Supplemental Material

Clinical Pharmacogenetics Implementation Consortium Guidelines for Human Leukocyte Antigen B (HLA-B) Genotype and Allopurinol Dosing

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CPIC Updates

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are published in full on the PharmGKB website (www.pharmgkb.org). Relevant information will be periodically reviewed and updated guidelines will be published online.

Focused Literature Review

We searched the PubMed database (1966 to October 2011) for keywords ((HLA OR HLA-B OR HLA-B58 OR HLA-B*5801) AND (allopurinol)), and retrieved fifty articles. Of those fifty the majority were review articles. We identified nine primary studies of the pharmacogenomics of allopurinol hypersensitivity and one meta-analysis. The recent meta-analysis of HLA-B*5801 and allopurinol-induced SJS/TEN(1) stated that in their literature review they found only six relevant primary studies in their database search that included MEDLINE, Pre-MEDLINE, Cochrane Library, EMBASE, International Pharmaceutical Abstracts (IPA), CINAHL, PsychInfo, the WHO International, Clinical Trial Registry, and ClinicalTrial.gov from their inceptions to June 2011(2-7). The additional three studies we have included in our corpus of literature include those that used a genome-wide association study (GWAS) design and were published after June 2011(8-10).

To construct an HLA-B*57801 minor allele frequency table based on ethnicity, allele frequency information was obtained from Allele Frequency Net Database (www.allelefrequencies.net). It is an online repository for HLA allele frequencies from both previously published and unpublished sources. All previously published data were manually checked against the original publications to verify the HLA-B*5801 allele frequencies. In some cases, sample sizes or allele frequencies were updated to reflect only subjects successfully genotyped for HLA-B*5801 (rather than the total sample size of the study) or to correct errata in the original publication. The combined analysis included 38979 Caucasians, 5811 Black or Africans, 882 Middle Easterners, 3318 Hispanic or Latino and 11531Asians.

Genetic Test Interpretation and Available Test Options

Commercially available genetic testing options change over time. Several platforms based on different genotyping technology that may assist in evaluating options are available and are described on the Pharmacogenetic Tests section of PharmGKB (http://pharmgkb.org/search/geneticTestList.action).

The commercial testing for HLA-B*5801 appears to be less widespread in availability at present than that of HLA-B*5701 (the allele associated with abacavir hypersensitivity). Testing procedures are similar than for HLA-B*5701(11) and may include sequencing or sequence specific priming PCR. Commercially available genetic testing options change over time.

Example CPT codes from Immunogenetics laboratory, Puget Sound Blood Center, USA are 83890, 83894 (x32), 83898 (x32), 83912.

Levels of Evidence linking genotype to phenotype

The evidence summarized in Supplemental Table S4 has been graded using the three-tiered system required by the Clinical Pharmacogenetics Implementation Consortium(12), as modified slightly from Valdes *et al.*(13):

> **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.

Every effort was made to present evidence from high-quality studies, which provided the framework for the strength of therapeutic recommendations in Table 2.

Strength of Recommendations

The dosing recommendations are simplified to allow rapid interpretation by clinicians, as adapted from the rating scale for evidence-based therapeutic recommendations on the use of allopurinol. As previously described for CPIC guidelines(12), three categories were chosen for recommendations: 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, for recommendations in-between strong and weak where there is room for differences in opinion as to the need for the recommended course of action. CPIC's dosing recommendations are based weighing the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Overall, the dosing recommendations are simplified to allow rapid interpretation by clinicians.

> A: Strong recommendation for the statement
>
> B: Moderate recommendation for the statement

C: Optional recommendation for the statement

Supplemental Table S1. Frequencies of alleles[1] in major race/ethnic groups[2]

Population Group	Total patients	Average HLA-B*5801 carrier frequency (%)
Asian	11531	6.1
Black or African American	5811	4.3
Caucasian	38979	0.75
Hispanic or Latino	3318	1.2
Middle Eastern	882	3.7

[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---detailed file table of HLA-B*5801 alleles in defined race/ethnic groups

