

Human Y chromosome variation in the genome sequencing era

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Abstract

The properties of the human Y chromosome – male-specificity, haploidy, and escape from crossing-over - make it an unusual component of the genome, and have led to its genetic variation becoming a key part of studies of human evolution, population history, genealogy, forensics and male medical genetics. Next-generation sequencing (NGS) technologies have driven recent progress in these areas. In particular, NGS has yielded direct estimates of mutation rates and an unbiased and calibrated molecular phylogeny of unprecedented detail. Moreover, the availability of direct-to-consumer NGS services is fuelling a rise of ‘citizen scientists’, whose interest in resequencing their own Y chromosomes is generating a wealth of new data.

Introduction

Most human nuclear chromosomes are inherited from both parents; only the Y chromosome is not. The unique role of this chromosome as a genetically dominant sex-determining factor leads it to be constitutively **haploid** and male-specific, which allows it to escape the reshuffling effects of crossing over for most of its length. In turn, these qualities have profound influences on its structure, mutation processes, and diversity within and between populations. Haploidy has its strongest influence upon Y-chromosomal repeated sequences. The Y chromosome is not constrained by the requirement of chromosomal pairing for most of its length, which has allowed repeat sequences to accumulate¹ (Box 1). These repeat sequences in turn promote frequent chromosomal rearrangements via intrachromosomal recombination, leading to a high degree of structural variation²⁻⁴. Male-specificity means that the patterns of diversity of the Y chromosome in populations reflect the

peculiarities of past male behaviours, including dominance of men in some cultures, and marriage rules that influenced how men and women moved between social groups⁵. There are also practical implications arising from this male-specificity, particularly in forensic DNA analysis⁶ and in genetic genealogy⁷. Finally, many common diseases are sexually dimorphic in their prevalence, progress and severity⁸, and the Y chromosome might play some part in this. It might also directly influence male fertility⁹ and affect male health via somatic instability¹⁰.

All these insights derive from two decades of steady progress in Y-chromosomal variant discovery and analysis, exploiting the fact that the allelic states of variants can be combined into haplotypes because of the absence of crossing over in the male-specific region of the Y chromosome (MSY; sometimes known as the non-recombining region of the Y, NRY; Box 1). However, until recently, such analyses have been affected by bias. Early studies involved discovering variants in small samples before genotyping them in larger samples, leading to strong biases because additional variants present in the larger samples were not accounted for¹¹. Some of these problems could be alleviated by performing combined analyses of slowly-mutating single-nucleotide polymorphisms (SNPs) and more rapidly-mutating **short-tandem repeats** (STRs). SNPs define stable haplotypes, known as **haplogroups**¹², which can be used to build a robust **phylogeny** using the principle of **maximum parsimony**. Deploying multiple STRs, which are variable in all populations and therefore lack **ascertainment bias**, can then reveal the level of variation within these haplogroups¹³, and also provide some information about their time-depths (that is, the time since the haplogroup-defining mutation occurred)¹⁴; older haplogroups will harbour higher STR haplotype diversity. Although such combined Y-SNP plus Y-STR studies have flourished, spawning the sub-discipline of male **phylogeography**, they have substantial limitations. For example, in addition to the inevitably incomplete resolution of the SNP-defined phylogeny, it has been debated whether a

'genealogical' STR mutation rate measured in families¹⁵ or a three-fold slower 'evolutionary' rate calibrated by historical events¹⁶ should be used; consequently, there is a three-fold variation in deduced time estimates depending on the approach adopted. Owing to these and other limitations, this era of phylogeographic studies is not reviewed here.

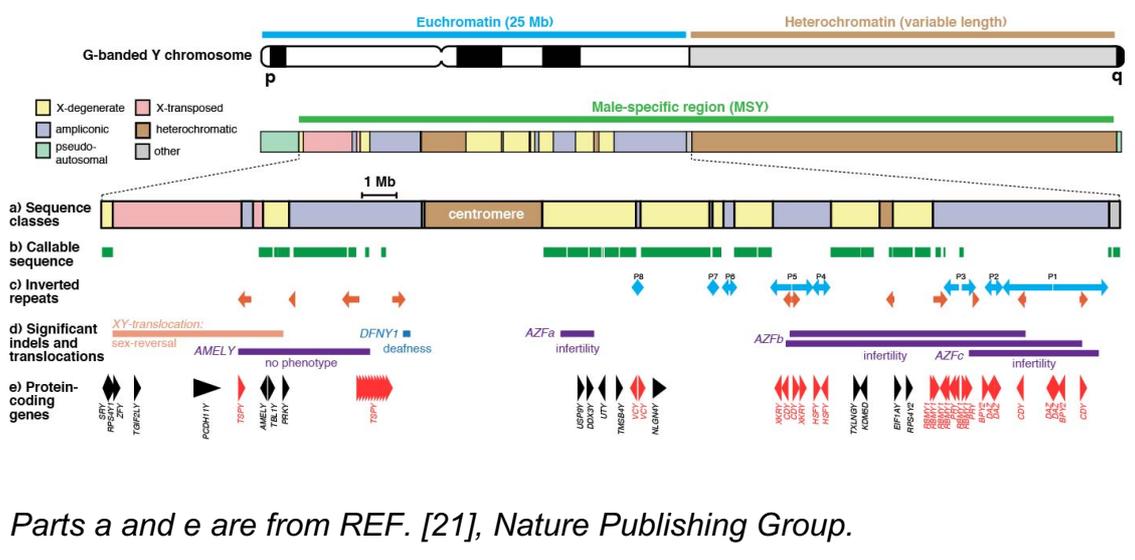
The best way to identify variation on the Y chromosome is to sequence it. However, with rare exceptions¹⁷⁻¹⁹, this approach was not used until 2010 when the availability of next-generation sequencing (NGS) platforms began to make **resequencing** cost-effective²⁰. In this Review, we discuss the advantages and limitations of NGS in variant discovery, and the resulting MSY phylogenies and their time calibration. We then describe recent insights from MSY data into population and evolutionary genetic questions, including male-mediated expansions and genealogical investigations, where the robust NGS-based phylogenetic structures and improved calibration have revealed major new events and changed our interpretation of others. Also covered are the medical consequences of MSY variation, and their implications for population genetics, where NGS is just beginning to be applied, and is starting to identify the basis of some Y-linked disorders. We conclude with perspectives for the future, including the potential impact of new sequencing technologies, possible insights from ancient DNA (aDNA) data, and challenges in understanding the functional roles of the Y chromosome.

