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Evolutionary and Medical Consequences of Archaic Introgression into Modern Human Genomes

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Abstract

The demographic history of anatomically modern humans (AMH) involves multiple migration events, population extinctions and genetic adaptations. As genome-wide data from complete genome sequencing becomes increasingly abundant and available even from extinct hominins, new insights of the evolutionary history of our species are discovered.

It is currently known that AMH introgressed with archaic hominins once they left the African continent. Current out of African human genomes carry fragments of archaic origin. This review focuses on the fitness consequences of archaic interbreeding in current human populations. We discuss new insights and challenges that researchers face when interpreting the potential impact of introgression on fitness and testing hypotheses about the role of selection within the context of health and disease.

Keywords: archaic introgression, fitness, natural selection, Neanderthal, Denisova, anatomically modern humans.

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Widespread interbreeding between hominins

The demographic history of anatomically modern humans (AMH) is complex, and involves a large number of migrations, genetic admixtures and introgressions, population extinctions and genetic adaptations, which overlap both in time and in space (see Figure 1). Due to this complexity, the evolutionary history of humankind is still far from being fully understood (Nielsen et al., 2017). During the last 30 years, the most accepted demographic scenario for explaining recent evolution of AMH has been the Out of Africa model (OOA). According to this model, AMH evolved in Africa around 100-200 thousands years ago (kya) in East Africa and migrated to the rest of the world. Classical "pure" OOA assumes that admixture with other archaic populations such as Neanderthals or Denisovans, present at the time of the rise of AMH, either did not occur or was negligible (Lalueza-Fox & Gilbert, 2011).

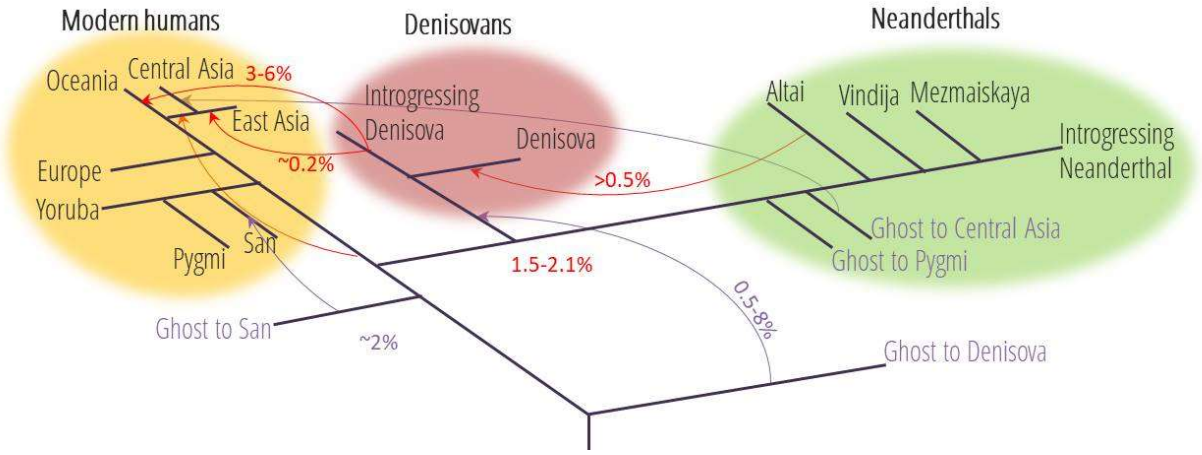

Figure 1. Family tree of the four groups of early humans living in Eurasia 50,000 years ago and the inferred gene flow between the groups due to interbreeding (based on Prüfer et al., 2014; Mondal et al., 2016; Hsieh et al., 2016; Medina-Gomez et al., 2017). The direction and estimated magnitude of inferred gene flow events are shown. Branch lengths and timing of gene flows are not scaled. The dashed line indicates that it is uncertain whether Denisovan gene flow into modern humans in mainland Asia occurred directly or via Oceania. Light violet color indicates introgression events from unknown archaic populations (Ghost).

