cases and controls were at least 18 years of age, HIV-1-infected, and had previously initiated nevirapine-containing therapy. Cases had experienced one or more of the following cutaneous or hepatic adverse events within the first 8 weeks of initiating nevirapine: severe cutaneous toxicity [grade III or IV categorized by National Institute of Allergy and Infectious Disease (NIAID) Division of AIDS criteria] [19]; symptomatic grade ≥3 hepatic transaminase elevation [alanine transaminase (ALT) or aspartate aminotransferase (AST) >5× upper limit of normal (ULN)]; or acute hepatic failure.

Potential cases and controls were excluded for: 150 or less CD4 T cells/μl at last available date within 6 months before initiating nevirapine; acute viral hepatitis; use of

immunomodulatory medications within the first 8 weeks of nevirapine therapy; no hepatic transaminase data within 6 months prior to initiating nevirapine; or previous participation in the 2NN long-term follow-up study. Potential cases were also excluded for: hepatotoxicity or rash that the investigators judged unrelated to nevirapine; initiation of abacavir or trimethoprim/sulfamethoxazole within 2 weeks prior to or within 8 weeks after initiating nevirapine; and ALT or AST values greater than 5 × ULN (grade >3) prior to initiating nevirapine. Potential controls were excluded for: development of grade ≥ 1 rash within 18 weeks of initiating nevirapine or any cutaneous condition potentially attributable to nevirapine; ALT or AST values greater than 2.5× ULN within 18 weeks of starting nevirapine; any hepatobiliary adverse event possibly due to nevirapine; or any systemic reaction (e.g. flu-like symptoms, arthralgia, myalgia, or conjunctivitis) attributable to nevirapine during the first 18 weeks of treatment.

Cases and controls were matched 1:2, respectively, on CD4 T-cell count within 50 cells/μl, sex, and self-reported race. Site personnel were asked to enrol three potential matched controls per case. Final matching was done centrally. Controls that did not match were excluded. The study was approved by the Institutional Review Board at each site, and all participants provided written informed consent. The study was registered at ClinicalTrials.gov (NCT00310843).

Study design

The study involved a screening visit and a subsequent entry and blood sampling visit. A total of 1536 patients were enrolled, of whom 647 failed screening based on eligibility criteria or case-control matching requirements.

Genotyping

Genomic DNA was isolated from peripheral blood mononuclear cells using Invitrogen iPrep (Invitrogen Corporation, Carlsbad, California, USA). Single-nucleotide polymorphisms (SNPs) were assayed in drug absorption, disposition, metabolism, and elimination (ADME) and major histocompatibility complex (MHC) genes (including 10-kb upstream and downstream regions), based on dbSNP version 128 and Genome NCBI build version 36 (SNP list available upon request). Some MHC-region SNPs were selected from Illumina MHC Mapping Panel and MHC Exon-Centric Panel (Illumina Inc., San Diego, California, USA). Assay was finalized based on primer designability and validation score. Genotyping was performed using Illumina BeadArray technology (Illumina Inc.): success rate 88.0–93.4% for SNPs, 99.4–100% for patient samples, reproducibility 100% between duplicates. We excluded participants with disagreement between sex indicated by genotype and clinical records.

HLA-A, *HLA-B*, *HLA-C*, and *HLA-DPB*, *HLA-DQB*, and *HLA-DRB* typing of all samples was performed with LIFECODES HLA DNA typing kits using Luminex xMAP technology and a reverse SSO protocol (Tepnel Lifecodes Corporation, Stamford, Connecticut, USA). DNA amplification and hybridization conditions followed manufacturer's protocol.

Statistical analysis

HLA alleles and SNPs were analyzed for association with adverse events in the total population and in each race group separately. Validity of self-reported race was supported by principal component analysis of SNP data with two principal components defining three clusters. Concordance with self-reported race was greater than 96%.

Fisher's exact test was used to analyze association of HLA alleles with adverse events in the three race groups and *P* values were corrected for multiple testing by dividing uncorrected *P*

values by number of alleles with greater than 1% frequency. All alleles with homogeneous odds ratios (ORs) (Breslow-Day test *P* value >0.01) among the three race groups were tested for association with adverse events in the total population by Cochran-Mantel-Haenszel test.

After filtering SNPs with call rates below 80%, minor allele frequencies less than 1%, or for controls not in Hardy–Weinberg equilibrium ($P < 0.001$), retained SNPs were tested for association with adverse events by allelic test, genotypic test, Cochran-Armitage trend test, and tests for dominant-effect and recessive-effect models, as implemented in PLINK (version 1.06) [20,21]. All tests were adjusted for multiple testing. Linkage disequilibrium was based on r^2 values.

