Pharmacogenetics in drug allergy: Updated (Role of Pharmacist in Clinical implementation)

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Is it possible to incorporate pharmacogenetic testing in routine clinical practice?

Patient: “Here is my pharmacogenomics card, please give me a medication properly.”

Doctor: “Yes, of course”

Name: Patient 2
Pharmacogenomics test: HLA-A, HLA-B, HLA-DR
Pharmacogenomics result: AAT-PK31 (GT, GT)
Pharmacogenomics interpretation: High risk for Carbamazepine/Ltn-carbamazepine-induced SJS/TEN

Sukasem C. and Chantratita W. Pharmacogenomics. 2016

4th fl. Division of Pharmacogenomics and Personalized Medicine

11,684 cases
**Updated PGx markers (DME) in SEA populations, 2018**

*(Sukasem C. and Medhasi S. Springer Nature, 2018)*

<table>
<thead>
<tr>
<th>PGx genes</th>
<th>Drugs</th>
<th>Surrogate Labs</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2B6</td>
<td>Efavirenz (EFV)</td>
<td>EFV level</td>
<td>Thai</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Clopidogrel</td>
<td>Platelet aggregation (ADP)</td>
<td>Thai, Malaysian, Singaporean,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vorchonazole (VCZ)</td>
<td></td>
</tr>
<tr>
<td>CYP2C9 and VKORC1</td>
<td>Warfarin</td>
<td>INR</td>
<td>Thai</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Risperidone (Ris)</td>
<td>Tamoxifen</td>
<td>Thai</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ris level, Tamoxifen</td>
<td></td>
</tr>
<tr>
<td>UGT1A1</td>
<td>Irinotecan</td>
<td>CBC</td>
<td>Thai, Singaporean,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ta2rolimus level</td>
<td></td>
</tr>
<tr>
<td>CYP3A5</td>
<td>Tacrolimus</td>
<td>Tacrolimus level</td>
<td>Thai</td>
</tr>
<tr>
<td>TPMT</td>
<td>6-MP, Azathioprine</td>
<td>TPMT enzyme activity 6-MP level</td>
<td>Thai</td>
</tr>
<tr>
<td>DPYD</td>
<td>5-FU</td>
<td>CBC</td>
<td>Thai, Singaporean,</td>
</tr>
</tbody>
</table>

**Updated PGx markers (HLA) in SEA populations, 2018**

*(Sukasem C. and Tempark T. Springer Nature, 2018)*

<table>
<thead>
<tr>
<th>Drugs</th>
<th>HLA-markers</th>
<th>Other factors</th>
<th>Ethnicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>HLA-B<em>15:02 (B</em>75 serotype: B*15:21)</td>
<td>Co-med (Depakine)</td>
<td>Thai, Vietnamese, Singaporean, Malay, Indonesia</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>HLA-A<em>02:07, HLA-A</em>33:03, HLA-B<em>15:02, HLA-B</em>44:03</td>
<td></td>
<td>Thai</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>HLA-B<em>15:02, HLA-B</em>15:13</td>
<td>CYP2C9, CYP2C19, Co-med (Omeprazole)</td>
<td>Thai, Malay</td>
</tr>
<tr>
<td>Ox-carbazepine</td>
<td>HLA-B*15:02</td>
<td></td>
<td>Thai</td>
</tr>
<tr>
<td>Phenoarbital</td>
<td>HLA-A<em>01:01, HLA-B</em>13:01</td>
<td></td>
<td>Thai</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>HLA-B*58:01</td>
<td>High dose, Female, Renal impairment, Elderly</td>
<td>Thai</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>HLA-B*35:05</td>
<td>CD4 level, CCHCR1</td>
<td>Thai</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>HLA-B<em>15:02, HLA-C</em>06:02, HLA-C<em>08:01, HLA-B</em>13:01</td>
<td></td>
<td>Thai</td>
</tr>
<tr>
<td>Dapsone</td>
<td>HLA-B*13:01</td>
<td></td>
<td>Thai</td>
</tr>
</tbody>
</table>

**Identify who is at risk for Severe cutaneous adverse drug reactions (SCARs) of treatment**

To avoid ADR-B (appropriate drug)

- Idiosyncratic ?
- Unpredictable ?
- Dose independent ?

**CADR: ADR-B**

![Type IV: Delayed Hypersensitivity Reactions](image)

**Human leukocyte antigen (HLA)**

- Located on the short arm of chromosome 6
- HLA is the name of the major histocompatibility complex (MHC) in humans.
- HLA is a class of surface membrane protein
- “Presenting” possible antigen to T and B cells
**Pharmacogenetics for Carbamazepine (HLA B*15:02)**

- A case-control study reported a strong association between HLA-B*1502 and SJS/TEN and suggested a 100% negative predictive value (Hun Chinese).
- 44 cases (SJS/TEN): 101 controls.
- 100% HLA-B*1502 in case group.
- 2.97% HLA-B*15-02 in control group.

