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Review

The 39,XO mouse as a model for the neurobiology of Turner syndrome and sex-biased neuropsychiatric disorders

Phoebe M.Y. Lynn, William Davies *

Behavioural Genetics Group, School of Psychology and Department of Psychological Medicine, University of Cardiff, UK

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Abstract

Turner syndrome (TS) is a developmental disorder most frequently arising from the loss of a complete X chromosome (karyotype 45,XO). The disorder is characterised by physiological abnormalities (notably short stature and ovarian dysfunction), emotional anomalies (including heightened anxiety) and by a neuropsychological profile encompassing deficits in visuospatial skills, memory, attention, social cognition and emotion recognition. Moreover, TS subjects are at significantly increased risk of developing attention deficit hyperactivity disorder (ADHD) and autism. At the neuroanatomical level, TS subjects display abnormalities across a number of brain structures, including the amygdala, hippocampus and orbitofrontal cortex. The TS phenotype arises due to reduced dosage of X-linked genes, and may also be modulated by parental origin of the single X chromosome. In this review, we discuss the utility of a mouse model of TS, the 39,XO mouse, in which the parental origin of the single X chromosome can be varied. This model provides the opportunity to investigate the effects of X-linked gene dosage/parent-of-origin effects on neurobiology in the absence of gross physiological abnormalities. Initial findings indicate that several features of the TS behavioural phenotype may be accurately recapitulated in the mouse. Furthermore, as X-linked gene dosage/imprinting can influence sex-specific neurobiology, investigations in the 39,XO mouse are also likely to offer insights into why certain neuropsychiatric disorders (including ADHD and autism) affect the sexes differently.

Keywords: ADHD; Amygdala; Autism; Brain; Genomic imprinting; Haploinsufficiency; X-inactivation; X chromosome

Contents

* Corresponding author at: Department of Psychological Medicine, Cardiff University, Henry Wellcome Building, Heath Park, Cardiff CF14 4XN, UK. Tel.: +44 29 2074 4837; fax: +44 29 2074 4005.
E-mail address: daviesw4@cardiff.ac.uk (W. Davies).

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1. Turner syndrome

Turner syndrome (TS) is a chromosomal disorder affecting approximately 1 in 2500 live female births, in which there is a partial or complete loss of one X chromosome [63]. Approximately 60% of TS individuals have complete loss of one X chromosome (X-monosomy, karyotype 45,XO), whilst around 30% have cryptic mosaicism where a proportion of cells, including those in the brain, can have additional sex-linked sequences (e.g. a complete second X chromosome) besides the single X chromosome. The remaining 10% of TS individuals have structural abnormalities in one X chromosome, including for example, deletions of Xp and Xq (short and long arms of the X, respectively) [87].

Physiologically, three systems are disproportionately affected within TS females: skeletal, reproductive and lymphatic [75]. Skeletal changes include short stature and cubitus valgus (unusual bend of the elbows); reproductive abnormalities include ovarian dysgenesis and infertility (although some TS females can produce oestrogen spontaneously, allowing successful reproduction); lymphatic problems include oedema, coarctation of the aorta and horseshoe kidneys. TS subjects also exhibit deficits in certain aspects of neuropsychological functioning (described in detail later). The physiological and neuropsychological abnormalities associated with TS presumably arise due to haploinsufficiency for one or more products of X-linked genes that normally escape X-inactivation (the epigenetic process by which, in the somatic cells of 46,XX females, one of the two X chromosomes is randomly inactivated). To elaborate briefly, in humans, about 15% of X-linked genes escape X-inactivation and are expressed from the inactivated X chromosome [11]; such genes will therefore be expressed from both X chromosomes in 46,XX subjects, but only from one X chromosome in TS subjects. As their expression will be approximately halved in TS subjects, they represent candidates for X-monosomy effects.

In addition to effects due to haploinsufficiency, the TS phenotype may vary according to the parental origin of the single X chromosome. In ~70% of 45,XO TS cases, the single X chromosome is of maternal origin (45,$X^{m}O$) whereas in the remainder of cases it is of paternal origin (45,$X^{p}O$) [87]. Phenotypic differences between 45,$X^{p}O$ and 45,$X^{m}O$ subjects have been described with regard to cardiovascular abnormalities and neck webbing [12] as well as with regard to certain neurobiological parameters (again, described in more detail later). These so-called parent-of-origin effects (POE) can be explained by the presence of X-linked imprinted genes [17]. Imprinted genes undergo an epigenetic process whereby one of their alleles is silenced whilst the other is expressed, depending on its parental origin [18,20], and they may influence brain development/function and vulnerability to mental disorders [21,45]. Some imprinted genes are only, or predominantly, expressed from their paternally inherited allele (paternally expressed genes), whilst others are only expressed from their maternally inherited allele (maternally expressed genes). Thus, 45,$X^{p}O$ subjects will benefit from the action of paternally expressed X-linked genes (and will lack expression from maternally expressed X-linked genes), whereas the reverse is true for 45,$X^{m}O$ subjects.

X-linked imprinting is not the only mechanism that may give rise to phenotypic differences between 45,$X^{p}O$ and 45,$X^{m}O$ subjects; Henn and Zang [36] suggested that the presence of cryptic mosaicism, specifically, the presence of Y-linked sequences in 45,$X^{m}O$ (but not in 45,$X^{p}O$) subjects might be sufficient to explain between group differences. In order to dissociate Y-linked effects from X-linked imprinted effects as candidate molecular mechanisms underlying 45,$X^{p}O$ and 45,$X^{m}O$ differences as effectively as possible, 45,$X^{m}O$ subjects should routinely be tested for masculinisation and/or the presence of Y-linked sequences [80].

2. The neuropsychology of Turner syndrome

The specific neuropsychological deficits associated with TS include attentional problems, memory impairments, visuospatial processing problems, deficits in fear recognition, anxiety and impairments in social cognition, and motor functioning problems [27,63,69,76]. Both hormonal and environmental factors could feasibly contribute towards these deficits. However, the TS neuropsychological profile does not mirror that of women with ovarian failure, nor is it fully corrected by oestrogen supplementation, arguing against a solely hormonal basis [74]. Some aspects of the TS phenotype (notably the anxiety and social cognition abnormalities) may arise due to subjects being treated differently by others due to their short stature and physical abnormalities. However, 46,XX females of short stature have not been found with the same deficits as observed in TS subjects [27]. These findings suggest that the neuropsychological profile of TS is likely to have a significant genetic component. Given this, one may expect some overlap between the neuropsychological profile of TS females and normal males, who both possess a single X chromosome. Indeed, males, like TS subjects, score lower than females on aspects of attentional, memory and social cognitive function [34,81]. However, males do not seem to exhibit the deficit in fear recognition characteristic of TS females [33].

2.1. IQ and arithmetic skills

The general neuropsychological profile of TS includes lower performance IQ, but equivalent (or nearly equivalent) verbal IQ