Published in final edited form as:
Dev Disabil Res Rev. 2009 ; 15(4): 318–327. doi:10.1002/ddrr.86.

Effects of Sex Chromosome Aneuploidies on Brain Development: Evidence From Neuroimaging Studies

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Abstract

Variation in the number of sex chromosomes is a relatively common genetic condition, affecting as many as 1/400 individuals. The sex chromosome aneuploidies (SCAs) are associated with characteristic behavioral and cognitive phenotypes, although the degree to which specific individuals are affected can fall within a wide range. Understanding the effects of different dosages of sex chromosome genes on brain development may help to understand the basis for functional differences in affected individuals. It may also be informative regarding how sex chromosomes contribute to typical sexual differentiation. Studies of 47,XXY males make up the bulk of the current literature of neuroimaging studies in individuals with supernumerary sex chromosomes, with a few small studies or case reports of the other SCAs. Findings in 47,XXY males typically include decreased gray and white matter volumes, with most pronounced effects in the frontal and temporal lobes. Functional studies have shown evidence of decreased lateralization. Although the hypogonadism typically found in 47,XXY males may contribute to the decreased brain volume, the observation that 47,XXX females also show decreased brain volume in the presence of normal pubertal maturation suggests a possible direct dosage effect of X chromosome genes. Additional X chromosomes, such as in 49,XXXXY males, are associated with more markedly decreased brain volume and increased incidence of white matter hyperintensities. The limited data regarding effects of having two Y chromosomes (47,XYY) do not find significant differences in brain volume, although there are some reports of increased head size.

Keywords

sex chromosome; aneuploidy; neuroimaging; brain; development

Sex is the single greatest discriminating morphometric factor in biology [Ropers and Hamel, 2005]. Overall brain size in humans is robustly dimorphic, with males having an approximately 10% greater volume. Sexual dimorphism of the developing brain is especially pertinent for child psychiatry, given that nearly all neuropsychiatric disorders of childhood demonstrate striking sex differences with respect to age of onset, prevalence, and symptom patterns [Giedd et al., 1997]. Factors giving rise to sexual dimorphism may thus also act as risk factors or protective agents for neurodevelopmental disorders, and understanding the development of sexual dimorphism may provide insights into the pathogenesis of neurodevelopmental disorders.

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Biological contributions to sex differences include sex differences in gonadal secretions that affect the brain and direct effects of the sex chromosome genes. The relative ease of manipulating hormone levels in animal models has led to a preponderance of literature and discussion about the effects of hormones on the brain. However, a growing body of literature [Arnold, 2004] is now suggesting that differences in the neural expression of X and Y genes may be more prominent than previously appreciated [Vawter et al., 2004; Weickert et al., 2009]. The X chromosome, in particular, has also been of great interest in cognition because of the disproportionately high number of X chromosome genes that are expressed in the brain, and the high number of syndromes affecting cognitive function that are associated with genes on the X chromosome [Ropers and Hamel, 2005; Skuse, 2005].

The X chromosome has many more genes than the Y chromosome. A species-specific complex process of X-inactivation occurs early in development in order to maintain dosage equivalence of most X chromosome genes. However, approximately 15% of X chromosome genes escape inactivation [Carrel and Willard, 2005], raising the question of whether dosage effects may contribute to sex differences. One way to explore dosage effects of genes on the X and Y chromosomes is to study naturally occurring populations with sex chromosome aneuploidies (SCAs).

Variation in the number of sex chromosomes is a relatively common genetic condition, affecting as many as 1/400 individuals [Nielsen and Wohlert, 1990; Ratcliffe, 1994]. Potential karyotypes include one or more additional X chromosomes, Y-chromosomes, or both. Individuals can also have too few sex chromosomes: approximately 1/2,000 women is born with partial or total loss of one X chromosome, known as Turner syndrome [Stochholm et al., 2006] (46,XO).

