Temple University
Department of Biology

-The Doctoral Dissertation Defense-

TITLE

"Dynamics of natural selection on human genomic variants"

Alyssa M. Pivirotto

TIME AND PLACE

Friday, April 26, 2024
1:00 PM
In Bio-Life, room 234

Refreshments served at 12:30 PM
Any questions, please contact the Biology Department @ 215-204-8854

Dissertation Committee
Dr. Jody Hey, Advisory Chair, Department of Biology, Temple University
Dr. Sudhir Kumar, Examining Committee Chair, Department of Biology, Temple University
Dr. Rob Kulathinal, Department of Biology, Temple University
Dr. Christina Bergey, External Examiner, Rutgers University

Abstract: Evolutionary adaptation in humans is shaped primarily by the selection of beneficial alleles. Classical population genetic theory predicts that alleles under selection will experience a rapid increase in frequency. However, the effects of weakly deleterious and neutral alleles propelled to high frequency due to drift complicates the identification of sites under positive selection. Evolutionary probability uses vertebrate alignments and divergence times to estimate a site's evolutionary history, assigning probability values to each potential amino acid at that site. For each mutation, a probability value can be calculated indicating whether the mutation is favored or disfavored evolutionarily. Because sites under selection will increase in frequency more quickly than they would due to genetic drift alone, it is expected that both beneficial and deleterious mutations will be younger on average than neutral variants of the same frequency. In chapter two, this was found to be true for the disfavored, deleterious mutations which were younger on average. Notably, beneficial mutations were found to be older on average than neutral mutations of the same frequency. One possible model suggests that the enrichment of old, beneficial alleles segregating in modern humans can be explained due to linked, weakly deleterious variants hindering the fixation of beneficial mutations until recombination allows for the escape of the beneficial mutation. Assessing allele age estimation methods is crucial for understanding the potential selection a mutation is undergoing. While whole genome sequencing data is becoming increasingly accessible, a large amount of the currently available data for large population datasets exists in the form of whole exome sequencing data. In chapter three, the accuracy of three allele age estimators, Genealogical Estimation of Variant Age (GEVA), Relate, and time of coalescence is tested for accuracy for both whole genome and whole exome sequencing datasets. Relate was found to outperform both other estimators of allele age for both a simple (Pearson: 0.64) and complex (Pearson: 0.68) demography model with the estimates based on whole exome data having an average drop in performance of 16 percent in comparison with the whole genome estimates. Beyond investigating segregating variants, phylogenetic methods such as evolutionary probability allow for the analysis of fixed candidate variants and the investigation into potential mechanisms by which these favored alleles arose. In chapter four, derived sites which have become fixed in modern humans where non-human primates all share the ancestral amino acid are identified. Utilizing the fixed, derived sites and the corresponding evolutionary probability values, it can be tested if adaptation occurs due to novel, low evolutionary probability mutations. A second hypothesis can also be tested where instead adaptation occurs due to a mutation to a more evolutionarily stable amino acid. It was found that while the majority of substitutions in modern humans are both arising by way of novel amino acids, however this is no evidence that these substitutions are driving phenotypic adaptation in modern humans.