IMMUNOGENETICS AND PHARMACOGENOMICS OF ALLERGIC DISEASES

CLARA GORODEZKY

Head of the Dept. of Immunology & Immunogenetics, InDRE
Fundacion Comparte Vida, A.C.
Mexico City

XXII World Allergy Congress
Cancún, México
December 4-8, 2011
Allergic Diseases and Associated phenotypes are polygenic & multifactorial

NOT EVERYTHING IS GENETICS!!

1. All features result of the interaction between environment and host genetics

2. The relationship patient-physician is relevant

3. More than diseases, there are patients, each of them with their own way of responding vs. The same unchaining agent

Genetic control of the immune response
The development of these diseases represent an interaction between genetic and environmental processes, which may be influenced by age.
Role of T-CD4 cells in the immune response against allergens

Allergenic peptide

TH2

Mast cell

IgE

IL-4, IL-13

NK

IL-5

Eos.

Type I Hypersensitivity

Late phase response

B
Factors and Cells Involved in the Induction of Th2, Th1 & Th0 Cells

### APC
- MHC class II
- Soluble antigens
- Low dose
- Mucose
- Co-stimulation
- APCs

### IL-12
- CD45RA+
- Th1

### IFN-γ
- CD45R0+
- Th0

### IL-10
- PGE2
- Th0

### IL-4
- Th2

### Mast cell
- CD4+

### CD-4+ CD8+ TCRαβ

### NK

---

**Th1**
- IL-12
- IFN-γ

**Th0**
- IL-10
- PGE2
- IL-4

**Th2**
- IL-4
Approaches for Gene Discovery

**Candidate gene association studies**  (1970s-present)
- **Advantages:** Hypothesis-driven; easy to interpret; detects genes with modest effects
- **Disadvantages:** Limited to what we know; Cannot discover novel genes or pathways; Requires LD between markers and causal agents

**Genome-wide linkage studies**  (1980-1990s)
- **Advantages:** Genome-wide; Can discover novel genes & pathways; Requires relatively few genetic markers; Does not rely on LD; Can detect genes harboring rare risk variants
- **Disadvantages:** Requires families; Poor resolution; Low power to detect genes with modest effects

**Genome-wide association studies**  (2007-present)
- **Advantages:** Genome-wide; can discover novel genes & pathways; Excellent resolution; Can detect loci with modest effects
- **Disadvantages:** Requires dense marker typing & large sample sizes; Requires LD; Limited to common variants

**Re-sequencing in genes, exomes, or whole genomes**  (ongoing)
- **Advantages:** Reveals all variations
- **Disadvantages:** Costly; Large sample sizes; Computationally & analytically challenging; Difficult to interpret
The Human MHC : HLA
July, 2011

Total alleles = 6403
Proteins = 4174

Prof. Jean Dausset †,
June 6, 2009
SOME GENES INVOLVED IN THE EXPRESSION OF ALLERGIC DISEASES

Willian Cookson, Nature 402: 88, 1999
**Combined Results of Meta-Analyses of Asthma GWAS in European, African Caribbean & Latino Samples (EVE) & European Samples (Gabriel)**

<table>
<thead>
<tr>
<th>GENE/REGION</th>
<th>RACE/ETHNIC GROUPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>17q21(ORMDL3/GSDML)</td>
<td>All</td>
</tr>
<tr>
<td>IL1RL1/IL18R1 (chr. 2)</td>
<td>All</td>
</tr>
<tr>
<td>TSLP (chr. 5)</td>
<td>All</td>
</tr>
<tr>
<td>IL33 (chr 9)</td>
<td>All</td>
</tr>
<tr>
<td>SMAD3 (chr. 15)</td>
<td>Euro, Euro-Am,</td>
</tr>
<tr>
<td>RORA (chr. 15)</td>
<td>Euro, Euro-Am</td>
</tr>
<tr>
<td>HLA-DQ (chr. 6)</td>
<td>All</td>
</tr>
<tr>
<td>PYHINI (chr 1)</td>
<td>Afr-Am/Afr.Caribbb</td>
</tr>
<tr>
<td>IL2RB (chr. 22)</td>
<td>Euro</td>
</tr>
<tr>
<td>SLC22A5 (chr 5)</td>
<td>Euro</td>
</tr>
<tr>
<td>IL13 (chr 5)</td>
<td>Euro</td>
</tr>
</tbody>
</table>

