Natural Selection in Human Populations

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Introduction

Natural selection, the process by which heritable individual differences that contribute to variation in survival and reproduction lead to changes in attributes of a population (see *Oxford Bibliographies* article Natural Selection), has been an important force in human evolution. Selection has played an essential role in human differentiation from apelike ancestors and in the adaptation of humans to diverse environments around the world (see *Oxford Bibliographies* article Human Adaptability). The study of natural selection in humans has largely fallen in the realm of population genetics (see *Oxford Bibliographies* article Population Genetics). Many forms of natural selection—including positive selection (the increase in frequency of advantageous alleles), purifying selection (the removal of deleterious alleles), and balancing selection (the maintenance of polymorphism due to heterozygote advantage or frequency-dependent selection)—have been examined in humans. Particular emphasis has been placed on positive selection and its role in producing geographic variation and local adaptation (see *Oxford Bibliographies* article Adaptation), and on detecting natural selection from population-genetic data (see *Oxford Bibliographies* article Detecting Natural Selection in the Genome).

General Overviews

Several reviews have considered the population-genetic study of natural selection in human populations, emphasizing to a different extent the driving selective pressures, statistical methods for detecting natural selection from patterns of genetic variation, and observations in human data. Some overviews focus on the particular patterns of human genetic variation, interpreting them in relation to processes of natural selection and the history of natural selection in humans (Sabeti, et al. 2006; Fu and Akey 2013; Lachance and Tishkoff 2013; Scheinfeldt and Tishkoff 2013). Others consider the detection of evidence of natural selection in general, using humans as an example of population-genetic methods (Kreitman 2000; Nielsen 2005; Vitti, et al. 2013). Reviews often place an emphasis on specific mechanisms of natural selection, their consequences for human genetic variation, and the evidence of their importance (Sabeti, et al. 2006; Fu and Akey 2013; Key, et al. 2014).

Fu, W., and J. M. Akey. 2013. Selection and adaptation in the human genome. *Annual Review of Genomics and Human Genetics* 14:467–489.

A review emphasizing processes of natural selection and their effects on human genetic variation.

Key, F. M., J. C. Teixeira, C. de Filippo, and A. M. Andres. 2014. Advantageous diversity maintained by balancing selection in humans. *Current Opinion in Genetics and Development* 29:45–51.

A review of balancing selection in humans and methods for identifying it.

Kreitman, M. 2000. Methods to detect selection in populations with applications to the human. *Annual Review of Genomics and Human Genetics* 1:539–559.

A discussion of tests of selection and the ways in which they identify signatures of multiple forms of selection, with an emphasis on scenarios in humans and *Drosophila*.

Lachance, J., and S. A. Tishkoff. 2013. Population genomics of human adaptation. *Annual Review of Ecology, Evolution, and Systematics* 44:123–143.

A review focusing on specific selection pressures and adaptations that have had a significant impact in human evolution.

Nielsen, R. 2005. Molecular signatures of natural selection. *Annual Review of Genetics* 39:197–218.

A review of the patterns that different forms of natural selection leave in population-genetic data.

Sabeti, P. C., S. F. Schaffner, and B. Fry, et al. 2006. Positive natural selection in the human lineage. *Science* 312:1614–1620.

An overview of positive selection detection methods and observations in humans, with an emphasis on selection at different time scales.

Scheinfeldt, L. B., and S. A. Tishkoff. 2013. Recent human adaptation: Genomic approaches, interpretation and insights. *Nature Reviews Genetics* 14:692–702.

A review of signatures of natural selection in humans and the effort to identify candidate alleles and their functional consequences.

Vitti, J. J., S. R. Grossman, and P. C. Sabeti. 2013. Detecting natural selection in genomic data. *Annual Review of Genetics* 47:97–120.

A review focusing on methods of detecting different forms of natural selection, with examples from humans.

Natural Selection on Different Time Scales

Studies of natural selection in human populations examine different time periods in human evolution by considering different comparisons: between humans and chimpanzees, between humans and archaic hominins, and among different human

populations.

