HLA-B*1301 Association with Dapsone Induced Hypersensitivity Reaction among Leprosy Patients in China
Introduction

• Since the discovery of dapsone (4,40-diaminodiphenylsulfone, DDS) in the 1940s, it has been widely used for the treatment of leprosy.

• Although the risk of dapsone-dependent side effects is very low if the plasma concentration is below 5 mg/L, some of the reported side effects include methemoglobinemia, hemolysis, agranulocytosis, and dapsone-induced hypersensitivity reactions (DIHR) (Zhu and Stiller, 2001).
Introduction

• DIHR is a life-threatening drug reaction, which has been reported in about 2% leprosy patients on dapsone therapy with 12.5% mortality, constituting one of major causes of mortality in leprosy patients. (Shen et al., 2011; Pandey et al., 2007)

• DIHR, clinically manifesting with fever, rash, lymphadenopathy, and hepatitis, is categorized under the drug-induced hypersensitivity syndrome (DIHS) or drug rash with eosinophilia and systemic symptoms (DRESS) syndromes. (Kumari et al., 2011; Kardaun et al., 2007; Sener et al., 2006).
Introduction

• Unlike other drug reactions, DIHR usually presents with low hemoglobin and a higher risk of liver involvement including cholestatic or hepatocellular disease, or both. (Richardus and Smith, 1989; Zhu and Stiller, 2001).
Introduction

• Although the exact mechanism of DIHR remains unclear, numerous reports have described the associations between human leukocyte antigens (HLA, especially MHC I) and drug eruptions in patients with various diseases (Pavlos et al., 2012; Chung et al., 2004; Mallal et al., 2002), and some HLA profiles are useful tools in diagnosing and, moreover, in preventing life-threatening adverse drug reactions (Chung et al., 2004; Mallal et al., 2008).
Introduction

- Dapsone is metabolized via acetylation and N-hydroxylation.
- Previous studies proved that genetic polymorphism of human NAT2 determined slow acetylator status and is a predisposing factor for allergic diseases and drug adverse reactions (Gawronska-Szklarz et al., 1999; Zielinska et al., 1998).
- Cytochrome P450 2C9 (CYP2C9) was also shown to be the initial step in the formation of toxic intermediate metabolites of sulfonamides, which are analogues of dapsone, that can induce hemolytic anemia and skin rash (Winter et al., 2000; Wolkenstein et al., 2005).
Methods

• Among 1058 cases of leprosy patients were screened in this study, 21 cases (1.98%) met the enrollment criteria for DIHR according to Richardus and Smith’s criteria (Richardus and Smith., 1989). The socio-demographic characteristics of the DIHR patients, dapsone-tolerant patients, and healthy controls are summarized.

• MHC I region typing and gene polymorphisms of related metabolism enzymes were detected in 122 leprosy patients exposed to dapsone and 96 healthy controls in Southern China.
Results

• There were no significant differences in terms of age, sex, and ethnicity among the three groups (age: p=0.713, sex: p=1.000, ethnicity: p=1.000).

• Patients presented with clinical signs of DIHR at a median of 28±8.5 days (range 15~42 days) after starting dapsone.

• The most common documented clinical signs of DIHR were fever (100%) and rash (100%), with 15 (71.4%) having maculo-papular eruptions and 6 (28.6%) having vesiculopapules. Lymphadenopathy was noted in 16 (76.2%) of cases.
Results

• The abnormal laboratory profiles involved elevated levels of serum liver enzymes and hypoalbuminemia in all cases, low hemoglobin in 18 cases (85.7%), leukocytosis in 18 cases (85.7%), and eosinophilia in 10 cases (47.6%).
• Patients were asked to cease dapsone therapy when they were suspected of having DIHR and treated with systemic corticosteroids at average dose 0.5-1mg/kg of prednisolone.
• One patient died of toxic hepatitis and subsequent hepatic failure. All other patients recovered within 2-4 weeks and their skin eruptions subsided in $21.6 \pm 8.7$ days (10-38 days) on average.
Table 1: **Demographic data for the cases and controls**

<table>
<thead>
<tr>
<th>Variable</th>
<th>leprosy patients with DIHR (n=21)</th>
<th>DDS-tolerant leprosy patients (n=105)</th>
<th>Healthy controls&lt;sup&gt;1&lt;/sup&gt; (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age[years mean±SD]</td>
<td>38.2±11.7</td>
<td>40.3±11.8</td>
<td>39.5±10.7</td>
</tr>
<tr>
<td>Male[no. %]</td>
<td>11(52.4%)</td>
<td>55(52.4%)</td>
<td>53(53.0%)</td>
</tr>
<tr>
<td>Female[no. (%)]</td>
<td>10(47.6%)</td>
<td>50(47.6%)</td>
<td>47(47%)</td>
</tr>
<tr>
<td>DDS-exposure duration(weeks)</td>
<td>&lt; 8</td>
<td>&gt;8</td>
<td>_</td>
</tr>
<tr>
<td>Han Chinese</td>
<td>12(57.1%)</td>
<td>55(52.4%)</td>
<td>52(52.0%)</td>
</tr>
<tr>
<td>Non-Han Chinese</td>
<td>9(42.9%)</td>
<td>50(47.6%)</td>
<td>48(48.0%)</td>
</tr>
<tr>
<td>Miao group</td>
<td>4(19.0%)</td>
<td>22(21.0%)</td>
<td>20(20.0%)</td>
</tr>
<tr>
<td>Tu group</td>
<td>2(9.5%)</td>
<td>12(11.4%)</td>
<td>12(12.0%)</td>
</tr>
<tr>
<td>Zhuang group</td>
<td>2(9.5%)</td>
<td>12(11.4%)</td>
<td>12(12.0%)</td>
</tr>
<tr>
<td>Buyi group</td>
<td>1(4.8%)</td>
<td>4(3.8%)</td>
<td>4(4.0%)</td>
</tr>
</tbody>
</table>

<sup>1</sup> Healthy controls: healthy non-leprosy controls not exposed to Dapsone
Results

- **HLA-B*1301** and **HLA-Cw*0304** were present in significantly higher frequency in DIHR patients than in either dapsone-tolerant patients or healthy controls.

