SUPPLEMENT TO:

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *HLA* Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update

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TABLE OF CONTENTS

GUIDELINE UPDATES

The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *HLA* genotype and use of carbamazepine and oxcarbazepine is published in full on the CPIC website (http://cpicpgx.org) and the PharmGKB website (www.pharmgkb.org). Information will be reviewed periodically and updated guidelines published online.

UPDATES IN SUPPLEMENT

- Updated literature search from January 2013 to June 2016 for *HLA-B*15:02* and carbamazepine.
- Expanded literature search to include *HLA-A*31:01* and oxcarbazepine.
- Updated evidence linking *HLA-B*15:02* to carbamazepine-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).
- Added evidence linking *HLA-B*15:02* to oxcarbazepine-induced SJS/TEN and evidence linking *HLA-A*31:01* to carbamazepine-induced SJS/TEN, drug reaction with eosinophilia and systemic symptoms (DRESS), and maculopapular exanthema (MPE).
- Added a section on the proposed mechanism for carbamazepine-induced SJS/TEN in *HLA-B*15:02* positive patients.
- Added resources to facilitate incorporation of *HLA* genotype results into electronic health records with clinical decision support and updated allele frequency information (see https://cpicpgx.org/guidelines/guideline-for-carbamazepine-and-hla-b/).

LITERATURE REVIEW

A search was conducted on the PubMed database (1966 to June 17, 2016) for keywords ([HLA] AND [carbamazepine]), ([HLA] AND [oxcarbazepine]), ([HLA] AND [eslicarbazepine]), and ([HLA] AND [lamotrigine]). The ([HLA] AND [carbamazepine]) search yielded 238 articles, the ([HLA] AND [oxcarbazepine]) search yielded 14 articles, the ([HLA] AND [eslicarbazepine]) search yielded two articles, and the ([HLA] AND [lamotrigine]) search yielded 30 articles. Study inclusion criteria included publications that explored the association between *HLA-B*15:02* or *HLA-A*31:01* genotypes and severe cutaneous adverse drug reactions

with any of the aforementioned antiepileptics. Non-English manuscripts were excluded. Following application of these inclusion criteria, 82 publications were reviewed.

A table of frequencies of the *HLA-B*15:02* and *HLA-A*31:01* alleles in different ethnic populations around the world was assembled from several sources (see ***HLA-A* and *HLA-B* Allele Frequency Table** online). Frequencies were included from the Allele Frequencies in Worldwide Populations website (http://www.allelefrequencies.net/), which lists frequency data for *HLA* alleles from over 200 different samples and populations. Allele frequencies were also obtained by conducting a search of the PubMed database (2000 to 2016) using the following criteria: ([HLA-B*1502] AND [frequency]) and ([HLA-A*3101] AND [frequency]). Studies from both sources were considered for inclusion if the following criteria were met: 1) the ethnicity of the population was clearly indicated; 2) allele frequencies were reported; and 3) the sample population consisted of at least 100 individuals.

OTHER CONSIDERATIONS

Allele Frequency vs. Allele Carriage Rate

Representation of *HLA* in a given population can be described in terms of either allele frequency (the total number of copies of the allele in the relevant population), or by allele carriage rate (the percentage of individuals who have the allele in the population or prevalence). This concept differs from other genes because *HLA* is inherited in a co-dominant fashion and to take into account those who are homozygous or have two copies of a given *HLA* allele. The representation of homozygosity in any given population may have been driven by a number of evolutionary factors that select against this ("the heterozygous advantage") (1, 2). For carbamazepine-induced SJS/TEN and abacavir hypersensitivity, there is no current evidence to suggest a gene-dose effect or that carrying more than one copy of the *HLA* risk allele is associated with a higher risk; however, for some other phenotypes (e.g., dapsone hypersensitivity and *HLA-B*13:01*), being homozygous portends a higher risk of disease (3).

