Drugs That Cause Hypersensitivity Reactions:

*Personalising Medicine & Predicting the Unpredictable*

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Perth, Western Australia

AVOIDING CATASTROPHIC DRUG TOXICITIES: AACC July 22, 2009
Genetics & Adverse Drug Reactions

“If it were not for the great variability among individuals, medicine might as well be a science and not an art”

Sir William Osler, 1892
Personalizing Medicine = defining optimal diagnostic, management & treatment strategies for the individual patient

**Pharmacogenetics**
- specific tests to prevent toxicity (e.g., HLA-B*5701 screening for abacavir hypersensitivity)
- guide dosing of drugs
- HLA and other immune markers to guide vaccine development and predict response

**Pharmacoeecology**
- individualizing the patient’s environment to optimize therapeutic outcome
- PK/PD interactions with drugs, herbal medicines and nutritional supplements
- food effects on drugs (absorption/bioavailability)
- adherence (cultural & socioeconomic influences)
- intercurrent disease of host state (e.g., organ failure, pregnancy)
- diurnal variation in pharmacokinetics/dynamics
- individual drug taking behaviour

**Personalized Prescription**

*Phillips E, Mallal S* Personalized Medicine 2009, 6(4), 393-408
Goals

- Define drug hypersensitivity reactions by epidemiological and immunological classifications and how these fit into broader context of adverse drug reactions
- Discuss new insights into the pharmacogenetics of drug hypersensitivity reactions
- Discuss clinical applications of pharmacogenetics to prevent drug hypersensitivity and the associated hurdles
### Characteristics of Drug Reactions

<table>
<thead>
<tr>
<th>Classification</th>
<th>TYPE A = Pharmacological</th>
<th>TYPE B = “Bizarre”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictable</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Dose Dependent</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Host Dependent</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Host Dependent (Genetic factors)</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Immunologic basis</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Examples</td>
<td>Gastrointestinal intolerance, seizures with penicillin etc</td>
<td>Allergic and idiosyncratic syndromes, hypersensitivity syndromes</td>
</tr>
</tbody>
</table>
Classification of ADRs

Drug Reaction

Predictable Reactions (dose dependent)

Unpredictable Reactions (less dose dependent)

Clinical Syndromes
- Reactive Metabolite Syndromes (e.g., Drug Hypersensitivity Syndrome)
  - Drug Hypersensitivity Syndrome
  - Hepatitis
  - SJS/TEN

Gell Coombs
- Type I
- Type II
- Type III
- Type IVa-d

“IDIOSYNCRATIC”

Pseudoallergic
- ASA
- Vancomycin
- Contrast
TYPE B REACTIONS: Associated Drugs

- **Anticonvulsants**
  - phenytoin, phenobarbital, carbamazepine
  - lamotrigine

- **Antimicrobials**
  - sulfonamides (sulfa antimicrobials), penicillins, dapsone
  - nitrofurantoin, minocycline, metronidazole

- **Allopurinol**

- **Antiinflammatories** (eg oxicam-NSAIDS, Valdecoxivib)

- **Antiretrovirals**

- **Alternative medicines**
  - Chinese herbals etc.

- **Antineoplastics**

- **mAbs**
  - “Ximab” (infliximab, rituximab) > “Zumab” (omalizumab) > “Mumab” (adalimumab)
Pharmacogenetics

Drug → Disease → Gene

**TYPE A**

**Dose Dependent Disease**

- Drug Efficacy or toxicity
- Often multifactorial (e.g., age, gender, BMI, concurrent medications)
- Often related to polymorphism(s) in drug metabolizing enzymes (e.g., CYP) or pharmacodynamic factors
- e.g., Warfarin, efavirenz, clopidogrel

**TYPE B**

**Dose Independent Disease**

- HLA & Drug Hypersensitivity

1. **abacavir hypersensitivity** (HLA-B*5701)
2. carbamazepine SJS/TEN (HLA-B*1502)
   - phenytoin SJS/TEN (HLA-B*1502)
3. allopurinol SJS/TEN/HSR (HLA-B*5801)
4. ximelagatran hepatotoxicity (HLA-DRB1*07; DQA1*02)
5. nevirapine rash and rash associated hepatitis (class I (HLA-DRB1*0101 + CD4+, HLA-B*1402, HLA-Cw8, HLA-B*3505))
6. Flucloxacillin cholestatic liver disease (HLA-B*5701)