Ober & Yao, 2011
# EPITOPES OF DIFFERENT ALLERGENS

<table>
<thead>
<tr>
<th>Antigens</th>
<th>Allergen</th>
<th>Size</th>
<th>T-cell Epitope</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dust</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Dermatophagoides pteronyssinus</em></td>
<td>Der p 1</td>
<td>24 kDa, 222 aa</td>
<td>45-6794-104, 117-143</td>
</tr>
<tr>
<td></td>
<td>Der p 1</td>
<td>110-119, 110-131</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Der p 1</td>
<td>1-4, 1-56, 15-94, 57-130</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(5 different)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Der p 2</td>
<td>15 kDa, 129 aa</td>
<td>1-15, 11-24, 20-33, 29-42</td>
</tr>
<tr>
<td><strong>Felis domesticus</strong></td>
<td>Fel d 1</td>
<td>17 kDa, 70+92 aa</td>
<td>39-52, 53-66</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9-21, 22-35, 57-70</td>
</tr>
<tr>
<td><strong>Seasonal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Betula verucosa</em></td>
<td>Bet vI</td>
<td>17 kDa,</td>
<td>159 aa</td>
</tr>
<tr>
<td>(4 different)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Lolium perene</em></td>
<td>Lol p 1</td>
<td>34 kDa, 240 aa</td>
<td></td>
</tr>
<tr>
<td>(4 different)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Phleum partense</em></td>
<td>Phl p 1</td>
<td>34 kDa, 240 aa</td>
<td></td>
</tr>
<tr>
<td><em>Poa pratensis</em></td>
<td>rKBG60</td>
<td>28 kDa, 268 aa</td>
<td></td>
</tr>
<tr>
<td><strong>Venoms (insects)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Apis mellifera</em></td>
<td>Api m 1(PLA₂)</td>
<td>19 kDa, 134 aa</td>
<td></td>
</tr>
<tr>
<td>Bee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Food</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Chicken</em></td>
<td>Ovalbumin</td>
<td>43 kDa, 385 aa</td>
<td></td>
</tr>
</tbody>
</table>

*van Nerven y col, Trends Immunol; 2007*
CHRISTALOGRAFIC STRUCTURE OF BETUL BIRCH POLLEN
Class II Molecule
<table>
<thead>
<tr>
<th>Allergen</th>
<th>Mol. Mass.</th>
<th>HLA</th>
<th>IgE+ (%)</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amb a 5</td>
<td>5</td>
<td>DR2</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>Lol p 2</td>
<td>11</td>
<td>DR3</td>
<td>47</td>
<td>5.3</td>
</tr>
<tr>
<td>Lol p 3</td>
<td>11</td>
<td>DR3</td>
<td>43</td>
<td>3.5</td>
</tr>
<tr>
<td>Lol p 3</td>
<td>11</td>
<td>DR3</td>
<td>57</td>
<td>18</td>
</tr>
<tr>
<td>Amb a 6</td>
<td>11.5</td>
<td>DR5</td>
<td>85</td>
<td>35</td>
</tr>
<tr>
<td>Amb a 6</td>
<td>11.5</td>
<td>DR5</td>
<td>40</td>
<td>23</td>
</tr>
<tr>
<td>Alt a 1</td>
<td>14</td>
<td>DR4</td>
<td>26</td>
<td>1.9</td>
</tr>
<tr>
<td>Der p 2</td>
<td>15</td>
<td>DR3</td>
<td>19</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Bet v 1</td>
<td>17</td>
<td>DR52</td>
<td>62</td>
<td>2.5</td>
</tr>
<tr>
<td>Bet v 1</td>
<td>17</td>
<td>DRB3*0101</td>
<td>51</td>
<td>2.5</td>
</tr>
<tr>
<td>Fel d 1</td>
<td>17</td>
<td>DR1</td>
<td>16</td>
<td>2.0</td>
</tr>
<tr>
<td>Der p 1</td>
<td>24</td>
<td>DR3</td>
<td>16</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Lol p 1</td>
<td>34</td>
<td>DR3</td>
<td>36</td>
<td>7.3</td>
</tr>
<tr>
<td>Lol p 1</td>
<td>34</td>
<td>DR3</td>
<td>33</td>
<td>3.1</td>
</tr>
</tbody>
</table>
Susceptibility is linked to a recessive gene that has a high penetrance (0.54).

