THE HUMAN Y CHROMOSOME, IN THE LIGHT OF EVOLUTION

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Most eukaryotic chromosomes, akin to messy toolboxes, store jumbles of genes with diverse biological uses. The linkage of a gene to a particular chromosome therefore rarely hints strongly at that gene's function. One striking exception to this pattern of gene distribution is the human Y chromosome. Far from being random and diverse, known human Y-chromosome genes show just a few distinct expression profiles. Their relative functional conformity reflects evolutionary factors inherent to sex-specific chromosomes.

DIOECIOUS
Having separate male and female organisms.

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In many DIOECIOUS taxa, karyotype determines sex. To mediate this developmental decision, sex-chromosome pairs have arisen independently among such lineages from separate pairs of ordinary autosomes[1]. The sex chromosomes of one taxon can, therefore, differ phylogenetically and structurally from those of another. The mammalian sex chromosomes, for example, are not specifically related to those of birds, insects or plants.

Despite their many origins, the sex chromosomes of diverse life forms are strikingly alike. Ever-hemizygous chromosomes (that is, the Y chromosome (hereafter the Y) in XY or the W chromosome in ZW systems) tend to be small, gene-poor and rich in repetitive sequence. Their non-sex-specific partners, the X chromosome (hereafter the X) and Z chromosome, tend to be more autosome-like in form and content, and in many cases undergo dosage compensation to equalize gene activity between the sexes. This gross convergence of sex chromosomes among disparate lineages hints that common factors drive their evolution. Such factors are increasingly well understood, thanks largely to studies of the mammalian sex chromosomes and of the human Y in particular. Here, we review how studies of the human Y have already cast a spotlight on the role of evolution in moulding the distinctive biological properties of sex chromosomes.

Classes of human Y-chromosome genes

A typical eukaryotic chromosome encodes a motley assortment of gene products; functionally related genes do not tend to jointly occupy particular chromosomes. It is curious, then, that one of the shortest human chromosomes — the Y — might contain the longest human genomic region, in which genes show only a few distinct expression profiles. To the extent that tissue specificity reflects functionality, the human Y thus harbours remarkably low gene-functional diversity. In fact, if classified jointly by location and apparent function, known human Y genes boil down to pseudoautosomal loci and three basic classes of non-recombining, male-specific loci.

The pseudoautosomal regions (PARs) at the ends of the human Y comprise ~5% of its sequence (this fraction, consistently small, varies among mammals)[2,3]. In male meiosis, the PARs of the X and Y recombine with each other at high, if subregionally varied, rates[4,5]. Accordingly, PAR genes, like autosomal genes, are shared freely between the sexes. Although highly recombinogenic relative to the human genome as a whole, the human PARs generally resemble autosomes in base composition, and in gene density and diversity. About a dozen pseudoautosomal genes, most of them on the short arm, have been identified. Most of these genes elude X inactivation, as would be expected of genes with sex-uniform dosage. Curiously, two genes on the long arm human PAR, *SYBL1* (synaptobrevin-like 1) and *HSPRY3* (sprouty (*Drosophila*) homologue 3), reportedly undergo X and Y inactivation in females and males, respectively, which indicates that this region might have a complex evolutionary history that involves recent X-to-Y translocation[6].

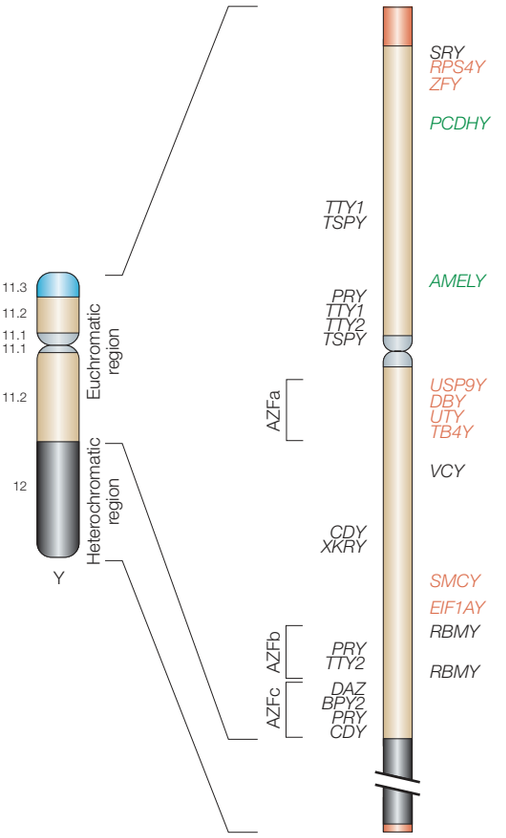

Figure 1 | **Active genes on the human Y chromosome.** Yellow bar, euchromatic portion of the non-recombining region of the Y chromosome (NRY); black bar, heterochromatic portion of the NRY; grey bar, centromere; red bars, pseudoautosomal regions (genes omitted). Genes named to the right of the chromosome have active X-chromosome homologues. Genes named to the left of the chromosome lack known X homologues. Genes in red are widely expressed housekeeping genes; genes in black are expressed in the testis only; and genes in green are expressed neither widely, nor testis specifically (*AMELY* (amelogenin Y) is expressed in developing tooth buds, whereas *PCDHY* (protocadherin Y) is expressed in the brain). With the exception of the *SRY* (sex-determining region Y) gene, all the testis-specific Y genes are multicopy. Some multicopy gene families form dense clusters, the constituent loci of which are indistinguishable at the resolution of this map. Three regions often found deleted in infertile men, AZFa, b, c (azoospermia factor region a, b, c), are indicated.