Pooled grouping	Ethnicity	HLA-B*5801 allele frequency (%)	Sample size
Asian	China Beijing Shijiazhuang Tianjian Han	6	618
Asian	China Canton Han	8.9	264
Asian	China Guangdong Province Meizhou Han	17	100
Asian	China Guangxi Region Maonan	4.2	108
Asian	China Guangzhou	8.5	102
Asian	China Guangzhou Han	4.7	106
Asian	China Guizhou Province Bouyei	8.3	109
Asian	China Guizhou Province Shui	1.5	153
Asian	China Inner Mongolia Region	8.8	102
Asian	China North Han	2.9	105
Asian	China Qinghai Province Hui	2.3	110
Asian	China South Han	8.9	284
Asian	China Southwest Dai	7.7	124
Asian	China Tibet Region Tibetan	1.6	158
Asian	China Yunnan Province Bulang	0.4	116
Asian	China Yunnan Province Han	7.4	101
Asian	China Yunnan Province Hani pop 2	2.7	150
Asian	China Yunnan Province Jinuo	0.5	109
Asian	China Yunnan Province Lisu	0.7	111
Asian	China Yunnan Province Nu	1.9	107
Asian	China Yunnan Province Wa	1.7	119
Asian	Indonesia Java Western	5.9	236
Asian	Indonesia Sundanese and Javanese	6	201
Asian	Japan Central	0.4	371
Asian	Japan pop 3	0.5	1018
Asian	Hong Kong Chinese	7.3	569
Asian	Russia Tuva pop 2, Siberian	6.7	169
Asian	South Korea pop 3	6.5	485
Asian	Singapore Chinese	10.4	149
Asian	Singapore Riau Malay	5	132
Asian	Singapore Thai	8.6	100
Asian	Taiwan Han Chinese	10.6	504
Asian	Taiwan Minnan pop 1	8.8	102
Asian	Taiwan pop 2	10	364
Asian	Taiwan pop 3	10.1	212
Asian	Taiwan Tzu Chi Cord Blood Bank	9.8	710
Asian	Thailand	7.7	142

Asian	Thailand Northeast pop 2	7.9	400
Asian	USA Asian	7.4	358
Asian	USA Asian pop 2	5.7	1772
Asian	Vietnam Hanoi Kinh pop 2	6.5	170
Asian	India Andhra Pradesh Golla	7.2	111
Black or African American	Cameroon Beti	3.7	174
Black or African American	Kenya	8	144
Black or African American	Kenya Luo	7	265
Black or African American	Kenya Nandi	10	240
Black or African American	Mali Bandiagara	2.2	138
Black or African American	Senegal Niokholo Mandenka	6.9	165
Black or African American	South Africa Natal Zulu	4	100
Black or African American	Uganda Kampala	4	161
Black or African American	Uganda Kampala pop 2	6	175
Black or African American	USA African American	6.4	252
Black or African American	USA African American Bethesda	2.6	187
Black or African American	USA African American pop 3	3.2	564
Black or African American	USA African American pop 4	3.51	2411
Black or African American	USA African American pop 8	3.6	605
Black or African American	Zimbabwe Harare Shona	4.4	230
Caucasian	Australia New South Wales Caucasian	4.9	134
Caucasian	Austria	0.8	200
Caucasian	Azores Terceira Island	1.2	130
Caucasian	Croatia	1.3	150
Caucasian	Czech Republic	1.4	106
Caucasian	England North West	0.5	298
Caucasian	France Corsica Island	4.5	100
Caucasian	France Southeast	1.6	130
Caucasian	Georgia Tibilisi	1.4	109
Caucasian	Germany pop 6	0.81	8862
Caucasian	Ireland Northern, Caucasian	0.3	1000
Caucasian	Ireland South, Caucasian	0.4	250
Caucasian	Italy Sardinia pop3	6.4	100
Caucasian	Macedonia pop 4	0.9	216

Caucasian	Madeira	1.6	185
Caucasian	Poland	1	200
Caucasian	Poland DKMS	0.65	20653
Caucasian	Romania	1.3	348
Caucasian	Serbia pop 2	0.5	102
Caucasian	Spain Gipuzkoa Basque	0	100
Caucasian	USA Caucasian Bethesda	0	307
Caucasian	USA Caucasian pop 2	1.1	265
Caucasian	USA Caucasian pop 4	1.02	1070
Caucasian	USA Eastern European	0.8	558
Caucasian	USA European American pop 2	0.9	1245
Caucasian	USA Philadelphia Caucasian	1.9	141
Caucasian	USA San Antonio Caucasian	0.3	222
Caucasian	Wales, Caucasian	0.5	1798
Hispanic or Latino	Guatemala Mayan	0.7	132
Hispanic or Latino	Mexico Guadalajara Mestizo pop 2	1	103
Hispanic or Latino	Mexico Oaxaca Mixtec	0	103
Hispanic or Latino	USA Hispanic	1.1	234
Hispanic or Latino	USA Hispanic pop 2	1.45	1999
Hispanic or Latino	USA Mexican American Mestizo	0.9	553
Hispanic or Latino	USA South Texas Hispanic	0.4	194
Middle Eastern	Iran Baloch	4	100
Middle Eastern	Israel Arab Druze	1.5	101
Middle Eastern	Jordan Amman	1.4	146
Middle Eastern	Oman	6.8	118
Middle Eastern	Saudi Arabia Guraiat and Hail	4.6	213
Middle Eastern	Tunisia	4	100
Middle Eastern	Tunisia pop 3	3.4	104
Other	Australia Cape York Peninsula Aborigine	1	103
Other	Australia Yuendumu Aborigine	0	191
Other	Israel Ashkenazi and Non Ashkenazi Jews	3.2	146
Other	USA North American Native	0.8	187
Other	USA Alaska Yupik	0	252

