The RHDGen Network

Genetics of Rheumatic Heart Disease (RHD)
The RHDGen Network

- Rationalé for RHDGen Network
- Proposed Activities
- Organisation
- Progress
Africa is the RHD Capital of the World
Figure 2: Pathogenetic pathway for ARF and RHD

Environmental factors, especially overcrowding

Precipitating event: infection with a strain of group A streptococcus carrying specific virulence factors

Repeated group A streptococcus infections

Susceptible host

Priming of immune response

First episode of ARF

Repeated or ongoing infections possibly driving the valvular inflammatory response

Episodes of recurrent ARF

Molecular mimicry between group A streptococcus antigens and host tissues

Exaggerated T-cell mediated immune response

Genetically-determined host factors

RHD

Carapetis. Lancet 2005;366:155
### Acute Rheumatic Fever occurrence in DZ vs MZ Twin Pairs

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio (95% CI)</th>
<th>No. of events</th>
<th>MZ</th>
<th>DZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irvine Jones 1933</td>
<td>55.00 (0.83, 3650.69)</td>
<td>2/2</td>
<td>0/5</td>
<td></td>
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<tr>
<td>Wilson 1937</td>
<td>5.00 (0.15, 166.59)</td>
<td>2/2</td>
<td>2/4</td>
<td></td>
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<tr>
<td>Taranta 1959</td>
<td>9.00 (0.86, 94.24)</td>
<td>3/16</td>
<td>1/40</td>
<td></td>
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<tr>
<td>Kaufmann 1938</td>
<td>10.00 (1.10, 90.90)</td>
<td>5/27</td>
<td>1/45</td>
<td></td>
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<tr>
<td>Stevenson 1953</td>
<td>57.00 (0.79, 4123.85)</td>
<td>1/1</td>
<td>0/9</td>
<td></td>
</tr>
<tr>
<td>Reed 1964</td>
<td>5.25 (2.55, 10.83)</td>
<td>36/127</td>
<td>11/157</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>6.39 (3.39, 12.06)</td>
<td>49/175</td>
<td>15/260</td>
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</tbody>
</table>

Odds ratio of concordance for acute rheumatic fever according to type of zygosity in a random-effects synthesis of data from studies included in the meta-analysis.

Engel M et al. PLoS ONE 2011 6(9):e25326
Which genes are involved in increasing or decreasing your risks for developing RHD
Proposed activities

• To recruit 2,500 cases and 3,500 controls
  - Case-control (discovery of variants): 1500 cases and 1500 controls
  - Trio study (replication study) 1000 cases and 2000 controls

• To identify genetic variants affecting susceptibility and resistance to RHD

• To train a group of scientists and clinicians in genomic studies of multifactorial disease

• To build a network for phenotyping of RHD

• To address ethical, legal and social issues that are relevant to Africa
Genotyping strategy

• GWAS is the preferred strategy for detecting common variants that are associated with RHD: ‘common variant, common disease’ hypothesis ($500 per sample)

• Whole genome sequencing would be ideal but the cost is prohibitive at this stage ($4000 to $5000 per sample)
Other scientific spin-offs

• Genetics of non-cardiac manifestations of acute rheumatic fever (ARF): Sydenham chorea, arthritis, skin changes

• Genetics of cardiovascular risk factors as quantitative traits: ECG and echo measurements, blood pressure, body size

• Opportunity for Immunology of ARF and RHD

• Platform for studies of ELSI
Progress

• Identification of the first 1,500 index cases is complete

• Standard operating procedures for the laboratory are being finalised

• Awaiting ethics committee approvals

• Start date for collection of DNA: 01 July 2013
Finally...

• We have already recruited 60% of probands required for the study

• The RHDGen Health Scholars Program will develop genomic teams of clinicians and scientists in 8 African countries

• RHDGen is a platform for the development of cardiovascular genetics in African populations