Most of the remainder of the human Y recombines with neither the X nor any other chromosome. This non-recombining region of the Y (NRY) consists largely of highly repetitive sequences that are rich in transposons and other elements whose replication and/or expression is unlikely to directly benefit the human host[7]. Of the ~60-megabase (Mb) human NRY, ~35 Mb are euchromatic. Most of the remainder is a block of heterochromatin on the long arm. Nearly one-half of the euchromatic portion of the NRY has been sequenced through the publicly funded Human Genome Project. Representative sequencing of the entire euchromatic NRY is expected to be completed within this year. So far, 21 distinct genes or gene families that are expressed in healthy tissues have been identified in the human NRY. These group into three salient classes — classes 1, 2 and 3 — largely on the basis of expression profile and homology to the X.

The eight known class 1 genes are single copy, are expressed widely in the body and have like-functioning X-linked homologues. Class 2 also has eight known members, each of which is multicopy, expressed only in the testis and without an active X homologue (FIG. 1, TABLE 1). Class 3 contains the human NRY genes that blur an otherwise sharp bipartition defined by classes 1 and 2. Most prominent among these is the *SRY* (sex-determining region Y) gene, the master trigger of male embryonic differentiation. The single-copy *SRY* gene is expressed in the embryonic BIPOTENTIAL GONAD — where it initiates the development of the testis — and also in the adult testis. The X carries the *SOX3* (SRY-box 3) gene, an active homologue of *SRY*[8,9]. Two other notable class 3 NRY genes are *AMELY* (amelogenin Y) and *PCDHY* (protocadherin Y). Unlike the widely expressed class 1 and testis-specific class 2 genes, *AMELY* and its X homologue, *AMELX* (amelogenin X), are expressed only in developing tooth buds[10]. Similarly, *PCDHY* and its X homologue, *PCDHX* (protocadherin X), are expressed mainly in the brain[11,12]. The remaining NRY genes are *RBMY* (RNA-binding motif protein Y) and *VCY* (variable charge Y, previously called *BPY1*), which have features of both classes 1 and 2. Like class 1 genes, they have active X homologues (named *RBMX* (RNA-binding motif protein X) and *VCX* (variable charge X), respectively); like class 2 genes, they are expressed from multiple copies, but in the testis only. The single-copy X homologue of *RBMY* is widely expressed and dosage compensated[8,9], whereas the many X homologues of *VCY* are expressed only in the testis (and so are inactive in females)[13].

Converging theoretical and empirical evidence shows how and why the gene content of the NRY reflects the region's distinctive history. Altogether, the three gene classes of the region show markedly limited functional themes — in stark contrast to the genic miscellany of other human chromosomes. This remarkable functional specialization highlights two evolutionary processes inherent to Ys: genetic decay and the accumulation of genes that specifically benefit male fitness.

Degeneration of the Y chromosome

The mammalian sex chromosomes are thought to have arisen from an ordinary pair of autosomes ~300 million years ago[14]. Until then, ambient temperature during embryonic development might have determined the sex of mammalian ancestors, as in many modern reptiles and other descendants of bony fish[15]. The foremost sex-chromosome bearers in this CLADE are, notably, birds and mammals — both HOMEOTHERMS, for whom temperature might have ceased to be useful as a signal for developmental switching. In mammals, sex chromosomes probably arose with the differentiation of *SRY* from its homologue, *SOX3*, which persists on the mammalian X[8,9]. Sequence and expression comparisons indicate that *SRY* and *SOX3* descend from a specific progenitor gene,

BIPOTENTIAL GONAD
The last embryonic tissue precursor that can differentiate into either the ovary or the testis.

CLADE
An organismal lineage comprising an ancestor and all its descendants.

HOMEOTHERM
An organism that uses cellular metabolism specifically to stabilize its own body temperature.

Table 1 | **Classification of human Y-chromosome genes**

Gene category	Genes	Known/putative function(s)	Expression specificity	Multiple copies on Y?	Has active X homologue?	X homologue inactivated in female?
Pseudoautosomal	Many	Equivalently diverse as autosomal genes	Diverse	No	Yes	Yes (except *SYBL1*, *HSPRY3*)
NRY class 1	*RPS4Y*, *ZFY*, *USP9Y*, *DBY*, *UTY*, *TB4Y*, *SMCY*, *EIF1AY*	Housekeeping	Broad	No	Yes	No
NRY class 2	*TTY1*, *TSPY*, *PRY*, *TTY2*, *CDY*, *XKRY*, *DAZ*, *BPY2*	Spermatogenesis	Testis	Yes	No	NA
NRY class 3	*SRY*	Male determination	Testis	No (yes in some rodents)	Yes	Yes
	RBMY	Spermatogenesis	Testis	Yes	Yes	Yes
	AMELY	Tooth development	Tooth bud	No	Yes	Maybe
	VCY	Unknown	Testis	Yes	Yes	NA
	PCDHY	Unknown	Brain	No	Yes	No

(NRY, non-recombining region of the Y chromosome; NA, not applicable.)

with the more derived *SRY* having gained and kept the male-determining function[9]. The emergence of a dominant and PENETRANT sex-determining allele of the proto-*SOX3*/*SRY* gene would have effectively rendered an autosome pair into sex chromosomes, starting a long and dramatic evolutionary process. Over aeons, the mammalian X and Y diverged, with the gross structure of the X changing remarkably little, while the Y rapidly degenerated[1,14,16,17].