Proposed Mechanism for HLA-B*15:02-mediated SJS/TEN in Response to Carbamazepine

Current research suggests that carbamazepine binds non-covalently to the B pocket of the HLA-B*15:02 peptide binding groove and that the B pocket residues Arg62, Asn63, Ile95, and Leu156 contribute to drug-HLA interactions (4). Other members of the B75 serotype implicated in carbamazepine SJS/TEN (as described in the following section) also share these B pocket residues. However, other mechanisms by which carbamazepine and its metabolites bind to the HLA molecules cannot be discounted and may account for differences in the presentation of clinical symptoms between different patients (5).

T-cell receptor (TCR) sequencing of blister-fluid derived T cells from patients with *HLA-B*15:02*-associated carbamazepine SJS/TEN has identified a shared $CD8^+$ TCR clonotype that bears a common CDR3 sequence that is found in the peripheral blood of carbamazepine SJS/TEN patients but not in peripheral blood of drug tolerant controls or in blister fluid from patients with SJS/TEN secondary to another drug. Thus, although the crystal structure of HLA-B*15:02 bound to peptide drug and TCR has not been solved and the role of a peptide remains to be determined, the immunopathogenesis of *HLA-B*15:02*-associated carbamazepine SJS/TEN likely depends upon the concomitant involvement of both a specific HLA allotype and a specific TCR clonotype (6).

HLA-B75 Serotype

Relevant to the proposed mechanism for *HLA-B*15:02*-associated carbamazepine SJS/TEN, HLA molecules of the same B75 serotype (e.g., HLA-B*15:08, HLA-B*15:11 and HLA-B*15:21) with similar peptide binding properties have also been associated with carbamazepine SJS/TEN, particularly HLA-B*15:11 in populations such as Japanese and Koreans where HLA-B*15:02 is less prevalent (7-9). Currently, carbamazepine-induced SJS/TEN has not been associated with less frequently carried B75 serotype alleles such as *HLA-B*15:30* and *HLA-B*15:31*; however, given the structural similarity and shared peptide binding properties, the risk for this should also be considered. If a patient developed SJS/TEN despite a negative *HLA-B*15:02* and/or *HLA-A*31:01* result, full *HLA-B* typing may provide further insight, particularly if the test reveals the presence of another B75 serotype allele.

Other Aromatic Anticonvulsants

Several drugs structurally similar to carbamazepine and oxcarbazepine have also been associated with drug-induced cutaneous adverse reactions in *HLA-B*15:02* positive patients or are thought to be associated with greater risk, including phenytoin, eslicarbazepine acetate, and lamotrigine. For a detailed discussion of *HLA-B*15:02* and phenytoin, please refer to the previously published CPIC guideline (10). Eslicarbazepine acetate is an antiepileptic drug used in Europe and America. It is a prodrug which is activated to (S)-licarbazepine, an active metabolite of oxcarbazepine. As of this report, there have been no cases reported of eslicarbazepine-induced cutaneous adverse reactions associated with *HLA-B*15:02*; however, based on its structural similarity to oxcarbazepine, caution should be used in patients positive for *HLA-B*15:02*. Lamotrigine has also been associated with SJS/TEN, particularly with rapid dose escalation or when used in combination with valproic acid. A 2015 meta-analysis involving four studies in Han Chinese patients found a statistical association between *HLA-B*15:02* and lamotrigine-induced SJS/TEN, with an odds ratio of 4.98 (11).

Available Genetic Test Options and Interpretation

Commercially available genetic testing options change over time. Information that may assist in evaluating options is available below. 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/.

HLA alleles are extremely diverse and typically consist 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 (**Supplemental Figure S1**). These nucleotide sequence differences translate to a peptide exhibiting 27 amino acid substitutions in the variant allele (**Supplemental Figure S2**). Comparison of the *HLA-A*31:01* allele with the reference *HLA-A*01:01* reveals 46 differences within the open reading frame of the gene (**Supplemental Figure S3**). These nucleotide sequence differences translate to a peptide exhibiting 33 amino acid substitutions in the variant allele (**Supplemental Figure S4**).

