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The Genetic Basis for Sex Differences in Human Behaviour: Role of the Sex Chromosomes

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Summary

The nature of the mechanisms underlying observed sex differences in human behaviour continues to be debated. This review concentrates on the thesis that genes on the sex chromosomes other than those directly controlling sex determination, and whose functions are, at least in part, independent from hormonal influences, play a significant role in determining gender differences in behaviour. To provide an adequate basis for examining this issue, the current understanding of the nature of sex determination, differences in behaviour and the influences of sex hormones are evaluated. The possible contribution to behavioural differences of those X-linked genes which escape inactivation, or which may be subjected to imprinting, is discussed. The review concludes with a summary of the genetic basis for two sexually disparate types of behaviour.

Introduction

That human males and females tend to behave differently is an undeniable fact, and indeed a welcome one. It is also generally recognised that both nature and nurture make profound contributions to this divergence, and attempts to unravel their interaction have formed the basis for an extensive literature. In this review, we have focused on evaluating the roles of the human X and Y chromosomes in conferring such sex differences. Although we will concentrate on proximal events and processes, we will also, inevitably, consider some of the downstream consequences of these.

Although a significant proportion of all human genes are expressed at elevated levels solely in the brain (e.g. Saito-Hisaminato *et al*. 2002), the direct influence of genetics on brain development and behaviour is currently poorly understood. Genes are likely to be involved in determining the pattern of neural formation in the brain throughout development, with differing patterns of expression predisposing an area of the brain to respond to certain tasks, rather than directly coding for task-specific products; but their potential for influencing behaviour is unequivocal.

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Behavioural Sex Differences: Societal Stereotypes or Biologically Based?

It can be argued that many of the perceptions regarding sex differences in behaviour are heavily influenced by stereotypes that are, in the main, unfounded. Nevertheless, considerable evidence has amassed to show that such stereotypes may be based upon genuine disparities between male and female cognition and behaviour, which can be measured empirically. Indeed, it would be remarkable if the obvious anatomical and physiological dichotomy between the sexes arising from evolutionary sexual selection wasn't paralleled, at least to some extent, at the behavioural level. There are, of course, huge variations in the traits of individuals *within* each sex, and many cases of overlap *between* the sexes. Yet studies have shown differences between the sex averages for many characteristics, including the risk for specific psychiatric disorders.

In terms of behavioural and cognitive differences in the normal population, it has repeatedly been

reported that females perform better than males in various tasks that assess verbal skills such as word learning and memory (e.g. Fenson *et al*. 1994; Kramer *et al*. 1997). In terms of academic achievement, international education figures from 43 developed countries, published by the Organisation for Economic Co-operation and Development in 2003, showed a consistent picture of women achieving better results than men at every level, particularly in literacy assessments (see http://www.standards.dfes.gov.uk/ and http://www.oecd.org/home/ for recent statistics). Females are also consistently found to be superior to males in tests of social skills, again from an early age (e.g. Dunn *et al*. 1991). They show, for example, more empathy, sensitivity to facial expressions, and more highly developed theory of mind (see Baron-Cohen, 2002, for review).

In contrast, males tend to perform better than females in tasks requiring some sorts of spatial skills, and more generally, they have a greater ability to 'systemise'. Baron-Cohen (2002) introduces this term to encompass all situations in which prediction and control of a system enable superior performance. Males generally obtain higher scores on tests in engineering and physics, although academically females have closed the gap in achievement even in these subjects over recent years. Males achieve greater success than females in construction tasks, the Embedded Figures task, map reading and other activities involving consideration of an 'input-operation-output' process (e.g. Galea & Kimura, 1993; Geary, 1996; Kimura, 1999). An interesting blurring of this simplistic distinction that is often drawn between male-typical and female-typical skills is the fact that women are, in fact, better at some spatial tasks than men. As Voltaire declared 'I hate women because they always know where things are'. That is, females generally have a superior memory for objects, locations and landmarks than males, performing 60-70% better in tasks set by Silverman & Eals (1992).

Males are widely acknowledged to show more physical aggression than females, and have also been found to display higher rates of risk-taking and sensation-seeking behaviour (e.g. Rosenblitt *et al*. 2001). In recent USA crime statistics, males were 10 times more likely than females to commit murder, and over 5 times as likely to be under 'correctional supervision' for criminal offences (see http://www.ojp.usdoj.gov/bjs/).

There are also significant differences between the sexes in the incidence and features of many psychiatric disorders. Unipolar depression, anxiety, eating disorders, panic disorder and phobias are all more frequently reported in women. Alcohol dependence, autism spectrum disorders, antisocial personality disorder, attention deficit and hyperactivity disorder (ADHD), and mental retardation are all more common in males (Sikich & Todd, 1988).

Reasons for such differences in behaviour and cognition are still under active investigation, however, and are likely to be numerous and varied, involving both genetic and environmental factors. In order to explore the issues cogently, it is fundamentally important to recognise that there are evolutionary forces driving the genetic mechanisms and biological substrates that are involved in sexual differentiation and behavioural dimorphism.

Structural Studies of the Brain Support a Biological Basis for Behavioural Differences

At the gross level, the brain, both in terms of its size and structure, is highly dimorphic between the sexes. The average male brain weighs around 11% more, and this difference remains significant when controlling for males' overall greater physical size (see Swaab & Hofman, 1984). The female brain is not, however, simply a downsized version of the male brain – the volumes of specific regions, relative to the cerebrum, are known to differ between males and females. For instance, the volumes of the frontal and medial paralimbic cortices are larger in women; the fronto-medial cortex, amygdala and hypothalamus, on the other hand, are larger in men (e.g. see Witleson, 1991). The difference in size can be substantial – the 3rd interstitial nucleus of the anterior hypothalamus, INAH3, a cell group in the medial preoptic region of the hypothalamus, is three times larger in males, for example (LeVay, 1991).

There is also evidence for sexual dimorphisms in regions that affect cognitive function. Results have suggested that females have proportionally larger Wernicke and Broca language-associated regions compared with males; these anatomical differences may correlate with the superior language skills demonstrated by females (Paus *et al*. 1996). This result is consistent with imaging studies reporting that female brains contain significantly

more grey matter than male brains in a language-related cortical region in the cerebral cortex (Schlaepfer *et al*. 1995) and recent imaging studies have further suggested sex differences in cerebral development and function in adolescence (Yurgelun-Todd *et al*. 2002). Other areas known to diverge include the suprachiasmatic nucleus of the hypothalamus, the massa intermedia and certain regions of the neocortex (Witelson, 1991). There are also notable sexually dimorphic patterns in the vasopressin innervation of the brain, which may or may not promote sex differences in behaviour (see DeVries & Boyle, 1998 for discussion).

The most significant sexual dimorphism of the human brain, however, appears to relate to brain lateralisation and cerebral dominance. It is now widely accepted that the two hemispheres are more asymmetrically organised for speech and spatial functions in men than in women; this may account for some sexual dimorphisms in cognitive functions (e.g. Johnson *et al*. 2002). Damage to one brain hemisphere has sometimes had a lesser effect in women than a comparable injury has in men. For instance, Kimura & Harshman (1984) found that verbal tasks such as vocabulary and digit span (both involving verbal memory) were impaired by both left- and right-hemisphere damage in females, but only by left-hemisphere damage in males, suggesting more bilateral organisation of the relevant functions in females. Furthermore, whereas aphasic speech disorders occur most often in women when damage is to the front of the brain, this is true for men when the posterior of the brain is damaged (e.g. see Kimura, 1992). Perceptual techniques that probe for brain asymmetry sometimes show smaller asymmetries in women. Such functional asymmetry could partly be explained by claims that parts of the corpus callosum, a major neural system that connects the two hemispheres, may be more extensive in women with potentially more connective fibres and hence more inter-hemispheric communication (Holloway *et al*. 1993).

Taken altogether, the evidence suggests that men's and women's brain develoment follows significantly different trajectories from very early in life. During development, sex hormones may direct such differentiation (Kimura, 1992), and this is discussed in detail later; however, genetic, non-hormonal signals may also trigger specific examples of sexual differentiation of the brain (Arnold, 1996). This thesis is supported bytwo arguments: firstly, direct genetic control of sexual differentiation in behaviour may be as likely to evolve as hormonal control; secondly, neural and non-neural sexual dimorphisms have been reported that are not well explained by classical theories of steroid-dependent sexual differentiation (e.g. Beyer *et al*. 1992).

