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Review article

Mapping the effect of the X chromosome on the human brain: Neuroimaging evidence from Turner syndrome

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ABSTRACT

In addition to determining sex, the X chromosome has long been considered to play a crucial role in brain development and intelligence. Turner syndrome (TS) is caused by the congenital absence of all or part of one of the X chromosomes in females. Thus, Turner syndrome provides a unique "knock-out model" for investigating how the X chromosome influences the human brain in vivo. Numerous cutting-edge neuroimaging techniques and analyses have been applied to investigate various brain phenotypes in women with TS, which have yielded valuable evidence toward elucidating the causal relationship between the X chromosome and human brain structure and function. In this review, we comprehensively summarize the recent progress made in TS-related neuroimaging studies and emphasize how these findings have enhanced our understanding of X chromosome function with respect to the human brain. Future investigations are encouraged to address the issues of previous TS neuroimaging studies and to further identify the biological mechanisms that underlie the function of specific X-linked genes in the human brain.

1. Introduction

In addition to determining physical phenotypes (e.g., skin color, body height or biological sex), genotype plays a crucial role in various cognitive/behavioral abilities (McGue and Bouchard, 1998; Plomin, 1991; Plomin et al., 1994). The brain serves as a valuable endophenotype that bridges the gap between molecular genetics and complex behaviors (Plomin and Kosslyn, 2001; Thompson et al., 2002).

In previous decades, many cutting-edge neuroimaging techniques have been applied to investigate human brain structure and function in vivo. Numerous recent studies have combined both genetic and neuroimaging analyses to identify associations between genetic variations and neuroimaging phenotypes of the human brain. This line of research is referred to as imaging genetics; it may provide valuable insight into the mechanisms of how specific genes affect brain endophenotypes and ultimately shape cognitive/behavioral functions during normal development and/or in complex brain disorders (Bigos and Weinberger, 2010).

1.1. X chromosome

The X chromosome is one of two sex chromosomes in humans and contains approximately 1000 genes (~4% of the human genome) (Ross et al., 2005). In typically developing (TD) women with a normal karyotype (46, XX), one of the two X chromosomes is randomly inactivated, leading to equal expression of X-linked genes with men (46, XY). However, a subset of genes escapes the X-inactivation (Carrel et al., 1999; Disteche, 1999) (Fig. 1), most of which are located on the tips of the X chromosome, namely, the pseudoautosomal regions (PARs). In contrast to the majority of the X chromosome genes, genes in these PARs remain capable of meiotic recombination with the same homological region on the Y chromosome; thus, either sex may receive two copies of genes in PARs (Heard and Disteche, 2006; Helena Mangs and Morris, 2007).

Notably, the X chromosome has long been considered to play a crucial role in the development of the human brain and intelligence (Johnson et al., 2009; Lehrke, 1972; Turner, 1996). As demonstrated by genomic data, many X-linked genes are involved in postsynaptic protein coding, which is essential for neuronal plasticity and cognitive processes (Laumonnier et al., 2007; Swingland et al., 2012). Moreover, X-linked genes have been demonstrated to have increased gross expression level in brain tissues in both humans and mammals, which further supports an essential role of the X chromosome in brain development and mental functioning (Nguyen and Disteche, 2006). Animal studies

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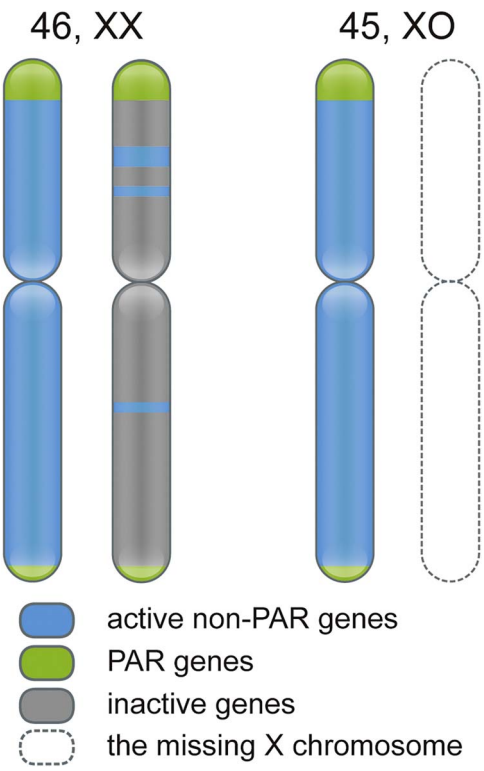

Fig. 1. Schematic structures of X chromosomes in typically developing (TD) and 45, XO Turner syndrome (TS) women. In TD women, one of the two X chromosomes is inactivated, which is referred to as X-inactivation. However, a number of X-linked genes escape from this process and remain active on the inactivated X chromosome. These genes were shown in color on the inactivated X chromosome in 46, XX women, with genes within pseudoautosomal regions (PAR) colored green and other genes colored blue. In contrast, there is no X-inactivation process in 45, XO TS women as a result of the congenital loss of one X chromosome. Essentially, the 45, XO TS women lack the expression or activities of the escaped genes on the inactivated X chromosome compared with TD women.

have demonstrated the involvement of X-linked genes, particularly in cognition-related molecular pathways. For example, increased fear reactivity was reported in 39, XO mice compared with normal 40, XX mice, which indicates a dosage effect of the X chromosome on emotional processing (Isles et al., 2004). At the gene level, overexpression of the X-linked gene NR2B facilitated learning and memory in transgenic mice (Tang et al., 2001).

