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Genomic signatures of sex-biased demography: progress and prospects

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Sex-biased demographic events have played a crucial role in shaping human history. Many of these processes affect genetic variation and can therefore leave detectable signatures in the genome because autosomal, X-linked, Y-linked, and mitochondrial DNA inheritance differ between sexes. Here, we discuss how sex-biased processes shape patterns of genetic diversity across the genome, review recent genomic evidence for sex-biased demography in modern human populations, and suggest directions for future research.

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Introduction

Human demographic history has been shaped by a complex assortment of processes, many of which are sex-biased. Some, such as modern marriage practices, can be readily investigated through observation or interview. Others are either cryptic or have been operating over a much longer timescale, and are therefore difficult or impossible to characterize with ethological or archeological methods. Fortunately, because autosomal, X-linked, Y-linked, and mitochondrial DNA inheritance differ between sexes, variation across these markers provides the complete signal of sex-biased processes that have left signatures in the genome [1,2]. Here, we review sex-biased demographic processes and discuss how they can be detected in the genome. The effect of sex-biased processes on phylogenetic reconstructions based on the Y chromosome and mitochondrial genome have been reviewed elsewhere [e.g., 3]. Throughout this review we instead focus on factors that affect the relative effective population size of males and females — most commonly estimated using nucleotide diversity (Box 1). We highlight recent genomic evidence for sex-biased demography in modern human populations and suggest avenues for future research.

Sex-biased processes: theory and expectations

The effective population size, N_e, which can be thought of as a measure of the number of breeding individuals in a population, is central to understanding the effects of evolutionary forces on a population [4,5]. In a constant, randomly mating, diploid population with an equal number of males and females, a Poisson distribution of offspring numbers, and nonoverlapping generations, N_e is expected to follow a 4:3:1:1 ratio across the autosomes, X chromosome, Y chromosome, and mitochondrial genome (mtDNA), respectively [4]. This ratio follows directly from the number of each of the respective chromosomes in the population and because of the equal sex ratio, and can be most clearly understood by considering a single genetic male and a single genetic female (Figure 1). In these two individuals, there are four copies of the autosomal genome (two in the male and two in the female), three copies of the X chromosome (one in the male and two in the female), and a single copy of the Y chromosome (from the male). While males and females both carry mitochondrial genomes, only females transmit mitochondria to offspring, and therefore only females contribute to the effective number of mitochondrial genomes in the population. Real human populations, however, differ substantially from this idealized population in a number of ways that cause measurable differences in the relative effective population size among regions of the genome. These departures can be caused by at least five sex-biased forces that drive differences between males and female effective population sizes: (1) unequal sex ratios; (2) differences in reproductive skew between the sexes; (3) sex-biased migration and dispersal patterns; (4) sex differences in generation time; and (5) sex-biased admixture and introgression (see Box 2 for other processes that can effect relative N_e across the genome) [2,4,6–10].

Sex ratios and reproductive success

Unequal sex ratios and differences in reproductive success both affect the relative N_e of males and females (N_m and N_f, respectively) and thus both affect the effective population size of markers with sex differences in inheritance in similar ways [4,8,10] (Figure 1). Ratios of N_e on the X chromosome to that of the autosomes (X/A ratios)

Box 1 Estimating effective population size using genomic data.

A variety of methods have been used to estimate effective population sizes from genomic data. By far the most commonly used is average pairwise nucleotide diversity, π, the expected value for this under the infinite sites model is:

$$\pi = 4N_e\mu,$$

where μ is the mutation rate [4,83]. Because of its relationship with N_e, nucleotide diversity is a versatile measure that reflects a wide range of processes affecting population history. In practice, nucleotide diversity is typically calculated by summing the number of pairwise differences among chromosome copies in a sample and dividing by the number of comparisons [84].

A second approach, employed by Keinan and colleagues [79], leverages F_{ST}, a measure of population differentiation, to estimate the amount of genetic drift that has occurred between a pair of populations since they split. While F_{ST} estimates from different parts of the genome can be used to estimate sex differences in gene flow [9,85–87], Keinan and colleagues [79,88] developed a method to compare F_{ST} among three pairs of populations, with one population whose size has roughly remained stable over time serving as a reference point, to estimate the amount of genetic drift unique to each population. This can then be used to estimate the post-divergence N_e of each population [79].