Primary Roles of Sex Chromosomal Genes in Determining Sex

It is a well-established fact that the complement of sex chromosomes is the primary source of sex-specific variation in genomic sequence. The Y chromosome is only around 65Mb long and represents less than 2% of the haploid genome. It has two pseudoautosomal regions at either end (PAR1 at Ypter and PAR2 at Yqter), within which exist about a dozen genes, mostly within PAR1. These PARs allow localised recombination to take place between the X and Y chromosomes during meiosis. Between them is the region previously designated as the non-recombining region of the Y (NRY). Recent evidence, however, suggests that extensive gene conversion occurs between the lengthy palindromes that exist in this segment and, to reflect this, it is now referred to as the male-specific region, MSR (Rozen *et al*. 2003; Skaletsky *et al*. 2003). The unique properties of the Y chromosome and the discovery of many new Y-polymorphic markers have combined to provide a powerful tool for investigating human evolution (e.g. see Jobling & Tyler-Smith, 2003). The euchromatic segment of the MSR comprises only about 23Mb, and embraces 78 protein-coding units for 27 distinct proteins or protein families representing fewer than 40 genes. In some XX male sexual dysgenics, illegitimate pairing occurs in the paternal meiosis between the MSR and the X (usually the short arm), sometimes involving exchange between homologous sequences proximal to the PAR boundary, such as the protein kinase genes (*PRKX* and *PRKY*), or between *Alu* repeats. The consequence of such exchanges is that a section of the non-autosomal region of the Y chromosome is transferred to the X chromosome (e.g. Schiebel *et al*. 1997). Studies of such individuals allowed the presumptive 'testis determining factor' (TDF) to be localised to a highly conserved 35kb region adjacent to

PAR1. The locus responsible is now known as the sex-determining region of the Y, *SRY*, first described by Sinclair *et al*. (1990).

In mice, conclusive evidence for the role of the *Sry* locus was provided by the demonstration that it induced sex reversal when introduced, via oocyte injection, to an XX embryo (Koopman *et al*. 1991), and that it has both the spatial and temporal expression consistent with its identity as the TDF (e.g. McLaren, 1998). The expression of *SRY*, in a normal male, stimulates the undifferentiated gonad, containing both Mullerian and Wolffian ducts, to develop into the testis. Within the Wolffian ducts, the Sertoli cells are stimulated to secrete Anti-Mullerian hormone (*AMH*), which causes the Mullerian duct to regress, while the Leydig cells are stimulated to secrete testosterone. This combination of events results in the development of the male phenotype. It has been proposed that the autonomous entry of germ cells into meiosis initiates the default ovarian pathway and blocks testis development, whereas *SRY* expression opposes this pathway by initiating testis cord formation prior to meiosis, which sequesters germ cells inside cords and arrests them in meiosis (Yao *et al*. 2002). If, however, *SRY* is not present, *DAX1* (a testis-expressed nuclear receptor) expression silences the male pathway genes leading to ovary differentiation and inducement of the female phenotype by female pathway genes (Bardoni *et al*. 1994). A duplication of *Dax1* on an active female X chromosome has been known to override male development even in the presence of *Sry* (Swain *et al*. 1998). Nevertheless, under normal conditions, the presence of SRY initiates the development of the male phenotype (See Figure 1).

Current evidence has implicated a range of other genes in a complex sex determination cascade, with expression levels of *SOX9* (chromosome 17), *SF1* (steroidogenic factor1; chromosome 9), *WT1* (Wilm's tumor 1; chromosome 11), *WNT4* (wingless gene family member 4; chromosome 1), and *AMH* (anti-Mullerian hormone; chromosome 19) also contributing to the sex determination pathway (e.g. see Luo *et al*. 1994; Morohashi *et al*. 2000; Nachtigal *et al*. 1998; Jordan *et al*. 2001; Mishina *et al*. 1996). *DMRT1* (Doublesex and MAB-3 related transcription factor 1; chromosome 9) is another autosomal gene that appears to be involved in testis differentiation – this is indicated by 46XY patients who have gonadal dysgenesis caused by a deletion of the area of the short arm of the chromosome harbouring this gene (as well as the nearby *DMRT2* gene) (Raymond *et al*. 1999). The *DMRT1* locus is of special interest, however, because it shows sexually dimorphic expression during the embryogenesis of mammals, birds and a reptile (*Alligator mississippiensis*). Furthermore, *Drosophila* and *C.elegans* also have related genes that play a role in their sexual development, leading Smith *et al*. (1999) to conclude that *DMRT1* represents an ancient and highly conserved component of vertebrate and invertebrate sexual determination.

It seems probable that, in mammals, the sex chromosomes arose initially through the emergence of a dominant, and penetrant, sex-determining allele of the proto *SRY* gene, catalysing extensive evolutionary divergence. The X-linked *SOX3* locus is thought to represent the ancestral gene from which *SRY* was derived (Foster & Graves, 1994). Molecular analysis suggests that the Y chromosome lost the ability to recombine with the X in a step-wise fashion, as a result of a series of inversions dating from about 300 million years ago (Lahn & Page, 1999). These events will have served to isolate wide regions of the chromosome from exchange with the rest of the genome via recombination.

This halting of recombination removes a key mechanism for maintaining the integrity of the chromosome, rendering genes in non-recombining regions liable to accumulate destructive mutations, whose potential defects are sheltered by intact X-homologues and hence not selectively expelled (Charlesworth, 1978, 1996). 'Muller's Ratchet' theorises that such neutral or slightly detrimental events can be incrementally fixed by speciation events. Smaller Y chromosomes may also confer an advantage in the race to fertilization.

Because the male-specific region of the Y has been shrinking and accumulating retroviral and heterochromatic sequences, rather than maintaining the functionality of many loci, Germaine Greer has commented that "men are the products of a damaged chromosome." More thoughtful investigation, however, would suggest that the Y is perhaps not so much a 'damaged chromosome' as a vector of male-specific genes, streamlined by evolutionary selection.

To compensate for the deterioration of many Y chromosomal genes, and the consequent imbalance in output