The Human-Chimp Lineage

Comparisons with our closest living relatives, chimpanzees, provide information about genetic changes unique to the human lineage. Of particular interest are loci that are likely to have undergone positive selection along the human lineage, as these loci might contribute to phenotypic and functional changes unique to humans (O'Bleness, et al. 2012). Methods to detect genomic regions under positive selection along the human lineage often involve sequence comparisons between related species, using approaches such as the ratio of nonsynonymous to synonymous substitutions (Nielsen, et al. 2005) and consideration of genetic diversity in humans at sites that differ between humans and chimpanzees (Enard, et al. 2002). They can involve comparisons that search for regions conserved through most of mammalian history but that have undergone rapid evolution along the human-specific lineage (Hubisz and Pollard 2014). Comparisons to chimpanzees can also reveal ancient instances of balancing selection, in which genetic polymorphism has been maintained on both the human and chimpanzee lineages since the time of the common ancestral species (Leffler, et al. 2013). Some studies extend beyond DNA sequence variation to consider other phenomena that likely also played an important role in generating differences between humans and chimpanzees: notably gene loss, gain, or duplication (Demuth, et al. 2006; Wang, et al. 2006; Wu, et al. 2011), and positive selection on regulatory regions (see Selection on Regulatory Elements).

Demuth, J. P., T. De Bie, J. E. Stajich, N. Cristianini, and M. W. Hahn. 2006. The evolution of mammalian gene families. *PLoS One* 1:e85.

An article comparing gene family evolution across multiple mammals, inferring gene gains and losses in the human lineage.

Enard, W., M. Przeworski, and S. E. Fisher, et al. 2002. Molecular evolution of FOXP2, a gene involved in speech and language. *Nature* 418:869–872.

An article describing human-specific amino acid changes in a gene that when mutated produces disorders in human language development.

Hubisz, M. J., and K. S. Pollard. 2014. Exploring the genesis and functions of human accelerated regions sheds light on their role in human evolution. *Current Opinion in Genetics & Development* 29:15–21.

A review describing the methods for detecting regions of the genome that have experienced accelerated evolution in humans since the split with chimpanzees.

Leffler, E. M., Z. Gao, and S. Pfeifer, et al. 2013. Multiple instances of ancient balancing selection shared between humans and chimpanzees. *Science* 339:1578–1582.

A paper that uses haplotypes shared between humans and chimpanzees to report on long-term balancing selection in the human and chimpanzee lineages.

Nielsen, R., C. Bustamante, and A. G. Clark, et al. 2005. A scan for positively selected genes in the genomes of humans and chimpanzees. *PLoS Biology* 3:e170.

A study using comparisons with chimpanzee orthologs to identify genomic regions and categories of genes with large numbers of derived nonsynonymous mutations in humans.

O'Bleness, M., V. B. Searles, A. Varki, P. Gagneux, and J. M. Sikela. 2012. Evolution of genetic and genomic features unique to the human lineage. *Nature Reviews Genetics* 13:853–866.

A review of positive selection and human trait evolution since the common ancestors with chimpanzees and other great apes.

Wang, X., W. E. Grus, and J. Zhang. 2006. Gene losses during human origins. *PLoS Biology* 4:e52.

An investigation of the impact of gene loss on human evolution, providing case studies of its adaptive effects.

Wu, D. D., D. M. Irwin, and Y.-P. Zhang. 2011. De novo origin of human protein-coding genes. *PLoS Genetics* 7:e1002379.

An article identifying new protein-coding genes originating on the human lineage, emphasizing their potential phenotypic importance.

Humans and Archaic Hominins

The human evolutionary tree includes multiple branches of extinct hominins. Neanderthals and their recently described sister population, known as Denisovans, share a common ancestor with humans between five hundred thousand and eight hundred thousand years ago. Technological advances have produced the first ancient human sequences, enabling direct genomic comparisons of humans and extinct hominins. By considering alleles derived in the human lineage (Prüfer, et al. 2014) or searching for long stretches of the genome in which ancient samples fall outside current human variation (Prüfer, et al. 2014; Racimo, et al. 2014), the analysis of ancient genomes has enabled inferences about traits that have evolved uniquely along the modern human lineage. Advances in sequencing of ancient samples have also led to the sampling of groups of individuals from more recent prehistoric populations. Considering multiple samples from a single ancient population can provide direct evidence of changes in allele frequency at phenotypically associated loci over short time scales, or deviations in frequency from a null model. For example, studies of prehistoric genomes suggest evidence of positive selection on genes related to pigmentation and lactose tolerance during the European Neolithic and Bronze Age (Gamba, et al. 2014; Mathieson, et al. 2015).