A variety of companies provide clinical testing services for the detecting of *HLA-B*15:02* and *HLA-A*31:01*. 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* or *HLA-A*31:01* and reported as the diplotype of *HLA-B* or *HLA-A* alleles, respectively.

Genotyping is another common approach in which the sequence variants that define *HLA-B*15:02* and *HLA-A*31:01* 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* and *HLA-A*31:01.* As the test is specific for *HLA-B*15:02* or *HLA-A*31:01*, the test will only report its presence or 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

The evidence summarized in **Supplemental Tables S1 and S2** is graded on a scale of high, moderate, and weak, based upon level of evidence:

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Based on the levels of evidence for major findings, the strength of therapeutic recommendations are assigned accordingly (**Tables 2 and 3, main manuscript**).

STRENGTH OF RECOMMENDATIONS

CPIC uses a slight modification of a transparent and simple system for recommendations adopted from the rating scale for evidence-based recommendations on the use of antiretroviral agents (12):

> **Strong**: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.
>
> **Moderate**: There is a close or uncertain balance as to whether the evidence is high quality and the desirable effects clearly outweigh the undesirable effects.
>
> **Optional**: The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.
>
> **No recommendation**: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

RESOURCES TO INCORPORATE PHARMACOGENETICS INTO AN ELECTRONIC HEALTH RECORD WITH CLINICAL DECISION SUPPORT

Clinical decision support (CDS) tools integrated into electronic health records (EHRs) can help guide the optimal use of pharmacogenetic test results at the point of care (13-17). Please refer to the CPIC website for this guideline (https://cpicpgx.org/guidelines/guideline-for-carbamazepine-and-hla-b/) for resources to support the adoption of this guideline's recommendations into an EHR. Based on the capabilities of various EHRs and local preferences, we recognize that approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for incorporating the use of *HLA* genotype results to guide the rational use of carbamazepine and oxcarbazepine in an EHR.

Effectively incorporating pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. Pharmacogenetic results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR (18, 19). To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted phenotype (**Table 1, main manuscript**). Because clinicians must be able to easily find the information, the interpreted phenotype may be documented as a problem list entry, in a patient summary section, or in the adverse drug reaction section; these phenotypes are best stored in the EHR at the "person level" that links to both the inpatient and outpatient record rather than at the date-centric "encounter level." Additionally, results should be entered as standardized and discrete terms to facilitate using them to provide point-of-care CDS (13, 20).

Because pharmacogenetic results have lifetime implications of clinical significance that may expand as more knowledge becomes available, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. To facilitate this process, CPIC provides gene-specific figures and tables that illustrate how *HLA* pharmacogenetic test results could be entered into an EHR, example EHR consultation/genetic test interpretation language, and widely used nomenclature systems for genes and drugs relevant to the guideline (see the following online resources: ***HLA-B* Genotype Table**, ***HLA-A* Genotype Table**, ***HLA* Gene Resource Mappings Table**, **Carbamazepine Drug Resource Mappings Table**, and **Oxcarbazepine Drug Resource Mappings Table**).

Point-of-care CDS should be designed to effectively notify clinicians of prescribing implications at any time after the test result is entered into the EHR. CPIC also provides gene-drug specific tables and example pre- and post-alert language that provide guidance to achieve these objectives with diagrams that illustrate how point-of-care CDS should be entered into the EHR (see the following online resources: **Carbamazepine Pre- and Post-test Alerts and Flow Charts** and **Oxcarbazepine Pre-and Post-test Alerts and Flow Charts**).