   - Locharenkul et al. Epilepsia 2008;49:2087-91
4. Kindmark et al. Pharmacogenomics J 2008;8:186-95
6. Daly et al. Nature Genetics. Published online May 31, 2009
Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir

S. Mallal, D Nolan, C Witt, G Masel, A M Martin, C Moore, D Sayer, A Caskey, C Mamotte, D Maxwell, F James, F T Christiansen

Summary

Background The use of abacavir—a potent HIV-1 nucleoside-analogue reverse-transcriptase inhibitor—is complicated by a potentially life-threatening hypersensitivity syndrome in about 6% of cases. Genetic factors influencing the immune response to abacavir might confer susceptibility. We aimed to find associations between MHC alleles and abacavir hypersensitivity.

Interpretation Genetic susceptibility to abacavir hypersensitivity is carried on the 57:1 ancestral haplotype. In our population, withholding abacavir in those with HLA-B*5701, HLA-DR7, and HLA-DQ3 should reduce the prevalence of hypersensitivity from 9% to 2.5% without inappropriately denying abacavir to any patient.

Lancet 2002; 359: 727–32

Lancet March 2, 2002

Genetic variations in HLA-B region and hypersensitivity reactions to abacavir

Seth Hethington, Avana R Hughes, Michael Moutafier, Denise Shortto, Katherine L Baker, My basename Sneath, Eric Lai, Krista Davies, Aligal Handley, David J Cow, Mary E Ring, Michael Strout, Chris Bowman, Linda Tournoud, Allan D Roses

Hypersensitivity to abacavir affects about 4% of patients who receive the drug for HIV-1 infection. We did a retrospective, case-control study to identify multiple markers in the vicinity of HLA-B associated with abacavir hypersensitivity. Abacavir hypersensitivity occurred more frequently among patients than controls by Fisher’s exact test. These included HLA-B57 (39 [46%] of 84 vs. five of 118 [4%]; odds ratio 23.6 [95% CI 3.0, 183.0]).

Lancet March 30, 2002
A marker for Stevens–Johnson syndrome

Stevens–Johnson syndrome and the related disease toxic epidermal necrolysis are life-threatening reactions of the skin to particular types of medication\(^1\text{-}^3\). Here we show that there is a strong association in Han Chinese between a genetic marker, the human leukocyte antigen HLA–B*1502, and Stevens–Johnson syndrome induced by carbamazepine, a drug commonly prescribed for the treatment of seizures. It should be possi-

Table 1 Frequency of HLA alleles in patients with Stevens–Johnson syndrome

<table>
<thead>
<tr>
<th>HLA allele</th>
<th>CBZ-SJS</th>
<th>CBZ-tolerant</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>B*1502</td>
<td>44 (100%)</td>
<td>3 (3%)*</td>
<td>5 (8.6%)†</td>
</tr>
<tr>
<td>Cw*0801</td>
<td>41 (83.2%)</td>
<td>17 (16.8%)</td>
<td>13 (14%)</td>
</tr>
<tr>
<td>A*1101</td>
<td>26 (51.8%)</td>
<td>51 (50.6%)</td>
<td>53 (57%)</td>
</tr>
<tr>
<td>DRB1*1202</td>
<td>33 (75%)</td>
<td>12 (11.9%)</td>
<td>18 (19.4%)</td>
</tr>
<tr>
<td>B<em>1502, Cw</em>0801</td>
<td>41 (83.2%)</td>
<td>3 (3%)*</td>
<td>7 (7.6%)</td>
</tr>
<tr>
<td>B<em>1502, A</em>1101</td>
<td>26 (51.8%)</td>
<td>2 (2%)</td>
<td>6 (6.5%)</td>
</tr>
<tr>
<td>B<em>1502, DRB1</em>1202</td>
<td>33 (75%)</td>
<td>1 (1%)</td>
<td>5 (5.4%)</td>
</tr>
<tr>
<td>B<em>1502, Cw</em>0801, A<em>1101, DRB1</em>1202</td>
<td>23 (66%)</td>
<td>0 (0%)</td>
<td>3 (3.2%)</td>
</tr>
</tbody>
</table>

Frequencies (by number and percentage) of individual or combined loci of the B*1502 ancestral haplotype are shown in patients with carbamazepine-induced Stevens–Johnson syndrome (CBZ-SJS; n = 44), and in carbamazepine-tolerant (n = 101) and normal subjects (n = 93). For methods, see supplementary information.

