SEX CHROMOSOMES AND BRAIN GENDER

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Abstract | In birds and mammals, differences in development between the sexes arise from the differential actions of genes that are encoded on the sex chromosomes. These genes are differentially represented in the cells of males and females, and have been selected for sex-specific roles. The brain is a sexually dimorphic organ and is also shaped by sex-specific selection pressures. Genes on the sex chromosomes probably determine the gender (sexually dimorphic phenotype) of the brain in two ways: by acting on the gonads to induce sex differences in levels of gonadal secretions that have sex-specific effects on the brain, and by acting in the brain itself to differentiate XX and XY brain cells.

Differences between the brains of males and females have long been thought to be caused by differences in hormones secreted by the gonads of each sex[1,2]. In mammals, the fetal male's testes secrete testosterone, which acts on the brain to cause masculine patterns of development and to differentiate the brain from that of the female. The potency of these effects could give the impression that all meaningful sex differences in the brain, and in brain diseases, are induced by gonadal secretions. This viewpoint is unnecessarily restrictive if it inhibits consideration of other mechanisms that are known to operate in other organs or other animals. In this review, I attempt to place the sexual differentiation of the brain in the broader context of the evolution of the sex chromosomes, which are the ultimate origin of all sexually dimorphic signals in birds and mammals. This provides insights that are not offered by the classic dogma of gonadal dependence of brain sexual differentiation.

The sex chromosomes are unusual in that they are differentially represented in the two sexes and, therefore, have been subject to sex-specific evolutionary pressures[3]. These pressures favour X and Y genes that are sexually antagonistic — in other words, that are more adaptive in one sex than the other[4,5]. The implications of this sexual bias in X and Y genes are usually discussed with regard to the primary sex organs, the gonads[6]. The brain is also an important sex organ because it controls functions and behaviours that are advantageous in one sex but not the other, and contains structures that are adaptive mostly in one sex. What is the role of the sex chromosome genes in the sexual differentiation of the brain, and where do these genes act? Does the sex difference in the genetic constitution of brain cells lead to sex differences in adaptive brain functions? Alternatively, are the sex differences in the complement of genes maladaptive, thereby creating pressure to evolve sex-specific mechanisms to counteract them? To approach these questions, I discuss theories regarding the selection pressures on X and Y genes, and then summarize recent evidence on the role of sex chromosome genes in determining brain gender.

The evolution of sex chromosomes

In birds and mammals, the sex chromosomes differ in size and in the type of genes that they contain (FIG. 1). The human Y chromosome, for example, is about one-third of the size of the X chromosome, and Y-chromosome genes encode only 27 proteins, in contrast to about 1,500 proteins that are encoded by X-chromosome genes[7,8]. The tips of the human X and Y chromosomes, the pseudoautosomal regions (PARs), pair and recombine during meiosis, so that the X and Y PARs are fully homologous in gene content. The rest of the sex chromosomes, however, do not recombine and, therefore, have adopted separate evolutionary paths.

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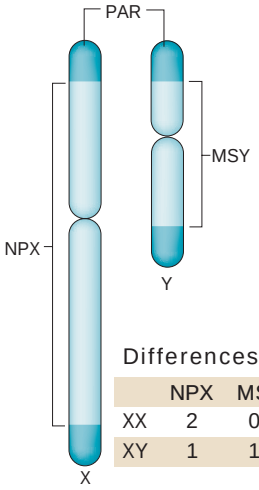
doi:10.1038/nrn1494



Differences between XY and XX

	NPX	MSY	PAR	Xp	X mosaic
XX	2	0	2	1	Yes
XY	1	1	2	0	No

Figure 1 | **Genetic differences between XX and XY cells.** At each end of the human X and Y chromosomes are the pseudoautosomal regions (PAR), which recombine during meiosis and therefore contain the same genes. The non-pseudosomal portion of the X (NPX) chromosome and male-specific portion of the Y (MSY) chromosome do not recombine with each other, and therefore contain genes that are no longer alleles. Sex differences between XX and XY organs arise because of differences in dosage of NPX and MSY genes, and because females but not males inherit the paternal X chromosome imprint (Xp). Sex differences are also created because XX organs are a mosaic of cells that express different alleles at polymorphic X loci, whereas XY organs are not mosaic for this reason (see FIG. 2).