Gamba, C., E. R. Jones, and M. D. Teasdale, et al. 2014. Genome flux and stasis in a five millennium transect of European prehistory. *Nature Communications* 5:5257.

A study using ancient DNA to describe transitions in pigmentation phenotypes and adult lactose tolerance, reporting evidence for positive selection.

Mathieson, I., I. Lazaridis, and N. Rohland, et al. 2015. Genome-wide patterns of selection in 230 ancient Eurasians. *Nature* 528:499–503.

An article examining ancient European populations to search for positive selection in modern Europeans by use of population allele frequencies and genetic differentiation.

Prüfer, K., F. Racimo, and N. Patterson, et al. 2014. The complete genome sequence of a Neanderthal from the Altai Mountains. *Nature* 505:43–49.

A paper providing a high-coverage sequence of a Neanderthal, reporting fixed sequence differences between archaic hominins and humans.

Racimo, F., M. Kuhlwilm, and M. Slatkin. 2014. A test for ancient selective sweeps and an application to candidate sites in modern humans. *Molecular Biology and Evolution* 31:3344–3358.

A study describing a method to detect positive selection unique to the human lineage from ancient hominin genomes and producing a catalogue of candidate genes.

Local Adaptation

The selection pressures active in different environments generate distinct adaptations. As human populations dispersed across the world, they encountered a variety of differences across environments, including differences in altitude, climate, food sources, pathogens, and sun exposure. These environmental variations and their resulting selective pressures have led to population differentiation and population-specific phenotypes (Kamberov, et al. 2013; Perry, et al. 2014). Examples of local adaptation have been identified in human populations that reside in extreme environments. For example, in populations living at high altitude, alleles that are favorable in hypoxic conditions have increased in frequency (Huerta-Sánchez, et al. 2014), as have alleles permitting adult lactose consumption in pastoral communities (Tishkoff, et al. 2007). Complex traits that are affected by large numbers of loci exhibit environmentally specific signatures of positive selection (Parra 2007; Turchin, et al. 2012; Perry, et al. 2014), and positive selection conferring local adaptation can be recent for such traits (Field, et al. 2016). Positive selection conferring local adaptation can occur for novel alleles, for alleles that have been maintained by balancing selection prior to the onset of positive selection (de Filippo, et al. 2016), or for alleles introduced via admixture (Huerta-Sánchez, et al. 2014).

de Filippo, C., F. M. Key, and S. Ghirotto, et al. 2016. Recent selection changes in human genes under long-term balancing selection. *Molecular Biology and Evolution* 33:1435–1447.

A proposal of a new mode of selection in which balancing selection provides the variation upon which positive selection can act in a new environment, with application to differences in modern human populations.

Field, Y., E. A. Boyle, and N. Telis, et al. 2016. Detection of human adaptation during the past 2000 years. *Science* 354:760–764.

A method to detect recent polygenic selection based on the genomic pattern of rare variants, with application in modern Europeans.

Huerta-Sánchez, E., X. Jin, and Z. Bianba, et al. 2014. Altitude adaptation in Tibetans caused by introgression of Denisovan-like DNA. *Nature* 512:194–197.

A study arguing that positive selection conferring altitude adaptation in high-altitude Tibetans traces to introgression from archaic hominins.

Kamberov, Y. G., S. Wang, and J. Tan, et al. 2013. Modeling recent human evolution in mice by expression of a selected EDAR variant. *Cell* 152:691–702.

A confirmation that an allele inferred to be under strong positive selection in East Asian populations produces phenotypes in a mouse model that accord with human phenotypes connected to the EDAR gene.

Parra, E. J. 2007. Human pigmentation variation: Evolution, genetic basis, and implications for public health. *Yearbook of Physical Anthropology* 50:85–105.

An examination of the genetic architecture of the geographically variable trait of skin pigmentation in the context of selective pressures.

