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Archaic hominin introgression into modern human genomes

Omer Gokcumen

Department of Biological Sciences, North Campus, University at Buffalo, Buffalo, New York

Correspondence
Omer Gokcumen, Department of Biological Sciences, North Campus, University at Buffalo, Buffalo, NY 14260.
Email: omergokc@buffalo.edu

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Abstract

Ancient genomes from multiple Neanderthal and the Denisovan individuals, along with DNA sequence data from diverse contemporary human populations strongly support the prevalence of gene flow among different hominins. Recent studies now provide evidence for multiple gene flow events that leave genetic signatures in extant and ancient human populations. These events include older gene flow from an unknown hominin in Africa predating out-of-Africa migrations, and in the last 50,000–100,000 years, multiple gene flow events from Neanderthals into ancestral Eurasian human populations, and at least three distinct introgression events from a lineage close to Denisovans into ancestors of extant Southeast Asian and Oceanic populations. Some of these introgression events may have happened as late as 20,000 years before present and reshaped the way in which we think about human evolution. In this review, I aim to answer anthropologically relevant questions with regard to recent research on ancient hominin introgression in the human lineage. How have genomic data from archaic hominins changed our view of human evolution? Is there any doubt about whether introgression from ancient hominins to the ancestors of present-day humans occurred? What is the current view of human evolutionary history from the genomics perspective? What is the impact of introgression on human phenotypes?

KEYWORDS
anthropological genetics, enisovans, genomics, molecular anthropology, neanderthals

1 | INTRODUCTION

Recent advances in ancient genomics—nothing short of revolutionary—coupled with the vast increase in the human genome variation data have allowed researchers to readdress a fundamental question:

Where does extant human genetic variation come from?

It has been known for some time that a single African ancestral population survived a severe population bottleneck. Thus, it was thought that virtually all-extant human genetic variation could be traced back to this ancestral population. In fact, earlier, locus-specific studies, such as the investigations on the mitochondrial DNA diversity, supported this scenario. However, recent genome-wide studies have challenged this relatively straightforward story of human evolution. These studies revealed branches of the human evolutionary tree that diverged much earlier and connected to each other across time. There is now evidence that ancient hominin populations, including ancestors of anatomically modern humans, Neanderthals, Denisovans (the enigmatic hominin, which was recently identified as a distinct lineage based on genomic evidence), and yet-to-be-discovered hominin populations split, diverged, and reconnected, sharing their genetic material with each other over and over again. The image of humankind as a separate, distinct group with a well-defined evolutionary lineage is being replaced by stories of *introgression*—that is, gene flow among isolated groups of hominin species. The genetic variation humans carry today can be traced back to multiple ancient populations, not all of them *Homo sapiens*.

Given that other reviews have already detailed studies on introgression in the human lineage (Ackermann, Mackay, & Arnold, 2016; Dannemann & Racimo, 2018; Racimo, Sankararaman, Nielsen, & Huerta-Sánchez, 2015; Vattathil & Akey, 2015; Wall & Yoshihara Caldeira Brandt, 2016), this review aims to answer specific questions about introgression that are relevant to anthropological thinking based on recent findings.

2 | WHAT IS INTROGRESSION AND WHY DO WE CARE ABOUT IT?

Introgression (or introgressive hybridization) is gene flow from the gene pool of one distinct biological taxon (often a species) to another by hybridization (Anderson & Hubricht, 1938). Though the concept of introgression may seem relatively simple, it refers to a very specific process and can be easily misunderstood. For introgression to occur, two biological entities[1] with a relatively recent common ancestor (e.g., the ancestors of modern humans and Neanderthals) need to split and remain isolated from each other for enough time that their gene pools could become distinctively divergent. Thus, the gene pool of the receiving population often harbors alleles distinguishable as introgressed and nonintrogressed.

Introgression, as specific a process as it is, turns out to be both common and evolutionarily crucial (Feder, Egan, & Nosil, 2012; Harrison & Larson, 2014; Suarez-Gonzalez, Lexer, & Cronk, 2018). It is plausible, for example, that by studying the introgressed genomic variation, one can estimate the strength, duration, and timing of interactions between different populations across time (e.g., de Manuel et al., 2016). Moreover, introgression can introduce new, potentially adaptive or maladaptive genetic variation to a population, providing natural experiments to understand the genetic bases of phenotypic variation and adaptive processes (Racimo, Marnetto, & Huerta-Sánchez, 2017; e.g., Kim, Huber, & Lohmueller, 2018). Thanks to the abundance of genome-wide datasets, investigating the signatures of introgression across the genome has become an important focus in human evolutionary genetics research.

3 | HOW HAVE GENOMIC DATA FROM ARCHAIC HOMININS CHANGED OUR VIEW OF HUMAN EVOLUTION?

The place of Neanderthals in human evolutionary history has been a major area of discussion since this species was first recognized as a distinct cousin to modern-day humans (King, 1864). Up until more quantitatively robust genomic evidence added to this debate in the 2000s, the majority of insights about the relationship between modern human ancestors and Neanderthals came from the fossil record (Tattersall, 1999). Despite being incomplete and biased towards Eurasian specimens, the fossil record revealed two general and robust trends (Klein, 1995; Liu et al., 2010; Stewart & Stringer, 2012; Storm et al., 2005; Stringer & Gamble, 1993; Swisher 3rd et al., 1996). First, the oldest modern human-like fossils are mostly located in Africa. Second, there are very old hominin fossils with distinct non-modern features and ambiguous and disputed phylogenetic classifications scattered across Eurasia and Oceania.

Two opposing views emerged from these general trends and dominated the debate on modern human origins in the latter part of the 20th Century, namely the *out-of-Africa* and *multiregionalism* models (Figure 1). The former took an orthodox view, tracing back modern humans to a single ancestral population in Africa, which later moved out of Africa to replace all other hominin species, including Neanderthals (Stewart & Stringer, 2012; Tattersall, 2009). The opposing *multiregionalist* view imagined a world where following the earlier migrations of the ancestral *Homo erectus* populations out of Africa, multiple human sub-species evolved in local ecological contexts in different parts of the globe (Wolpoff, Hawks, & Caspari, 2000; Wolpoff, Thorne, Smith, Frayer, & Pope, 1994). These groups, multiregionalists argued, later blended to form the relatively homogenous extant human population. In their own rights, these opposing views explained different aspects of the fossil record, with the out-of-Africa model representing the mainstream view at the time (Tattersall, 2009). However, the quantitative noise that is inherent in the fossil record eventually reduced this debate to methodological minutiae with no synthesis in sight. Then, entered genetics.