- In particular, **HLA–B*1301** was found in 90% of DIHR patients and was present in only 6.9% of dapsone-tolerant patients, with a sensitivity of 90% and specificity of 93.1% (AUC: 0.92). If either **HLA-B*1301** or **HLA B*1313** was present, the sensitivity and specificity were 100% and 92.2%, respectively (AUC: 0.961).
Results

• The most common of these three-loci MHC I combined haplo types in DIHR patients was HLA-A*1101-B*1301-Cw*0304 (68.4%), however, it was present in only 1.0% of dapsone-tolerant patients.

• Within DIHR patients and dapsone-tolerant patients, the presence of HLA- B*1301 and HLA-C*0304 alleles had a positive predictive value for DIHR of 76%, and the absence of this combination of alleles had a negative predictive value of 99.0%, while the presence of the HLA-B*1301 haplotype alone was associated with positive and negative predictive values for DIHR of 72.0% and 97.9%, respectively.
Table 2: Frequency of HLA alleles in cases and controls

<table>
<thead>
<tr>
<th>HLA allele</th>
<th>leprosy patients with DIHR (n=20)</th>
<th>DDS-tolerant leprosy patients (n=102)</th>
<th>Healthy controls¹</th>
<th>OR[95% CI]</th>
<th>pc</th>
</tr>
</thead>
<tbody>
<tr>
<td>B*1301</td>
<td>18 (90%)</td>
<td>7 (6.9%)</td>
<td>11 (11.5%)</td>
<td>²122.1 [ 23. 5-636.2]</td>
<td>²6.038×10⁻¹²</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>³69.6 [ 14.2-341.0]</td>
<td>³1.961×10⁻¹¹</td>
</tr>
<tr>
<td>B*1313</td>
<td>2 (10%)</td>
<td>1 (1.0%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C*0304</td>
<td>19 (95%)</td>
<td>22 (21.6%)</td>
<td>24 (25%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B<em>1301, C</em>0304</td>
<td>17 (85%)</td>
<td>6 (5.9%)</td>
<td>4 (4.2%)</td>
<td>⁴90.667 [20.7-397.8]</td>
<td>⁴4.280×10⁻¹¹</td>
</tr>
<tr>
<td>B<em>1301 or B</em>1313</td>
<td>20 (100%)</td>
<td>8 (7.9%)</td>
<td>11 (11.5%)</td>
<td>⁵470.0 [25.9-8521.3]</td>
<td>⁵8.320×10⁻¹⁵</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>⁶154.6 [18.8-1267.4]</td>
<td>⁶4.040×10⁻¹³</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(analysis of the haplotype of linkage disequilibrium for HLA-A<em>1101-B</em>1301-Cw*0304); 9 failure in genotyping for HLA A in 1 leprosy patient with DIHR and 1 DDS-tolerant leprosy patient.</td>
<td></td>
</tr>
<tr>
<td>A<em>11:01, B</em>13:01, C*03:04</td>
<td>13 (68.4%, n=19)</td>
<td>3 (3.0%, n=101)</td>
<td></td>
<td>⁷70. 8 [15.8-317.8]</td>
<td>⁷1.668×10⁻⁸</td>
</tr>
</tbody>
</table>

¹ Healthy controls: healthy non-leprosy controls not exposed to Dapsone; 2,4,5,7 cases/dapsone-tolerant controls; 3,6 cases/healthy controls; 8 cases/dapsone-tolerant controls (analysis of the haplotype of linkage disequilibrium for HLA-A*1101-B*1301-Cw*0304); 9 failure in genotyping for HLA A in 1 leprosy patient with DIHR and 1 DDS-tolerant leprosy patient.
Results

• There was no significant association among any of the genotypes or phenotypes of CYP 2C9 (including the single nucleotide polymorphisms of its promoter) and NAT2 with occurrence of DIHR.
Conclusions & Discussion

• The major finding of this study was that the presence of the HLA-B*1301 haplotype is strongly associated with development of DIHR. It supports an important and immediately applicable clinical role for HLA typing in this setting.

• However, several limitations are present in this study. First, although the study was carried out in several geographical areas in China, further studies among patients with different ethnic backgrounds are needed.
Conclusions & Discussion

• Second, the sample size for this study may not be large enough for the subgroup analysis to show potential associations between HLA alleles and subgroups of DIHR, even though current data showed a statistical significance and strong association between HLA B*1301 and DIHR in Southern Chinese.

• Third, for the difficulty of samples collection, in this study, non-leprosy patient with DIHR and other dapsone related side effects were not investigated, whether these finding in leprosy patients can be used to non-leprosy patients with DIHR should be confirmed.
Conclusions & Discussion

In summary, \textit{HLA-B*1301} could be a useful biomarker to predict DIHR before administering dapsone to leprosy patients in the Chinese population. The mechanism of DIHR appears immunologically related with HLA but not with metabolism of dapsone. Further studies are needed to investigate the molecular mechanisms of HLA subtypes and DIHR in leprosy patients.

A large-scale prospective study is necessary to verify the value of HLA-B*1301 as a predictive biomarker for DIHR.
Acknowledgments

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