The Role of the *Y* Chromosome in Brain Function

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Abstract: In mammals, sex differences are evident in many aspects of brain development, brain function and behaviour. Ultimately, such differences must arise from the differential sex chromosome complements in males and females: males inherit a single X chromosome and a Y chromosome, whilst females inherit two X chromosomes. One possible mechanism for sexual differentiation of the brain is *via* male-limited expression of genes on the small Y chromosome. Many Y-linked genes have been implicated in the development of the testes, and therefore could theoretically contribute to sexual differentiation of the brain indirectly, through influencing gonadal hormone production. Alternatively, Y-linked genes that are expressed in the brain could directly influence neural masculinisation. The present paper reviews evidence from human genetic studies and animal models for Y-linked effects (both direct and indirect) on neurodevelopment, brain function and behaviour. Besides enhancing our knowledge of the mechanisms underlying mammalian neural sexual differentiation, studies geared towards understanding the role of the Y chromosome in brain function will help to elucidate the molecular basis of sex-biased neuropsychiatric disorders, allowing for more selective sex-specific therapies.

INTRODUCTION

There is a substantial body of evidence showing that female and male mammals (including humans) differ with respect to many aspects of their physiology and behaviour. Neuropsychological studies in man (to use the term in its loosest sense) have demonstrated that males tend to outperform females on behavioural tasks tapping visuospatial and navigational skills, whereas females tend to score more highly on tasks assaying verbal and social proficiency [1]. Females also tend to exhibit superior performance in assays of object location memory [2,3], emotion recognition [4,5] and empathy [6], whilst males are more likely to exhibit higher levels of aggression and behavioural disinhibition [1,7]. A combination of early *post mortem* studies and more recent *in vivo* neuroimaging work has identified a number of brain structures whose anatomy is sex-specific, and whose different function in males and females may underlie the behavioural effects described above [8]; these include the amygdala (larger in males), the hippocampus (larger in females), the corpus callosum (larger in females, but see [9]) and regions of the cerebral cortex. With respect to the latter structure, women tend to have larger paralimbic and fronto-orbital areas, whereas men generally have a larger fronto-medial cortex [10]. Sexual dimorphisms have also been reported in the hypothalamus, an area implicated in sexual preference and numerous sex-related behaviours. Simon Le Vay's work in particular has demonstrated that the interstitial nuclei of the anterior hypothalamus region 3 is approximately three times larger in heterosexual men than in homosexual men and heterosexual women [11]. Whilst many brain and behavioural findings regarding sex differences in humans are robust, and have been recapitulated in animal models [12-14], the magnitude, functional relevance, and even the veracity of others has been a matter for some debate [15]. Inconsistent findings between studies may be due to i) small effect size, ii) failure to take into account stage of the female menstrual cycle, iii) poorly specified phenotypes of interest, and iv) more general phenomena such as differential matching for IQ and social status between the sexes. The advent of more refined behavioural/neuropsychological testing procedures, and more sophisticated imaging techniques will improve the identification and characterisation of sexually dimorphic brain and behavioural substrates.

Sexual differentiation, the process by which females and males acquire their distinctive physiologies, is a downstream consequence of the fact that the sexes possess different chromosomal complements [16]. In mammals, males possess a single X chromosome (invariably inherited from their mother) and a single Y chromosome (inherited from their father), and, as such, have the karyotype 46,XY. Females, in contrast, inherit two X chromosomes, one from either parent (karyotype 46,XX). There are therefore three possible mechanisms through which sex-linked gene expression could contribute to sexual dimorphism in brain and behaviour (reviewed in [17]). Firstly, as females possess two X chromosomes, as opposed to the male's one, genes which escape the process of X-inactivation will be expressed approximately twice as highly in female than male tissues; the most contemporary estimates suggest that ~20% of all X-linked genes on the human X chromosome may escape X-inactivation to some extent [18,19]. Secondly, as the two sexes differ with respect to the parental origins of their X

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chromosomes, any so-called imprinted genes on this chromosome may exhibit sexually dimorphic expression; the degree to which an X-linked imprinted gene exhibits sexually dimorphic expression will depend upon whether it is preferentially expressed from the paternally or maternally inherited allele and whether or not it is subject to X-inactivation [20]. The third possible genetic mechanism through which sexual differentiation of the brain may occur, and the one upon which the remainder of this review will focus, is *via* the male-limited expression of genes in the non-recombining region (NRY) of the Y chromosome (i.e. those genes that are Y-unique) [17]. Our discussion shall consider: i) the structure and genetic complement of the Y chromosome, ii) how the genes upon it may shape male brain function and behaviour through indirect or direct means and how we may dissociate between the two possibilities, and iii) the role of the Y chromosome in engendering vulnerability to male-biased neuropsychiatric disorders.

THE Y CHROMOSOME

Despite its profound effects on sexual differentiation (see later), the brain effects mediated by the Y chromosome have not attracted the same amount of interest as those mediated by its larger and cognition-gene rich counterpart, the X; this may be because of the former's small size and low gene content [21]. In humans the X chromosome is ~155Mb in size and houses ~1500 genes, whereas the Y chromosome is just ~60Mb in size and houses ~350 genes, many of which are pseudogenes. Alternatively, it may be because, unlike the X chromosome, it is not subject to the intrinsically interesting epigenetic process of silencing, or because its repetitive structure means that it is not readily amenable to genetic and genomic studies.