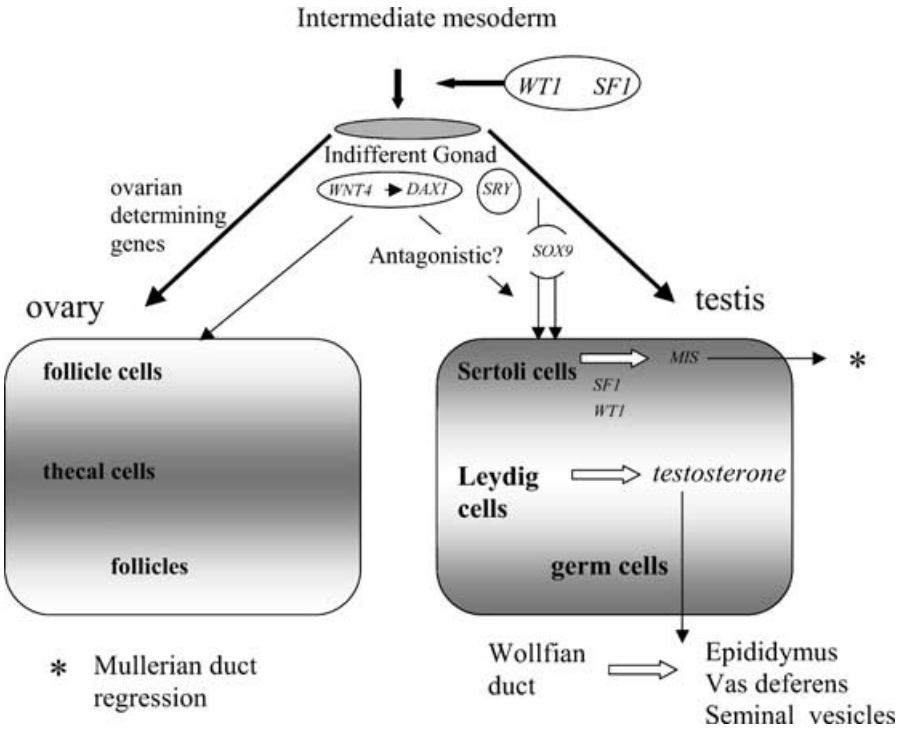

Figure 1 An overview of the genes whose roles have been implicated in gonad development. *SF1*, (*NR5A1*) steroidogenic factor 1 WT1, Wilms tumour 1; *DAX1* (*NR0B1*), DSS-AHC critical region on the X chromosome 1, also known as dosage-sensitive sex-reversal. (DSS); *SOX3*, SRY-related HMG box 3; *SOX9*, SRY-related HMG box 9; SRY, sex determining region on the Y-chromosome; *MIS* (*AMH*), Mullerian duct inhibiting substance. There appear to be three classes of transcription factors; firstly, those general factors whose roles intervene at various stages (e.g. SF1 and WT1), secondly, those like SRY and SOX9 appear to be specific to testis development and finally factors such as DAX1 which generally antagonise testis development and promote ovary development (e.g. see Swain & Lovell-Badge, 1999). Additional roles for transcription factors WNT4, GATA4 and FOG1 (*ZFPM1*) in gonad development have been confirmed recently (see Jordan *et al*. 2001; Tevosian *et al*. 2002).

from the former X/Y homologous alleles, logic and a large body of research suggest that further processes for coping with this imbalance have been conscripted by evolution (Charlesworth, 1996). In the case of mammalian lineages, 'X-inactivation' emerged as a mechanism by which the female embryo, at an early stage of its development, randomly inactivates all but one X chromosome in each cell. The cell lines descended from each parent cell retain their pattern of either paternal or maternal inactivation. A simplified interpretation of the mechanism envisages the initial silencing of transcription as spreading from an inactivation centre to embrace almost the entire chromosome, while subsequent maintenance of inhibition is thought to occur locus by locus through processes involving both DNA methylation and histone modification. The locus implicated in initial events, *XIST*, is expressed only from the inactive X (Xi). In mice *Tsix* is a 40kb sequence, extending across the *Xist* locus on the antisense DNA strand, which can be transcribed into an antisense RNA in female mammals. A role as an antagonist blocking *Xist* action is suggested by the gene's differential methylation on the active and inactive X, and by the correlation of loss of *Tsix* expression with the upregulation of *Xist* on the subsequently inactive X in mice. The converse is true of expression of the two transcripts on the active X (Stavropoulos *et al*. 2001). However, there is evidence that the mode of *Tsix* action in mice is not shared by humans (Migeon, 2003).

Recent estimates conclude that as many as 1/5 genes located on the X-chromosome appear to escape inactivation (Carrel *et al*. 1999). The distribution of such 'escapees' seems to be non-random, with an apparent

excess residing on Xp (X-chromosome, short arm). Some escapees have been shown to have lost their Y homologue, causing females to have two active copies whilst males have only one. This suggests that their recruitment into X-inactivation may have suffered an evolutionary time lag after the loss of an active Y-linked counterpart. It is possible that dosage is simply not important for these genes; alternatively, greater dosage in females might be important for a sex-specific reason, for instance as a requirement for normal ovarian function. The repercussions of this process for differences in sex-specific behaviour are discussed below, but first we consider the traditional, but rapidly changing, view that hormones are the only biological influence required to explain sex differences in behaviour and cognition.

Sex Differences in Behaviour at the Mercy of Hormones?

Many of the first studies demonstrating a relationship between gonadal hormones and behaviour and the brain were conducted on animals. Testosterone, secreted by the testes in male mammals (beginning in the fetal stage and continuing after birth), has been shown to trigger male-specific brain development that leads to anatomical differences in the male brain and a follow-on effect on sexually dimorphic behaviours and functions (e.g. Goy & McEwen, 1980; Arnold & Gorski, 1984). The primary method by which sex hormones bring about sexual dimorphisms in the human brain is thought to be by differential cell death (Jacobson, 1991, Hutchinson & Pilgrim, 1994).

Androgens also inhibit the development of female-typical behavioural characteristics, which are often maintained by ovarian hormones. For example, whereas male rodents deprived of androgens are less likely to mount females and more likely to be sexually receptive to males (lordosis), the sexual behaviour of female rodents and primates with increased androgen levels resembles that of a normal androgenised male. However, there is no simple correlation between levels of hormones present and degree of behaviour exhibited. Variations have been shown to relate to the timing of exposure, the organism's sensitivity to the hormones and, importantly, modification by environmental factors. Gonadal hormones also affect sexually dimorphic behaviours not directly implicated as being geared towards reproduction, such as aggression and cognition. For example, in rats and primates, exposure to high levels of androgen during sensitive periods of brain development is associated with increased aggression and 'rough play' (Beatty, 1992). In relation to cognition, female rats given masculinising hormones during critical periods of development learn the 'radial-arm maze' as well as normal males, and significantly better than normal females or even castrated males (Williams & Meck, 1991). This spatial superiority, characteristic of males in many species, is thought to relate to the use of geometric cues with which females struggle more, on average, than males.

In humans, there are cases where female embryos have been exposed to masculinising hormones, for example due to maternal ingestion of particular androgenising drugs (e.g. progestins or diethylstilbestrol – DES) during pregnancy. Also, in one form of Congenital Adrenal Hyperplasia (CAH), there is early fetal overproduction of adrenal androgens. In both situations, prenatal exposure to androgens seems to lead to masculinised behaviours such as aggression and increased spatial ability, as well as male-typical toy play and sexual preference (Reinisch, 1981; Ehrhardt *et al*. 1985; Meyer-Bahlburg *et al*. 1985). How much this behaviour in CAH girls can be attributed to parents' adaptation of behaviour, which might arise unconsciously as a reaction to the male-like appearance of the child's genitalia, is debated however (Slijper, 1984).

Opposite-sex twin pairs represent a potentially useful, and more commonly available, opportunity for studying intrauterine hormonal influences, as female co-twins may be exposed to high levels of testosterone by virtue of sharing the womb with a male. Studies have found such females to have higher than average levels of male-type behaviour, such as spatial ability (Cole-Harding *et al*. 1988) and sensation seeking (Resnick *et al*. 1993). Other studies, however, have found no evidence of such an effect (Rose *et al*. 2002). Whether the male co-twin is correspondingly rendered more feminised in his behaviour is a question that has been largely ignored. The socio-developmental influences on behaviour of having an opposite-sex as opposed to a same-sex twin are difficult to distinguish. Studies using singletons with an older brother as a

control, however, have generally found that any tendency in girl members of opposite-sex twin pairs towards masculinised behaviour is accounted for by environmental opposite-sex sibling effects rather than *in utero* hormonal crossovers (Henderson & Bernebaum, 1997). Hines *et al*. (2002), however, have found evidence for a linear relationship between levels of testosterone (within the normal range) in pregnant women and the subsequent gender role behaviour of their preschool daughters.

Hormones secreted by the hypothalamus and pituitary glands direct sexual maturation at puberty. The physical changes in height, weight and body shape that take place during this period are well–documented (e.g. Veldhuis, 2003). In terms of behaviour, though, hormonal fluctuations in females may be especially relevant to mood disorders, which are twice as common in females as they are in males. Of course, the normal fluctuations in female hormones cannot be sufficient to explain mood disorders, or depression, given that many women do not suffer from any serious mood disturbances. It is probable, however, that clinically diagnosed depression is simply the extreme of a continuous trait in the population. Perhaps those women with a greater genetic vulnerability to develop depression are particularly vulnerable at these key stages in their reproductive cycles (e.g. Steiner *et al*. 2003).

An interesting natural experiment, demonstrating the crucial role of sensitivity to hormones, and not simply their presence, arises in human sufferers of Testicular Feminisation Syndrome (TFM). This is an X-linked recessive disorder, caused by the lack of a functional androgen receptor gene at Xq11-q13 (Imperato-McGinley *et al*. 1990), and resulting in a biological incapacity of end-organs to recognise the presence of normal male hormones. Consequently, affected individuals have a normal male XY karyotype, but display a female physical phenotype, including external genitalia, but lacking a uterus. Behaviour can also be overtly feminised, but the condition is quite heterogeneous and few studies have concentrated on the behavioural characteristics.