However, genomic studies of ancient DNA have revealed that AMH interbred with other hominid lineages, such as Neanderthals and Denisovans, present in Eurasia up to ~30,000–50,000 years ago (Kelso & Prüfer, 2014; Quach & Quintana-Murci, 2017; Vattathil & Akey, 2015). Whole-genome sequences from ancient specimens have revealed the presence of DNA of Neanderthal ancestry accounting for ~2% of the genome in Europeans to ~4% in Asians (Green

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et al., 2014). In contrast, DNA introgressed into modern humans from Denisovans is found mostly in Australo-Melanesians, who may account for up to 6% of Denisovan DNA in their genomes and, to a lesser extent, in South East Asians (Mallick et al., 2016). These estimates are averages across the modern human genome. However, specific regions of the genome may have degrees of Neanderthal ancestry as high as 64% in Europeans and 62% in Asians.

New studies based on current genetic diversity are suggesting that the events of archaic introgression in AMH did occur out of Africa with other hidden ”ghost” archaic populations (Mondal et al., 2016). Furthermore, there is growing evidence that archaic introgression occurred also within Africa (Labuda et al., 2000; Hammer et al., 2011; Lachance et al., 2012; Hsieh et al., 2016; Xu et al., 2017; Zanolli et al., 2017), raising the exciting possibility that other unknown archaic groups may have contributed to human genetic diversity. Therefore, recent work suggests that apparently distinct species can exchange the genetic material along their evolutionary history (Mallet et al., 2016). The biological implications of such introgression, including their consequences on modern human health is reviewed in the following sections.

Selection against introgressed regions at the level of genomes and individual loci

Introgressed alleles in a foreign genetic background frequently have the negative fitness effects regardless of the amount of adaptive introgression. Martin and Jiggins (2017) made two important considerations when dealing with models of selection against introgressed genomic tracts. First, as many of the factors that influence selection -such as recombination rate and gene density- are interdependent, the models that account for combined effects of both factors are more feasible, especially if they incorporate specific predictions such as the decline in selective sweep strength with increasing distance from selected loci. Juric et al. (2016) modelled the level of Neanderthal ancestry in human populations as a function of the recombination distance from nearby selected alleles and estimated both the density of selected loci and the strength of selection. Second, interpretations of the landscape of ancient introgression into human species may vary depending on underlining assumptions. For example, the majority of models assume that introgressed blocks are selected independently of each other in the genetic background of the recipient population. However, Harris and Nielsen (2016) showed that much of the selection against introgression may occur in early generations, since early generation hybrids should have complex ancestries in which epistasis can lead to non-additive fitness effects. Another

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assumption pointed out in this study is that weakly deleterious mutations segregating in the donor population would be the main driver of selection against Neanderthal introgression in humans. Under such a model, the lower effective population size in Neanderthals would have led to the accumulation of weakly deleterious alleles that, once introgressed into humans, would reduce the relative fitness of the hybrid. However, in such context, even if both species bear recessive deleterious alleles but at differing sites, hybrids might have enhanced overdominant fitness variation regardless these deleterious recessives, which leads to the conclusion that Neanderthal introgression may have initially been favoured by selection in humans (Harris & Nielsen, 2016).

Disproportionate role for sex chromosomes in species differences and hybrid incompatibility constitutes a consistent pattern in speciation (Presgraves, 2008; Qvarnström & Bailey, 2009). The compelling evidence of these processes has been reported in the genomes of non-African humans, which have sequences devoid of introgressed variation ("deserts") from Neanderthals and Denisovans, possibly driven by selection against introgression described by Sankararaman et al. (2014; 2016). Furthermore, the authors indicated that the introgression landscape of Neanderthal and Denisovan in modern humans is similar. Of particular interest is a significant reduction in admixture associated with genes showing testes-specific expression, suggesting that admixture may have led to reduced male fertility and supporting evidence of reduced introgression on sex chromosomes (Sankararaman et al., 2014; Sankararaman et al., 2016). However, this genomic evidence must be interpreted with caution (Garrigan et al., 2012). When selection against introgression occurs at a large number of loci throughout the genome, its combined effects on many loci can leave detectable patterns, even though selection on any individual locus may be weak (Martin & Jiggins, 2017). Moreover, weaker signals of introgression have been observed in parts of the genome with high gene density and/or low recombination (Sankararaman et al., 2016), agreeing with theoretical work, which predicted that the strength of selection against introgression depends on the density of selected sites and the recombination rate (Barton & Bengtsson, 1986).

