

## Sex Chromosomes: Does it Affect the Way You Think?

Sir,

Understanding differences in the brain of a male and female has always been an area of research among neuroscientists. There are a considerable number of sex-related differences noted in the neuroanatomical structures, neurophysiological functions, and psychosocial aspects, which are

controversial partly due to the varied methodologies used to study these domains among males and females and partly due to environmental factors.<sup>[1]</sup> The brain development is affected by the gonadal sex hormones and adrenal hormones secreted during puberty and prepubertal period, respectively. Various studies over the past decade indicate that X chromosome has an

independent influence on the cognitive-behavioral and neuroanatomical domains in the humans.<sup>[2,3]</sup> It is indeed, challenging to understand the effect of X chromosome on the developing brain in the prepubertal period, when there is a minimal effect of the sex hormones.

Studies have shown that either a deficient complement of X chromosome (XO, Turner syndrome [TS]) or supplementary complement (XXY, Klinefelter syndrome [KS]) has a profound effect on the regional brain volumes and on the cognitive, socioemotional, and other neurobiological functions, thus making persons with TS and KS one of the favorite models to study the effect of the sex chromosomes on brain. A recent study showed an increase in the total gray and white matter in the male groups as compared with the female groups on whole-brain voxel-based morphometric comparison.<sup>[4]</sup> The anatomical localization of these findings correlated with the region-specific cognitive-behavioral functions, for example, TS and KS group, showed lower scores on the overall intellectual and verbal abilities as compared to typically developing males and females.

An important question arises whether we can use sex chromosome aneuploidies as true models to understand the dose-dependent effect of X chromosome on brain structures? One of the important phenomena seen in X chromosome biology is mosaicism. The pattern of mosaicism may vary in the brain tissue, which may result in a different pattern of the gene expression, thereby causing a confounding effect on the anatomical-behavioral domains. Like X chromosome, Y chromosome has also been shown to have effect on brain anatomy and neuropsychological functions. Studies have shown the deleterious effect of an extra Y chromosome in XYY males on the size of the brain and possible association of an extra Y chromosome with behavioral traits such as anxiety and antisocial traits.<sup>[5]</sup> Similarly, 47 XXX female, where there is no Y chromosome, shows more severe decrease in the size of the brain than males with KS (XXY).<sup>[5]</sup> Various Y chromosome-related genes have been associated with different brain regions, for example, sex-determining region on the Y gene expression has been seen in the medial rostral hypothalamus, frontal and the temporal cortex.<sup>[6]</sup> A steroid sulfatase enzyme-coding gene, superior temporal sulci, is found to be associated with neurodevelopmental disorders such as attention-deficit hyperactivity disorder and autism spectrum disorders.<sup>[6]</sup> Studying whether male-pattern brain development and cognitive functions are a direct consequence of Y chromosome-related gene expression or an indirect result of the genetic interactions between X and Y chromosome would give a more comprehensive picture of the neuroanatomical correlates of an X chromosome gene dosage.

An important strategy, which can be used to study the effect of sex chromosomes, is by studying the effect of X chromosome on the brains of monozygotic/dizygotic twins, which would allow exploring the role of environmental factors in a controlled genetic setting. Similarly, understanding the effect of X chromosome on a phenotypically female to male transsexual or Y chromosome on male to female transsexual in individuals of gender identity disorder would minimize the confounding factors.

In summary, understanding the influence of sex chromosomes on brain anatomy and physiology is interesting yet difficult amounting to the complexities of the chromosomal gene expressions involved and their relation to the human behavior. Such studies have clinical significance and would help us in better understanding of the pathophysiology of various gender-specific neuropsychiatric disorders.

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#### Conflicts of interest

There are no conflicts of interest.

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