*Odds ratio (CBZ-SJS/CBZ-tolerant; 2.504 95% CI, 1.264–4.922); corrected P value, P = 3.13x10^-2.
†Odds ratio (CBZ-SJS/normal; 8.95 95% CI, 6.09–12.36); P = 1.39x10^-2.
WARNING
SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE

SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH TEGRRETOL. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH TEGRRETOL. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH TEGRRETOL UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE WARNINGS AND PRECAUTIONS/LABORATORY TESTS).

- HLA-B*1502 prevalent in Han Chinese (10-15%) vs Caucasians (<0.1%)
- Not predictive for development of carbamazepine SJS/TEN in Caucasian population*

*Alfirevic et al Pharmacogenomics 2006;7:813
*Clinical cross-reactivity occurs in approximately 70-80%*
March 15, 2005 (4134-9)

**HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol**

Shuen-Iu Hung^ab, Wen-Hung Chung^abc,d, Lieh-Bang Liou^e, Chen-Chung Chu^f, Marie Lin^g, Hsien-Ping Huang^h, Yen-Ling Lin^i, Joung-Liang Lai^j, Li-Cheng Yang^k, Hong-Shang Hong^l, Ming-Jing Chen^m, Ping-Chin Lai^n, Mai-Szu Wu^o, Chia-Yu Chu^p, Kuo-Hsiung Wangl, Chien-Hsiun Chen^q, Cathy S. J. Fann^r, Der-Yuan Wu^b, and Yuan-Tsong Chen^t

^aInstitute of Biomedical Sciences, Academia Sinica, Taipei 11529, Taiwan; Departments of Dermatology, Rheumatology, Allergy, and Immunology, and Nephrology, Chang Gung Memorial Hospital, Taipei 11007, Taiwan; Department of Medical Research, Mackay Memorial Hospital, Taipei 11049, Taiwan. ^bDepartment of Immunology and Rheumatology, Taichung Veterans General Hospital, Taichung 40705, Taiwan; Departmennt of Dermatology, National Taiwan University Hospital, Taipei 10002, Taiwan; Department of Dermatology, Taipei Medical University Hospital, Taipei 11031, Taiwan. ^cDepartment of Dermatology, Taipei Medical University Hospital, Taipei 11031, Taiwan.

Table 3. Frequencies of individual or combined loci of HLA-B*5801 extended haplotype in patients with allopurinol-induced SCAR, allopurinol tolerant control, and general population control

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Allopurinol-SCAR (n = 51)</th>
<th>Tolerant control (n = 135)</th>
<th>Odds ratio</th>
<th>Pc value*</th>
<th>General population control (n = 93)</th>
<th>Odds ratio</th>
<th>Pc value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>B*5801</td>
<td>51 (100)</td>
<td>20 (15)</td>
<td>580.3</td>
<td>4.7 × 10⁻²⁴</td>
<td>19 (20)</td>
<td>393.5</td>
<td>8.1 × 10⁻¹⁶</td>
</tr>
<tr>
<td>Cw*0302</td>
<td>48 (94)</td>
<td>19 (14)</td>
<td>97.7</td>
<td>1.4 × 10⁻¹⁹</td>
<td>19 (20)</td>
<td>62.3</td>
<td>2.5 × 10⁻¹³</td>
</tr>
<tr>
<td>A*3303</td>
<td>34 (67)</td>
<td>24 (18)</td>
<td>9.3</td>
<td>2.2 × 10⁻⁴</td>
<td>20 (22)</td>
<td>7.3</td>
<td>4.7 × 10⁻²</td>
</tr>
<tr>
<td>DRB1*0301</td>
<td>33 (65)</td>
<td>17 (13)</td>
<td>12.7</td>
<td>2.8 × 10⁻⁶</td>
<td>14 (15)</td>
<td>10.3</td>
<td>8.5 × 10⁻⁴</td>
</tr>
<tr>
<td>B<em>5801, Cw</em>0302</td>
<td>48 (94)</td>
<td>19 (14)</td>
<td>97.7</td>
<td>1.4 × 10⁻¹⁹</td>
<td>19 (20)</td>
<td>62.3</td>
<td>2.6 × 10⁻¹³</td>
</tr>
<tr>
<td>B<em>5801, Cw</em>0302, A*3303</td>
<td>34 (67)</td>
<td>17 (13)</td>
<td>13.9</td>
<td>5.4 × 10⁻⁷</td>
<td>16 (17)</td>
<td>9.6</td>
<td>1.7 × 10⁻³</td>
</tr>
<tr>
<td>B<em>5801, Cw</em>0302, DRB1*0301</td>
<td>30 (59)</td>
<td>11 (8)</td>
<td>16.1</td>
<td>7.4 × 10⁻⁷</td>
<td>10 (11)</td>
<td>11.9</td>
<td>7.8 × 10⁻⁴</td>
</tr>
<tr>
<td>B<em>5801, Cw</em>0302, A<em>3303, DRB1</em>0301</td>
<td>21 (41)</td>
<td>9 (7)</td>
<td>9.8</td>
<td>0.039</td>
<td>9 (10)</td>
<td>6.5</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate percentage.