Given the overwhelming evidence for the importance of sex hormones in sexual dimorphism, it might appear that there is little need to look for other, non-hormonal, explanations of sex-specific brain development and behaviour, beyond the direct genetic effects of *SRY* and its gene partners on testis development. Some instances of sexual differentiation, however, cannot be attributed to gonadal steroids alone. For example, in many relevant respects, marsupials resemble eutherian mammals. The male is the heterogametic sex (XY) whereas the female is homogametic (XX), and the location and timing of *SRY* expression are consistent with its role as a testis-determining factor. Yet, studies of the tammar wallaby, *Macropus eugenii*, have found that the development of some sex-specific structures precedes gonadal differentiation and is robust to experimental treatment with steroids (Renfree & Short, 1988). For instance, before gonadal differentiation, genetic males develop scrotal anlagen and gubernaculum whereas genetic females develop mammary and pouch anlagen. Indeed, recent studies using tissue from mouse brains have shown that sexual dimorphism in the expression levels of some X-linked, as well as autosomal, genes precedes gonadal differentiation, thus indicating that these differences are not hormonally-directed (Dewing *et al*. 2003). Furthermore, cross-sex development cannot be induced by treatment with exogenous steroids (Shaw *et al*. 1988). Because there are several such cases of sexual differentiation that cannot be easily explained by steroidal influences alone, it seems logical to speculate that there may be direct genetic effects on sex-specific behaviour. We next, therefore, consider evidence that the expression profile of some genes may differ between the sexes, and that these loci may thereby represent candidates likely to be involved in the genetic basis of behavioural differences.

The Significance of X-inactivation

When looking for genes with differential expression between the sexes, the obvious starting points are those loci located on the X and Y chromosomes. (Figure 2 illustrates the localisation of some of the key loci implicated in sex determination and behaviour that are discussed below).

Apart from its direct role in sex determination, the human Y chromosome has evolved to carry a combination of male-specific fertility genes and a limited range of housekeeping genes with homologues on the human X. While not denying the possibility that differential expression of these in the two sexes may be significant,

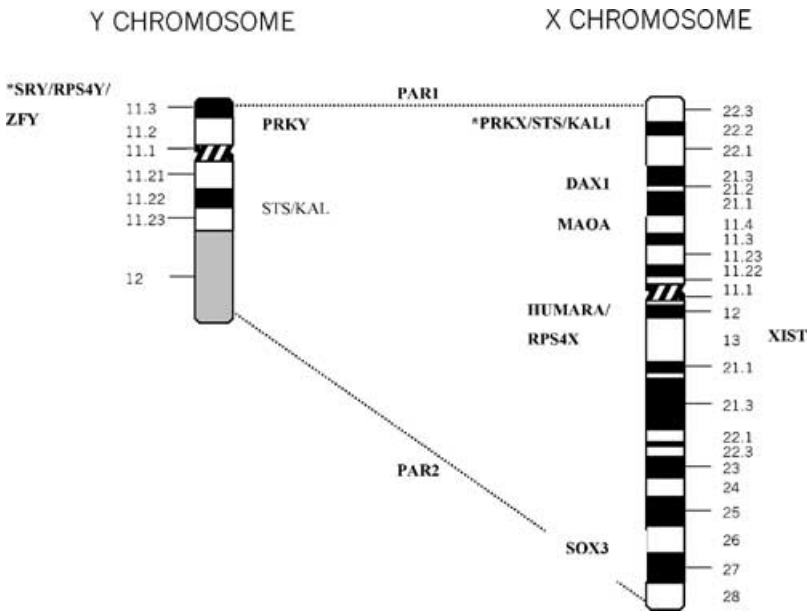

Figure 2 Ideograms of human X and Y chromsomes indicate locations of some key loci referred to in the text, including those implicated in sex determination. The names of the loci and their cytogenetic map positions. On the Y chromosome: *SRY*, sex determining region Y – Yp11.3, adjacent to the pseudoautosomal boundary; *ZFY*, zinc finger protein – Yp11.3; *PRKY*, protein kinase, Y-linked - Yp11.2. The Y long arm harbours non-active homologous sequences corresponding to the *STS*, steroid sulphatase (microsomal), arylsulfatase C, and *KAL1*, Kallmann syndrome, genes. On the X chromosome: *PRKX*, protein kinase X-linked – Xp22.3; *STS*, steroid sulphatase (microsomal), arylsulfatase C, Xp22.32; *KAL1*, Kallmann syndrome gene 1, Xp22.32; *DAX1* (official symbol, *NR0B1*) nuclear receptor subfamily 0, group B, member 1 - Xp21.3; *ZFX*, zinc finger protein, X-linked – Xp22.1; *MAOA*, monoamine oxidase A – Xp11.3; *AR* (alternative symbol, *HUMARA*), androgen receptor – Xq12; *RPS4X*, ribosomal protein S4, X-linked – Xq13; *XIST*, X (inactive)-specific transcript – Xq13.2; *SOX3*, *SRY* (sex determining region Y)-box 3 – Xq26-q27. PAR1 and PAR2 refer to the short arm and long arm pseudoautosomal regions, respectively. (*Note: *SRY* is located 2.30 Mb from the telomere, about 60 Kb distal to *RPS4Y* and 180 Kb distal to *ZFY*, with *PRKY* a further 4.6 Mb towards the centromere. On the X chromosome, *PRKX* is about 3.2 Mb from the telomere, with *STS*, at 6.5 Mb, and *KAL1*, at 8.0 Mb, located proximally). (information based on links to the following URL – Entrez map viewer: http://www.ncbi.nlm.nih.gov/UniGene/clust).

it is also important to acknowledge that the human X has up to 1,000 genes, some of which could potentially contribute significantly to sexual dimorphism beyond those involved in the sex determination process itself. In particular, an understanding of which genes do and do not escape X-inactivation may be crucial to evaluating their potential contribution to sexually dimorphic characteristics.

Broadly speaking, then, X-inactivation is the means by which males and females are rendered *more similar* in terms of gene expression; however, it also provides an opportunity for sex *differences* to arise, resulting from expression differentials of genes that escape inactivation. As previously mentioned, estimates of the number of these 'escapees' have increased such that it is now thought that up to one in five (i.e. about 200) genes on the inactive X are expressed (Carrel *et al*. 1999). X-linked genes that escape inactivation can be subdivided into two groups: those that have Y homologues and those that do not.

Several genes located proximal to PAR1 have been found to escape inactivation, either completely or partially. These include the Kallman syndrome (*KAL1*)

and steroid sulphatase (*STS*) gene. Neither have Y homologues in humans, though the Y chromosome does harbour non-functional pseudogenes (e.g. see Disteche, 1995, 1999). It has been speculated that such loci may have been part of a more extensive pseudoautosomal region that has been lost as a result of a series of pericentric inversions of the ancestral Y chromosome (Fraser *et al*. 1987; Page *et al*. 1987; Lahn & Page, 1999) and it was originally thought that escape from inactivation was attributable to their position close to the PAR. Subsequently, however, an increasing number of genes positioned far from PAR1, such as Zinc Finger Protein X-linked (*ZFX*) and Ribosomal Protein S4 (*RPS4X*), have been shown to escape inactivation. Both have functional Y homologues (*ZFY* and *RPS4Y* respectively), which, though not identical to the sequence on the X, suggest balanced expression of the gene product in males and females (Disteche, 1999). Even when genes escaping inactivation have homologues on the Y chromosome, however, it has been reported that, in mice, the contribution to expression levels in the brain made by the Y-linked gene is often smaller than that made by the X-linked gene (Xu *et al*. 2002). Thus, sex differences in summed expression levels may remain, even for X-linked genes with functional Y equivalents. Furthermore, and with particular relevance to behaviour, there is some evidence that X and Y homologues may not be expressed at the same stages of brain development and in the same tissues. This raises an important possible mechanism whereby male and female brain function could differ for genetic reasons (Xu *et al*. 2002).