Heteromorphic sex chromosomes in sexually reproducing organisms have evolved many times in response to similar selection pressures[9,10]. The triggering events seem to be mutations that cause a dominant sex-determining allele to emerge on an AUTOSOME. Early in the mammalian radiation, for example, mutations of the gene *Sox3* are thought to have produced a new gene, *Sry*, which forces the differentiation of testes rather than ovaries[3,11,12]. The chromosome that carried the new testis-determining gene would therefore have been restricted to males, an event that triggered a remarkable and inevitable change in the evolutionary pressures on that chromosome, the proto-Y, and its partner, the proto-X. Genes that were tightly linked to *Sry* would have been freed from any requirement to be adaptive in females, so that male-benefit sexually antagonistic alleles (good for males, bad for females) would be strongly selected[5,10,13]. Sexually antagonistic alleles produce sexual dimorphisms. The Y chromosomes of various species harbour genes that are essential for male functions such as spermatogenesis[14–16], supporting the conclusion that the proto-Y chromosome would have evolved clusters of genes that were important for males[6,7]. However, most Y-chromosome genes retain a high degree of homology with X-linked genes, forming X–Y gene pairs or 'partners'[17] — former alleles that no longer recombine. The maintenance of homology is evidence that the paired genes still have a similar function, and that expression of the Y gene balances the dosage difference in the X gene, which often escape inactivation (see below).

AUTOSOME
Any chromosome in a cell that is not a sex chromosome.

Male-specific pressures on the Y chromosome caused a region that was spatially linked to *Sry* to diverge from the X chromosome, leading to a loss of homology and recombination of those portions of the two chromosomes. The loss of recombination was important because it led to progressive degeneration of the Y chromosome and the subsequent evolution of dosage compensation of the X chromosome[10,17,18]. If a Y-linked gene was lost, pressure would have been created in males to upregulate the expression of the X partner gene, to keep the gene dosage at a functional level relative to autosomal genes with which it interacts. A counter-pressure would have been created for female-specific downregulation of gene expression to compensate for the double genomic dose of X genes in females. The need for dosage compensation of X-linked genes seems to be widespread among organisms, and diverse compensation mechanisms have evolved[19]. In mammals, one of the two X chromosomes is transcriptionally silenced, or inactivated, in each non-germline (somatic) cell[20]. The choice of which X chromosome to inactivate in each cell is random, so that females are a fine-grain mosaic of cells that express the alleles encoded on either X chromosome[21]. This mosaicism might itself lead to sex differences in tissue function, as discussed below (FIG. 2). 'X inactivation' is regulated according to developmental stage or tissue type[22–24], and some X genes escape inactivation[25,26]. The double genomic dose of such 'X escapees' could, therefore, cause constitutive sex differences in the expression of those genes[27]. Factors other than genomic dose might regulate expression of such genes, so the inevitability of sex differences in expression of X escapees is open to question.

The X chromosome, like the Y, is specialized for sex-specific functions because it is influenced by sex-specific selection pressures[28]. Male-benefit genes might be concentrated on the X chromosome because any recessive male-benefit allele will be expressed fully from the single X chromosome of males and be immediately available for strong selection, but will be rarely expressed in females if the locus is highly polymorphic[3,4,29,30]. Some evidence supports this predicted preference of male-benefit genes for the X chromosome[29,31]. Hemizygous exposure in males, together with female selection of intelligent males, has been used to explain the unusual concentration of genes that are required for brain function on the primate X chromosome[32]. However, other forces will tend to make the X chromosome enriched with female-benefit genes. X-chromosome genes spend twice as much of their evolutionary life in females as they do in males. So, alleles that are good for females might be favoured on the X chromosome if they are not very bad for males. In addition, genes that are good for males but bad for females could find it difficult to survive on the X chromosome. Diverse evidence from several species (humans, mice, *Drosophila melangaster* and *Caenorhabditis elegans*) suggests that male-biased genes (testis genes, or genes that are expressed more strongly in males) are under-represented on the X chromosome, whereas ovary- and placenta-enriched genes are over-represented[29,33–37]. So, the X chromosome has a sexual bias in gene content, but in specific instances the bias can favour genes that benefit either sex[29].

