HLA Mismatches

Professor Steven GE Marsh

Anthony Nolan Research Institute
HLA Mismatches

- HLA Genes, Structure, Polymorphism
- HLA Nomenclature
- HLA Mismatches in HSCT
- Defining a mismatch
HLA Mismatches

- HLA Genes, Structure, Polymorphism
- HLA Nomenclature
- HLA Mismatches in HSCT
- Defining a mismatch
DR Sub-region haplotype Diversity

 DR1  
 DRB1  DRB6  DRB9  DRA
 Serogroup
 DR51  
 DRB1  DRB6  DRB5  DRB9  DRA
 DR52  
 DRB1  DRB2  DRB3  DRB9  DRA
 DR8   
 DRB1  DRB9  DRA
 DR53  
 DRB1  DRB7  DRB8  DRB4  DRB9  DRA

β chain gene  Pseudogene  Associated β chain gene  α chain gene
HLA Polymorphism

Class II

Class I

B C A
Polymorphism located in exons 2 & 3
Polymorphism located in exon 2
HLA Class I
Number of HLA alleles, March 2013

<table>
<thead>
<tr>
<th>HLA</th>
<th>Number of Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-A</td>
<td>2244 (24)</td>
</tr>
<tr>
<td>HLA-B</td>
<td>2934 (49)</td>
</tr>
<tr>
<td>HLA-C</td>
<td>1788 (9)</td>
</tr>
<tr>
<td>HLA-E</td>
<td>11</td>
</tr>
<tr>
<td>HLA-F</td>
<td>22</td>
</tr>
<tr>
<td>HLA-G</td>
<td>50</td>
</tr>
<tr>
<td>HLA-DRA</td>
<td>7</td>
</tr>
<tr>
<td>HLA-DRB</td>
<td>1418 (20)</td>
</tr>
<tr>
<td>HLA-DQA1</td>
<td>50</td>
</tr>
<tr>
<td>HLA-DQB1</td>
<td>323 (7)</td>
</tr>
<tr>
<td>HLA-DPA1</td>
<td>37</td>
</tr>
<tr>
<td>HLA-DPB1</td>
<td>185</td>
</tr>
<tr>
<td>HLA-DMA</td>
<td>7</td>
</tr>
<tr>
<td>HLA-DMB</td>
<td>13</td>
</tr>
<tr>
<td>HLA-DOA</td>
<td>12</td>
</tr>
<tr>
<td>HLA-DOB</td>
<td>13</td>
</tr>
<tr>
<td>MICA</td>
<td>92</td>
</tr>
<tr>
<td>MICB</td>
<td>40</td>
</tr>
<tr>
<td>TAP1</td>
<td>12</td>
</tr>
<tr>
<td>TAP2</td>
<td>12</td>
</tr>
</tbody>
</table>
HLA-B 2010

HLA-B Amino Acid Polymorphism Heat Map
IMGT/HLA Database

RELEASE 3.11.0.1, 2013-02-11

The IMGT/HLA Database provides a specialist database for sequences of the human major histocompatibility complex (HLA) and includes the official sequences for the WHO Nomenclature Committee For Factors of the HLA System. The IMGT/HLA Database is part of the international ImMunoGeneTics project (IMGT®).

The database uses the 2010 nomenclature designations in all tools. To aid in the adoption of the new nomenclature, all search tools can be used with both the current and pre-2010 allele designations. The pre-2010 nomenclature designations are only used where older reports or outputs have been made available to download.

Latest Developments
- HLA-DPB1 T-Cell Epitope Algorithm
- What's new in the latest release

Latest Publications
  The IMGT/HLA Database
  Nucleic Acids Research (2013) 41:D1222-7 (Download PDF File)

Sponsors
The IMGT/HLA Database is sponsored by a number of institutes and companies, for further details of all our supporters and how you can help please see the funding page.

Lead Sponsorship of the IMGT/HLA Database by;

Further Sponsorship;

[Logos of sponsors]
HLA Mismatches

- HLA Genes, Structure, Polymorphism
- HLA Nomenclature
- HLA Mismatches in HSCT
- Defining a mismatch
### HLA Allele Nomenclature Pre-2010

<table>
<thead>
<tr>
<th>Gene</th>
<th>Type</th>
<th>Subtype</th>
<th>Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA - A *</td>
<td>24</td>
<td>02 01 02</td>
<td>L</td>
</tr>
</tbody>
</table>

- **Separator**
- **Subtype**
  - Differences outside the coding sequence, introns, 3', 5'
- **Gene**
  - Corresponds to the serological antigen or allele family
- **Type**
- **Silent substitution**
- **Expression**
  - L = Low
  - N = Null
  - S = Secreted
  - Q = Questionable
HLA - A * 24 : 02 : 01 : 02  L