The rampant attrition of gene activity from evolving Ys has long been noted. In fact, MEROHAPLODIPLOID sex determination (for example, XX:XO) is thought to represent a relatively stable endgame in sex-chromosome evolution[18]. Potential causes and mechanisms of Y-specific degeneration have drawn heated speculation. Why and how have large X and Y regions stopped recombining with each other? And why might Y genes tend to decay once they stop recombining with their X counterparts?

Recent results indicate that, on the evolutionary lineage leading to humans, the mutually non-recombining portions of the human Xs and Ys greatly expanded several times, each time converting a block of previously freely recombining sequence into X- and Y-specific regions[14]. The striking similarity in gene order seen among disparate mammalian Xs, compared with the relative scrambling of genes seen among mammalian Ys (FIG. 2), indicates that such coarse blockwise (versus smooth) consolidation of Y-haplotype linkage was probably caused by serial, large-scale inversion of much of the Y itself. Such inversions would have disrupted alignment, and thus recombination, between progressively larger regions of the Xs and Ys. At least four multigene inversions seem to mark the human Y lineage: the first ~300 million years ago and the last ~30 million years ago[14] (FIG. 3). Consolidating linkage across wide swathes of the chromosome, such inversions might have swept to fixation in ancestral populations either by GENETIC DRIFT, or by selection if they bound together alleles that conferred benefit only in the presence of the sex-determining gene. That gene, *SRY*, seems to have been the first active gene on the Y to cease recombination with the X, as ranked by silent divergence between X and Y homologues[14]. The history of Y gene rearrangement (as well as gain and loss) varies among mammalian lineages (FIG. 2); such variation will prove phylogenetically informative as more non-human mammalian Y sequences become available.

But why do NRY genes tend to decay? Several models point to their lack of recombination as a key factor. Edmund Wilson, and later Hermann Muller, proposed that the NRY accumulates null alleles because intact X homologues shelter them[19,20]; such defunct loci are not selectively purged as they would be if rendered homozygous by recombination. A more general theory by Muller, dubbed "Muller's ratchet" (and extended by Brian Charlesworth and others), holds that, in the face of largely harmful mutations, only recombination can adequately regenerate highly fit alleles (that is, crossover between harmful variants that occupy different sites in a locus can yield a repaired allele)[21,22]. William Rice invoked Muller's ratchet in considering tight linkage across multiple loci, not all of which carry beneficial alleles; he gave the name "genetic hitchhiking" to the spread of potentially harmful alleles that are linked to selectively favoured alleles, with a concomitant reduction in local nucleotide diversity[23].

Human NRY haplotypes are — as predicted by such models — nearly static, strikingly poor in variation (despite relatively frequent mutation, apparently owing to greater male than female germ-cell turnover in mammals) and greatly eroded in function relative to other genomic regions[24]. By recombination, such other regions can maintain diverse, highly fit haplotypes that readily spread by selection, thanks to the greater, and thus less genetic-drift-prone, EFFECTIVE POPULATION SIZE of diploid versus haploid regions. Although the details of relevant models spur debate, most evolutionary biologists agree that recombination shuffles alleles so that well-adapted haplotypes can readily replace ill-adapted ones. Indeed, experimentally restricting local recombination in laboratory fruitfly populations has been shown to threaten their long-term genetic integrity[25].

PENETRANCE
The frequency of affected individuals among the carriers of a particular genotype.

MEROHAPLODIPLOID
Characterized by one sex lacking part, but less than half, of the diploid chromosome set typical of the other sex.

GENETIC DRIFT
The random fluctuation of allele frequencies across generations in a finite population.

EFFECTIVE POPULATION SIZE (N_e). The theoretical number of organisms or copies of a locus for which the genetic variation in a given sample of the organisms or copies can be explained solely by mutation and genetic drift; N_e is related to, but never exceeds, the actual population size (N).

