Predicting immune-mediated adverse drug reactions and emerging immunogenetic discoveries

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Immune-mediated adverse drug reactions

• ADRs a major health problem
  – 6-7% hospitalizations
  – 100,000 deaths/year in US
  – Primary cause of drug withdrawal from market
  – 20% of ADRs are immune-mediated with often greater health care cost

• Type 1 (Type A)
  – Dose dependent, “predictable”
  – Related to drug’s pharmacological action

• Type 2 (Type B - idiosyncratic)
  – “unpredictable”
  – inappropriate immuno-allergic reaction

Karnes et al. Annual Review of Pharmacology and Toxicology. 2019
Severe immune-mediated adverse drug reactions

• Types of serious reactions:
  • usually delayed, T cell-mediated
  • Stevens-Johnson syndrome (SJS)
  • Toxic epidermal necrosis (TEN)
  • Drug induced liver injury (DILI)
  • Hypersensitivity syndromes (HSS)

• SJS/TEN
  • Mortality rate up to 50%
  • No treatment guideline, highlighting lack of evidence-based treatment

• HLA alleles can be used to predict severe IM-ADRs to certain anti-epileptics, antibiotics, HAART, and other drugs

Karnes et al. *Annual Review of Pharmacology and Toxicology*. 2019
Published Genome-Wide Associations through 12/2013
Published GWA at $p \leq 5 \times 10^{-8}$ for 17 trait categories
<table>
<thead>
<tr>
<th>Drug (references)</th>
<th>HLA allele</th>
<th>Adverse reaction</th>
<th>Prevalence of ADR</th>
<th>Carriage rate (%) of HLA-4 allele&lt;sup&gt;a&lt;/sup&gt;</th>
<th>OR</th>
<th>NPV (population)</th>
<th>PPV (population)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir (46, 47, 110, 137)</td>
<td>B*57:01</td>
<td>Hypersensitivity reaction</td>
<td>8% of population (3% true, 2–7% false positive HSR)</td>
<td>5–8 (European) &lt;1 (Sub-Saharan African) &lt;1 (Southeast Asian) 2–3 (African American)</td>
<td>960</td>
<td>100%</td>
<td>55%</td>
<td>13</td>
</tr>
<tr>
<td>Allopurinol (58, 129, 138–145)</td>
<td>B*58:01</td>
<td>SJ/S/TEN, DRESS/DIHS</td>
<td>1–4/1,000</td>
<td>1–6 (European) 10 (Sub-Saharan African) 10–15 (Southeast/South Asian) 4 (African American)</td>
<td>580</td>
<td>100% (Han Chinese)</td>
<td>3% (Han Chinese)</td>
<td>250</td>
</tr>
<tr>
<td>Carbamazepine (50, 109, 117–120, 146–151)</td>
<td>B*15:02</td>
<td>SJ/S/TEN</td>
<td>&lt;1–6/1,000</td>
<td>&lt;0.1 (European) 10–15 (Southeast Asian) &lt;1 (African)</td>
<td>&gt;1,000</td>
<td>100% (Southeast Asian)</td>
<td>2–8%</td>
<td>1,000</td>
</tr>
<tr>
<td>Carbamazepine (54, 56, 112, 122, 152, 153)</td>
<td>A*31:01</td>
<td>DRESS/DIHS</td>
<td>0.05%</td>
<td>&lt;6 (European) &lt;1 (Sub-Saharan African)</td>
<td>57.6</td>
<td>99.9%</td>
<td>0.89%</td>
<td>3,334</td>
</tr>
<tr>
<td>Dapsone (67)</td>
<td>B*13:01</td>
<td>DRESS/DIHS</td>
<td>1–4/100</td>
<td>0 (European) 2–30 (Southeast Asian)</td>
<td>20</td>
<td>99.8%</td>
<td>7.8%</td>
<td>84</td>
</tr>
<tr>
<td>Flucloxacillin (43)</td>
<td>B*57:01</td>
<td>Drug-induced liver injury</td>
<td>8.5/100,000</td>
<td>5–8 (European) &lt;1 (Sub-Saharan African) &lt;1 (Southeast Asian) 2–3 (African American)</td>
<td>81</td>
<td>99.9%</td>
<td>0.12%</td>
<td>13,819</td>
</tr>
<tr>
<td>Methimazole/ carbenbazole (32, 65, 154)</td>
<td>B*38:02</td>
<td>Agranulocytosis</td>
<td>Unknown</td>
<td>5–15 (China, Taiwan) &lt;1 (European) &lt;1 (African)</td>
<td>266–753</td>
<td>99.9%</td>
<td>7–30%</td>
<td>211–238</td>
</tr>
<tr>
<td></td>
<td>B*27:05</td>
<td></td>
<td></td>
<td>4–8 (European) &lt;2 (China) &lt;1 (Africa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine (4, 155)</td>
<td>C*04:01</td>
<td>DRESS</td>
<td>Unknown</td>
<td>15–30 (average prevalence across races)</td>
<td>3–7</td>
<td>95–97%</td>
<td>5–27%</td>
<td>Variable</td>
</tr>
<tr>
<td>Oxcarbazepine (156–158)</td>
<td>B*15:02</td>
<td>SJ/S/TEN</td>
<td>Unknown</td>
<td>&lt;0.1 (European) 10–15 (Southeast Asian) &lt;1 African</td>
<td>27.9</td>
<td>99.9% (Han Chinese)</td>
<td>0.73% (Han Chinese)</td>
<td>&gt;5,000</td>
</tr>
</tbody>
</table>