Linkage disequilibrium (LD), the nonrandom association of alleles [89], can also be used to estimate effective population size [90,91]. By comparing measures of LD across the genome, one can estimate the ratio of male and female N_e [92,93], though this includes more assumptions, particularly nonoverlapping generations and a Poisson distribution of offspring, than diversity [93]. These measures are not equivalent, however, and provide estimates on different timescales. In particular, F_{ST} is a function of polymorphism since population divergence, while π reflects polymorphism along an entire lineage [29]. LD, on the other hand, can reflect both recent and ancient N_e depending on the measure and data used [94].

Box 2 Other processes influencing diversity ratios.

Sex-biased demographic processes are not the only phenomena to differentially affect regions of the genome with different inheritance types (Figure 1). A number of other processes can impact diversity ratios, including population size changes, mutation bias, and natural selection [2,6].

In cases where population size changes over time, the effective population size of the population in question is approximated by the harmonic mean of the effective population sizes across previous generations [95]. This has the important implication that periods of lowest effective size will most strongly effect N_e and that populations recovering from a bottleneck will have much lower effective sizes than similarly sized populations that have remained at constant size [4,7]. Population size changes will therefore differentially affect DNA markers with different inheritance types. In particular, diversity on the X chromosome responds more quickly and dramatically to population size changes than the autosomes because of its relatively smaller effective population size [82]. This effect is even more pronounced in uniparentally inherited markers because of their even smaller relative sizes [82].

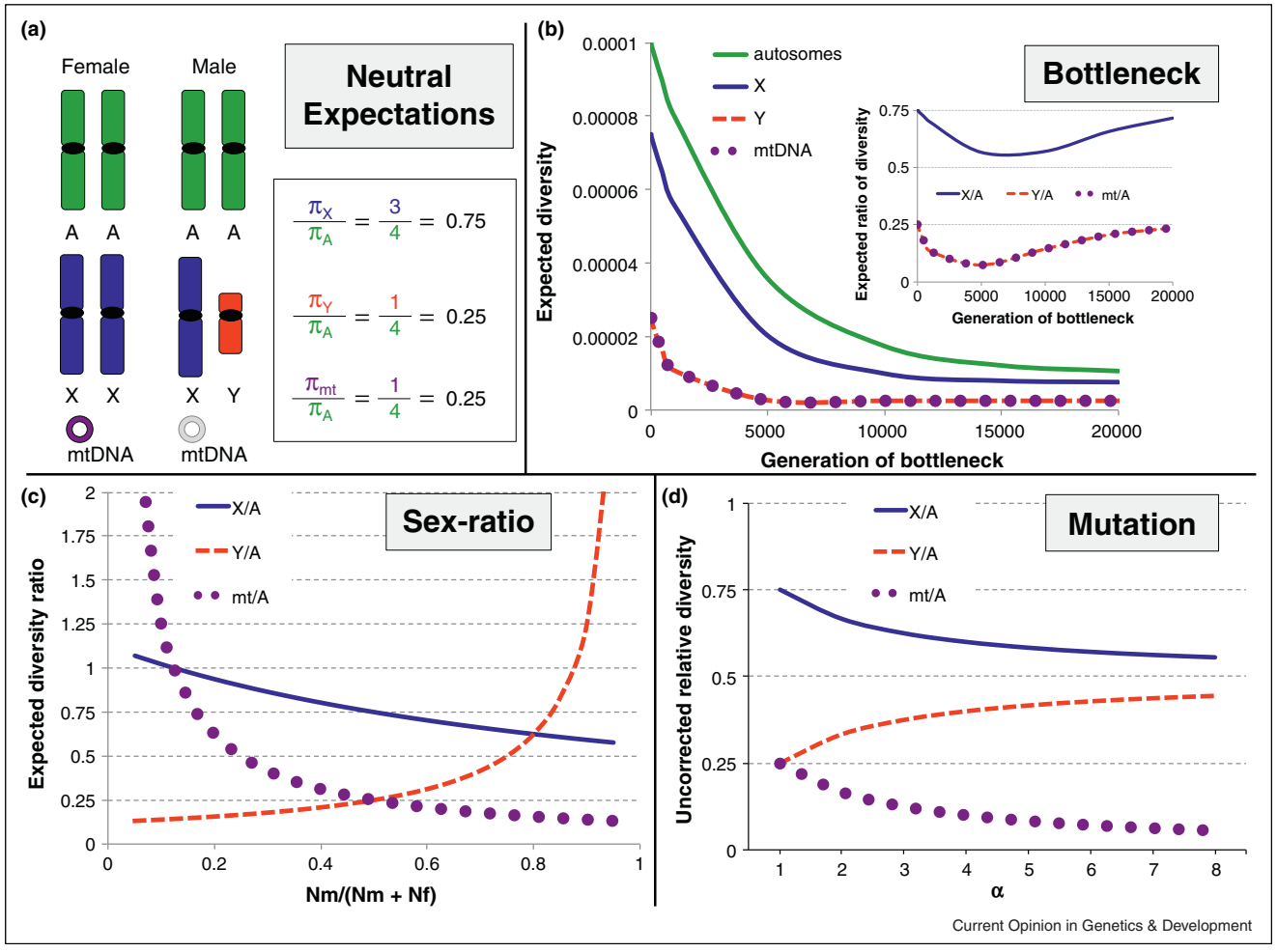
Humans, like all mammals, exhibit male mutation bias — a higher mutation rate in males than females resulting from a greater number of germline cell divisions in males than females [96]. Relatively speaking, male mutation bias will increase diversity in genomic regions in the following order: Y chromosome $\gg$ autosomes $>$ X chromosome. Because of its profound impact on relative diversity estimates, it is important to correct for male mutation bias. This is typically achieved by normalizing diversity estimates using divergence from an outgroup [28•,78••,79,97–99]. However, the magnitude of male mutation bias is not uniform among lineages [100–102] and choice of outgroup can affect relative diversity estimates [78••,97,98].