Box 1: Evolution and genetic and physical structure of the Y chromosome

Presence of a Y chromosome normally leads to a male phenotype via the expression of the Y-linked gene *SRY* (*sex-determining region, Y*), whose product acts on an enhancer of the autosomal gene *SOX9* to cause formation of **Sertoli cells** and thus trigger differentiation of the testis¹¹⁹. Although the human sex chromosomes differ greatly in size, structure and gene content,

they originated from a pair of homologous autosomes. The process of their divergence began around 180 million years ago¹²⁰ when the proto-Y chromosome acquired its dominant sex-determining function, and continued via a series of segmental inversions that successively shut down recombination with the X chromosome¹²¹. In the absence of genetic exchange, the Y chromosome degenerated and lost material: it is around 60 Mb in size, compared with the ~150-Mb X chromosome. There are two segments of sequence homology (pseudoautosomal regions), at the tips of the short and long arms, in which meiotic crossing over between the X and Y occurs. Between these regions the male-specific region of the Y chromosome (MSY) escapes from crossing over. Of this region, around half is a variably-sized block of **heterochromatin**, and the remaining ~23 Mb of **euchromatin** is composed of three major sequence classes²¹ (see the figure, part a): (i) The X-degenerate (XDG) class - 8.6 Mb of sequences diverged to differing degrees from the ancestral proto-X chromosome; (ii) the X-transposed region (XTR) - a 3.4-Mb interrupted block of DNA transferred from the X chromosome¹²² since the human lineage diverged from the human-chimpanzee common ancestor; and (iii) intrachromosomal repeats of high sequence similarity, termed ampliconic regions, totalling 10.2 Mb. The high interchromosomal and intrachromosomal similarity of the last two of these classes makes interpreting resequencing data difficult, and there are only 9.99 Mb²⁶ of the sequence in which variants are unambiguously **callable** (see part b of the figure). Among the repeated sequences are large direct and inverted repeats, including eight **palindromes** (labelled P1-P8 in part c of the figure), which promote frequent rearrangements via non-allelic homologous recombination (NAHR; see the figure, part d). These rearrangements include deletions that are associated with reduced fertility^{79,123}. The MSY's ~78 protein-coding genes²¹ (see the figure, part e; this compares to ~1000 genes in the corresponding region of the X chromosome¹²⁴) reflect its sequence classes: the XDG segments contain single-copy genes that have X-linked

gametologues and are mostly ubiquitously expressed; and the ampliconic regions contain multi-copy genes that are mostly testis-specific in expression. Despite its exemption from crossing over, the MSY is far from being recombinationally inert: **gene conversion** occurs frequently within the ampliconic regions¹²⁵⁻¹²⁷, and occasionally between highly similar non-pseudoautosomal sequences on the X and Y chromosomes¹²⁸⁻¹³⁰. However, because most hypervariable **minisatellites** owe their variability to crossover **hotspots**¹³¹, these dynamic loci are absent from the male-specific region of the Y chromosome, where crossover cannot occur.



Technological transformation

Sequence-based phylogenies

Sequence data, in principle, lead to a robust phylogeny with branch lengths that are proportional to numbers of mutations (SNPs), and thus to time (Figure 1a). However, in practice, sequencing the Y chromosome is not without its difficulties. Even with the availability of a high-quality reference sequence²¹, the complex repeated structure of the Y-chromosome and the short (<200-bp)

reads produced by most current technologies make unambiguous mapping (i.e. alignment to the reference genome) possible only in the unique regions of the chromosome; these discontinuous segments dispersed along the MSY add up to about 10 Mb in total length (Box 1). Some studies have enriched specifically for 0.5-3.7-Mb subsets of these regions²²⁻²⁴, whereas others have sequenced the entire genome and subsequently extracted the relevant reads bioinformatically^{4,20,25-27}. Sequencing depth (the number of sequence reads covering a particular genomic position) is also important, because the low depth used in several early studies is likely to result in less efficient discovery of rare variants that are present in just one or a few individuals; as these variants lie on terminal branches of the phylogeny, such branches would be artefactually shortened²⁸. Several other technical factors also influence the final set of variants and thus the phylogenetic tree, such as the sequencing platform, the variant calling algorithm, and filtering and validation strategies. Consequently, results presented in different studies cannot be simply or reliably combined or compared; instead, a new analysis starting from the sequence reads is required.

NGS data have also been used for the systematic discovery of Y-STRs. One study genotyped 4,500 Y-STRs and estimated mutation rates for 702 of them²⁹. Although the short reads resulted in the longest and most variable Y-STRs being under-ascertained, this approach illustrates the great potential for large-scale Y-STR studies. Structural Variants (SVs, including Copy Number Variants (CNVs) and inversions) are enriched on the Y compared with other chromosomes^{2,30}, probably as a consequence of its repeated structure (Box 1). Sequence-based analyses are beginning to reveal the full extent of this form of variation^{4,31,32}, and the greater tolerance for gene loss on the Y chromosome compared with the autosomes.

Despite these complexities, the SNP-based callsets and phylogenies produced by independent studies are highly congruent^{24,26,33}. Inconsistencies can generally be explained by differences in the samples used, segments of

the chromosome included, or expected low levels of false-positive and false-negative calls.

Calibrating phylogenies

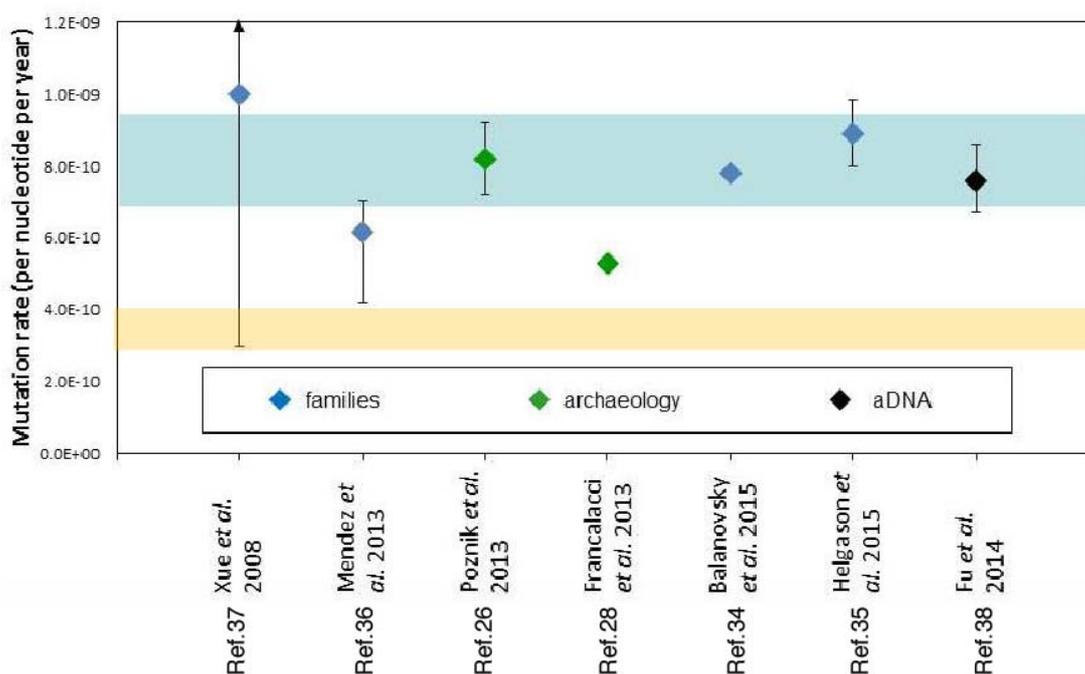
In addition to producing a phylogeny with a robust structure, NGS data result in branches whose lengths are based on the number of mutations on each branch; if the mutation rate is known and has been constant, this information can be converted into time to generate a calibrated phylogeny (Figure 1).