Perry, G. H., M. Foll, and J. C. Grenier, et al. 2014. Adaptive, convergent origins of the pygmy phenotype in African rainforest hunter-gatherers. *Proceedings of the National Academy of Sciences USA* 111:E3596–E3603.

An investigation using haplotype statistics and population differentiation to infer that the pygmy phenotype might have arisen via positive selection favoring shorter stature.

Tishkoff, S. A., F. A. Reed, and A. Ranciaro, et al. 2007. Convergent adaptation of human lactase persistence in Africa and Europe. *Nature Genetics* 39:31–40.

A classic example of recent positive selection and adaptation in human populations, namely adult lactose tolerance.

Turchin, M. C., C. W. K. Chiang, and C. D. Palmer, et al. 2012. Evidence of widespread selection on standing variation in Europe at height-associated SNPs. *Nature Genetics* 44:1015–1019.

A study of positive selection on a polygenic trait, reporting evidence for adaptive genetic differences in loci associated with height in northern and southern European populations.

Genetic Signatures of Positive Selection

Studies of positive selection in humans rely on theoretical predictions linking population-genetic models of positive selection to detectable signatures in population-genetic data. Many types of signatures have been examined.

Shifts in Allele Frequency

Natural selection acting in a genomic region alters the frequencies of selected alleles and the distribution of allele frequencies at sites in the region: the site-frequency spectrum (SFS). Positive selection tends to decrease the probability that a selected allele is sampled at moderate frequency, and it tends to increase the probability that it is sampled at low or high frequency. By contrast, purifying selection increases the probability of sampling at low frequency and decreases the probability of sampling at moderate or high frequency. Studies of site-frequency spectra in coding regions have indicated that selection acts differently on different categories of sites, suggesting purifying selection on nonsynonymous variants (Bustamante, et al. 2005; Boyko, et al. 2008; Ronen, et al. 2013). The SFS is altered from a null pattern both by selection and by demographic phenomena, and uses of the SFS to search for signatures of positive selection often benefit from taking demographic phenomena into account (Eyre-Walker, et al. 2006; Boyko, et al. 2008).

Boyko, A. R., S. H. Williamson, and A. R. Indap, et al. 2008. Assessing the evolutionary impact of amino acid mutations in the human genome. *PLoS Genetics* 4:e1000083.

A study in which the demographic history is first estimated and a distribution of selection coefficients is then inferred.

Bustamante, C. D., A. Fledel-Alon, and S. Williamson, et al. 2005. Natural selection on protein-coding genes in the human genome. *Nature* 437:1153–1157.

An article examining protein-coding genes to infer the strength of selection on nonsynonymous variants.

Eyre-Walker, A., M. Woolfit, and T. Phelps. 2006. The distribution of fitness effects of new deleterious amino acid mutations in humans. *Genetics* 173:891–900.

An article using allele frequencies to infer the distribution of selection coefficients in the presence of a demographic model, with an application to human nonsynonymous polymorphisms.

Ronen, R., N. Udpa, E. Halperin, and V. Bafna. 2013. Learning natural selection from the site frequency spectrum. *Genetics* 195:181–193.

An article using machine learning methods to determine features of the SFS affected by selection.

Diversity Signatures of Linked Selection

Positive selection acting on variable sites in the genome accelerates the time to fixation of a selected allele, producing a “selective sweep.” Because the sojourn time of a favored allele is shorter than that of a neutral allele, fewer recombination events are expected on chromosomes carrying the selected allele during its rise in frequency relative to neutral sites. Therefore, genetic variants that are proximal in the genome to the selected allele, though they might be neutral or even slightly deleterious, might “hitchhike” to high frequency as a result of linkage to the advantageous allele (Maynard Smith and Haigh 1974; Stephan, et al. 1992). When neutral alleles near a selected site are driven to high frequency, genetic diversity in the region is reduced at the end of the sweep (Begun and Aquadro 1992). This local dip in genetic diversity near a selected site and the concomitant increase in high-frequency derived alleles can be used to infer the presence of a sweeping allele (Fay and Wu 2000).

Begun, D. J., and C. F. Aquadro. 1992. Levels of naturally occurring DNA polymorphism correlate with recombination rates in D. melanogaster. *Nature* 356:519–520.

An article finding substantial loss of genetic diversity in regions surrounding a potentially favored mutation in *Drosophila*.