TABLE S1. EVIDENCE LINKING *HLA-B*15:02* GENOTYPE WITH CARBAMAZEPINE- AND OXCARBAZEPINE-INDUCED CUTANEOUS ADVERSE REACTIONS

Type of Experimental Model	Clinical Phenotype	Major Findings	References	Level of Evidence[a]
Carbamazepine and *HLA-B*15:02*				
In vitro	N/A	PBMCs from 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 (21)	Moderate
In vitro	SJS/TEN	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 (4)	Moderate
Clinical	SJS/TEN	Prospective screening of *HLA-B*15:02* reduces the incidence of carbamazepine-induced SJS/TEN compared to historical data.	Chen, *et al.* 2011 (22) Chen, *et al.* 2014 (23)	High
Clinical	SJS/TEN	Significant association between *HLA-B*15:02* genotype and patients with carbamazepine-induced SJS/TEN compared to carbamazepine-tolerant patients and/or healthy controls.	**Supports statement:** Chung, *et al.* 2004 (24) Hung, *et al.* 2006 (25) Man, *et al.* 2007 (26)	High

			Locharernkul, *et al.* 2008 (27) Mehta, *et al.* 2009 (28) Tassaneeyakul, *et al.* 2010 (7) Wu, *et al.* 2010 (29) Chang, *et al.* 2011 (30) Then, *et al.* 2011 (31) Wang, *et al.* 2011 (32) Zhang, *et al.* 2011 (33) Kulkantrakorn, *et al.* 2012 (34) Shi, *et al.* 2012 (35) Neuman, *et al.* 2012 (36) Amstutz, *et al.* 2013 (37) He, *et al.* 2013 (38) Cheung, *et al.* 2013 (39) Lin, *et al.* 2013 (40)	

			Aggarwal, *et al.* 2014 (41) Chong, *et al.* 2014 (42) Khor, *et al.* 2014 (43) Kwan, *et al.* 2014 (44) Sun, *et al.* 2014 (45) Genin, *et al.* 2014 (46) Hsiao, *et al.* 2014 (47) Toh, *et al.* 2014 (48) Wang, *et al.* 2014 (49) Nguyen, *et al.* 2015 (50) Yang, *et al.* 2015 (51) Teh, *et al.* 2016 (52) **Indeterminate (inadequate statistical power to detect low frequency variant):** Alfirevic, *et al.* 2006 (53)	

			Kashiwagi, *et al.* 2008 (54) Kaniwa, *et al.* 2008 (55) Kano, *et al.* 2008 (56) Ikeda, *et al.* 2010 (57) Kaniwa, *et al.* 2010 (8) Kim, *et al.* 2011 (9) Niihara, *et al.* 2012 (58) Park, *et al.* 2016 (59)	
Clinical	DRESS/MPE	No significant association between *HLA-B*15:02* genotype and patients with carbamazepine-induced **non-SJS/TEN cutaneous adverse drug reaction** compared to carbamazepine-tolerant patients and/or healthy controls.	Alfirevic, *et al.* 2006 (53) Hung, *et al.* 2006 (25) Man, *et al.* 2007 (26) Kashiwagi, *et al.* 2008 (54) Kano, *et al.* 2008 (56) Ikeda, *et al.* 2010 (57) Wu, *et al.* 2010 (29) Wang, *et al.* 2011 (32) Niihara, *et al.* 2012 (58)	High

			Amstutz, *et al.* 2013 (37) Li, *et al.* 2013 (60) Lin, *et al.* 2013 (40) Sun, *et al.* 2014 (45) Hsiao, *et al.* 2014 (47) Locharernkul, *et al.* 2008 (27) Chong, *et al.* 2014 (42) Nguyen, *et al.* 2015 (50)	
Clinical	SJS/TEN	Cases of patients with carbamazepine-induced SJS/TEN and *HLA-B*15:02* genotype.	Lonjou, *et al.* 2006 (61) Odueyungbo, *et al.* 2010 (62) Elzagallaai, *et al.* 2011 (63) Wang, *et al.* 2012 (64) Techasatian, *et al.* 2015 (65) Tan, *et al.* 2015 (66) Bellon, *et al.* 2016 (67)	Moderate