Clinical variables were tested for association with adverse events by conditional logistic regression. HLA alleles and *CYP2B6* SNPs associated with cutaneous adverse events, clinical variables, and their two-way product terms were used as explanatory variables in multiple logistic regression models. For *CYP2B6* SNPs, an additive effect was assumed, with 0, 1, or 2 encoding the number of risk alleles. Forward and backward elimination were used to select variables associated with cutaneous adverse events.

Results

Patient characteristics

The study enrolled 889 participants from 2006 to 2008 at 76 sites in 11 countries (Argentina, Australia, Canada, France, Germany, Netherlands, Spain, Taiwan, Thailand, UK, and US), including 276 evaluable cases (175 with cutaneous adverse events, 101 with hepatic adverse events) and 587 evaluable controls (Fig. 1). Self-reported race (Asian, African, or European descent and herein referred to as Asian, Black, or White) agreed with the SNP data. Among Asians, 74.3% were Thai and among Whites, 31% self-identified as Hispanic/Latino. Demographic variables and baseline characteristics are shown in Table 1. Baseline CD4 T-cell counts were greater than 250 and 400 cells/ml in 69.7 and 48.7% of women and men, respectively; 71.8% of all participants had prior antiretroviral exposure. No demographic or clinical variable was significantly associated with adverse events.

Associations with ADME gene and major histocompatibility complex polymorphisms

A total of 2744 SNPs across ADME and MHC genes (see supplemental material, http://links.lww.com/QAD/A139) were assessed for associations with adverse events in each race group and among all participants. In analyses controlled for population stratification among all participants, two linked SNPs in *CYP2B6* [rs2054675 and rs3786547 (r^2 = 0.982)] were significantly associated with cutaneous adverse events after correcting for multiple comparisons (Fig. 2a). Both were in linkage disequilibrium with rs3745274 (*CYP2B6* 516G→T; $r^2 > 0.90$) (Fig. 2b), which is known to predict delayed plasma nevirapine clearance [9–15].

For *CYP2B6* 516G→T, increasing T-allele count (0, 1, 2) was significantly associated with progressively increased risk of cutaneous adverse events in Blacks and Whites, with a weak trend in Asians (P=0.0025, P=0.021, and P=0.12, respectively, Cochran-Armitage trend test). Among Asians, the association was stronger for rs2054675 and rs3786547 (both P = 0.041). The association with 516G→T was particularly strong in Blacks, in whom the OR for 516TT homozygosity relative to 516GG homozygosity was 5.92 [95% confidence interval (CI) 1.53–26.8]. No SNP was significantly associated with hepatic adverse events after correcting for multiple comparisons (Fig. 2c).

There were possible associations between cutaneous adverse events and MHC polymorphisms *(HLA-B, HLA-C, CCHCR1, TCF19)*, although none withstood multiple

comparisons (Fig. 2a). We found no statistically significant association between *ABCB1* 3435C→T and nevirapine-associated cutaneous or hepatic adverse events, although the OR for hepatic adverse events among Blacks was 0.50 (95% CI 0.14–1.76; *P*= 0.27).

Associations with HLA alleles

A total of 863 patients were HLA typed. *HLA-Cw*04* was significantly associated with cutaneous adverse events among all study participants, most notably among Blacks and Asians (Fig. 3a). *HLA-B*35* was strongly associated with cutaneous adverse events in Asian and Thai participants, but not in non-Thai Asians (mainly Taiwanese); there was a weak association with *HLA-B*35* among Whites that did not withstand multiple testing correction. In analyses that excluded individuals with concomitant cutaneous and hepatic adverse events, OR for cutaneous adverse events increased from 5.65 to 7.31 for *HLA-B*35* in Thai participants and from 2.51 to 2.98 for *HLA-Cw*04* among all participants (data not shown). Among Asians, but not Blacks or Whites, the OR for cutaneous adverse events was markedly increased among those carrying both *HLA-Cw*04* and *HLA-B*35* (OR 18.34, 95% CI 5.10–65.99). Among Whites, a weak association between cutaneous adverse events and the relatively infrequent *HLA-Cw*15* was no longer apparent when considering patients with only isolated cutaneous adverse events.

