Chronic Granulomatous Disease
Genetics & Carrier Issues

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Potential genetic defects

- X-Linked
  - CYBB
- Autosomal Recessive
  - NCF1
  - CYBA
  - NCF2
  - NCF4
Genetics

90% of patients have CYBB or NCF1 variants
**Genetics**

**Point Mutation**—change of individual letter in a book, causes you to read word incorrectly and change meaning

**Deletion**—deleting chapter of book, sometimes chapter before or after is deleted too
McLeod Syndrome

- No kell antigen on RBC’s
- Acanthocytosis
  - Abnormal shaped RBC’s
- Can be sensitized to transfusions and have future reactions
- Neuropsychological impairment later in life
- Cardiovascular impairment later in life
Genetics

- McLeod
  - Acanthocytosis
  - Absent Kx
  - Neurological

- Duchenne Muscular Dystrophy

- CGD
  - Granuloma
  - Infection

- Retinitis Pigmentosa
We know it’s X-linked, why do we need to know more?
Table 1. Results of Univariate and Bivariate Cox Regression Models Showing the Association between Dihydrorhodamine Fluorescence Values and Mortality among Patients with Chronic Granulomatous Disease.

<table>
<thead>
<tr>
<th>Model Covariates</th>
<th>Hazard Ratio for Death (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydrorhodamine &lt;225 AU</td>
<td>5.46 (1.26–23.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydrorhodamine &lt;225 AU</td>
<td>4.83 (1.34–10.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>History of liver abscess</td>
<td>3.76 (1.11–21.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Model 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydrorhodamine &lt;225 AU</td>
<td>4.89 (1.12–21.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Increase in alkaline phosphatase &gt;0.25 U/liter/yr</td>
<td>5.49 (2.05–14.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Model 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydrorhodamine &lt;225 AU</td>
<td>4.52 (1.01–20.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Decline in platelet slope &gt;9000 platelets/mm³/yr</td>
<td>1.56 (0.56–4.36)</td>
<td>0.40</td>
</tr>
</tbody>
</table>
Genetics
# Genetics

<table>
<thead>
<tr>
<th>Mutation</th>
<th>No. of Families</th>
<th>Total No. of Patients</th>
<th>O$_{2}^-$ Production</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>gp91phox — missense mutations</td>
<td>32</td>
<td>39</td>
<td>6.76±2.18 (0.44–60.65)</td>
<td>—</td>
</tr>
<tr>
<td>Amino acids 1–309, except His222</td>
<td>13</td>
<td>18</td>
<td>14.42±4.67 (2.09–60.65)</td>
<td>—</td>
</tr>
<tr>
<td>Amino acids 310–570, plus His222</td>
<td>19</td>
<td>21</td>
<td>1.53±0.24 (0.44–4.37)</td>
<td>&lt;0.001‡</td>
</tr>
</tbody>
</table>

Table 2. Production of Reactive Oxygen Intermediates According to Mutation Associated with Chronic Granulomatous Disease.
Genetics

**Need for genetic classification**
- Confirm diagnosis
- Location of variant in protein vs intron vs promoter region vs large deletion
- Genetic counseling/family planning

**Future**
- Use in CRISPR/Cas9 gene therapy
- ? Interferon responsive variant
X-Linked Carriers

Just carriers of the disease...

DONT WORRY,
X-Linked Carriers

**Reported complications**
- Autoimmune manifestations
- Discoid lupus erythematosus
- Raynaud phenomenon
- Oral aphthous ulcers

*Most literature based on case reports*
X-Linked Carriers

Maybe we shouldn’t just forget about carriers?

X-linked carriers of chronic granulomatous disease: Illness, lyonization, and stability

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X-Linked Carriers

A. Distribution according %DHR+

B. Plot of %DHR+ by age in female carriers of CGD
X-Linked Carriers
X-Linked Carriers

- Average DHR 39% in carriers with autoimmune or inflammatory manifestations
- Autoimmunity alone was not associated with DHR

<table>
<thead>
<tr>
<th>TABLE I. AIMs in CGD carriers</th>
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<tbody>
<tr>
<td><strong>Clinical features</strong></td>
</tr>
<tr>
<td>DLE</td>
</tr>
<tr>
<td>Granulomatous colitis (Crohn-like disease)</td>
</tr>
<tr>
<td>SLE</td>
</tr>
<tr>
<td>Hypothyroidism/hyperthyroidism</td>
</tr>
</tbody>
</table>

*Number of carriers with AIMs: more than 1 condition might be diagnosed in each female subject.
X-Linked Carriers

**DHR and Infections**

*FIG 3. Risk of infection and AIMs. Probabilities are based on %DHR⁺ values. A logistic regression model was used to estimate the probability of infection or AIM as a function of %DHR⁺ value. P values tested whether the %DHR⁺ value is a significant predictor for infection or AIM.*
X-Linked Carriers

Is a carrier’s X-inactivation/DHR stable over time?

[Graph showing the percentage of DHR+ over age for twin sisters A and B, with correlation coefficients r=0.83 and r=0.5.]
X-Linked Carriers

Mom vs daughter? Sisters?
X-Linked Carriers

1. **Skewed inactivation and DHR<20%**
   - Highly correlated with infections
2. **DHR unrelated to autoimmune/inflammatory manifestations**
3. **High correlation in X-inactivation between twins and sister**
4. **“Generational resetting”—no correlation between mom and daughter DHR%**
5. **DHR % is not stable over time**
X-Linked Carriers

What does this mean?
What do we do with this information?

- Not always asymptomatic—establish with experienced immunologist if having infectious or autoimmune complications

What if asymptomatic?

- Reasonable to establish with experienced immunologist to get baseline DHR—<20% associated with infection

But DHR changes with time?

- Reasonable to follow repeat DHR every few years
CGD Associated Colitis
Treatment

Questions