Three broad approaches have been used to estimate the Y-SNP mutation rate, two of which use genealogies³⁴⁻³⁷ and historical or archaeological dates^{26,28} and are equivalent to the approaches used for Y-STRs. The third approach makes use of aDNA sequences of known ages³⁸, which carry fewer mutations from the root of the Y phylogeny than do present-day sequences because they had less time to accumulate such mutations³⁹ (Box 2). The three approaches give reasonably consistent estimates: however, there is a 15% difference between the most reliable current genealogy-based point estimate³⁵ of 8.9×10^{-10} and the corresponding aDNA-based point estimate³⁸ of 7.6×10^{-10} mutations per base per year, illustrating the remaining uncertainty. It currently remains unclear which estimate is more reliable, though the latter is more compatible with independently-dated events such as the out-of-Africa expansion and the peopling of the Americas⁴.

Box 2. The Y-SNP mutation rate

Like any part of the genome, the Y chromosome accumulates SNPs through mutation, but it does this at a higher average rate because it passes between generations exclusively via sperm rather than eggs, and spermatogenesis is more mutagenic than oogenesis. This higher rate of mutation is thought to be because of the larger numbers of cell divisions, and hence DNA replications,

that occur in the male germline¹³². Direct measurement of the Y-SNP mutation rate began in 2008 using a **deep-rooting** Chinese pedigree sampling 13 Chinese meioses³⁷ (see the figure: vertical bars show the 95% confidence interval, where this is given, and the colour of each point indicates whether it was derived from family studies, archaeological evidence or aDNA) and was subsequently extended to clan-based genealogies³⁴ and additional pedigrees³⁶, including a study that examined 1365 Icelandic meioses³⁵.



Two archaeological calibration points have been used: a population expansion in Sardinia 7.7 kya²⁸; and an expansion of Y chromosomes in the Americas 15 kya²⁶. These two calibration points give different estimates of mutation rate, illustrating the complexity of linking archaeological and genetic events. The estimation of mutation rates from ancient DNA (aDNA) requires an ancient sequence that is both accurately dated and old enough to be 'missing' many mutations³⁹: a seemingly unlikely combination. Yet fortunately one such sequence has been reported, from a 45,000-year-old femur from Ust'-Ishim in western Siberia³⁸. The estimates from each approach, based on

the largest datasets and most widely-accepted archaeological calibration, are reasonably consistent and their confidence intervals all overlap (see the figure, where this consensus Y rate (blue shading) is contrasted with the autosomal rate¹³³ (buff shading)). Divisions of the spermatogonia (the stem-cells of spermatogenesis), continue throughout a man's life, so increasing paternal age leads to an increasing SNP mutation rate³⁵. This implies that cultural differences between populations that influence the average age at which a man fathers children may alter the effective mutation rate.

The constancy of the mutation rate over time and in different places is difficult to assess. The number of male-line mutations increases with paternal age³⁵, therefore variation in male generation time might plausibly lead to mutation rate variation⁴⁰, which on the Y chromosome could lead to different root-to-tip branch lengths for different lineages. Such variation has been reported, with haplogroup E-M96 (sub-Saharan Africa) and O-P186 (East Asia) branch lengths being longer²⁴ (possibly reflecting higher average paternal ages), and haplogroup A1b-M6 (found in parts of Africa) being shorter³³ than expected. The calibrated phylogeny presented here (Figure 1a) lacks the deepest-rooting known haplogroup³⁶, A00³⁶), because that lineage was not present in the 1000 Genomes Project samples. However, a subsequent NGS-based study estimated that A00 diverged 275 (95% CI: 241-305) thousand years ago (kya)⁴¹. The same study examined ~120 kb of Y-chromosomal DNA from a Neanderthal from El Sidrón, Spain and demonstrated that the Neanderthal lineage formed an **outgroup** to all known modern humans, diverging 588 (95% CI: 447-806) kya (Figure 1b).

Some of the observations that emerge from calibrated phylogenies are to be expected, such as geographically-specific haplotype distributions (Figure 1c). However, these phylogenies also provide striking new insights. For instance, the timing of a major expansion of the lineages outside Africa 50-60 kya (Fig 1a) corresponds to the estimated time of Neanderthal **admixture** in non-

Africans³⁸, which itself is likely to mark the major expansion of modern humans out of Africa. Thus, this male lineage expansion could simply result from the general population expansion of modern humans. However, note the importance of the Y-chromosomal mutation rate used in calibration (Figure 1); if 8.7×10^{-10} mutations per base per year had been used instead of 7.6×10^{-10} per base per year, a more recent Y-chromosomal expansion would have been inferred, and a more complex demographic model with male lineage expansion lagging behind geographical spread would be necessary.

Insights into population genetics

Prior to recent progress in population genomics⁴², the Y chromosome and maternally-inherited **mitochondrial DNA** (mtDNA) were the highest-resolution tools for human population genetic studies, and their patterns of diversity were widely used to interpret the human past⁴³. However, both have disadvantages for this purpose, as they each represent just one realisation of the evolutionary process, and are strongly influenced by **genetic drift** and sex-biased behaviours, and potentially by positive selection. Their real utility comes from their uniparental modes of inheritance, which can provide insights into past social structure and the potentially different behaviours of men and women - of considerable interest to historians, archaeologists and anthropologists, for example.

Some of these sex-influenced behaviours have been investigated by analysis of Y-chromosomal diversity, albeit with the traditional Y-SNP plus Y-STR approaches. For example, differences in the reproductive biology of men and women, including the length of reproductive life and the resources invested in offspring, contribute to greater variance in the number of offspring of men⁴⁴. This variance is expected to result in a lower male effective population size through genetic drift, which can be strongly enhanced in some populations by social structures⁵ that endow small numbers of men with high status.

Unusually frequent Y-STR haplotype clusters have been interpreted⁴⁵ as signals of past patrilineal dynasties, including that founded by Genghis Khan⁴⁶, the Chinese Qing dynasty⁴⁷, and the Irish early medieval Uí Néill dynasty in Europe⁴⁸.

Furthermore, customs surrounding marriage practices can influence the migration behaviours of the sexes, thus affecting Y-chromosome diversity. For example, around 70% of human societies are patrilocal^{49,50} – following marriage, the couple makes their home near the man's birthplace, rather than the woman's. This practice is expected to increase the geographical differentiation of Y haplotypes, and to have the opposite effect on mtDNA haplotypes⁵¹. Indeed, studies of patrilocal and matrilineal tribes⁵² have confirmed the expected effects of these marriage practices on Y chromosome and mtDNA diversity.

Finally, when populations of different origins mix, the contributions of men and women are often unequal⁵³. This sex-biased admixture can result from a sex bias in the composition of one population, or from the social exclusion from sexual interaction of one or the other sex from a particular population. Studies of many populations in the Americas have shown the dramatically male-biased contribution of Europeans compared to indigenous or African-derived populations⁵⁴⁻⁵⁶.

