Supplemental Material

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *HLA-B* Genotypeand Carbamazepine Dosing

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Table of Contents

CPIC Updates

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are published in their entirety on the PharmGKB website (www.pharmgkb.org). These guidelines will be updated periodically based on new literature and published online.

Focused Literature Review

A search was conducted on the PubMed database (1966 to December 2012) and the Ovid MEDLINE (1950 to December 2012) database for keywords ([HLA or HLA-B or *HLA-B*15:02*] AND [carbamazepine]). A more general search was also conducted using the search terms ([carbamazepine hypersensitivity] OR [carbamazepine Stevens-Johnson]).

A table of frequencies of the *HLA-B*15:02* allele in different ethnic populations around the world was assembled from several sources. Frequencies were included from the Allele Frequencies in Worldwide Populations website (http://www.allelefrequencies.net/) which lists frequency data for *HLA-B*15:02* from 100 different samples and populations. Where possible, the original paper from which the allele frequencies were obtained was reviewed for the inclusion criteria listed below. Allele frequencies were also obtained by conducting a search of the PubMed database (1966 to June 2012) and Ovid MEDLINE (1950 to June 2012) using the following criteria: ([HLA or HLA-B or *HLA-B*15:02*] AND [genotype or allele or frequency]) with filter limits set to retrieve "full-text" and "English" literature. Studies from both sources were considered for inclusion if, 1) the ethnicity of the population was clearly indicated; 2) either allele frequencies or alleles for *HLA-B* genotypes were reported; 3) the method by which *HLA-B* was genotyped was reliable and proven; 4) the sample population consisted of at least 50 individuals; 5) the study represented publication of novel data, not literature reviews or meta-analyses of previously published data; and 6) the population studied did not have a concomitant disease (such as an autoimmune condition) that would be expected to result in a distribution of *HLA-B* alleles that were different from the general population. In instances where genotype data from large cohorts of ethnically-diverse individuals were reported without respect to ethnicity, studies were only considered if one ethnicity was ≥95% of the majority. In some cases, sample

sizes or allele frequencies were updated to reflect only subjects successfully genotyped for *HLA-B* (rather than the total sample size of the study) or to correct errata in the original publication. The combined analysis included 271 Africans, 371 non-Caucasian Americans, 14,397 East Asians, 30,640 Europeans including Caucasians worldwide, 491 Middle Easterners, 201Oceanians, and 235South or Central Asians (Supplemental Tables S1 and S2).

Other Considerations

HLA-A*31:01

*HLA-A*31:01* has also been associated with carbamazepine hypersensitivity reactions (1, 2). This includes not only SJS and TEN (3, 4), but also other phenotypes including maculopapular exanthema (MPE) and DRESS (drug reactions with eosinophilia and systemic symptoms).Thus, unlike *HLA-B*15:02* where the association is specific for SJS/TEN, *HLA-A*31:01* is associated a wider range of phenotypes. The association with *HLA-A*31:01* has also been shown in a larger number of ethnicities including Han Chinese, Japanese, South Korean and Caucasian (5-7), and in two independently replicated Genome-wide Association studies (GWAS) in Japanese and Caucasian populations (7, 8). The OR for the *HLA-A*31:01* association was approximately 9, whereas for *HLA-B*15:02* it is approximately 113(2).

Yip et al. have systematically reviewed both alleles and discussed the clinical utility for evaluating *HLA-A*31:01* as compared to *HLA-B*15:02*. They found that, in order to avoid one case of carbamazepine-induced cutaneous adverse drug reaction, the number of patients required for *HLA-A*31:01* screening is smaller than that required for *HLA-B*15:02*. However, if just SJS/TEN is considered, then the numbers are in favor of *HLA-B*15:02* screening.

It is unclear why the severity of the cutaneous adverse drug reactions associated with the two alleles differ (2). It is also unclear why the *HLA-A*31:01* association is found in more populations than the *HLA-B*15:02* association. It may be related to the fact that the background frequency of the *HLA-A*31:01* allele is higher than the *HLA-B*15:02* allele in many populations. The frequency of *HLA-B*15:02* is extremely low in the Japanese, Korean and European populations, ranging from (0.002 – 0.02) (2).

Other AntiepilepticsWithAn Aromatic Ring

Several drugs structurally and therapeutically similar to carbamazepine have also been associated with drug-induced adverse cutaneous reactions and *HLA-B*15:02*.