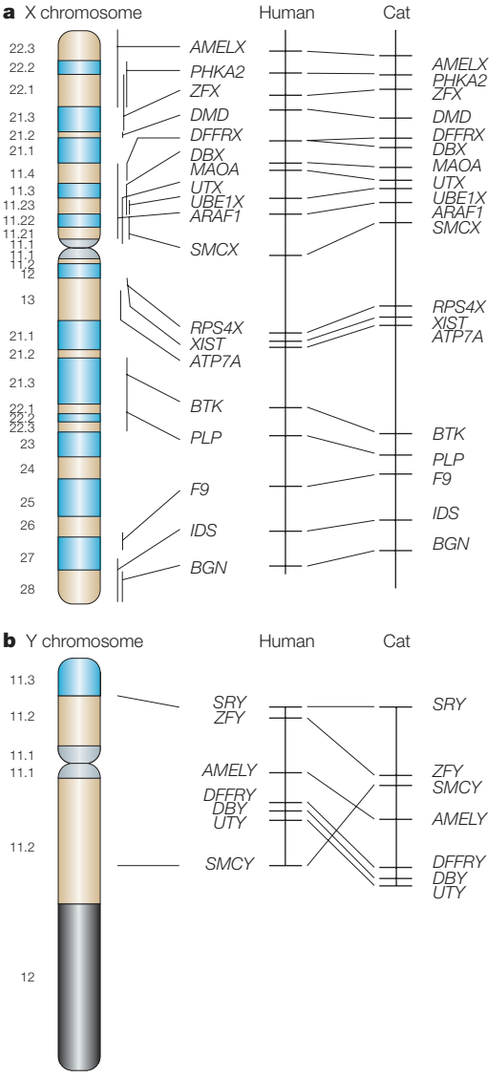

Figure 2 | **Sex chromosomes in mammals.** The radiation hybrid maps show **a** | conservation of locus order in disparate mammalian X chromosomes (cat and human) compared with **b** | the relative rearrangement of Y chromosomes in the same taxa. A similar comparison of the human Y to those of other primates (omitted for simplicity) reveals more recent taxon-specific rearrangements[108].
Adapted from REF. 109.

The functional blight of NRYs might also explain their characteristic shrinkage and/or accumulation of non-essential — perhaps even parasitic — retroviral and heterochromatic sequences. Many gene-like NRY loci are not expressed in humans, as in many other taxa with XY systems, whereas their X counterparts remain active. This observation belies the pervasive decay that is associated with overly robust linkage. Nevertheless, a handful of non-recombining homologue pairs remain active on both chromosomes. Bucking the decay trend, these genes attest to the common ancestry of the Xs and Ys. Two alternative scenarios might account for their persistence in the NRY.

PARALOGUE
A locus that is homologous to another within the same haploid genome.

Persistence of XY-chromosome homologues

In the first scenario, X-homologous NRY genes might have functions crucial to both sexes. Such genes persist, with little differentiation, if proper development requires their double dosage (two X copies in females, or X and Y copies in males)[26]. In that case, X and Y homologues should function roughly equivalently, and, to maintain sex-uniform dosage, the former should elude X inactivation. Class 1 human NRY genes meet these conditions. They and their X homologues encode widely expressed housekeeping proteins, many of which are crucial to viability[26]. The observed ratio of protein-to-nucleotide divergence between such XY homologues is significantly lower than that for other neighbouring loci — consistent with the idea that selection has conserved the functional similarity of X and Y copies[26]. Finally, the X homologues of nearly all these class 1 NRY genes elude X inactivation[26–28].

In the second scenario, NRY genes persist because they have specialized in male-specific functions, such as somatic masculinization or spermatogenesis. As such, they differ significantly in function from their X homologues (which presumably preserve ancestral functions). An exemplar is *SRY*, which apparently differentiated from its widely expressed X homologue, *SOX3*, to gain and maintain a key function in male development[8,9]. Another is the testis-specific class 3 gene *RBMY*, the X homologue of which, *RBMX*, is expressed in diverse tissues[29,30]. Presumably, in both cases, the progenitor of the XY-homologue pair was widely expressed. During subsequent evolution, the X homologue (*SOX3* or *RBMX*) maintained this expression status, whereas the activity of the Y homologue (*SRY* or *RBMY*) became testis-specific (and thus male-specific). Other examples of NRY genes that have adopted specialized male functions are reported in the mouse. Three mouse NRY genes, *Zfy* (zinc-finger protein), *Ube1y* (ubiquitin-activating enzyme E1) and *Usp9y* (ubiquitin-specific protease 9), show testis-specific expression, whereas their X homologues are expressed in many other tissues[31–33].

Accumulation of spermatogenic genes

Although NRY genes with X homologues clearly attest to ancestral XY homology, the evolutionary origins of class 2 NRY genes (which lack X homologues) are less obvious. Early clues to the history of these testis-specific genes came from studies of the *CDY* (chromodomain protein Y) and *DAZ* (deleted in azoospermia) genes. Both have specific autosomal PARALOGUES: *CDYL* (chromodomain protein Y-like) and *DAZL* (deleted in azoospermia-like), respectively. These autosomal genes are found throughout mammals, whereas *CDY* and *DAZ* are found only on primate Ys. These observations indicate that early mammals might have had only *DAZL* and *CDYL*, the paralogues of which arose *de novo* at some point and were maintained on the primate Y lineage[26,34–36]. *DAZ* and *DAZL* are spliced alike, which indicates that *DAZ* might have reached the Y by inter-chromosomal transposition of *DAZL*[35]. *CDY* is an intronless version of *CDYL*, which indicates that *CDY* might have arisen by retroposition of *CDYL* mRNA[36].