Interestingly, analysis of an Aboriginal Australian haplogroup C-M130 lineage illustrates the contrast between the Y-SNP plus Y-STR and sequencing approaches to population-genetic questions. The former method suggested that this lineage had diverged from haplogroup C-M130 chromosomes in the Indian subcontinent around 5 kya⁵⁷, implying gene flow into Australia around this time. By contrast, sequencing demonstrated a divergence time close to 50 kya⁵⁸ and thus no evidence for Holocene period male gene flow into Australia, and this older time is more likely to be correct^{24,27,59}.

Sequencing approaches have yet to be widely applied to the types of studies discussed above, but as costs fall further, the number of sequencing-based

analyses is likely to increase. Currently, studies are emerging in which novel variants discovered by resequencing are applied in large population samples⁶⁰, but NGS approaches have already had a direct impact in some areas, as described in the following sections.

Male-mediated expansions

Several Y-chromosome resequencing studies^{4,23,26,27,61} have concurred in finding bursts of expansion⁴⁵ within specific lineages within the last few thousand years. Examples include the expansion of haplogroup Q1a-M3 in the Americas at ~15 kya, the time of initial human colonisation; expansion of two independent haplogroup E1b-M180 lineages in Africa at ~5 kya, which pre-dates the demographic and geographical expansions of Bantu speakers, but the lineages were subsequently carried by them; and expansion in Western Europe of lineages within haplogroup R1b-L11 ~4.8–5.9 kya, possibly associated with technological advances in the Bronze Age (Fig. 1). This last expansion had been recognised previously but, based on Y-SNP and Y-STR analysis, had been interpreted as an older, Neolithic event⁶². The Bronze Age Yamnaya culture has been linked by genome-wide aDNA evidence to a massive migration from the Eurasian Steppe, which may have replaced much of the previous European population^{63,64}. The haplogroup R1b-L11 expansion is also evident in a European-focused population sequencing study⁶¹, which finds additional recent European expansions involving haplogroups I1-M253 and R1a-M17.

Population-based interpretations of demographic history using **Bayesian skyline plots** (BSPs) provide a way to visualise changing past population size and, when both Y-chromosome and mtDNA sequences are considered, allow a comparison of male and female effective population sizes. BSPs based on the sequences of Y chromosomes and mtDNAs from a global sample set²⁷ (Figure 2) demonstrate contrasting temporal profiles for Y and mtDNA, with the contraction and recent expansion in male effective

population sizes very evident, but absent from the mitochondrial BSP. In addition, estimates of the effective population size for mtDNA are consistently more than twice as high as those for the Y chromosome, emphasizing the greater variance in reproductive success of males.

Over the past few years, sequence data for ancient Y chromosomes have been accumulating³⁹ and, although the geographical and temporal distribution is patchy, these data promise to add much to our understanding of sex-biased processes in the past. For example, a number of dramatic shifts in Y haplogroup frequencies have been shown to have occurred in Europe over the past ~35 thousand years (Figure 2c).

Genealogical studies and patrilineal surnames

The historical case regarding President Thomas Jefferson's (1743-1826) alleged paternity of at least one of the children of Sally Hemings (1773-1835), a slave at his Virginia estate, was arguably the catalyst for the use of Y-chromosomal analysis in family history. Sharing of Y haplotypes⁶⁵ between attested male-line descendants of Jefferson's paternal uncle and those of his alleged son supported the paternity case. More generally, a relationship between Y haplotypes and patrilineal surnames has been investigated and supported using Y-SNP plus Y-STR approaches. Studies of this relationship in different countries have revealed the effects of past social structures on Y-chromosome diversity. In England⁶⁶ and Spain^{67,68}, the probability of sharing a Y-haplotype between two men who share a surname is inversely proportional to the frequency of the surname in the population – common surnames, founded many times, have high Y diversity, while rare ones tend to have low diversity. However, in Ireland⁶⁹ common surnames are as likely as rare surnames to have low Y diversity, which probably reflects medieval dynastic social structures. The clear relationship between Y-haplotypes and surnames attests to low non-paternity rates in the studied populations, which specific

studies seem to confirm^{70,71}.

The surname-Y haplotype relationship has practical implications. Predicting a surname from a Y haplotype would be useful in no-suspect criminal cases⁶, and this has been shown to be feasible in principle⁷², though in practice would require very large databases of surnames with associated Y haplotypes. Privacy concerns have been raised about the anonymity of enrolment into medical genomic studies, as surnames of participants appear to be predictable from publically available whole-genome sequence data in combination with public non-genetic data⁷³. The Y chromosome is nevertheless a standard tool for forensic investigators, and the most common approach is to investigate whether or not there is a match between samples of interest using Y-STRs (Box 3).

Box 3: The Y chromosome as a forensic tool

The Y chromosome's male specificity makes it potentially useful in forensic DNA analysis^{6,134}, particularly in cases of male-on-female sexual assault¹³⁵, where the victim's DNA can be in great excess. If human individual identification via Y-DNA analysis were possible, this would indeed be a valuable tool. In principle, NGS could offer such discriminating power if a large proportion of the Y could be reliably sequenced, but in forensic practice the small amounts of often damaged DNA, the relatively high cost of sequencing, and in some countries legal or ethical restrictions, prohibit this approach. Instead, forensic DNA testing generally relies upon length-based analysis of STRs.

The workhorse of most forensic DNA analysis is a set of ~15 - 21 STRs on the autosomes [www.cstl.nist.gov/strbase/multiplx.htm]. The high discriminating power this set provides comes from two factors: (i) the STRs have high mutation rates (typically around 0.1% per STR per generation

[www.cstl.nist.gov/strbase/mutation.htm]), leading to high allelic diversity, and (ii) they are independently inherited, leading to a very low probability (typically $\sim 10^{-18}$ to 10^{-25}) that two random individuals will share a genotype (DNA profile) by chance. The first factor also applies to the Y chromosome, but the second does not: all Y-STRs are permanently linked together, and they evolve as a haplotype by mutation alone⁶. This greatly reduces the degree of inter-individual discrimination they offer: indeed, close patrilineal relatives are expected to share the same Y-STR profile, unless a mutation has occurred among the set of tested STRs. This situation is exacerbated by the recent rapid expansions of male lineages in some parts of the world⁴⁵ (see main text).

One approach to this problem has been to seek examples of Y-STRs that have particularly high mutation rates. One study analysed 186 bioinformatically-identified STRs in ~ 2000 father-son pairs in order to estimate mutation rates¹³⁶, and identified a subset of 13 RM (rapidly-mutating) Y-STRs, each mutating at $>1\%$ per generation. This set is capable of distinguishing between fathers and sons in $\sim 49\%$ of pairs based on mutation¹³⁷, and thus allows Y-STR analysis to approach the level of individual identification. The application of NGS approaches to Y-STRs promises to further enhance discrimination power, by discovering additional RM Y-STRs²⁹, increasing the number of simultaneously analysed STRs in routine typing, and also adding information about their internal sequence variation.

