Genetic Variation at the N-acetyltransferase (*NAT*) Genes in Global Populations
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Abstract
Functional variability at the N-acetyltransferase (*NAT*) genes is associated with adverse drug reactions and cancer susceptibility in humans. Previous studies of small sets of ethnic groups have indicated that the *NAT* genes have high levels of amino acid variation that differ in frequency across ethnic groups. I hypothesize that this functional variation may be adaptive in different environments and is maintained due to natural selection. Although we can only speculate about the selective forces acting on the NAT genes in the past, it is possible that the observed pattern of phenotypic variation is associated with exposure to environmental, specifically dietary, toxins.
The objectives of the present study are to characterize nucleotide variation at the *NAT* drug-metabolizing genes (*NAT1, NAT2*) in global human populations, including many previously under-represented African populations, and to understand the role that natural selection has played in shaping variation at *NAT1* and *NAT2* in human populations living in different environmental settings. We have resequenced ~3000 bp for both of the *NAT1* and *NAT2* gene regions, in 182 African individuals and 155 individuals from a representative global panel (HGDP-CEPH), and have identified Single Nucleotide Polymorphisms (SNPs) at each locus (*NAT1* (48) and *NAT2* (46)). We have inferred haplotype phase and characterized patterns of haplotype diversity for each *NAT* locus. We have characterized nucleotide diversity and linkage disequilibrium for this ethnically diverse population dataset, as well as performed several tests of selective neutrality. This work will contribute to our understanding of how variation at the *NAT* loci may have been adaptive for dealing with changes in diet and exposure to toxins during human evolution.