*HLA-DRB1*01* was significantly associated with hepatic adverse events in Whites (Fig. 3b). This HLA allele was infrequent among Blacks and rare among Asians. In analyses that excluded individuals with coincident cutaneous and hepatic adverse events, OR for hepatic adverse events among Whites increased from 3.02 to 3.63 for *HLA-DRB1*01.* Similarly, *HLA-DQB1*05* was significantly associated with hepatic adverse events among Whites only, despite its high frequency among Asians and Blacks but not when considering isolated hepatic adverse events (data not shown). We found no association between *HLA-Cw*08* (present in 7% of participants) and cutaneous or hepatic adverse events.

Associations with *CYP2B6* and HLA combinations

Major associations with genetic polymorphism in *CYB2B6* and *HLA* are summarized in Fig. 4a. Relationships between *HLA-Cw*04* and *CYP2B6* 516G→T and effects of clinical variables, including age, sex, CD4 T-cell count, race, plasma HIV-1 RNA, and antiretroviral history, were examined. By logistic regression analysis that adjusted for *HLA-Cw*04* and CYP2B6 516G→T, the only clinical variable associated with cutaneous adverse events was prior antiretroviral status (OR 0.57 for antiretroviral experienced, 95% CI 0.37–0.87; *P*= 0.0097; data not shown), particularly history of abacavir use in Whites (*P*= 0.010; data not shown), which was independent of *HLA-Cw*04* and *CYP2B6* 516G→T. History of use for stavudine were not associated with cutaneous or hepatic adverse events. Patients carrying both *CYP2B6* 516TT and *HLA-Cw*04* were at highest risk in the total population (OR 6.31, 95% CI 2.53–15.73), and in Blacks and Asians analyzed separately (Fig. 4b).

Among Asians, the three-way combination of *HLA-Cw*04, HLA-B*35,* and *CYP2B6* 516G→T was too infrequent to evaluate. Our matching of cases and controls on CD4 T-cell count prevented direct assessment of its relationship with adverse events. In post hoc analyses stratified by CD4 T-cell count, the latter did not contribute to adverse event risk in the presence of risk HLA alleles or SNPs.

Concomitant hepatic and cutaneous adverse events

Among the 276 evaluable cases, 74 were known to have had concomitant hepatic and cutaneous adverse events. We repeated the above analyses, limited to this subgroup of cases. After correcting for multiple comparisons, none of the above HLA alleles or SNP

associations was significantly associated in this subgroup of cases, and no additional significant associations were identified (data not shown).

Discussion

The present study characterizes associations between genetic variants and symptomatic hepatic and cutaneous reactions among HIV-1 patients who had initiated nevirapine with relatively high CD4 T-cell counts (>150 cells/μl). We convincingly demonstrated that polymorphisms in *CYP2B6* and multiple HLA loci were associated with a higher likelihood of risk for nevirapine-related adverse events. We also showed that genetic predictors of cutaneous versus hepatic adverse events differ, and that relationships between genetic variants and adverse events vary by race.

This is the first study that *CYP2B6* variants affect risk for nevirapine-associated adverse events. Major metabolic pathways for nevirapine involve hydroxylation by CYP2B6 and CYP3A4 [22,23]. In addition, nevirapine induces CYP2B6 and CYP3A4 expression over several weeks, increasing its own clearance [23]. Previous studies associated *CYP2B6* 516G→T with increased plasma nevirapine concentrations [9–15], but separate analyses found no relationship between plasma nevirapine concentrations and adverse events [24]. It is possible that previous analyses missed a true association with plasma nevirapine concentrations. Alternatively, a metabolite, rather than parent compound, may mediate toxicity. With loss of *CYP2B6* function, more nevirapine may be shunted through pathways that generate minor metabolites. Consistent with this hypothesis, a rodent model implicated a quinine methide of nevirapine formed in the skin following sulfation of the 12-hydroxy metabolite [25]. Among 129 SNPs in 11 sulfotransferase and sulfatase genes assayed herein, none were significantly associated with adverse events. We found no association between *CYP2B6* variants and hepatic adverse events, consistent with limited previous data [7,8] and with a rat model [26].

Cutaneous adverse events were associated with MHC class I alleles *(HLA-B*35* and *HLA-Cw*04)* and hepatic adverse events with MHC class II alleles *(HLA-DRB1*01* and possibly *HLA-DQB1*05*). These findings suggest distinct mechanisms with CD8 T cells (i.e. MHC class I) possibly more important for cutaneous adverse events, and CD4 T cells (i.e. MHC class II) more important for hepatic adverse events. The increased ORs observed when concomitant hepatitis and rash cases were excluded support this concept. Without more direct evidence, however, this hypothesis is tentative, as HLA associations do not prove causation. We suspect that associations with other polymorphisms in the MHC locus reflect linkage with risk HLA alleles.

