The Genetics of Pemphigus

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No conflicts
**Definition:**

**Autoimmunity** is the failure of an organism to recognize its own constituent parts as "self", which results in an immune response against its own cells and tissues.

- >100 human autoimmune diseases
- 10-20% of population
- 3rd highest disease burden
Autoimmune Disease

- Genes
- Immune Regulation
- Environment

Susceptibility to disease is **COMPLEX**

- *multifactorial*
- *polygenic*
Genetics

- Genetic basis of disease
  
  *what is the evidence?*

- Identification of disease susceptibility genes
  
  *what genes cause disease?*

- Exploration of functional pathways
  
  *how do genes cause disease?*
Genetics

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## Population Studies

<table>
<thead>
<tr>
<th>Population</th>
<th>Incidence per $1 \times 10^6$</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA Jewish</td>
<td>32</td>
</tr>
<tr>
<td>Jews (Jerusalem)</td>
<td>16.1</td>
</tr>
<tr>
<td>Greek</td>
<td>9.3</td>
</tr>
<tr>
<td>Bulgarian</td>
<td>4.7</td>
</tr>
<tr>
<td>Southern Indians</td>
<td>4.4</td>
</tr>
<tr>
<td>USA non-Jewish</td>
<td>4.2</td>
</tr>
<tr>
<td>Malaysian</td>
<td>2.0</td>
</tr>
<tr>
<td>Saudi Arabian</td>
<td>1.6</td>
</tr>
<tr>
<td>French</td>
<td>1.3</td>
</tr>
<tr>
<td>German</td>
<td>0.98</td>
</tr>
<tr>
<td>Finnish</td>
<td>0.76</td>
</tr>
</tbody>
</table>

World-wide Incidence - PV

<table>
<thead>
<tr>
<th>Population</th>
<th>Incidence per $1 \times 10^6$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>range: 0.76 - 32 per million</td>
</tr>
</tbody>
</table>


**Female Predominance in Autoimmune Disease**

<table>
<thead>
<tr>
<th>Literature</th>
<th>1.1 : 1 - 2.25 : 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinha study</td>
<td>2 : 1</td>
</tr>
</tbody>
</table>

Pemphigus Incidence Worldwide
Autoimmune Co-Morbidity

21% of all PV pts report having a co-morbid autoimmune diseases

Sinha study

48% of all PV patients report having one or more relatives with autoimmune disease.

No concordance rates available for monozygotic vs dizygotic twins


Sinha study
Autoimmune Clusters

Cluster 1
PV
AITD
RA
DM1

Cluster 2
PV
AITD
RA
SLE

Autoimmune Comorbidity

Family History of Comorbidity

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Disease Susceptibility Genes

*Inheritance is polygenic*

- HLA genes
- non HLA genes
Disease Susceptibility Genes

Inheritance is polygenic

- HLA genes
- non HLA genes
HLA and PV

> 95% of PV patients type as:

- DR4
- DR6

Relative Risk (RR) = 15.2 - 127.1

*a ratio of the probability of the disease occurring in the presence of the allele vs in its absence*
Lee *et al.* Disease relevant HLA class II alleles isolated by genotypic, haplotypic, and sequence analysis in North American Caucasians with pemphigus vulgaris. *Hum. Immunol.* 68(7):630
Disease Susceptibility Genes

Inheritance is polygenic

- HLA genes
- non HLA genes
non HLA genes

Strategies to identify risk loci:

- candidate gene screen
  *the usual suspects*

- genome wide screen
  *shotgun strategy*
  
  genome-wide association study (GWAS)  
  next-generational sequencing
Candidate Gene Screen

- IGHC  

- IGKC  
  no association

- DSG3  

- TNFα, TGFβ, IL-10  
  no association

- TAP2*C, TAP2*D  

- PTPN22  
Genome Wide Screen

**Genome Wide Association Studies (GWAS)**

discovery driven

Genome Wide Screen

Next-gen Sequencing

Exome

Whole genome
Genetics

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The Ternary Complex

Pathway to Disease

Genes

Autoimmune Disease

Immune Regulation

Environment

HLA

T Cell

B Cell

Dsg3

Dsg1

Keratinocyte
HLA and PV

Cytokines
- ↑ IL-1α, IL-1β, IL-6, IL-8, IL-13, IL-21, IL-23, and TNF-α

Antioxidants
- ↓ Total antioxidant capacity (TAC)

Autoantibodies
- cluster together based on anti-Dsg3, anti-TPO, mAChR3, -4, -5 reactivity
- ↑ levels in serum

Gene expression
- cluster together (unbiased)
Gene Expression

PV blood

Microarray experiment – gene chip

AFFYMETRIX HuU133A array
(>54,000 transcripts)

1. HLA-driven genes

2. HLA-independent genes

3. Protective genes

PV

- HLA-driven genes
- HLA-independent genes

HLA+ CR

- HLA-driven genes
- Protective genes

1. Immune system processes
2. Cell structural process
3. Biogenesis + metabolic processes
Genetics - Clinical Relevance

- Identify individuals at risk *develop new genetic screening tests*
- Predict course of disease *early intervention*
- Predict response to therapy *tailored therapy*
- Understand disease mechanisms *new therapeutic targets*

New era of *personalized* medicine

*Innovation plan:* Patient crowd-sourced study
Pemphigus Vulgaris – a mobile health perspective

- **New App** currently under development in Sinha lab
- Allows user-friendly delivery of patient survey
- iOS 9+/Android

- Monitor patient condition and disease activity in *real-time*
  - Faster data collection
  - Increased data accuracy
  - Photo capable; med log, sleep log, food log

- Ensure *secure* / HIPAA compliant data transmission

- **Empower** patients with resources and care options
  - Access to providers, research opportunities

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Thank you!!

And remember to donate **BLOOD**!

Patients
Family members