**Genomics investigation of human genes associated with diseases at higher rates in African Americans.**

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We seek support to initiate an innovative line of research on health disparity. Our long-term goal is to develop functional assays in the model organism of *Saccharomyces cerevisiae* for human genes associated with diseases at higher rates in African Americans (DHRAA). To achieve this goal, Miss Clegg will focus on a list of candidate genes.

Polymorphisms in human genomes are known to be associated with DHRAAs. For example, sickle-cell disease is caused by semi-recessive mutations in the hemoglobin gene [[1](#_ENREF_1)]. This disease has a high-incidence in AADPs because the mutant alleles of the hemoglobin genes exist at high frequencies in AADPs. The high frequency of the mutant hemoglobin alleles can be attributed to resistance to malaria, an adaptive advantage found in heterozygous carriers [[1](#_ENREF_1)]. Kidney diseases occurs disproportionally high in AADPs, and have been linked to several genetic factors [[2](#_ENREF_2)]. Recently, one form of kidney disease, a spectrum of nondiabetic end stage kidney disease (ESKD) that is a DFHAA, was linked with missense mutations in *APOL1* gene [[3](#_ENREF_3)]. These disease variants occur at higher frequencies in two western African populations and have a role in fighting parasitic trypanosome [[3](#_ENREF_3)].

Because most gene variants associated with DFHAAs likely exist in high frequencies in AADPs, these gene variants could be under selection and are outcomes of trade-off during evolution. This reasoning lead us to hypothesize that recently selected gene variants in AADPs may account for some DFHAAs, and will be addressed by the proposed activities.

## Aim . Evaluate a list of candidate human genes and examine their allele distributions in AADPs.

This candidate gene approach is an alternative approach to the computational approach in the first aim. Our tentative list of candidate DHRAA genes includes MSH2, MSH3, WRN, SOD2, SIRT1, TOR1, CHECK2, CYP2D6, cytochrome b5, and p53. We will retrieve the polymorphism data in these genes from the dbSNP database (http://www.ncbi.nlm.nih.gov/projects/SNP/). MSH2 and MSH3 are known to cause the hereditary non-polyposis colorectal cancer, and a functional assay for MSH2 has been established in yeast [[4](#_ENREF_4)]. Polymorphism in WRN, SOD2, and SIRT1 have been associated with life history traits in humans [[5](#_ENREF_5), [6](#_ENREF_6)]. Polymorphism in autophagy pathway is another candidate, because it is recently linked to human aging [[7](#_ENREF_7)]. One genetic polymorphism in cytochrome b5 has been reported to be unique in African Americans [[8](#_ENREF_8)], and slightly higher activities have been observed in African Americans compared with Caucasians [[9](#_ENREF_9)], although a causal relationship between these two findings has not been established. We will pay special attention to MSH2 alleles that are enriched in African Americans, because our BIO125 course, Molecular Biology and Genomics, has developed a functional assay using humanized yeast with MSH2 pathogenic alleles [[4](#_ENREF_4)].

We will use ms and mbs to generate posterior distributions of both neutral and selective evolution for both human and yeast homologs, and the posterior distributions will be calculated using parameters *S*, *D*, and *H*. Given that whole genome sequences are available in both *S. cerevisiae* and *S. paradoxus*, we will also apply the joint coalescence and phylogenic approach to infer natural selection – a method that is recently developed [[10](#_ENREF_10)].

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