Our results support the association between *HLA-B*3505*, *HLA-Cw*0401*, and nevirapine-associated cutaneous adverse events previously reported among Thai populations [16,17]. In analyses comprising 147 cases and 185 controls, Chantarangsu *et al.* [17] identified an association between *HLA-B*3505* and nevirapine-associated cutaneous adverse events (OR 18.96); also predictive were *HLA-Cw*0401* (OR 5.36) and the *HLA-Cw*0401-HLA-B*3501* haplotype (OR 12.12). Similarly, Likanonsakul *et al.* [16] reported an association between *HLA-Cw*04* and cutaneous adverse events among 39 cases and 60 controls. Our data confirmed strong associations between *HLA-B*35*, *HLA-Cw*04*, and cutaneous adverse events among Asians, particularly in Thai participants, and extended the *HLA-Cw*04* association to Black and White populations. The study results also showed that among *HLA-Cw*04* carriers, cutaneous adverse events were increased with concomitant *CYP2B6* 516G→T. In contrast, this study did not find significant associations with *HLA-B*35* in Blacks and Whites, perhaps reflecting its infrequency in these populations [27].

The results of our study also support the association between *HLA-DRB1*0101* and nevirapine-associated adverse events reported in the Western Australian HIV Cohort [4]. That study included 26 cases (25 Whites) who experienced ALT elevation, fever, and/or rash with nevirapine and 209 controls. *HLA-DRB1*0101* was significantly associated with hepatic/systemic reactions (OR 4.8), but not with isolated cutaneous adverse events. The association was only apparent in patients with at least 25% CD4 T cells [4]. The current study confirmed the association between *HLA-DRB1*01* and hepatic adverse events among Whites. We did not find any significant association with *HLA-DRB1*01* in Blacks and Asians, perhaps because *HLA-DRB1*01* is infrequent in these populations [27]. Results also indicated an association between *HLA-DQB*05* and hepatic adverse events in Whites, likely reflecting linkage between *HLA-DRB1*01* and *HLA-DQB1*05* [27]. However, among individuals with isolated hepatic adverse events the association with *HLA-DQB*05* was no longer significant, whereas the *HLA-DRB1*01* association increased.

This analysis did not replicate findings from studies in Sardinia and Japan that suggested an association between *HLA-Cw*08* and nevirapine-associated hypersensitivity [5,6]. Two previous studies involving individuals of African descent suggested that *ABCB1* 3435C→T was associated with decreased nevirapine-associated hepatic adverse events [5,6]. Whereas we found no statistically significant association between *ABCB1* 3435C→T and nevirapine-associated adverse events, the ORs for *ABCB1* 3435C→T and hepatic adverse events among Blacks was consistent with previous studies. There was no such association in Asians or Whites despite increased T-allele frequencies.

Our study had limitations. Matching on CD4 T-cell count, sex, and race allowed more efficient discovery of genetic associations, but prevented assessment of these variables independently. Excluding individuals with mild or equivocal adverse events prevented us from assessing whether the same genetic variants predict less severe events. The retrospective design excluded individuals who died from any cause and limited the types of data we could reliably collect. The associations identified cannot be generalized to individuals with less than 150 CD4 T cells/μl, an exclusion criterion in our study. Although we performed extensive genotyping focused on ADME genes and MHC region, important HLA and non-HLA polymorphisms may have been missed. High-resolution HLA typing would likely increase ORs and specificities for at least some associations identified, but would likely not increase sensitivity.

Clinically useful markers for serious adverse events must be highly sensitive. Unfortunately, the genetic variants identified herein lacked sensitivity, and therefore have little or no clinical utility for patients initiating nevirapine-containing regimens. Among Asians with cutaneous adverse events, 80% were *HLA-B* 35*-negative; among all participants with cutaneous adverse events, 62% were *HLA-Cw* 04-negative;* and among Whites with hepatic adverse events, 56% were *HLA-DRB1*01-negative.* Among all participants with any adverse event, 48% had neither an HLA risk allele (*HLA-Cw*04, -B*35, -DRB1*01*) nor homozygosity for *CYP2B6* 516TT This suggests additional, not yet identified risk factors. It is almost certain that some adverse events in the present study were unrelated to nevirapine, further limiting our ability to assess how effectively genetic testing would prevent true nevirapine reactions.

