Genomic Opportunities for Studying Sickle Cell Disease

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What questions are we asking?

- Connecting genotype with phenotype is the fundamental aim of genetics.
- What affects the risk of disease outcome in sickle cell disease
  - Genomic factors which enhance damage
  - Genomic factors which protect against damage
  - Modulation environmental factors

Why now?

- **Genotyping** has become technically feasible – many things go into decisions, but the technology is available to heavily interrogate and define the genome
- **Phenotyping** – the observable expression of genes which produce noticeable characteristics -- lags way behind
  - Primary and secondary processes are confounded
  - Disease outcomes evolve over time
- "Multiple hypothesis" testing problem creates major computational challenges

What kinds of populations should we go after?

Genotype to phenotype (G2P)

- Hypothesis-generating approach
- Large numbers of individuals
- **Well-defined** phenotyping essential
- Computational approaches challenging – modifiers of Mendellian disease

Phenotype to genotype (P2G)

- Hypothesis-testing approach
- Need enrichment for phenotype
- Families and genetically informative populations are most useful
  - African
  - Enrich for haplotypes (Benin, CAR, Senegal..)

What are phenotypes in SCD/

- Processes which lead to organ damage
  - Hemolysis
  - Vaso-occlusion
  - Thrombosis
  - Inflammation
- Processes which are NOT phenotypes (too many underlying causes) and thus not now susceptible to G2P or P2G
  - Death
  - Pain

Today's work

- What are the highest priority questions?
- Can we begin to phenotype well enough to make it worthwhile developing cohorts? This requires knowing what the questions are.
- If we were to invest in systematic approaches to interrogate genetics, genomics and environmental factors, how would this be designed?
- How far should we be going in genomics?
- Who needs to be on the teams?
- **Everything must be shared.**