Phenytoin and fosphenytoin, the parenteral prodrug of phenytoin, are FDA approved for the treatment of tonic-clonic seizures, partial seizures, statusepilepticus and for seizure prevention. Positive *HLA-B*15:02* has been reported to occur less frequently in phenytoin/fosphenytoin-induced Stevens-Johnson Syndrome (SJS) / toxic epidermal necrolysis (TEN) than in carbamazepine-induced SJS/TEN though this is supported currently by only limited data (9-11).

Oxcarbazepine is the keto-analog of carbamazepine. As with carbamazepine, oxcarbazepine has been used in the treatment of partial seizures with and without generalization and in the treatment of neuropathic pain. As of this report, three cases have been reported of oxcarbazepine-induced SJS in individuals positive for *HLA-B*15:02* (12-14). There is also one case report tying oxcarbazepine to MPE without progression to SJS/TEN in a patient of Han Chinese decent (15).

Eslicarbazepine acetate is an antiepileptic drug used in Europe and America. It is a prodrug which is activated to eslicarbazepine, an active metabolite of oxcarbazepine. As of this report, there have been no cases reported of eslicarbazepine-induced SJS/TEN; however, based on its structural similarity to oxcarbazepine, caution should be used in susceptible individuals positive for *HLA-B*15:02*.

Lamotrigine has been associated with SJS/TEN, particularly with rapid dose escalation or when used in combination with valproic acid. There are conflicting reports regarding its association with *HLA-B*15:02*. In one study of three lamotrigine-induced SJS in a Han Chinese population, none were associated with *HLA-B*15:02* (16), but in a separate study in the same population, two of the six lamotrigine-induced SJS were positive for *HLA-B*15:02* (17).

Available Genetic Test Options and Interpretation

Commercially available genetic testing options change over time. Information that may assist in evaluating options is available below, as well as on the Pharmacogenetic Tests section (http://pharmgkb.org/resources/forScientificUsers/pharmacogenomic_tests.jsp) of PharmGKB.Furthermore, the Genetic Testing Registry (GTR) provides a central location for voluntary submission of genetic test information by providers and is available at http://www.ncbi.nlm.nih.gov/gtr/. At the time of this publication, no genetic test information has been submitted to the GTR regarding HLA-B*15:02.

The *HLA-B*15:02* allele is a complex variant consisting of numerous nucleotide and resultant amino acid substitutions. Comparison of nucleotide sequences for a reference *HLA-B* allele with that of *HLA-B*15:02* reveals 42 differences within the open reading frame of the gene (Figure S1). These nucleotide sequence differences translate to a peptide exhibiting 27 amino acid substitutions in the variant allele (Figure S2).

A variety of companies provide clinical testing services for the detecting of *HLA-B*15:02*. They primarily employ two different detection methods. One is direct sequencing of the gene. Alleles are assigned by comparison of the sequence to the known variants that define *HLA-B*15:02* as detailed in Figure S1 and reported as the diplotype of both *HLA-B* alleles.

Genotyping is another common approach in which the sequence variants that define *HLA-B*15:02* are directly detected through a panel of DNA tests. Allele specific polymerase chain reaction(PCR) is commonly employed where PCR primers specific for each nucleotide variant are used. The PCR products can then be detected using gel electrophoresis or other methods. A variety of other genotyping methods may also be used to directly detect each of the nucleotide variants for *HLA-B*15:02*. As the test is specific for *HLA-B*15:02*, the test will only report its presence and absence as opposed to the full diplotype available through sequencing.

Another option is the genotyping of one or more single nucleotide polymorphisms (SNPs) that are near the HLA-B locus and in linkage disequilibrium with the *HLA-B*15:02* allele. However, as this test is indirect and depends upon linkage disequilibrium which may vary between

different populations, it may have lower accuracy. It also requires genotyping and may not be any faster or less expensive than genotyping of the specific defining variants.

Levels of Evidence

Supplemental Table S3 summarizes the evidence for association of SJS/TEN to *HLA-B*15:02*. The evidence is graded on a scale of high, moderate, and weak, modified slightly from Valdes et al. (18):

> **High:**Consistent results from well-designed, well-conducted studies.
>
> **Moderate:**Sufficient to determine effects, but limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.
>
> **Weak:**Insufficient to draw meaningful conclusions regarding health outcomes because of limited number or power of studies, important flaws in study design or execution, gaps in the chain of evidence, or lack of information.

CPIC's dosing recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines.(19) Some of the factors that are taken into account include *in vitro*studies of carbamazepine-stimulated T cellsfrom patients with *HLA-B*15:02* alleles, and retrospective and prospective clinical outcome data for carbamazepine.