Natural selection can also leave genomic signatures that confound estimates of sex-biased demographic processes. In particular, because recessive alleles on the sex chromosomes are directly exposed to selection in males, natural selection is expected to be more efficient in driving beneficial alleles to fixation and eliminating deleterious alleles [103–105]. Both types of selection result in disproportionately reduced diversity in and around functional elements on the sex chromosomes. This is most clearly illustrated by the commonly observed positive relationship between X/A diversity ratios and distance from genes [78••,98,99,106]. It is therefore critical to filter functional elements and, in many cases, windows around them before conducting demographic analyses.

reach a minimum of approximately 9/16 when there is a single breeding female, a substantially higher variance in reproductive success in females than males, or a combination of the two (Figure 1). In the opposite case, X/A ratios achieve a maximum of approximately 9/8 when there is an extremely female-biased sex ratio or high variance in male reproductive success. Y/A and mt/A ratios, on the other hand, range between 1/8 and infinity, for small and large effective population sizes of the transmitting sex (males for Y and females for mtDNA, respectively; Figure 1).

With few exceptions, sex ratios are very similar across modern human populations, with an average of 105–107 male births for every 100 female births [11], suggesting that the effects of differential reproductive success between the sexes may have a larger effect on N_m and N_f than the absolute number of males and females. Among modern human populations, there is a tremendous range in the variance in sex-specific reproductive success among populations [12,13]. Males typically exhibit higher variance than females, but the degree of difference between the sexes varies by population, largely stemming from differences in marriage practices [12]. In particular, populations practicing strict monogamy tend to exhibit approximately equal ratios of male to female variance in reproductive success, while men in societies practicing serial monogamy or polygyny tend to have a higher variance in reproductive success than females, particularly in more sedentary populations [12–14]. Interestingly, however, other factors can mediate the effects of these marriage practices on N_m and N_f, so that marriage system does not directly predict reproductive variance. For example, in a historical sample of Finnish populations, men who remarried had 25% more offspring born than men who married only once, but this difference disappeared when the measure changed to number of offspring surviving to reproductive age or number of grandchildren born [15]. In the case of polygyny, Evans and Charlesworth [16•] found that the effects