In humans, X-linked gene defects have been disproportionately identified in various psychiatric disorders and particularly in mental retardation (Ropers and Hamel, 2005; Skuse, 2005). Empirically ascertaining the patterns in which the X chromosome influences human brain structure and function is of particular importance for understanding sex differences in the brain and cognition for elucidating sex-specific incidences and symptom presentation for many neuropsychiatric disorders (Cahill, 2006; Holden, 2005). However, empirically investigating how the X chromosome influences the human brain remains technically challenging, particularly in vivo.

1.2. Turner syndrome

Turner syndrome (TS) is a human disorder caused by a partial or complete absence of one X chromosome in women, which occurs in ~1 per 2500–3000 live female births (Sybert and McCauley, 2004). Approximately half of TS individuals exhibit a complete loss of one X chromosome, termed X-monosomy (45, XO karyotype) (Fig. 1), whereas approximately 10% of TS individuals exhibit structural abnormalities in one of the two X chromosomes (e.g., deletions on Xp and Xq or an isochromosome with two q arms) or more complex X chromosome abnormalities (Sybert and McCauley, 2004). The remaining TS individuals have a cryptic mosaicism and exhibit more than one cell line, such as a 45, XO cell line and either a 46, XX cell line or other cell lines (Sybert and McCauley, 2004).

The common TS physical manifestations include short stature, gonadal dysgenesis, and infertility (Hong and Reiss, 2014; Ranke and Saenger, 2001). The cognitive phenotypes of TS are characterized by severe deficits in multiple cognitive domains, including visual-spatial ability, mathematical processing, and social cognition (Hong et al., 2009; Hong and Reiss, 2014). Regarding general intelligence, numerous TS studies have demonstrated a lower performance IQ in contrast to a within-normal verbal IQ in TS individuals (Garron, 1977; Lahood and Bacon, 1985; Pennington et al., 1982; Rovet, 1993; Shaffer, 1962; Silbert et al., 1977; Temple et al., 1996). Specifically, verbal cognition, such as phonological processing, receptive vocabulary, and reading comprehension, are well preserved in TS; however, several non-verbal abilities, including attention, working memory, cognitive flexibility, visual-spatial skills, executive function, and abstract reasoning, have been demonstrated to be worse compared with TD women (Ross et al., 1996; Skuse et al., 1997; Temple and Carney, 1995). In addition, poor mathematical processing and social skills have frequently been reported in TS girls (Hong et al., 2011; McCauley et al., 2001; Mccauley et al., 1987; Rovet and Ireland, 1994; Rovet et al., 1994; Skuse et al., 1997). Difficulties in these domains may severely affect academic achievement and adaptive functioning of TS individuals.

Both physical and psychological features highly vary across women with TS as a result of the varied structural defects on the X chromosome or mosaicism (Bharath et al., 2010). In general, small deletions on the X chromosome or mosaicism likely manifest fewer and subtler TS features, whereas large deletions, critical region deletions, or non-mosaicism karyotypes may result in the full spectrum of TS features. Accordingly, most typical TS phenotypes are expected to occur in women with TS who express a 45, XO karyotype, i.e., X-monosomy.

Interestingly, TS individuals can be regarded as a natural human "knock-out model" of the X chromosome and, therefore, represent a valuable opportunity to investigate the function of the X chromosome in humans. Many neuroimaging techniques have been applied to TS individuals, which have provided valuable insight into the role of the X chromosome in human neural systems (Hong and Reiss, 2014; Printzlau et al., 2017). For example, structural and diffusion magnetic resonance imaging (MRI) studies have demonstrated specific abnormalities in the cortical gray matter (GM), subcortical nuclei, and the white matter (WM) in TS individuals. In addition, specific alterations in human brain activity/function have been identified using various functional neuroimaging techniques, such as positron emission tomography (PET) and functional MRI (fMRI). A list of previously published neuroimaging studies of TS is provided in Supplementary Table 1.

This review aims to summarize the recent progress in TS-related neuroimaging studies and to emphasize how these findings have enhanced our understanding of the influences of the X chromosome in the human brain. In addition, current issues and future considerations in this field are elaborated. The neuroimaging findings of TS are herein organized into five categories: 1) GM morphometry; 2) WM integrity; 3) functional activity/connectivity; 4) brain-behavior relationships; and 5) confounding factors. Issues and future considerations cover four topics: 1) neuroimaging brain phenotypes; 2) relating brain abnormalities to cognitive deficits; 3) differentiating between genetic and hormonal effects; and 4) investigating beyond the TS model.

2. Neuroimaging findings in TS

2.1. GM morphometry

Structural MRI (sMRI) is the most frequently used neuroimaging modality for studying TS individuals. This particular type of MRI can provide an image contrast between brain tissues (i.e., GM, WM, and