The initial impact of genetics on our understanding of human origins was considerable, yet theoretically rudimentary, as it was framed via the contemporary anthropological discussions. The first genetic studies on human variation showed that the majority of extant human genetic variation with the deepest phylogenetic branches reside in Africa, supporting the out-of-Africa model (Cann, Stoneking, & Wilson, 1987; Seielstad, Bekele, Ibrahim, Touré, & Traoré, 1999; Tishkoff et al., 2009). Another piece of the puzzle was put in place when the sequence of maternally inherited mitochondrial DNA from a Neanderthal was shown to be considerably different from the millions of documented human mitochondrial DNA sequences (Serre et al., 2006). The multiregional model suggested that if Neanderthals contributed to the human gene pool substantially then at least some humans should carry mitochondria inherited from Neanderthals. Thus, at the beginning of the 21st Century, mainstream anthropological genetics squarely agreed with the out-of-Africa model: modern humans originated from a single African ancestral population and spread across the world, replacing all other closely related groups of hominins, including Neanderthals. As it turns out, this model was incomplete.

The next phase of anthropological genomics has been nothing short of paradigm-shifting. Before ancient hominin genomes were sequenced, sophisticated analyses of the then recently available genome-wide datasets gave early signs for the insights to come: a small but observable number of unusually divergent haplotypes (i.e., multiple alleles in linkage disequilibrium with each other) within

[1] I am refraining from using the term "species" here and note that the term "biological entity" was used to describe such closely related lineages (see the excellent review by Harrison and Larson (2014) for a more thorough discussion). As this audience knows well, the species concept in anthropology has always been murky; in this review, I will use "population" to designate groups with distinctive gene pools, (e.g., Neanderthal and modern human populations) to avoid committing to either the *lumper* or *splitter* camps.

the extant human gene pool (Hammer, Woerner, Mendez, Watkins, & Wall, 2011; Plagnol & Wall, 2006; Templeton, 2002). One remarkable early study suggested that 5% of the human genome have coalescent dates that are older than what can be explained by a single African ancestral population and invoked multiple ancient admixture events, including one from Neanderthals (Plagnol & Wall, 2006).

Direct evidence soon followed with the publication of genome-wide data from a Neanderthal individual (Green et al., 2010). The authors showed that extant Eurasian populations share significantly more derived alleles with Neanderthals than sub-Saharan African populations, a subtle difference only visible with the statistical power gained by analyzing millions of alleles across the genome. The most plausible interpretation of this observation is that Neanderthals contributed to the Eurasian but not the African gene pool. Shortly after, genome-wide data were published from another ancient hominin, a Denisovan individual (Meyer et al., 2012). This Siberian hominin was almost as genetically distinct from Neanderthals as it was from modern humans. What was more surprising, however, was that Oceanian populations share more derived alleles with Denisovans than other populations, suggesting a potential Denisovan introgression into Oceanic populations.

Two different ancient genomes led to the discovery of two independent introgression events in the human lineage - *what are the odds?* Subsequent studies (Kuhlwilm et al., 2016; Meyer et al., 2016; Posth et al., 2017; Prüfer et al., 2014; Slon et al., 2018) have revealed several more introgression events among archaic hominins and the ancestors of modern humans in what a Nature editorial defined as an "interbreeding bonanza" (Callaway, 2016). The debate of human evolution shifted from the more generic out-of-Africa and multiregionalism models to extremely quantitative genomic discussions of the timing, extent, and origin of introgressions into modern human ancestors (Wolf & Akey, 2018). The emerging picture of the human evolutionary tree now has several connections between its branches.

4 | IS THERE ANY DOUBT ABOUT WHETHER INTROGRESSION FROM ANCIENT HOMININS TO THE ANCESTORS OF PRESENT-DAY HUMANS OCCURRED?

The scenario for the Neanderthal introgression into humans is rather simple (Figure 2). In a hypothetical introgression scenario, a male Neanderthal has a female offspring with a female human individual. This "hybrid" offspring would carry one Neanderthal copy and one human copy for each of her chromosome pairs. Through the independent assortment of chromosomes, the eggs of this hybrid individual would carry a random combination of Neanderthal and human chromosomes. Moreover, because the process of recombination can shuffle genetic material between homologous chromosomes during gamete formation, the Neanderthal chromosomes in her eggs may carry a small portion of human DNA fragments and vice versa. Assuming that this hybrid individual lived and produced offspring with humans, the resulting second generation will be less Neanderthal and more human, carrying a smaller number of Neanderthal pieces in her chromosomes. Also assuming that her offspring successfully produce more offspring, her descendants will increase in numbers in the population, but by each generation, they carry fewer and shorter fragments of Neanderthal DNA in their genomes. Indeed, today we estimate that virtually all Eurasians (billions of individuals) each carry hundreds of different neanderthal pieces scattered across their chromosomes (Vernot & Akey, 2014).

Despite being conceptually simple, studying Neanderthal introgression in the genome is painfully convoluted. The genomic signature of introgression is only visible in a tiny fraction of the human genome that fits the following criteria:

1. The shared allele is derived in the Neanderthal lineage. More than 99.5% of the nucleotides are identical in human and Neanderthal genomes (Prüfer et al., 2014),[2] and as such, the majority of genomic locations are not informative about the introgression process.
2. The shared allele is polymorphic in humans—some individuals must have the Neanderthal allele while others carry the ancestral human allele. If the allele is fixed in the human lineage, we cannot tell whether it was fixed after Neanderthal introgression (unlikely) or if it was already derived and became fixed in Human-Neanderthal ancestor (more likely).
3. The shared allele is identical-by-descent in the human and Neanderthal lineages, that is, the derived allele did not evolve independently in the human and Neanderthal lineages.[3]
4. The sharing of these alleles is due to recent gene flow from Neanderthals to humans, and not because of incomplete lineage sorting (i.e., ancient alleles that remain polymorphic since before Human-Neanderthal populations split). This is an important point as more than 95% of polymorphic derived alleles shared with Neanderthals are due to incomplete lineage sorting, and thus less than 5% of shared alleles are informative about introgression (Lin, Pavlidis, Karakoc, Ajay, & Gokcumen, 2015).