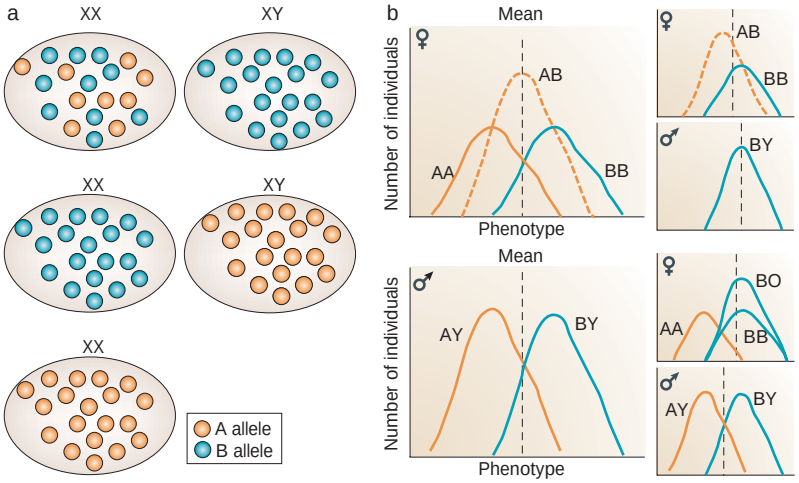


Figure 2 | **The implications of X mosaicism for brain gender.** Diagrams show the theoretical effect of X mosaicism on sexual dimorphism when X loci are highly polymorphic. The illustrations show a case in which only two alleles are present in the population, but the sex difference is more pronounced if the locus has numerous alleles. **a** | In females, organs are a mosaic of cells that express either allele (heterozygote, top XX diagram), or a single allele (homozygous, middle and bottom XX diagrams). By contrast, males will be hemizygous for either allele. **b** | Left, the distribution of phenotypes in a population of females and males caused by the X-linked trait, assuming some variability of phenotype for each X allele (A and B). If the effects of two alleles are averaged in females, the male population will be more variable than that of females, but will have the same mean. Upper right, if the A allele is lethal, males that are hemizygous for A will be removed from the population, as will homozygous AA females, resulting in a mean difference in the trait (as occurs in Rett syndrome[62]). Lower right, if the A allele is not lethal but A cells cannot compete against B cells during development, AB heterozygous females will express the B allele exclusively (BO), causing a sex difference in the phenotypic mean.

Are genes that are required for brain function in one sex also concentrated differentially on the sex chromosomes and, if so, how might they influence brain development? In a sexually reproducing species with heteromorphic sex chromosomes, the male must evolve male-specific neural mechanisms to produce and deliver sperm, whereas the female must evolve the means by which to produce eggs and receive sperm. For optimal reproduction in a complex vertebrate, sex differences in the brain are required to coordinate the exchange of gametes (pair-bonding, courtship and copulation), and to engage in sex-specific territoriality, aggression, parental care, sociality and cognition. The concepts discussed above suggest that the genes that control such sexual dimorphisms in the brain would be enriched on the sex chromosomes.

XX versus XY organs. The genetic differences between XX and XY cells and organs stem from the presence or absence of Y genes, and from X gene dosage, mosaicism and parental imprint[38] (FIG. 1). The Y gene that has the strongest masculinizing effect on the brain is *Sry*. This gene causes testicular development and the consequent production of high levels of testosterone, which causes permanent masculinization during brain development and reversible masculinization of male functions in adulthood[1,2]. Male mice that differ only in the strain origin of their Y chromosome have different levels of testosterone in their blood[39,40], suggesting that Y alleles (*Sry* or others) also modulate testosterone levels. Male mice with different Y chromosomes also show large differences in offensive aggression, possibly because of direct effects of Y-linked genes on the brain, although effects that are mediated by strain differences in testosterone are difficult to exclude[41–45]. At least eight Y-linked genes are expressed in the mouse brain[27], including *Sry* itself [46–50]. The male-specific effects of Y gene expression are reduced by the expression of a functionally similar X partner gene[27,51,52]. In some cases, however, the X–Y gene pairs can be differentially regulated, causing an imbalance of X and Y gene products between the sexes[27,53]. Also, the small number of Y genes in many mammals reduces the number of possible male-specific effects of Y genes.