*The Pc values were adjusted by using Bonferroni’s correction for multiple comparisons to account for the observed alleles.

-HLA-B*5801 present in 9-11% Han Chinese but also present in other races (Caucasian 1-6%; African 2-4%; Japanese <0.4%)

-Some studies suggest some generalizability across European and Japanese populations
Strong association but only small proportion of HLA-B*5701 positive patients will develop flucloxacillin DILI

-Extremely low positive predictive value (1.26%) therefore assuming Caucasian population carriage rate of HLA-B*5701 of 6-8% would need to screen over 1000 patients to prevent one case

-Other factors (off chromosome 6) may be important (ST6GAL1 which encodes sialic acid transfer enzyme)

### Table 1 Distribution of HLA-B*5701 genotypes

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
<th>P value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n = 64)</td>
<td>4 (6.3)</td>
<td>60 (93.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases (n = 51)</td>
<td>43 (84.3)</td>
<td>8 (15.7)</td>
<td>8.97 × 10⁻¹⁹</td>
<td>80.6 (22.8–284.9)</td>
</tr>
<tr>
<td>Replication cases (n = 23)</td>
<td>20 (87.0)</td>
<td>3 (13.0)</td>
<td>6.62 × 10⁻¹³</td>
<td>100.0 (20.6–485.8)</td>
</tr>
</tbody>
</table>

Replication cases were those exposed to co-amoxiclav concurrently with flucloxacillin (n = 7) and flucloxacillin DILI cases recruited after the GWA study (n = 16). Percentages are shown in parentheses. P values are uncorrected.
Associations may differ across race, phenotype, study design and underlying immune status

• HLA-DRB1*0101 + CD4% > 25 and rash associated hepatitis (Martin et al AIDS 2005)
• HLA-Cw8-B14 haplotype in Sardinians (Littera et al AIDS 2006)
• HLA-Cw8 in Japanese (Gatanaga et al AIDS 2007)
• HLA-DRB1*01 in French population with efavirenz or nevirapine rash

**HLA-B*3505 allele is a strong predictor for nevirapine-induced skin adverse drug reactions in HIV-infected Thai patients**
Soranun Chantarangsuan, Taisei Mushiroda, Surakameth Mahasirimongkol, Sasisopin Kiertiburanakul, Sornuek Sungkanuparp, Weerawat Manosuthi, Woraphot Tantisiriwat, Angkana Charoenyingwattana, Thanyachai Sura, Wasun Chantratita and Yusuke Nakamura
Pharmacogenetics & Genomics 2009
NEVIRAPINE HYPERSENSITIVITY
(rash of varying severity, fever, hepatitis, multisystem disease)

Genetic susceptibility conferred by Class I MHC marker(s) eg. HLA-B*1402, HLA-Cw8, HLA-B*3505

Genetic susceptibility conferred by Class II MHC marker(s) eg. HLA-DRB1*0101
+ Sufficient levels of CD4+ T cells

Sufficient levels of relevant metabolite
(distinct from dose dependent or “Type A” adverse drug reactions)

- Nevirapine disposition (?Role of CYP3A4/CYP2B6/CYP2C9) and drug transporters (P-glycoprotein(MDR1)) and polymorphisms in drug metabolizing and drug transporter genes that differ across ethnicity

Phillips E, Mallal S. Current Opinion in Molecular Therapeutics 2009; 11(3);231-242
Host-Drug-Infection Interactions: A Complex Dynamic