Even with current technologies, it is not possible to identify individual alleles in a given modern genome that fit these criteria. Instead, we rely on quantitative population genetics approaches to ask specific questions about introgression. Svante Pääbo's group directly investigated Neanderthal introgression in a landmark paper (Green et al., 2010), documenting the first genome-wide sequencing data from a Neanderthal individual. The authors used a simple but clever strategy to compare the relative contribution of Neanderthals to individual

[2]These comparisons are conducted in segments of the DNA where the sequence alignment and thus variation calling is robust and have low false positive rates. A good portion of the genome is *terra incognita* for such short-read sequence-based variation analyses due to complications stemming from simple repeats, segmental duplications, structural variations, retrotranspositions, and assembly errors, etc (Chaisson et al., 2018; Kronenberg et al., 2018; Lin & Gokcumen, 2019; Miller et al., 2017; Sedlazeck, Lee, Darby, & Schatz, 2018). It is likely that this limitation in our approach may hinder our ability to investigate important variation between and within species that may explain some of the phenotypic variations. However, with regard to human evolutionary history, there is no reason to believe that this methodological shortcoming bias the results with regard to evolutionary history in a fundamental way.

[3]Note that most studies assume that recurrence is a minor contributor to allele sharing.

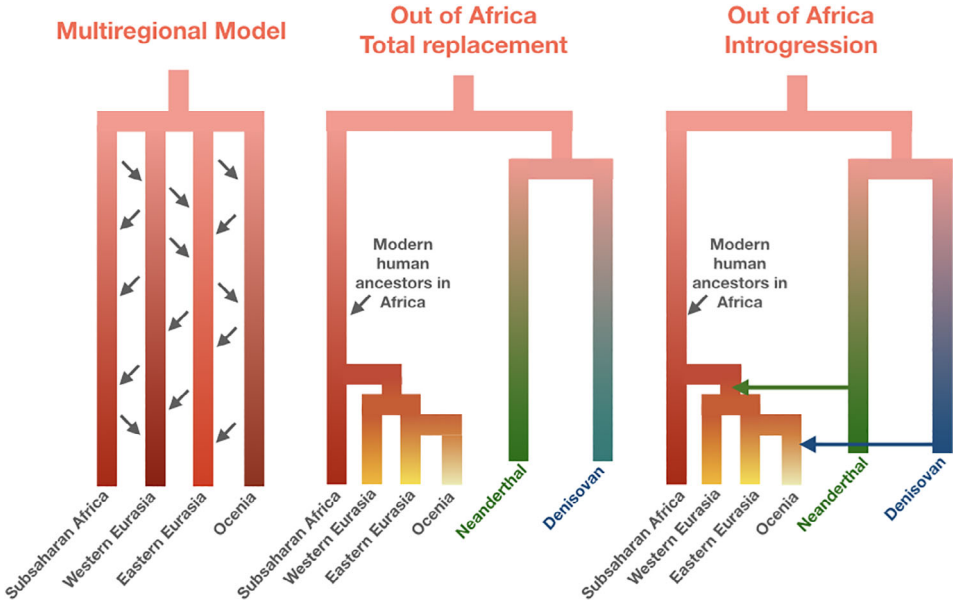

FIGURE 1 Cartoon schematics of the three broad models of recent human evolution discussed in this article

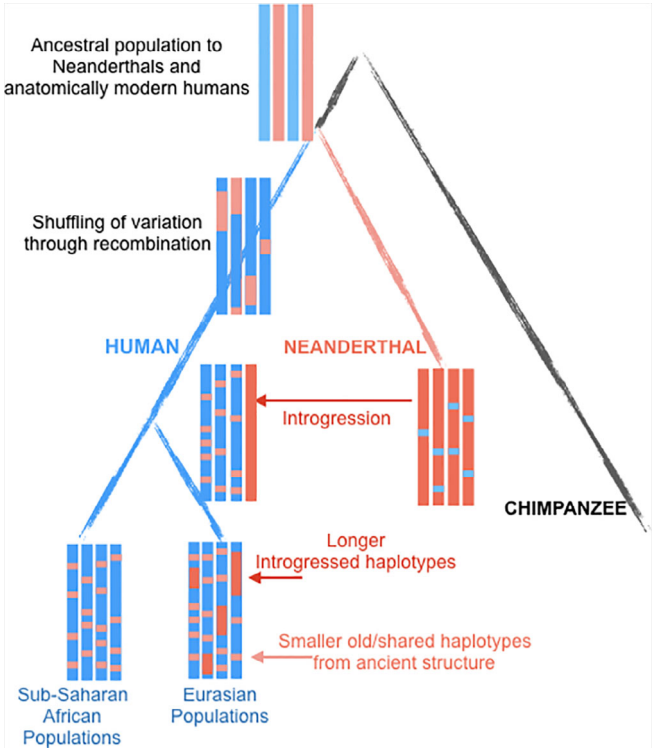

FIGURE 2 A simple schematic of Neanderthal introgression. The orange/red pieces on the chromosomes show the segments of DNA that are shared with Neanderthal chromosomes. Note that smaller pieces can be traced back to the ancestral population of Humans and Neanderthals while the signature of introgression is in longer haplotypes that can be traced back to the much recent introgression event

human genomes using Patterson's D statistics (Durand, Patterson, Reich, & Slatkin, 2011); specifically, they showed that genomes of individuals with Eurasian ancestry share significantly more Neanderthal-derived polymorphic alleles as compared to the genomes of individuals with sub-Saharan African ancestry. They surmised that this difference is due to Neanderthal introgression into the ancestors of the Eurasian population, assuming that sub-Saharan Africans have no introgressed alleles from Neanderthals. This major breakthrough provided the first direct evidence that Neanderthals contributed to the human gene pool.

It is important to summarize a technical issue regarding the analysis of introgression in human genomes. The genome carries a vast amount of information (more than three billion base pairs); derived alleles that fit the criteria that inform about introgression are a fraction of this number. For example, the Green et al. (2010) study reported the comparison between the genomes of one San individual and one French individual; they found that these genomes share 95,347 and 103,612 derived alleles with Neanderthals, respectively. Based on the assumption that there was no Neanderthal introgression into the ancestral population of the San, all the shared alleles in this genome must stem from incomplete lineage sorting (i.e., these are ancient variations maintained since before human-Neanderthal divergence). By the same logic, a similar amount of allele sharing due to incomplete lineage sorting is expected between the French and the Neanderthal genomes. Only the remaining number of alleles in the French genome (103,612–95,347 = 8,265) provide evidence for introgression. In other words, only 0.0002755% of base pairs in this genome were informative about Neanderthal introgression.