A potentially larger constitutive genetic difference between XX and XY cells involves X-linked genes. X inactivation might eliminate sex differences in X-linked gene expression caused by differences in genomic dose, because both male and female cells would express a single dose of X genes. However, several important sex differences probably persist. The first and most obvious difference is that because X inactivation is incomplete and varies according to tissue type and developmental stage[22,23,25], genes that escape inactivation can be expressed at a higher level in females[26,27]. Second, the mosaicism of expression of inactivated X-linked genes leads to sex differences in organ function if the X gene is polymorphic (FIG. 2). In that case, the female's tissues, including the brain, are typically a mosaic of cells in which different X alleles are expressed, whereas the male's tissues express a single variant at each locus. A good example of a sex difference created by X mosaicism is the retinal spectral sensitivity of new world primates[54–59]. Two opsin genes encode visual pigments in the retina, determining the range of wavelengths that is detected by cone photoreceptors. One gene is autosomal and the other is X-linked. Because the X gene is polymorphic, females are often heterozygous at that locus and, therefore, are trichromatic (one autosomal and two X-encoded alleles), whereas males are always dichromatic. A similar polymorphism in humans apparently leads to sex differences in colour perception[60]. Importantly, the X locus polymorphism seems to have been maintained throughout millions of years of new world primate evolution, across several species, indicating that the polymorphism is adaptive. Although the reason for this is not clear, the favoured explanation is not based on a female-specific selection pressure, but rather that trichromacy leads to superior foraging ability[58]. In this case, a functional sex difference seems to be a by-product of X inactivation coupled to gene polymorphism that is maintained by forces that are not sex-specific.

An unusually large number of X-linked genes are involved with brain development and function[32], so mosaicism of polymorphic X alleles could contribute to sex differences in brain function. Female brains are a mosaic of cells expressing alternate alleles at polymorphic loci, so that the differences in effects of various alleles are blunted (FIG. 2b). Males, on the other hand, express the single hemizygous allele, and as a group will

have more variable brain phenotypes[59]. For example, the reported higher variance among males in tests of mental function can be explained by the mosaicism of polymorphic X-linked brain alleles in females[32,61]. However, such mosaicism could cause sex differences not only in the variance of brain traits, but also in the mean of traits. If males are more variable than females because of X-linkage, and one of the two population extremes is removed, then the trait mean for males and females will differ (FIG. 2b). Such an interaction explains the sex difference in Rett syndrome, a form of severe mental retardation that occurs almost exclusively in females[62]. Rett syndrome results from deleterious mutations in the X-linked gene *MECP2*. The mutations are lethal in hemizygous males but not in females, owing to the protection that is offered by the proportion of female cells that express the non-mutated allele. In other cases, a dysfunctional X allele might not be lethal by itself, but could merely place cells carrying the allele at a competitive disadvantage so that cells that express the disadvantageous allele in females will be differentially lost during development (FIG. 2b). So, the allele would be under-represented in females relative to males, leading to an average sex difference in traits that are influenced by the gene.

A third difference between XX and XY cells arises from imprinting — differential expression of either the maternal or the paternal allele of a given gene. Males exclusively inherit X genes with a maternal genomic imprint, whereas females have cells containing both the maternal and paternal imprint on X genes (FIG. 1). Although it is currently not clear which X genes receive such a parental imprint, evidence indicates that there is a parental imprint and that this influences somatic phenotype. For example, XO embryos that receive the X chromosome from the father are delayed in their development relative to XO embryos that receive the maternal X chromosome[63].