Fay, J. C., and C.-I. Wu. 2000. Hitchhiking under positive Darwinian selection. *Genetics* 155:1405–1413.

A paper developing a frequency-based method for detecting positive selection from the principle that selective sweeps result in an excess of high-frequency derived mutations.

Maynard Smith, J., and J. Haigh. 1974. The hitch-hiking effect of a favourable gene. *Genetical Research* 23:23–35.

A classic paper introducing the hitchhiking phenomenon and providing initial theoretical results for its associated reduction in genetic diversity.

Stephan, W., T. H. E. Wiehe, and M. W. Lenz. 1992. The effect of strongly selected substitutions on neutral polymorphism: Analytical results based on diffusion theory. *Theoretical Population Biology* 41:237–254.

An article that considers the impact of selective sweeps on genetic diversity, with theoretical predictions about the reduction in diversity around a selected locus.

Haplotype Signatures

When a selected allele rises quickly to a high frequency, fewer recombination events occur on the selected haplotype background than under neutrality. This phenomenon results in long unbroken haplotypes that share the selected allele. Early haplotype signatures of positive selection focused on presence of a high-frequency haplotype (Hudson, et al. 1994). More recently, statistical inference of recent positive selection has often been performed by scanning the genome for regions of aberrant haplotype structure with heuristic scores indicating the presence of long haplotypes shared by a favored allele (Sabeti, et al. 2002; Voight, et al. 2006). Such tests have been successfully applied in humans to identify regions under positive selection in many populations (Pickrell, et al. 2009; International HapMap 3 Consortium 2010).

Hudson, R. R., K. Bailey, D. Skarecky, J. Kwiatowski, and F. J. Ayala. 1994. Evidence for positive selection in the superoxide dismutase (Sod) region of *Drosophila melanogaster*. *Genetics* 136:1329–1340.

An article developing the idea that a high-frequency haplotype provides evidence for positive selection.

International HapMap 3 Consortium. 2010. Integrating common and rare genetic variation in diverse human populations. *Nature* 467:52–58.

A survey of human genetic variation scanning for a composite pattern of multiple haplotype-based signals of recent positive selection, uncovering genomic regions related to immunity, olfaction, and pigmentation.

Pickrell, J. K., G. Coop, and J. Novembre, et al. 2009. Signals of recent positive selection in a worldwide sample of human populations. *Genome Research* 19:826–837.

A study of genomic regions under positive selection in different worldwide human populations, comparing geographic regions using haplotype-based summary statistics.

Sabeti, P. C., D. E. Reich, and J. M. Higgins, et al. 2002. Detecting recent positive selection in the human genome from haplotype structure. *Nature* 419:832–837.

A study proposing the use of extended regions of homozygosity to identify genomic regions that are putatively under positive selection in humans.

Voight, B. F., S. Kudaravalli, X. Wen, and J. K. Pritchard. 2006. A map of recent positive selection in the human genome. *PLoS Biology* 4:e72.

An article devising a test to identify genomic regions that have low haplotype diversity in a manner that is indicative of positive selection.

Population Differences

Human adaptation to regionally specific environments drives differentiation between populations. In particular, specific regions of the genome that confer environment-specific adaptations are likely to be more differentiated on average than the rest of the genome (Lewontin and Krakauer 1973; Akey, et al. 2002; Barreiro, et al. 2008; Coop, et al. 2009). Because both neutral genetic drift and positive selection can lead to genetic differentiation in spatially distributed populations, excess phenotypic differentiation as computed by a quantitative trait measure QST analogous to the standard genetic differentiation measure FST can reveal that selection on quantitative, polygenic traits drives differences between populations at multiple loci (Whitlock 2008; Leinonen, et al. 2013; Berg and Coop 2014).

Akey, J. M., G. Zhang, K. Zhang, L. Jin, and M. D. Shriver. 2002. Interrogating a high-density SNP map for signatures of natural selection. *Genome Research* 12:1805–1814.

A report of a genome-wide catalogue of regions in the human genome with excess locus-specific genetic differentiation compared to the genomic average.

Barreiro, L. B., G. Laval, H. Quach, E. Patin, and L. Quintana-Murci. 2008. Natural selection has driven population differentiation in modern humans. *Nature Genetics* 40:340–345.