In my opinion, this technical issue is important to highlight for two reasons. First, though interesting with regard to human evolution, the actual number of differences between two human genomes due to Neanderthal introgression is almost negligible, and it is debatable whether the reports of Neanderthal contributions on the order of 1–4% from genome-based ancestry tracking companies are an accurate representation. Second, even small biases in false negative or false positive rates in variation calling, assumptions on demographic histories of hominin populations, or differences in mutation rate estimates, if systemic, can significantly bias analysis of introgression in

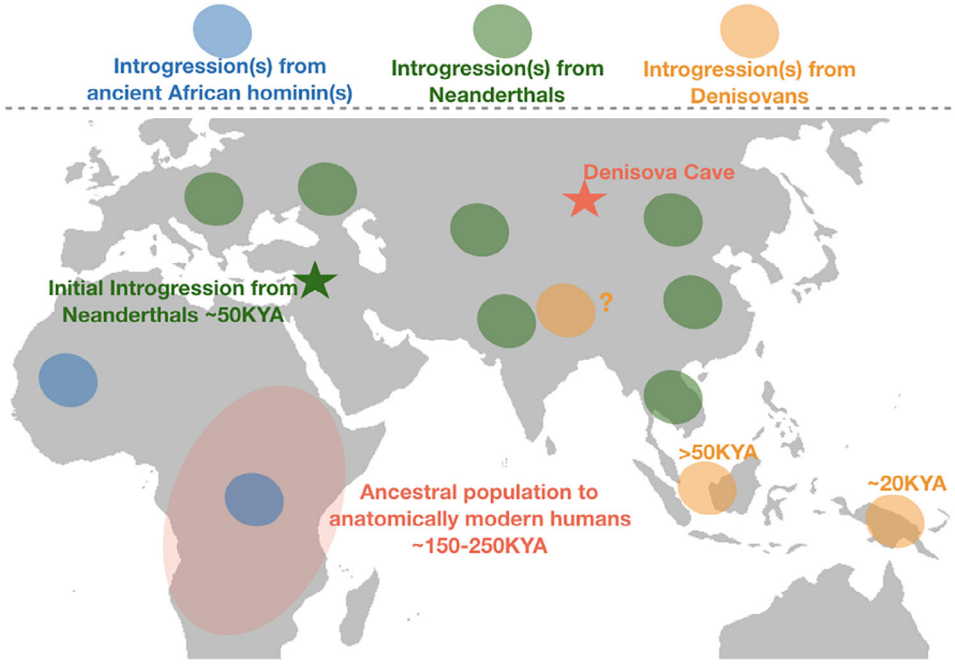

FIGURE 3 The approximate locations and dates of known or predicted introgression events. Note that the picture is still blurry and the exact locations and dates of the introgression events are yet to be fully elucidated

human populations.[4] Indeed, such arguments were the basis of initial skepticism in the community about the argument that Neanderthals contributed a considerable amount of genetic material to the Eurasian gene pool.

One such rebuttal argued that spatial population structure in human ancestral human populations could explain the observed differences in the allele sharing with Neanderthals without invoking introgression (Eriksson & Manica, 2012). They argued for a scenario where the ancestors of present-day Eurasians may have separated from other modern human populations in Africa, prior to migrations out of Africa, and that this ancestral group harbored slightly more Neanderthal alleles simply as a result demographic history and drift. Another argument can be made that the recently appreciated variation in the mutational processes between different human populations (Harris & Pritchard, 2017) may have contributed to the differences in the amount of Neanderthal allele sharing, complicating the introgression scenario. These are legitimate concerns; however, haplotype-level analyses provide a second and so-far undisputed evidence for introgression.

[4]The issue of false-negatives and false-positives in variation calling in ancient hominin genomes are particularly relevant for two reasons. *First*, well-studied effect of contamination from different sources can introduce systematic biases (Gilbert, Bandelt, Hofreiter, & Barnes, 2005)—especially given that the majority of ancient DNA researchers are of Eurasian descent. However, several clever bioinformatic methodologies were devised to minimize such contamination as detailed in excellent reviews (Skoglund et al., 2014; Willerslev & Cooper, 2005). *Second*, ancient DNA is more scarce and fragmented than modern DNA, and thus the data from this source material result in a smaller number of shorter sequences (Glocke & Meyer, 2017; Rohland, Glocke, Aximu-Petri, & Meyer, 2018). As a result, the assembly from ancient genomes are not technically possible (yet). Instead, ancient sequences are mapped to reference genomes from the closest species, in the case of ancient hominins to human reference genomes (de Filippo, Meyer, & Prüfer, 2018). It is plausible that both of these issues can create biases that affect investigation of introgression. Nevertheless, the general consensus in the community at this point is that these biases are randomly affecting the analysis without creating systematic deviations for measurements of introgression.

Once it was suggested that Neanderthals might have contributed genetic material to ancestors of present-day humans, the next clear step was to identify the specific segments of DNA that were introgressed. This is conceptually possible to do because individual variations in the human genomes do not independently travel from one generation to another; instead, variants that are physically close to each other are in *linkage disequilibrium*—they segregate together. This linkage is only broken by chromosomal recombination over generational time (see Veeramah & Hammer, 2014). Thus, the alleles introgressed from Neanderthals should be found together in clusters in the genome.

Such an analysis identified hundreds of segments in the human genome that harbor dozens—sometimes hundreds—of proximate derived variants that match the Neanderthal genome (Sankararaman et al., 2014; Vernot & Akey, 2014), and in the case of Oceanic populations, the Denisovan genome (Browning, Browning, Zhou, Tucci, & Akey, 2018; Vernot et al., 2016). Moreover, the size of these segments can give clues about the time of the introgression event. The longer the amount of time for recombination to work on these segments, the smaller they become. Inversely, the longer the putatively introgressed segments, the more recent the admixture event occurred. Indeed, the introgressed segments identified in various human genomes point to recent admixture events postdating out-of-Africa migrations, and in the case of Denisovans, as recent as 20,000 years before present. These particular dates effectively rule out the potential contribution of ancient population structure in Africa as an explanation for the observed allele sharing trends between extant human populations and ancient hominins. The discovery of hundreds of large segments of DNA with hundreds of alleles shared with Neanderthals or Denisovans provides strong support for the introgression scenario, leading to the current consensus in the field that introgression has been a considerable force shaping extant

human genetic variation. The debate now hinges on the timing, strength, and functional effects of introgression in the human lineage.

5 | WHAT IS THE CURRENT VIEW OF HUMAN EVOLUTIONARY HISTORY FROM THE GENOMICS PERSPECTIVE?