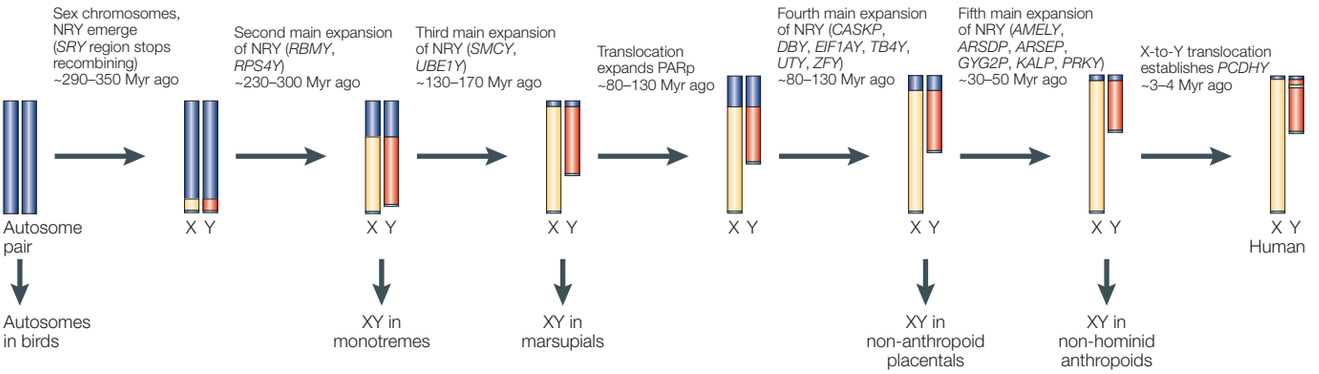

Figure 3 | **Human sex-chromosome evolution.** The figure shows the overall shrinkage of the Y chromosome and the blockwise expansion of its non-recombining region (NRY), probably mediated by serial large-scale inversion as posited by Lahn and Page[14]. Main events are noted and roughly dated (Myr ago, millions of years ago), with new NRY genes placed in parentheses, and phylogenetic branches indicated by arrows. Blue regions are freely recombining. Yellow regions are X-chromosome specific. Red regions are Y-specific (NRY). The green region represents *PCDHX/Y* (protocadherin X/Y)-containing sequence that has translocated from the X to the NRY (some other likely translocations are omitted for simplicity). The diagram is not drawn to scale and centromeres are omitted, as their locations are uncertain for many evolutionary stages. (PARp, short arm pseudoautosomal region.)

The gain and retention of genes that specifically benefit male fecundity — and promote spermatogenesis in particular — seems to be a global theme in Y evolution. Biologists have long suspected, and sometimes confirmed, the great importance of male-specific chromosomes in spermatogenesis[34,37–45]. Male fruitflies that lack a Y, for example, produce no fertile sperm[39,42]. Factors that potentially drive the accumulation of spermatogenic function in Ys have drawn much speculation. Ronald Fisher posited a selective advantage in sequestering, within a male-specific portion of the genome, any genes that benefit males but harm females[46]. This sexual antagonism model was invoked to account for the Y linkage of ornamentation genes in guppies[47] (FIG. 4); these genes probably enhance male attractiveness and fecundity, but would reduce fecundity in female carriers, as female ornamentation increases predation risk without effectively boosting mating chances.

Sexual antagonism might plausibly explain the accumulation of spermatogenic genes on Ys, because such genes clearly benefit males but might harm females. Indeed, women that carry Y fragments are especially prone to gonadoblastoma, a form of ovarian tumour[48,49]. However, impairment of female fitness by spermatogenic genes could alternatively be mitigated, potentially at low metabolic cost, by transcriptionally silencing these genes in females, instead of moving them to the Y. This possibility makes the sexual antagonism model less generally compelling.

Accordingly, we invoke an additional argument — "constant selection" — to further explain the preferential accumulation on the Y of any spermatogenesis genes that might be nearly neutral in females. Studies in several taxa indicate that genes that drive sperm production evolve unusually rapidly, presumably owing to fierce rivalry among sperm from one or multiple males, whose fecundity tends to vary more than that of females[50–52]. Under such stringent selection for winning strategies in the race for fertilization, alleles that enhance sperm success might readily spread in a population. Their actual selective advantage, however, is likely to vary with chromosomal linkage. If they are Y linked, such alleles are always favoured, because they are expressed in each generation; if they are autosomal or X linked, they can selectively spread only when male-transmitted — roughly every other generation for autosomal loci and every third generation for X loci. So, generation-invariant selection on spermatogenic genes might intensify the overall selective advantage for their gain, retention and adaptive change on the male-specific NRY. Whether such intensified advantage actually makes allelic fixation significantly more likely on the NRY than elsewhere in the genome remains to be fully modelled. The several-fold lower effective population size of the NRY than of the X or an autosome, for example, might diminish the advantage of constant selection, because small populations allow non-advantageous alleles a greater chance to drift to fixation in place of advantageous alleles[53].

Amplification of gene copy number might be a second counter to the decay of NRY genes. Most class 2 genes exist in multiple copies on the Y, although current counts are inexact[26]. Gene amplification might buffer against harmful mutations: although mutations accumulate to impair the function of single copies, other intact copies might carry out a gene family's spermatogenic duties and, also, seed further amplification. Notably, the great density of long-repeat sequences throughout the NRY might mediate frequent amplification of repeat-flanked genic regions[26,54,55].

Altogether, NRY genes have two distinct origins and three distinct evolutionary fates. Their origins are: descent from the proto-Y, which was extensively homologous with the X, or specific recruitment to the Y from elsewhere in the genome. The three evolutionary fates of NRY genes are: functional decay, preservation in ancestral (typically housekeeping) form, or specialization in male-specific function.

Figure 4 | **Example of a Y-chromosome-linked trait.** Male (top) and female (bottom) guppies (*Poecilia reticulata*). Colourful male ornamentation, which enhances both sexual attractiveness to females and visibility to would-be predators, reflects the expression of Y-chromosome-linked genes.
Photo courtesy of N.M.P.

Despite degeneration, some Ys (for example, that of the fruitfly *Drosophila miranda*) seem to have ballooned in size through large translocations from autosomes[56]. Such a translocation apparently occurred in an early placental mammal ancestor, shortly after the placental–MARSUPIAL split[57,58] (FIG. 3). This translocation generated new XY-homologous sequence, which then encountered the factors that drive ongoing XY differentiation. Recombination was eventually suppressed in much of the new Y-linked portion; most genes in the region then decayed, and their X homologues became subject to inactivation in females.