Overall, the dosing recommendations are simplified to allow rapid interpretation by clinicians. We chose to use a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of retroviral agents (http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf)(20): strong, where "the evidence is high quality and the desirable effects clearly outweigh the undesirable effects"; moderate, in which "there is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects; and optional, in which the desirable effects are closely balanced with undesirable effects and there is room for differences in opinion as to the need for the recommended course of action.

Strong recommendation for the statement

Moderate recommendation for the statement

Optional recommendation for the statement

Supplemental Table S1. Worldwide Allele Frequencies1 of HLA-B*15:02- Summary by Race/Ethnic Group[2]

Race/Ethnic Designation	Allele Frequency	Sample Size
African	0.0	271
Non-Caucasian American	0.0039	371
East Asian	0.043	14,397
European	0.000057	30,640
Middle Eastern	0.0045	491
Oceanian	0.107	201
South/Central Asian	0.0134	235
[1]Average allele frequencies are reported based on the average from the actual numbers of subjects with each allele reported in multiple studies.		
[2]Race/ethnic group designations correspond to those indicated in Supplemental Table S2.		

Supplemental Table S2. Worldwide Allele Frequencies of *HLA-B*15:02*-Detailed by Sample

HGDP-CEPH Grouping	Population/Ethnicity	Allele Frequency	Sample Size
Africa	Morocco NadorMetalsa pop 2(21)	0	73
Africa	Morocco SettatChaouya (22)	0	98
Africa	South Africa Natal Zulu (23)	0	100
Americas	Mexico City Mestizo (24)	0.008	121
Americas	Mexico Puebla Mestizo (24)	0.005	99
Americas	Mexico Sinaloa Mestizo(24)	0	56
Americas	Brazil Belo Horizonte Caucasian(23)	0	95
East Asia	China Beijing pop 2 (25)	0.1287	826
East Asia	China Beijing Shijiazhuang Tianjian Han (26)	0.024	618
East Asia	China Canton Han (27)	0.073	264
East Asia	China Guangdong Province (28)	0.035	100
East Asia	China Guangxi Region Maonan (29)	0.148	108
East Asia	China Guizhou Province Bouyei (30)	0.155	109
East Asia	China Guizhou Province Miao pop 2 (30)	0.042	85
East Asia	China Guizhou Province Shui (30)	0.156	153
East Asia	China Inner Mongolia Region (31)	0.015	102
East Asia	China North Han (32)	0.019	105
East Asia	China Qinghai Province Hui (31)	0.027	110
East Asia	China Southwest Dai (25)	0.069	124
East Asia	China Yunnan Province Bulang(33)	0.358	116
East Asia	China Yunnan Province Han (34)	0.124	101
East Asia	China Yunnan Province Hani pop 2 (33)	0.1	150
East Asia	China Yunnan Province Jinuo (35)	0.238	109

East Asia	China Yunnan Province Lisu (36)	0.123	111
East Asia	China Yunnan Province Nu (36)	0.09	107
East Asia	China Yunnan Province Wa (35)	0.21	119
East Asia	Japan Central (37)	0.001	371
East Asia	Japan pop 3 (38)	0.001	1,018
East Asia	Malaysia(39)	0.081	75
East Asia	Singapore Chinese (8, 23)	0.057	149
East Asia	South Korea pop 3 (40)	0.002	485
East Asia	South Korea pop 8 (41)	0.022	7,096
East Asia	Taiwan pop 2 (42)	0.052	364
East Asia	Taiwan pop 3 (43)	0.06	212
East Asia	Taiwan Tzu Chi Cord Blood Bank (44)	0.042	710
East Asia	Thailand Northeast pop 2(45)	0.084	400
Europe	Cuba Caucasians(8, 23)	0	70
Europe	Bulgaria (46)	0	55
Europe	Germany pop 6 (47)	0.0002	8,862
Europe	Ireland Northern (48, 49)	0	1,000
Europe	Poland DKMS(50)	0	20,653
Middle East	United Arab Emirates pop 2(51)	0.006	373
Middle East	Oman (8, 23)	0	118
Oceania	Indonesia Sundanese and Javanese(52)	0.107	201
South/Central Asia	India Mumbai Marathas(53)	0.01	72
South/Central Asia	India Mumbai Maratha (53)	0.019	91
South/Central Asia	India North pop 2 (54)	0.01	72

Supplemental TableS3.Evidence linking *HLA-B*15:02* genotype with carbamazepine-induced SJS/TEN.

