Human genetics: A look in the mirror

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Who are we? Where did we come from? How did we get here? Throughout the ages, humans have sought answers to these questions, pursuing wisdom through religion, philosophy, and eventually science. Evolutionary analyses published by *Genome Biology and Evolution (GBE)* allow us to peer into the mirror and better understand ourselves as a species, bringing us closer than ever to uncovering the answers to these long-held questions. GBE's latest virtual issue on human genetics highlights some of the most exciting research published in the journal

within the last year and a half, demonstrating the wide variety of evolutionary approaches to this avenue of research as well as a number of fascinating insights into our own biology.

Taking over a decade to complete, the original Human Genome Project cost nearly $3 billion and involved the collective effort of hundreds of scientists. Since then, advances in sequencing technology have resulted in an explosion in human genetics and genomics research, with an estimated one million human genomes sequenced to date. While this wealth of data has the potential to answer some of our most fundamental questions, unlocking its mysteries has necessitated the invention of new analytic and computational methods and the integration of techniques and ideas from diverse biological sciences, including physiology, anatomy, medicine, population genetics, bioinformatics, and computational, molecular, and evolutionary biology.

A key area of investigation involves identifying ways in which humans differ from other primates—in other words, what makes us human? Several studies published over the last 18 months suggest that part of the answer may be found in transcriptional regulation and changes in gene expression. Edsall et al. (2019) evaluated differences in chromatin accessibility, which impacts access of the transcriptional machinery to the DNA, across five primates including humans. They found high levels of differentiation across species, as well as classes of sites that differed based on selection, genomic location, and cell type specificity. More specifically, Swain-Lenz et al. (2019) found that differences in chromatin accessibility near genes involved in lipid metabolism may provide a mechanistic explanation for the higher levels of body fat observed in humans compared to other primates. Arakawa et al. (2019) showed that human-specific increases in the transcription of four structural protein genes may give rise to morphological features specific to human skin, including increased thickness and strength compared to the skin of other primates. Finally, a catalog of proteins involved in

transcriptional regulation by Perdomo-Sabogal and Nowick (2019) showed that certain types of transcription factors are associated with genes under positive selection, including those associated with schizophrenia, eye development, and fertility in humans.

Another area of interest is the role of mutation in shaping the human genome and our evolutionary history. For example, there has been considerable debate over how much of the human genome is subject to natural selection. It has been argued that this fraction cannot be too large, or else humans would suffer a loss of fitness due to the number of deleterious mutations. However, Galeota-Sprung et al. (2020) countered this argument by showing that the mutational load would be tolerable even if much of the human genome were subject to selection. Additional analyses by Castellano et al. (2020) revealed how the recombination rate, gene density, and mutation rate interact to shape patterns of DNA diversity across humans and other closely related homininae. A study by Prendergast et al. (2019) further uncovered unique biases in mutations that occur at adjacent nucleotide sites in humans, suggesting the existence of distinct evolutionary forces acting on such sites and identifying differences in these forces across human populations.

A particularly fascinating topic in this field is concerned with investigating genetic differences between human populations and their association with the natural history of these groups. For example, Harris et al. (2019) found that the ancestors of Native Americans carried the ancestral, rather than the derived, version of an ancient polymorphism that predates the split with Neanderthals. This polymorphism encompasses the fatty acid desaturase genes, and thus those with Native American ancestry may be at risk for low levels of nutrients derived from dietary omega-3 and omega-6 fatty acids. Jonnalagadda et al. (2019) identified a number of alleles associated with iris color and skin pigmentation in South Asians, while Vicuña et al. (2019) discovered genetic variants that may have helped the Andean Native American

ancestors of people living in the Atacama Desert in northern Chile to adapt to high arsenic levels in the water. Analysis of another desert-dwelling population by Eaaswarkhanth et al. (2020) showed evidence for positive selection of a genomic region encompassing the TNKS gene in Kuwaiti individuals. Because this gene influences metabolic traits and hypertension risk, selection for this haplotype may have provided an advantage to Kuwaiti ancestors living in the desert of the Arabian Peninsula but has health implications for their modern day descendants.

Indeed, as revealed by these studies, one of the greatest potential benefits of this line of inquiry is the elucidation of new knowledge that informs our understanding of human health and disease. Reher et al. (2019) found that genes of the major histocompatibility complex, which helps the immune system recognize foreign substances, retain higher levels of diversity than other genes. This was true in both archaic and modern humans, even though archaic humans and Neanderthals had reduced levels of genetic diversity compared to modern humans. Lin and Gokcumen (2019) characterized fine-scale structural variation in the human genome and revealed hotspots that were associated with both adaptive and biomedically relevant variants. For example, they identified hotspots associated with alpha and beta hemoglobin gene clusters as well as idiopathic short stature. Finally, a study by Liu et al. (2019) of samples taken from within a single tumor of a patient with hepatocellular carcinoma showed that the mitochondrial genome was evolving neutrally, providing evidence that refutes the hypothesis that selection acts on mitochondrial DNA to promote tumor development.

Together, this selection of manuscripts highlights some of the latest findings and new approaches in the study of human genetics, a field that promises to help define who we are as a species and to reveal mysteries of human migration and adaptation that may otherwise have been lost to human history.

More information: Casey McGrath et al. Human Genetics: A Look in the Mirror, *Genome Biology and Evolution* (2020). DOI: 10.1093/gbe/evaa139