The study of family history is an enormously popular hobby, and DNA analysis has been enthusiastically embraced by the so-called 'genetic genealogy' community^{7,74}. There are many direct-to-consumer DNA testing companies that offer Y-chromosome analysis and some of these run 'surname projects' that bring together men who share surnames to also share their DNA data. Initially these companies typed only Y-STRs, but driven by competition they

have moved via SNP typing to Y-chromosome sequencing. For a few hundred US dollars the company Family Tree DNA offers 'Big-Y' (targeted resequencing of 11.5 - 12.5 Mb of Y-DNA), and Full Genomes Corporation offers 'Y Elite 2' (14 Mb resequenced), both providing a list of called SNPs to customers. Some services offer whole-genome sequencing (Full Genomes Corp), or the interpretation of genome sequences (e.g. YFull), and will extract Y sequence variants, including >500 Y-STR genotypes. The wealth of sequence data emerging from this 'recreational' genomic activity derives from a biased set of males who have the money and interest to fund it, but if made widely available could nonetheless add greatly to Y chromosome sequence variation data. Genealogists themselves can hope for molecularly-based family trees with improved time-scales compared to the current STR-based estimates, and it may also be possible to tie these into historical figures from aDNA data. There is also scope for growth of 'citizen science', in which people who are not academics trained in population genetics can make valuable contributions to the scientific literature; past examples have included using early 1000 Genomes Project data to identify new variants within haplogroup R1b-L11 (ref. 75) and a study focussed on haplogroup Q3-L275, a rare West Asian lineage that has been little studied by academics but is of particular interest to citizen scientists because it exceeds 5% frequency in Ashkenazi Jews⁷⁶, a community strongly engaged in such analyses.

Medical consequences of Y variation

The previous sections have mostly assumed, implicitly or explicitly, that the Y chromosome can be regarded as a **neutral** locus influenced solely by demographic events, where it makes no biological difference which Y haplotype a man carries. However, the Y chromosome has a primary function in determining male sex via *SRY* (Box 1), and also carries >70 other genes. These genes can vary in sequence, copy number or other aspects between men. In this section, we first review what is known about the phenotypic and

medical consequences of Y-chromosomal variation, and then discuss the implications of these consequences for its use in population studies. Many such consequences depend on a known gene or region of the chromosome, or on the copy number (ploidy) of the whole chromosome. In these cases, sequencing the chromosome adds little to our understanding. But in cases where the genetic basis of a phenotype is unclear, sequence data can reveal this basis.

Simple genetic conditions influenced by the Y chromosome

Given the role of *SRY* in determining male sex, *SRY* loss of function via deletion or point mutation would be expected to lead to a female phenotype, and *SRY* gain of function via translocation to another chromosome would result in a male phenotype. These consequences are indeed seen in rare sex-reversed XY female and XX male individuals^{77,78}.

Further to its sex-determining role, studies of men with spermatogenic failure have shown that three regions of the Y chromosome are required for spermatogenesis and thus male fertility; these regions were defined by deletions designated *AZFa*, *AZFb* and *AZFc*⁷⁹ (Box 1). Each region contains more than one gene, and no specific gene has been unambiguously identified as responsible for the phenotype. The best-understood region is *AZFa*, which contains just two genes, *USP9Y* and *DDX3Y*. Deletion of both genes results in a complete lack of germ cells (Sertoli-cell-only syndrome) in all known cases⁸⁰. By contrast, deletion or disruption of *USP9Y* alone is associated with spermatogenic phenotypes ranging from azoospermia (undetectable sperm) to normozoospermia (normal sperm), presumably owing to differences in genetic background or environment⁸⁰. Deletion or disruption of *DDX3Y* alone has not yet been reported, but functional studies in **induced pluripotent stem cells (iPSCs)** carrying an *AZFa* deletion have shown that introduction of *DDX3Y* can restore germ-cell formation, which suggests a key role for *DDX3Y* in this process⁸¹. Such work provides one model for the dissection of the gene

functions within the *AZFb* and *AZFc* regions, while future large-scale NGS surveys may reveal small disruptive mutations that lead to some aspects of these phenotypes or, alternatively, inactivate a gene without phenotypic consequences.

Anomalies in sex differentiation and spermatogenesis are, when severe, not transmissible, and so generally cannot lead to simple heritable disorders. Only a single such condition has been reliably mapped to the MSY: a form of male-specific deafness (designated *DFNY1* because it was the first Y-linked deafness locus identified) reported in a single extended Chinese pedigree⁸². However, sequencing of the affected Y chromosome demonstrated that its basis was not a mutation in a Y-chromosomal gene, but instead an insertion of 160 kb from chromosome 1 carrying a known dominant deafness-associated locus, *DFNA49*⁸³, a conclusion that would have been difficult to reach without NGS data.

Complex genetic conditions influenced by the Y chromosome

Over the past decade or so, **genome-wide association studies (GWAS)** have identified over 30,000 associations between specific SNPs and traits (32,234 unique SNP–trait associations on 6th March 2017; <http://www.ebi.ac.uk/gwas/>), an average of about one per 100 kb. Strikingly, not a single one of these trait-associated SNPs is located on the Y chromosome, where 100 would be expected even if just the ~10 Mb of unique sequence were considered. Although the Y chromosome is often neglected by such studies, and some Y-SNP associations have been reported by targeted investigations, for example in coronary artery disease⁸⁴, it remains unclear whether the lack of reported genetic associations is truly biological, or is explained by current methodological limitations such as the different settings needed for identifying variants in haploid versus diploid regions. Nevertheless, complex influences of Y-chromosomal loci on spermatogenesis have been

detected, affecting the process more subtly than the high-penetrance *AZFa-c* deletions. Unusually high or low (<21 or >55) numbers of copies of *TSPY* double the risk of spermatogenic failure^{85,86}. A partial deletion within *AZFc* (designated “*gr/gr*”, 1.6 Mb) removes four genes belonging to three gene families without eliminating any gene family entirely, and is also associated with a doubling of the risk of spermatogenic failure. It accounts for ~2% of severe spermatogenic failure, although <2% of men with the deletion are affected^{87,88}. Nevertheless, the *gr/gr* deletion is fixed in some haplogroups, for example, D2-M55, which is present in 36% of Japanese males⁴ but has only minor phenotypic effects⁸⁹, suggesting the possibility of compensating variants elsewhere on such Y chromosomes. In addition, the *gr/gr* deletion was associated with a twofold increased risk of testicular germ cell tumours, at least in a sample of predominantly European ancestry⁹⁰. While these insights have been derived without using NGS, future long-read NGS approaches should provide a fuller understanding of the structures of the partial deletions and how they relate to phenotypic variation, and might also shed light on the postulated compensating variants.

Y-chromosomal aneuploidy

Constitutional variation in the number of copies of the Y chromosome has long been noted, with the most common aneuploidies being Turner Syndrome (45,X; 1 in 2,000) and XYY Syndrome (47,XYY; 1 in 1,000). Phenotypic anomalies can affect both morphology (for instance, height, brain structure) and behaviour (such as risk of autism spectrum disorder and attention-deficit/hyperactivity disorder)⁹¹, and there is significantly higher mortality from a wide range of diseases^{92,93}. However, such individuals also have reduced or increased dosage for the ~20 protein-coding genes in the **pseudoautosomal** regions, and, while early work suggested that the Turner Syndrome phenotype cannot be fully explained by the lack of a second copy of *PAR1*⁹⁴,

specific MSY genes remain to be convincingly implicated.