Evidence for the role of purifying selection in shaping introgression landscape come from particular categories of genes experiencing different amounts of introgression as previously demonstrated for non-human species (Fontaine et al., 2015; Janoušek et al., 2015; Runemark et

al., 2018; Schumer et al., 2016). This is also true for the autosomal regions deficient in both Neanderthal and Denisovan ancestries, which contain a significant enrichment of genes transcribed in meiotic germ cells (Jégou et al., 2017). The phenotypic traits and the type of selective regime acting on them are summarized in Figure 2, and their corresponding genomic regions are listed in Supporting Table. Taking into account that there has been strong selection against archaic introgression among protein-coding genes (Fu et al., 2016; Sankararaman et al., 2016; Vernot & Akey, 2014), functional regions contributing to the uniqueness of some modern human traits could be identified if they are strongly depleted of archaic ancestry (Vernot et al., 2016). For example, no Neanderthal ancestry has been detected around the forkhead box protein P2 (FOXP2) gene, mutations of which are associated with language disorders (Konopka & Roberts, 2016). Similarly, Neanderthals and Denisovans carry a single copy of AMY1 gene, encoding an amylase enzyme responsible for starch digestion. In contrast, AMH carry multiple copies of the gene and there is no evidence of Neanderthal introgression. This has been interpreted as an evidence that the production of larger amounts of salivary amylase for starch digestion has been under positive selection to modern humans compared to archaic species (Perry et al., 2015). Moreover, regions depleted of both Neanderthal and Denisova ancestry are enriched for genes expressed in specific brain regions (e.g. the ventral frontal cortex-ventrolateral prefrontal cortex in infants and the striatum in adulthood; Vernot et al., 2016). Another genomic study of Chintalapati et al. (2017) on small indels introgressed from Neanderthal demonstrated that negative selection affected these variants more than other variants segregating in modern humans and confirmed that deletions evolved under more constraint than insertions, the vast majority of them laying in the intronic regions. Besides, introgressed variants that may influence on the phenotype of their carriers were identified (Supporting Table). Among them, an introgressed deletion associated with a decrease in the time to menarche may constitute an example of a former Neandertal-specific trait contributing to modern human phenotypic diversity (Chintalapati et al., 2017; Supporting Table).

Further evidence of the deleterious effect of Neanderthal introgression can be identified at the expression level. Analysis of gene expression of Neanderthal alleles in current individuals shows a significant downregulation at testes and brain compared to other tissues (Dannemann et al., 2017; McCoy et al., 2017).

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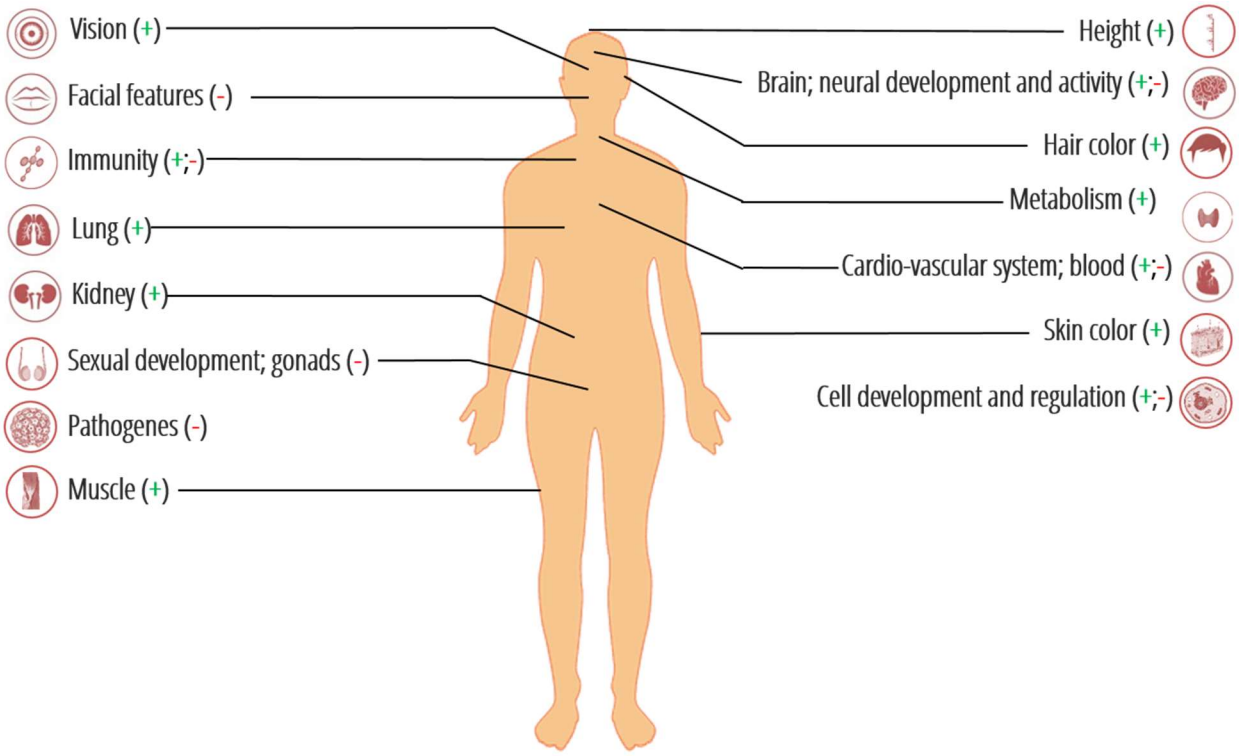