Developmental mechanisms

The evolutionary concepts discussed above do not specify the molecules or developmental mechanisms that lead to sex differences in the brain. If male-benefit genes accumulate on the Y chromosome, for example, and favour the development of male-specific brain functions, evolutionary theory does not predict the mechanisms by which these genes act, merely that they act in a male-specific fashion. There are two main mechanisms available. Either the gene acts in brain cells to alter brain phenotype, or it acts on another tissue that in turn induces sex differences in the brain. The most likely non-brain site of action is the gonads. In mammals, once the testes have differentiated by the action of *Sry*, they secrete testosterone, which makes non-gonadal tissues more masculine in their functions[64,65]. For example, the penis and scrotum, and neural systems that innervate them, differentiate because of the direct action of androgens on perineal tissues[66]. Testosterone, and/or its metabolite oestradiol, also act directly on the brain to induce permanent masculine differentiation of neural circuits. Later in life, for example during puberty and in adulthood, sex differences in gonadal hormones contribute to sex differences in brain function. The effects of gonadal hormones are profound and probably constitute the main, or for some dimorphisms the only, mechanism by which sex differences occur in the brain[64]. For example, in specific cases a neural phenotype is masculinized completely by giving XX females testosterone, or de-masculinized completely by blocking the action of testosterone in XY males. In those cases, the genetic difference between XX and XY brain cells does not seem to interfere with the dominant masculinizing effects of testosterone or its metabolites. However, most sex differences in the brain have not been carefully studied, and in cases that have been studied, the potent effects of gonadal hormones do not rule out a minor role for other factors.

A brain site of X or Y gene action?

To what extent do X and Y genes act not only on the gonads, but also on the brain, to cause sex differences? To answer this question, it becomes important to measure the phenotype of individuals that differ in the complement or dose of X and Y genes. To isolate the direct actions of sex chromosome genes on the brain from the indirect actions that are mediated by gonadal secretions, the strategy is either to measure neural phenotype before gonadal hormones become effective, or to make gonadal secretions identical in animals that differ in their complement of sex chromosomes. However, identical hormonal levels are difficult to achieve in practice.

Sex chromosomes induce sex differences in various organs before the gonads begin to secrete steroid hormones. In several mammalian species, male embryos are larger than female embryos, and in mice both X and Y genes contribute to the sex difference[63,67,68]. In the wallaby, X-linked genes cause genitalia (scrotum, mammary tissue, pouch) to differentiate before the gonads[69,70]. Sex differences in gene expression are detected in the embryonic mouse brain before the gonads differentiate[71]. In all of these cases, the sex differences occur before the initial stages of gonadal differentiation, including the differentiation of the hormone-secreting cells of the testes. So, these examples cannot be explained as a result of gonadal hormone action. When mesencephalic or diencephalic cells are cultured from rat or mouse embryos, the XX and XY cultures show differences in phenotype. In this case, the cells are harvested from the embryos after testicular differentiation but before the testes are thought to secrete high levels of testosterone, so the difference is attributed to an effect of the sex chromosomes in the brain[72,73] (FIG. 3). Null mutations of the tumour suppressor gene *p53* (*Trp53*) in mice cause failure of neural tube closure before gonadal differentiation. The mutation differentially affects females, suggesting that neural tube closure is different in XX and XY brains, an idea that might provide a clue to explain the higher incidence of neural tube closure defects in female humans[74–77]. Questions for future study include whether these pre-gonadal differences in XX and XY brains influence the later development of brain function, and how these differences interact with the large sex-specific effects of gonadal steroids.

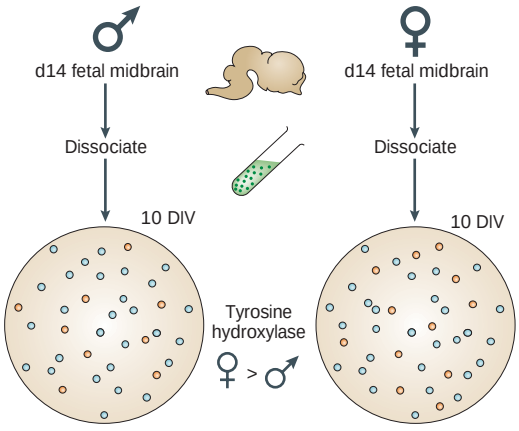


Figure 3 | **Sex chromosome effect on dopamine neurons.** When rat fetal cells are harvested from embryonic midbrain and plated out as dissociated cell cultures, XX cultures develop more tyrosine hydroxylase-positive (dopaminergic) neurons than XY cultures. The cells are removed from the fetus before the testes produce large amounts of testosterone, so the sex difference is attributed to brain-autonomous factors encoded by the sex chromosomes[72,73]. A similar difference in mice is also attributed to a difference in sex chromosome complement[83]. d14, day 14 ; DIV, days *in vitro*.