Oxcarbazepine and *HLA-B*15:02*				
Clinical	SJS/TEN	Significant association between *HLA-B*15:02* genotype and patients with oxcarbazepine-induced SJS/TEN compared to oxcarbazepine-tolerant patients or healthy controls.	**Supports statement:** Chen, *et al.* 2017 (68) **Indeterminate (inadequate statistical power to detect low frequency variant):** Amstutz, *et al.* 2013 (37)	High
Clinical	DRESS/MPE	No significant association between *HLA-B*15:02* genotype and patients with oxcarbazepine-induced **non-SJS/TEN cutaneous adverse drug reaction** compared to oxcarbazepine-tolerant patients and/or healthy controls.	**Supports statement:** Hu, *et al.* 2011 (69) He, *et al.* 2012 (70) Lv, *et al.* 2013 (71) Sun, *et al.* 2014 (45) Wang, *et al.* 2014 (72) Chen, *et al.* 2017 (68) **Indeterminate (inadequate statistical power to detect low frequency variant):**	High

			Amstutz, *et al.* 2013 (37)	
Clinical	SJS/TEN	Cases of patients with oxcarbazepine-induced SJS/TEN and *HLA-B*15:02* genotype.	Chen, *et al.* 2009 (73) Hung, *et al.* 2010 (74) Sun, *et al.* 2014 (45)	Moderate
Clinical	DRESS	Case of a patient with oxcarbazepine-induced DRESS and *HLA-B*15:02* genotype.	Shankarkumar, *et al.* 2009 (75)	Weak
Clinical	MPE	Cases of patients with oxcarbazepine-induced MPE and *HLA-B*15:02* genotype.	Wang, *et al.* 2012 (64) Wang, *et al.* 2014 (72)	Weak

DRESS: drug reaction with eosinophilia and systemic symptoms; MPE: maculopapular exanthema; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis

[a]Rating scheme described in the **Supplemental Material**.

TABLE S2. EVIDENCE LINKING *HLA-A*31:01* GENOTYPE WITH CARBAMAZEPINE- AND OXCARBAZEPINE-INDUCED CUTANEOUS ADVERSE REACTIONS

Type of Experimental Model	Clinical Phenotype	Major Findings	References	Level of Evidence[a]
Carbamazepine and *HLA-A*31:01*				
In vitro	N/A	HLA-A*31:01 restricted the activation of carbamazepine-specific CD8(+) T-cells that were derived from a patient with *HLA-A*31:01* genotype who presented with a generalized maculopapular exanthema with eosinophilia and lymphocytosis 6 days after starting carbamazepine.	Lichtenfels, *et al.* 2014 (76)	Weak
Clinical	DRESS	Significant association between *HLA-A*31:01* genotype and patients with carbamazepine-induced DRESS compared to carbamazepine-tolerant patients and/or healthy controls.	**Supports statement:** Hung, *et al.* 2006 (25) Kashiwagi, *et al.* 2008 (54) Kim, *et al.* 2011 (9) McCormack, *et al.* 2011 (77) Ozeki, *et al.* 2011 (78) Niihara, *et al.* 2012 (58)	High

			Amstutz, *et al.* 2013 (37) Genin, *et al.* 2014 (46) Hsiao, *et al.* 2014 (47) **Indeterminate (inadequate statistical power to detect low frequency variant):** Shirzadi, *et al.* 2015 (79)	
Clinical	MPE	Significant association between *HLA-A*31:01* genotype and patients with carbamazepine-induced MPE compared to carbamazepine-tolerant patients and/or healthy controls.	**Supports statement:** Hung, *et al.* 2006 (25) Kashiwagi, *et al.* 2008 (54) Hsiao, *et al.* 2014 (47) McCormack, *et al.* 2011 (77) Ozeki, *et al.* 2011 (78) Niihara, *et al.* 2012 (58)	Moderate