THE HUMAN Y CHROMOSOME

The human Y chromosome, like the autosomes and the X chromosome, consists of a short (Yp) and a long (Yq) arm (~11.5Mb and ~48.5Mb respectively) separated by a centromere (Fig. **1**). At either end of the chromosome are regions which can recombine during meiosis with their equivalents on the X chromosome; as this recombinatory behaviour is reminiscent of that of the autosomes, these terminal domains are designated pseudoautosomal regions (or PARs). PAR1 is located on Yp, and contains ~10 genes. PAR2 is located on Yq and contains ~15 genes. Together, the PARs comprise ~5% of the basepair content of the chromosome. The remaining 95% of the chromosome constitutes the non-recombining region (NRY) referred to earlier (also known as the male-specific region or MSY). Currently, 156 transcription units (distinct regions of DNA which are transcribed into RNA) have been found on human NRY, 78 of which are protein-coding (27 distinct proteins or protein families) [22]. Genes on NRY fall into two categories: those that are expressed throughout the body (including the brain) and those that are expressed mainly, or exclusively, in testes and are likely to affect testis development and/or spermatogenesis. Microarray analysis comparing gene expression in *post mortem* male and female brains has suggested that ~20% of NRY-linked genes are expressed in this tissue, though this figure is probably an underestimate given sensitivity issues and the possibility of cross-hybridisation with closely related X-linked sequences [23]. The human NRY comprises three different types of euchromatic sequences (i.e. those which are likely to be transcribed)[22]: i) X-transposed sequences which have ~99% homology to equivalent regions on the X chromosome (although importantly they do not recombine) and are characterised by low gene and high repeat density ii) ampliconic sequences which exhibit a high degree of similarity (99.9%) to other NRY sequences and include genes mainly expressed in testes; these regions are usually large allowing for gene conversion, a phenomenon of non-reciprocal recombination between Y chromosome sequences that has resulted in eight large palindromes in the ampliconic sequences iii) X-degenerate sequences, which include single-copy genes and pseudogenes with an X chromosome homologue. X-degenerate genes are generally ubiquitously expressed - indeed, it is noteworthy that no ubiquitously expressed gene has yet been found amongst the other two types of sequence.

As the NRY does not recombine, it is generally passed unchanged from father to son with both sharing the same Y-linked polymorphism profile (or 'haplotype'). As Y-linked haplotypes tend to vary across geographical regions, and even between neighbouring countries due to the differential fixation of *de novo* mutations, haplotype analyses have been important in addressing questions regarding human origins and patterns of migration [24]. The utility of haplotype analyses to neurobiological studies, and the caveats associated with their use are discussed later.

THE Y CHROMOSOME IN RODENT MODELS

The Y chromosome of the most genetically amenable mammal, the mouse, is around the same size as its human equivalent (50-60Mb). As in man, it comprises two arms separated by a centromeric region, a minute Xp, and a long Xq. However, unlike in man, there is just one PAR, located at the Xq telomere [25]. The majority of the mouse Y chromosome has recently been sequenced [26]. This analysis has shown that the X-degenerate portion of the mouse Y is even more degenerate than that of the human Y, whilst the ampliconic portion of the mouse Y has expanded massively to cover ~95% of the chromosome with highly repetitive sequence. Many of the genes on the mouse Y chromosome have human orthologues and a large proportion influence testis development (e.g. *Sry*) [27,28] and/or spermatogenesis (e.g. *Eif2s3y*) [29]; consistent with the latter, the murine Y chromosome is highly condensed in somatic cells, becoming transcriptionally active only in germ cells [30]. Systematic deletion of Y-linked genes or gene families in mouse mutants has begun to unravel which genes are responsible for particular aspects of germ cell development [31]. As the sequencing of the Y chromosome of a second rodent, the rat, is ongoing it would be premature to draw any general conclusions about its structure. However, comparative studies of the rat and mouse Y chromosomes have noted the presence of species-specific repetitive sequences [32]. Moreover, it has been shown that *TSPY*, whose product is involved in spermatogenesis, is a functional gene in both rats and man, but is pseudogenic in the mouse [33].