A paper describing global population differentiation, emphasizing genomic regions that might show an excess of differentiation or homogeneity owing to positive or negative selection.

Berg, J. J., and G. Coop. 2014. A population genetic signal of polygenic adaptation. *PLoS Genetics* 10:e1004412.

A method identifying selection on traits governed by multiple loci by considering allele frequency shifts in groups of loci associated with a specific phenotype.

Coop, G., J. K. Pickrell, and J. Novembre, et al. 2009. The role of geography in human adaptation. *PLoS Genetics* 5:e1000500.

An article identifying loci under positive selection by examining patterns of genetic differentiation among many populations.

Leinonen, T., R. S. McCairns, R. B. O'Hara, and J. Merilä. 2013. QST–FST comparisons: Evolutionary and ecological insights from genomic heterogeneity. *Nature Reviews Genetics* 14:179–190.

A review on QST and FST comparisons with emphasis on applications.

Lewontin, R. C., and J. Krakauer. 1973. Distribution of gene frequency as a test of the theory of the selective neutrality of polymorphisms. *Genetics* 74:175–195.

A classic paper proposing locus-specific excess genetic differentiation as evidence for positive selection.

Whitlock, M. C. 2008. Evolutionary inference from QST. *Molecular Ecology* 17:1885–1896.

A review on the use of phenotypic and genotypic measures of differentiation, QST and FST, with emphasis on interpretations.

Spatial and Environmental Patterns

The differing environments of different human populations produce population-specific selective pressures on complex phenotypes. Because many of these phenotypes are governed by multiple loci of small effect throughout the genome, subtle shifts in allele frequencies across the genome are expected as a result of such pressures (Novembre and Di Rienzo 2009; Hancock, et al. 2010a; Hancock, et al. 2010b). Empirical studies therefore make use of known phenotypic differences hypothesized to be beneficial under different local environments—such as climatic variables, altitude, and latitude—to uncover locally positively selected loci, comparing the distribution of a spatial variable with the distribution of genotypic variables (Coop, et al. 2010; Jeong and Di Rienzo 2014).

Coop, G., D. Witonsky, A. Di Rienzo, and J. K. Pritchard. 2010. Using environmental correlations to identify loci underlying local adaptation. *Genetics* 185:1411–1423.

A method for detecting human local adaptation through correlations of environmental variables with genotypes.

Hancock, A. M., G. Alkorta-Aranburu, D. B. Witonsky, and A. Di Rienzo. 2010a. Adaptations to new environments in humans: The role of subtle allele frequency shifts. *Philosophical Transactions of the Royal Society of London B: Biological Sciences* 365:2459–2468.

A review emphasizing the detection from correlations with environmental variables of loci that contribute to local adaptation.

Hancock, A. M., D. B. Witonsky, and E. Ehler, et al. 2010b. Human adaptations to diet, subsistence, and ecoregion are due to subtle shifts in allele frequency. *Proceedings of the National Academy of Sciences USA* 107:8924–8930.

An article highlighting a set of related phenotypes associated with ecological adaptation, with adaptation proceeding by allele frequency shifts at many loci genome wide.

Jeong, C., and A. Di Rienzo. 2014. Adaptations to local environments in modern human populations. *Current Opinion in Genetics & Development* 29:1–8.

A review on the genetic architecture of complex adaptive human phenotypes that vary spatially.

Novembre, J., and A. Di Rienzo. 2009. Spatial patterns of variation due to natural selection in humans. *Nature Reviews Genetics* 10:745–755.

A review of methods and results concerning human population differentiation driven by environmental variation.

Admixture Patterns

Many human populations have experienced admixture, in which two or more previously isolated source populations exchanged genes, as a result of colonization, spatial expansion, or social practices involving marriage customs. The genomes of admixed individuals contain a mixture of components originally deriving from their parental populations, with the lengths of genomic tracts from specific source populations reflecting the time since admixture occurred. Within an admixed population, the excess of ancestry from a given source at a genomic position (Tang, et al. 2007; Bryc, et al. 2010; Jeong, et al. 2014) or long tracts of a single ancestry (Sankararaman, et al. 2014; Racimo, et al. 2015; Gittelman, et al. 2016) can indicate positive selection acting on the allele from that source, as a consequence of the fact that ancestry from the source has been preferentially preserved. Alternatively, a paucity of putatively introgressed regions might suggest purifying selection (Sankararaman, et al. 2014).