Figure 1



Genomic signatures of population history. Many processes acting on a population leave genomic signatures. **(a)** In an ideal population with a constant mutation rate across the genome (see text for additional details), N_e, and therefore nucleotide diversity (Box 1), is expected to follow a 4:3:1:1 ratio across the autosomes, X chromosome, Y chromosome, and mitochondrial genome (mtDNA), respectively, based on the number of each chromosome in males and females. Both males and females have mtDNA, but only the mother's is transmitted to offspring, and so only female mtDNA contributes to diversity. **(b)** A population bottleneck can affect relative diversity ratios among genomic regions, even if there is no sex-bias. This is because the relative N_e of different types of DNA determine how quickly they reach equilibrium after a population size change [82] (Box 2). Here, we plot expected diversity over time after a 90% reduction in N_e, using equations from Pool and Nielsen [82], assuming a uniform mutation rate across the genome of $\mu = 0.0001$. The *x*-axes represent number of generations after the instantaneous reduction in population size, while the *y*-axes represent expected diversity and expected diversity ratios (inset). **(c)** The effects of unequal sex ratios on the expected diversity ratios, using equations from Hedrick [6]. The *x*-axis represents the fraction of males in the population ($N_m/(N_m + N_f)$) and the *y*-axis represents the expected diversity ratio. When the number of males is large relative to females, the Y/A ratio will approach $N_m/8$ and the mt/A ratio will approach 1/8. A large excess of females will lead to the opposite expectation. **(d)** Male-mutation bias can profoundly affect diversity estimates in population that is otherwise at equilibrium, if not accounted for (Box 2). The ratio of male mutation rate to female mutation rate, α, is plotted on the *x*-axis, while the expected diversity ratio, uncorrected for this mutation bias, is plotted on the *y*-axis.

of polygyny on reducing N_m diminished with decreasing mate stability over time — that is, as the rate of male replacement increases, so does N_m. Furthermore, though most modern societies can be described as polygynous, most human reproduction, even in polygynous populations, occurs in long-term, monogamous pairings [14,17].

Generation time

Generation time, which can be thought of as the mean difference in age between parent and offspring, can also drive sex differences in N_e. If all other parameters are equal between the sexes, the sex with the longer generation time will have a lower effective population size [10]. However, as other parameters deviate from equilibrium,

generation time can interact with them in relatively complex ways [10]. For example, men in many societies experience nonzero, or even substantial, fertility late in life, that is, after the age of menopause in women [18]. This is often associated with polygyny in which older men are able to monopolize access to younger, reproductive women [18]. If this is the case, this system implies stable polygyny with higher variance in reproductive success among males, which, interacting with a longer male generation time, might therefore result in a lower N_m than that predicted by either process by itself. In addition, men and women exhibit substantially different age-related changes in mutation rate [19,20]. This produces opposing forces on ratios of nucleotide diversity, which are often used to estimate N_e: as male generation time increases, diversity decreases the most on the Y chromosome, intermediately on the autosomes, and the least on the X chromosome (N_e of the mtDNA is not affected by N_m), but as the mutation rate increases with age, more diversity is introduced to those chromosomes in the same relative order (i.e., the most on the Y and the least on the X chromosome) [21•]. This leads to the counterintuitive result that maternal age will have a stronger influence on relative diversity than paternal age [21•].

Migration and admixture

Migration, admixture, and introgression can, in some ways, be thought of as behaving in the same way along a continuum, ranging from migration among subpopulations (least pronounced effects) to admixture among human populations that have been separated for hundreds or thousands of years to archaic admixture among hominin species, in which alleles originally only present in one species introgress into a second species (most pronounced effects). In all three cases, a male-bias — when more males migrate than females — will increase N_m and have effects similar to the processes described above, where N_e across the genome will increase the most on the Y chromosome, intermediately on the autosomes, and the least on the X chromosome. A female bias, on the other hand, will increase N_f and will affect genomic regions in the opposite order of males. However, if the groups studied are sub-populations of a larger population, expectations for these measurements across the entire population (as opposed to within a subpopulation) are reversed [9]. The reason that the effects of migration and admixture fall along a continuum is that with increasing population separation, more population-specific genetic drift will occur, and subsequent gene flow will be more likely to introduce novel alleles. Interestingly, this process can lead to a phenomenon in which an abrupt increase in migration, particularly after complete isolation, can cause higher than expected peaks in N_e that persist for very long periods of time [22•]. It is thus important to consider the effects of changes in migration patterns, even if they have occurred in the distant past [22•,23]. While numerous methods exist for detecting migration and admixture between populations and species [24], sex-biased admixture requires careful consideration. In particular, mean admixture on the X chromosome fluctuates over time after a single admixture event, so that estimations of sex-specific ancestry based on the relative time the X chromosome spends in males and females (1/3 and 2/3, respectively) fails to capture true admixture estimates in most situations [25•].