Somatic loss of the Y (LOY) in blood cells has also been noted for decades⁹⁵, but its full health implications have only been identified more recently¹⁰, although without using NGS. LOY is the most common known acquired human mutation in surveyed populations⁹⁶, and its frequency increases with age (Figure 3A), and is associated with smoking⁹⁷. It has also been associated with decreased survival time from all causes (Figure 3B), including cancer (Figure 3C)⁹⁶, and with increased risk of Alzheimer disease (Figure 3D)⁹⁸; these associations have been replicated in some but not all studies⁹⁹⁻¹⁰². The SNP rs2887399 near *TCL1A* on chromosome 14 is associated with LOY risk (OR = 1.55, 95% CI = 1.36–1.78; P = 1.37×10^{-10})¹⁰¹ and more recently 18 additional associated genomic regions have been identified^{102,103}. While the mechanistic relationship between LOY and disease, and the importance of specific Y genes or Y haplotype background remain to be fully understood, a tumour suppressor role for *TMSB4Y* has been proposed¹⁰³, as has a model whereby LOY might provide an indicator of the increased aneuploidy of other chromosomes¹⁰². If specific Y-chromosomal genes or haplotypes are relevant, NGS data should in the future contribute to understanding their importance.

Can Y variation be considered neutral?

The lack of recombination on the MSY means that selection on any variant anywhere on the chromosome affects the entire MSY, and some of the known variants change functional elements. For example, the abundant structural variation on the Y chromosome includes a recurrent 2.5-4.0-Mb deletion removing *AMELY*, *PRKY* and *TBL1Y*, and sometimes *PCDH11Y*^{104,105}, with rarer equivalent duplications¹⁰⁶. One form of the deletion (Box 1) reaches 2% frequency in South Asia^{104,105}, and no phenotypic consequences have been identified, although further studies focusing on men harbouring the deletion

are needed. Another partial deletion within *AZFc* (*g1/g3* or *b2/b3*, 1.8 Mb) removes five genes belonging to three gene families, one more than the *gr/gr* deletion, yet is widespread and fixed in haplogroups such as N-M231, and is associated with normal spermatogenesis^{88,107,108}. Thus, variants with substantial effects on Y gene content can apparently have negligible phenotypic consequences and allow neutral or near-neutral evolution.

Overall, genetic diversity on the Y chromosome is lower than expected when simple demographic models are fitted to the diversity of other chromosomes, an observation that could be explained by strong purifying selection¹⁰⁹ or a more complex demography including severe male-specific bottlenecks⁴. Protein-coding sequences on the Y show particularly low levels of diversity, with less non-synonymous than synonymous variation and an average of one amino acid difference per chromosome across 16 unique genes on Y chromosomes from diverse haplogroups¹¹⁰. Purifying selection undoubtedly removes a small proportion of Y lineages from the population, but there is currently little evidence for significant variation in its efficiency between haplogroups (for a counter-example, see ref. 111), nor for biologically-based positive selection. Thus, while higher-powered studies are needed, there currently seems to be little evidence for differential non-neutral evolution of Y haplogroups, and few consequences for analyses that assume neutrality.

Perspectives

Over the past few years, improved sequencing technologies have greatly enriched our knowledge of Y-chromosomal variation, and these tools are continuing to develop. As a result, data generation is becoming cheaper and easier, with benefits for all areas that depend on large sequence databases, from evolutionary genetics to genealogy and forensics. Here, we discuss examples of how next-generation sequencing will continue to affect our understanding of the Y-chromosome.

Long-read sequencing

Technologies generating individual reads, or synthetic reads, that can be tens of kilobases in length are now starting to be used¹¹², and will provide access to more of the repeated regions of the chromosome. Although these regions are not expected to substantially improve phylogenetic reconstruction or dating, they are likely to reveal details of incompletely understood mutational processes, and to have particular relevance to functionally important genes on the Y chromosome, which are abundant in the repeated regions. Long reads help to resolve complex repeated regions and also allow effective *de novo* assembly¹¹³, which together may reveal sequences carried by some Y chromosomes but absent from the reference sequence.

The increasing influence of aDNA

The logical way to investigate Y-chromosomal history is to genotype or sequence Y chromosomes from each geographical area and time interval of interest, and to document the changes over space and time. Before NGS, PCR-based aDNA studies were too laborious and prone to contamination to make this approach feasible. However, NGS has transformed the field and, consequently, aDNA studies are now beginning to reveal the complexity of history¹¹⁴ and seem sure to continue to do so, with increasing resolution. aDNA data from outside Europe are particularly needed, both to address current questions such as the origins of the extreme expansions identified from present-day Y chromosomes^{4,27,61}, and to reveal the unknown features of the histories elsewhere. Even within Europe, there are still few full ancient Y sequences³⁹, and although the origin of the predominant haplogroup R1b-L11 might be related to the Yamnaya migration, the common Western European R1b-L11 chromosomes are not represented among the Yamnaya genotypes

available thus far^{4,115}, revealing a substantial gap in our understanding of the Bronze Age expansion.

Understanding the function of Y-chromosome genes

Although a catalogue of the protein-coding genes on the Y chromosome exists, many aspects of their function remain unknown. What, if any, phenotype is associated with loss or duplication of each gene? How does each gene contribute to the Turner and XYY syndrome phenotypes? What is the full range of phenotypic consequences of somatic LOY, which genes and mechanisms are most relevant, and do the consequences vary between haplogroups? Why do the *gr/gr* and *b2/b3* deletions have such different functional consequences, and why do *gr/gr* deletion phenotypes vary between haplogroups? To what extent do haplogroup differences influence the traits investigated by genome-wide association studies? In addition to the protein-coding genes, the Y chromosome yields many non-coding transcripts and contains additional regulatory elements annotated as functional. How can their functions best be investigated?

Genome-wide association studies are, in reality, usually autosome-wide association studies (AWAS), ignoring the X and Y chromosomes¹¹⁶ despite the abundance of X- and Y-chromosomal SNPs on most genotyping arrays. Perhaps the single greatest current opportunity in the Y-chromosomal field is to use the millions of genotype–phenotype datasets already available to investigate the roles of the sex chromosomes in common diseases and phenotypes, analyses that will be particularly challenging for the Y chromosome because of its extreme **population stratification**.