Another approach to the study of sex chromosome effects has been to manipulate the complement of sex chromosomes in mice of the same gonadal type. For example, mice with Y chromosomes that lack the testis-determining gene *Sry* develop ovaries[78]. If a functional *Sry* transgene is added back onto an autosome, the male is reconstituted (XY$^-$*Sry*) but *Sry* is no longer Y-linked[79]. Mating XY$^-$*Sry* males with XX females produces two types of male (with sex defined by gonadal type), XY$^-$*Sry* and XX*Sry*, and two types of female, XY$^-$ and XX. This makes it possible to assess the effects of the sex chromosomes in mice with either ovarian or testicular hormones[38]. To remove the sexually dimorphic effects of gonadal secretions in adults, the four genotypes can be studied in gonadectomized adult mice that have been treated equally with testosterone[80,81], or in neonatal mice[82]. Mice with testes are generally more masculine in many traits (male copulatory behaviour, social exploration, and structure of specific regions of the hypothalamus, cortex and spinal cord) than mice with ovaries, independent of their sex chromosome complement. This confirms the long-standing idea that sex differences in brain and behaviour are induced by gonadal secretions. However, in the lateral septum of adult mice, XY$^-$*Sry* and XX*Sry* males have different numbers of vasopressinergic fibres, and a similar difference was found in XX and XY$^-$ females[80]. This difference is attributable to the difference in sex chromosome complement in these animals. The results do not exclude the possibility that the sex chromosome effect is mediated by differences in gonadal secretions between XX and XY animals of either sex. However, such a gonadal explanation seems unlikely because higher androgen levels, for example, in XY animals would have caused a group difference in several of the hormone-sensitive sexual dimorphisms measured.

XX and XY brain cells also seem to behave differently *in vitro*. When mesencephalic cells harvested from embryonic day 14 mouse embryos are dissociated in cell culture, the XY cultures develop more dopamine neurons than the XX cultures, independent of the gonadal type of the embryo[83] (FIG. 3). In this case the effect cannot be explained by group differences in gonadal secretions, because XY$^-$ cultures derived from females are more masculine than XX*Sry* cultures derived from males. It is not yet known whether the sex chromosome effect can also be detected in dopamine neurons *in vivo*.

In some studies, only the number of X chromosomes has been manipulated. For example, female mice with a single X chromosome (XO) are more fearful than XX females during specific behavioural tests, a difference that is ascribed to haploinsufficiency of an X-linked gene[84]. Although a neural site of action of the X-linked gene has not been established, this result supports the importance of X-linked-gene dosage in brain function, and raises the possibility that this contributes to sex differences in the brain.

Studies in birds. Like mammals, birds have sex chromosomes that differ greatly in size, but in this case females are heterogametic (ZW) and males are homogametic (ZZ). The small W chromosome is similarly thought to have evolved when its genes became female-determining. Several W-linked genes are interesting candidates for an ovary-determining gene, but none has been proven to carry out that role[85–89]. Some evidence also points to a testis-determining role for Z genes[90,91]. The mechanism, if any, for dosage compensation in birds has also not been resolved[86,92–94], and some Z genes are expressed at a higher level in the brains of males than females[53,95]. Moreover, some W genes are expressed only in the brains of females[95]. So, sex differences in the expression of W or Z genes could cause sex differences in brain phenotype