The majority of extant genetic variation in humans can be traced back to a relatively homogenous ancestral population in Africa (Malaspinas et al., 2016; Mallick et al., 2016) that likely went through a severe bottleneck (a dramatic reduction in the size of the population) roughly 100,000 to 200,000 years before present, culling most of the genetic variation in the process (Mallick et al., 2016). At some point in our history, our population consisted of just 10,000 reproducing individuals[5] (Takahata, 1993) or even less (Tenesa et al., 2007). We almost became extinct—probably multiple times. As a result, the majority of the genetic variations observed in present-day human genomes (>90% based on our estimates) are actually mutations accumulated since this bottleneck event (Li & Durbin, 2011; Manica, Amos, Balloux, & Hanihara, 2007). Among the small number of variants that predate this bottleneck reside those that were introgressed from different hominins. Investigation of such genetic variants in different human populations in comparison to available ancient hominin genomes point to at least three distinct hominin populations that contributed to the present-day human gene pool (Dannemann & Racimo, 2018; Wolf & Akey, 2018) (Figure 3). However, to understand these introgression events, it is crucial to understand the structure of both the genetic variation of modern humans, and that of ancient hominin species.

5.1 | On structure in Africa

One of the complications of investigating introgression in hominin species, especially in Africa, is the blurry line between "introgression" and "deep genetic structure." The former is defined as gene flow from a highly divergent population (possibly a different species, depending on the way you categorize species), while the latter refers to the presence of structured divergent genetic variation within a population. Data from the genomes of relatively recent inhabitants of different African geographies (the remains were dated within 10,000 years before present) suggest the presence of deeper lineages that are now lost among extant African populations (Schlebusch et al., 2017; Skoglund et al., 2017). In other words, human genetic variation in Africa 10,000 years ago was more diverse and included more divergent haplotypes than what is observed today. These small populations were measurably different from extant African populations, and most of the genetic variation unique to them is not found in extant African populations. This indicates that there is a substantial deep genetic structure in Africa that is mostly invisible when only analyzing the limited samples from extant human genomes. This genetic structure includes haplotypes that coalesce *before* the separation of Khoe-San populations with other African populations, ~250,000–350,000 years ago (Schlebusch et al., 2017). Thus, at least some of the haplotypes in extant human populations that are older than the post-bottleneck population that we described above can be explained by this ancient genetic structure, and not introgression.

5.2 | "Ghost" encounter(s) in Africa

Given the lack of any genome-wide data from an ancient hominin in Africa, one of the methodological challenges is to distinguish between haplotypic variation that descended from the "deep genetic structure" that I described above and haplotypic variation that descended from an introgression event. The difference is one of time. The former should be dated back to hundreds of thousands of years (the divergence time of most distinct anatomically modern human haplotypes) and the latter should be in the range of millions of years (the divergence time of anatomically modern humans and the source ancient hominin lineage[s] in Africa).

It has been widely accepted that several hominin species have lived in Africa contemporaneously with anatomically modern humans (e.g., *Homo* naledi [Dirks et al., 2017]). Indeed, small but significant deviations from expected linkage disequilibrium and demographic trends invoke introgression from archaic hominin(s) in Africa (Durvasula & Sankararaman, 2018; Hammer et al., 2011; Hsieh et al., 2016; Lorente-Galdos et al., 2019; Xu et al., 2017). A relative consensus of the admittedly small number of studies is that the source of this introgression is a now-extinct hominin population that diverged from the modern human lineage between 0.5 and 2 million years before present. The timing and location of the introgression event are not clear. For example, our own study found one likely introgressed haplotype overlapping the salivary *MUC7* gene that is shared among all African populations, suggesting that at least one introgression event happened before the ancestral human population dispersed in Africa (Xu et al., 2017). We estimated that this introgression happened roughly 100,000 years before present and that the source hominin population diverged from anatomically modern humans about two million years before present. Other studies using sophisticated genome-wide approaches, found concordant evidence of such haplotypes across the genome (Durvasula & Sankararaman, 2018; Lorente-Galdos et al., 2019). A recent model-based approach suggests that a population-specific introgression(s) may have happened as recently as 30,000 years before present affecting ancestors extant African populations (Hsieh et al., 2016). All of these dates, however, are highly sensitive to demographic models, mutation rate estimates, and recombination rate assumptions. Thus, a clearer, more definitive picture requires direct sequencing of ancient genomes from African ancient hominins and older anatomically modern human remains from Africa. Regardless, there is accumulating evidence that anatomically

[5]Here, I am referring to *effective population size*, which refers to the size of an *idealized* population. This population has random mating, constant population size over time, equal number of offspring for each parent pair, concurrent birth every generation. These simplications are, of course, unrealistic, but extremely useful to understand the evolution of genetic variation in a population. It is important to note that the actual population size is generally larger than effective population size.

modern human genomes harbor segments from an unknown hominin population(s) that lived in Africa.

5.3 | On Neanderthal evolutionary history

Even before genomic data, the fossil record solidly established that Neanderthals were a Eurasian population (Howell, 1957; Mellars, 2015). They evolved in Eurasia (likely in Europe) ~400,000 years ago, and later spread across Eurasia (Higham et al., 2014; Pinhasi, Higham, Golovanova, & Doronichev, 2011). Since then, genomic data provided new insights into the relationships between different Neanderthal populations, albeit these insights are limited to the number of samples sequenced to date (Rogers, Bohlender, & Huff, 2017; Wolf & Akey, 2018). Briefly, we know that at least two highly distinct Neanderthal populations walked Eurasia—one in Europe (best represented by the Vindija Neanderthal Genome) and another in Siberia (represented by the Altai Neanderthal Genome) (Prüfer et al., 2014; Prüfer et al., 2017). These two populations were already diverged from each other as early as 120,000 years before present and remained divergent (Peyrégne et al., 2019).

There are other surprising twists to the Neanderthal story. When a bone fragment that is ~90,000 years old from the Denisova cave (the same cave where the Siberian Altai Neanderthal specimen was found) was sequenced, it was discovered that the genome belongs to an offspring of a Neanderthal mother and a Denisovan father (we will talk about Denisovans in the next section) (Slon et al., 2018). *Again, what are the odds?* This incredible discovery shows that introgression between different hominin subpopulations is commonplace. Moreover, it was found that the Neanderthal alleles found in this genome match better to the European Neanderthal genomes than they do to the Altai Neanderthal genomes. This speaks to a population replacement of the Eastern Neanderthals by the European Neanderthals sometime between 140,000 years before present (i.e., the age of the divergent Altai Neanderthal) and 90,000 years before present (i.e., the age of the hybrid individual). Even the very small number of Neanderthal genomes paint a picture of their complex evolutionary history, which also involved interaction with modern human ancestors.