Gene
Type
Corresponds to the serological antigen or allele family

Subtype
Silent substitution

Separator

Differences outside the coding sequence, introns, 3´, 5´

Expression
L = Low
N = Null
S = Secreted
Q = Questionable

HLA Allele Nomenclature 2010
HLA Nomenclature

A*24020101 → A*24:02:01:01
A*2499 → A*24:99
A*24:100
A*24:101
A*020199 → A*02:01:99
A*02:01:100
The nomenclature system needs:

- To be expandable
- To encode relatedness
- To encode ambiguity
- To be usable
<table>
<thead>
<tr>
<th>Level</th>
<th>HLA Nomenclature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serology</td>
<td>A2</td>
</tr>
<tr>
<td>Low level of resolution</td>
<td>A*02</td>
</tr>
<tr>
<td>Medium level</td>
<td>A*02:01/02:05/02:09/02:40/02:43N…</td>
</tr>
<tr>
<td>High level</td>
<td>A*02:01:01/02:09</td>
</tr>
<tr>
<td>Allele level</td>
<td>A*02:01:01:01</td>
</tr>
</tbody>
</table>
NMDP Codes

Using medium level resolution typing it is possible to exclude some but not all alleles from a group, hence the National Marrow Donor Program (NMDP) codes.

B*15:01 or B*15:02 = B*15AB

B*15:01/15:02/15:05/15:15/15:21/15:45/15:56/15:70 = B*15FGR
New Nomenclature

Allele Code:
/46:01

/46:01

**ACTIVATED** for use at:

B*15:SGEM
Peptide binding domain Nomenclature

• There were requests from the HLA community to give an official nomenclature for groups of alleles which share the same peptide binding domains

• The following allele string of A*02 alleles share the same $\alpha_1$ and $\alpha_2$ domains

A*02:01:01/02:01:02/02:01:03/02:01:04/02:01:05/02:01:06/
02:01:07/02:01:08/02:01:09/02:01:10/02:01:11/02:01:12/02:01:13/02:01:14/02:01:15/02:01:17/
02:01:18/02:01:19/02:01:21/02:01:22/02:01:23/02:01:24/02:01:25/02:01:26/02:01:27/02:01:28/
02:01:29/02:01:30/02:01:31/02:01:32/02:01:33/02:01:34/02:01:35/02:01:36/02:01:37/02:01:38/
02:01:39/02:01:40/02:01:41/02:01:42/02:01:43/02:01:44/02:01:45/02:01:46/02:01:47/02:01:48/
02:01:49/02:01:50/02:01:51/02:01:52/02:01:53/02:01:54/02:01:55/02:01:56/02:01:57/
02:01:58/02:01:59/02:01:60/02:01:61/02:01:62/02:01:63/02:01:64/02:01:65/02:01:66/02:01:67/
02:01:68/02:01:69/02:01:70/02:01:71/02:01:72/02:01:73/02:01:74/02:01:75/02:01:76/02:01:77/
02:01:78/02:01:79/02:01:80/02:01:81/02:01:82/02:01:83/02:01:84/02:01:85/02:01:86/02:01:87/
02:01:88/02:01:89/02:01:90/02:01:91/02:01:92/02:01:93/02:01:94/02:01:95/02:01:96/02:01:97/
02:01:98/02:01:100/02:01:101/02:01:102/02:01:103/02:01:104/02:01:105/02:01:106/02:01:107/
02:01:108/02:01:109/02:01:110/02:01:111/02:01:112/02:01:113/02:01:114/02:01:115/02:01:116/
02:01:117/02:01:118/02:01:119/02:01:120/02:01:121/02:01:122/02:01:123/02:01:124/02:01:125/
02:01:126/02:01:127/02:01:128/02:01:129/02:01:130/02:01:131/02:01:132/02:01:133/02:01:134/
02:01:135/02:01:136/02:01:137/02:01:138/02:01:139/02:01:140

• This can now be abbreviated as A*02:01P
Identical exons 2 & 3 Class I – exon 2 Class II

- There were requests from the HLA community to give an official nomenclature for groups of alleles which share exons 2 & 3 for Class I and exon 2 for Class II

- The following allele string of A*02 alleles share the same exon 2 and 3 sequences

A*02:01:01:01/02:01:01:02L02:01:01:03/02:01:08/02:01:11/02:01:14/02:01:15/02:01:21/02:09/02:43N/02:66/02:75/02:83N/02:89/02:97:01/02:97:02/02:132/02:134/02:140