In birds, two sex differences in the brain are attributed to the direct action of sex chromosome-linked genes. The most studied is the sex difference in the neural song circuit of zebra finches[64,96]. Males, but not females, sing a courtship song, and the forebrain neural song circuit is much larger in males than in females. Because most sex differences in the brain are attributed to the action of gonadal hormones, researchers have attempted to sex-reverse the song-system phenotype by giving male hormones to females, or by blocking testicular hormones in males. These experiments have been unable to cause complete sex reversal, although treating females with oestradiol causes marked (but partial) masculinization of the song circuit morphology, resulting in these females singing. Manipulations of steroid hormone action in males have not caused large changes in sexual phenotype[97–101], leaving open the possibility that other agents cause sexual differentiation. The song circuit is feminine in genetic females that have significant amounts of testicular tissue, which is induced to develop by pharmacological treatments that also block ovarian development[96,102]. These experiments suggest that ovarian secretions are not required for the

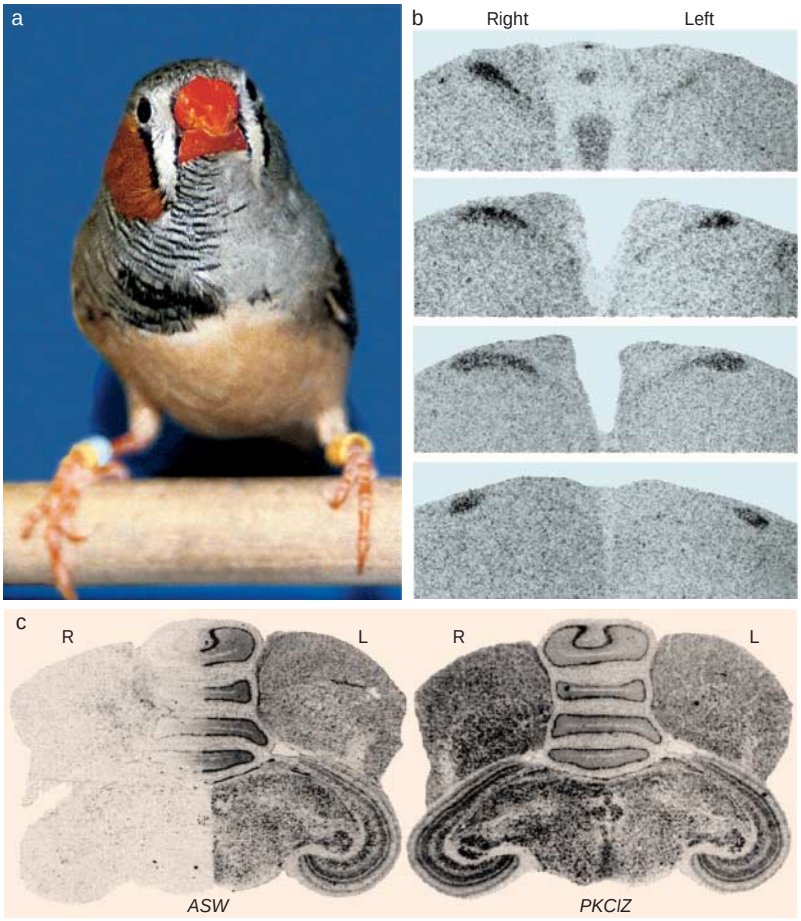


Figure 4 | **The case of the half-male, half-female finch.** Observations of a single gynandromorphic zebra finch lend credence to the view that adaptive sex differences can be caused by the direct action of sex chromosome genes in brain cells[94]. **a** | The zebra finch had male plumage (black breast stripes and bar, brown cheek patch) and a testis on the right side, and grey female plumage and an ovary on the left. Genetic tests showed that W-linked genes, normally only present in females, were higher on the left. **b** | The song nucleus HVC, marked by *in situ* hybridization for androgen receptor, was larger on the right side than on the left. The lateral difference in brain sexual phenotype is attributed to genetic differences between the two sides. **c** | *In situ* hybridization showed that the W-linked *ASW* gene (left), normally expressed only in the female brain, was expressed predominantly on the left half of the brain (dark areas). A sharp line in the middle divided the level of expression in the two halves of the brain. The Z-linked gene *PKCIZ* (right) was expressed more on the right than the left side of the brain, a difference normally found in ZZ males compared with ZW females. Reproduced, with permission, from REF. 95 © (2003) National Academy of Sciences USA.

feminine development of this circuit, and that testicular hormones are not sufficient to induce masculine brain differentiation in genetic females.