The existence of genes on the X chromosome that escape inactivation and which do not appear to have any functional equivalent on the Y chromosome is a clear potential source of genetically-based sexual dimorphism. For instance, Eukaryotic Translation Initiation Factor 2 (*EIF2G*), Sedlin (*SEDL*) and Co-factor Required for SP1 transcriptional activation Subunit 2 (*CRSP2*) are all X-linked genes that seem not to be inactivated on Xi, yet do not have equivalent loci on the Y chromosome (for recent summaries of such loci see Carrel *et al*. 1999; Craig *et al*., in press). For all such genes, therefore, whereas females carry two active alleles, males carry only one. Thus, the female genome produces up to twice as much of the protein coded for by these loci as the male genome. It follows that this dosage imbalance is a fundamental source of differences in the genetic output of the two sexes, and such disparity is likely to have phenotypic consequences, particularly given the involvement of some of these loci in the control of transcription and translation.

Research suggests, therefore, that sex differences may result from escapee genes whether or not they have Y homologues. Indeed, De Vries *et al*. (2002), studying mice with the male determining *Sry* gene translocated onto an autosome, have provided direct evidence that sex chromosomal genes contribute directly to differences between male and female brains. Furthermore, the fact that they are hemizygous for X-linked genes that have no Y homologue means that the male sex as a whole may generally be exposed to extremes of phenotypes that are controlled by alleles on the X chromosome. Females, in contrast, have two alleles, each of which is usually inactivated in 50% of cells, and the effects of the two are averaged and thus likely to be less extreme. This may help to explain the commonly recognised, yet infrequently discussed, phenomenon that males exhibit greater variance in the population than females for a large number of traits (see Hedges & Nowell, 1995).

Although random inactivation would predict that females should have about 50% of cells with an active paternal X and 50% with an active maternal X, skewed patterns of inactivation may arise. This could occur simply by chance, particularly if tissues develop from relatively few cells. In some cases, however, extremely skewed inactivation patterns result from mutations, including deletions or translocations, affecting the X-chromosome (see Heard, Clerc, & Avner, 1997). There are also reports of pedigrees in which skewed X-chromosome inactivation segregates with mutations affecting the XIST locus (Plenge *et al*. 1997). Skewed inactivation has been known to cause differences in X-linked disease expression between monozygotic (MZ) twin girls. Examples include two MZ twin pairs discordant for haemophilia B, one pair discordant for the fragile-X phenotype, six pairs discordant for Duchenne Muscular Dystrophy, and six pairs discordant for red-green colour vision deficiency (e.g. Burn *et al*. 1986; Tiberio, 1994; Brown & Robinson, 2000). There have also been suggestions that skewed inactivation may be a causal factor in twinning and might explain a corresponding excess of female

twins (Burn *et al*. 1986), topics that remain controversial. While skewing of X-inactivation should be expected to cause female monozygous twins to be, on average, more discordant in the manifestation of X-linked QTLs than their male counterparts, it also follows that dizygous male twins should be more divergent for X-linked traits than dizygous females. Both of these predictions for some aspects of cognition and language development in twins, measured between 2 and 4 years, appear to be borne out (see Loat *et al*. 2004).

Evidence for X-linked Genes Implicated in Behaviour

There is some evidence that there may be an X-linked gene for social cognition, which undergoes parental imprinting. On tests of social cognitive dysfunction in X0 Turner's syndrome girls, Skuse *et al*. (1997) discovered that subjects who inherited their single X from their father ($45X^{p}$) attained significantly higher scores than females who were $45X^{m}$, suggesting that the paternal allele conferred an advantage in cognitive abilities enabling socialization. They also found, and other studies have confirmed (e.g. Dunn *et al*. 1991), that normal boys possessed poorer social cognitive skill than normal girls. The data could thus be interpreted to support the existence of a gene conferring an advantage in the set of cognitive skills necessary for enhanced reciprocal social communication, but which is maternally imprinted. Such a locus would be transcribed only from the paternal X-linked allele, and therefore not expressed in males. In spite of the high interest in, and significance of, these studies, they have not yet been adequately replicated.

The X chromosome has, in recent years, also been implicated (controversially or otherwise) in a number of other behavioural traits including: homosexuality, affective disorders, general cognitive ability and antisocial behaviour, as well as having a large number of loci assigned to it that are associated with mental retardation (see Table 1). Furthermore, it has been argued that a concentration on the X chromosome of loci implicated in brain function has an evolutionary explanation based upon selection for high cognition skills in males (Zechner *et al*. 2001).

Overall, then, there appear to be compelling reasons to investigate different behavioural consequences depending on sex chromosome complement. We conclude, therefore, with a review of the genetic basis for two sexually disparate types of behaviour.

Sex Differences in General Cognitive Ability (g)

The term 'General cognitive ability' ('g') (Plomin, 1999) refers to what is common between measures of spatial ability, verbal ability, processing speed and memory. Standard IQ tests that combine a total score from a diverse set of cognitive measures, however, index 'g' relatively well. Although there are significant sex differences in intellectual function, these do not seem to lie in overall levels of intelligence, but more in patterns of ability, as discussed previously.

Sex differences in the aging of brain areas that are essential to higher cognitive function have also been detected, suggesting that the impact of gender on cognition also varies with age (Murphy *et al*. 1996). Evidence that hormones affect specific cognitive abilities comes from studies that show that cognitive performance is modifiable in adulthood by the hormonal status of participants. For instance, women at the low oestrogen phase of the menstrual cycle show enhanced spatial cognition (Hampson, 1990), whilst at the high oestrogen phase they display enhanced motor skills (Hampson & Kimura, 1988). Women on oestrogen replacement therapy also showed enhanced verbal memory, but no change in spatial memory. Conflicting data on this subject exist, however, and might reflect differing research methodologies. There is, nevertheless, considerable evidence that genes contribute significantly to 'g', converging on the conclusion that 'g' has a heritability of about 50% (Plomin, 1999). Sorting the results by age has shown that heritability increases from about 20% in infancy to 40% in childhood and more than 60% in later life. This highlights the presumptive importance of environmental stimuli, with infants being more susceptible to environmental manipulation during the formative years. Similarly, heritability differs between the sexes, verbal cognitive ability in particular showing greater heritability for boys than girls (Galsworthy *et al*. 2000). Plomin (1999) suggests that research based on an assumption of many quantitative trait loci, QTLs, will be important, as the average effect-size of genetic

Table 1 X-linked traits associated with behaviour and cognition

Behaviour	Locus/Loci	Location	References
Non-syndromic X-linked retardation	*RPS6KA3/RSK2* *ARX* *IL1RAPL1*	Xp22	Ropers *et al*. (2003)
Antisocial personality	*MAOA*	Xp11.4	Brunner *et al*. (1993); Caspi *et al*. (2002)
Non-syndromic X-linked retardation	*TM4SF2*	Xp11.4	Ropers *et al*. (2003)
Socialisation skills		Xp21.1-p11.4 ?	Skuse *et al*. (1997); Naumova *et al*. (1998)
Non-syndromic X-linked retardation	*OPHN1* *ACSL4/FACL4* *PAK3* *RPS6KA3*	Xq22	Ropers *et al*. (2003) Zechner *et al*. (2001)
Non-syndromic X-linked retardation	*AGTR2*	Xq24	Ropers *et al*. (2003)
Non-syndromic	*ARHGEF6*	Xq26	Ropers *et al*. (2003)
X-linked retardation	*FMR2/FRAXE*	Xq28	Ropers *et al*. (2003)
Non-syndromic X-linked retardation	*GDI1* *MECP2* *SLC6A8*		
?Manic-depressive illness, X-linked 2	*MAFD2/MDX*	Xq28	See Baron *et al*. (1993)
Male homosexuality		Xq28	Hamer *et al*. (1993)

In addition to the above and mental retardation associated with fragile sites at Xq27.3 (*FRAXA*) and at Xq28 (*FRAXE*), On-line Mendelian Inheritance in Man (OMIM) lists 25 X-linked loci associated with mental retardation (designated MRX) and 15 for mental retardation associated with defined syndromes (designated MRXS) – see http://www3.ncbi.nlm.nih.gov/Omim/.

effects is likely to be small for complex traits. Each QTL may account for less than 1% of the variance, and gene interactions will further complicate the task of finding genes for 'g'. The putative existence of genes for 'g' that have additive effects has, however, made the search for such genes theoretically achievable. Given the evidence that the X chromosome appears to have at least its fair share of potential QTLs for g, and certainly an excess of genes associated with mental impairments (Zechner *et al*. 2001), it follows that sex differences in the expression of X-linked genes important in behaviour are to be anticipated.