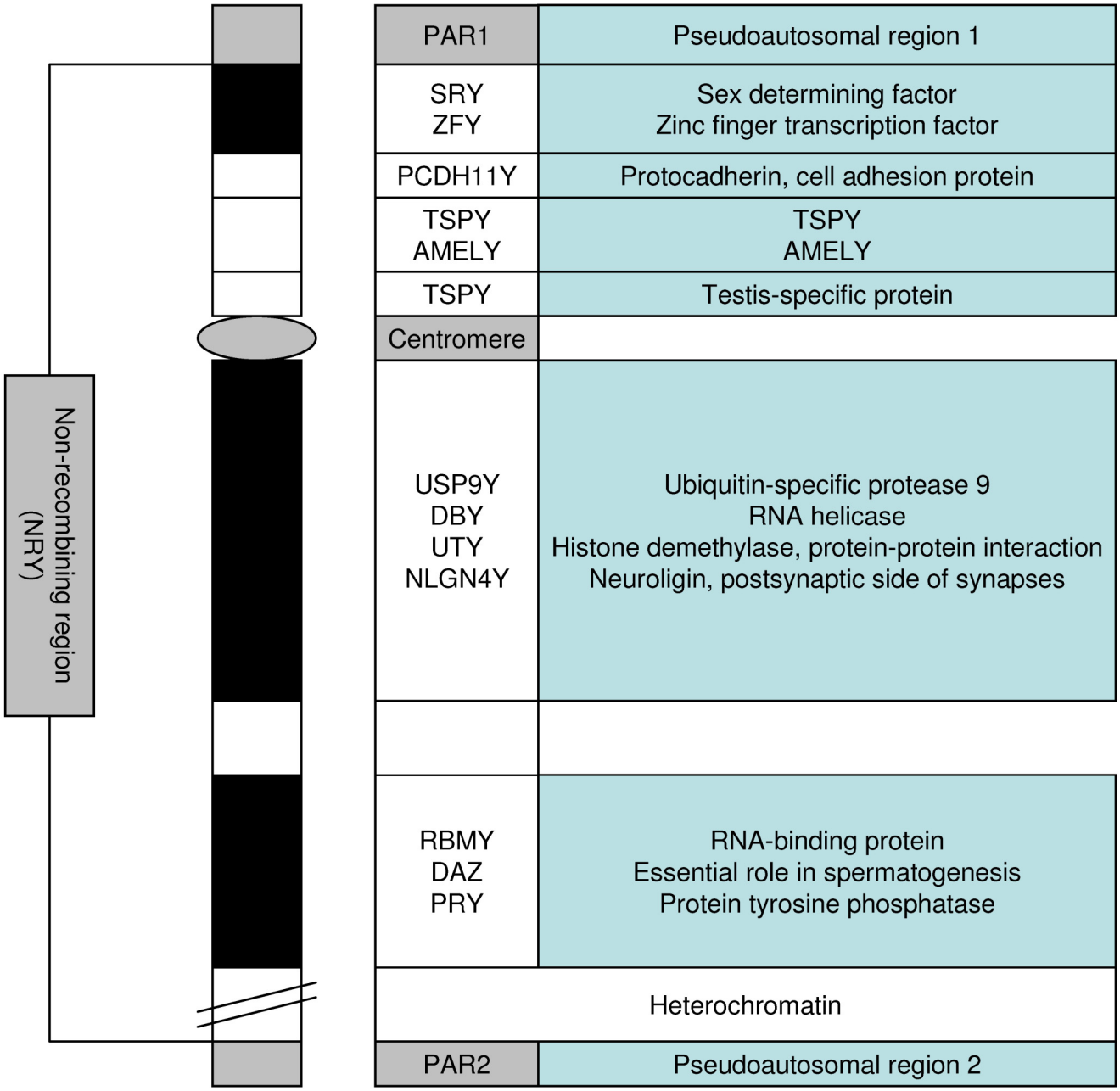

Fig. (1). Schematic of the human Y chromosome showing key structural features and genes.

SRY: The Sex-Determining Gene

Early work by Jacobs and Strong (amongst others) showed that, in mammals, in contrast to nematode worms and fruit flies, it was the inheritance of the Y chromosome (even in the presence of multiple X chromosomes) that initiated testis development and conferred male-typical physiological and behavioural traits [34]. Consequently, substantial effort was invested in trying to identify the locus responsible for the so-called testis-determining factor (TDF) within the critical sex-determining region of the Y. In 1990, a seminal Nature paper by Sinclair and colleagues reported a novel gene candidate for the TDF in man; this gene, located at Yp11.3, encoded a protein with a DNA-binding motif present in high motility group (HMG) proteins, and was designated *SRY* (for Sex-determining Region on the Y) [35]. The fact that this gene was deleted in 40,XY mice who appeared female provided converging evidence for its role as the crucial determinant of maleness [36]. Interestingly, *SRY* is the sole X-degenerate gene which is not ubiquitously expressed (it is predominantly expressed in testis). The precise molecular mechanisms through which *SRY* confers a male phenotype are beyond the scope of this review, and have been considered in detail elsewhere [37]. Briefly, data from mice suggests that during an expression period from embryonic day 10.5-12.5, Sry interacts with SF1 synergistically to upregulate *Sox9* gene expression, ultimately leading to Sertoli cell differentiation and subsequent testes development [38]. Once *Sry* expression declines, Sox9 levels are maintained at a high level, inducing, in combination with a collection of other proteins (notably WT1, SF-1 and GATA4), the expression of Anti-Mullerian hormone, the function of which is to prevent the