Figure 2. The prevalent phenotypic impact of introgressed variants from ancient genomes over modern human organs and systems (see Supporting Table for details).
+ - advantageous variation;
- - detrimental variation.

Genomic signatures of adaptive introgression from archaic to modern humans

The footprint of purifying selection against archaic alleles is widespread in the human genome. Nevertheless, given that archaic species evolved for long times in environments for which early AMH were not biologically adapted, interbreeding between anatomically modern humans with archaic species could have facilitated adaptation to specific environments (Racimo et al., 2015; Gittelman et al., 2016; see Supporting Table). This evolutionary process could bring variants at a higher frequency than *de novo* mutations, providing linked blocks of sequence with multiple functional mutations, potentially including co-adapted alleles (Hedrick, 2013). This process, known as adaptive introgression, has risen to prominence based on a series of high profile examples in human genomes (Kelso & Prüfer, 2014; Racimo et al., 2015; Vattathil & Akey, 2015) (see Figure 2). For example, genes involved in functions related to keratin filaments, sugar metabolism, muscle contraction, body fat distribution, enamel thickness and oocyte meiosis have been targeted by adaptive introgression from Neanderthals (Sankararaman

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et al., 2014; Racimo et al., 2017; Zanolli et al., 2017). Genes involved in the variation of skin pigmentation and hair morphology (BNC2, MC1R) also show the signature of positive selection as the result of adaptation to diverse habitats with different degree of insolation (Dannemann & Kelso, 2017; Ding et al., 2014; Frost et al., 2017). Advantageous immune variants introduced into the modern human population from archaic genomes have substantially contributed in the present-day diversity of immune genes (Mendez et al., 2012; Mendez et al., 2013; Deschamps & Quintana-Murci, 2016; Nédélec et al., 2016; Quach et al., 2016; Racimo et al., 2015). Since innate immunity genes have evolved under stronger purifying selection than the rest of the genome (Deschamps et al., 2016), this enrichment of introgressed alleles suggests the presence of strong positive selection at the immune system. Similarly, EGLN1 and EPAS1 genes, associated with hemoglobin concentration and response to hypoxia, display a high degree of Denisovan ancestry in Tibetans, suggesting that this population acquired advantageous alleles for high altitude life through ancient admixture (Hu et al., 2017; Huerta-Sánchez et al., 2014; Tashi et al., 2017). In contrast to these evidences of positive selection, evidence for balancing selection in humans is largely circumstantial (Quach & Quintana-Murci, 2017). However, host defense genes such as those encoding several membrane glycoproteins, the KIR regions that coevolve with HLA ligands, and other genes encoding proteins involved in cell migration or innate immunity, apparently are subject to this otherwise rare selective regime (Andrés et al., 2009; DeGiorgio, Lohmueller, & Nielsen, 2014; Leffler et al., 2013; Norman et al., 2007; Single et al., 2007). The HLA region, a paradigm of balancing selection in humans, harbors functional variants that were probably introgressed from Neanderthals and Denisovans (Abi-Rached et al., 2011). An alternative explanation by Yasukochi and Ohashi (2017) based on phylogenetic analysis do not support the introgression hypothesis and conclude that it is highly likely that supposedly introgressed allelic lineage HLA-B*73 has been maintained in the direct ancestors of modern humans (Yasukochi & Ohashi, 2017).