Recent genomic evidence for sex-biased demographic processes in humans

Male-specific population bottlenecks

One of the most common results from studies of modern human populations is that the effective population size of females is, and has been for much of human history, larger than that of males [26,27,28•]. In a study of six populations across Africa and Eurasia, Hammer and colleagues [28•] found substantially higher than expected ratios of X/A diversity, consistent with an overall greater N_f than N_m averaged across the entire history of each lineage [29]. More recently, Wilson Sayres and colleagues [30••] found extremely low ratios of Y/A diversity in African and European populations, consistent with a combination of a very low N_m and strong purifying selection on the Y. Lippold and colleagues [26] further showed, using a global sample of 51 populations, that N_f has likely been greater than N_m throughout much of human history, dating back to before the bottleneck of populations migrating out of Africa. Data from the Arabian Peninsula also support an excess of N_f across the Out-of-Africa bottleneck, as lineages that diverged soon after dispersing out of Africa exhibit higher than expected X/A diversity ratios [31].

Interestingly, the difference between N_m and N_f has not remained constant over time and many populations appear to have experienced an extreme male-specific bottleneck and subsequent exponential expansion in the last 10 000 years [26,32,33••,34•]. Karmin *et al.* [33••] estimated that, in Europe, this bottleneck occurred between 8 and 4 thousand years ago, during which N_f was as much as 17 times greater than N_m. The processes causing this bottleneck remain unclear. The spread of agriculture likely played some role, as it is associated with a shift to patrilocality (female dispersal) and patrilinearity, as well as changes in population size [13,23,27,35,34•,35–38]. For example, African pygmy populations and closely related non-pygmy agricultural populations exhibit strong differences in relative N_e, with agricultural populations exhibiting much stronger genetic signatures of patrilocality [39]. In Europe, analyses of ancient DNA revealed that patrilocality was associated with the spread of farming during the Neolithic expansion [35,40].

A shift to patrilocality associated with agriculture is insufficient to explain this pattern by itself, however, as many of these male-specific bottlenecks occurred well after the emergence of agriculture [26,32,33••]. An additional

possibility is that other cultural practices associated with the Neolithic transition, such as the accumulation of wealth, power, and social prestige, led to an increased variance in heritable male reproductive success [1,33,38]. Batini and colleagues [32] note that male demographic shifts in Europe and the Middle East coincide with the emergence of elites and major developments in weaponry.

Impact of modern cultural practices on diversity

Modern marriage practices can also leave sex-biased signatures in the genome. Guillot and colleagues [41•] explored the genetic consequences of Asymmetric Prescriptive Alliance (APA), a set of marriage rules common in eastern Indonesia in which men marry their mother's brother's daughter (MBD) and women transfer from wife-giver to wife-taker communities. They estimated that people in the Indonesian community Rindi have historically adhered to this set of rules approximately 50–60% of the time [41•]. Interestingly, this flexibility in adherence appears to have buffered against the substantial reductions in genetic diversity expected under strict adherence [41•].

South Tyroleans, a European alpine population, participate in an inheritance system called *Geschlossener Hof* ('closed holding'), which leaves an unexpected signature in the genome [42]. South Tyroleans, like other alpine populations, are patrilocal, but in *Geschlossener Hof*, a farm is only transferred to a single son, while other sons either stay on the farm as employees or relocate [42]. This increased male mobility, despite patrilocality and patrilinearity, reduces Y chromosome differentiation among subpopulations — the opposite of the pattern expected for patrilocal groups [42].