Karnes et al. Annual Review of Pharmacology and Toxicology. 2019
CPIC guidelines for IM-ADRs

Table 2 Recommended therapeutic use of abacavir in relation to HLA-B genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Implications for phenotypic measures</th>
<th>Recommendations for abacavir</th>
<th>Classification of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncarrier of HLA-B*57:01</td>
<td>Low or reduced risk of abacavir hypersensitivity</td>
<td>Use abacavir per standard dosing guidelines</td>
<td>Strong</td>
</tr>
<tr>
<td>Carrier of HLA-B*57:01</td>
<td>Significantly increased risk of abacavir hypersensitivity</td>
<td>Abacavir is not recommended</td>
<td>Strong</td>
</tr>
</tbody>
</table>

HLA-B, human leukocyte antigen B. *Rating scheme described in Supplementary Data online.

Table 2 Recommended therapeutic use of allopurinol by HLA-B genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Implications for phenotypic measures</th>
<th>Recommendations for allopurinol</th>
<th>Classification of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncarrier of HLA-B*5801 (*X/X) 2</td>
<td>Low or reduced risk of allopurinol-induced SCAR</td>
<td>Use allopurinol per standard dosing guidelines</td>
<td>Strong</td>
</tr>
<tr>
<td>Carrier of HLA-B<em>5801 (HLA-B</em>5801/<em>X, HLA-B</em>5801/HLA-B*5801)</td>
<td>Significantly increased risk of allopurinol-induced SCAR</td>
<td>Allopurinol is contraindicated</td>
<td>Strong</td>
</tr>
</tbody>
</table>

HLA-B, human leukocyte antigen B; SCAR, severe cutaneous adverse reaction. *Rating scheme described in Supplementary Table S4 online. HLA-B genotype other than HLA-B*5801 is indicated by *X.

Table 2 Recommendations for carbamazepine therapy based on HLA-B and HLA-A genotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Implication</th>
<th>Therapeutic recommendation</th>
<th>Classification of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B<em>15:02 negative and HLA-A</em>31:01 negative</td>
<td>Normal risk of carbamazepine-induced SJS/TEN, DRESS, and MPE</td>
<td>Use carbamazepine per standard dosing guidelines</td>
<td>Strong</td>
</tr>
<tr>
<td>HLA-B*15:02 positive</td>
<td>Greater risk of carbamazepine-induced SJS/TEN, DRESS, and MPE</td>
<td>If patient is carbamazepine-naive and alternative agents are available, do not use carbamazepine</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Other aromatic anticonvulsants have very limited evidence, if any, linking SJS/TEN, DRESS, and/or MPE with the HLA-A*31:01 allele, and thus no recommendation can be made with respect to choosing another aromatic anticonvulsant as an alternative agent.

https://cpicpgx.org/guidelines/
HLA Imputation using GWAS data
Comparison of HLA imputation programs to sequenced HLA alleles in 3,265 samples

- Overall concordance rates similar in Whites
  - 0.975 (SNP2HLA)
  - 0.939 (HLA*IMP:02)
  - 0.976 (HIBAG)

- Accuracy decreases with African ancestry, decreasing allele frequency, lower genomic coverage, limited reference panels
Phenome-wide association studies (PheWAS)