Bryc, K., A. Auton, and M. R. Nelson, et al. 2010. Genome-wide patterns of population structure and admixture in West Africans and African Americans. *Proceedings of the National Academy of Sciences USA* 107:786–791.

A paper detecting genomic regions under selection in African Americans by comparing locus-specific ancestry proportions to genome-wide ancestry levels in the admixed population.

Gittelman, R. M., J. G. Schraiber, B. Vernot, C. Mikacenic, M. M. Wurfel, and J. M. Akey. 2016. Archaic hominin admixture facilitated adaptation to out-of-Africa environments. *Current Biology* 26:3375–3382.

A study of genomic regions introgressed from archaic hominins that are likely under selection in diverse human populations.

Jeong, C., G. Alkorta-Aranburu, and B. Basnyat, et al. 2014. Admixture facilitates genetic adaptations to high altitude in Tibet. *Nature Communications* 5:3281.

An article describing an excess of high-altitude population ancestry surrounding loci associated with hemoglobin concentration in Tibetans, suggesting an admixture-based mechanism for high-altitude adaptation.

Racimo, F., S. Sankararaman, R. Nielsen, and E. Huerta-Sánchez. 2015. Evidence for archaic adaptive introgression in humans. *Nature Reviews Genetics* 16:359–371.

A review describing methods to detect selected genomic regions that have resulted from gene flow with archaic humans.

Sankararaman, S., S. Mallick, and M. Dannemann, et al. 2014. The genomic landscape of Neanderthal ancestry in present-day humans. *Nature* 507:354–357.

A paper using Neanderthal sequences to identify genomic regions in humans that are introgressed from archaic populations, suggesting evidence for both positive and negative selection on those regions.

Tang, H., S. Choudhry, and R. Mei, et al. 2007. Recent genetic selection in the ancestral admixture of Puerto Ricans. *American Journal of Human Genetics* 81:626–633.

A study of selection in admixed Puerto Ricans, developing early methods for detecting selection in admixed populations.

Selection on Regulatory Elements

Variation in gene expression and epigenetic variation can be exposed to the action of natural selection (King and Wilson 1975, Wray 2007). Numerous signatures of regulatory phenomena have been studied in humans, including patterns in transcription-factor binding sites and in human-accelerated genomic regions that result from positive selection on regulatory elements. Studies support the widespread importance of natural selection on human regulatory variation (Lappalainen and Dermitzakis 2010; Arbiza, et al. 2013; Enard, et al. 2014), including its roles in producing local adaptations that differentiate human populations (Fraser 2013) and in giving rise to skeletal and brain phenotypes that differ between humans and chimpanzees (Sholtis and Noonan 2010).

Arbiza, L., I. Gronau, and B. A. Aksoy, et al. 2013. Genome-wide inference of natural selection on human transcription factor binding sites. *Nature Genetics* 45:723–729.

An article providing evidence of selection on gene regulation since the human-chimpanzee divergence through the analysis of transcription-factor binding sites.

Enard, D., P. W. Messer, and D. A. Petrov. 2014. Genome-wide signals of positive selection in human evolution. *Genome Research* 24:885–895.

A study finding stronger evidence for positive selection near regulatory elements than that seen at protein-coding substitutions.

Fraser, H. B. 2013. Gene expression drives local adaptation in humans. *Genome Research* 23:1089–1096.

A study demonstrating a significant role for positive selection on gene expression in producing local adaptation across human populations.

King, M.-C., and A. C. Wilson. 1975. Evolution at two levels in humans and chimpanzees. *Science* 188:107–116.

A classic paper presenting the hypothesis that phenotypic differences between chimpanzees and humans might be driven by gene expression and regulatory changes rather than by DNA sequence differences alone.

Lappalainen, T., and E. T. Dermitzakis. 2010. Evolutionary history of regulatory variation in human populations. *Human Molecular Genetics* 19:R197–R203.

A review describing different types of selection on human regulatory elements.