Recent admixture

Genetic analyses have been used to refine understanding of historical processes leading to population admixture and have shown that this admixture is often sex-biased. These analyses have been particularly important in understanding the long-term genetic consequences of colonialism and the Atlantic slave trade. In the Caribbean, population admixture stems from a history of colonialism, in which European contact led to the decimation of native populations due to disease, forced labor, and warfare, and an influx of enslaved Africans to replace the declining number of native laborers [43,44]. Patterns of admixture vary according to each population's specific colonial history [43,45]. However, most populations exhibit a sex-bias, with significant ancestry from European men and Native American and African women [46,47].

Beleza and colleagues [48] studied populations in the Cape Verde Islands in West Africa, where populations are known to be highly admixed and are primarily descended from European men and African women as a result of the Atlantic slave trade. Overall, they found that admixture followed known settlement patterns, with higher levels of African ancestry on the first islands to be settled and gradually decreasing across the archipelago, following the migration of admixed peasants [48]. There was a single exception to this pattern: Fogo Island, which was one of the first islands to be settled, had much lower admixture than expected given its slave labor system. The authors hypothesize that this discrepancy might result from differential reproductive success between two groups, one composed by the offspring of European men and 'domestic' enslaved African women, who later became the a major ruling group, and the other composed by 'rural' enslaved people who experienced much higher mortality and were continuously replaced by other enslaved people from the African mainland [48].

Archaic admixture and introgression

Interest in hominin introgression has surged with the rapidly accumulating genetic evidence that *Homo sapiens* interbred with other species of archaic hominins [49–57].

Genomic analyses suggest multiple pulses of Neanderthal [58–60] and Denisovan [61] introgression, as well as at least one pulse of introgression from *H. sapiens* into Neanderthals [62]. These studies have also shown that archaic alleles are not uniformly distributed across the genomes of modern humans. Rather, many regions of the genome exhibit 'deserts' of admixture, in which evidence of introgression is significantly reduced or absent [60–64]. Notably, the X chromosome contains significantly less introgression than the autosomes and no archaic haplotypes have been found on modern human Y chromosomes or mtDNA [61,64–68].

Given that levels of detected introgression are associated, in part, with regions of the genome characterized by different inheritance patterns, an obvious question is whether there was a sex bias in hybridization among hominins. Juric and colleagues [69••] estimated, assuming no selection, that levels of admixture observed on modern human X chromosomes and autosomes are consistent with about three times as many reproductive events involving a Neanderthal male and a human female than the opposite pairing. Low levels of X-linked introgression have alternatively been proposed to result from reduced hybrid fertility because archaic ancestry was depleted in regions containing testis-specific genes [61,64,70]. In an analysis of Y chromosome coding regions from a Neanderthal found in El Sidrón, Spain, Mendez and colleagues [68] similarly concluded that hybrids might have experienced reduced viability. This conclusion was based on the absence of this Neanderthal Y chromosome haplotype in modern humans and substitutions with predicted functional effects in three genes involved in maternal immune response during gestation. However, hybrid incompatibility is not required to explain patterns of introgression.

Models of genome-wide purifying selection against weakly deleterious introgressed alleles, and the direct exposure of recessive deleterious alleles on the X chromosome in males are also compatible with observed patterns of introgression [69••,71].

While these results are exciting, much more work is needed for a complete understanding of archaic introgression. In particular, models that integrate selection with sex-biased demography will play an important role in explaining the differences in observed introgression on the X chromosome versus the autosomes. Moreover, because drift is likely to remove haplotypes from non-recombining markers with small effective population sizes, the recovery of mtDNA and Y-linked DNA from ancient samples in and near hybrid zones will provide better evidence to inform our understanding of sex-bias in archaic introgression and the viability of hybrid individuals.

Future directions

The recent availability of thousands of genomes from modern and ancient populations around the world has provided an unprecedented level of insight into human origins, evolution, demography, and dispersal [33••,34•,54,72–77]. However, despite the ubiquity of sex-biased demographic processes throughout human history, the genomic exploration of these processes has not kept pace [but see 30••,31,33••,34•,78••,79]. This is due, in no small part, to the range of technical and biological challenges inherent in inferring sex-bias from genomic data (Box 3). In particular, the interaction of multiple demographic and selective processes can leave confounding signatures in the genome.