			Amstutz, *et al.* 2013 (37) Fricke-Galindo, *et al.* 2014 (80) **Indeterminate (inadequate statistical power to detect low frequency variant):** Li, *et al.* 2013 (60) Song, *et al.* 2014 (81) Shirzadi, *et al.* 2015 (79)	
Clinical	SJS/TEN	Significant association between *HLA-A*31:01* genotype and patients with carbamazepine-induced SJS/TEN compared to carbamazepine-tolerant patients.	**Supports statement:** Ozeki, *et al.* 2011 (78) McCormack, *et al.* 2011 (77) Genin, *et al.* 2014 (46) **Indeterminate (inadequate statistical power to**	High

			detect low frequency variant): Hung, *et al.* 2006 (25) Kim, *et al.* 2011 (9) Niihara, *et al.* 2012 (58) Shi, *et al.* 2012 (35) Amstutz, *et al.* 2013 (37) Genin, *et al.* 2014 (46) Hsiao, *et al.* 2014 (47) Park, *et al.* 2016 (59)	
Clinical	DRESS	Cases of patients with carbamazepine-induced DRESS and *HLA-A*31:01* genotype.	Mizumoto, *et al.* 2012 (82) Anjum, *et al.* 2014 (83) Segert, *et al.* 2016 (84)	Weak
Oxcarbazepine and *HLA-A*31:01*				
Clinical	DRESS/MPE	No significant association between *HLA-A*31:01* genotype and patients with oxcarbazepine-induced non-SJS/TEN cutaneous	**Supports statement:** Chen, *et al.* 2017 (68)	Moderate

		adverse drug reaction compared to oxcarbazepine-tolerant patients or healthy controls.	**Indeterminate (inadequate statistical power to detect low frequency variant):** Amstutz, *et al.* 2013 (37)	
Clinical	SJS/TEN	No significant association between *HLA-A*31:01* genotype and patients with oxcarbazepine-induced SJS/TEN compared to oxcarbazepine-tolerant patients or healthy controls.	**Supports statement:** Chen, *et al.* 2017 (68) **Indeterminate (inadequate statistical power to detect low frequency variant):** Amstutz, *et al.* 2013 (37)	High

DRESS = drug reaction with eosinophilia and systemic symptoms; MPE = maculopapular exanthema; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis

[a]Rating scheme described in the **Supplemental Material**

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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 GACAAGCTGGAGCGCGCTGACCCCCCAAAGACACACGTGACCCACCACCCCCATCTCTGACCATGAGGCCACCCTGAGGTGCTGGGCCCTGGGTTTCTACC
HLA-B*1502      GAGACGCTGCAGCGCGCGGACCCCCCAAAGACACATGTGACCCACCACCCCCATCTCTGACCATGAGGCCACCCTGAGGTGCTGGGCCCTGGGCTTCTACC

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
```

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 (85).

```
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
```

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 (85).

```
cDNA                    10         20         30         40         50         60         70         80         90        100
 A*01:01:01:01      ATGGCCGTCA TGGCGCCCCG AACCCTCCTC CTGCTACTCT CGGGGGCCCT GGCCCTGACC CAGACCTGGG CGGGCTCCCA CTCCATGAGG TATTTCTTCA
 A*31:01:02:01      ATGGCCGTCA TGGCGCCCCG AACCCTCCTC CTGCTACTCT TGGGGGCCCT GGCCCTGACC CAGACCTGGG CGGGCTCCCA CTCCATGAGG TATTTCACCA

 cDNA                   110        120        130        140        150        160        170        180        190        200
 A*01:01:01:01      CATCCGTGTC CCGGCCCGGC CGCGGGGAGC CCCGCTTCAT CGCCGTGGGC TACGTGGACG ACACGCAGTT CGTGCGGTTC GACAGCGACG CCGCGAGCCA
 A*31:01:02:01      CATCCGTGTC CCGGCCCGGC CGCGGGGAGC CCCGCTTCAT CGCCGTGGGC TACGTGGACG ACACGCAGTT CGTGCGGTTC GACAGCGACG CCGCGAGCCA

 cDNA                   210        220        230        240        250        260        270        280        290        300
 A*01:01:01:01      GAAGATGGAG CCGCGGGCGC CGTGGATAGA GCAGGAGGGG CCGGAGTATT GGGACCAGGA GACACGGAAT ATGAAGGCCC ACTCACAGAC TGACCGAGCG
 A*31:01:02:01      GAGGATGGAG CCGCGGGCGC CGTGGATAGA GCAGGAGAGG CCTGAGTATT GGGACCAGGA GACACGGAAT GTGAAGGCCC ACTCACAGAT TGACCGAGTG