Y-chromosome genes and disease

A striking feature of the human NRY is that its two largest gene classes correspond to two disorders: Turner syndrome (TS) and male infertility. Turner syndrome results from a 45,XO karyotype[59–61]. Most such embryos die *in utero*, accounting for roughly one-tenth of recognized human foetal deaths. TS is detected in about 1 out of 3,000 human live-births[62]. Short stature, failure of gonadal development and diverse macroanatomic anomalies typify the syndrome[59–61].

The TS karyotype can be seen as the lack of either an X, relative to XX females, or a Y, relative to XY males. Recognizing this, Malcolm Ferguson-Smith argued in 1965 that the syndrome reflects the haploinsufficiency of "TS genes", which he predicted would be common to the Xs and Ys and would elude X inactivation[60]. Class 1 human NRY genes and their X homologues meet these conditions and are considered to be TS candidates. Their widespread expression is consistent with the broad range of symptoms observed in TS patients. Pseudoautosomal genes might also contribute to TS, as they occupy both the Xs and Ys and typically elude female X inactivation[2]. Indeed, a gene called short stature homeobox (*SHOX*), identified recently in the freely recombining region of the human sex chromosomes, seems to contribute to the short stature of TS individuals[63,64]. The syndrome highlights the crucial importance of the Y in body-wide housekeeping functions and underscores the incompleteness of human Y degeneration. In the mouse, whose Y degeneration seems relatively more advanced, XO individuals reportedly show no salient phenotype.

The second common Y-associated disorder is male infertility. About 1 out of 1,000 human males is infertile, owing to spermatogenic failure[65]. Remarkably, newly arisen Y deletions account for ~10% of such cases[34,44], which is consistent with a rate of *de novo* partial Y deletion of at least 10^{-4}. Class 2 genes, which are testis-specific in expression and male-specific in the genome, are probably important for spermatogenesis. Deletion mapping in infertile men has defined particular Y regions that are involved in fertility. Three such regions — AZFa, b, c (azoospermia factor region a, b and c) — are well characterized (FIG. 1); deletion within any one region might severely impair spermatogenesis[34,43,44]. Among the three, AZFc deletion is by far the most common. The need for an intact Y for spermatogenesis might largely reflect the presence of testis-specific genes in these regions. Still, the possibility cannot be ruled out that the more widely expressed Y genes might also be required for male fertility. For example, lesions of *USP9Y* (previously known as *DFFRY*) or *DBY* (DEAD/H (Asp-Glu-Ala-Asp/His)-box polypeptide Y) genes, which are both widely expressed class 1 genes in AZFa, have been linked to spermatogenic failure[66,67].

In summary, two principal Y-associated disorders reflect the two most salient functional themes of the human Y, again highlighting the two main gene classes therein.

Class 3 genes

The active human NRY genes that fit neither class 1 nor 2 have provoked considerable curiosity, and some functional and phylogenetic inquiry. Five such genes are known; perhaps other putative coding sequences on the NRY will, upon more thorough expression assay in a broad range of tissues, prove to be additional class 3 genes. In general, these genes seem to be in various states of evolutionary limbo. Some (for example, *RBMY* and *SRY*) clearly reflect the evolutionary trend of the Y for male-specific fitness and, thus, most resemble class 2 genes; in some rodents, *Sry* is multicopy[68], as are human class 2 genes and *RBMY*. Other class 3 genes, especially those that recombined recently, might still decay and join the ranks of evolutionarily informative — if functionally inert — NRY pseudogenes. Some such genes, however, might reflect the influence of additional evolutionary factors at work on the NRY. Here, within the broad context of mammalian Y history, we speculate on potential biological roles and evolutionary histories of the most intriguing class 3 genes.

MARSUPIAL
Non-placental mammal whose liveborn young suckle in maternal pouches.