Nevirapine is generally well tolerated when initiated in patients who are treatment-naïve and have lower CD4 T-cell counts (<250 cells/μl in women, <400 cells/μl in men) [2]. These cut-offs may reduce nevirapine-related symptomatic hepatotoxicity to approximately 1% [28]. We show that both ADME and HLA variants affect risk for nevirapine-associated adverse events. These genetic variants, however, identified only a minority of adverse event

cases. Continued search for additional genetic predictors is warranted, as are studies of underlying pathogenic mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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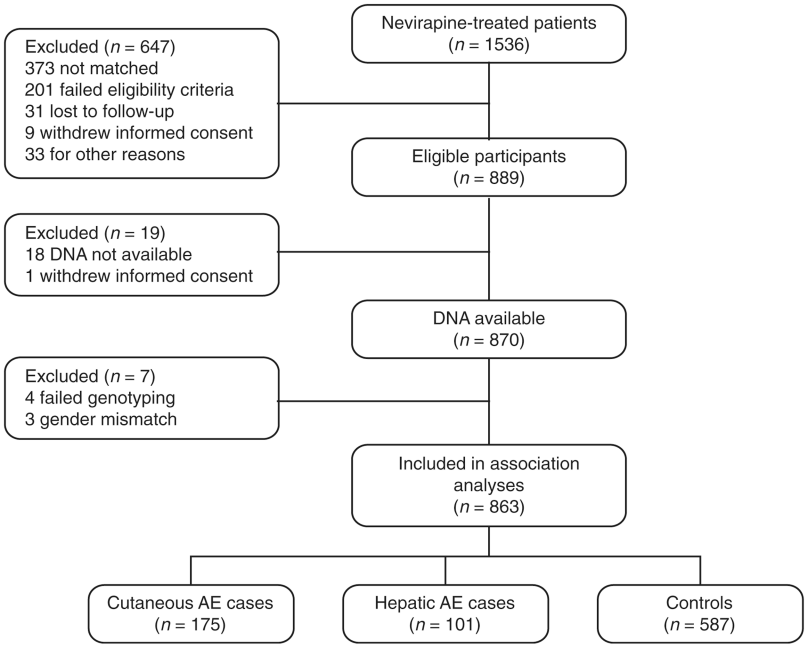
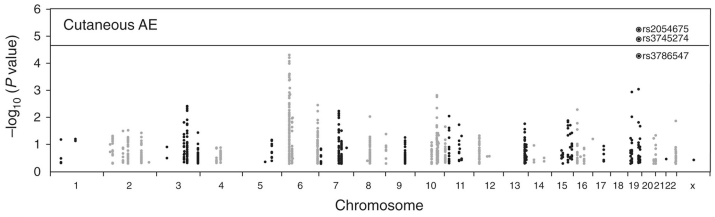


Fig. 1.
Disposition of study volunteers. AE, adverse events.

(a)



(b)

SNP[a]	Alleles[b]	Population	Minor Allele Frequency Case	Control	OR (95% CI)[c]	*P* value[c,d]
rs2054675	C/T	Asian	0.345	0.253	1.55 (1.04–2.33)	0.0205
(Flanking 5 UTR)		Black	0.648	0.427	2.48 (1.30–4.72)	0.0034
		White	0.325	0.218	1.72 (1.16–2.55)	0.0039
		Total			1.76 (1.36–2.27)	8.2×10^{-6} (0.019)[e]
rs3786547	C/T	Asian	0.345	0.253	1.55 (1.04–2.33)	0.0205
(Intron)		Black	0.667	0.429	2.67 (1.39–5.11)	0.0014
		White	0.312	0.217	1.63 (1.10–2.42)	0.009
		Total			1.74 (1.34–2.25)	1.2×10^{-5} (0.029)
rs3745274	T/G	Asian	0.336	0.264	1.41 (0.93–2.11)	0.055
(Non-synonymous		Black	0.648	0.401	2.75 (1.44–5.24)	0.0012
coding)		White	0.312	0.221	1.59 (1.07–2.37)	0.0125
		Total			1.66 (1.29–2.15)	5.5×10^{-5} (0.13)

[a] Chromosome location shown in parenthesis.
[b] Minor/major allele based on allele frequency in the total population.
[c] Odds ratios (OR), 95% confidence interval (CI), and one-tailed *P* values calculated by Fisher's exact test for race populations and by Cochran-Mantel-Haenszel test for total population.
[d] *P* value from Breslow-Day test for OR heterogeneity among three race populations is 0.67 for *rs2054675*, 0.35 for *3786547*, and 0.22 for *rs3745274*.
[e] Corrected *P* value shown in parenthesis and obtained by dividing the one-tailed CMH *P* value by 2336, the number of SNPs used in association analysis for total population.