All frequency data was extracted from http://www.allelefrequencies.net/

Allele frequency net: a database and online repository for immune gene frequencies in worldwide populations(14).

Supplementary Table S3: Available Testing Options

Test site	Method
Immunogenetics laboratory, Puget Sound Blood Center, Washington USA http://www.psbc.org/lab_immunogenetics/test25.htm	sequence specific priming PCR
UMass Memorial Medical Center, Clinical Laboratories, Massachusetts, USA http://www.umassmemoriallabs.org/lab-services/histocompatibility-hla	
Transplant Immunology and Histocompatibility Laboratories UT Southwestern Medical Center, Texas, USA http://www.utsouthwestern.edu/utsw/cda/dept131762/files/487379.html	high resolution sequence based typing
Immco, Buffalo, New York, USA and Burlington, Ontario, Canada www.immcodiagnostics.com	
Pharmigene, Inc., Taipai, Taiwan and California, USA http://www.pharmigene.com/genetic_tests/genetic_tests_Allopurinol.htm	RT-PCR & SYBR Green based detection method

Supplemental Table S4

Evidence Linking Genotype with Phenotype

Type of Experimental Model (in vitro, in vivo preclinical, or clinical)	Major Findings	References	Level of Evidence
Clinical	Presence of HLA-B*5801 is predictive of	Hung et al(2),	High

clinically diagnosed allopurinol SCAR	Kaniwa et al.(3), Kang et al.(4), Lonjou et al(5), Tassaneeyakul et al.(6), Tohkin et al.(10)

(1) Somkrua, R., Eickman, E.E., Saokaew, S., Lohitnavy, M. & Chaiyakunapruk, N. Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *BMC medical genetics* **12**, 118 (2011).

(2) Hung, S.I. *et al.* HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci U S A* **102**, 4134-9 (2005).

(3) Kaniwa, N. *et al.* HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis. *Pharmacogenomics* **9**, 1617-22 (2008).

(4) Kang, H.R. *et al.* Positive and negative associations of HLA class I alleles with allopurinol-induced SCARs in Koreans. *Pharmacogenet Genomics* **21**, 303-7 (2011).

(5) Lonjou, C. *et al.* A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet Genomics* **18**, 99-107 (2008).

(6) Tassaneeyakul, W. *et al.* Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. *Pharmacogenet Genomics* **19**, 704-9 (2009).

(7) Jung, J.W. *et al.* HLA-B58 can help the clinical decision on starting allopurinol in patients with chronic renal insufficiency. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* **26**, 3567-72 (2011).

(8) Cristallo, A.F. *et al.* A study of HLA class I and class II 4-digit allele level in Stevens-Johnson syndrome and toxic epidermal necrolysis. *International journal of immunogenetics* **38**, 303-9 (2011).

(9) Genin, E. *et al.* Genome-wide association study of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Europe. *Orphanet journal of rare diseases* **6**, 52 (2011).

(10) Tohkin, M. *et al.* A whole-genome association study of major determinants for allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients. *Pharmacogenomics J*, (2011).

(11) Martin, M.A., Klein, T.E., Dong, B.J., Pirmohamed, M., Haas, D.W. & Kroetz, D.L. Clinical pharmacogenetics implementation consortium guidelines for hla-B genotype and abacavir dosing. *Clinical pharmacology and therapeutics* **91**, 734-8 (2012).

(12) Relling, M.V. & Klein, T.E. CPIC: Clinical Pharmacogenetics Implementation

Consortium of the Pharmacogenomics Research Network. *Clinical pharmacology and therapeutics* **89**, 464-7 (2011).

(13) Valdes, R., Payne, D.A. & Linder, M.W. . Laboratory analysis and application of pharmacogenetics to clinical practice. *The National Academy of Clinical Biochemistry (NACB) - Laboratory Medicine Practice Guidelines* 2010.

(14) Gonzalez-Galarza, F.F., Christmas, S., Middleton, D. & Jones, A.R. Allele frequency net: a database and online repository for immune gene frequencies in worldwide populations. *Nucleic acids research* **39**, D913-9 (2011).