Conclusions

The technological revolution of the last few years has allowed multi-megabase

sequences of Y-chromosomal DNA to be determined from large population samples, with consequent unbiased ascertainment of variation. The resulting time-calibrated phylogeny reveals male expansions at the time of the migration of modern humans out of Africa around 60,000 years ago, and also in the last few millennia, probably corresponding to technology-driven population expansions. aDNA investigations are beginning to reveal the complexity of changes in Y chromosome lineage distributions and frequencies over time. In genealogical studies, the male-line inheritance of the Y chromosome makes it an excellent tool for studies of male family history, creating a burgeoning area of citizen science in which NGS technologies are being enthusiastically applied. The Y chromosome has not been implicated at all in genome-wide association studies, and only in a single simple heritable disorder, but is central to disorders of sex determination and spermatogenesis. Mosaic somatic loss of the Y chromosome in aging men has been associated with increased risk of cancer mortality and Alzheimer Disease. With high-quality genome sequences of millions of men expected to be available in the next few years^{117,118}

[\[www.nhlbi.nih.gov/research/resources/nhlbi-precision-medicine-initiative/topmed/wgs\]](http://www.nhlbi.nih.gov/research/resources/nhlbi-precision-medicine-initiative/topmed/wgs), we look forward to a detailed phylogeny that links all their Y chromosomes, helps us to understand our shared history, and reveals the clear-cut or subtle phenotypic consequences of carrying one type of Y chromosome instead of another.

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Figures and Legends

Figure 1. Calibrated Y-chromosomal phylogeny. A mutation rate of 7.6×10^{-10} mutations per base per year was used for calibration. (a) The schematic tree represents data on 60,555 Y-SNPs in 1244 present-day chromosomes from the 1000 Genomes Project⁴. Labels on the branches and below the triangles are haplogroup names in the form 'Haplogroup-key defining mutation'. Labels outlined in black indicate haplogroups that have undergone rapid recent expansions (see text). Haplogroups represented by many chromosomes are collapsed into triangles where the triangle height represents the coalescence time and the width the frequency in the sample. An expansion of haplogroup R2a-M124 in a more standard format is shown in the dotted box in the top right-hand corner. (b) Phylogeny including Neanderthal and the most divergent human lineage⁴¹, A00; note the different timescale from (a). (c) Geographical distribution of the major lineages, shown by pie-charts in which the sectors are coloured to correspond to the haplogroups in part (a). Three-letter labels are abbreviated population code-names¹³⁸. ACB, African Caribbeans in Barbados; ASW, Americans of African ancestry in the south-west United States; BEB, Bengali from Bangladesh; CDX, Chinese Dai in Xishuangbanna, China; CEU, northern Europeans from Utah; CHB, Han Chinese in Beijing, China; CHS, southern Han Chinese; CLM, Colombians from Medellin, Colombia; ESN, Esan in Nigeria; FIN, ancestry in the south-west United States; BEB, Bengali from Bangladesh; CDX, Chinese Dai in Xishuangbanna, China; CEU, Utah Residents (CEPH) with Northern and Western European Ancestry; CHB, Han Chinese in Beijing, China; CHS, southern Han Chinese; CLM, Colombians from Medellin, Colombia; ESN, Esan in Nigeria; FIN, Finnish in Finland; GBR, British in England and Scotland; GIH, Gujarati Indian from Houston, Texas; GWD, Gambian in the Western Divisions in the Gambia; IBS, Iberian population in Spain; ITU, Indian Telugu from the United Kingdom; JPT, Japanese in Tokyo,

Figure 2: Comparison of demographic histories of females and males revealed by mtDNA and Y-chromosome analysis.

a) Bayesian skyline plots (BSPs) of effective population size against time based on sequences of mtDNAs, in 320 individuals, with different world regions indicated by colours. The major expansion is between ~20 and ~14 kya. b) BSPs for Y chromosomes in the same samples, with colouring as in part (a). Important features are an early expansion at ~60 kya and a contraction and rapid expansion within the last 10 ky. Note the difference in scales of the y-axes, and the greater female effective population size reflected in mtDNAs. Parts a and b are adapted with permission from REF. [27], [CSHL Press]. c) Frequencies of four selected Y haplogroups in ancient DNA samples from Europe, showing the recent rise of haplogroup R1b, and previous high frequencies of the currently rare haplogroups I2 and G. Ancient data are from the summary at www.ancestraljourneys.org, and modern data from ref. 138. Parts a and b are adapted from REF. 27.

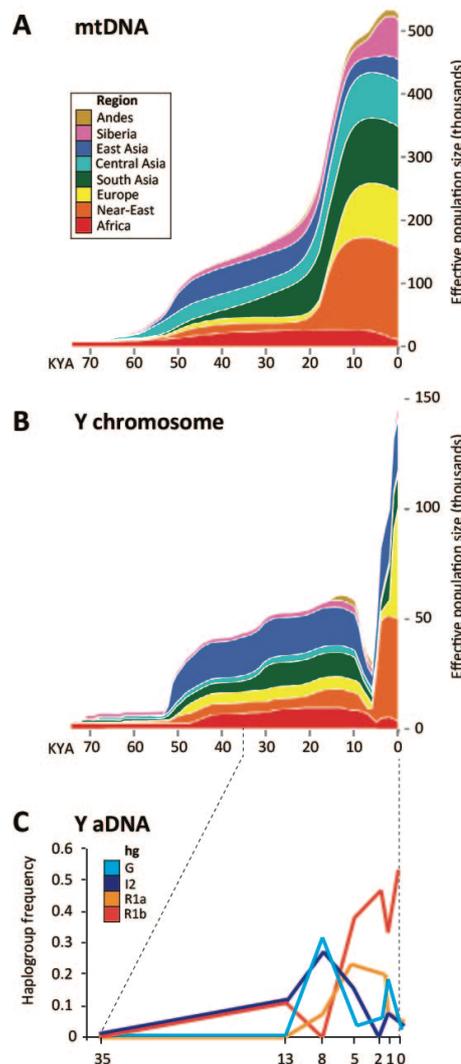
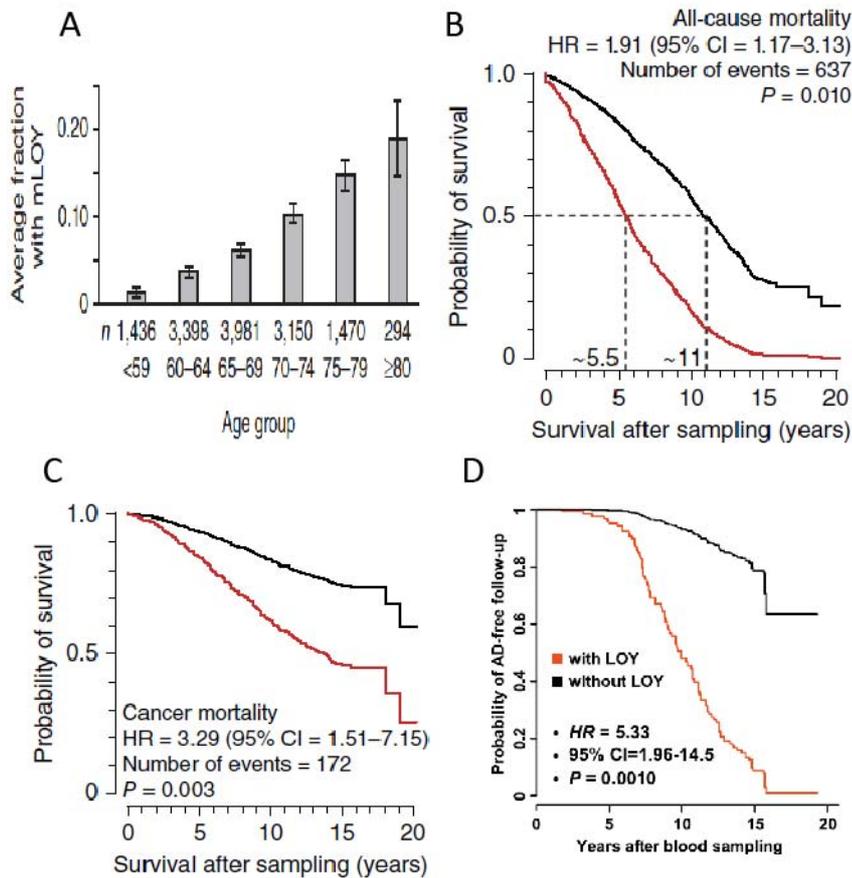