EHR resources such as BioVU

Phenome Wide Association Study
(1 SNP compared to ALL Phenotypes)

allele G patients group
allele A patients group

linked through a one-directional hash algorithm

allele G patients phenotype  allele A patients phenotype

compare ALL DIAGNOSIS to find differences between cases and controls
PheWAS of HLA Variation

• Imputed HLA genomic variation from European ancestry individuals
  • 29,712 patients from BioVU
• Genotyped on the HumanExome BeadChip
  • 2,061 HLA tag SNPs
• Tested association with 1,545 phenotypes
• Data for four and two digit HLA alleles and amino acid changing variants

HLA PheWAS Results

- 66 four-digit HLA allele-phenotype associations significant in both discovery and replication cohorts
  - Strongest HLA-DQB1*03:02 and type 1 diabetes (odds ratio 4.31[3.57-5.19], p=4.50x10^{-53})

- 62 two-digit HLA allele-phenotype associations significant
  - HLA-DQA1*01 and T1D (OR 0.32 (0.26-0.39), p=8.19x10^{-32}).

- 1223 significant associations amino acid changing variants
  - T1D and an alanine/valine substitution at position 57 of HLA-DQB1 (OR 0.20 [0.17-0.25], p=2.6x10^{-60})

- Data replicate many known phenotypic associations
  - Primarily autoimmune diseases

- Provide comprehensive, publicly-available catalog of clinical phenotypes associated HLA variation

Karnes et al. Science Translational Medicine. 2017
PheWAS plot of four digit HLA allele associations

null
Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing

Risk for late-onset Alzheimer's disease (LOAD), the most prevalent dementia, is partially driven by genetics. To identify LOAD risk loci, we performed a large genome-wide association meta-analysis of clinically diagnosed LOAD (94,437 individuals). We confirm 20 previous LOAD risk loci and identify five new genome-wide loci (ICK, ACE, ADAM10, ADAMTS1, and WWOX), two of which (ADAMTS10, ACE) were identified in a recent genome-wide association (GWAS)-by-familial-proxy of Alzheimer's or dementia. Fine-mapping of the human leukocyte antigen (HLA) region confirms the neurological and immune-mediated disease haplotype HLA-DR15 as a risk factor for LOAD. Pathway analysis implicates immunity, lipid metabolism, tau binding proteins, and amyloid precursor protein (APP) metabolism, showing that genetic variants affecting APP and Aβ processing are associated not only with early-onset autosomal dominant Alzheimer's disease but also with LOAD. Analyses of risk genes and pathways show enrichment for rare variants (P = 1.32 × 10⁻⁶), indicating that additional rare variants remain to be identified. We also identify important genetic correlations between LOAD and traits such as family history of dementia and education.
HLA PheWAS in eMERGE

- PheWAS performed in 83,717 individuals with EMR data
- Adjusted for gender, site, PC, and PC2
- ~500,000 regressions in total
- 1,338 PheWAS Codes greater than 500 Cases
- 531 Significant PheWAS Codes
- lowest p-value: $7.3 \times 10^{-52}$ for T1D with ophthalmic manifestations
- Led by Dr. Ian Byrell Stanaway, UW and Dr. Vivek Naranbhai, Massachusetts General Hospital, Harvard

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-A</td>
<td>40</td>
</tr>
<tr>
<td>HLA-B</td>
<td>92</td>
</tr>
<tr>
<td>HLA-C</td>
<td>31</td>
</tr>
<tr>
<td>HLA-DPB1</td>
<td>27</td>
</tr>
<tr>
<td>HLA-DQA1</td>
<td>16</td>
</tr>
<tr>
<td>HLA-DQB1</td>
<td>20</td>
</tr>
<tr>
<td>HLA-DRB1</td>
<td>50</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>276</strong></td>
</tr>
</tbody>
</table>
**B*27:05 and AS**

- Rheumatoid arthritis and other inflammatory polyarthropathies
- Uveitis, noninfectious or NOS
- Rheumatoid arthritis
- Juvenile rheumatoid arthritis
- Hypothyroidism
- Hypothyroidism NOS
- Other arthropathies

**DQA1*03:03 and RA**

- Hypothyroidism
- Hypothyroidism NOS
- Cardiac dysrhythmias
- Abnormal electrocardiogram (ECG) [EKG]
- Acute pain
- Ankylosing spondylitis