Type of Experimental Model (*in vitro, in vivo* preclinical, or clinical)	**Major Findings**	**References**	**Level of Evidence**
In vitro	PBMCs from Han Chinese carbamazepine-induced SJS/TEN patients, all HLA B*15:02 positive, have significantly higher levels of interferon gamma and granulysin when cultured with carbamazepine, compared to carbamazepine-tolerant patients (2 HLA-B*15:02 positive and 9 HLA-B*15:02 negative)	Ko*et al.*2011(55)	Moderate
In vitro	Patients with carbamazepine-induced SJS/TEN and *HLA B*15:02* positive mounted a cytotoxic T lymphocyte response. This response was absent in carbamazepine-tolerant *HLA B*15:02* positive patients	Wei*et al.* 2012 (56)	Moderate
Clinical	Prospective screening of *HLA-B*15:02* reduces the incidence of clinical diagnosed SJS/TEN compared to historical data in a Han Chinese population	Chen *et al.*2011(57)	High

Clinical	Significant association between *HLA-B*15:02* genotype and Han Chinese patients with carbamazepine-induced SJS/TEN compared to carbamazepine tolerant patients and/or healthy controls	Chung *et al.*2004(58), Hung *et al.*2006(5), Man *et al.*2007(59), Wang *et al.*2011(60), Zhang*et al.* 2011(61), Lin*et al.* 2012(62)	High
Clinical	Significant association between *HLA-B*15:02* genotype and Malay patients with carbamazepine-induced SJS/TEN compared to healthy controls	Chang*et al.* 2011(63), Then*et al*. 2011(64)	High
Clinical	Significant association between *HLA-B*15:02* genotype and Thai patients with carbamazepine-induced SJS/TEN compared to carbamazepine-tolerant patients	Kulkantrakorn*et al*. 2012(65), Locharernkul*et al*. 2008(10), Tassaneeyakul*et al*. 2010(66)	High
Clinical	No significant association between *HLA-B*15:02* genotype and Japanese patients with carbamazepine-induced SJS/TEN compared to carbamazepine-tolerant patients	Ikeda*et al.* 2010(67), Kaniwa*et al.*2008(68), Kaniwa*et al*. 2010(69), Kano *et al*. 2008(70)	High
Clinical	No significant association between *HLA-B*15:02* genotype and Han Chinese patients with carbamazepine- induced non-SJS/TEN cutaneous adverse drug reaction compared to carbamazepine-tolerant patients and/or healthy controls	Hung*et al*. 2006(5), Man*et al*. 2007(59), Wang *et al*. 2011(60)	High

Clinical	No significant association between *HLA-B*15:02* genotype and Japanese patients with carbamazepine-induced non-SJS/TEN cutaneous adverse drug reaction compared to carbamazepine-tolerant patients	Ikeda*et al.*2010(67), Kano *et al*. 2008(70)	High
Clinical	Significant association between *HLA-B*15:02* genotype and Central Chinese patients with carbamazepine- induced SJS/TEN compared to carbamazepine-tolerant patients and healthy controls	Wu *et al*. 2010(71)	Moderate
Clinical	Significant association between *HLA-B*15:02* genotype and Indian patients with carbamazepine- induced SJS/TEN compared to healthy controls	Mehta *et al*. 2009(72)	Moderate
Clinical	No significant association between *HLA-B*15:02* genotype and Korean patients with carbamazepine-induced SJS/TEN compared to carbamazepine-tolerant patients	Kim *et al*. 2011(4)	Moderate
Clinical	No significant association between *HLA-B*15:02* genotype and Caucasian patients with carbamazepine-induced non-SJS/TEN cutaneous adverse drug reaction compared to carbamazepine-tolerant patients	Alfirevic*et al*. 2006(73)	Moderate

Clinical	No significant association between *HLA-B*15:02* genotype and Central Chinese patients with carbamazepine-induced non-SJS/TEN cutaneous adverse drug reaction compared to carbamazepine-tolerant patients and/or healthy controls	Wu *et al*. 2010(71)	Moderate
Clinical	No significant association between *HLA-B*15:02* genotype and Thai patients with carbamazepine-induced non-SJS/TEN cutaneous adverse drug reaction compared to carbamazepine-tolerant patients and healthy controls	Locharernkul*et al*. 2008(10)	Moderate
Clinical	No significant association between *HLA-B*15:02* genotype and Caucasian patients with carbamazepine-induced SJS/TEN compared to carbamazepine-tolerant patients	Alfirevic*et al*. 2006(73)	Moderate
Clinical	Case report of 12 patients (8 Caucasians and 4 Asian ancestry) with carbamazepine-induced SJS/TEN. Only the 4 with Asian ancestry had *HLA B*15:02* genotype	Lonjou*et al*. 2006(74)	Moderate
Clinical	Case reports of Asian patient with carbamazepine-induced SJS/TEN and *HLA B*15:02* genotype	Elzagallaai*et al*. 2011(75), Odueyungbo*et al*. 2010(76) Wang *et al*. 2012(77)	Moderate

