RHDGen Progress Report

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Mayosi Research Group
Goals

- Recruit 2,500 cases of RHD and 3,500 non-RHD ethnically-matched adult controls;
- Conduct a case-control GWAS
  - by genotyping 5 million single nucleotide polymorphisms (SNPs) in 1,500 RHD cases and 1,500 controls;
- Replication of findings in a further 1,000 cases and 2000 parental controls (Trio Study);
- Train 16 scientists/clinicians in genomics and ethics at masters, doctoral and post-doctoral levels;
- Address ethical, legal and social issues that are relevant to Africa.
Sampling Framework

- RHD cases from hospitals in 8 sub-Saharan countries
- Controls: Mostly community-based
Experimental design

• **Phase 1:** GWAS of 1500 cases and 1500 controls to discover SNPs associated with susceptibility and resistance to RHD (i.e., the Discovery Cohort)

• **Phase 2:** family-based GWAS of an independent set of 1000 trios to replicate the findings of the first phase (i.e., the Replication Cohort)

• **Phase 3:** combined case-control study of 2500 cases and 2500 controls or pseudo-controls derived from the first two phases in order to discover genetic variants of modest effect and confirm the findings of the first two phases (i.e., the Meta-analysis).
## Recruitment Sites

<table>
<thead>
<tr>
<th>Site</th>
<th>Principal Investigator</th>
<th>Status</th>
<th>Date of Initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>101 - Cape Town</td>
<td>Bongani Mayosi</td>
<td>Recruiting</td>
<td>Oct 2013</td>
</tr>
<tr>
<td>201 - Zambia</td>
<td>John Musuku</td>
<td>Recruiting</td>
<td>Sep 2014</td>
</tr>
<tr>
<td>301 - Namibia</td>
<td>Chris Hugo-Haman</td>
<td>Recruiting</td>
<td>Oct 2014</td>
</tr>
<tr>
<td>401 - Nigeria</td>
<td>Fidelia Bode-Thomas</td>
<td>Recruiting</td>
<td>Sep 2014</td>
</tr>
<tr>
<td>601 - Kenya</td>
<td>Steve Ogendo</td>
<td>Recruiting</td>
<td>Feb 2015</td>
</tr>
<tr>
<td>701 - Sudan</td>
<td>Ahmed El-Sayed</td>
<td>Recruiting</td>
<td>Feb 2015</td>
</tr>
<tr>
<td>801 - Uganda</td>
<td>Charles Mondo</td>
<td>Ethics approved</td>
<td>May 2015</td>
</tr>
</tbody>
</table>
# Recruitment

<table>
<thead>
<tr>
<th>Site</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cape Town</td>
<td>676</td>
<td>735</td>
</tr>
<tr>
<td>Zambia</td>
<td>92</td>
<td>0</td>
</tr>
<tr>
<td>Namibia</td>
<td>145</td>
<td>0</td>
</tr>
<tr>
<td>Nigeria</td>
<td>69</td>
<td>64</td>
</tr>
<tr>
<td>Kenya</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Sudan</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1076</strong></td>
<td><strong>800</strong></td>
</tr>
</tbody>
</table>

- **Trios**: 35 across 4 sites
Monthly Case Recruitment

www.RHDAfrica.org
Cumulative Case Recruitment

www.RHDAfrica.org
Phenotype
Pilot phase

- DNA Extraction: 1,670 specimens
- 1,094 specimens sent for first GWAS analysis to Guillaume Pare (McMaster) in April 2015
- 2.5 M Illumina chip
- Challenges:
  - Sample couriering
  - QA issues
  - QC issues
RHDGen Health Scholars’ Programme

• Appointments:
  – 1 x Postdoctoral Fellow (Zambia)
  – 2 x MSc studentships in empirical ethics awarded (Malawi / Cameroon)
  – 2 x MSc studentships in molecular genetics awarded (Kenya / Zimbabwe)
  – 1 x PhD studentship in molecular genetics awarded (Burundi)
  – O/S: PhD studentships in statistical genetics (x 1), and bioinformatics (x1)

• 7 x MMed Fellows appointed:
  • 1 x each recruiting centre (outside SA)
Challenges

• Delayed site initiation
  – October 2013 to May 2015
  – Ethics approval delay
  – Admin problems including financial issues
  – Infrastructure
Challenges

- **Recruitment**
  - Small number of fully active sites
  - Site specific challenges e.g. small patient pool, distance from hospitals, loss to follow up
  - Trios are not as many as initially thought:
    - e.g. Nakita found only 22 out of 500 at Cape Town alone. May well have to revise the target to only 200 trios.
  - REMEDY: n=1,500: currently only 26% of these have been enrolled
## Challenges

Based on actual numbers of CRFs in RHDGen Dbase

<table>
<thead>
<tr>
<th>Site</th>
<th>No of pts in REMEDY</th>
<th>Recruited into RHDGen</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>101 - Cape Town</td>
<td>489</td>
<td>276</td>
<td>56</td>
</tr>
<tr>
<td>201 - Zambia</td>
<td>127</td>
<td>35</td>
<td>28</td>
</tr>
<tr>
<td>301 - Namibia</td>
<td>277</td>
<td>49</td>
<td>18</td>
</tr>
<tr>
<td>401 - Nigeria</td>
<td>143</td>
<td>44</td>
<td>31</td>
</tr>
<tr>
<td>501 - Mozambique</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>601 - Kenya</td>
<td>305</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>701 - Sudan</td>
<td>185</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>1568</strong></td>
<td><strong>413</strong></td>
<td><strong>26</strong></td>
</tr>
</tbody>
</table>

*Potential Enrollees > 1,000*
Challenges

- Recruitment
  - REMEDY: n=1,500: currently only 26% of these have been enrolled
  - Small number of fully active sites
  - Site specific challenges e.g. small patient pool, distance from hospitals, loss to follow up
  - Trios are not as many as initially thought. Nakita example where only 22 out of 500 at Cape Town alone. May well have to revise the target to only 200 trios.
Challenges

• Possible solutions:
  – All sites should be fully active
  – Outreach/Partnerships
  – REMEDY
MMED Meeting

- Recruitment review
- Science aspects to be discussed within postgraduate projects as part of RHDGen
- Come up with innovative methods (collectively) to improve recruitment to meet the (new) recruitment target date of June 2016.
Community Engagement Activities

- Heldeberg college Health Awareness Week – opportunity to highlight RHD and the importance of sore throat management