**HOST**
- HLA
- Immune response genes
- Control of infection
- Vaccine design

**PATHOGEN**
- Chronic persistent DNA viruses (CMV, EBV, HHV-6, Herpes viruses) and/or HIV

**DRUG**
- Pharmacodynamics
- Pharmacokinetics
- Drug Efficacy
- Drug Toxicity

**Drug resistance**
- Drug Efficacy
Classic 3 ring Target – HSV not drug

Atypical Target – 2 ring dusky center

Mucositis & Atypical target

Blistering of TEN
HLA-B*1502 & Carbamazepine: Phenotype is Important

Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

- associated with severe skin syndromes (SJS/TEN in Han Chinese)
- NOT associated with drug hypersensitivity (fever/rash/internal organ involvement) or disease in Caucasians
Drug Hypersensitivity & HLA: Immunogenetic Models

Carbamazepine

- Class I MHC
  - HLA-B*1502
  - CD8+
- Specific for disease (SJS/TEN) & Race (Han Chinese)

Nevirapine

- Class I MHC
  - CD8+
- Metabolic differences between race driving differences in phenotype

Abacavir

- Class I MHC
  - HLA-B*5701
  - CD8+
- Specific for disease, generalizable across race
Prerequisites for Widespread Incorporation of HLA Pharmacogenetic Testing

Implications differ according to drug...
<table>
<thead>
<tr>
<th>Prerequisites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
</tr>
<tr>
<td>• HLA allele is strongly associated with the toxicity, and the negative predictive value of the test is high*</td>
</tr>
<tr>
<td>• The number of patients needed for testing to prevent a case of toxicity is low*</td>
</tr>
<tr>
<td>• HLA allele is prevalent in a large, non-disenfranchised population*</td>
</tr>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>• Drug exhibits favorable attributes, such as good efficacy, convenience in dosing and administration, tolerability and pill burden*</td>
</tr>
<tr>
<td>• Alternative drug(s) that do not require pharmacogenetic testing are either absent or have negative attributes*</td>
</tr>
<tr>
<td>Drug toxicity</td>
</tr>
<tr>
<td>• Toxicity is severe and persistent* (ie, not isolated mild rash)</td>
</tr>
<tr>
<td>• Toxicity is readily and accurately phenotyped*</td>
</tr>
<tr>
<td>• An adjunctive diagnostic test, such as skin patch testing, can improve phenotypic precision</td>
</tr>
<tr>
<td>Environment</td>
</tr>
<tr>
<td>• Champions available (eg, clinical academics, industry [if drug not off patent*], professional bodies, regulatory agencies, guideline committees, patient advocacy groups, laboratory providers and the media), willing and able to drive pharmacogenetic test development and implementation</td>
</tr>
<tr>
<td>Generation of high-level evidence</td>
</tr>
<tr>
<td>• Case-control studies with estimated predictive values based on the assumed prevalence of the HLA allele</td>
</tr>
<tr>
<td>• Population-based cohort studies with directly calculated predictive values of the test</td>
</tr>
<tr>
<td>• Open screening studies</td>
</tr>
<tr>
<td>• Supportive experimental data</td>
</tr>
<tr>
<td>• Blinded randomized controlled trials</td>
</tr>
<tr>
<td>• Evidence across ethnic groups and geographical areas to determine the clinical settings that the test may be applied to</td>
</tr>
<tr>
<td>• Cost-effectiveness data</td>
</tr>
<tr>
<td>Development and availability of appropriate laboratory support</td>
</tr>
<tr>
<td>• No patent restriction on use of the test</td>
</tr>
<tr>
<td>• Development of simple, inexpensive, robust, unambiguous laboratory tests</td>
</tr>
<tr>
<td>• Rapid and simple report and interpretation</td>
</tr>
<tr>
<td>• Development of reagents (eg, mAbs, PCR-based kits)</td>
</tr>
<tr>
<td>• Global distribution and commercialization of allele-specific test</td>
</tr>
<tr>
<td>• Allele-specific quality assurance targeted to avoid false-negative results and consequent morbidity or mortality</td>
</tr>
<tr>
<td>• Reimbursement of test</td>
</tr>
<tr>
<td>Design and implementation of appropriate clinical systems</td>
</tr>
<tr>
<td>• Education of clinicians, nurses, pharmacists, phlebotomists and patients</td>
</tr>
<tr>
<td>• Systems to ensure appropriate and routine triggering of ordering of the test</td>
</tr>
<tr>
<td>• Systems in the clinic to ensure the correct blood samples are sent to the correct laboratory for analysis</td>
</tr>
<tr>
<td>• Systems to ensure test results and correct interpretation is rapidly transmitted to, retained by and acted on by the healthcare team and patient</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug/HLA association</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC</td>
</tr>
<tr>
<td>ABC</td>
</tr>
<tr>
<td>CBZ</td>
</tr>
<tr>
<td>ALL</td>
</tr>
<tr>
<td>NEV</td>
</tr>
</tbody>
</table>