SJS: Stevens-Johnson Syndrome; TEN: Toxic Epidermal Necrolysis

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HLA-B Reference ATGCTGGTCATGGCGCCCCGAACCGTCCTCCTGCTGCTCTCGGCGGCCCTGGCCCTGACCGAGACCTGGGCCGGCTCCCACTCCATGAGGTATTTCTACA
HLA-B*1502      ATGCGGGTCACGGCGCCCCGAACCGTCCTCCTGCTGCTCTCGGGAGCCCTGGCCCTGACCGAGACCTGGGCCGGCTCCCACTCCATGAGGTATTTCTACA

HLA-B Reference CCTCCGTGTCCCGGCCCGGCCGCGGGGAGCCCCGCTTCATCTCAGTGGGCTACGTGGACGACACCCAGTTCGTGAGGTTCGACAGCGACGCCGCGAGTCC
HLA-B*1502      CCGCCATGTCCCGGCCCGGCCGCGGGGAGCCCCGCTTCATCGCAGTGGGCTACGTGGACGACACCCAGTTCGTGAGGTTCGACAGCGACGCCGCGAGTCC

HLA-B Reference GAGAGAGGAGCCGCGGGCGCCGTGGATAGAGCAGGAGGGGCCGGAGTATTGGGACCGGAACACACAGATCTACAAGGCCCAGGCACAGACTGACCGAGAG
HLA-B*1502      GAGGATGGCGCCCCGGGCGCCATGGATAGAGCAGGAGGGGCCGGAGTATTGGGACCGGAACACACAGATCTCCAAGACCAACACACAGACTTACCGAGAG

HLA-B Reference AGCCTGCGGAACCTGCGCGGCTACTACAACCAGAGCGAGGCCGGGTCTCACACCCTCCAGAGCATGTACGGCTGCGACGTGGGGCCGGACGGGCGCCTCC
HLA-B*1502      AGCCTGCGGAACCTGCGCGGCTACTACAACCAGAGCGAGGCCGGGTCTCACATCATCCAGAGGATGTATGGCTGCGACGTGGGGCCGGACGGGCGCCTCC

HLA-B Reference TCCGCGGGCATGACCAGTACGCCTACGACGGCAAGGATTACATCGCCCTGAACGAGGACCTGCGCTCCTGGACCGCCGCGGACACGGCGGCTCAGATCAC
HLA-B*1502      TCCGCGGGTATGACCAGTCCGCCTACGACGGCAAGGATTACATCGCCCTGAACGAGGACCTGAGCTCCTGGACCGCGGCGGACACGGCGGCTCAGATCAC

HLA-B Reference CCAGCGCAAGTGGGAGGCGGCCCGTGAGGCGGAGCAGCGGAGAGCCTACCTGGAGGGCGAGTGCGTGGAGTGGCTCCGCAGATACCTGGAGAACGGGAAG
HLA-B*1502      CCAGCGCAAGTGGGAGGCGGCCCGTGAGGCGGAGCAGCTGAGAGCCTACCTGGAGGGCCTGTGCGTGGAGTGGCTCCGCAGATACCTGGAGAACGGGAAG

HLA-B Reference GACAAGCTGGAGCGCGCTGACCCCCCAAAGACACACGTGACCCACCACCCCATCTCTGACCATGAGGCCACCCTGAGGTGCTGGGCCCTGGGTTTCTACC
HLA-B*1502      GAGACGCTGCAGCGCGCGGACCCCCCAAAGACACATGTGACCCACCACCCCATCTCTGACCATGAGGCCACCCTGAGGTGCTGGGCCCTGGGCTTCTACC

HLA-B Reference CTGCGGAGATCACACTGACCTGGCAGCGGGATGGCGAGGACCAAACTCAGGACACTGAGCTTGTGGAGACCAGACCAGCAGGAGATAGAACCTTCCAGAA
HLA-B*1502      CTGCGGAGATCACACTGACCTGGCAGCGGGATGGCGAGGACCAAACTCAGGACACCGAGCTTGTGGAGACCAGACCAGCAGGAGATAGAACCTTCCAGAA