Resistance is linked to a dominant HLA-DQ gene with a higher penetrance (0.778).

**Therapy Perspective**

Select the antigenic fractions of allergens that may induce IgE specific suppression.

```
**Ag** -> **TH2**

**IL-4**
**IL-5**
**IL-6**
**IL-13**

**B** -> **IgE**

**Specific IgE**

**DQ-Linked Is gene**

**IL-2/IFN-γ**

**B** -> **IgA (IL-5)**
**IgG (IL-4, 5, 6)**
**IgG (IL-4, 5)**
```
The common goal is to decrease Th2 responses that lead to allergic disease!
PHARMACOGENOMICS

PHARMACOLOGY

GENOMICS

[Images of various medical and scientific equipment and samples]
¿DO ALL INDIVIDUALS RESPOND THE SAME WAY TO DRUG TREATMENTS?

$Rx + ☻ = ☻$

$Rx + ☻ = ☻$

$Rx + ☻ = ☻$

?????
PHARMACOGENOMICS

Study and analysis of the individual genetic variability, related to:

- drug response
- drug design and development
- therapeutic design to achieve successful results in clinical assays
- more effective and less dangerous therapies for the patient
Pharmacogenetics Vs. Pharmacogenomics

Studies the influence of much or the entire genome on drug activity, identifying what drugs are effective in which patients.

Both terms are confounding in the day to day practice and are used indistinctly!!

Studies the influence of genetic factors on drug activity, identifying what drugs are effective in which patients.

Interaction of our Genes with the Environment
INDIVIDUAL RISK:

DRUG INEFFECTIVENESS/TOXICITY

GENES + ENVIRONMENTAL FACTORS INTERACTIONS

Gender, ethnicity, diet, nutrition, función organic function, drug interaction, tobacco, coffee & alcohol intake, concomitant diseases, disease severity

• GENETIC FACTORS

The most important are......

MHC, Receptor, Transport & other genes & drug metabolizing enzymes (DMEs)

(15 a 30%-95%)
INTER-INDIVIDUAL VARIATION TO DRUG RESPONSES

* Non efficacy of Treatment: 25-80%
Efficacy 51.5%


• Adverse Drug Reactions (ADR) USA (1994)

  6.7% hospitalization (2,216,000 patients)
  0.32% Fatal reactions (106,000 patients)
  4-6 Deaths

Lazarou et al. 1998; JAMA 279:1200
### Examples of Associations between Drug Response and Genetic Variants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Variable Clinical Effect</th>
<th>Genes with Associated Variants</th>
<th>Possible Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine and mercaptopurine</td>
<td>Bone marrow aplasia</td>
<td>TPMT</td>
<td>Hypofunctional alleles</td>
</tr>
<tr>
<td></td>
<td>Reduced therapeutic effect at standard doses</td>
<td></td>
<td>Wild-type alleles</td>
</tr>
<tr>
<td>Some antidepressants and β-blockers</td>
<td>Increased side effect risk</td>
<td>CYP2D6</td>
<td>Hypofunctional alleles</td>
</tr>
<tr>
<td></td>
<td>Decreased efficacy</td>
<td></td>
<td>Gene duplication</td>
</tr>
<tr>
<td>Omeprazole</td>
<td><em>Helicobacter pylori</em> cure rate</td>
<td>CYP2C19</td>
<td>Hypofunctional alleles</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Neutropenia</td>
<td>UGT1A1</td>
<td>Decreased expression due to regulatory polymorphism</td>
</tr>
<tr>
<td>HIV protease inhibitors</td>
<td>Central nervous system levels</td>
<td>MDR1</td>
<td>Altered P-glycoprotein function</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Blood pressure lowering and heart rate slowing</td>
<td>ADRB1</td>
<td>Altered receptor function or number</td>
</tr>
<tr>
<td>Inhaled β₂-agonists</td>
<td>Bronchodilation</td>
<td>ADRB2</td>
<td>Altered receptor function or number</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Blood pressure lowering</td>
<td>ADD1</td>
<td>Altered cytoskeletal function by adducin variants</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Anticoagulation</td>
<td>VKORC1</td>
<td>Variant haplotypes in regulatory regions leading to variable expression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP2C9</td>
<td>Coding region variants causing reduced S-warfarin clearance</td>
</tr>
<tr>
<td>Abacavir</td>
<td>Immunologic reactions</td>
<td>HLA variants</td>
<td>Altered immunologic responses</td>
</tr>
<tr>
<td>QT-prolonging antiarrhythmatics</td>
<td>Drug-induced arrhythmia</td>
<td>ion-channel genes</td>
<td>Exposure of subclinical reduction in repolarizing currents by drugs</td>
</tr>
<tr>
<td>General anesthetics</td>
<td>Malignant hyperthermia</td>
<td>RYR1</td>
<td>Anesthetic-induced increased release of sarcoplasmic reticulum calcium by mutant channels</td>
</tr>
<tr>
<td>Inhaled steroids</td>
<td>Bronchodilation</td>
<td>CRHR1</td>
<td>Unknown</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors (statins)</td>
<td>Low-density lipoprotein cholesterol lowering</td>
<td>HMGCR</td>
<td>Altered HMG-CoA reductase activity</td>
</tr>
</tbody>
</table>