Sholtis, S. J., and J. P. Noonan. 2010. Gene regulation and the origins of human biological uniqueness. *Trends in Genetics* 26:110–118.

A review of regulatory evolution in humans, combining information about annotation of regulatory elements and human-accelerated regions to study human-specific traits.

Wray, G. A. 2007. The evolutionary significance of cis-regulatory mutations. *Nature Reviews Genetics* 8:206–216.

A review of phenotypic changes produced through natural selection on regulatory mutations, with examples in humans and other species.

Selection and Disease

As humans dispersed throughout the world, populations encountered new pathogens that provided new and potentially quite strong selection pressures. Pathogenic agents provide many of the best-known examples of selective pressures in human evolutionary history, shaping genome-wide patterns of variation and leading to specific responses in biological functions such as immunity (Kwiatkowski 2005; Barreiro and Quintana-Murci 2010; Fumagalli, et al. 2011; Enard, et al. 2016). Some studies have considered the genetic response to a specific disease such as malaria (Kwiatkowski 2005), whereas others have considered genomic patterns, finding an excess of genetic loci under selection in genes related to molecular functions associated with disease (Barreiro and Quintana-Murci 2010). Direct immunological assays have provided evidence that natural selection in response to pathogens might proceed differently in different populations (Nédélec, et al. 2016). The interaction of natural selection with genetic variation that contributes to disease has been of interest more generally beyond the study of pathogen-driven selection (Di Rienzo 2006), for example in the analysis of the relationship between demographic phenomena and natural selection in producing genome-wide patterns of mildly deleterious genetic variation (Lohmueller 2014). It has also been examined in evaluating the relative influence of demographic and selective phenomena on patterns in specific disease-associated loci (Novembre, et al. 2005).

Barreiro, L. B., and L. Quintana-Murci. 2010. From evolutionary genetics to human immunology: How selection shapes host defence genes. *Nature Reviews Genetics* 11:17–30.

A review of the genomic signatures of selective pressures from pathogens during human evolution.

Di Rienzo, A. 2006. Population genetics models of common diseases. *Current Opinion in Genetics & Development* 16:630–636.

A review of population-genetic phenomena influencing the geographic distribution of genetic diseases, including the relationship of disease variation to positive and purifying selection acting on disease-associated variants.

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Challenges

Although human genomic sequencing has spurred much interest in the role of evolutionary forces in shaping genetic diversity, robust detection of positive selection in genomic and phenotypic data remains challenging. We focus on three pressing problems: accounting for confounding evolutionary forces, understanding the evolutionary mechanisms for adaptation in humans, and linking genomic signatures of selection to the selected phenotypes. (1) Inference of the occurrence of natural selection in humans can be influenced by other evolutionary forces that affect genetic variation. Demographic phenomena can alter allele frequencies and linkage disequilibrium patterns; for example, population bottlenecks can increase linkage disequilibrium and can confound haplotype scans (Teshima, et al. 2006). More generally, adaptive and non-adaptive processes can generate similar patterns of genetic variation, making them difficult to distinguish (Jensen 2014). Genome scans for outlier loci with unusual diversity patterns have sometimes been performed, but these methods might be susceptible to false positives or low power (Kelley, et al. 2006). (2) Though most research on human adaptation has focused on positive selection and selective sweeps, it has been argued that classic strong selective sweeps might be rare in humans (Hernandez, et al. 2011). If sweeps are rare, then weaker “soft” selective sweeps or coordinated allele frequency shifts driven by simultaneous selection acting on many loci might be more salient phenomena (Pritchard, et al. 2010, Schrider and Kern 2017). (3) It has become increasingly common to assess the connection between selection on complex traits and the identification of loci that influence phenotypes (Lohmueller 2014). Studies also consider signals of selection in sets of polymorphic sites that have a common functional significance, such as disease-associated loci from genome-wide association studies (Berg and Coop 2014, cited under Population Differences). When functional significance cannot be assigned in advance to selected loci, it is often unclear how to identify the phenotypes affected by natural selection. Integrating selection studies with functional genomics might prove to be important in linking selection signals to specific phenotypes (Storz and Wheat 2010).

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A study showing that genomic scans for positive selection can be confounded by demographic phenomena that generate similar signatures.

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