(c)

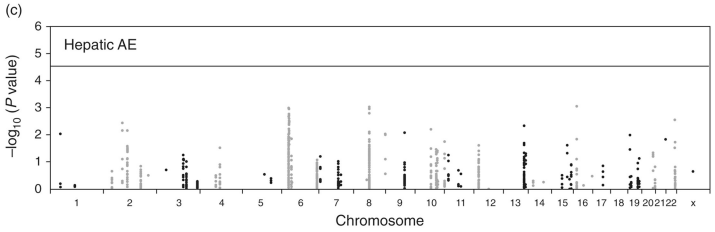


Fig. 2.

Associations between single-nucleotide polymorphisms and adverse events. Panel (a) is a Manhattan plot of the results for cutaneous adverse events (AEs) compared with controls. Panel (b) shows *CYP2B6* SNPs associated with cutaneous AEs. Panel (c) is a Manhattan plot of the results for hepatic AEs compared with controls. In panels (a) and (b), the $-\log_{10}$ *P* values were plotted against chromosome positions. Lines indicate a Bonferroni corrected *P* value of 0.05. Panel (a) represents 2336 SNPs. Panel (c) represents 2058 SNPs. The three SNPs labeled are in *CYP2B6.*

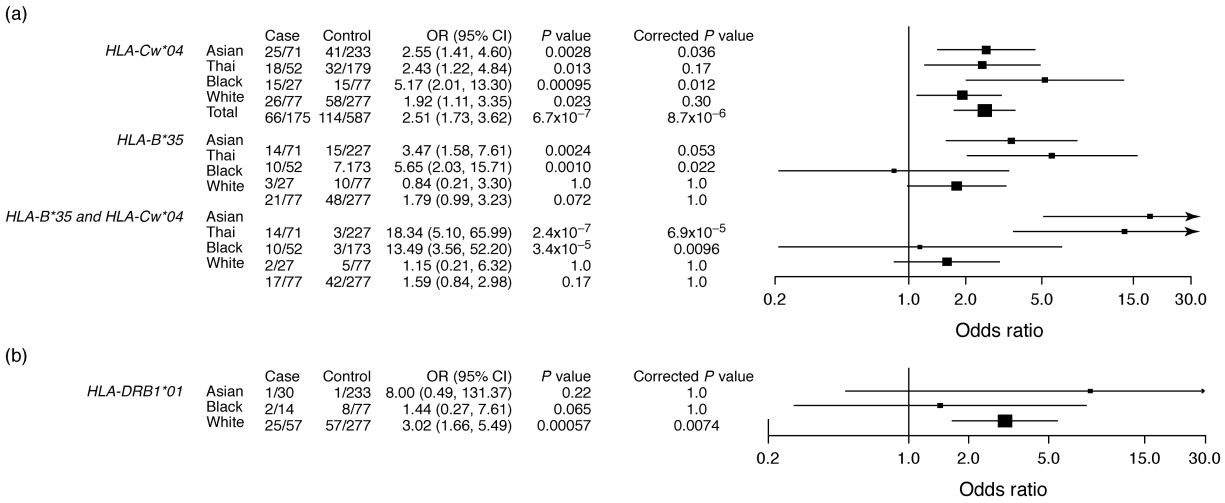


Fig. 3.

Associations between HLA alleles and nevirapine-related adverse events. Panel (a) shows cutaneous adverse events (AEs). Panel (b) shows hepatic AEs. Odds ratios (OR) and two-tailed *P* value were calculated by Fisher's exact test in race groups for all HLA alleles, and by Cochran-Mantel-Haenszel (CMH)test in the total population for *HLA-Cw*04.* All Thai participants were also included in the Asian group and were excluded from the CMH test. *P* values were corrected by Bonferroni procedure and corrected P value = Pvalue/*n*, where *n* is 22 for *HLA-B*35,* 13 for *HLA-Cw*04,* 13 for *HLA-DRB1*01,* and 286 for *HLA-B35-Cw*04.* Cases and controls are presented as numbers of participants (*n*) with the indicated genotypes divided by the numbers of cases or controls. Height of a square is proportional to the sample size. Horizontal lines represent 95% confidence intervals (CIs).