Figure 3. Loss of Y (LOY) in blood samples and its medical consequences. (a) LOY increases with age. The fraction of men with LOY is shown for different age groups; error bars show 95% confidence intervals. (b) LOY is associated with increased mortality from all causes. The numbers above the horizontal axis are the 50% survival times for this elderly cohort, and are 5.5 years shorter for men with LOY. (c) LOY is associated with cancer mortality. (d) LOY is associated with increased probability of diagnosis with Alzheimer Disease (AD).

Part a is from REF. [101], Nature Publishing Group. Parts b and c are from REF. [96], Nature Publishing Group. Part d is adapted with permission from REF. [98], [Elsevier].



Glossary terms

Admixture: The mixing of distinct parental populations resulting in a new hybrid population.

Bayesian skyline plot: A plot of effective population size against time, summarizing the demographic history of a population.

Callable: Describes DNA sequence in which reliable genotype calls can be made in next-generation sequencing because of unambiguous mapping of reads to the reference sequence.

Euchromatin: The part of the genome that is in an extended conformation and which contains transcriptionally active DNA.

Gametologues: Similar sequences on the X and Y chromosomes, which share an origin in the ancestral autosomal pair from which the current X and Y have evolved.

Gene conversion: A nonreciprocal exchange of sequence information between one DNA molecule and another. Non-allelic gene conversion is active between repeat sequences on the Y chromosome.

Genetic drift: The random fluctuation of allele frequencies in a population due to chance variations in the contribution of each individual to the next generation.

Genome-wide association studies: Studies of many common genome-wide variants (usually SNPs) in different individuals to determine if any variant is associated with a trait

Haplogroups: related sets of Y-chromosomes collectively defined by specific slowly-mutating binary polymorphisms (usually SNPs).

Haploid: Of a chromosome, having one copy per cell.

Heterochromatin: A highly condensed, transcriptionally inert segment of the genome, often composed of repeated DNA sequences. On the Y, found mainly near the centromere and in the distal half of the long arm.

Hotspots: short (few kilobases) regions of the genome in which meiotic crossing over is significantly elevated over the genome average.

Induced pluripotent stem cells - a type of stem cell that can be directly generated from adult cells and differentiated into many cellular types.

Maximum parsimony: A method for selecting the best evolutionary tree from a set of alternatives on the basis of which contains the fewest mutational changes.

Minisatellites: DNA sequence containing a variable number (~10 to >1000) of tandemly-arranged repeat units, each typically 10–100 bp in length.

Mitochondrial DNA (mtDNA): The circular, maternally-inherited genome carried by the mitochondrion, a cellular organelle.

Neutral: Describing genetic variation that has no effect on selective fitness.

Phylogeny: A tree-like diagram that represents the evolutionary relationships among a set of sequences.

Phylogeography: Analysis of the geographical distributions of different clades within a phylogeny, such as haplogroups in the Y phylogeny.

Pseudoautosomal: Describing the behaviour of two regions of the sex chromosomes that display inheritance from both parents due to crossing over between the X and Y chromosomes in male meiosis.

Resequencing: Taking a particular known sequence from an existing source, or an entire genome, and determining it in several different individuals as a means to discover sequence variation.

Sertoli cells: Cells located in the walls of the seminiferous tubules of the testis, which act to support the development of sperm.

Short-tandem repeat (STR): A DNA sequence containing a number (usually ≤ 50) of tandemly repeated short (2–6-bp) sequences, such as $(GATA)_n$. Often polymorphic, and also known as a microsatellite.

Ascertainment bias: Bias in a dataset caused by the way that DNA sequence variants are identified, or samples are collected.

Outgroup: A lineage or species that is more distantly related to a group of lineages or species than any of them is to each other.

Population stratification: Systematic differences in allele frequencies

between subgroups within a population.

Deep-rooting: Describing a human pedigree containing the descendants of common ancestors who lived several or many generations ago.

Author Biographies

Mark A. Jobling

Mark Jobling is a Professor in the Department of Genetics at the University of Leicester, UK. His research is in the area of human genetic diversity and the forces that pattern it, from mutation dynamics to cultural factors in populations. He has a long-term interest in the Y chromosome and its many peculiarities, exploiting this male-specific marker in studies of population history, sex-biased admixture, mutation processes, forensic analysis and genetic genealogy. His current research projects exploit the power of next-generation sequencing in evolutionary and forensic applications in humans and other animals.

Chris Tyler-Smith

Chris Tyler-Smith heads the Human Evolution team at The Wellcome Trust Sanger Institute, UK. His interests are in understanding worldwide genetic variation in humans (including on the Y chromosome) and closely-related species such as gorillas or chimpanzees, and how this information can be used to understand the human past. How have humans spread around the world, diverged, mixed, and adapted to their environments throughout prehistoric and historic times? Investigating these questions involves both generating and analyzing new genomic data, and in some cases functional studies such as in people with natural gene knockouts or in genetically modified mice.

Key Points

1. As a consequence of its key role in male sex determination, the Y chromosome has unique genetic properties that lead to it carrying highly-informative haplotypes that evolve largely by the simple accumulation of mutations.
2. Advances in technology have allowed approximately 10 Mb of Y-chromosomal DNA to be sequenced from large population samples, with consequent unbiased ascertainment of their genetic variation.
3. Y-chromosomal sequences can be assembled into a robust phylogeny, which can be calibrated using estimates of the mutation rate from family studies, known archaeological events, or ancient DNA samples.
4. The calibrated Y-chromosomal phylogeny reveals male expansions corresponding to the migration of modern humans out of Africa around 60,000 years ago, the colonisation of the Americas around 15,000 years ago, and more recent technology-driven population expansions.
5. The Y chromosome has a specialist role in forensic genetics, allowing male-specific DNA profiles to be compared at increasingly high resolution.
6. In genealogical studies, the male-line inheritance of the Y chromosome makes it a perfect tool for studies of male family history, creating a burgeoning area of citizen science.
7. The Y chromosome is central to disorders of sex determination and spermatogenesis. Recently, mosaic somatic loss of the Y chromosome in aging men has been associated with increased risk of cancer mortality and Alzheimer Disease.