*ADD1 = the gene encoding α-adducin; ADRB1 = the gene encoding the β₁-adrenergic receptor; ADRB2 = the gene encoding the β₂-adrenergic receptor; CRHR1 = the gene encoding corticotropin-releasing hormone receptor-1; CYP2C19 = the gene encoding the 2C19 cytochrome P450 isoform; CYP2C9 = the gene encoding the 2C9 cytochrome P450 isoform; CYP2D6 = the gene encoding the 2D6 cytochrome P450 isoform; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; HMGCR = the gene encoding HMG-CoA reductase; MDR1 = the gene encoding P-glycoprotein; RYR1 = the gene encoding the skeletal muscle calcium-release channel; TPMT = the gene encoding thiopurine methyltransferase; UGT1A1 = the gene encoding uridine diphosphate glucosyltransferase 1 family, polypeptide A1; VKORC1 = the gene encoding vitamin K epoxide reductase complex, subunit 1.*
### Table 1. US FDA or EMEA drug pharmacogenomic labeling: constitutive genetic variants.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene target</th>
<th>Information</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoridazine</td>
<td>CYP2D6</td>
<td>ADRs: W&amp;P Test not required</td>
<td>QT prolongation, torsades de pointes</td>
</tr>
<tr>
<td>Codeine</td>
<td>CYP2D6</td>
<td>ADRs: W&amp;P Test not required</td>
<td>Apnea among children from breastfeeding mothers</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>CYP2D6</td>
<td>ADRs: W&amp;P Test not required</td>
<td>Dose reduction for PMs</td>
</tr>
<tr>
<td>Tamoxifene</td>
<td>CYP2D6–CYP2C19</td>
<td>Lower response rate: W&amp;P Test not required</td>
<td>Loss of efficiency among PMs and with CYP2D6 inhibitors</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>CYP2C19</td>
<td>ADRs: W&amp;P Test not required</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Warfarin</td>
<td>CYP2C9</td>
<td>ADRs: W&amp;P Individualized dosing: W&amp;P Test not required</td>
<td>Risk of bleeding</td>
</tr>
<tr>
<td>Warfarin</td>
<td>VKORC1</td>
<td>ADRs: W&amp;P Individualized dosing: W&amp;P Test not required</td>
<td>Risk of bleeding</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>UGT1A1</td>
<td>ADRs: W&amp;P Individualized dosing Test not required</td>
<td>Diarrhea, neutropenia</td>
</tr>
<tr>
<td>Azathioprine and 6-mercaptopurine</td>
<td>TPMT</td>
<td>ADRs: W&amp;P Individualized dosing Test not required</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>DPD</td>
<td>ADRs: contraindication Test not required</td>
<td>Orodigestive – neutropenia</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>CCR5</td>
<td>Nonresponse Test required</td>
<td>For CCR5-negative patients</td>
</tr>
<tr>
<td>Rasburicase</td>
<td>G6PD</td>
<td>ADRs: contraindication Test not required</td>
<td>Hemolysis in G6PD-deficient patients</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>HLA-B*1502</td>
<td>ADRs: W&amp;P Test not required</td>
<td>Severe immunoallergic cutaneous</td>
</tr>
<tr>
<td>Abacavir</td>
<td>HLA-B*5701</td>
<td>ADRs: W&amp;P Test not required</td>
<td>Hypersensitivity reactions</td>
</tr>
</tbody>
</table>