(a)

Adverse event	Genotype markers	Patient race
Hepatic	*HLA-DRB1*01*	White
Rash	*HLA-Cw*04*	White, Black, Asian
	*HLA-B*35*	Asian
	CYP2B6 polymorphisms	White, Black, Asian
Rash	*HLA-B*35* and *HLA-Cw*04*	Asian (Thai)
	CYP2B6 G516T and *HLA-Cw*04*	White, Black, Asian

(b)

		Case	Control	OR (95% CI)	*P* value
Total population	*CYP2B6 516TT* and *HLA–Cw*04*$^+$	14/60	10/261	6.31 (2.53, 15.73)	6.2×10^{-5}
	CYP2B6 516GT and *HLA–Cw*04*$^+$	24/70	38/289	3.37 (1.83, 6.23)	6.1×10^{-5}
	CYP2B6 516GG and *HLA–Cw*04*$^+$	28/74	64/315	2.40 (1.40, 4.11)	0.0012
	CYP2B6 516TT and *HLA–Cw*04*$^-$	16/62	34/285	2.42 (1.22, 4.80)	0.0095
	CYP2B6 516GT and *HLA–Cw*04*$^-$	46/92	173/424	1.48 (0.94, 2.32)	0.085
Asian	*CYP2B6 516TT* and *HLA–Cw*04*$^+$	4/25	4/105	4.81 (1.11, 20.78)	0.044
	CYP2B6 516GT and *HLA–Cw*04*$^+$	9/30	11/112	3.94 (1.45, 10.68)	0.014
	CYP2B6 516GG and *HLA–Cw*04*$^+$	12/33	25/126	2.31 (1.00, 5.21)	0.0063
	CYP2B6 516TT and *HLA–Cw*04*$^-$	6/27	16/117	1.80 (0.63, 5.15)	0.37
	CYP2B6 516GT and *HLA–Cw*04*$^-$	18/39	68/169	1.27 (0.63, 2.57)	0.59
Black	*CYP2B6 516TT* and *HLA–Cw*04*$^+$	9/14	2/23	18.90 (3.07, 116.21)	0.00062
	CYP2B6 516GT and *HLA–Cw*04*$^+$	6/11	8/29	3.15 (0.75, 13.29)	0.15
	CYP2B6 516GG and *HLA–Cw*04*$^+$	0/5	5/26	0.61 (0.06, 6.10)	0.56
	CYP2B6 516TT and *HLA–Cw*04*$^-$	4/9	9/30	1.87 (0.40, 8.61)	0.45
	CYP2B6 516GT and *HLA–Cw*04*$^-$	3/8	31/52	0.41 (0.09, 1.89)	0.28
White	*CYP2B6 516TT* and *HLA–Cw*04*$^+$	1/21	4/133	1.61 (0.17, 15.17)	0.52
	CYP2B6 516GT and *HLA–Cw*04*$^+$	9/29	19/148	3.06 (1.21, 7.69)	0.023
	CYP2B6 516GG and *HLA–Cw*04*$^+$	16/36	34/163	3.04 (1.42, 6.48)	0.005
	CYP2B6 516TT and *HLA–Cw*04*$^-$	6/26	9/138	4.30 (1.38, 4.80)	0.016
	CYP2B6 516GT and *HLA–Cw*04*$^-$	25/45	74/203	2.18 (1.13, 4.19)	0.028

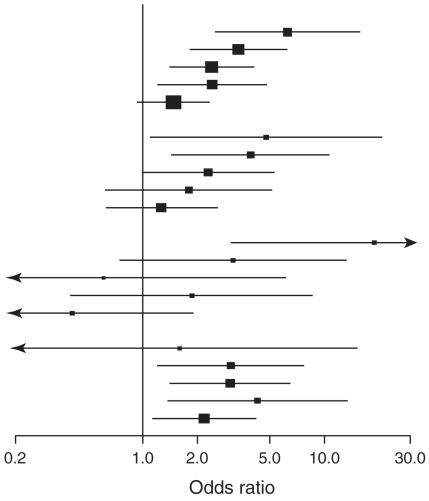


Fig. 4.

