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AfroSickle: *Network News*

To Promote Science and Improve Patient Care for SCD in Africa

Project Convener:

R. Cooper
rcooper@lumc.edu

Project Coordinators:

Nallely Mora
namora@lumc.edu

Helen Nde
hnde@luc.edu

Welcome!

Pardon our interval of silence. Progress has continued but other life events have intervened. Several projects under development are described below and we welcome – actually very much need – your feedback and opinions.

Network News: Headlines

- Plans for NIH Submission on Genetics of SCD
- Ibadan HU Trial
- A Second Potential Genetic Study of SCD
- New NHLBI Center on Translational Research and Implementation Science Open for Business
- Published Papers

Network News: The Stories

Plans for NIH Submission on Genetics of SCD

Based on joint discussions between Neil Hanchard (Baylor), Bamidele Tayo (Loyola) and Richard Cooper (Loyola) we have a working draft of the aims for an NIH grant. The "headline message" is that we propose to define the segregating variability at genetic loci known to influence the clinical course of SCD in multiple African populations. The basic idea is to undertake deep sequencing in the following set of genes. First, as outlined previously by Neil, we will attempt to determine whether Hb S mutation occurred once in the evolutionary history of our species (with the resulting variation in background haplotypes reflecting complex structural reorganization at this locus. The following paragraph summarizes this argument:

> *We will leverage the extensive reach of our network to explore a long-standing conundrum of SCD genetics. Local sickle (HbS) haplotypes, classically defined by RFLP sites across the β-globin locus, are the linchpin of our understanding of the*

origin(s) of the sickle mutation and have long been correlated with SCD severity. Recent observations of long-range HbS haplotypes - driven by recent selective sweeps in response to malarial endemicity - and extensive local diversity at the β-globin gene cluster, hint at a previously underappreciated complexity to HbS haplotypes. This has implications for both the origins of the HbS mutation and the identification of cis-acting factors influencing SCD variability. We propose the application of targeted, long-range sequencing to decipher the complexity of HbS haplotypes in ? 5 African countries, representing four classical βs haplotypes, with the ultimate goal of relating this complexity to the clinical variability in SCD in these populations.

The following paragraph describes the rationale for one of the Specific Aims:

We hypothesize that a detailed genomic exploration of sickle β-globin gene cluster diversity will reveal common cis events that underlie the association between classical Bs haplotypes and clinical outcomes.

In addition we will examine sequence variation at loci influencing Hb F and enzyme systems the influence hemolysis. This work will be coordinated by G. Lettre and S. Offori-Acquah, in the US/Canada, and sickle cell centers in Ghana, Nigeria, Cameroon and Kenya. While we do not propose to capture "all" segregating variability in Africa, we will make the argument that if a comparison of these groups suggests that most of what can impute to be significant has been observed, then we have a reasonable proxy for other African groups. It would, needless to say, be helpful to have representation from populations in Central African Republic and Congo, for example. Extensive sequencing is expensive to do and tedious to clean and analyze, so there are limits. Clearly additional analyses could be carried out using genotyping arrays. In addition, we

will propose to "nest" this study within the Genome Diversity in African Population project.

In the next phase we will work out the sampling design together with the co-investigators in Ghana, Nigeria, Cameroon and Kenya. We recognize that differential survival to adulthood could bias the distribution of variants that we find, and we may need to include a set of non-SS individuals to be sure our estimates are not far from the population means.

Ibadan HU Trial

The study has now been registered at ClinicalTrials.gov under the name "*Risk Clinical Stratification of Sickle Cell Disease in Nigeria, Assessment of Efficacy/Safety of Hydroxyurea Treatment."* Its ClinicalTrials.gov Identifier is NCT02149537. The url link to the online info is www.clinicaltrials.gov/ct2/show/NCT02149537. The trial will start recruiting patients in July 2014. Enrollment of participants into the cross-sectional phase continues.

A Second Potential Genetic Study of SCD

We have now had several conversations about the potential for a large age-stratified survey of Hb and genetic variants. This would be used to create a "synthetic" cohort, i.e., define the survival patterns to adulthood in relation to Hb phenotype and other genotypes that influence survival. Several members of our Network have substantial data on this question and we have agreed to try to pool together the existing data and write a short description of what a formal project would look like, particularly in regard to sample size and between population or study site variability. (In other words, survival patterns may be very different in Kumasi compared to Kano . . .).

New NHLBI Center on Translational Research and Implementation Science Open for Business

The Institute has formally created the program headed by George Mensah – a friend and collaborator of many of ours. The following quote from the press release suggests the potential direction of the Center:

> *CTRIS also will be the focal point for NHLBI's global health activities, examining global health issues through the lens T4 translation research and implementation science. As an example, Dr. Mensah referenced a 2013 publication he co-authored in the Journal of the American Medical Association. The paper measured the burden of diseases, injuries, and leading health risk factors in the United States from 1990 to 2010 and compared these measurements with those of the 34 countries in the Organization for Economic Co-operation and Development (OECD) countries. Despite a large investment in biomedical research by the U.S., its position based on all mortality-based metrics declined between 1990 and 2010 to 27th or 28th among the 34 OECD countries. But that's not all.*
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> *"Ask the question, 'How are we doing in heart attacks?' You'll see that we've invested the most money in heart attack research; yet in terms of the summary measure of health, we rank 17th. How did that happen? If you look at chronic lung disease, we rank 16th. The only category in which we come first is in how much money we spend per person every year. It is tempting to attribute these differences to differences in healthcare system between the U.S. and the OECD countries, but we know it is more complex than that," Dr. Mensah added.*
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> *NHLBI leadership in this arena is crucial because heart disease is the leading contributor to premature mortality in the U.S. and OECD countries; and chronic lung disease and sickle cell disease are two of the top four diseases with the greatest potential for reducing years lived with disability in these countries.*

"With research, perhaps we can begin to explain what's really driving the differences," he added.

There will be a "think tank" meeting for the Center in September and Gbenga Ogedegbe (NYU) and Richard Cooper (Loyola) have been invited to attend.

Published Papers

The paper on Hb F, BCL11A and SCD hospitalizations appeared in March. Click here for that and more ASN publications. A manuscript is in preparation to describe the genetic and Hb phenotype distributions in our baseline cohort from Ibadan.

R. Cooper