Fortunately, a number of theoretical developments have made this endeavor more tractable [9,10,25•,78••,80]. Moreover, while the careful collection, assembly, and analysis (Box 3) of novel data from the whole genome (autosomes, sex chromosome, and mitochondrial genome) is necessary for a complete understanding of human sex-biased demography in many regions of the world, we feel that currently available data can be leveraged to address many interesting questions about sex-bias. Population genomic datasets containing markers with different inheritance patterns are becoming increasingly available [e.g., 73], making possible the detailed investigation of sex-biased processes on a global scale.

We suggest, therefore, that the future is bright for the genomic study of sex-biased demography and that there are numerous fruitful avenues for future research. Further modeling and simulation work will be especially critical for fully characterizing how demographic and selective forces interact with each other. In addition, while some work has given tantalizing insight into sex-bias in the human Out-of-Africa migration [79,81•], virtually nothing is known about sex-bias in other major dispersals. Furthermore, a better understanding of sex differences in archaic introgression can provide insight into the social structure and behavior of these dispersing humans, as well as other hominin species. Finally, humans exhibit remarkable cultural diversity — understanding the full

Box 3 Technical challenges and considerations when investigating sex-biased processes.

While the incorporation of genomic data from the autosomes, X chromosome, Y chromosome, and mitochondrial genome is crucial for the inference of sex-biased demography, genomic analysis of the sex chromosomes and mtDNA present numerous technical challenges that require careful consideration.

Inflating and deflating X-linked diversity. Regions that recombine are expected to have higher levels of diversity than regions where recombination is reduced or absent. While recombination has been suppressed between the majority of the X and Y chromosomes, it still occurs in the pseudoautosomal regions (PARs) [107]. These regions must therefore be filtered to prevent an artificial inflation of diversity on the X chromosome. While a strict PAR boundary has typically been assumed, recent evidence instead indicates that genetic diversity is elevated not only in the PAR, but across the PAR boundary, as well as in a recently X-transposed region [108], and so extra care should be taken to remove these regions to avoid inflating estimates of X-linked diversity. In contrast, many regions of the X chromosome, particularly those containing ampliconic genes, exhibit evidence of extreme selective sweeps [70,109] and need to be filtered because they will deflate estimates of neutral X-linked diversity.

Variation on the Y chromosome. The Y chromosome is full of repetitive elements and palindromic sequences [110] that provide challenges for unique read mapping and can result in over-calling variation in these regions. Moreover, the X and Y chromosomes share many gametologs [111] — homologous genes that diverged due to the suppression of recombination between the sex chromosomes — so special care should be taken to ensure gametolog-specific mapping to avoid inflating estimates of diversity in and near these sequences. Further, because it is largely nonrecombining, natural selection will act to decrease diversity in all neutral Y-linked regions [30••]. While special attention can be paid to avoid inflating estimates of sex-linked diversity due to mis-mapping, the biological process of selection acting to decrease Y-specific diversity requires using modeling to accurately take into account.

Heteroplasmy. The mitochondrial genome (mtDNA) is typically mapped as a haploid locus, because mitochondria are haploid, but each cell has thousands of copies of mtDNA and can maintain multiple mtDNA variants in each cell — a phenomenon called heteroplasmy [112]. In the presence of heteroplasmy and calling mtDNA variation under the strict assumption that it is a haploid genome, heteroplasmic sites may be removed as low-confidence, which will reduce estimates of mtDNA diversity.

Sex chromosome aneuploidy. Approximately 1 in 400 people has an atypical number of X and Y chromosomes [113]. Failing to correctly assess sex chromosome ploidy will result in faulty assumptions during DNA sequence mapping and variant calling, and will affect estimates of diversity based on the total number of chromosome copies. As population datasets grow in size, the likelihood of including individuals with sex chromosome aneuploidies increases, and so effort must be made to identify aneuploidies to ensure that statistics are calculated correctly.

range of effects that these behaviors have the genome will be key to using the genome to unravel cultural patterns in past populations.

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