development of the mullerian ducts into the uterus. From approximately embryonic day 15 in rodents, Leydig cells in the developing testes synthesize testosterone, which is essential for the development of male genitalia [39]. In mammals, testosterone can affect masculinisation of the brain substantially in critical pre- and peri-natal periods (organisational effects) and in later postnatal life (activational effects). Testosterone exerts its effects either through its metabolite, estradiol, acting at estrogen receptors or directly by acting on androgen receptors. Conversion of testosterone to estradiol takes place locally in the brain through aromatisation by the P450 enzyme [40]. In rodents, brain areas that are sensitive to the influence of testosterone/estradiol include the medial amygdala, the medial preoptic area, the paraventricular nucleus, and the anteroventral periventricular nucleus of the hypothalamus [41,42]. In humans, masculinisation of the brain is thought to be caused primarily by the direct effects of testosterone on androgen receptors, and not through its aromatisation to estradiol [43]. Testosterone has been shown to influence a wide range of cognitive functions, notably visuospatial ability, object recognition and working memory, in both humans and rodents. Administering high levels of testosterone to female rats *in utero* improved their subsequent visuospatial performance [44], whilst performance on various behavioural tasks assaying visuospatial and working memory and object recognition has been shown to be impaired in gonadectomised male rats [45-48]. In humans, males with a higher level of testosterone have been reported to have superior visuospatial abilities [49]. Importantly, therefore, in mammals, *SRY* (and indeed any other Y-linked gene which affects testis development and subsequent gonadal hormone secretion) could influence the development of male-specific neurobiology by indirect means. In marsupials like the tammar wallaby many somatic sex differences are evident prior to testicular formation, implying that in this group, there is a greater degree of hormonal independence in sexual differentiation than in mammals (and, therefore a greater reliance on direct sex-linked gene effects)[50].

SRY in the Brain

Although *SRY* is chiefly expressed in the testes, it is also expressed to some extent in other tissues including heart, liver and kidney, and certain brain regions [51,52]. Hence, besides influencing male-specific traits indirectly, theoretically it could influence neurodevelopment and brain function in a direct cell-autonomous manner. In humans, *SRY* expression has been described in the medial rostral hypothalamus, frontal and temporal cortex [52]. In adult rodents, the gene is expressed in the hypothalamus and midbrain (notably the substantia nigra and the ventral tegmental area) [53,54]. In mice at least, the gene is expressed in two different forms depending upon developmental stage: during embryogenesis, circular (and untranslated) transcripts are produced, whilst linear (and translatable) transcripts are produced thereafter [55]. The transition between expressed forms is presumably due to a developmental switch in promoter usage, but the evolutionary and functional reasons behind it remain to be investigated. In mice and humans, *Sry* is a single copy gene; in contrast, in rats and certain other rodent species multiple Y-linked copies of the S*ry* gene have been reported [56-58]. Six *Sry* copies have been identified in the NRY of *Rattus norvegicus*: *Sry1*, *Sry2*, *Sry3*, *Sry3B*, *Sry3B1*, and *Sry3C*; all six copies have a conserved opening reading frame and the difference between them is less than 2% [56]. Our initial gene expression analyses have shown that in rat brain *Sry2* is the predominant transcript (>90% of transcripts), whilst *Sry1* may be expressed at low levels in some strains (unpublished observations). These findings mirror the results from other rat tissues: in testis, *Sry2* constitutes ~50% of all *Sry* transcripts, whilst in the adrenal glands the *Sry* transcript pool is almost exclusively of the *Sry2* variety [56].

The expression of *Sry* in brain and adrenal tissue rich in catecholaminergic cells led Milsted and colleagues to test whether the protein might be influencing the expression of genes important in catecholamine biosynthesis. Their *in vitro* assays showed that Sry appeared to bind at the promoter region of the gene encoding tyrosine hydroxylase (the rate-limiting enzyme in dopamine biosythesis) to enhance its transcription [59]. These data suggest that one way in which Sry acts to confer maleness is through affecting development of the dopaminergic system; they further imply that SRY (dys)function may contribute towards the male bias in certain conditions with a known catecholaminergic basis e.g. ADHD, addiction and hypertension [60-62]. Future work might be directed towards identifying other key transcriptional targets for Sry in the brain by using chromatin immunoprecipitation for example.

DOWNSTREAM BRAIN AND BEHAVIOURAL FUNCTIONS OF *SRY*

As mentioned above, Sry may influence brain and behaviour either indirectly, *via* effects on testis development and subsequent hormone secretion, or directly *via* its expression in neural tissue. The downstream effects of Sry on brain function and behaviour may be most readily addressed using rodents, and in this section, we describe two model systems which have recently been used to some effect.

i) 4-Core Genotype Cross

One mouse model which may be used to identify *Sry*-dependent and *Sry*-independent sexually dimorphic phenotypes is the so-called '4-core genotype cross' (comprehensively reviewed by Arnold and Chen [63]). *Sry*-dependent phenotypes may be due to indirect effects of the protein (*via* effects on testis differentiation and function) or to direct effects on brain function. *Sry*-independent phenotypes are due to the influence of sex-linked genes other than *Sry*. The model makes use of a variant of the Y^{129} chromosome deleted for *Sry* (*Tdy*^{m1} mutation [64]), designated Y^-, and an autosomally located ubiquitously expressed *Sry* transgene. A cross between a 40,XY^-*Sry* male (i.e. a mouse with the deletion of the Y-linked *Sry* gene, and an autosomal transgene) and a 40,XX female generates 'four core genotypes': 40,XX (chromosomally and gonadally female), 40,XX*Sry* (chromosomally female, but gonadally male due to the presence of the autosomal *Sry* transgene), 40,XY^- (chromosomally male, and gonadally female due to loss of endogenous *Sry* expression), and finally, 40,XY^-*Sry* (chromosomally and gonadally male). The key point about the model is that through the use of pre-planned comparisons, *Sry*-dependent and independent processes may be dissociated. Specifically, a difference in a particular brain or behavioural parameter between 40,XX and 40,XX*Sry*