The study of a single, lateral GYNANDROMORPHIC finch supports a role for the genetic sex of brain cells in determining the sexual phenotype of this system[95] (FIG. 4). This animal had male plumage on the right side of the bird and female plumage on the left, sharply dividing the animal along the midline. On the right side was a testis, and on the left an ovary, suggesting that the genetic mechanisms that control gonadal development were also lateralized. Genetic tests showed that W-linked genes were present in the genome on the left side more than on the right. In the brain, the W-linked genes were expressed at a high level on the left and a low level on the right, again sharply dividing the brain down the middle (FIG. 4). The song circuit was more masculine on the right side, a difference that is attributed to the lateral genetic difference in sex chromosome genes, rather than to the levels of gonadal hormones, which would have influenced both sides equally (FIG. 4). However, the left (genetically female) song circuit was larger than in normal females, suggesting that a factor from the genetically male side, perhaps hormonal, partially masculinized the female side. Oestradiol, which is known to be a masculinizing agent in this system, might be secreted at a higher level in the male forebrain[99], so that the masculinizing signal could have been a sex steroid derived from the brain itself [103]. (A similar sexually dimorphic neural synthesis of oestradiol might contribute to sex differences in the rodent hippocampus[104–107].) If the brain in males is normally the source of a hormonal masculinizing signal, then production of the signal must be sexually differentiated. In zebra finches, this differentiation occurs presumably by the sex-specific action of Z or W genes.

The genetic sex of brain cells might also contribute to sexual differentiation in the quail[108]. Male-to-female and female-to-male transplantation of embryonic brain tissue in quail do not have equivalent effects. Genetic males with female brain tissue do not develop normal gonads, suggesting that a genetically male brain is required for normal gonadal development.

Summary and conclusions

Genes that are found on the sex chromosomes influence sexually dimorphic brain development both by causing sex differences in gonadal secretions and by acting in brain cells themselves to differentiate XX and XY brains. Because it is easier to manipulate hormone levels than the expression of sex chromosome genes, the effects of hormones have been studied much more extensively, and are much better understood, than the direct actions in the brain of sex chromosome genes. Although the differentiating effects of gonadal secretions seem to be dominant, the theories and findings discussed above support the idea that sex differences in neural expression of X and Y genes significantly contribute to sex differences in brain functions and disease.

All of the sexually dimorphic signals, whether gonadal or brain-autonomous, are likely to induce sex differences in cellular functions that are adaptive in one organ or at one point of development, but maladaptive in another context[109]. Any maladaptive sex differences that arise will create a sex-specific pressure to compensate for sex differences in the brain. For example, the evolution of X inactivation is a female-specific response to the maladaptive sex differences in gene dosage that arose because of male-specific adaptive changes in the Y chromosome. Alternatively, a sex difference created as a by-product of inevitable mosaicism of X gene expression might have negative adaptive value, and could favour the evolution of sex-specific mechanisms to counteract it. So, in some cases, sex differences caused by gonadal hormonal effects on the brain or by the direct action of sex chromosome

GYNANDROMPORPHIC
Having both male and female morphological characteristics.

genes in the brain might compensate for other sex differences rather than creating adaptive sex differences themselves[109].

Many neurological and psychiatric diseases differ in incidence or severity between the sexes. Some of these diseases are known to involve X-linked genes[32]. The vulnerability of males to mutations of X-linked genes is an obvious source of sex differences in diseases. However, more subtle variation of the same loci probably accounts for some of the differences in psychological and neural function among populations of males and females. Recent improvements in methods to manipulate and measure gene action will lead to further insights on the role of X and Y genes in brain gender.

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Acknowledgements

Thanks to Paul Burgoyne, Geert De Vries, Emilie Rissman, Robin Lovell-Badge, Amanda Swain, Eric Vilain, Robert Agate, Jun Xu, Xuqi Chen, Yuichiro Itoh, Barbara Finlay, Andrew Sinclair and Jennifer Graves for discussions of the ideas summarized here. Supported by the National Institutes of Health.

Competing interests statement

The author declares no competing financial interests.

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