This can now be abbreviated as A*02:01:01G
Nomenclature for Factors of the HLA System

Nomenclature of HLA Alleles

Early in their study it was recognised that the genes encoding the HLA molecules were highly polymorphic and that there was a need for a systematic nomenclature. The HLA complex is located within the 6p21.3 region on the short arm of human chromosome 6 and contains more than 220 genes of diverse function. Many of the genes encode proteins of the immune system. The naming of new HLA genes and allele sequences and their quality control is the responsibility of the WHO Nomenclature Committee for Factors of the HLA System, which first met in 1968, and laid down the criteria for successive meetings. This committee meets regularly to discuss issues of nomenclature and has published 19 major reports documenting firstly the HLA antigens and more recently the genes and alleles. The standardisation of HLA antigenic specifications has been controlled by the exchange of typing reagents and cells in the International Histocompatibility Workshops.

- How an allele is named
- HLA Nomenclature Reports
- HLA Nomenclature Updates
- Nomenclature Committee
- HLA Workshops
- Access sequence alignments and files

Since 1999 when a large number of HLA allele sequences were first analysed and named, the job of curating and maintaining a database of sequences has been of prime importance. The dissemination of new allele names and sequences is of paramount importance in the clinical setting and through the work of the HLA Informatics Group and in collaboration with the European Bioinformatics Institute, we are able to provide public access to the data through the web sites http://www.ebi.ac.uk/imgt/hla/ and here at http://hla.alleles.org. The IMGT/HLA Database collects both new and confirmatory sequences, which are then expertly analysed and curated before being named by the Nomenclature Committee. The resulting sequences are then included in the tools and files made available from both the IMGT/HLA Database and this site. These regular
HLA Mismatches

- HLA Genes, Structure, Polymorphism
- HLA Nomenclature
- HLA Mismatches in HSCT
- Defining a mismatch
International Histocompatibility Working Group in Hematopoietic Cell Transplantation
Established 1996
Funded by the National Institutes of Health, AI069197

International collaboration:
42 laboratories
435 transplant centers
10 transplant and donor registries
18 countries

Database for the 16th WS:
25,963 unrelated donor transplants (21,777 accepted)
Impact of Number of HLA Mismatches on Survival
# Effect of Number of HLA Mismatches on Outcome

Tally treated as a categorical variable

<table>
<thead>
<tr>
<th>Number of Mismatches</th>
<th>Grades III-IV aGVHD OR (95% CI), P value</th>
<th>Relapse HR (95% CI), P value</th>
<th>Survival HR (95% CI), P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (N=10896)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1 (N=6171)</td>
<td>1.50 (1.38-1.62), &lt;0.001</td>
<td>1.03 (0.96-1.1), 0.35</td>
<td>1.25 (1.20-1.31), &lt;0.001</td>
</tr>
<tr>
<td>2 (N=2620)</td>
<td>1.83 (1.64-2.03), &lt;0.001</td>
<td>1.07 (0.97-1.18), 0.19</td>
<td>1.50 (1.41-1.59), &lt;0.001</td>
</tr>
<tr>
<td>3 (N=1264)</td>
<td>2.07 (1.80-2.39), &lt;0.001</td>
<td>1.17 (1.01-1.34), 0.03</td>
<td>1.76 (1.63-1.89), &lt;0.001</td>
</tr>
<tr>
<td>4+ (N=745)</td>
<td>2.59 (2.18-3.07), &lt;0.001</td>
<td>1.07 (0.88-1.29), 0.50</td>
<td>1.91 (1.74-2.10), &lt;0.001</td>
</tr>
</tbody>
</table>

*The risks of severe acute GVHD and mortality increase as the number of mismatched HLA loci increases.*

*Useful for risk assessment prior to HCT.*
HLA Mismatches

• HLA Genes, Structure, Polymorphism
• HLA Nomenclature
• HLA Mismatches in HSCT
• Defining a mismatch
What is a mismatch?

- A2 versus A24
- A*02:01 versus A*03:01
- A*02:01 versus A*02:05
What is a mismatch?