mice (or between 40,XY$^-$ and 40,XY$^-$ mice) would imply an effect which was dependent upon the presence of the *Sry* transgene. In contrast, a difference between 40,XX and 40,XY$^-$ mice (or between 40,XX*Sry* and 40,XY$^-$*Sry* mice) who are matched for gonadal sex but not for sex chromosome complement, would imply an *Sry*-independent sex-linked gene effect; the precise mechanism underlying this effect could then be elucidated using alternative models such as the 39,XO mouse [65].

Documented *Sry*-dependent brain and behavioural phenomena include progesterone receptor expression in the anteroventral periventricular nucleus, the medial preoptic nucleus, and the ventromedial nucleus [66], cortical thickness [67] and various sexual behaviours including degree of mounting, latency to mount and latency to thrust [68]. A dosage-dependent *Sry* effect on sexual behaviours is consistent with the observation that male mice with an additional Y chromosome (41,XYY) have shorter latencies to intromit, and to ejaculate than their 40,XY counterparts [69]. Our own ongoing work has shown that the expression of an *Sry* transgene may shape cognition, in that 40,XX*Sry* and 40,XY$^-$*Sry* mice made fewer errors in learning a maze-based task than animals without the transgene (unpublished results). Given that in mammals, the vast majority of known effects of the Y chromosome, are hormonally-mediated, most *Sry*-dependent effects, including those described above, are likely to be mediated *via* effects on testis differentiation and subsequent hormone (notably testosterone) release. There is a substantial literature describing the important and wide-ranging organisational and activational effects of testosterone on sexual differentiation of the brain [70].

Direct sex-linked gene effects (i.e. *Sry*-independent effects) have, to date, been described upon a multitude of measures including: autoimmune disease vulnerability [71], neural tube defects [72], nociception [73], habit formation [62], differentiation and development of mesencephalic dopaminergic neurons [74] and vasopressin immunoreactivity in the lateral septum [68,75].

ii) Knockdown of *Sry* Expression

To address the difficulty inherent in the 4-core genotype model of ascribing *Sry*-dependent effects to direct or indirect (hormonally-mediated) influences, one may turn to another model system. Specifically, the effects of artificially downregulating *Sry* expression at key brain sites in order to ascertain the effects on previously identified *Sry*-dependent phenotypes could be examined. If *Sry* downregulation has no effect on the phenotype of interest, it may be concluded that the phenotype is likely to be gonadal hormone-dependent; conversely, if the downregulation is effective, one might conclude that the phenotype is dependent upon the action of brain-expressed *Sry*. Recently, Dewing *et al.* used antisense oligonucleotides to knock down *Sry* expression in the rat substantia nigra [53]. This manipulation led to a decrease in tyrosine hydroxylase expression in this brain region (consistent with the previous data suggesting Sry as a transcriptional activator) and motor deficits. As the authors pointed out these results demonstrated 'a direct male-specific effect on the brain by a gene encoded only in the male genome'. Furthermore, they speculated that the results may be of relevance to the molecular pathogenesis of Parkinson's Disease which is more common in males [76], and which is characterised by motoric dysfunction and dopaminergic neuron loss in the substantia nigra. One exciting question which follows from this is whether, besides influencing motor function, Sry may directly influence behavioural (cognitive) endophenotypes, particularly those sensitive to dopaminergic manipulation; monitoring the brain and behavioural effects of knocking down *Sry* expression in the rat ventral tegmental area for example may help to address this point.

In addition to looking in animal models, we may also gain insights into the brain and behavioural functions of *SRY* by looking at humans with deletions of, or inactivating mutations in, the gene. However, as these mutations will abrogate *SRY* function in all tissues, as in the 4-core genotype cross, it will not be possible to dissociate between indirect and direct *SRY* effects. As these subjects are relatively rare, no comprehensive brain and behavioural analyses have been performed on them to date. Case studies of 46,XY females with *SRY* mutations and consequent gonadal dysgenesis [28,77-79] report that, in terms of psychosexual behaviour, such subjects tend to exhibit a female-typical profile in that they are attracted to men [79]. This observation indicates that *SRY* may play a fundamental role in sexual preference. Future work examining the behavioural/cognitive profiles of subjects with reduced or enhanced *SRY* dosage (notably 46,XY females or 46,XX males respectively) will help to clarify the role of *SRY* in brain function.

THE BRAIN AND BEHAVIOURAL EFFECTS OF THE SEX-LINKED *STS* GENE

A second sex-linked gene that has relatively well-defined effects on brain and behaviour is *Sts*, encoding the enzyme steroid sulfatase. Steroid sulfatase is responsible for the desulfation of various neuroactive steroids, notably of the GABAergic modulator dehydroepiandrosterone sulphate (DHEAS) to DHEA [80]. The enzyme is expressed most highly during embryogenesis in the placenta and the liver and in the cortex, thalamus and hindbrain [81]. In mice, *Sts* is the only known PAR gene [82,83], and is therefore expressed from both the X and Y chromosomes.