*W&P section of the summarized product characteristics [104,105]. ADR: Adverse drug reaction; EMEA: European Medicines Agency; PM: Poor metabolizer; W&P: Warnings and precautions.*
PHARMACOGENOMICS

All patients with the same diagnosis

1. Genetic profile for toxicity with usual dose of drug A
   - Treat with lower dose of drug A or alternative drug

2. Genetic profile for favorable response to drugs C and D
   - Genetic profile for favorable response to drugs A and B

Severe allergic or hypersensitivity reaction to drugs are common and preclude necessary treatment. Association between allergy or hypersensitivity to a medication and HLA type.

HLA typing allows risk stratification of the patients.
Drugs associated to SJS and TEN

Antiepileptic agents: Carbamazepine; Phenytoin; Phenobarbital; Lamotrigine; Allopurinol; Nevirapine

Anti-inflammatories of oxicam family

Sulfonamides

SJS: Stevens Johnson Syndrome
TEN: toxic epidermal necrolysis
<table>
<thead>
<tr>
<th>HLA Antigen</th>
<th>Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HLA-B*5701</strong></td>
<td>Hypersensitivity to Abacavir</td>
</tr>
<tr>
<td><strong>HLA-B*1502</strong></td>
<td>Carbamazepine induced SJS or TEN</td>
</tr>
<tr>
<td><strong>HLA-B*5801</strong></td>
<td>Allopurinol induced SJS or TEN</td>
</tr>
<tr>
<td><strong>HLA-DRB1*01</strong></td>
<td>Nevirapine</td>
</tr>
<tr>
<td><strong>HLA-DRB1*07</strong></td>
<td>Ximelagatran</td>
</tr>
<tr>
<td><strong>HLA-A29,B12,DR7</strong></td>
<td>Sulfonamides</td>
</tr>
<tr>
<td><strong>HLA-A2,B12</strong></td>
<td>Oxicam</td>
</tr>
<tr>
<td><strong>HLA-DQA1*0102</strong></td>
<td>Lumiracoxib</td>
</tr>
</tbody>
</table>

**SJS**: Stevens Johnson Syndrome  
**TEN**: toxic epidermal necrolysis
HIV infection treatment

HAART highly active antiretroviral therapy

- **NRTI** Nucleoside analogue Reverse Transcriptase Inhibitor
- **NNRTI** Non Nucleoside analogue RTI
- **HIV Protease Inhibitors**
Ziagen, Abacavir Sulfate: (1S,cis)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1)

Ziagen, an oral medication taken twice daily, is a nucleoside analogue reverse transcriptase inhibitor (NRTI) and is taken in combination with other anti-HIV medications.

The combination helps to lower the amount of HIV found in the blood.
The allergy, frequently referred to as an abacavir hypersensitivity reaction (AHR), is a serious side effect that occurs in up to 8 percent of those taking the drug. Symptoms, including fever, rash and shortness of breath, often worsen with continued use of the drug. These symptoms can be fatal, especially if the drug is stopped and then restarted.
Proportion of patients stopping ABC therapy in the first 6 weeks
Before/after introduction of prospective HLA-B*5701 typing

Rauch et al. CID 2006
HLA-B*5701 Testing - The Panel recommends HLA-B*5701 testing prior to initiating abacavir therapy to reduce the risk of hypersensitivity reaction (AI).

HLA-B*5701 + patients should not be prescribed abacavir (AI), and the positive status should be recorded as an abacavir allergy in the patient's medical record (AII).

When HLA-B*5701 screening is not readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of abacavir-associated hypersensitivity reaction (CIII).
Carbamazepine has both antiepileptic and psychotropic properties.

**Indications:**
- Epilepsy
- Pain syndromes: Trigeminal neuralgia and glossopharyngeal neuralgia.
- Manic depressive illness unresponsive to lithium.
FDA alert 12/12/2007 recommends HLA-B*1502 typing before prescribing Carbamazepine to patients of Asian origin
SJS/TEN and HLA-B*1502 Allele

Retrospective case-control studies have found that in Chinese patients there is a strong association between the risk of developing SJS/TEN with carbamazepine treatment and the presence of HLA-B*1502.