Association between polymorphisms and related adverse events. Panel (a) shows major association between genetic polymorphisms and nevirapine-related adverse events (AEs). CYP2B6 polymorphisms include rs2054675, rs3786547, and rs3745274. Panel (b) shows associations between *CYP2B6* 516G→T, *HLA-Cw*04*, and cutaneous AEs. The lowest risk genotype (*CYP2B6* 516GG and lacking *HLA-Cw*04*) was the reference for calculating odds ratios (OR) and two-tailed *P* values by Fisher's exact test for race groups and by Cochran-Mantel-Haenszel test for total population. A continuity correction was made to calculate OR by adding one to all cells of a contingency table if a cell harbours zero. Cases and controls are presented as numbers of participants with the indicated genotypes divided by the numbers of cases or controls. Height of a square is proportional to sample size. Horizontal lines represent 95% confidence intervals (CIs).

Table 1

Baseline characteristics of study participants.

	Black			Asian			White			Total		
	Hepatic (*n*=14)	**Rash (*n*=27)**	**Control (*n*=77)**	**Hepatic (*n*=30)**	**Rash (*n*=71)**	**Control (*n*=233)**	**Hepatic (*n*=57)**	**Rash (*n*=77)**	**Control (*n*=277)**	**Hepatic (*n*=101)**	**Rash (*n*=175)**	**Control (*n*=587)**
Age, years (SD)	40.6 (9.1)	37.1 (8.4)	38.4 (7.3)	38 (9.2)	38.3 (8.6)	39.5 (9.2)	47.6 (11.5)	45 (9.4)	46.9 (10)	43.8 (11.3)	41.1 (9.6)	42.8 (10.0)
Women [*n*(%)]	12 (85.7)	22 (81.5)	48 (62.3)	19 (63.3)	34 (47.9)	113 (48.5)	12 (21.1)	22 (28.6)	64 (23.1)	43 (42.6)	78 (44.6)	225 (38.3)
CD4 T cellsper μ1 [*n* (SD)]	401 (276)	322 (120)	366 (175)	385 (265)	415 (232)	412 (247)	549 (287)	437 (186)	471 (227)	480 (287)	410 (201)	434 (232)
Women (>250cells/μl) [*n* (%)]	6 (50.0)	16 (72.7)	36 (75.0)	9 (47.4)	24 (70.6)	74 (65.5)	8 (66.7)	19 (86.4)	49 (76.6)	23 (53.5)	59 (75.6)	159 (70.7)
Men (>400 cells/μl) [*n* (%)]	1 (50.0)	1 (20.0)	8 (27.6)	6 (54.5)	16 (43.2)	50 (41.7)	29 (64.4)	26 (47.3)	115 (54.0)	36 (62.1)	43 (44.3)	173 (47.8)
HIV, $\log_{10}$ copies/ml (SD)	3.8 (1.4)	3.0 (1.4)	3.2 (1.5)	2.9 (1.6)	2.8 (1.4)	3.1 (1.6)	3.2 (1.5)	3.5 (1.2)	2.9 (1.5)	3.2 (1.4)	3.2 (1.4)	3.0 (1.5)
Body weight [kg (SD)]	72 (22)	72 (16)	76 (19)	55 (9)	57(11)	57(10)	73 (13)	66 (12)	73 (14)	67 (16)	63 (13)	67(15)
HCV-positive [*n* (%)]	0 (0.0)	2 (7.4)	2 (2.6)	1 (3.3)	0 (0.0)	3(1.3)	1 (1.8)	9 (11.7)	19 (6.9)	2 (2.0)	11 (6.3)	24 (4.1)
HBV-positive [*n* (%)]	1 (7.1)	2 (7.4))	3 (3.9)	0 (0.0)	1 (1.4)	4(1.7)	4 (7.0)	8 (10.4)	21 (7.6)	5 (5.0)	11 (6.3)	28 (4.8)
Treatment-native [n(%)]	8 (57.1)	7 (25.9)	24 (31.2)	16 (53.3)	13 (18.3)	98 (42.1)	15 (26.3)	14 (18.2)	48 (17.3)	39 (38.6)	34 (19.4)	170 (29.0)
ALT, fold ULN [average(SD)]	0.7 (0.4)	0.5 (0.3)	0.6 (0.4)	0.6 (0.4)	0.7 (0.7)	0.7 (0.7)	0.7 (0.5)	0.8 (0.8)	0.7 (0.5)	0.7 (0.5)	0.8 (0.7)	0.7 (0.6)
AST, fold ULN [average(SD)]	0.7 (0.2)	0.7 (0.6)	0.8 (0.3)	0.7 (0.4)	0.8 (0.8)	0.8 (0.3)	0.7 (0.3)	0.8 (0.6)	0.8 (0.4)	0.7 (0.3)	0.8 (0.6)	0.8 (0.6)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B; HCV, hepatitisC; ULN, upper limit of normal; SD, standard error.