Sex Differences in Antisocial Behaviour

Moffitt *et al*. (2001) suggest that over a lifetime, antisocial disorder is 2.4 times more prevalent in males than females, and more males than females are diagnosed with conduct disorder at every age. Males are also more physically and verbally aggressive at every age, with the highest rates of convicted offending in males, significantly exceeding those in females.

In animals, the relationship between testosterone and aggression has been demonstrated through correlational and experimental studies (Turner, 1994). In humans, however, the data are more conflicting. The situation is typified by a study performed by Turner (1994), which showed that testosterone was positively correlated with aggressive behaviour in 12-13 year old boys, but not in 15-16 year old boys. Other research has suggested that aggression and testosterone are indeed positively correlated (Archer, 1991). Recent evidence has suggested that the maximum effect of testosterone on aggression might show a time-lag of around 6 hours (van Honk *et al*. 1999). If previous studies were conducted without allowing for time-lags, a higher correlation might be expected than currently observed. Although women have relatively lower levels of both testosterone and aggression, there is yet little evidence to suggest that the relationship between these differs in size and/or direction between the sexes (Kemper, 1990).

Evidence also points to a higher heritability of aggression in males, whereas common environment may be more important in females (Miles & Carey, 1997;

Vierikko *et al*. 2003). However, as is the case for most behaviours, a definitive estimate of the magnitude of the genetic contribution to aggression is difficult to assess, as heritability depends on the range of both genetic and environmental factors in the population being studied.

The first evidence for a link between a specific locus and sexual dimorphism in antisocial behaviour came from studies of a Dutch pedigree, in which several males exhibited borderline mental retardation associated with impulsive aggression and inappropriate behaviour induced by stress. The trait is X-linked, co-segregating with a dinucleotide repeat at the monoamine oxidase A (*MAOA*) locus (Xp21-p11). All affected males showed elevated excretion of MAOA substrates, and reduced excretion of expected MAOA products, resulting from a nonsense mutation causing a truncated and non-functional protein (Brunner *et al*. 1993). Obligate female carriers were found to be unaffected. MAOA regulates the levels of serotonin, dopamine and noradrenaline, abnormalities in the metabolism of all of which have been associated with aggressive tendencies. Knock-out mice for *MAOA* also show elevated aggressive tendencies (see Craig, 1994).

Of particular interest is the recent discovery of an interaction between genetic, environmental and hormonal predispositions towards aggression. Caspi *et al*. (2002) studied the effect of a polymorphism for "high" and "low" *MAOA* expression. It was found that those boys having the low activity allele, and who were maltreated, were much more likely to develop antisocial behaviour ($p = 0.85$), conduct disorder, a disposition towards violent behaviour, or be convicted for a violent offence than were those with high MAOA activity. Maltreatment increased the risk of criminality by 50%, but high expression of *MAOA* seemed to afford a protective effect against the negative and aggressive consequences of a maltreated childhood. The difficulty in gauging the correct proportions of risk factors for aggressive behaviour might be a direct result of the complexity of such interactions.

In Conclusion

Men and women, then, *are* different from each other in a number of important respects. These differences go far beyond the basics of anatomy, and are manifested in many aspects of cognition, behaviour, and disorders thereof. The historical perspective of the male's role as being that of the hunter-gatherer, competing with other males for food, resources and females, and making little personal investment in the rearing of children, is consistent with the male-specific development of traits such as aggression, competitiveness and spatial awareness. For females, on the other hand, child rearing and the ability to survive within a cooperative society may have been of more importance, encouraging the development of communicative and social skills. Although these sex-typed roles have undergone a massive cultural overhaul in recent generations, the evolutionary time lag is such that their influence on behaviour will continue to be seen for many future generations. The effects of evolution may also extend to differences in criteria of mate selection and 'sexual mentality'. Contemporary observations are generally that males are more superficial, attracted primarily by beauty and youth, but are also sexually opportunistic, whilst women are attracted by wealth and status. An evolutionary interest in achieving, in the case of men, the maximum rate of reproduction with partners who have good fitness for child-bearing, or, in the case of women, choosing partners with good resources and the best genes for successful offspring, would help to explain these different priorities.

For thousands of years, males and females have been under divergent pressures of selection, and it is therefore unsurprising that genes on the sex chromosomes should have evolved along divergent paths, influencing sex-typed behaviour directly as well as indirectly, via the control of hormones and brain maturation. The most plausible model to explain the aetiology of the discrepancies between male and female-typical behaviour, then, invokes all of these factors, which in turn interact with the rich background of familial environments and socio-cultural norms against which these biological mechanisms are acting. It is this interaction of an organism with its environment, and the pattern of reactions to stimuli, that enable survival. Undoubtedly, a full account of how sex differences arise must take into consideration the sex-specific differences in life experience, as well as the sex-specific responses to these experiences. These patterns are strongly mediated by

genetic and hormonal predisposition, but, as in recent findings of gene-environment interactions, the presence or absence of certain external stimuli can be crucial as to whether the differences in biological substrates show any discernible and consistent effect. It can only serve to enhance the sensitivity of detection of these substrates to take into account all of the possible sources of variation in individual responses to environmental stimuli.

Ultimately, then, to claim that men and women are different is not to claim that they are unequal, and in accepting this, the constantly increasing body of empirical proof of these differences should not be seen as a threat. A greater understanding of how and why males and females do not behave and think in the same way will not only further understanding of behaviour and psychopathology in general, but also enable a greater understanding of how best to adapt environments to achieve as good a quality of life as possible in diverse areas, from development of a successful educational system to prevention and treatment of mental disorders.

References

Archer, J. (1991) The influence of testosterone on human aggression. *British J Psychology* **82**, 1–28.

Arnold, A. P. & Gorski, R. A. (1984) Gonadal steroid induction of structural sex differences in the central nervous system. *Annu Rev Neurosci* **7**, 413–442.

Arnold, A. P. (1996) Genetically triggered sexual differentiation of brain and behavior. *Horm Behav* **30**, 495–505.

Bardoni, B., Zanaria, E. & Guioli, S. *et al*. (1994) A dosage sensitive locus at Xp21 is involved in male to female sex reversal. *Nat Genet* **7**, 497–501.

Baron, M., Freimer, N. F. & Risch, N. *et al*. (1993) Diminished support for linkage between manic depressive illness and X-chromosome markers in three Israeli pedigrees. *Nat Genet* **3**, 49–55.

Baron-Cohen, S. (2002) The extreme male brain theory of autism. *Trends Cog Sci* **6**, 248–254.

Beatty, W. W. (1992) Gonadal hormones and sex differences in non-reproductive behaviours. In: *Handbook of behavioural neurobiology* (eds. A. A. Gerall, H. Moltz & I. L. Ward), pp. 85–128. New York: Plenum Press.

Beyer, C., Kolbinger, W. & Froehlich, U. *et al*. (1992) Sex differences of hypothalamic prolactin cells develop independently of the presence of sex steroids. *Brain Research* **593**, 253–256.

Brown, C. J. & Robinson, W. P. (2000) The causes and consequences of random and non-random X-chromosome inactivation in humans. *Clin Genet* **58**, 353–63.

Brunner, H. G., Nelen, M. & Breakefield, X. O. *et al*. (1993) Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. *Science* **262**, 578–580.

Burn, J., Povey, S. & Boyd, Y. *et al*. (1986) Duchenne muscular dystrophy in one of monozygotic twin girls. *J Med Genet* **23**, 494–500.

Carrel, L., Cottle, A. A. & Goglin, K. C. *et al*. (1999) A first-generation X-inactivation profile of the human X chromosome. *Proc Natl Acad Sci U.S.A* **96**, 14440–14444.

Caspi, A., McClay, J. & Moffitt, T. E. *et al*. (2002) Role of genotype in the cycle of violence in maltreated children. *Science* **297**, 851–854.

Charlesworth, B. (1978) Model for evolution of Y chromosomes ad dosage compensation. *Proc Natl Acad Sci U.S.A* **75**, 5618–5622.

Charlesworth, B. (1996) The evolution of chromomsal sex determination and dosage compensation. *Curr Biol* **6**, 149–162.