Phillips E, Mallal S, Current Opinion in Molecular Therapeutics 2009;11:231-42
Translating Research in Genomic Medicine into the Clinic & Beyond

- **STEP 1** – The discovery & turning this into a health application
  - 2002 – HLA-B*5701 association in two independent groups
  - Imprecision of clinical phenotype (false positive clinical diagnosis) cast doubt on generalizability of HLA-B*5701 to “all” abacavir HSR. Patch testing developed to identify those with true immunologically medicated HSR

- **STEP 2** - Development of high level clinical evidence (randomized) in support of test. Basic science to support biological plausibility
  - 2002-present: genetic and cellular studies support plausibility of association
  - 2005-2008 – PREDICT-1, SHAPE & observational studies provide robust clinical evidence

- **STEP 3** - Diffusion of research and delivery to clinic depends on efficiency and quality assurance of laboratory testing and reporting
  - 2005 - PCR-based techniques readily applicable methodology (rapid, inexpensive)
  - 2005-2008 - HLA-B*5701 quality assurance program roll-out
  - 2008 – HIV Treatment guidelines/product information change to incorporate recommendation for baseline testing & reimbursement

- **STEP 4** – Evaluating performance of the test in real clinical practice
  - 2008 + - Multiple observational studies Pharmacoeconomic evaluation
  - Post “PREDICT-1” clinical quality assurance

Phillips E, Mallal S  Personalized Medicine 2009;6:393-408
Predicting Drug Hypersensitivity in Clinical Practice: The Abacavir Example

- Guanosine nucleoside analogue used in antiretroviral therapy, approved by regulatory agencies 1998/1999
- Hypersensitivity syndrome characterized by fever, malaise +/- skin rash was characterized in pre-marketing phase, not fatal unless drug reintroduced; affected approximately 6-8% of predominantly Caucasian population
- Robust clinical management program for drug
- Early clues such as familial case reports and rarity in Blacks suggested genetic association
- 2002 – two independent groups reported strong association with HLA-B*5701
- 2008 – screening for hypersensitivity has rolled out into much of developed world
## HLA-B*5701 and Abacavir Hypersensitivity: A Comparison of Two Studies

### Mallal et al, 2002

<table>
<thead>
<tr>
<th>HSR</th>
<th>Pos PV</th>
<th>Neg PV</th>
<th>Sens</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSR</td>
<td>14</td>
<td>4</td>
<td>78%</td>
<td>97%</td>
</tr>
<tr>
<td>No HSR</td>
<td>5</td>
<td>177</td>
<td>74%</td>
<td>98%</td>
</tr>
</tbody>
</table>

### Hetherington et al, 2002*

<table>
<thead>
<tr>
<th>HSR</th>
<th>Pos PV</th>
<th>Neg PV</th>
<th>Sens</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSR</td>
<td>36</td>
<td>29</td>
<td>55%</td>
<td>99%</td>
</tr>
<tr>
<td>No HSR</td>
<td>8</td>
<td>649</td>
<td>82%</td>
<td>96%</td>
</tr>
</tbody>
</table>

*Caucasians only

Observed sensitivity and specificity
PV assumes prevalence of ~9%


Early Problems with “Phenotype”

• Early studies have observed variable sensitivity of *HLA-B*5701

- Definition of abacavir hypersensitivity reaction (ABC HSR)
- Nonspecificity of clinical phenotyping → false positive clinical diagnosis
- Differences in white and nonwhite races

Mallal et al. Lancet 2002
Hughes et al. Pharmacogenomics 2004

![Bar chart showing sensitivity of HLA-B*5701](chart.png)
## Phenotypic Uncertainty of Abacavir HSR