5.4 | Neanderthal introgression in Western Asia

The universal presence of Neanderthal introgression in all Eurasian populations, but its absence in sub-Saharan African populations points to a single definitive introgression event (Green et al., 2010), which likely happened just after the ancestral Eurasians split from the more diverse sub-Saharan African populations but before they split into smaller groups and migrated through the coasts of Eurasia. Based on this, the geographic setting for this introgression event should be Western Asia (possibly the Levant) ~50,000 years ago, where modern humans and Neanderthals first met (Hovers, 2006; Shea, 2003). Of course, a closer look into the region's genomic make-up complicates this rather simple observation.

There is no direct DNA evidence from this region corresponding to this period from either anatomically modern humans or Neanderthals (Taskent & Gokcumen, 2017). Moreover, there seems to be a structure in the distribution of Neanderthal introgression in the genomes of extant populations in western Asia (Lazaridis et al., 2016). Peoples from the Levant seem to have lower amounts of Neanderthal introgression, while peoples from Anatolia and Iran have introgression levels similar to other Eurasian populations (Taskent et al., 2017; Vyas & Mulligan, 2019). Two plausible explanations have been put forward. First, it is possible that multiple populations migrated out of Africa and that only one of them interacted with both Neanderthals. Thus, the variation in levels of Neanderthal introgression that we observe in extant Western Asia may be the result of different ancestries that can be traced back to these different ancestral populations (Lazaridis et al., 2016). A second, mutually compatible explanation would be that recent gene flow from populations south of the Saharan desert diluted the Neanderthal introgression in specific Western Asian populations. Indeed, sub-Saharan and Neanderthal ancestry proportions are negatively correlated with each other in Western Asian populations (Taskent et al., 2017). Moreover, recent ancient genome data suggest population replacements of some Western Asian populations, most notably ancient Egyptian populations, by sub-Saharan African populations. Regardless of the current distribution of Neanderthal alleles in the region, the introgression detected in Eurasians more closely resembles Western Neanderthals (e.g., Vindija Neanderthals). Thus, the current model is that Western Neanderthals expanded into Western Asia, and were then absorbed by expanding anatomically modern human groups.

5.5 | Subsequent Neanderthal introgression(s)

While opening new windows into our past—to amazing views—ancient genomics also reminds us how little we appreciate the complexity of human history. The muddy reality keeps usurping our well described, precise models. For example, while the community was still constructing a narrative to explain the observed introgression in extant populations, Fu et al. (2015) published the genome sequence of a ~40,000-year-old anatomically modern human excavated from Eastern Europe (Peştera cu Oase, Romania). This genome harbors massive Neanderthal genome pieces in its genome, indicating that this individual likely had a Neanderthal grandparent 4–6 generations back. This indicates another introgression event in Eastern Europe, after the first migrants out of Africa expanded multiple migratory branches into different parts of Eurasia. Further complicating the issue, this Oase individual did not contribute any genetic material to extant Europeans. Six months after the publication of the Oase genome, another study found evidence for gene flow from early humans to eastern Neanderthals (represented by the Altai Neanderthal genome) (Kuhlwilm et al., 2016). As exemplified by these studies, multiple introgression events occurred among multiple Neanderthal and anatomically modern human populations across the Eurasian continent, but the signatures of these interactions are mostly lost in extant human populations.

With the availability of thousands of extant human genomes, along with multiple ancient Neanderthal sequences, there is a renewed effort to discern between the subtle signatures of Neanderthal introgression that can be traced back to different periods and geographies. An earlier study suggested that there might be observably higher levels of

Neanderthal alleles in East Asian populations, invoking a distinct introgression event after the ancestral population of East Asians separated from other Eurasian populations (Wall et al., 2013). More recent studies used sophisticated model-based and machine-learning approaches to claim a single introgression event cannot explain the distribution of Neanderthal alleles in extant human genomes (Mondal, Bertranpetit, & Lao, 2019; Villanea & Schraiber, 2019).

It is now clear from ancient genome work (Dannemann & Racimo, 2018), as well as pioneering biological anthropology studies (Tattersall & Schwartz, 1999), that it was culturally and biologically possible for Neanderthal and human populations to produce offspring. Thus, it is a distinct possibility that Neanderthals did not become extinct in the traditional sense. Instead, the isolated, small Neanderthal populations across Eurasia were absorbed by anatomically modern humans throughout their expansive growth across Asia and Europe; the signatures of these distinct Neanderthal populations should be hidden in modern human genomes. However, these signatures are difficult to disentangle from each other and we may have to wait for more Neanderthal genomes to be published to paint a more definitive picture of the complex history of Eurasia in the last 100,000 years.

5.6 | The Denisovans in the islands?

One of the most fascinating developments in the field of ancient genomics is the discovery of the *Denisovans* as a separate hominin lineage. A humble finger bone excavated from the Denisova cave in Siberia, the same location where the Altaian Neanderthal remains were found, yielded sequences that match neither the human nor the Neanderthal genome perfectly (Meyer et al., 2012). Instead, it revealed a distinct lineage that split from the modern human lineage ~700,000 years ago, and from Neanderthals just after that split. What is possibly more surprising than the discovery of this new lineage was that extant populations inhabiting the island nations of Southeast Asia and Oceania show signatures of multiple introgression events from at least three distinctive Denisovan populations (Browning et al., 2018; Jacobs et al., 2019; Mondal et al., 2019; Vernot et al., 2016). Moreover, some of these introgression events were as recent as 30,000 years before present (perhaps even more recently) and, thus are population-specific, affecting only populations in Papua (Jacobs et al., 2019). This more recent introgression event was preceded by additional admixture events from Denisovans to ancestors of extant Asian populations, as well as populations that now live in the west of the Wallace Line, like the Papuans. This line that marks a major shift in ecological trends stopped many species of plants and animals (Mayr, 1944), but apparently stopped neither modern humans nor Denisovans alleles. How, where, and when a Siberian (and maybe also Tibetan [Chen et al., 2019]) hominin population introduced large segments of their genomes to the ancestors of the extant sea-faring populations of the southeast Eurasia and Ocenia remains a major anthropological puzzle.

5.7 | On fossils and genomes

The stories of human evolution that can be narrated from fossil remains and ancient genomes do not always overlap. I have already presented you with a complicated history of recent human evolution based on genomic evidence; this evidence is often complementary to what is observed in the fossil record. For example, there is fossil evidence that humans and Neanderthals co-inhabited in Eurasia in a period coinciding with the out-of-Africa migrations (Higham et al., 2014). Similarly, there are interesting fossils remain in Africa whose dates make them potential candidates for being the source of the divergent haplotypes observed in extant African genomes (Dirks et al., 2017). However, not everything fits neatly.