The occurrence of higher rates of these reactions in countries with high freq. of B*1502 suggests that the risk may be increased in allele+ individuals of any ethnicity.

Chung et al. Nature 428, 486, 2004
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 TEGRETOL. 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 TEGRETOL. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH TEGRETOL UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK.
Variation in the prevalence of HLA-B*1502

**ASIA.**

>15% of the population is pos. in Hong Kong, Thailand, Malaysia, and parts of the Philippines.

About 10% in Taiwan & 4% in North China.

South Asians, including Indians, have intermediate prevalence of HLA-B*1502, 2-4%.

B*1502 is in <1% in Japan & Korea.

B*1502 is absent/low in non Asians (e.g., Caucasians, African-Americans, Hispanics, Mexicans and Amerindians).
Prior to initiating Tegretol therapy, testing for HLA-B*1502 should be performed in patients of populations in which HLA-B*1502 may be present.

In deciding which patients to screen, the given prevalence of B*1502 may offer a rough guide, keeping in mind the limitations of these figures due to wide variability in rates even within ethnic groups, the difficulty in ascertaining ethnic ancestry, and the likelihood of mixed ancestry.

Tegretol should NOT be used in B*1502 patients, unless the benefits clearly outweigh the risks. B*1502 - patients, are thought to have a low risk of SJS/TEN.
B*1502 genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management.

Many *1502+ Asian patients treated with Tegretol will not develop SJS/TEN, and these reactions can still occur infrequently in HLA-B*1502- patients of any ethnicity.
Genetic Architecture of Asthma and Allergic Diseases

A. Monogenic. - Caused by highly penetrant <1% rare mutations

- **SPINK5** (Netherton syndrome)
- **STAT3** (Hyper-IgE syndrome)

B. Complex diseases or phenotypes w/low freq. (1-5%) risk alleles w/ intermediate effect sizes

- **FLG** (Atopic dermatitis)
- **ORMDL3/GSDML** (Asthma)
- **TSLP, IL33, IL1RL1, HLA-DR/-DQ, IL13** (Asthma and allergic disease)

Complex diseases & phenotypes with common disease risk alleles (>5%), w/ very low effect sizes & penetrance

**GWAS**

**Sequence**

Frequency size of risk allele
Allopurinol is a xanthine oxidase inhibitor which reduces serum and urinary uric acid concentrations.

Treatment of primary or secondary gout

Patients with leukemia, lymphoma and other malignancies who are receiving cancer therapy which causes elevations of uric acid levels.
ZYLOPRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR OTHER SIGNS WHICH MAY INDICATE AN ALLERGIC REACTION

In some instances a skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial, and purpuric lesions, as well as Stevens-Johnson syndrome (erythema multiforme exudativum), and/or generalized vasculitis, irreversible hepatoxicity, and, on rare occasions, death.
HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol.


Study: 51 patients with allopurinol-SCAR and 228 controls:

135 allopurinol-tolerant subjects and 93 healthy subjects were genotyped for 823 SNPs in genes related to drug metabolism and immune response.

The initial screen revealed strong association between allopurinol-SCAR and SNPs in the MHC region, including BAT3 (encoding HLA-B associated transcript 3), MSH5 (mutS homolog 5), and MICB (MHC class I polypeptide-related sequence B) (P <10^{-7}).
HLA -A, B, C, DRB1 typing was performed.

HLA-B*5801 was present in 100%/51 patients with allopurinol-SCAR but only in 20 (15%) of 135 tolerant patients

RR=580.3 ; p= 4.7 x 10^{-24}

and in 19 (20%) of 93 of healthy subjects

RR= 393.51  p= 8.1 x 10^{-18}

HLA -A*3303, Cw*0302, DRB1*0301 were in Δ with HLA-B*5801
A genome-wide study identifies HLA alleles associated with lumiracoxib-related liver injury.

