Collaborative African Genomics Network

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Broad Objectives *CAfGEN*

- A retrospective study on the genomics of paediatric HIV disease progression among long-term non-progressors using children with rapidly progressive disease as controls

- A prospective genomics study on HIV/TB disease progression in children

- Establishment of genomics capacity and provision of enabling technology in Botswana and Uganda

- Community engagement and education in both countries to support current and future genomics research
Sample Collection from two Paediatric Cohorts

1. **Retrospective HIV/AIDS cohort (CP1):**
   HIV-infected children at the phenotypic extremes of HIV disease progression: 500 long-term non-progressors (LTNPs) and 500 rapid progressors (RPs)

2. **Prospective HIV/TB cohort (CP1):**
   2000 HIV-infected children followed over time for progression to active TB
Retrospective HIV/AIDS Cohort (CP2): Approach

- **Aim:** To identify host genetic variants within the coding regions of candidate genes and throughout the genome that influence disease progression.

- Assess genes that have already been associated with HIV disease progression in other populations: Class I HLA and chemokine receptors, comparing LTNPs to RPs

- Using whole-exome sequencing, identify new host genes affecting paediatric HIV disease among 200 LTNPs and 200 RPs

- Promising variants will be replicated in the remaining 300 LTNPs and 300 RPs
**Candidate gene studies**
(N=200 LTNPs/200 RPs)
Sanger sequencing/allelotyping
**Chemokine receptors - UB**
Class I HLA alleles - MakCHS

**Novel variant ‘enrichment’ study**
(N=200 LTNPs/200 RPs)
Whole Exome Sequencing
MakCHS (50%); BCM (50%)

**Potential variant pool**
Identification of candidate variants (P< 0.01)

**Replication**
(N = 300 LTNPs/300 RPs)
Genotype top candidates variants in remaining cohort
UB and MakCHS

**Validation of identified variants**
Sanger Sequencing
UB

*All analyses will be undertaken by **CAfGEN** trainees assisted by faculty at BCM and Makerere/UB*
Aim: To identify genes that show differential expression with the progression to active TB disease in HIV co-infected children.

Integrate genome-wide genotyping with RNA sequencing to look for SNPs that are causally linked to the progression to active TB in HIV-infected children.

Strong candidate genes must show both a change in transcript abundance with the transition from inactive to active disease AND...

The level of expression of the gene must be influenced by the underlying SNP genotype

Approach adds substantial statistical power to establish the association of SNPs (genotype) with the progression to active TB disease (clinical phenotype) thereby requiring fewer samples than a typical GWAS.
CP3 Approach

120 active TB progressors
DNA & paired RNA samples
Core project 1

RNA sequencing & Differential expression analysis
BCM by CAFGEN trainees

Genome-wide SNP genotyping
BCM by CAFGEN trainees

Expression QTL and Integrated Genomic analysis
UB, BCM, MakCHS

Targeted Replication
100 active TB ‘cases’
/100 baseline ‘controls’
UB
Overall Progress Summary

- Program was funded in Jan 2014
- Two-year graduate level training at the Genomics Research Training Program (GRTP) at BCM started in June 2014 in part-fulfillment of PhD for 3 candidates from BW and 3 candidates from UG
- Equipment procured:
  - Illumina MiSeq sequencer for MakCHS
  - ABI 3500 capillary sequencer for UB
  - Freezerworks for both UB/MakCHS
- MTA between BCM and MakCHS
- Community Advisory Boards active at both sites
- 5 IRB approvals for all sites
- Recruitment commenced in Uganda in June 2014 and in Botswana in October 2014
Patients and Samples

- Retrospective study we aimed to recruit 500 HIV RPs and 500 LTNPs; and so far:
  - 457 of the 500 RPs
  - All 500 LTNPs

- Prospective study aimed to recruit 2000 HIV infected children at baseline and follow them for at least 18 months for development of active TB: so far we have screened 773 and recruited 771
  - Botswana – Screened 443 and enrolled 406 With 1 TB incident
  - Uganda – Screened 510 and enrolled 479 With 1 TB incident

- Also aimed to recruit 100 patients with active TB at baseline:
  - So far we have recruited 4 Uganda and 2 Botswana
Sample Processing

- University of Botswana received 393 retrospective samples of which 268 have had DNA extracted, quantified, quality controlled and archived
  - Received 312 samples for the prospective study
- MakCHS has received 500 retrospective samples of which all 500 have had DNA extracted, quantified, quality controlled and archived
  - Received all 408 samples for the prospective study
- 150 samples (100 Bw and 50 Ug) were successfully shipped from Uganda to BCM in March for sequencing
- First 50 samples are currently in Whole Exome sequencing pipeline in Human Genome Sequencing Center at BCM
- Additional samples will be shipped by June 2015
Continental Training

- In January 2015, UB held a week-long genetic association course with application to analysis of sequence and genotype data for 12 participants from Botswana, South Africa, and Uganda

- Several of short in-house trainings have been held at the Baylor COEs in Uganda COE and Botswana, including:
  - Protocol training for study team members
  - GCP and HSP training for study team members
  - GCLP training for laboratory staff
  - SOPs and clinical quality management plan trainings for study team members
Community Engagement and Education

- Awarded an Engaging Science Grant from the Wellcome Trust to educate media and public on genes and heredity in Botswana using media workshops and comic books
  - Community Stakeholders Workshop: 37 participants
  - Media Workshop (Journalists & Cartoonists): 24 participants
  - Comic books under development - first of 4 books due in May 2015
Next Steps

- Establish Genomics Training Programmes at UB/MakCHS
  - MakCHS – Department approval at the final stage
  - Provision for the Department of Genomics in UB
- Monitor trainees
- Shipment of samples across institutions for genomics
- Publish and disseminate Genome Adventures comic books
- Bioinformatics training in Makerere University in July/Aug 2015
Concluding Remarks

- We have made excellent progress so far

- Prospective study will require more time (6-12 months) to complete
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