There is growing evidence that some anatomically modern human groups left Africa earlier than it was thought (Harvati et al., 2019; Hershkovitz et al., 2018). *Were these earlier migrations doomed adventures? Did they leave any genetic traces behind? Did they also interact with Neanderthals?* Another inconsistency is the timing and location of the introgression of Denisovan alleles into Asian, Southeast Asian, and Oceanic populations. Based on the genetic evidence alone, one might conclude that Denisovans were a diverse and widespread population. The fossil record is scarce, however, and fragmentary fossil pieces have been found only in two locations—one in Siberia and another in the Tibetan plateau (Chen et al., 2019). The lack of fossil remains from Southeast Asia and Oceania is puzzling. Thus, the likely ecological setting of Denisovan population(s) remains enigmatic. It was argued, for example, that Denisovans were cold-adapted (Racimo et al., 2017). *If so, does the source of recent introgression observed in Oceanic populations, which live in much warmer climates, indicate the presence of a yet another population related to, but distinct from, Denisovans?*

Finally yet importantly, I would like to note that almost each new genome sequence from an ancient hominin led to massive and unexpected revelations. In parallel, the past decade was full of new and exciting fossil discoveries, including *Homo naledi* in South Africa (Dirks et al., 2017), *Homo florensis* in Indonesia (Brown et al., 2004), and *Homo luzonensis* in the Philippines (Détroit et al., 2019). Moreover, the fossil record in East Asia—especially in China—has been scrutinized with a new lens based on the recent genomic evidence (Bae, Douka, & Petraglia, 2017). *Were some of these previously discovered East Asian specimens Denisovans?* Collectively, the period spanning 200,000 to 50,000 years before present emerges as a colorful world where myriad human-like populations, some isolated and some interacting with each other, cohabited. However, what we can infer about it from extant human genomes is limited, and new ancient genome data from this period will likely produce exciting revelations that we can only imagine.

6 | WHAT IS THE IMPACT OF INTROGRESSION ON HUMAN PHENOTYPES?

6.1 | Did introgression from other hominin populations into anatomically modern humans contribute to phenotypic variation in extant human populations?

The immediate answer based on a quick look at the genome-wide trends of functional variation is that it is negligible. A more thoughtful, careful answer is that the very few loci shown to be evolving under

positive selection in different extant human populations, mostly involved in immunity and metabolism-related traits, often harbor haplotypes introgressed from ancient hominins.

6.2 | Genome-wide depletion of functional sequences among the introgressed haplotypes

Let us start with the genome-wide trends of the Neanderthal introgression. As we mentioned before, haplotypes introgressed from Neanderthals constitute 1–3% of Eurasian genomes (Lohse & Frantz, 2014; Prüfer et al., 2017). Collectively, these introgressed pieces are distributed *away* from functionally important coding and regulatory sequences (Sankararaman et al., 2014; Vernot & Akey, 2014). This observation indicates that after an introgression event, negative selection weeds out functionally relevant Neanderthal alleles.[6] It is important to reiterate that the actual difference between Neanderthal genomes and human genomes is small (<1% overall) and that the majority of important functional sequences have been conserved across all hominins. For example, virtually no major difference is observed between the coding sequences of housekeeping genes (i.e., genes essential for the maintenance of basic cellular function) among primates, let alone among hominins. On top of this, there is depletion of derived Neanderthal alleles affecting functional sequences among humans. Thus, the overall functional impact of Neanderthal introgression on human biological variation is small.

Independent of the overall functional impact of Neanderthal introgression, the underlying evolutionary reasons for the negative selection acting on Neanderthal-derived sequences in the human gene pool provide a fascinating area of study. The first possibility is hybrid incompatibility; when coupled in homologous chromosomes, the human and Neanderthal versions of a gene may be less fit than when Neanderthal or human versions occur homozygously. Thus, after an introgression event, the individuals heterozygously carrying a human and Neanderthal version of genes with hybrid incompatibility would suffer from a fitness cost and have fewer viable offspring. Such a selective force would be particularly profound in loci affecting reproduction and gamete formation. Indeed, there is evidence for particular depletion of introgressed sequences in the X-chromosome, among testis-expressed genes, and regions of the genome that regulate gamete formation (i.e., meiosis) (Jégou, Sankararaman, Rolland, Reich, & Chalmel, 2017; Sankararaman et al., 2014; Vernot & Akey, 2014).

The second possibility is that Neanderthal populations had less healthy genomes. Because their effective population sizes were much smaller than compared to contemporary human populations, drift likely allowed a higher number of deleterious alleles to remain in the Neanderthal population (Harris & Nielsen, 2016; Juric, Aeschbacher, & Coop, 2016; Steinrücken, Spence, Kamm, Wieczorek, & Song, 2018). These alleles often overlap with coding and regulatory sequences and can have drastic effects, especially when carried homozygously. When these alleles were introduced to the larger human population, selection became a relatively more prominent force, eliminating the detrimental Neanderthal alleles (and associated haplotypes) from the population.

[6]A similar observation was made for haplotypes introgressed from Denisovans.

6.3 | The small number of introgressed fragments have an observable effect on population-specific adaptive biological variation

This subtitle is a little contradictory. I just established above that the Neanderthal contribution to overall functional human genetic variation is very limited. It is true that only a very small number of Neanderthal (or Denisovan) introgressed alleles have a functional impact that is currently observable in extant human populations (Vernot & Akey, 2014). Smaller still is the number of those functional variants that confer some adaptive advantage (Racimo et al., 2015). However, in fact, what is true for the introgressed variants can be generalized for all genetic variation. That is, most genetic variants are not functionally or adaptively relevant (Ohta, 1992). Therefore, among all adaptive genetic variation in extant human populations, introgressed variants occupy a considerable space (Gittelman et al., 2016).

Our understanding of how genetic variation affects common human phenotypic variation is still in its infancy.[7] There is growing evidence showing that hundreds of genes function in concert (Boyle, Li, & Pritchard, 2017), and that genetic variation interacts with other variants across the genome (Carlborg & Haley, 2004), as well as with environmental variables, resulting in varying, and sometimes population-specific, functional effects (Li & Keating, 2014; Martin et al., 2017). Variation introgressed from Neanderthals (or other ancient hominins) is not an exception and more work needs to be completed to get a clearer picture of the functional impacts of introgression in specific human populations. Nevertheless, some general trends are emerging. For example, a correlation between Neanderthal alleles and clinically relevant phenotypic variation indicates that genetic variants introgressed from Neanderthals may explain susceptibility for depression and actinic keratosis (lesions due to sun exposure), among other traits (Simonti et al., 2016). Moreover, most of the functional Neanderthal introgressed alleles seem to affect regulatory sequences rather than the coding sequences (Dannemann, Prüfer, & Kelso, 2017; McCoy, Wakefield, & Akey, 2017). In other words, rather than changing the proteins themselves, the effects of introgressed alleles are most visible in levels of gene expression.