 cDNA                   310        320        330        340        350        360        370        380        390        400
 A*01:01:01:01      AACCTGGGGA CCCTGCGCGG CTACTACAAC CAGAGCGAGG ACGGTTCTCA CACCATCCAG ATAATGTATG GCTGCGACGT GGGGCCGGAC GGGCGCTTCC
 A*31:01:02:01      GACCTGGGGA CCCTGCGCGG CTACTACAAC CAGAGCGAGG CCGGTTCTCA CACCATCCAG ATGATGTATG GCTGCGACGT GGGGTCGGAC GGGCGCTTCC

 cDNA                   410        420        430        440        450        460        470        480        490        500
 A*01:01:01:01      TCCGCGGGTA CCGGCAGGAC GCCTACGACG GCAAGGATTA CATCGCCCTG AACGAGGACC TGCGCTCTTG GACCGCGGCG GACATGGCAG CTCAGATCAC
 A*31:01:02:01      TCCGCGGGTA CCAGCAGGAC GCCTACGACG GCAAGGATTA CATCGCCTTG AACGAGGACC TGCGCTCTTG GACCGCGGCG GACATGGCGG CTCAGATCAC

 cDNA                   510        520        530        540        550        560        570        580        590        600
 A*01:01:01:01      CAAGCGCAAG TGGGAGGCGG TCCATGCGGC GGAGCAGCGG AGAGTCTACC TGGAGGGCCG GTGCGTGGAC GGGCTCCGCA GATACCTGGA GAACGGGAAG
 A*31:01:02:01      CCAGCGCAAG TGGGAGGCGG CCCGTGTGGC GGAGCAGTTG AGAGCCTACC TGGAGGGCAC GTGCGTGGAG TGGCTCCGCA GATACCTGGA GAACGGGAAG

 cDNA                   610        620        630        640        650        660        670        680        690        700
 A*01:01:01:01      GAGACGCTGC AGCGCACGGA CCCCCCCAAG ACACATATGA CCCACCACCC CATCTCTGAC CATGAGGCCA CCCTGAGGTG CTGGGCCCTG GGCTTCTACC
 A*31:01:02:01      GAGACGCTGC AGCGCACGGA CCCCCCCAAG ACGCATATGA CTCACCACGC TGTCTCTGAC CATGAGGCCA CCCTGAGGTG CTGGGCCCTG AGCTTCTACC

 cDNA                   710        720        730        740        750        760        770        780        790        800
 A*01:01:01:01      CTGCGGAGAT CACACTGACC TGGCAGCGGG ATGGGGAGGA CCAGACCCAG GACACGGAGC TCGTGGAGAC CAGGCCTGCA GGGGATGGAA CCTTCCAGAA
 A*31:01:02:01      CTGCGGAGAT CACACTGACC TGGCAGCGGG ATGGGGAGGA CCAGACCCAG GACACGGAGC TCGTGGAGAC CAGGCCTGCA GGGGATGGAA CCTTCCAGAA

 cDNA                   810        820        830        840        850        860        870        880        890        900
 A*01:01:01:01      GTGGGCGGCT GTGGTGGTGC CTTCTGGAGA GGAGCAGAGA TACACCTGCC ATGTGCAGCA TGAGGGTCTG CCCAAGCCCC TCACCCTGAG ATGGGAGCTG
 A*31:01:02:01      GTGGGCGTCT GTGGTGGTGC CTTCTGGACA GGAGCAGAGA TACACCTGCC ATGTGCAGCA TGAGGGTCTC CCCAAGCCCC TCACCCTGAG ATGGGAGCCG