CBZ-induced SJS/TEN was strongly associated with HLA-B*1502 (OR=2504)


**Association between HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in a Thai population**

We thank Tae Joon Park, Da Hye Youn, and the other authors of the original study for their permission to use their data for this analysis.

**Table 2. Frequencies of certain HLA-D alleles in CBZ-induced SJS/TEN and CBZ-induced skin patients**

<table>
<thead>
<tr>
<th>HLA-D alleles</th>
<th>CBZ-induced SJS/TEN (%)</th>
<th>CBZ-induced skin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>004</td>
<td>10</td>
<td>6.3</td>
</tr>
<tr>
<td>005</td>
<td>5</td>
<td>1.5</td>
</tr>
<tr>
<td>006</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>007</td>
<td>10</td>
<td>7.6</td>
</tr>
<tr>
<td>008</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>009</td>
<td>10</td>
<td>7.6</td>
</tr>
<tr>
<td>010</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>011</td>
<td>10</td>
<td>7.6</td>
</tr>
<tr>
<td>012</td>
<td>0</td>
<td>0.1</td>
</tr>
</tbody>
</table>

**B-1502 allele with OR of 54.76 (95% CI 14.62-205.13)**

**HLA-B* 15:02 for screening CBZ-induced SCARs**

Sukasem et al. Annu Rev Genomics Hum Genet. 2018

**Most Reported Suspected Drugs with SCARs (1994-2016 June)**

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>No of SCAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHENOBARBITAL</td>
<td>439</td>
</tr>
<tr>
<td>COLOCHROME</td>
<td>581</td>
</tr>
<tr>
<td>HUUMAGDA</td>
<td>625</td>
</tr>
<tr>
<td>AMOXICILLIN</td>
<td>672</td>
</tr>
<tr>
<td>PARACETAMOL</td>
<td>2095</td>
</tr>
<tr>
<td>NEVIRAPINE CONTAINING</td>
<td>1399</td>
</tr>
<tr>
<td>CARBAMAZEPINE</td>
<td>2061</td>
</tr>
<tr>
<td>PHENTYON</td>
<td>545</td>
</tr>
<tr>
<td>ALLOGULIN</td>
<td>2082</td>
</tr>
<tr>
<td>CD-TRIMAZADIC</td>
<td>2909</td>
</tr>
</tbody>
</table>

**Thai Pharmacovigilance**

- **Carbamazepine: HLA-B* 15:02**
  - National Health Security Office (NHSO)
  - 2010

- **Allopurinol: HLA-B* 58:01**
  - Allopurinol is the most common cause of Steven-Johnson syndrome and toxic epidermal necrolysis in Europe and local

**Thai population (n=986)**

- **HLA-B* 15:02 (Carbamazepine) = 15.92%**
- **HLA-B* 58:01 (Allopurinol) = 16.43%**

Puangpatch and Sukasem et al. Frontier genetics, 2015

**โครงการนำร่อง “การป้องกันสิ่งแวดล้อมรังสี Steven-Johnsson syndrome (SJS) และ Toxic epidermal necrolysis (TEN) จากยา Carbamazepine/Oxcarbazine โดยการประเมินความเสี่ยงทางทันตกรรมชนิด HLA-B*15:02”**

ดุลยกรรม 2556 ถึงปี 2558

**Caution:**

Thai-language text is not accurately translatable and may not convey the intended meaning. Please consult a Thai-speaking expert for more accurate translation.
**CASE 1: CBZ-induced DRESS (test prior)**
A female got CBZ after negative HLA-B* 15:02 screening >>> DRESS

Association between HLA-B Alleles and Carbamazepine-Induced Maculopapular Exanthema and Severe Cutaneous Reactions in Thai Patients

**HLA-B*15:02 and SJS/TEN; OR = 70.91**
95% CI 19.67–255.65, p = 4.46 × 10⁻¹³

No association of HLA-B*15:02 and CBZ-induced DRESS (n=5)
HLA-A*33:03 for DRESS (unpublished data)

**CASE 2: To confirm (test after)**
- A female with CBZ-induced DRESS
- Test to confirm diagnosis
- Negative HLA-B*15:02 (HLA-B* 27:06/58:01)

**CBZ-SCAR: HLA-B* 15:02**
**Phenotype specificity**
- HLA-B* 15:02>>CBZ-SJS/TEN
- No DRESS or MPE

**Clinical implementation:**
- Clinical interpretation>>do not over clinical interpretation

**Specific HLA-B* 15:02 Screening**
- Male, 15 years (dyskinesia)
- Specific HLA-B* 15:02 Screening Negative HLA-B* 15:02 (Low risk)
- CBZ-induced SJS (14 days)

**Allelic HLA-B genotyping**

**Change from a Low risk to be a High risk of CBZ-SJS/TEN**
**HLA-B*15:02 and carbamazepine-induced Stevens-Johnson syndrome: pooled-data and in silico analysis**