Aggression in mice is highly sexually dimorphic, with males exhibiting a far greater tendency to attack their conspecifics. A genetic study aiming to identify and characterise the Y chromosomal correlates of this sexual dimorphism localised the underlying region to the Y-PAR [84]. As the only known PAR gene, *Sts* immediately became an excellent genetic candidate for these effects on aggression. Follow-up pharmacological studies targeting the steroid sulfatase axis seem to confirm a role for the enzyme in the brain processes underlying aggression [85]. Besides influencing aggression, parallel genetic and pharmacological studies have demonstrated that steroid sulfatase may influence attention and impulsivity in mice [86,87]. As an aside, work by Maxson has shown that the NRY region of several pairs of inbred mouse strains can have differential effects on offense, suggesting *Sry* as a plausible positional candidate for effects on aggression [88].

Work in rats has shown that steroid sulfatase can influence learning and memory [89] and hippocampal

acetylcholine release [90]. However, as *Sts* is non-pseudoautosomal in rats and has no detectable Y homologue [91], these neurobiological effects must be attributable to the X-linked *Sts* gene.

In man, subjects with deletions of the *STS* gene, or inactivating mutations within it, and thus presenting with the disorder X-linked ichthyosis, appear to display heightened vulnerability to autism and to predominantly-inattentive subtype ADHD [92]. Moreover, the *STS* gene has been associated with ADHD [93], suggesting that steroid sulfatase may underlie attentional processes in both rodents and humans. *STS* is located on the distal short arm of the X chromosome (Xp22.3), very close to PAR, and it escapes X-inactivation [94]. Unlike in the rat, in man, X-linked *STS* has a homologue located on the long arm of the Y chromosome, although a succession of base substitutions, and small insertions and deletions appear to have rendered this Y-linked version a non-expressed pseudogene [95]. The fact that *STS* escapes X-inactivation (and is therefore expressed from both X chromosomes), and that it has no functional Y homologue, could potentially explain the reported higher activity of the enzyme in female than male tissues [96,97]. Furthermore, this sex difference in steroid sulfatase activity could explain why males and females are differentially vulnerable to disorders of attention and impulse control such as ADHD and pathological gambling.

THE EFFECTS OF OTHER Y-LINKED GENES ON BRAIN AND BEHAVIOUR

SRY and *STS* are perhaps the best characterised genes resident on the Y chromosome in terms of their brain and behavioural functions, although it must be acknowledged that in many respects our knowledge about the role of these two genes is lacking. However, there are several other Y-linked genes in NRY, which, in that they are expressed in the brain, could also potentially contribute towards neural sexual differentiation. Xu and colleagues described six NRY genes (*Dby* (now *Ddx3y*) *Ube1y*, *Smcy* (now *Kdm5d*), *Eif2s3y*, *Uty*, and *Usp9y*) which were expressed at one or more developmental stages in male and 40,XY female mouse brain (the latter indicating a lack of requirement for testicular secretions)[98]. Of the genes analysed, all had an X-linked homologue, which was definitively known to escape X-inactivation in three cases (*Smcx/Kdm5c*, *Utx* and *Eif2s3x*). In several cases, the expression of the Y homologue in males was much lower than its X-linked homologue, and as such was not sufficient to ensure dosage compensation between the sexes. A further intriguing possibility when considering the genetic mechanisms underlying sexually dimorphic brain phenotypes, is that X and Y-linked homologues, in addition to being expressed at different levels, are expressed at different developmental stages and/or in different brain regions. Indeed, recent work by Xu *et al.* has shown that the paralogues *Utx* and *Uty* are differentially expressed in the paraventricular nucleus of the hypothalamus (high *Uty* expression) and in the amygdala (high *Utx* expression), possibly as a consequence of differential epigenetic marks [99]. To our knowledge, no comprehensive survey comparing the relative spatiotemporal expression dynamics of X and Y homologues has yet been performed, although it has been shown that that there is some consistency in the expression patterns of *Eif2s3y* and *Eif2s3x*, with highest expression of both in the thalamus, hypothalamus, hippocampus and cerebellum [100]. The expression patterns for many mouse NRY genes are now documented in resources such as the Allen Brain Atlas: of the Y-linked genes mentioned above, *Ube1y* and *Eif2s3y* are highly expressed throughout the hypothalamus. As the pituitary gland is pivotal in the secretion of hormones underlying sex-specific physiology, it would be worthwhile examining the expression of Y-linked genes in specific endocrine cell types of this tissue. In many cases, the brain and behavioural functions of NRY-linked genes are obscure, a fact probably attributable to the structural nature of the Y chromosome precluding the development of knockout models. Insights into the range of neural functions underpinned by NRY genes are likely to come from Y-chromosome mutant mice (in which Y-linked genes are spontaneously deleted or duplicated); alternatively, insights may come from a comparison of normal male mice and 39,X^mO mice [65], the two groups only differing in the fact that the latter has no Y chromosome.