Cole-Harding, S., Morstad, A. L. & Wilson, J. R. (1988). Spatial ability in members of opposite-sex twin pairs. *Beh Genet* **18**, 710.

Craig, I. (1994) Misbehaving monoamine oxidase gene. *Curr Biol* **4**, 175–177.

Craig, I., Mill, J. S., Craig, G. *et al*. (2004) Application of micro-arrays to the analysis of the inactivation status of human X-linked genes expressed in lymphocytes. *Eur J Hum Genet*, in press

Dewing, P., Shi, T., Horvath, S. & Vilain, E. (2003) Sexually dimorphic gene expression in mouse brain precedes gonadal differentiation. *Brain Res Mol Brain Res* **118**, 82–90.

De Vries, G. J. & Boyle, P. A. (1998) Double duty for sex differences in the brain. *Behavioural Brain Research* **92**, 205–213.

De Vries, G. J., Rissman, E. F., Simerly, R. B. *et al*. (2002). A model system for study of sex chromosome effects on sexually dimorphic neural and behavioural traits. *J Neurosci* **22**, 9005–9014.

Disteche, C. M. (1995) Escape from X inactivation in human and mouse. *Trends Genet* **11**, 17–22.

Disteche, C. M. (1999) Escapees on the X chromosome. *Proc Natl Acad Sci U.S.A* **96**, 14180–14182.

Dunn, J., Brown, J. & Slomkowski, C. *et al*. (1991) Young children's understanding of other people's feelings and beliefs: individual differences and their antecedents. *Child Dev* **62**, 1352–1366.

Ehrhardt, A. A., Meyer-Bahlburg, H. F. & Rosen, L. R. *et al*. (1985) Sexual orientation after prenatal exposure to exogenous estrogen. *Arch Sex Behav* **14**, 57–77.

Fenson, L., Dale, P. S. & Reznick, J. S. *et al*. (1994) Variability in early communicative development. *Monogr Soc Res Child*

Dev **59**, 1–173.
Foster, J. W. & Graves, J. A. (1994) An SRY-related sequence on the marsupial X chromosome: implications for the evolution of the mammalian testis-determining gene. *Proc Natl Acad Sci U.S.A* **91**, 1927–1931.
Fraser, N., Ballabio, A. & Zollo, M. *et al*. (1987) Identification of an incomplete coding sequence for steroid sulphatase on the human Y-chromosome: evidence for an ancestral pseudoautosomal gene? *Development* **101**, 127–132.
Galea, L. A. & Kimura, D. (1993) Sex differences in route learning. *Pers Indiv Diff* **14**, 53–65.
Galsworthy, M. J., Dionne, G. & Dale, P. S. *et al*. (2000) Sex Differences in the etiology of early verbal and non-verbal development. *Dev Sci* **3**, 206–215.
Geary, D. (1996) Sexual selection and sex differences in mathematical abilities. *Behav Brain Sci* **19**, 229–284.
Goy, R. W. & McEwen, B. S. (1980) *Sexual differentiation in the brain*. London: MIT Press.
Hamer, D., Hu, S. & Magnuson, V. L. *et al*. (1993) A linkage between DNA markers on the X chromosome and male sexual orientation. *Science*, **261**, 321–325.
Hampson, E. (1990) Estrogen-related variation in human spatial and articulatory-motor skills. *Psychoneuroendocrinology* **15**, 97–111.
Hampson, E. & Kimura, D. (1988) Reciprocal effects of hormone fluctuations on human motor and perceptual spatial skills. *Behav Neurosci* **102**, 456–459.
Heard, E., Clerc, P. & Avner, P. (1997) X-chromosome inactivation in mammals. *Annu Rev Genet* **31**, 571–610.
Hedges, L. V. & Nowell, A. (1995) Sex differences in mental test scores, variability, and numbers of high-scoring individuals. *Science* **269**, 41–45.
Henderson, B. A. & Berenbaum, S. A. (1997) Sex-typed play in opposite-sex twins. *Dev Psychobiol* **31**, 115–123.
Hines, M., Golombok, S. & Rust, J. *et al*. (2002) Testosterone during pregnancy and gender role behavior of preschool children: a longitudinal, population study.
Holloway, R. L., Anderson, P. J. & Defendini, R. *et al*. (1993) Sexual dimorphism of the human corpus callosum from three independent samples: relative size of the corpus callosum. *Am J Phys Anthropol* **92**, 481–498.
Hutchison, J. B. & Pilgrim, C. (1994) Developmental regulation of sex hormones in the brain: can the role of gonadal steroids be redefined? *Neurosci* **60**, 843–855.
Imperato-McGinley, J., Ip, N. Y. & Gautier, T. *et al*. (1990) DNA linkage analysis and studies of the androgen receptor gene in a large kindred with complete androgen insensitivity. *Am J Med Genet* **36**, 104–108.
Jacobson, M. (1991) *Developmental Neurobiology*. New York: Plenum Press.
Johnson, B. W., McKenzie, K. J. & Hamm, J. P. (2002) Cerebral asymmetry for mental rotation: effects of response hand, handedness and gender. *Neuroreport* **13**, 1929–1932.
Jobling, M. A. & Tyler-Smith, C. (2003) The human Y chromosome: an evolutionary marker comes of age. *Nature Reviews Genetics*, **4**, 598–612.
Jordan, B. K., Mohammed, M. & Ching, S. T. *et al*. (2001) Up-regulation of WNT-4 signaling and dosage-sensitive sex reversal in humans. *Am J Hum Genet* **68**, 1102–1109.
Kemper, T. K. (1990) *Social Structure and Testosterone*. New Brunswick, NJ: Rutgers University Press.
Kimura, D. (1992) Sex Differences in the Brain. *Scientific American* **267**, 80–87.
Kimura, D. (1999) *Sex and Cognition*. Cambridge, Mass: MIT Press.
Kimura, D. & Harshman, R. A. (1984) Sex differences in brain organization for verbal and non-verbal functions. *Progress in Brain Research* **61**, 423–41.
Koopman, P., Gubbay, J. & Vivian, N. *et al*. (1991) Male development of chromosomally female mice transgenic for Sry. *Nature* **351**, 117–121.
Kramer, J. H., Delis, D. C. & Kaplan, E. *et al*. (1997) Developmental sex differences in verbal learning. *Neuropsych* **11**, 577–584.
Lahn, B. T. & Page, D. C. (1999) Four evolutionary strata on the human X chromosome. *Science* **286**, 964–967.
LeVay, S. (1991) A difference in hypothalamic structure between heterosexual and homosexual men. *Science* **253**, 1034–1037.
Loat, C., Asbury, K. & Galsworthy, M. *et al*. (2004) X inactivation as a source of behavioural differences in monozygotic female twins. *Twin Research* **7**, 54–61.
Luo, X., Ikeda, Y. & Parker, K. L. (1994) A cell-specific nuclear receptor is essential for adrenal and gonadal development and sexual differentiation. *Cell* **77**, 481–490.
McLaren, A. (1998) Assembling the mammalian testis. *Curr Biol* **8**, 175–177.
Meyer-Bahlburg, H. F., Ehrhardt, A. A. & Feldman, J. F. *et al*. (1985) Sexual activity level and sexual functioning in women prenatally exposed to diethylstilbestrol. *Psychosom Med* **47**, 497–511.
Migeon, B. R. (2003). Is Tsix repression of Xist specific to mouse? *Nat Genet* **33**, 337–338.
Miles, D. R. & Carey, G. (1997) Genetic and environmental architecture of human aggression. *J Pers Soc Psychol* **72**, 207–217.
Mishina, Y., Rey, R. & Finegold, M. J. *et al*. (1996) Genetic analysis of the Mullerian-inhibiting substance signal transduction pathway in mammalian sexual differentiation. *Genes Dev* **10**, 2577–2587.
Moffitt, T. E., Caspi, A. & Rutter, M. *et al*. (2001) *Sex differences in Antisocial Behaviour: conduct disorder, delinquency and violence in the Dunedin Longitudinal Study*. Cambridge: Cambridge University Press.
Morohashi, K., Mukai, T. & Kawabe, K. *et al*. (2000) Adrenocortical and gonadal differentiation regulated by transcrip-

tion factors, Ad4BP/SF-1 (NR5A1) and Dax-I (NROB1). *Endocrine Research* **26**(4), 953.