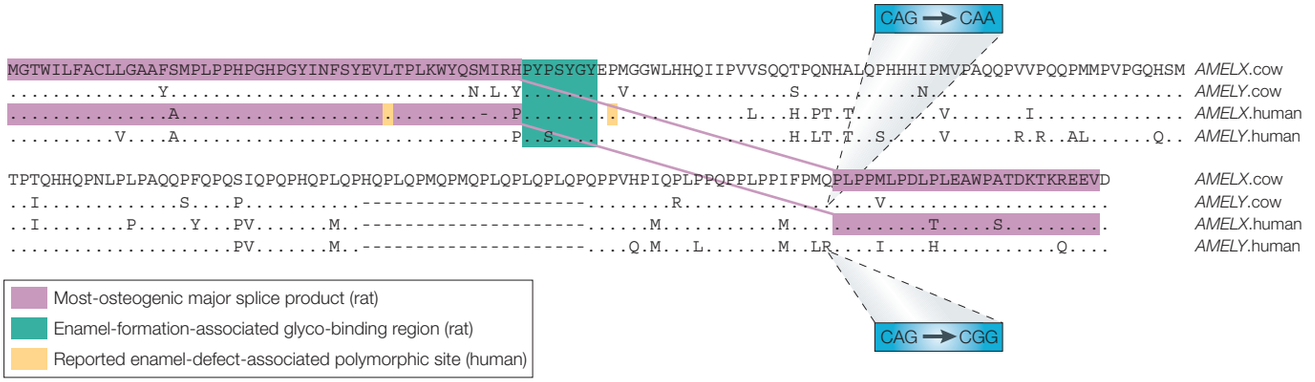

Figure 5 | **Amelogenin gene-splicing patterns.** Comparative alignment of cow X- (GenBank accession number M63499), cow Y- (M63500), human X- (M86932) and human Y- (M86933) chromosome-encoded amelogenins, excluding cow alternatively spliced exon 3 for simplicity. Dots indicate identity to cow X-derived sequence; hyphens indicate relative gaps. Purple regions, linked by lines to indicate mRNA splicing, are homologous to a highly osteogenic splice product in rat[88]. Blue boxes show inferred parallel mutations in the cow and human Y loci, which destroy an exonic splice site (ancestral CAG glutamine codon) that is crucial to the osteogenic transcript. Green regions (notably excluded from the osteogenic product) are homologous to the glyco-binding motif that is crucial for enamel formation in rat, as reported by Ravindranath *et al.* in REF. 110. Yellow sites have known variants associated with human X-linked enamel defects, as in REF. 75. Note that relative sequence similarities indicate that the cow and human *AMELY* (amelogenin Y) loci became non-recombining separately after cow–human divergence, consistent with the model posited in FIG. 3.

Amelogenin X/Y genes. Amelogenin proteins aggregate to scaffold the accretion of tooth enamel, which is the most densely mineralized vertebrate tissue[69,70]. Placental mammals express these proteins from an X locus and, in some taxa (for example, primate, cat, cow, deer and horse, but not murid or pig), more weakly from a Y locus[71–73]. In humans, some *AMELX* (but not *AMELY*) alleles reportedly segregate with enamel defects, although studies on the X inactivation status of the gene are inconclusive[74,75].

Given the expression profile of amelogenin, its active expression from Ys is puzzling. In the light of basic trends of Y-gene evolution, such conservation might reflect chance long-term persistence or, perhaps, adaptive evolution for some function specifically benefiting males. The latter possibility is particularly intriguing in the human case. Human *AMELX* and *AMELY* probably stopped recombining with each other between 30 and 50 million years ago — ample evolutionary time for Y-gene decay, as attested by the fact that all other known human X genes that ceased X–Y recombination during that time now lack active Y homologues[14]. Moreover, when aligned with one another, human *AMELX* and *AMELY* show, in addition to a single-codon gap, the most amino-acid replacements per synonymous nucleotide divergence of known human XY homologues, including those whose Y copies are pseudogenes. Likewise, partially sequenced deer amelogenin homologues show 3 frame-preserving gaps and 11 amino-acid differences, but no synonymous differences[76]. Such sequence divergence might be more consistent with differential adaptive protein evolution by the homologues than with chance persistence of functionally unconstrained *AMELY* loci.

If *AMELY* has persisted by adaptive evolution in the mode of other NRY genes, what male-specific benefit might it confer? Notably, to explain the evolution of genomic imprinting, David Haig, Laurence Hurst and others have modelled sexual antagonism as mediated through differences between maternal and paternal epigenetic regulation of early growth. They posit that promiscuous, nurturing mothers prefer (in the evolutionary sense) equitable offspring growth, whereas fathers prefer resource-intensive offspring growth at the expense of rival-fathered half-siblings[77,78]. Imprinting research has largely targeted systemic growth modifiers as candidates for such parental antagonism, but one could also predict localized processes such as mammalian tooth development as relevant to such conflict.

Namely, promiscuous mammal mothers might prefer relatively early teething of offspring in order to speed weaning and regain fertility. By contrast, fathers might prefer later teething, relative to other growth, in order to monopolize maternal resources. Indeed, first molar eruption age in HAPLORHINE primates reportedly correlates tightly with both weaning age and the inter-birth interval of the mother[79]. Furthermore, the delay typical of marsupial primary incisor eruption is widely deemed adaptive for prolonged suckling (K. Smith, personal communication).

Intriguingly, females in many primate populations teethe earlier overall than males[80–83] (albeit that females outpace males on other development fronts too). Moreover, there is anecdotal evidence of delayed tooth eruption in XYY males[84]. Such observations are grossly consistent with Y-linked tooth eruption delay, which might simply reflect systemic sex-differential growth. Alternatively, might *AMELY*, acting as a parentally antagonistic gene, delay male tooth eruption in at least some of the taxa that preserve it?

Yoh Iwasa, Hurst and others, have noted that sex-linkage, like imprinting, can mark alleles by parentage[85–87]. Although any inhibition of tooth eruption by *AMELY* would be manifest only in males, a Y harbouring such a parentally antagonistic gene would still be predicted to spread at the expense of other Y variants in some populations, perhaps as defined by the degree of POLYANDRY, distribution of litter size and other factors.

HAPLORHINE
A member of the clade comprising apes, monkeys and tarsiers only.

POLYANDRY
A population mating structure in which a female might mate with multiple males during her lifetime.

MEIOTIC DRIVE
Preferential transmission of one gamete genotype over another genotype, in which the genotypes in question might derive from the same meiosis.

