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Update on Genetic Susceptibility to DILI in Humans

March 19th, 2015

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University of North Carolina at Chapel Hill
DILIN
Drug-Induced Liver Injury Network

iDLIC

NIDDK
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

International SAE Consortium

https://dilin.dcri.duke.edu/

https://www.saeconsortium.org/
GWAS of Drug-Induced Liver Injury

HLA-B*57:01, a genetic risk factor for drug-induced liver injury

A genome-wide association study with lumiracoxib

Susceptibility to Amoxicillin-Clavulanate-Induced Liver Injury Is Influenced by Multiple HLA Class I and II Alleles

GASTROENTEROLOGY 2011;141:338–347
<table>
<thead>
<tr>
<th>Compound</th>
<th>No of cases</th>
<th>HLA allele</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flucloxacillin</td>
<td>51</td>
<td>B*57:01</td>
<td>80.6(22.8-284.9)</td>
<td>9x10^{-19}</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>201</td>
<td>A*02:01</td>
<td>2.3(1.8-2.9)</td>
<td>1.8x10^{-10}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DRB1<em>15:01-DQ B1</em>06:02</td>
<td>2.8(2.1-3.8)</td>
<td>3.5x10^{-11}</td>
</tr>
<tr>
<td>Lumiracoxib</td>
<td>41</td>
<td>DRB1<em>15:01-DQ B1</em>06:02</td>
<td>5.0(3.6-7.0)</td>
<td>6.8x10^{-25}</td>
</tr>
<tr>
<td>Lopatinib</td>
<td>35</td>
<td>DRB1<em>07:01-DQA1</em>02:01</td>
<td>2.9(1.3-6.6)</td>
<td>0.007</td>
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<tr>
<td>Ximelagatran</td>
<td>74</td>
<td>DRB1<em>07:01-DQA1</em>02:01</td>
<td>4.4(2.2-8.9)</td>
<td>6x10^{-6}</td>
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<tr>
<td>Ticlopidine</td>
<td>22</td>
<td>A*33:03</td>
<td>13.0 (4.4-38.6)</td>
<td>1.2 x 10^{-5}</td>
</tr>
</tbody>
</table>
“Phase 2” DILI Meta-GWAS

Total of 1,505 DILI Cases of Primarily European Ancestry
Omnibus (“all-cause”) DILI GWAS
(excluding flucloxacillin and amoxicillin/clavulanate)
899 cases and 10,605 controls
HLA-A*33:01 is the top associated HLA allele (OR~2.6 , pv=2*10^-8)
Drug-specific analysis: TERBINAFINE
14 Caucasian cases
HLA A-33:01 risk factor (OR ~40, p-value $10^{-10}$)

<table>
<thead>
<tr>
<th>SNP</th>
<th>ODDS</th>
<th>UCI</th>
<th>LCI</th>
<th>Pvalue</th>
<th>Pvalue.Fis</th>
<th>FreqCases</th>
<th>FreqCont.</th>
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<tbody>
<tr>
<td>HLA-B*14:02</td>
<td>13.99</td>
<td>36.2</td>
<td>5.405</td>
<td>5.40E-08</td>
<td>1.82E-05</td>
<td>0.25</td>
<td>0.03079</td>
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<td>0.7582</td>
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<td>HLA-A*33:01</td>
<td>40.53</td>
<td>131.4</td>
<td>12.51</td>
<td>6.78E-10</td>
<td>4.71E-07</td>
<td>0.2143</td>
<td>0.01058</td>
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<td>0.1939</td>
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<td>HLA-C*08:02</td>
<td>10.77</td>
<td>27.6</td>
<td>4.19</td>
<td>8.02E-07</td>
<td>0.000133</td>
<td>0.25</td>
<td>0.04226</td>
<td>1</td>
<td>0.5674</td>
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</table>
After eliminating terbinafine cases, HLA-A 33:01 remains weakly associated with “all-cause” DILI.
Other HLA results:
Rare HLA types* associated with specific drugs

<table>
<thead>
<tr>
<th>ETH</th>
<th>DRUG</th>
<th>HLA allele</th>
<th>MAT cases</th>
<th>MAT controls</th>
<th>NETdb</th>
<th>OR</th>
<th>PV</th>
<th># carriers</th>
<th># cases</th>
<th># DILIC</th>
<th># DILIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>nEU</td>
<td>TEUTHROMYCIN</td>
<td>HLA-A*02:02</td>
<td>0.06</td>
<td>0.0006</td>
<td>0.0009</td>
<td>101.8</td>
<td>6.77E-05</td>
<td>1</td>
<td>9</td>
<td>0</td>
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<td>MINOCYCLINE</td>
<td>HLA-B*35:02</td>
<td>0.06</td>
<td>0.0030</td>
<td>0.01</td>
<td>29</td>
<td>2.57E-08</td>
<td>4</td>
<td>25</td>
<td>3</td>
<td>27</td>
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<td>SEVOFLURANF</td>
<td>HLA-DRB1*08:03</td>
<td>0.10</td>
<td>0.0023</td>
<td>0.0024</td>
<td>145.4</td>
<td>9.84E-05</td>
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<td>VALPROICACID</td>
<td>HLA-DRB1*10:01</td>
<td>0.08</td>
<td>0.0067</td>
<td>0.0085</td>
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<td>15</td>
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<td>FRUTHROMYCIN</td>
<td>HLA-A*69:01</td>
<td>0.10</td>
<td>0.0040</td>
<td>0.0015</td>
<td>430</td>
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<td>10</td>
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<td>2</td>
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<td>LAMOTRIGINE</td>
<td>HLA-C*16:04</td>
<td>0.10</td>
<td>0.0004</td>
<td>0.0006</td>
<td>280.1</td>
<td>3.05E-05</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

*Accuracy of imputation is less reliable for rare HLA types!!!
HLA genes: role in immunity and drug hypersensitivity

- **HLA class I genes expressed on most cells**
  - A, B and C genes

- **HLA class II genes expressed on antigen presenting cells**
  - DR, DQ, DP genes

- **HLA proteins normally present peptide antigens to T cells**
  - May inappropriately present drug-peptide complexes or “neoantigens”
Mechanistic Basis of HLA-Mediated Drug Toxicities

PDB code 3UPR

David Ostrov, University of Florida
SULFAMETHOXAZOLE W/TRIMETHOPRIM:
27 Caucasian cases
Genome-wide significant signal on Chr9p (intergenic)
Ongoing Next-Gen Sequencing Studies

- Drug-Induced Liver Injury due to:
  - Isoniazid
  - Minocycline
  - Nitrofurantoin
  - Valproic Acid
  - Body-building supplements containing androgens
  - Sulfamethoxazole/trimethoprim (TBD)
- Cholestatic liver injury (targeting the “biliome”)

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- Minocycline
- Nitrofurantoin
- Valproic Acid
- Body-building supplements containing androgens
- Sulfamethoxazole/trimethoprim (TBD)
“Gene-to-Function”

“Function-to-Gene”

Cultured undifferentiated stem cells

Pluripotent

DNA
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Duke University
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- David Goldstein

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