What are major histocompatibility complex genes and why are they relevant to human health & evolution?

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Overview of the Major Histocompatibility Complex

Evolution of the MHC

MHC and human health

How/Why is the MHC so variable?
The Human Genome
Human Leukocyte Antigens (HLA)

The Major Histocompatibility Complex (MHC)
A tightly linked cluster of genes responsible for immune response and regulation, disease resistance and graft rejection
HLA matching is important for successful transplantation

but finding a perfect HLA match is challenging
The Human MHC
Two principal classes of MHC molecules

**MHC Class I molecules**
- expressed on surface of nucleated cells
- present peptides from intracellular pathogens

**MHC Class II molecules**
- expressed on immunocompetent cells
- present peptides from extracellular pathogens
Three dimensional structure
HLA Molecules

Up to 7 types of peptide presenting molecules
Both parental chromosomes are expressed equally

HLA heterozygotes can respond to a wider range of immunological challenges
# HLA Polymorphism

## Class I

<table>
<thead>
<tr>
<th>Locus</th>
<th>Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-A</td>
<td>&gt;400</td>
</tr>
<tr>
<td>HLA-B</td>
<td>&gt;700</td>
</tr>
<tr>
<td>HLA-C</td>
<td>&gt;200</td>
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</table>

## Class II

<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td>HLA-DRB1</td>
<td>&gt;500</td>
</tr>
<tr>
<td>HLA-DRB3</td>
<td>&gt;40</td>
</tr>
<tr>
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<tr>
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![HLA Polymorphism Diagram](image-url)
## HLA Diversity

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**Class II**

![HLA Diversity Diagram](image)
Genetics and Individual Identity
HLA genes are frequently used for paternity determination.
HLA genes are also used in forensics
HLA and Infectious Disease

In humans, there is evidence that the inheritance of particular MHC (aka HLA) alleles confers resistance to certain pathogens.

HLA-B53 and HLA-DRB1*1302 are found in individuals who are resistant to *Plasmodium falciparum* malaria (Hill *et al.*, 1992).
HLA and Infectious Disease

HIV-infected individuals with rare HLA types, exhibit lower viral loads and slower disease progression than infected individuals with common HLA types (Trachtenberg et al., 2003)
Gene function and rates of substitution

In most genes, $d_N < d_S$, due to functional constraints

If $d_N > d_S$, coding changes are more rapid, indicating positive selection
Evidence for positive selection in the peptide binding region of MHC molecules
High Rates of Nucleotide Substitution are Found in Peptide Binding regions

```
GAG  TAC  GTG  CGC
GAG  TTG  GTG  CGC
GAG  TTC  CTG  CAC
```

Exons: 1 2 3 4 5 6
Protein Domains: LP β₁ β₂ TM CYT
Neanderthals living in Europe developed the HLA receptor that provided them with immunity against many pathogens. The Neanderthals, which were resident in Europe, carried this receptor on their immune cells but the receptor is rare in Africans.

The receptor is thought to provide a distinct evolutionary advantage.
MHC and Infectious Disease

Disease progression is mediated by MHC class I alleles in SIV-infected macaques (Evans, Knapp et al., 1998)

Cotton-top tamarins exhibit limited MHC class I polymorphism and allelic variation and they are unusually susceptible to outbreaks of viral disease (Evans, Knapp et al., 1998)
Evidence for positive selection in primates

Fig. 7 Amino acid variability plot for 33 Masp-DRB alleles. The horizontal axis shows the amino acid position, and the vertical axis shows the number of different amino acids at a given position. The most variable sites in the rhesus macaque MHC (Slierendregt et al. 1992) are indicated by asterisks (*)
Mandrill MHC Class II Genes

34 different *Masp-DRB* sequences (~90% expressed)

1-7 sequences per individual, average number of sequences/individual is 4
Evidence for positive selection in primates

But, is this a reflection of recent events or selection in the past?
Baboon MHC Class II Genes

23 different *Paur-DRB* sequences

2-8 sequences per individual, average number of sequences/individual is 4

11 different haplotypes
Human v chimpanzee MHC genes

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<table>
<thead>
<tr>
<th>Patr-DRB1*0305</th>
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<tr>
<td>HLA-DRB1*0302</td>
</tr>
<tr>
<td>Patr-DRB1*0702</td>
</tr>
<tr>
<td>HLA-DRB1*0701</td>
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MHC Genes and Pathogen Resistance

MHC heterozygotes are, in theory, better able to respond to pathogens than MHC homozygotes.
HLA and Pregnancy Loss

Couples with high degree of HLA sharing may experience poor pregnancy outcome

- Implantation
- Pregnancy maintenance
Adaptation & Natural Selection

Generally, it is thought that the loss of genetic diversity can compromise the future ability of populations to survive in the face of changing environmental conditions.
Heritable True Fitness and Bright Birds

“General good health and freedom from parasites are often strikingly indicated in plumage and fur, particularly when these are bright rather than dull or cryptic”

(Hamilton & Zuk, 1982)
"There may be a large class of genes with effects on fitness…"

"The genes are those for resistance to various pathogens and parasites."

(Hamilton & Zuk, 1982)
Signalling MHC Genotypes

Odor cues?

Visual cues?
Signalling HLA Genotype

Odor cues

Women who were not taking contraceptive pills preferred the odor of HLA-disparate males (Wedekind et al., 1995)
Why are we attracted to particular partners?
“Opposites attract”
“Opposites Attract?”

European American couples are significantly more HLA-dissimilar than random pairs of individuals, but African American couples do not show a significant pattern of HLA-based dissimilarity (Chaix, Cao & Donnelly, 2008).

Rare instances of very high HLA similarity among non-mates suggest some couples may avoid extreme similarity, rather than favour dissimilarity… but too few samples to test rigorously… (Derti et al, 2010)
“Opposites Attract”

Couples shared fewer HLA alleles than expected by chance

Evidence for MHC-dependent mating preferences in Hutterites (Ober et al., 1994, 1996)
MHC and Mate Choice

News and Events

Smell the love
Limited MHC diversity has been found in some endangered species.
Summary

HLA/MHC genes are highly variable and play a key role in helping us deal with pathogens and disease.

Choosing partners with different HLA types from our own could ultimately provide our offspring with enhanced disease resistance.

A GOOD REASON FOR OPPOSITES TO ATTRACT
HLA and Pregnancy Loss

Couples with high degree of HLA sharing may experience poor pregnancy outcome.
Chacma baboons do not maximize MHC dissimilarity between potential or actual partners, but there is a high degree of MHC differentiation between troops.

When sex-biased dispersal is considered, MHC disassortative mate choice may not be critical for RS.
MHC genes are commonly studied for medical and forensic research, but they also have relevance for scientists interested in ecology, adaptation & animal behaviour.

Primates may use visual or olfactory signals to communicate important information about their MHC genotype for the purposes of mate choice and/or kin recognition.