Kanoot Jarathamisophon, Varomyin Tipmaraee, Antida Sangiamsaey, Chontaphat Sukasem, Pornprot Limprasert

- **Member of Serotype 75 as risk alleles**
  - 15:02, 15:08, 15:11 and 15:21
- **Specific HLA-B* 15:02 screening:** False negative to identify the high risk patients

**CASE 4:** A boy with positive HLA-B*15:02 with OXC

**HLA-B*15:02 and OXC-SJS/TEN (OR=27.9)**
Less severity than CBZ (NEUROLOGY, 2016)

**CBZ-PGX: Ethnic specificity**
- HLA-B* 15:02>>> Han Chinese, Thai, Indian, Malaysian, Singaporean, Vietnamese, SEA
- HLA-A* 31:01>>> Japanese, Korean, Caucasian and European

**CASE 5:** Requested HLA-B* 15:02 for a Japanese patient: False negative

**SCIENTIFIC REPORTS**

**Share risk marker (HLA-B* 15:02) between CBZ and OXC**

Risk and association of HLA with oxcarbazepine-induced cutaneous adverse reactions in Asians

**CASE 4:** A boy with positive HLA-B*15:02 with OXC

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- HLA-A* 31:01>>> Japanese, Korean, Caucasian and European

**Ethnic identification**


Carbamazepine-induced severe cutaneous adverse reactions and HLA genotypes in Koreans. (Kim SH, Epilepsy Res. 2011)

**HLA-A* 31:01>>> Caucasian, European, Japanese and Korean**
CASE 6: a female dead from CBZ-induced TEN

- Health professional awareness
- Counseling system
- Electronic Health Record (EHR)

Clinical implementation:
Clinician/Pharmacist/Nurse/Patients
  • Stakeholders, role and workflow
  • PGx card and personalized report

Personalized Medicine report
At least 3 copies for
  • Patient
  • Clinician
  • Pharmacist

Key messages: The Challenges of Success for Health

“Not just only the genetic screening but also the others”

1. PGx infrastructures and facilities: Laboratory and equipment
2. Pharmacovigilance system
3. Evidence-based PGx testing: PGx researches
4. Pharmacogenetics tools: Interpretation algorithm, Precision medicine report and Pharmacogenetics cards
5. Health Professionals: Educational training and raising awareness
6. Electronic health record (EHR)
7. PGx workflow for clinical service and counseling system

PPM workflow for clinical service and counseling system

Sukasem et al. Annu Rev Genomics Hum Genet. 2018
What you have to known for PGx-CBZ?

1. HLA-B*15:02 is strongly associated with CBZ-induced SJS/TEN
2. Phenotype specificity: HLA-B*15:02>CBSJ5/S/TEN
3. Share risk marker for aromatic group: CBZ>OXC
4. Ethnic specificity
   - HLA-B*15:02>Han Chinese, Thai, Indian, Malaysian, Singaporean, SEA
   - HLA-A*31:01>Caucasian, European, Japanese and Korean
5. Family of risk genes (HLA-B75 serotype=15:02, 15:08, 15:11 and 15:21)

Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update
Elizabeth J. Phillips,1 Chaosheng Sukamto,1,2 Michelle Whirl-Carrillo,3 David J. Milsark,4 Henry M. Dunnuberg,4 Warren Chauncey,4 Barry Goldspiel,4 Yuen-Tsong Chen,4,5 Bruce C. Carlson,4 Alfred J. George Jr.,4 Yasu Mushiroda,4,5 Terr Klein,4 Rosenn S. Gammal4 and Munir Pirmohamed4

Case study
- Female, 69 years (Seizure, HAP)
- PHY SR 100 mg 3 cap., HS. (29/9)
- 51.8 ug/ml, PHY- overdose (5/10)
- PHY-induced DRESS (28 days)
- PHY-induced hepatotoxicity
- PHY-induced encephalopathy

HLA-B*15:02 positive and risk of AED-induced SCARs

CADR: ADR
- X Idiosyncratic
- X Unpredictable
- X Dose independent
Key messages: **Opportunities for Health**

“PGx: The low hanging fruits, it is the innovative tools to maximize the efficacy and to decrease or eradicate the adverse drug reactions”

![Graph showing number of SJS/TEN reports by year in Thai Vigibase (1984-2016, June)]

**Health Professionals: Educational training and raising awareness**

**Building a strong interdisciplinary team**

**PGx-training center**

- 13 Ph.D. candidate
- 4 MS. Candidate

**Grants and Funding**

- Newton Fund
- The Royal Golden Jubilee Ph.D. Program
- ERASMUS MUNDUS
- GlaxoSmithKline
- FRANCO-THAI Chamber of Commerce
- NSTDA (IRN)
- NRCT
You are cordially invited to the PPM 7th Year Anniversary Celebration

“The PPM: Clinical Pharmacogenomics meeting”
Friday August 3rd, 2018

Auditorium Hall (Mini-theater), 5th Floor, Somdech Phra Debaratana Medical Center, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok

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