ASHG ANNUAL MEETING 2025
BOSTON, MA • OCTOBER 14-18

Presidential Symposium

Ancient genomes: Perspectives on human biology and disease, Janet Kelso

The genome sequences of now extinct humans offer a unique opportunity to study the human past. Advances in the retrieval and analysis of ancient DNA have made it possible for us to reconstruct the genomes of several Neandertals, as well as to identify a previously unknown Asian hominin group related to Neandertals, the "Denisovans". These archaic genome sequences have provided insights into Neandertals and Denisovans, and have also revealed their interactions with modern humans. For example, we have shown that there was gene flow between archaic humans and early modern humans, such that all present-day people outside of Africa carry approximately 2% Neandertal DNA, and that some populations, largely in Asia and Oceania, also carry DNA inherited from Denisovans. This introgressed DNA has both positive and negative outcomes for present-day carriers; underlying apparently adaptive phenotypes such as high altitude adaptation, as well as influencing immunity and disease risk. We have identified haplotypes inherited from Neandertals and Denisovans, and determined their functional consequences using public genome, gene expression, and phenotype datasets.

Pervasive findings of directional selection realize the promise of ancient DNA to elucidate human adaptation, David Reich

This talk will present a method for detecting evidence of natural selection in ancient DNA time-series data that leverages an opportunity not utilized in previous scans: testing for a consistent trend in allele frequency change over time. By applying this to 8433 West Eurasians who lived over the past 14000 years and 6510 contemporary people, we find an order of magnitude more genome-wide significant signals than previous studies: 347 independent loci with >99% probability of selection. Previous work showed that classic hard sweeps driving advantageous mutations to fixation have been rare over the broad span of human evolution, but in the last ten millennia, many hundreds of alleles have been affected by strong directional selection. Discoveries include an increase from ~0% to ~20% in 4000 years for the major risk factor for celiac disease at HLA-DQB1; a rise from ~0% to ~8% in 6000 years of blood type B; and fluctuating selection at the TYK2

tuberculosis risk allele rising from ~2% to ~9% from ~5500 to ~3000 years ago before dropping to ~3%. We identify instances of coordinated selection on alleles affecting the same trait, with the polygenic score today predictive of body fat percentage decreasing by around a standard deviation over ten millennia, consistent with the "Thrifty Gene" hypothesis that a genetic predisposition to store energy during food scarcity became disadvantageous after farming. We also identify selection for combinations of alleles that are today associated with lighter skin color, lower risk for schizophrenia and bipolar disease, slower health decline, and increased measures related to cognitive performance (scores on intelligence tests, household income, and years of schooling). These traits are measured in modern industrialized societies, so what phenotypes were adaptive in the past is unclear. We estimate selection coefficients at 9.9 million variants, enabling study of how Darwinian forces couple to allelic effects and shape the genetic architecture of complex traits.

The genetic architecture of complex traits through the lens of multi-ancestry genetic studies, Loic Yengo

To date, >90% of participants in genome-wide association studies (GWAS) have European ancestries, which has resulted in poor portability of genetic associations to other groups. Nevertheless, the number and size of multi-ancestry GWAS have continuously grown over the past 15 years with the promise to deliver insights that could not be discovered otherwise. In this presentation, we will discuss how multi-ancestry genetic studies have improved our understanding of the genetic architecture of complex traits, defined here as the joint distribution of frequencies and effect sizes of causal variants. Specifically, we will revisit evidence supporting that causal variants and their effect sizes are largely shared between human populations, discuss current limitations of that evidence and lay out future directions for multi-ancestry studies.

Genetic risk and gene regulation across changing environments, Francesca Luca

Human traits result from a complex interaction between Genotypes and Environmental exposures (GxE). Personal and global changes in environmental exposures can have profound effects on human health. Understanding human ability to respond to these environmental changes is key to comprehending the plasticity of human phenotypes and the factors that push this response toward pathological outcomes. Studies from my group and others have shown that environmental effects on complex traits are mediated by changes in gene expression and other gene regulatory mechanisms. I will provide a perspective on GxE for gene regulation and their impact on genetic risk for disease. We have identified GxE across different types of environments, including shifts in life-style, exposures to environmental contaminants and complex psychosocial experiences. These

results highlight the need for a paradigm shift that jointly accounts for genetic and environmental risk in human health and phenotype predictions.