Increasing evidence suggests that regulatory variants play a central role in adaptive processes (Fraser, 2013; Pickrell, 2014; Schaub et al., 2012). A compelling example of local adaptation detected on the expression level is at the apelin receptor gene APLNR. Apelin is a signal peptide that influences several aspects of cardiac, digestive, brain, and vascular function, including regulation of oxygen levels. This gene exhibits strong allele-specific expression favoring the Neanderthal allele in brain tissues, but allele-specific expression favoring the

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modern human allele in non-brain tissues (McCoy et al., 2017). There are also a number of examples of local adaptation driven by regulatory variants resulting in population differences in immune responses (Dannemann et al., 2017; Nédélec et al., 2016; Quach et al., 2016). Despite the evidence that functional archaic alleles (non-synonymous and associated with expression) have decreased in frequency over the past 8,500 years, four loci were identified where the archaic alleles associated with differential expression show large increases in frequency over time. Among these are introgressed alleles modifying expression of the OAS1/OAS2/OAS3 genes involved in innate immunity and whose tissue-specific effects suggest that they may be functionally relevant (Mendez et al., 2013; Dannemann et al., 2017). Archaic alleles in OAS1 are associated with higher expression in subcutaneous adipose tissue and sun-exposed skin, while higher expression in thyroid and pancreas and vagina is associated with archaic alleles in OAS2 and OAS3, respectively. In contrast, individuals carrying archaic alleles show down-regulation of OAS1 and OAS3 in esophagus mucosa and spleen, and individuals carrying archaic alleles show down-regulation of OAS2 in fibroblasts and OAS3 in fibroblasts as well as three brain regions (hippocampus, putamen, and caudate nucleus) (Dannemann et al., 2017). Other examples of local adaptation influencing the levels of expression include expression of gene ERAP2, involved in susceptibility to Crohn's disease; CCR1, limiting leukocyte recruitment and preventing inflammatory responses; HLA-DQA1, associated with susceptibility to celiac disease; and TLR1, associated with markedly lower levels of inflammatory response gene expression (Nédélec et al., 2016; Quach et al., 2016). Apparently, introgression from Neanderthals also contributed to the diversification of transcriptional responses to infection in human populations. The introgressed genetic segments in European genomes contain regulatory variants with effects on steady-state expression and responses to TLR7/8 stimulation and influenza virus (Quach et al., 2016; Quach & Quintana-Murci, 2017). Furthermore, the archaic variants of several eQTLs have been reported as potential candidates for adaptive introgression conferring better adaptation through the regulation of gene expression. Examples are the gene DARS associated with neuroinflammatory and white matter disorders (Nédélec et al., 2016); the archaic variants of OAS locus apparently associated with diverse flavivirus resistance phenotypes (Sams et al., 2016); and PNMA1 harboring a response eQTL for influenza virus and stimulating interferon production (Quach et al., 2016). Another regulatory archaic variant modifies the expression of TNPO3 in brain being associated with multiple autoimmune phenotypes (Dannemann et al.,

2017). All these studies clearly show that selection and archaic admixture affected substantially present-day inter-population differences in immune responses, at least in terms of transcriptional variability, supporting the notion that variation in gene expression has been an important vehicle for human adaptation (Fraser, 2013). Furthermore, it has been shown that the higher frequency archaic variants contribute significantly more to gene expression changes than lower frequency archaic variants. This suggests that at least some of the archaic alleles that modify gene expression may have been driven to higher frequencies by positive selection, supporting the idea that changes in gene expression are likely to have important adaptive effects in humans (Dannemann et al., 2017).

However, whatever the potential benefits of archaic introgression in the past, alleles of Neanderthal origin have been also associated with several neurological, dermatological, and immunological phenotypes, indicating an influence of ancient admixture on current disease risk in humans (Mozzi et al., 2017; Simonti et al., 2016; Taskent et al., 2017). For example, introgressed alleles associated to the immune system response can increase the risk of inflammation or autoimmunity under the environmental factors changing overtime (Barreiro & Quintana-Murci, 2010; Brinkworth & Barreiro, 2014; Corbett et al., 2018; Sironi & Clerici, 2010; S. C. Stearns, 2012). The case of celiac disease neatly illustrates the tradeoff between past selection and current maladaptation. Taskent et al. (Taskent et al., 2017) detected an evidence of Neanderthal introgression in the chemokine receptor (CCR) gene family constituting the risk alleles for celiac disease, which was possibly maintained by selective forces in early European population. Furthermore, population genetic analyses have shown that the high frequency of several risk alleles of genes associated with celiac disease such as IL12A, IL18RAP and SH2B3 (Hunt et al., 2008) in Europeans results from past positive selection events (Barreiro & Quintana-Murci, 2010; Zhernakova et al., 2010). Another example came from a nonsynonymous variant of the ZNF365D gene present in ~32% of Europeans and absent from Africans, which was inherited from Neanderthals and is associated with a higher risk of Crohn's disease (Sankararaman et al., 2014). Likewise, variants of TLR6-1-10 inherited from Neanderthals and Denisovans and present in Europeans and Asians have been associated with greater susceptibility to allergies (Dannemann et al., 2016).

