The Role of Genetics in Vasculitis

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2017 Vasculitis Foundation International Symposium
June 24, 2017
Relevant Financial Disclosures

Sharon A. Chung, MD MAS

- I have nothing to disclose.
Goals

- Not to provide an exhaustive list of all the genes that are felt to be important for all of the vasculitides

- What does “genetic” mean?

- What have we learned from genetic studies in vasculitis?

- Common questions
  - Will my children get vasculitis?
  - Are there genetic tests for vasculitis?
Is vasculitis a “genetic” disease?

What does “genetic” really mean?
Vasculitis is a genetically “complex” disease

Each genetic variant contributes a small amount to disease risk

<table>
<thead>
<tr>
<th>Vasculitis</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyarteritis nodosa</td>
<td>Hepatitis B infection</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>Hepatitis C infection</td>
</tr>
<tr>
<td>ANCA-associated vasculitis</td>
<td>Farming, silica dust, solvent</td>
</tr>
<tr>
<td></td>
<td>Medications (e.g., propylthiouracil, hydralazine)</td>
</tr>
<tr>
<td></td>
<td>Drugs (cocaine, levamisole)</td>
</tr>
</tbody>
</table>
Compare DNA to discover genetic variants more common in patients.
What diseases have been studied?

<table>
<thead>
<tr>
<th>Published genome-wide association studies</th>
<th>Candidate gene studies</th>
<th>Few studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behcet’s disease</td>
<td>CSS/EGPA HSP/IgA vasculitis</td>
<td>Polyarteritis nodosa</td>
</tr>
<tr>
<td>Kawasaki’s disease</td>
<td></td>
<td>Primary CNS vasculitis</td>
</tr>
<tr>
<td>GPA(WG)/MPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Takayasu’s arteritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giant cell arteritis (GCA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryoglobulinemic vasculitis</td>
<td></td>
<td></td>
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</table>
What has been found?

So what is on chromosome 6?

- Takayasu’s arteritis
- Behcet’s disease
- GPA/MPA
Human Leukocyte Antigen (HLA) genes

- Short arm of chromosome 6
- Strongest genetic signal for almost all autoimmune diseases
- Proteins that help identify self from non-self
  - Class I are on all cells
  - Class II are on specific cells of the immune system
  - Present foreign and self proteins to the immune system
- Are matched for organ and bone marrow transplants to prevent rejection
## Genetic associations in the MHC

### Vasculitis Gene Affected Unaffected

<table>
<thead>
<tr>
<th>Vasculitis</th>
<th>Gene</th>
<th>Affected</th>
<th>Unaffected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takayasu’s arteritis</td>
<td>HLA-B51</td>
<td>57%</td>
<td>18%</td>
</tr>
<tr>
<td>Behcet’s disease</td>
<td>HLA-B52</td>
<td>63%</td>
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### CSS/EGPA and GCA

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<th>Unaffected</th>
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</thead>
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<tr>
<td>CSS/EGPA</td>
<td>HLA-DRB1*04</td>
<td>39%</td>
<td>20%</td>
</tr>
<tr>
<td>GCA</td>
<td>HLA-DRB1*04</td>
<td>61%</td>
<td>24%</td>
</tr>
</tbody>
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<th>Unaffected</th>
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</thead>
<tbody>
<tr>
<td>GPA (anti-PR3+)</td>
<td>HLA-DPB1*04</td>
<td>73%</td>
<td>44%</td>
</tr>
</tbody>
</table>
What do these results tell us?

- Variation in different genes lead to different types of vasculitis

- Some vasculitides share risk genes
  - Common mechanism?
  - Non-HLA genes influence the type of vasculitis developed

- Variants are also frequent in unaffected individuals
  - Less useful for genetic testing

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Genes outside of the HLA are also important

- Different genes associated with different vasculitides
- Many regulate the immune system
- Help inform why vasculitis develops but not “testable”
Ok, so why do genetic studies?

- **Biology**
  - What pathways are important in disease development
    - Provide targets for drug development
    - Identify potential biomarkers for disease activity
  - Why certain patients develop certain manifestations (kidney vs. lung vs. skin vs. GI tract, etc.)

- **Medication response**
  - Identify individuals who are more likely to respond or develop toxicity to a specific medication
Will my children get vasculitis?

- Does vasculitis run in families? Somewhat; not well studied

- Some examples:
  - Behcet’s (in Turkey):
    - Sibling risk is 11.4-52.5x higher than general population
    - Overall frequency is ~1:1000 → sibling risk is ~1-5%
  - Kawasaki’s (in Japan):
    - Sibling risk is 10x higher than the general population
    - Risk for a child is 2x higher than general population
    - Overall frequency is ~1:500 → 2% sibling risk, 0.4% child risk
Does vasculitis run in families?