**B*15:01 and hypothyroidism**

- Hypothyroidism
- Hypothyroidism NOS
- Type 1 diabetes with ophthalmic manifestations

**DRB1*15:01 and MS**

- Type 1 diabetes with renal manifestations
- Type 1 diabetes with ophthalmic manifestations
- Type 1 diabetes with neurological manifestations
- Insulin pump user
- Lupus (localized and systemic)
- Scleroderma
- Myasthenia gravis
- Nephrotic syndrome
- Diabetes mellitus Type 2
- Hyperlipidemia
- Diabetes mellitus Type 1
- Hypercholesterolemia
### TABLE 1
Number of unique participant eMERGE IDs and reported demographics

<table>
<thead>
<tr>
<th>Medical center</th>
<th>Participants</th>
<th>Arrays Batches</th>
<th>Gender Male</th>
<th>Gender Female</th>
<th>African/Black</th>
<th>American Indian</th>
<th>Asian</th>
<th>White</th>
<th>Pacific Islander</th>
<th>Hispanic/Latino</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston Children’s</td>
<td>1,019</td>
<td>1</td>
<td>596</td>
<td>423</td>
<td>66</td>
<td>2</td>
<td>21</td>
<td>676</td>
<td>0</td>
<td>125</td>
<td>129</td>
</tr>
<tr>
<td>CCHMC</td>
<td>5,717</td>
<td>12</td>
<td>3,262</td>
<td>2,455</td>
<td>601</td>
<td>5</td>
<td>67</td>
<td>4,673</td>
<td>5</td>
<td>143</td>
<td>223</td>
</tr>
<tr>
<td>CHOP</td>
<td>10,465</td>
<td>21</td>
<td>5,630</td>
<td>4,835</td>
<td>4,666</td>
<td>7</td>
<td>161</td>
<td>4,890</td>
<td>3</td>
<td>321</td>
<td>417</td>
</tr>
<tr>
<td>Columbia</td>
<td>2,065</td>
<td>2</td>
<td>1,058</td>
<td>1,007</td>
<td>179</td>
<td>6</td>
<td>77</td>
<td>619</td>
<td>2</td>
<td>448</td>
<td>734</td>
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<tr>
<td>Geisinger</td>
<td>3,111</td>
<td>1</td>
<td>1,638</td>
<td>1,473</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>3,085</td>
<td>0</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Harvard</td>
<td>10,095</td>
<td>3</td>
<td>4,626</td>
<td>5,469</td>
<td>509</td>
<td>0</td>
<td>172</td>
<td>8,579</td>
<td>0</td>
<td>474</td>
<td>361</td>
</tr>
<tr>
<td>Kaiser/GHC/UW</td>
<td>3,316</td>
<td>3</td>
<td>1,428</td>
<td>1,888</td>
<td>109</td>
<td>12</td>
<td>89</td>
<td>2,922</td>
<td>6</td>
<td>69</td>
<td>109</td>
</tr>
<tr>
<td>Marshfield Clinic</td>
<td>4,756</td>
<td>5</td>
<td>1,878</td>
<td>2,878</td>
<td>2</td>
<td>3</td>
<td>12</td>
<td>4,690</td>
<td>0</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>10,256</td>
<td>16</td>
<td>5,193</td>
<td>5,063</td>
<td>23</td>
<td>18</td>
<td>21</td>
<td>8,810</td>
<td>0</td>
<td>1,043</td>
<td>341</td>
</tr>
<tr>
<td>Mt. Sinai</td>
<td>6,255</td>
<td>4</td>
<td>2,555</td>
<td>3,700</td>
<td>4,046</td>
<td>33</td>
<td>3</td>
<td>679</td>
<td>0</td>
<td>1,297</td>
<td>197</td>
</tr>
<tr>
<td>Northwestern</td>
<td>4,848</td>
<td>2</td>
<td>817</td>
<td>4,031</td>
<td>598</td>
<td>0</td>
<td>0</td>
<td>4,207</td>
<td>0</td>
<td>36</td>
<td>7</td>
</tr>
<tr>
<td>Vanderbilt</td>
<td>21,814</td>
<td>10</td>
<td>9,868</td>
<td>11,946</td>
<td>3,854</td>
<td>16</td>
<td>102</td>
<td>17,313</td>
<td>0</td>
<td>211</td>
<td>318</td>
</tr>
<tr>
<td>Total</td>
<td>83,717</td>
<td>38,549</td>
<td>45,168</td>
<td>14,662</td>
<td></td>
<td>104</td>
<td>725</td>
<td>61,143</td>
<td>16</td>
<td>4,194</td>
<td>2,873</td>
</tr>
</tbody>
</table>

