**ABSTRACT**

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Because Africa is exposed to varying degrees of ultraviolet radiation and modern humans have inhabited Africa for the last 200,000 years, many indigenous populations are adapted to their UV environments. To identify genetic loci associated with UV exposure in Africa, we have quantified skin pigmentation levels and genotyped 1,650 Africans from Ethiopia, Tanzania, and Botswana using the Illumina 5M plus exome SNP array. A GWAS analysis of 1,066 of these individuals from Ethiopia and Tanzania identified three significantly associated loci: *SLC24A5*, *DDB1*, and *FZR1. SLC24A5* is a gene previously identified as associated with light skin pigmentation. However, the other two genes are novel and are involved in UV exposure. *DDB1* is associated with the repair of UV damaged DNA, and mutations in this gene cause skin cancers in children. *FZR1* is involved in UV induced apoptosis. These genes may help explain why individuals with African ancestry are about 25 times less likely to develop skin cancer than individuals with primarily European ancestry.

We propose to use next generation sequencing along with *in vitro/in vivo* assays to identify functionally important variants within these candidate regions. Specifically, using targeted resequencing, we will sequence 384 individuals at the extremes of the phenotype distribution at candidate loci. We will use this data to impute genotypes in the full set of phenotyped samples in order to do fine-scale mapping. To distinguish functionally important regulatory variants, we will use reporter assays in melanocytes and we will use transgenic zebrafish to study the effect of variants in coding regions. This study will provide the preliminary data for an R01 grant to further characterize the genetic basis of skin pigmentation in Africa, to identify functionally important genetic variants, and the role that these loci, together with UV exposure, may play in melanoma risk among ethnically diverse populations.