GPA/WG (in Sweden):

- 1st degree relative risk is 1.6x higher than general population
- Overall frequency is ~ 60/million → 90/million
- Increased risk of other autoimmune diseases in 1st degree relatives:
  - Any autoimmune disease: ~ 1.3x higher
  - Multiple sclerosis: 2x higher (0.15% → 0.30%)
  - Rheumatoid arthritis: 1.5x higher (1% → 1.5%)
- GCA, TA, PAN, CSS/EGPA, HSP/IgAV, and others: case reports, but no formal estimates of familial risk
What does this tell us?

- Your family member (parent, sibling, child) is at:
  - Higher risk for developing vasculitis
  - Higher risk of developing another autoimmune disease
  - But the absolute risk is still **VERY LOW** (often 1% or less!)

- Genes are not the complete story
  - Other exposures (environmental?) are important

- Very different from other “Mendelian” diseases (e.g., familial breast cancer)
  - Single gene vs. multiple genes

- Don’t live in fear!
Are there genetic tests available to...

- help diagnosis/predict vasculitis?
  - Unfortunately, not at this time
    - Genetic risk variants are too common to be useful
    - Would not recommend genetic testing at this time
  - Future tests will likely need to look at multiple genes

- determine which medications I should or should not take?
  - TPMT testing for azathioprine (Imuran)
    - Absent 3 in 1000 individuals (azathioprine is toxic)
  - Need to study the influence of genetics in drug response for future clinical trials
What does the future hold?

- Whole genome (“next generation”) sequencing
  - Sequencing all of an individual’s DNA
  - Identify new and/or rare genetic variants that have more impact on developing vasculitis
  - Currently ~$1500/individual, but costs are dropping rapidly
    - Likely a common research tool in the future
How can you help?

- If are seen at a Vasculitis Clinical Research Consortium (VCRC) site:
  - Enroll in one of the genetic studies
    [http://rarediseasesnetwork.epi.usf.edu/vcrc/centers/index.htm](http://rarediseasesnetwork.epi.usf.edu/vcrc/centers/index.htm)

- If you are not seen at a VCRC site:
  - Enroll in the VCRC contact registry:
    [http://rarediseasesnetwork.epi.usf.edu/vcrc/registry/](http://rarediseasesnetwork.epi.usf.edu/vcrc/registry/)

- If you have already enrolled, thank you!
## Genetic differences: GPA and MPA

<table>
<thead>
<tr>
<th>Odds Ratios</th>
<th>GPA</th>
<th>MPA</th>
<th>Anti-PR3 (PRTN3)</th>
<th>Anti-MPO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HLA-DP</strong></td>
<td>5.39</td>
<td>1.6</td>
<td>7.03</td>
<td>1.55</td>
</tr>
<tr>
<td><strong>HLA-DQ</strong></td>
<td>1.2</td>
<td>1.6</td>
<td>1.15</td>
<td>1.53</td>
</tr>
<tr>
<td><strong>SERPINA1</strong></td>
<td>1.85</td>
<td>NA</td>
<td>1.89</td>
<td>NA</td>
</tr>
<tr>
<td><strong>PRTN3</strong></td>
<td>1.28</td>
<td>NA</td>
<td>1.30</td>
<td>NA</td>
</tr>
</tbody>
</table>

Larger odds ratios indicate stronger associations
NA = not associated

- Although GPA and MPA have similar manifestations, genetic associations are different
- Some associations are stronger with autoantibody status than with the clinical disease type
Why did I get this disease?
  • Does genetics play a role?

Will my children be affected?
  • Should my children undergo testing to see they will develop this disease?
What does the future hold?

- **Epigenetics (DNA methylation)**
  - A method of how the environment influences disease risk or activity
  - Influenced by age, environmental exposures, medications
  - Important in autoimmune diseases (RA, SLE, GPA/WG)

- High methyl diet
- Thin, not diabetic
- Obese, diabetic
- Demethylating

```
5’    C    G    C    G    3’
|      |      |      + CH₃    |      |
Unmethylated - gene expressed
```

```
5’    C    G    C    G    3’
|      |      |      CH₃    |
Methylated - gene repressed
```
We are in exciting era of genetic studies for vasculitis

Future studies: identify targets for diagnostic tests and less toxic medications

No genetic tests available to help diagnose disease, predict disease risk, or inform disease activity—yet!

Risk of vasculitis (and other autoimmune diseases) is higher for relatives of individuals with vasculitis, but remains VERY LOW

Please participate in a genetic study if the opportunity arises!
Thank you!

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