Note: eMERGE: Electronic Medical Records and Genomics.
HLA PheWAS in African Americans

- 14,662 African Americans
- 820 PheWAS codes greater than 200 cases in African Americans
- 120 HLA alleles MAF >= 0.01
- 820 x 120 = 98,400 tests

- Significant Phecodes:
  - African 167
  - Asian 19
  - European 754

- Significant Regressions:
  - African 236
  - Asian 21
  - European 4480
DQA1*05:01

Type 1 diabetes
Type 2 diabetes with ophthalmic manifestations

Diabetic retinopathy

Polyneuropathy in diabetes

A*66:01

Antirheumatics causing adverse effects in therapeutic use
**DRB1*01:03 and coagulation defects in pregnancy**

**DPB1*14:01 and GI anomalies**

**B*27:05 and AS**

**B*39:10 and thyroid cancer**
Sex bias in MHC I-associated shaping of the adaptive immune system

Tilman Schneider-Hohendorf, Dennis Görlich, Paula Savola, Tiina Kelkka, Satu Mustjoki, Catharina C. Gross, Geoffrey C. Owens, Luisa Klotsu, Klaus Dormair, Heinz Wiendl, and Nicholas Schwab

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Edited by K. Christopher Garcia, Stanford University, Stanford, CA, and approved January 12, 2018 (received for review September 14, 2017)

HLA associations, T cell receptor (TCR) repertoire bias, and sex bias have independently been shown for many diseases. While some immunological differences between the sexes have been described, they do not fully explain bias in men toward many infections/cancers, and toward women in autoimmunity. Next-generation TCR variable beta chain (TCRBV) immunosequencing of 824 individuals was evaluated in a multiparametric analysis including HLA-A/B/MHC class I background, TCRBV usage, sex, age, ethnicity, and TCRBV selection/expansion dynamics. We found that HLA-associated shaping of TCRBV usage differed between the sexes. Furthermore, certain TCRBVs were selected and expanded in unison. Correlations between these TCRBV relationships and biochemical similarities in HLA-binding positions were different in CD8 T cells of patients with autoimmune diseases (multiple sclerosis and rheumatoid arthritis) compared with healthy controls. Within patients, men showed higher TCRBV relationship Spearman’s rho in relation to HLA-binding position similarities compared with women. In line with this, CD8 T cells of men with autoimmune diseases also showed higher degrees of TCRBV perturbation compared with women. Converged selection and expansion of CD8 T cells in patients with autoimmune diseases, but especially in men, appears to be less dependent on high HLA-binding similarity than in CD4 T cells. These findings are consistent with studies attributing autoimmunity to processes of epitope spreading and expansion of low-avidity T cell clones and may have further implications for the interpretation of pathogenic mechanisms of infectious and autoimmune diseases with known HLA associations.

TCR binding amino acids of MHC molecules specifically influence the binding to and usage of TCR variable alpha (TCRAV) and TCRBV chains (19), and that the presence of specific TCR rearrangements is an indication of the HLA background of the host and also of previous exposure to pathogens (20). Dysregulation in the TCR–antigen–MHC complex can lead to autoimmunity (21) in the case of uncontrolled immune cell expansion or cross-reactivity between foreign and autoantigens. Hypoexpansions or low TCR avidity might lead to susceptibility to infections. Additionally, to combat tumor-associated immune system suppression, cancer patients can now be treated with T cell-relevant immune checkpoint inhibitors such as blockade of CTLA-4 (22) or PD-1 (23).