There are human orthologues of *Ddx3y*, *Kdm5d, Uty* and *Usp9y*, therefore investigations in mouse models into the neurobiological functions of these genes are likely to shed light upon their role in male brain development in humans. There appear to be species differences between mice and humans with regard to some Y-linked brain-expressed genes, in that *Ube1y* and *Eif2s3y* have no human counterparts, whilst *ZFY* appears to be expressed in the hypothalamus and cortex of adult humans [52], but is not expressed at any developmental stage in mouse brain [98]. Hence, it is likely that the nature of the neural sexual differentiation process is, to a greater or lesser extent, species-specific. One X-Y homologous gene pair which has received a lot of interest regarding its role in neurodevelopment is *PCDH11X/Y*. The homologous genes are located within a hominid-specific region of the sex chromosomes (Xq21.3 and Xp11.2), and encode members of the protocadherin superfamily responsible for cell-cell interactions during development of the central nervous system [101]. Not only are *PCDH11X* and its Y counterpart structurally different (and therefore possibly functionally distinct) but they have been shown to exhibit differential expression patterns, most likely because the two genes possess different promoter regions [101]. In the brain, transcripts from both *PCDH11X* and *PCDH11Y* are present most highly in the cortex [102], and also in several subregions including the amygdala, caudate nucleus, hippocampus and thalamus [101]. Interestingly, *PCDH11X* seems to be the preferential transcript in the cerebellum; in the heart, transcripts are predominantly from *PCDH11X*, whereas in the kidney, liver, muscle and testis transcripts come mainly from *PCDH11Y* [101]. Together these data indicate that *PCDH11X/Y* genes may play key modulatory roles in the sexual differentiation of a wide variety of organs (including the brain) in hominid mammals. Exactly how *PCDH11Y* may act in the brain to modulate function remains to be resolved, but work in prostate cancer cell culture suggests that it may influence neuroendocrine tissue transdifferentiation *via* classical Wnt signalling pathways [103].

Y CHROMOSOME EFFECTS ON VULNERABILITY TO NEUROPSYCHIATRIC DISORDERS

For most multigenic human disorders, the underlying substrates are unknown or their functions are poorly understood. Neuropsychiatric disorders, in particular, are likely to have a complex and multifactorial basis, with their development and course being influenced by genetic and environmental factors, and by interactions between the two. Whilst there is some controversy regarding the extent and specificity with which behaviour differs between the sexes in healthy populations, it is clear that many, if not all, neuropsychiatric disorders show some sort of sex-bias in their presentation, even allowing for possible ascertainment biases; this observation implies that male and female brains are somehow differentially sensitive to such disorders. This sex-bias may be evident in terms of the incidence of the disorder, its age-at-onset, its progress, its response to conventional therapeutics, its underlying neurobiology, or a combination of some or all of these. In terms of specific conditions, we know that males are more commonly affected by developmental disorders such as ADHD [104] and that they may be more severely affected by some disorders: for example, a recent longitudinal study following patients with schizophrenia for 20 years, has shown that female schizophrenic patients have a significantly better course of illness and better global functioning than male patients even taking into the account the earlier age-at-onset for men (the mean age of onset is approximately 4 years earlier for men than for women) [105]. In contrast, females are more prone to affective disorders with a later onset, usually during adolescence, such as unipolar depression and anxiety [106]. The observation that males and females differ in their susceptibility to neurodevelopmental disorders such as autism and ADHD suggests that sex-linked genes may be particularly important *in utero* in directly modulating critical neurodevelopmental processes (either directly or *via* effects on prenatal gonadal hormone levels).

Case or small-scale studies have suggested a role for Y chromosome genes in some neuropsychiatric disorders. For example, individuals with 47,XYY syndrome are at elevated risk of developing antisocial behaviour [107] and may be at increased risk of developing schizoaffective disorder [108], probably as a consequence of NRY gene over-expression. A potential role for Y-linked genes in the pathogenesis of schizophrenia is also supported by the observation of an isodicentric Y chromosome in a schizophrenic patient [109]. A case study has implicated Y-linked genes in ADHD susceptibility: in this case, the affected boy possessed a rare deletion of Yq with duplication of Yp [110]. Interestingly, the duplicated region included the *SRY* gene, suggesting that overdosage of this specific gene may be responsible (either directly or indirectly) for the observed behavioural phenotype. One important caveat with studies such as these is that the co-occurrence of a particular cytogenetic mutation and a particular neuropsychiatric manifestation does not necessarily imply that the two are linked.

Although studies examining rare Y-linked mutations or rare polyploidies such as those described above may provide important proof-of-principle data about the involvement of sex-linked genes in neuropsychiatric phenotypes, ideally we would like to know the extent to which common Y-linked genetic variants may predispose to male-biased mental illnesses within the general population. In order to address this question, association studies have compared Y chromosome haplogroups (i.e. a group of haplotypes that share a common ancestor) in patient and control cohorts. This experiment represents an indirect way of examining whether Y chromosome polymorphisms are involved in a disorder and assumes that a variant conferring susceptibility arose against a specific Y chromosome haplogroup background - due to the lack of recombination within the NRY, the susceptibility variant would be co-inherited with the variants that define this haplogroup. In association studies of this type, ensuring control and patient groups are adequately matched is vital, given that Y chromosome haplogroups may vary substantially with geographical region [111]. This matching process has been facilitated by the work of the Y Chromosome Consortium, a collaborative body dedicated to studying variation within the human Y chromosome. To date, the consortium has resolved nomenclature problems associated with Y-linked variants and has produced a parsimonious phylogenetic tree including all known Y chromosome haplogroups, the latest revised version of which contains 311 haplogroups and approximately 600 single nucleotide polymorphisms (SNPs) [112].