Further investigations are required, but the studies published to date have provided invaluable resources and increased our understanding of the molecular and cellular processes underlined by introgressed genetic variants and different selective regimes acting on them.

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Conclusions and perspectives

The ongoing deluge of sequencing data from thousands of individuals and different populations worldwide, including some archaic hominins, has provided new insight into the evolutionary history of our species. Genomic studies of introgression between early Eurasians and archaic human species, such as Neanderthals and Denisovans, are beginning to offer novel insights into the evolutionary and phenotypical consequences of hybridization. There is quite common evidence for widespread selection against introgression across the genome, but adaptive introgression may also be considered an important force driving adaptation of modern humans to new environments. However, additional human datasets advances, integration of different sources of information and development of new statistical and analytical methods are critical for understanding the biological and medical implications of much of such signals of selection.

Supporting Table illustrates that our knowledge of the functional consequences of the introgressed variation is essentially based on populations with European ancestry. Informative data from other ethnic groups and sequencing additional samples from ancient hominins will further deepen our knowledge of the contribution of archaic hominins to the diversity of human traits and complex diseases. Furthermore, it will help to identify the functional changes that have contributed to human adaptation and survival over time. Moreover, multigenerational prospective cohort studies from multiple human populations will allow direct measurements of genetic variation and selection intensity for common traits in contemporary populations, performed in a range of nutritional, cultural and geographic conditions, constituting the best way of characterization of the magnitude and importance of complex ecological, epidemiological, demographic and evolutionary shifts. In addition to the genome databases of European origins as the Framingham cohort in the USA, the Uppsala Birth Cohort in Sweden and the Lifelines Cohort in the Netherlands such cohorts now include H3Africa Initiative on Human Heredity and Health in Africa and the Tohoku Medical Megabank Project in Japan. Data desideratum supplemented with genomic and medical information will further increase our understanding of the antagonistic pleiotropic effects that contribute to the burden of non-infectious diseases and provide new clues to disease causes, potential therapies and possible adverse effects of novel therapies (Corbett et al., 2018).

In the case of integrating different sources of information, studies of genetic variants with regulatory effects on gene expression (eQTL) have already provided insight into the genetic and

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evolutionary determinants of population phenotypic diversity (Fairfax & Knight, 2014). One of the first global approaches is the GTEx project. GTEx explores the landscape of gene expression across 54 different tissues, providing the richest catalog of tissue-specific and shared eQTL (Ardlie et al., 2015; GTEx Consortium, 2017). It was already used in the analyses of expression patterns of introgressed haplotypes in the recent studies conducted by McCoy et al. (2017) and Dannemann et al. (2017). The future population genetic analyses should apply the extension of this across-tissue rationale to multiple populations from different ethnic backgrounds to provide a comprehensive picture of the physiological mechanisms underlying adaptation to environmental pressure and the maintenance of homeostasis.

In the case of new methods, the challenge for the future will be to develop robust statistical models and computational methods for detecting selection, quantifying the frequency of adaptive introgression more widely and understanding the circumstances where it is likely to play a predominant role in adaptation. An exciting future prospect is that our interpretations of observations in nature will be aided by simulation studies (Harris and Nielsen 2016) and empirical studies of the consequences of introgression for phenotype and fitness (McCoy et al. 2017). In this context, there are no accurate estimates of the timing of most of the signatures of selection now being detected in the human genome (lactase persistence as an exception; Field et al., 2016; Tishkoff et al., 2007), or good methods for estimating the ages and natures of the environments in which past selection occurred (Corbett et al., 2018). Future studies should be able to discriminate with confidence between different time-scales of selection, for example, as a result of the agricultural revolution 8,000–10,000 years ago or the industrial revolution 100–300 years ago.

In conclusion, the integration of all of these datasets into a clinical, epidemiological, and population genetics framework will provide new insights on the history of adaptations in the genus *Homo*, and the ways our genetic and non-genetic makeup, together with changes in our environment and cultural behaviors, influence phenotypic variation in both health and disease.

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