Accumulating evidence indicates that the majority of adaptive introgression affects biological systems that interact and respond to the environment: that is, metabolism and immunity. There are excellent studies that scrutinize adaptive introgression both at the locus-specific and genome-wide level (Dannemann & Kelso, 2017;

[7]One promising new development is the emergence of long-read sequencing technologies, which have the potential to fill in the gaps in human genetic variation, involving retrotransposons, short tandem repeats, structural variations, such as inversions, duplications, translocations, and large deletions, as well as smaller insertion–deletion variations (Chaisson et al., 2018; Huddleston et al., 2017; Sedlazeck et al., 2018). Most genome-wide association studies interrogate single nucleotide variants and are generally blind to other types of variants. It is likely based on that locus-specific and small number of genome-wide studies that such variation may significantly increase our ability to detect the genetic basis of phenotypic variation (Eaaswarkhanth, Pavlidis, & Gokcumen, 2014; Resendez et al., 2019; Saitou & Gokcumen, 2019).

Gittelman et al., 2016; Racimo, Marnetto, & Huerta-Sánchez, 2017). The former includes the striking example of the Denisovan *EPAS1* haplotype that likely confers high altitude adaptation in a Tibetan population—a poster child for adaptive introgression (Huerta-Sánchez et al., 2014). Multiple studies linked introgressed haplotypes with immune-related variation (Enard & Petrov, 2018; Quach et al., 2016)—including variation in the well-studied *HLA* locus (Abi-Rached et al., 2011). Introgression affecting the immune system can be explained by the diverse pathogenic pressures that hominin populations were exposed to; Neanderthal and Denisovan versions of immunity-related variants remain adaptively relevant for extant anatomically modern human populations. Similarly, other studies showed that there is an enrichment in metabolism genes among the small number of genic introgressed alleles (Khrameeva et al., 2014; Racimo, Gokhman, et al., 2017). The human migrants in Eurasia may have borrowed introgressed alleles that confer a metabolic advantage to the northern climate and ecology, to which the Neanderthals were likely well adapted. A similar local adaptation argument was made for putatively introgressed variants affecting pigmentation among Eurasians (Ding et al., 2014). The functional impact of Neanderthal and Denisovan introgression is not negligible within the context of overall adaptive variation observed among extant humans.

7 | AN EXCITING TOMORROW AND A WHOLE LOT OF GAPS TO FILL

It is an exciting time to be a geneticist. For the first time, we have the data and tools to directly glimpse the underappreciated complexity of our recent past as a species. This review should serve as a primer for the anthropology community on the rapidly accumulating genomic data on the introgression(s) from multiple distinct hominin populations into the anatomically modern human populations.

The research into introgression also highlights major gaps in the field. First is addressing the sampling bias in large human genetics studies; most human genetics studies focus on present-day peoples in western European countries and the U.S., which has long been criticized by the biological anthropological community (Reardon & TallBear, 2012). Fortunately, the limitations of this bias have been increasingly appreciated (Bolnick, Raff, Springs, Reynolds, & Miró-Herrans, 2016; Claw et al., 2018; Gokcumen, 2018). For example, extensive sampling of present-day populations that live in Papua New Guinea revealed previously hidden and surprisingly recent introgression from Denisovans into the ancestors of these populations (Jacobs et al., 2019). There are now attempts to collect samples through better-rationalized[8] strategies. Peoples of Africa, with their amazing diversity of cultures, languages, and histories, remain particularly underrepresented both as participants and leaders of genomic research (Campbell & Tishkoff, 2008). With more awareness and more inclusive sampling, I am confident that our community will lead the effort to fully expose our history ingrained in our genomes, old and new.

Another major gap in our knowledge comes from the dearth of sequences from ancient remains. Every new genome provides a revolutionary new insight into our history. Thus, the community excitedly awaits every new genome from ancient hominins. It would be especially exhilarating to see genomic data from remains excavated in Africa, Southeast Asia, and Oceania—geographies where climate has, so far, hindered successful DNA extractions. One of the related bottlenecks in the field, paralleling the general paucity of ancient remains, is that only a small number of groups have access to the samples, funds, expertise, facilities, and computational resources to properly conduct ancient genomics research. The need for customized computational pipelines necessary to analyze ancient genome data creates bottlenecks for most anthropology groups to comprehensively study ancient genomes. Such bottlenecks are likely hampering novel perspectives and approaches. As such, one clear future goal of the community should be training the next generation of biological anthropologists in genomics analyses, in general, and bioinformatics issues pertaining to ancient genome data, in particular.

When it comes to investigating the impact of ancient hominin introgression on phenotypic variation, the challenge is more general. The relationships between a genetic variant and phenotype are not straightforward; they are dependent on both genomic and environmental backgrounds (e.g., Resendez et al., 2019). However, there are increasing numbers of databases involving millions of participants, as well as concurrent mechanistic studies involving modified cell lines and model organisms (Visscher et al., 2017). It is my opinion that in the near future these studies will lead to a comprehensive and accurate understanding of the genetic basis of heritable traits and the mechanisms through which genetic variation affects cellular and organismal phenotypes. Within this general context, the functional impact of the complex evolutionary history of our species will become clearer.

The last decade painted a picture of our diverse ancestors, traveling, dying, surviving, and having lots of sex with each other to an extent that previously would have seemed almost impossible. However, if we use a wider lens, we would see that the emerging messiness of our evolutionary history is by no means unique. It is, instead, similar to what has been observed among our closest primate relatives (de Manuel et al., 2016; Rogers et al., 2019), and among animals—from butterflies to fish (Hedrick, 2013). Introgression is a major force in evolution that affects almost all species at one time or another and our history is not different.

Even our brains search for a simple origin story, what we find is a beautiful mess.

[8]The initial round of human genetic research relied on samples that may have prioritized convenience and accessibility over more thoughtful sampling schemes. Now, there is a growing understanding for the need for better custom-designed study-designs to answer specific questions regarding human genetic variation (Lachance & Tishkoff, 2013). These better designs involve a better understanding of the genetic basis of complex traits, the ethical considerations regarding sampling from and inclusion of indigenous populations (Gurdasani, Barroso, Zeggini, & Sandhu, 2019).

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Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Omer Gokcumen https://orcid.org/0000-0003-4371-679X

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