HLA-B Reference GTGGGCAGCTGTGGTGGTGCCTTCTGGAGAAGAGCAGAGATACACATGCCATGTACAGCATGAGGGGCTGCCGAAGCCCCTCACCCTGAGATGGGAGCCG
HLA-B*1502      GTGGGCAGCTGTGGTGGTGCCTTCTGGAGAAGAGCAGAGATACACATGCCATGTACAGCATGAGGGGCTGCCGAAGCCCCTCACCCTGAGATGGGAGCCA

HLA-B Reference TCTTCCCAGTCCACCGTCCCCATCGTGGGCATTGTTGCTGGCCTGGCTGTCCTAGCAGTTGTGGTCATCGGAGCTGTGGTCGCTGCTGTGATGTGTAGGA
HLA-B*1502      TCTTCCCAGTCCACCATCCCCATCGTGGGCATTGTTGCTGGCCTGGCTGTCCTAGCAGTTGTGGTCATCGGAGCTGTGGTCGCTACTGTGATGTGTAGGA

HLA-B Reference GGAAGAGTTCAGGTGGAAAAGGAGGGAGCTACTCTCAGGCTGCGTGCAGCGACAGTGCCCAGGGCTCTGATGTGTCTCTCACAGCTTGA
HLA-B*1502      GGAAGAGCTCAGGTGGAAAAGGAGGGAGCTACTCTCAGGCTGCGTCCAGCGACAGTGCCCAGGGCTCTGATGTGTCTCTCACAGCTTGA
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Supplemental Figure S1.Nucleotide coding sequence alignment of HLA-B*15:02 and the reference sequence. Nucleotide differences between the two sequences are highlighted in blue. This alignment was generated using the IMGT/HLA Database's alignment tool (www.ebi.ac.uk/imgt/hla/align.html) and visualized in Jalview.(78)

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HLA-B Reference MLVMAPRTVLLLLSAALALTETWAGSHSMRYFYTSVSRPGRGEPRFISVG
HLA-B*1502      MRVTAPRTVLLLLSGALALTETWAGSHSMRYFYTAMSRPGRGEPRFIAVG

HLA-B Reference YVDDTQFVRFDSDAASPREEPRAPWIEQEGPEYWDRNTQIYKAQAQTDRE
HLA-B*1502      YVDDTQFVRFDSDAASPRMAPRAPWIEQEGPEYWDRNTQISKTNTQTYRE

HLA-B Reference SLRNLRGYYNQSEAGSHTLQSMYGCDVGPDGRLLRGHDQYAYDGKDYIAL
HLA-B*1502      SLRNLRGYYNQSEAGSHIIQRMYGCDVGPDGRLLRGYDQSAYDGKDYIAL

HLA-B Reference NEDLRSWTAADTAAQITQRKWEAAREAEQRRAYLEGECVEWLRRYLENGK
HLA-B*1502      NEDLSSWTAADTAAQITQRKWEAAREAEQLRAYLEGLCVEWLRRYLENGK

HLA-B Reference DKLERADPPKTHVTHHPISDHEATLRCWALGFYPAEITLTWQRDGEDQTQ
HLA-B*1502      ETLQRADPPKTHVTHHPISDHEATLRCWALGFYPAEITLTWQRDGEDQTQ

HLA-B Reference DTELVETRPAGDRTFQKWAAVVVPSGEEQRYTCHVQHEGLPKPLTLRWEP
HLA-B*1502      DTELVETRPAGDRTFQKWAAVVVPSGEEQRYTCHVQHEGLPKPLTLRWEP

HLA-B Reference SSQSTVPIVGIVAGLAVLAVVVIGAVVAAVMCRRKSSGGKGGSYSQAACS
HLA-B*1502      SSQSTIPIVGIVAGLAVLAVVVIGAVVATVMCRRKSSGGKGGSYSQAASS

HLA-B Reference DSAQGSDVSLTA
HLA-B*1502      DSAQGSDVSLTA
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Supplemental Figure S2.Amino acid sequence alignment of HLA-B*15:02 and the reference sequence. Amino acid differences between the two sequences are highlighted in blue. This alignment was generated using the IMGT/HLA Database's alignment tool (www.ebi.ac.uk/imgt/hla/align.html) and visualized in Jalview.(78)

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