 cDNA                   910        920        930        940        950        960        970        980        990       1000
 A*01:01:01:01      TCTTCCCAGC CCACCATCCC CATCGTGGGC ATCATTGCTG GCCTGGTTCT CCTTGGAGCT GTGATCACTG GAGCTGTGGT CGCTGCCGTG ATGTGGAGGA
 A*31:01:02:01      TCTTCCCAGC CCACCATCCC CATCGTGGGC ATCATTGCTG GCCTAGTTCT CTTTGGAGCT GTGTTCGCTG GAGCTGTGGT CGCTGCTGTG AGGTGGAGGA

 cDNA                  1010       1020       1030       1040       1050       1060       1070       1080       1090
 A*01:01:01:01      GGAAGAGCTC AGATAGAAAA GGAGGGAGTT ACACTCAGGC TGCAAGCAGT GACAGTGCCC AGGGCTCTGA TGTGTCTCTC ACAGCTTGTA AAGTGTGA
 A*31:01:02:01      GGAAGAGCTC AGATAGAAAA GGAGGGAGCT ACTCTCAGGC TGCAAGCAGT GACAGTGCCC AGGGCTCTGA TATGTCTCTC ACAGCTTGTA AAGTGTGA
```

Figure S3. Nucleotide coding sequence alignment of *HLA-A*31:01* and the reference sequence (*HLA-A*01:01*). Nucleotide differences between the two sequences are highlighted in red. This alignment was generated using the IMGT/HLA Database's alignment tool (www.ebi.ac.uk/imgt/hla/align.html) and highlighted manually.

```
AA Pos.                -21        -11         -1          10          20          30          40          50          60          70
A*01:01:01:01          MAVM APRTLLLLLS GALALTQTWA GSHSMRYFFT SVSRPGRGEP RFIAVGYVDD TQFVRFDSDA ASQKMEPRAP WIEQEGPEYW DQETRNMKAH
A*31:01:02:01          MAVM APRTLLLLLL GALALTQTWA GSHSMRYFTT SVSRPGRGEP RFIAVGYVDD TQFVRFDSDA ASQRMEPRAP WIEQERPEYW DQETRNVKAH

AA Pos.                 80          90         100         110         120         130         140         150         160         170
A*01:01:01:01      SQTDRANLGT LRGYYNQSED GSHTIQIMYG CDVGPDGRFL RGYRQDAYDG KDYIALNEDL RSWTAADMAA QITKRKWEAV HAAEQRRVYL EGRCVDGLRR
A*31:01:02:01      SQIDRVDLGT LRGYYNQSEA GSHTIQMMYG CDVGSDGRFL RGYQQDAYDG KDYIALNEDL RSWTAADMAA QITQRKWEAA RVAEQLRAYL EGTCVEWLRR

AA Pos.                180         190         200         210         220         230         240         250         260         270
A*01:01:01:01      YLENGKETLQ RTDPPKTHMT HHPISDHEAT LRCWALGFYP AEITLTWQRD GEDQTQDTEL VETRPAGDGT FQKWAAVVVP SGEEQRYTCH VQHEGLPKPL
A*31:01:02:01      YLENGKETLQ RTDPPKTHMT HHAVSDHEAT LRCWALSFYP AEITLTWQRD GEDQTQDTEL VETRPAGDGT FQKWASVVVP SGQEQRYTCH VQHEGLPKPL

AA Pos.                280         290         300         310         320         330         340
A*01:01:01:01      TLRWELSSQP TIPIVGIIAG LVLLGAVITG AVVAAVMWRR KSSDRKGGSY TQAASSDSAQ GSDVSLTACK V
A*31:01:02:01      TLRWEPSSQP TIPIVGIIAG LVLFGAVFAG AVVAAVRWRR KSSDRKGGSY SQAASSDSAQ GSDMSLTACK V
```

Figure S4. Amino acid sequence alignment of HLA-A*31:01 and the reference sequence (HLA-A*01:01). Amino acid differences between the two sequences are highlighted in red. This alignment was generated using the IMGT/HLA Database's alignment tool (www.ebi.ac.uk/imgt/hla/align.html) and highlighted manually.

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