But how might *AMELY* actively delay teething? Recent work shows that a well-attested short amelogenin splice product might strongly promote bone and/or cartilage growth, rather than enamel formation, indicating a previously unsuspected regulatory function for the gene[88]. Intriguingly, a splice junction crucial to this product has been eliminated by separate mutations in both the human and cow *AMELY* loci, leaving them able to encode only the long transcripts generally associated with enamel-forming, but not osteogenic, function (FIG. 5). Notably, regulatory signals from the enamel organ are implicated in the early stages of tooth eruption, which is thought to involve programmatic turnover in local bone and cartilage tissues[89]. These observations are consistent with, if not clearly supportive of, our speculation that *AMELY* of some mammals might have diverged in function from *AMELX* in a manner benefiting males through teething delay.

Rare human Y lineages that lack *AMELY* have been reported[90]. In the context of our model, it will be of great interest to learn more about tooth eruption timing in these lineages.

Variable charge X/Y genes. These genes are the only known active human XY homologues that are both expressed exclusively in the testis. They form a large family: two reported Y-linked loci, which encode identical proteins, and roughly a dozen X-linked loci, the protein products of which vary mainly in the tandem iteration of an acidic ten-amino-acid motif present singly in the Y homologues[13]. The predicted VCX/Y proteins are 125–206 amino acids long, with an invariant highly basic amino-terminal segment. So, with predicted isoelectric points ranging from 4.3 to 9.4, these proteins probably vary greatly in net charge at living pH, prompting their name: variable charge, X and Y[13].

Human *VCX/Y*-derived probes hybridize well only in anthropoids, among those mammals assayed. The gene family thus seems to have arisen recently and/or evolved rapidly in the anthropoid lineage[13]. The cellular function(s) of VCX and VCY proteins are unknown. But in size, absolute charge and superficial structural features, VCX and VCY resemble chromatin-associated proteins such as histones and protamines; the latter mediate condensed DNA packaging in sperm[52].

More strikingly, however, the testis-specific expression, multiple copies of sex-linked homologues, variable motif iteration and phylogenetic novelty of *VCX/Y* recall the fruitfly X-linked *Stellate* (*Ste*) and Y-linked *crystal* ((*Su*)*Ste*) loci[91]. These genes, confined to *Drosophila melanogaster* and close relatives, are contentiously viewed as MEIOTIC DRIVE antagonists, with *Stellate* expression putatively hindering transmission of Y-bearing sperm in a dosage-dependent manner and *crystal* expression putatively suppressing such bias[92–94]. Sex-chromosome drive is theoretically predicted to arise readily and is generally well attested in the heterogametic sexes of flies, lepidopterans, birds and mammals[95]. Such drive, however, carries an unusual cost in skewing the sex ratio; this is predicted to favour the genome-wide emergence of drive modifiers.

Human *VCX* copies cluster near the Xp telomere, in the X region that most recently ceased to recombine with the Y[14]. There, two *VCX* clusters flank the *STS* (steroid sulphatase) gene[96,97]. Deletion-induced *STS* deficiency, seen mostly in males as the skin anomaly called ichthyosis, might mark *VCX*-deficient individuals, because whole-gene deletions often reflect unbalanced recombination among flanking *VCX* repeat clusters[13,98,99]. If *VCX* acts analogously to *Stellate*, males should overabound among offspring of VCX^{-}/VCY^{+} men. Sex-ratio assessment in X-linked ichthyotic pedigrees might, therefore, reveal any resulting meiotic drive. Several such pedigrees are at least partially reported[98,100–102]. Interestingly, before knowledge of *VCX/Y*, there was speculation of male-bias among offspring of ichthyosis-carrier females[103] (rather than of affected males, as expected in spermatogenic X versus Y drive). However, such speculation was disputed on the grounds of male-biased ascertainment and reporting[102]. Perhaps more concerted study of *VCX/Y* will ultimately provide a new window on human sex-linked meiotic drive — a phenomenon so far only cursorily studied[103,104].

Protocadherin X/Y genes. The recently characterized hominid *PCDHX/Y* loci encode protocadherins expressed mainly in the brain[11,12]. The X- and Y-derived protein sequences have diverged slightly from one another and show different cellular expression distributions, leading Patricia Blanco *et al.* to suggest that *PCDHY* might have gained a male-specific function in brain morphogenesis[12]; the nature of such a hypothetical function is unclear, although large-scale sexual dimorphism of the adult human brain is well attested[105]. Alternatively, considering that the *PCDHY* region is thought to have transposed to the Y from the X only ~3–4 million years ago[106], the gene might simply be in an early stage of functional degeneration.

Conclusion

Theodosius Dobzhansky's claim that "nothing in biology makes sense except in the light of evolution" is a mantra of the field[107]. Viewed practically, it might be an overstatement: much coherent insight into the functioning of living systems has been gained without explicitly invoking evolutionary arguments. However, reference to evolution is crucial to a working understanding of Y functionality. As discussed here, gross classification of the genes of the human Y elucidates much of its unusual history. And in turn, such evolutionary insight helps to elucidate the functional ranges of the molecules that those genes encode.

Links

DATABASE LINKS *SYBL1* | *HSPRY3* | *SRY* | *SOX3* | *AMELY* | *PCDHY* | *AMELX* | *PCDHX* | *RBMY* | *VCY* | *RBMX* | *VCX* | *Zfy* | *Ube1y* | *Usp9y* | *CDY* | *DAZ* | *CDYL* | *DAZL* | Turner syndrome | male infertility | *SHOX* | AZF | *DBY* | *Stellate* | *crystal*

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