Murphy, D. G. M., DeCarli, C. & McIntosh, A. R. *et al.* (1996) Sex Differences in human brain morphometry and metabolism: an *in vivo* quantitative magnetic resonance imaging and positron emission tomography study on the effect of aging. *Arch Gen Psychiatry* **53**, 585–594.

Nachtigal, M. W., Hirokawa, Y. & Enyeart-VanHouten, D. L. *et al.* (1998) Wilm's tumor 1 and DAX-1 modulate the orphan nuclear receptor SF-1 in sex-specific gene expression. *Cell* **93**, 445–454.

Page, D. C., Mosher, R. & Simpson, E. M. *et al.* (1987) The sex-determining region of the human Y chromosome encodes a finger protein. *Cell* **51**, 1091–1104.

Paus, T. & Otaky, N. & Caramanos, Z. *et al.* (1996) In vivo morphometry of the intrasulcal gray matter in the human cingulated, paracingulate and superior-rostral sulci: hemispheric asymmetries, gender differences and probability maps. *J Comp Neurol* **376**, 664–673.

Plenge, R. M., Hendrich, B. D. & Schwartz, C. *et al.* (1997) A promoter mutation in the XIST gene in two unrelated families with skewed X-chromosome inactivation. *Nat Genet* **17**, 353–356.

Plomin, R. (1999) Genetics and General Cognitive Ability. *Nature* **402**, C25–C29.

Reinisch, J. M. (1981) Prenatal exposure to synthetic progestins increases potential for aggression in humans. *Science* **211**, 1171–1173.

Raymond, C. S., Parker, E. D. & Kettlewell, J. R. *et al.* (1999) A region of human chromosome 9p required for testis development contains two genes related to known sexual regulators. *Hum Mol Genet* **8**, 989–996.

Renfree, M. B. & Short, R. V. (1988) Sex determination in marsupials: Evidence for a marsupial-eutherian dichotomy. *Phil Trans R Soc Lond* **322**, 41–53.

Resnick, S. M., Gottesman, I. I. & McGue, M. (1993) Sensation seeking in opposite-sex twins: an effect of prenatal hormones? *Behav Genet* **23**, 323–329.

Ropers, H.-H., Hoeltzenbein, M. & Kalscheuer, V. *et al.* (2003) Nonsyndromic X-linked mental retardation: where are the missing mutations? *Trends in Genetics* **19**, 316–320.

Rose, R., Kaprio, J. & Winter, T. *et al.* (2002) Femininity and Fertility In Sisters With Twin Brothers: Prenatal Androgenization? Cross-Sex Socialization? *Psychol Sci* **13**, 263–267.

Rosenblitt, J. C., Soler, H. & Johnson, S. E. *et al.* (2001) Sensation seeking and hormones in men and women: exploring the link. *Horm Behav* **40**, 396–402.

Rozen, S., Skaletsky, H. & Marszalek, J. D. *et al.* (2003) Abundant gene conversion between arms of palindromes in human and ape Y chromosomes. *Nature* **423**, 873–876.

Saito-Hisaminato, A., Katagiri, T. & Kakiuchi, S. *et al.* (2002). Genome-wide profiling of gene expression in 29 normal human tissues with a cDNA micro-array. *DNA Research* **9**, 35–45.

Schiebel, K., Winkelmann, M. & Mertz, A. *et al.* (1997) Abnormal interchange between a novel isolated protein kinase gene, *PRKY*, and its homologue, *PRKX*, accounts for one third of all (Y+)XX males and (Y-)XY females. *Hum Mol Genet* **6**, 1985–9189.

Schlaepfer, T. E., Harris, G. J. & Tien, A. Y. *et al.* (1995) Structural differences in the cerebral cortex of healthy females and male subjects: a magnetic resonance imaging study. *Psychiatry Res* **61**, 129–135.

Shaw, G., Renfree, M. B. & Short, R. V. *et al.* (1988) Experimental manipulation of sexual differentiation in wallaby pouch young treated with exogenous steroids. *Development* **104**, 689–701.

Sikich, L. & Todd, R. D. (1988) Are the neurodevelopmental effects of steroid hormones related to sex differences in psychiatric illness? *Psychiatric Development* **4**, 277–309.

Silverman, I. & Eals, M. (1992) Sex differences in spatial abilities: Evolutionary theory and data. In: *The Adapted Mind (*eds. J. H. Barkow, L. Cosmides, & J. Tooby), pp. 533–549. New York: Oxford University Press.

Sinclair, A. H., Berta, P. & Palmer, M. S. *et al.* (1990) A gene from the human sex-determining region encodes a protein with homology to a conserved DNA-binding motif. *Nature* **346**, 216–217.

Skaletsky, H., Kuroda-Kawaguchi, T. & Minx, P. J. *et al.* (2003) The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes. *Nature* **423**, 825–837.

Skuse, D. H., James, R. S. & Bishop, D. V. *et al.* (1997) Evidence from Turner's syndrome of an imprinted X-linked locus affecting cognitive function. *Nature* **387**, 705–708.

Slijper, F. M. (1984) Androgens and gender role behaviour in girls with congenital adrenal hyperplasia (CAH). *Prog Brain Res* **61**, 417–422.

Smith, C. A., McClive, P. J. & Western, P. S. *et al.* (1999) Conservation of a sex-determining gene. *Nature* **402**, 601–602

Stavropoulos, N., Lu, N. & Lee, J. T. (2001) A functional role for Tsix transcription in blocking Xist RNA accumulation but not in X-chromosome choice. *Proc Natl Acad Sci U.S.A* **98**, 10232–10237.

Steiner, M., Dunn, E. & Born, L. (2003) Hormones and mood: from menarche to menopause and beyond. *J Affect Disord* **74**, 67–83.

Swaab, D. F. & Hofman, M. A. (1984) Sexual differentiation of the human brain: A historical perspective. *Prog Brain Res* **61**, 361–374.

Swain, A., Narvaez, V. & Burgoyne, P. *et al.* (1998) Dax1 antagonises Sry action in mammalian sex determination. *Nature* **397**, 761–767.

Tiberio, G. (1994) MZ Female twins discordant for X-linked diseases: A review. *Acta Genet Med Gemellol* **43**, 207–214.

Turner, A. K. (1994) Genetic and hormonal influence on male violence. In: *Male Violence* (eds. J. Archer), New York: Routledge.

Van Honk, J., Tuiten, A. & Verbaten, R. *et al*. (1999) Correlations among Salivary Testosterone, Mood, and Selective Attention to threat in Humans. *Horm Beh* **36**, 17–24.

Veldhuis J. D. (2003) Neuroendocrine facets of human puberty. *Neurobiology of Aging* **24**, Suppl 1, S93–S119.

Vierikko, E., Pulkkinen, L. & Kaprio, J. *et al*. (2003) Sex Differences in genetic and Environmental Effects on Aggression. *Aggressive behaviour* **29**, 55–68.

Williams, C. L. & Meck, W. H. (1991) The organizational effects of gonadal steroids on sexually dimorphic spatial ability. *Psychoneuroendocrinology* **16**, 155–176.

Witelson, S. F. (1991) Neural sexual mosaicism: sexual differentiation of the human temporo-parietal region for functional asymmetry. *Psychoneuroendocrinology* **16**, 131–153.

Xu, J., Burgoyne, P. S. & Arnold, A. P. (2002) Sex differences in sex chromosome gene expression in mouse brain. *Hum Mol Genet* **11**, 1409–1419.

Yao H. H., Tilmann, C. & Zhao, G. Q. *et al*. (2002) The battle of the sexes: opposing pathways in sex determination. *Novartis Foundation Symposium* **244**, 187–98.

Yurgelun-Todd, D. A., Killgore, W. D. & Young, A. D. (2002) Sex differences in cerebral tissue volume and cognitive performance during adolescence. *Psychology Reports* **91**, 743–757.

Zechner, U., Wilda, M. & Kehrer-Sawatzki, H. *et al*. (2001) A high density of X-linked genes for general cognitive ability: a run-away process shaping human evolution. *Trends Genet* **17**, 697–701.

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