<table>
<thead>
<tr>
<th>Blinded Study</th>
<th>Abacavir Groups</th>
<th>Zidovudine or indinavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNA3005</td>
<td>19/268 (7%)</td>
<td>6/265 (2%)</td>
</tr>
<tr>
<td>CNA30024</td>
<td>27/324 (8%)</td>
<td>10/325 (3%)</td>
</tr>
<tr>
<td>Total Cases</td>
<td>46/592 (7.8%)</td>
<td>16/590 (2.7%)</td>
</tr>
</tbody>
</table>

Cases in CNA30024 as reported by Investigators in the ABC HSR CRF Module

Patch Testing Following Abacavir (ABC) Exposure

**Presentation by epidermal Langerhans cells**

**Local Reaction**

Prior ABC ingestion

Sensitization

CD8+

Day 0

**Alcohol dehydrogenase**

(Abacavir)

CYP450

ABC → Reactive Metabolite (Antigen)

Conjugation with host protein in skin

Presentation by epidermal Langerhans cells

>6 weeks later

Abacavir Skin Patch Testing

Patch testing

Previously assigned cases
- Carriers of 57.1 AH markers: 9/9
- Non-57.1 carriers (NNRTI+): 0/3
- Non-57.1 carriers (NNRTI-): 1 patient unavailable

Previously assigned tolerant
- Carriers of 57.1 AH markers: 0/5

3 previously assigned cases had diagnosis revised:
(1) Concurrent NNRTI therapy
(2) Negative patch test

**HLA-B*5701 and Abacavir Hypersensitivity**

Reclassified first 200 patients (*not available)

<table>
<thead>
<tr>
<th>HLA-B*5701</th>
<th>Pos</th>
<th>Neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSR</td>
<td>15</td>
<td>1*</td>
</tr>
<tr>
<td>No HSR</td>
<td>4</td>
<td>180</td>
</tr>
</tbody>
</table>

Sens 93.8%
Spec 97.8%

<table>
<thead>
<tr>
<th>Pos PV</th>
<th>Neg PV</th>
</tr>
</thead>
<tbody>
<tr>
<td>78.9%</td>
<td>99.4%</td>
</tr>
</tbody>
</table>

Patch Testing

- Useful for abacavir to phenotype patients with true immunologically mediated abacavir hypersensitivity
- NOT a predictive test: patients need previous systemic exposure to abacavir
- Diagnostic sensitivity (from PREDICT-1) = 87%
- Useful in practice to identify novel HLA allele associated abacavir hypersensitivity but NOT to rechallenge patients with clinical history consistent with abacavir hypersensitivity
- Sensitivity in other drug hypersensitivities (eg carbamazepine) appears much lower (50% or less)
- Positive in 30-50% of other drug associated disease (eg fixed drug eruption, acute generalized exanthematous pustulosis)

Shear et al. AIDS 2008;22:999-1007
Incorporation of a Pharmacogenetic Test into Clinical Practice

- High level evidence generalisable to diverse clinical settings
- Widespread availability of cost-effective and reliable laboratory tests
- Effective strategies to operationalise testing into routine clinical practice
Fall in Early Discontinuation of Abacavir after Introduction of Prospective Genetic Screening*


* p<.05

- HLA-B*5701

Screening eliminated true and false positive abacavir hypersensitivity

BUT NEED TO HAVE GOOD COMMUNICATION BETWEEN HEALTHCARE TEAM AND CHECK HLA-B*5701 RESULTS PRIOR TO STARTING ABACAVIR!!!!!
*Trottier et al. abacavir early discontinuation decreased from 13.6% to 5.6% after screening, IAS 2007, abstract MOPEB002)

+HLA-B*5701 + HSR from 12.2% to 0% (Zucman et al. JAIDS 2007; epub March 8)

^ABC HSR 6.5% historically to 0% post screening (Reeves et al. HIV Medicine March 2006)
*All 4/725 (0.8%) patients in ARIES study clinical diagnosed with HSR were patch test negative

• First RCT to look at clinical utility of a pharmacogenetic test to prevent a specific drug toxicity

• Problem of false positive clinical diagnosis of abacavir hypersensitivity was overcome by using strategy of skin patch testing (100% specific) to define the phenotype of true immunologically mediated abacavir hypersensitivity
Prospective, randomized (1:1), double-blind, multicenter study with 6-week observation period (>90% of HSR cases)

CONTROL

ABC-naive subjects (n=1956)

No screening (n=976)

1:1 Randomization

ABC was the only required drug for this study; Remainder of regimen was investigator-selected

Patients start ABC (n=913); Samples tested for HLA-B*5701 at the end of the study