Using the strategy outlined above, significant associations between particular Y chromosome haplogroups and male-biased behavioural traits (including alcohol dependence [113] and aggression [114]) have been reported, whilst a study examining the relationship between Y chromosome haplogroups and autism failed to find any association [115]. However, the results of studies like these must be interpreted with caution given that they often use small, heterogeneous samples with non-overlapping Y chromosome markers. In our ongoing work, we are testing the idea that Y chromosome variation may contribute to ADHD and schizophrenia vulnerability in men, by comparing the haplogroups of large samples of Caucasian patients and controls of U.K. origin. Preliminary analyses suggest that, whilst there is little evidence for association with either disorder, there is an apparent modifying effect of Y chromosome variants on cognitive performance (performance IQ) in the ADHD sample (unpublished results). An obvious, and important, question which arises from this finding, is whether the effect is generalisable to a non-clinical male sample - if it is, identifying and characterising the causal variant will be a priority. Such work would have important ramifications for explaining the evolutionary basis of cognitive sexual dimorphism.

With regard to specific candidate genes for the male-bias in neuropsychiatric disorders, numerous factors make the *PCDH11Y* gene an attractive proposition. Firstly, it appears to be expressed in males in a highly regulated and spatiotemporally dynamic manner and is involved in synapse formation and neuronal path finding in the brain, processes which go awry in a number of common male-biased mental conditions [116]. The fact that *PCDH11Y* is not expressed (or only weakly expressed) in the cerebellum, whereas it is expressed elsewhere in the brain, could potentially explain why males are especially vulnerable to disorders with known cerebellar pathology (e.g. ADHD and autism). Finally, as mentioned previously, *PCDH11Y* is specific to the hominid

lineages and is absent in non-human primates such as chimpanzees and gorillas [117]; moreover, the gene has shown accelerated sequence change in the hominid lineage [118]. For this reason, it has been proposed, most vociferously by Timothy Crow and colleagues, that aberrant expression of the protein encoded by *PCDH11Y* could predispose males to disorders of human-specific functions such as language (thought to be a correlate of cerebral asymmetry), theory of mind and problem-solving flexibility [119]. There is convincing evidence that these types of human-specific function are impaired in a number of male-biased disorders, notably schizophrenia and autism [6,120]. However, initial, relatively small, candidate gene studies examining possible association between SNPs within *PCDH11Y* and a number of neurospsychiatric disorders (autism, ADHD, bipolar disorder, obsessive-compulsive disorder and schizophrenia/psychosis) have failed to find evidence for a link to date [102,119]. It is formally plausible that variation in *PCDH11Y*, or on the Y chromosome in general, may be responsible for vulnerability to these disorders in specific sub-groups. Alternatively, it may be that it is the expression pattern of the gene (which may be modulated epigenetically *via* environmental influences) which is more important in modulating its effect on male disease vulnerability than its sequence.

A second candidate gene that could potentially influence neuropsychiatric phenotypes is *NLGN4Y*, the Y homologue of *NLGN4X*. These genes encode cell adhesion molecules which interact with β-neurexins at the postsynaptic membrane during the process of synaptogenesis [121]. Early findings that mutations in *NLGN4X* were present in families with mental retardation and autism spectrum disorders suggested a possible causal link between the disorders and the gene mutation [122, 123]. The results of subsequent studies have suggested that, if mutations in *NLGN4X* are pathogenic, they are likely to be rare, and are not likely to explain the majority of cases of autism [124-127]. In a study explicitly focussing on sequence variants in *NLGN4Y*, Yan and co-workers identified one mis-sense variant present in one autistic patient and his learning-disabled father out of a population of 335 autistic or mentally retarded males [128]. This result is consistent with the idea that mutations in the *NLGN4* genes may contribute to the etiology of autism, but only in a limited proportion of cases.

CONCLUSIONS

Despite its small size, and limited gene content, we have argued here that the Y chromosome may exert a considerable influence on brain function. As a consequence of its inheritance pattern, genes upon it may help to define male-specific brain phenotypes, and hence male-typical behaviours. An alternative perspective is that, in some cases, Y-linked genes may act to attenuate sex differences (e.g. where the Y homologue of an X-linked escaping inactivation performs a functionally equivalent role). In this context, Dewing and colleagues suggested that, in rats, '*Sry* could compensate for a factor that is only present in females and maintains tyrosine hydroxylase expression in substantia nigra neurons', positing high levels of estrogens in females as such a factor [53]. A major goal for future work will be to describe the brain functions of Y-linked genes in terms of their relevance to selective evolutionary forces acting on the chromosome, such as sexual antagonism. Further studies on the Y chromosome will provide insights into the biological basis of neural sexual differentiation (or lack thereof), and will clarify the molecular basis of sex biases in common neuropsychiatric disorders.

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