Most immune system dysfunctions show strong sex bias: men are more susceptible to many infectious diseases and cancers of nonreproductive organs, whereas autoimmune diseases are much more common in women (24, 25). Even in psychological disorders such as major depression (26) and in neurodegenerative diseases such as Alzheimer’s, recent studies have shown immune system involvement (27) and sex bias (28). Many studies have been conducted concerning either sex (25), HLA (29, 30), or TCR (31) associations with diseases. However, even though some sex differences in immune regulation have been reported (25, 32), it is still not completely clear why this bias exists. Multiparametric analysis of the influence of sex on HLA-mediated shaping of the TCR repertoire has been hindered by
<table>
<thead>
<tr>
<th>HLA Allele</th>
<th>Phenotype</th>
<th>All cases</th>
<th>All controls</th>
<th>Females OR</th>
<th>Females P</th>
<th>Males OR</th>
<th>Males P</th>
<th>Interaction P</th>
</tr>
</thead>
<tbody>
<tr>
<td>B*2705</td>
<td>Other inflammatory spondylopathies</td>
<td>223</td>
<td>23,403</td>
<td>1.60</td>
<td>0.082</td>
<td>8.12</td>
<td>3.4E-21</td>
<td>3.2E-06</td>
</tr>
<tr>
<td>DPB1*0301</td>
<td>Senile dementia</td>
<td>224</td>
<td>23,111</td>
<td>0.79</td>
<td>0.311</td>
<td>2.86</td>
<td>5.9E-06</td>
<td>1.0E-04</td>
</tr>
<tr>
<td>C*0702</td>
<td>Vitamin deficiency</td>
<td>1,966</td>
<td>21,062</td>
<td>1.04</td>
<td>0.572</td>
<td>0.67</td>
<td>8.3E-05</td>
<td>2.4E-04</td>
</tr>
<tr>
<td>B*0702</td>
<td>Vitamin deficiency</td>
<td>1,966</td>
<td>21,062</td>
<td>1.02</td>
<td>0.818</td>
<td>0.66</td>
<td>8.4E-05</td>
<td>4.6E-04</td>
</tr>
<tr>
<td>DQB1*0301</td>
<td>Congenital anomalies of urinary system</td>
<td>433</td>
<td>26,979</td>
<td>1.81</td>
<td>9.5E-05</td>
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<td>5.6E-04</td>
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<tr>
<td>DRB1*0401</td>
<td>Noninfectious gastroenteritis</td>
<td>814</td>
<td>20,452</td>
<td>1.03</td>
<td>0.789</td>
<td>0.54</td>
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<tr>
<td>DQB1*0301</td>
<td>Genitourinary congenital anomalies</td>
<td>657</td>
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<td>0.966</td>
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<tr>
<td>C*0602</td>
<td>Psoriasis</td>
<td>369</td>
<td>22,973</td>
<td>2.98</td>
<td>7.7E-14</td>
<td>1.44</td>
<td>0.049</td>
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<td>B*4002</td>
<td>Benign neoplasm of colon</td>
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<td>24,588</td>
<td>0.70</td>
<td>0.258</td>
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<td>DQB1*0202</td>
<td>Respiratory abnormalities</td>
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<td>20,833</td>
<td>1.65</td>
<td>5.5E-06</td>
<td>1.03</td>
<td>0.822</td>
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<tr>
<td>C*0602</td>
<td>Psoriasis and related disorders</td>
<td>384</td>
<td>22,973</td>
<td>2.84</td>
<td>3.9E-13</td>
<td>1.42</td>
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<tr>
<td>B*1401</td>
<td>Chronic liver disease and cirrhosis</td>
<td>1,173</td>
<td>22,347</td>
<td>2.43</td>
<td>1.9E-05</td>
<td>0.79</td>
<td>0.459</td>
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<td>A*1101</td>
<td>Cardiac arrest</td>
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<td>17,561</td>
<td>3.76</td>
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<td>DQA1*0102</td>
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<td>0.399</td>
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</tbody>
</table>

PheWAS: sex bias of HLA associations
Major Challenges for HLA association

• Power
  • Low prevalence of IM-ADRs
  • For discovery and replication
  • Need for clinical networks to drive research and guidelines

• Phenotyping
  • Syndromes may mimic IM-ADRs
  • Electronic medical records

• Influence of race and ethnicity in IM-ADRs
  • Availability of reference populations
  • Disparate frequency of alleles between race groups
  • Disparate allelic associations between race groups
Distribution of ancestry in the GWAS catalogue

- Disproportionate contribution of associations from African and Hispanic/Latin American categories compared to percentage of individuals

Morales et al. Genome Biology (2018)
Current and planned in-person enrollment centers (over the course of enrollment)
Future Directions

• KIR, TCR, BCR, HLA expression
  • Interaction of immunogenomic variation
• Assessment of Pleiotropy in PheWAS
• IPSC testing for patient-specific drug hypersensitivity
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