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The development of mental state attributions in women with X-monosomy, and the role of monoamine oxidase B in the sociocognitive phenotype ☆

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Abstract

We hypothesized that women with Turner syndrome (45,X) with a single X-chromosome inherited from their mother may show mentalizing deficits compared to women of normal karyotype with two X-chromosomes (46,X). Simple geometrical animation events (two triangles moving with apparent intention in relation to each other) which usually elicit mental-state descriptions in normally developing people, did not do so to the same extent in women with Turner syndrome. We then investigated the potential role in this deficit played by monoamine oxidase B enzymatic activity. MAO-B activity reflects central serotonergic activity, and by implication the functional integrity of neural circuits implicated in mentalizing. Platelet MAO-B was substantially reduced in Turner syndrome. However, contrary to prediction, in this (relatively small) sample there was no association between MAO-B enzymatic activity and mentalizing skills in participants with and without Turner syndrome.

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1. Introduction

Turner syndrome (TS) (Turner, 1938) is a genetic condition affecting approximately 1 in 2500 live female births. Women with TS have a single intact X-chromosome (a karyotype denoted as X-monosomy or 45,X) compared to two in normal females (46,XX) and an X and a Y sex chromosome (46,XY) in normal males. It is the sole example of a condition in which an entire chromosome can be deleted without lethal consequences. Studying women with X-monosomy holds promise for elucidating the role of X-linked genes in normal development. Our focus here is on genes that influence social adjustment, which is significantly impaired in a substantial minority of females with X-monosomy (Creswell & Skuse, 2000). We have also reported anomalies in some aspects of sociocognitive processing in women with Turner syndrome and no gross social adjustment difficulties (Lawrence, Campbell, et al., 2003; Lawrence, Kuntsi, Coleman, Campbell, & Skuse, 2003).

Our group has suggested at least two avenues of genetic research that could account for anomalies of social development in 45,X females. The first relates to the parental origin of the X-chromosome. There may be differential expression of maternal and paternal alleles as a consequence of epigenetic modification. This can potentially result in 'parent-of-origin' effects on sexually dimorphic phenotypic traits (genomic imprinting; Donnelly et al., 2000) because the X-chromosome is asymmetrical in respect of parental origin and inactivation status in males and females. Our earlier research found that X-monosomic females whose single X-chromosome was maternal in origin had greater social adjustment difficulties than those in whom it was paternal (Skuse et al., 1997). Recent evidence has been found for X-linked imprinting of specific gene expression in mice (Davies et al., 2005; Raefski & O'Neill, 2005), but not yet in humans. There is some emerging evidence for structural differences in cortical and subcortical brain regions associated with the processing of social cues, which vary according to the parental origin of the normal X-chromosome in X-monosomy (Cutter et al., 2005; Skuse, 2005).

1.1. MAO enzymes in relation to social function

A second possibility, pursued in the present paper, is that one or more non-imprinted X-linked genes may also be associated with impaired adjustment in X-monosomic females compared with 46,XX females because two copies may be needed for normal development of the female 'social brain'. Here there should be no parent-of-origin effect. Recent evidence supporting the hypothesis has shown that a key influence of such genes may be in modulating the functional integrity of amygdala-fusiform connectivity (Skuse, Morris, & Dolan, 2005). The location of candidate genes has been mapped to a 5 Mb region on the short arm (Xp: see Good et al.,