4378 SUBJECTS FROM 25 COUNTRIES WERE TYPED FOR DQA1*0102:

Caucasians (N=3557), Blacks (N=78), Hispanics (N=675) & others (N=68)

Results from follow-up of the genome-wide analysis of 67 SNPs to search for additional markers that associate with risk of liver enzyme elevations (peak ALT/AST > 3x U), showed strong DQA1*0102 carrier status.

Singer, Lewitsky et al, Nature Genetics, 2010:38. 632
## HLA Alleles Is Associated With Lumiracoxib In Patients With Inflammatory Diseases

<table>
<thead>
<tr>
<th>Liver Injury</th>
<th>% Carriers</th>
<th>% Non-Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular</td>
<td>76.5</td>
<td>45.9</td>
</tr>
<tr>
<td>Mixed</td>
<td>20.6</td>
<td>48.6</td>
</tr>
<tr>
<td>Cholestatic</td>
<td>2.9</td>
<td>5.4</td>
</tr>
</tbody>
</table>

\[ p=0.01 \]

\[ \text{OR for } >3x\text{ U} = 5.8; >5x\text{ U} = 11.1; >8x\text{ U} = 21.6; >10x\text{ U} = 24.1 \]

### DQA1*0102 patients freq by race:

- **Caucasian**: 35.4%  
- **Hispanic**: 21.2%  
- **Black**: 57.7%  
- **Other**: 38.7%
HLA Alleles Is Associated With Lumiracoxib In Patients With Inflammatory Diseases

A logistic regression model was applied with an indicator of liver enzyme levels as a dependent variable, variable number of copies of HLA as an independent variable, and sex, age, study as co-variants.

DRB1*1501 yielded the most significant result among Hispanics (p=0.0007; OR=6), similar to that obtained from the whole analysis (OR=5).

This association with the increase in liver enzymes was stronger than the one of DQA1*0102, however, all DRB1*1501 carriers were also DQA1*0102, ..which one is the primary susceptibility allele?
HLA Alleles Is Associated With Lumiracoxib In Patients With Inflammatory Diseases

It is important to emphasize, that results were compared with HLA DQA1* typed patients taking Naproxen and Ibuprofen, with no HLA association at all.

More studies are needed in patients from ethnic specific populations, taking Lumiracoxib for inflammatory diseases such as rheumatic diseases.

The FDA will soon provide an alert for HLA typing in patients, before taking Lumiracoxib.
HLA typing and Pharmacogenomics: It is already here!!

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

FDA alert 12/12/2007 recommends HLA-B*1502 typing before prescribing Carbamazepine to patients of Asian origin.

DHHS Treatment guidelines for HIV-1 infection in Adults and Adolescents (12/01/2007 update) recommends HLA-B*5701 typing before prescribing Abacavir.
It is already here

From NEJM, Feb. 2008, 358
HLA-B*5701 Screening for Hypersensitivity to Abacavir. Mallal et al.

Pharmacogenomic Biomarkers for Prediction of Severe Adverse Reactions. M. Ingelman-Sundberg, 2009
(7 listed, 3 HLA alleles).
HLA AND PERSONALIZED MEDICINE

pharmacogenomics
disease diagnostics
immunotherapy
infectious disease vaccines
tumor vaccines

http://www.pharmgkb.org
PharmGKB (Pharmacogen Base)
GOALS OF PHARMACOGENOMICS

* To identify the functional genes or polymorphisms associated with the individual response to drugs

* To obtain personalized drugs

* To improve the efficacy of disease therapeutics

* To avoid adverse drug reactions

* To select patients for clinical trials of new drugs and for better therapeutic strategies

* To design new drugs
Personalized Medicine
PERSONALIZED MEDICINE: THE FUTURE

GeneChip Analysis

SMART CARD

Alastair J.J. Wood

GENOME

(Confidential)
Serious adverse reactions to drugs in association with certain HLA alleles have been confirmed in some ethnic groups, but have not been investigated in other populations. It is also likely that additional associations may be established for other drugs with increasing awareness of possible immunogenetic predisposition.

AIM: The aim of this study is to establish an ongoing registry for compilation of data on the incidence of the association of HLA alleles and/or other immunogenetic factors with adverse drug reactions in various populations.
If it was not, because of the enormous variability among individuals, Medicine would be a science and not an art

Sir William Osler
1849-1919

PharmGKB (Pharmacogen Base)

http://www.pharmgkb.org