- A*02:01:01 versus A*02:01:22
- A*02:15N versus A*02:43N
- A*02:01 versus A*02:09
- DRB1*14:01 versus DRB1*14:54
DRB1*14:01 vs DRB1*14:54

The conundrum of HLA-DRB1*14:01/*14:54 and HLA-DRB3*02:01/*02:02 mismatches in unrelated hematopoietic SCT

A Pasi¹, R Crocchiolo², M Bontempelli³, C Caracassi⁴, G Carella⁵, L Crespiatico⁶, L Garbarino⁷, L Mascaretti⁸, B Mazzi⁹, G Mazzola¹⁰, V Miotti¹¹, B Porfiro¹², C Tagliaferri¹³, T Valentini¹⁴, C Vecchiato¹⁵, K Fleischhauer¹⁶,¹⁶, N Sacchi¹⁷, A Bosi¹⁸ and M Martinetti¹

BMT (2011) 46 916
Effect of T-cell-epitope matching at HLA-DPB1 in recipients of unrelated-donor haemopoietic-cell transplantation: a retrospective study

Katharina Fleischauer*, Bronwen E Shaw*, Theodore Gooley, Mari Malkki, Peter Bandy, Jean-Denis Bigmon, Valérie Dubois, Mary M Harowitz, J Alejandro Madrigal, Yasuo Morishima, Machteld Oudshoorn, Olle Ringden, Stephen Spellman, Andrea Velardi, Elisabetta Zino, Effie W Petersdorf, on behalf of the International Histocompatibility Working Group in Hematopoietic Cell Transplantation
DPB1 T-Cell Epitope Algorithm

Classification of HLA-DPB1 mismatches based on T-cell-epitope groups has been shown to identify permissive mismatches and non-permissive mismatches for HLA-DPB1 after unrelated-donor haemopoietic stem cell transplantation (HSCT). Classification of HLA-DPB1 mismatches based on T-cell-epitope groups may identify mismatches that might be tolerated (permissive) and those that would increase risks (non-permissive) after transplantation. This calculator allows you to enter the HLA-DPB1 typing of a patient and donor and view the predicted T-Cell epitopes and resulting prediction of the effect of mismatching when selecting appropriate donors for HSCT recipients.

The implementation of the DPB1 T-Cell Epitope algorithm has been written in collaboration with Katharina Fleischhauer, San Raffaele Scientific Institute, Italy and Bronwen Shaw, Anthony Nolan Research Institute, UK.

Disclaimer - This tool is being offered as a tool to predict T-Cell epitope matching at DPB1 as reported in:
- Fleischhauer K, Shaw BR, Gooley T, et al.
  Effect of T-cell-epitope matching at HLA-DPB1 in recipients of unrelated-donor haemopoietic-cell transplantation: a retrospective study.
  Nonpermissive HLA-DPB1 disparity is a significant independent risk factor for mortality after unrelated haematopoietic stem cell transplantation.
  Frequency and targeted detection of HLA-DPB1 T cell epitope disparities relevant in unrelated hematopoietic stem cell transplantation.
  A T-cell epitope encoded by a subset of HLA-DPB1 alleles determines nonpermissive mismatches for hematologic stem cell transplantation.

No information entered into this tool is collected or stored on our servers.
### Donor Typings: PROSPECTIVE-DONOR-1

<table>
<thead>
<tr>
<th>Allele</th>
<th>TCE Group</th>
<th>Predicted Immunogenicity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPB1*15:01</td>
<td>3</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>DPB1*04:02</td>
<td>3</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>

**The predicted immunogenicity of the DPB1 matching for this pair is: Permissive**

### Donor Typings: PROSPECTIVE-DONOR-2

<table>
<thead>
<tr>
<th>Allele</th>
<th>TCE Group</th>
<th>Predicted Immunogenicity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPB1*03:01</td>
<td>2</td>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td>DPB1*06:01</td>
<td>3</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>

**The predicted immunogenicity of the DPB1 matching for this pair is: Non-Permissive HvG**

### Donor Typings: PROSPECTIVE-DONOR-3

<table>
<thead>
<tr>
<th>Allele</th>
<th>TCE Group</th>
<th>Predicted Immunogenicity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPB1*02:01</td>
<td>3</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>DPB1*09:01</td>
<td>1</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>

**The predicted Immunogenicity of the DPB1 matching for this pair is: Non-Permissive HvG**
Conclusions

• Understanding the relevance of different HLA mismatches is in its infancy
• Studies have shown that certain genes/antigens/alleles may have a hierarchy but more studies are needed
• Very large datasets are needed for such studies to have power
• Access to well curated HLA data in the PROMISE data is essential for the understanding of HLA mismatching
• Coding of HLA data in terms of match or mis-match is complicated and best left to the experts analysing the research questions
Acknowledgements

Dr Browen Shaw, Anthony Nolan
Dr Neema Mayor, Anthony Nolan
Prof Alejandro Madrigal, Anthony Nolan
Prof Effie Petersdorf, Fred Hutchinson
Dr Irina Evseeva, Anthony Nolan
Melanie Smith, Anthony Nolan
James Robinson, Anthony Nolan
Carmen Ruiz, EBMT
Pamela Welson, EBMT