If HSR occurs, undergo patch test 6-8 weeks after event

SCREENING

Samples tested for HLA-B*5701 in real time (n=980)

Only HLA-B*5701- subjects start ABC (n=859)

HLA-B*5701+ subjects excluded from study (n=54)

Clinically Suspected and Immunologically Confirmed HSR in ITT evaluable population

Clinically Suspected HSR:
- 7.8% (66/847)
- OR 0.40 (0.25, 0.62)
- P < 0.0001

Immunologically Confirmed HSR:
- 3.4% (27/803)
- OR 0.03 (0, 0.18)
- P < 0.0001

Control arm:
- 0.0% (0/802)
- OR 0.03 (0, 0.18)
- P < 0.0001

Prospective HLA-B*5701 screening arm:
- 2.7% (23/842)

Clinically Suspected and Immunologically Confirmed HSR:
- 0.0% (0/802)
Abacavir Exposed >6 weeks
100%

Clinically suspected HSR 7.8%

Patch +ve
HSR 2.7%

HLA-B*5701 +ve
‘True’ HSR (3.1%)

HLA-B*5701 +ve
ABC Tolerant (2.6%)

Phillips E, Mallal S
Personalized Medicine
2009, 6(4), 393-408

**HLA-B*5701 Carriage Frequency**

- **INDIA** 5-20%
- **UK** ~8%
- **MIDDLE EAST** 1-2% (NB 5-7% Ashkenazi Jews)
- **AUSTRALIA** ~8%
- **US Caucasian** ~8%
- **US Asian** ~1%
- **US African-American** ~2.5%
- **US Hispanic** ~2%
- **S. AMERICAN Caucasian** 5-7%
- **W. EUROPE** 5-7%
- **MEDITERRANEAN** 1-2%
- **JAPAN** 0%
- **CHINA** 0% (NB 2.5% N.E. provinces)
- **THAILAND** 4-10%*
- **THAILAND B*57 carriage:**
  - Urban Bangkok 3.6%
  - Thai Dai Lue (NE Thai) ~11%
  - Southern Thai Muslim 3%
- **MEDITERRANEAN** 1-2%
- **S. AMERICAN Hispanic** ~2%
- **AFRICA** <1%

SHAPE Study Design

CASES

Black and White subjects with clinically-suspected ABC HSR (CS-HSR)

ABC skin patch test & HLA-B*5701

Positive

White: 130
Black: 69

Negative

White: 42
Black: 5

White: 85
Black: 63

CONTROLS

Black & White subjects enrolled in KLEAN, ALOHA, CNA30027, CNA30032

Identify ABC-tolerant subjects who provided PGx consent and sample

White: 202
Black: 206

HLA-B*5701 results available for all control subjects

High Negative Predictive Value of HLA-B*5701 Generalised Across Race

White:
- SPT-pos: 100% (n=42/42)
- Control: 96% (n=194/202)
- OR: White IC-HSR 1945 [110-34352]; CS-HSR 19[8-48]

Black:
- SPT-pos: 100% (n=5/5)
- Control: 99% (n=204/206)
- OR: Black IC-HSR 900 [30-21045]; CS-HSR 17[4-164]
Major Treatment Guidelines Revised to Reflect HLA-B*5701 Screening

<table>
<thead>
<tr>
<th>Preferred</th>
<th>NNRTI</th>
<th>EFV</th>
<th>ABC/3TC (for HLA-B*5701 negative patients) or TDF/FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>FPV/r BID</td>
<td>LPV/r BID</td>
<td>ATV/r</td>
</tr>
</tbody>
</table>

IAS Guidelines:  JAMA 2008;300(5):555-70
Pharmacogenetics and HLA: Predicting the Unpredictable?

- Type A reactions are predictable based on their pharmacological action therefore pharmacogenetic factors will only explain a proportion of the variability in drug response.
- Type B adverse drug reactions such as hypersensitivity reactions and severe skin syndromes are immunogenetically mediated.
- HLA associations are promising for prediction and hence prevention of these types of reactions but abacavir is currently the only drug where high level evidence exists and widespread screening has been implemented.
- Numerous clinical and laboratory hurdles must be overcome for successful integration of pharmacogenetic testing into a clinical setting.
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Campbell Witt  Richard Harrigan
Frank Christiansen  Andri Rauch
Rom Kreuger  Amalio Telenti
Susan Herrmann  Hansjakob Furrer
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