Prospective longitudinal studies of individuals with SCAs performed in Denver, Boston, Toronto, and Europe have found each of the karyotypes to be associated with an increased risk of behavioral and cognitive difficulties [Ratcliffe et al., 1982; Stewart et al., 1986 Nielsen and Wohlert, 1990; Bender et al., 1993a]. Most of the data from these reports is related to 47,XXY and to a lesser extent 47,XXX. Fewer participants with 47,XYY were identified in early prospective studies. Furthermore, participants with more than one additional X or Y chromosome generally were not included in group comparisons, but were often described on a case-by-case basis due to the rarity of these conditions.

For males with 47,XXY, IQ scores are generally reported to be in the average range, but they are depressed relative to siblings or matched controls. Their IQs are decreased by approximately a half to a full standard deviation, with greater verbal than non-verbal weaknesses. Similarly, for females with 47,XXX, IQ scores tend to fall about a standard deviation or 1.5 standard deviations below siblings or matched control participants [Ratcliffe et al., 1979; Stewart et al., 1979; Netley and Rovet, 1982; Walzer et al., 1986; Bender et al., 1991]. Very few prospective studies have included enough XYY participants to permit group comparisons. Walzer et al. [1991] reported IQ scores for XYY to be approximately a standard deviation below controls. Ratcliffe et al. [1982] reported similar findings. However, when data from the different early prospective studies were pooled, Netley [1986] reported no significant IQ differences between the XYY group and matched controls. Thus, there is less consistency with regard to overall cognitive functioning for this group.

Less is known about rarer forms of sex chromosome variation, such as 48,XXYY, 48,XXXY, 48XXXX, 49,XXXXY, and 49,XXXXX. Linden et al. [1995] reported on several cases of these rarer conditions and indicated that many of these individuals had IQ scores that fell into the intellectually disabled range. More recent studies of these rarer conditions have not included prospective birth cohorts, but instead have been characterized

by referred samples. These studies have sometimes relied on parent report of adaptive function (e.g., [Visootsak et al., 2007] or medical chart review of intelligence tests scores (e.g., [Tartaglia et al., 2008]). The results of current research converge with those of Linden et al., in which children with a greater number of supernumerary sex chromosomes experience greater impairment. For example, children with XXYY were reported to have adaptive functioning and IQ scores in the borderline to intellectually disabled range in two studies (about 1.5 to 2 standard deviations below the population mean) [Visootsak et al., 2007; Tartaglia et al., 2008]. For males with 48XXXY and 49XXXXY, cognitive and adaptive functioning appears to be somewhat lower, with adaptive functioning scores almost three standard deviations below the population mean based on one report [Visootsak et al., 2007]. However, it is important to emphasize that existing data are limited on children with 48XXXY and 49XXXXY and sometimes these conditions are collapsed into one group, as in [Visootsak et al., 2007].

In sum, there appears to be a decrease in cognitive functioning with each additional sex chromosome (with the results for XYY being less consistent). Existing data appear to support the suggestion by Polani [1977] that each additional sex chromosome reduces overall intellectual abilities by about a standard deviation, although the remarkably high degree of variability between individuals within each karyotype precludes this as a firm basis for prognosis.

A few groups have used brain imaging to explore how sex chromosome dosage may affect brain structure and activity. A handful of controlled comparisons are available of XO, XXY, XXX, and XYY individuals, while thus far only case studies and postmortem data have been reported for individuals with two or more additional chromosomes. We review data on brain structure associated with each of the SCVs besides 46,XO, which is being covered elsewhere in this issue.

47,XXY

The most common of the SCAs is 47,XXY, found in as many as 1/600 males [Nielsen and Wohlert, 1990; Ratcliffe, 1994]. The associated phenotypic characteristics were first described by Klinefelter et al. [1942], although the degree to which 47,XXY individuals exhibit these features can vary widely. One of the most common findings in 47,XXY is hypogonadic hypogonadism. For reasons that are not yet well understood, the testicles of individuals with 47,XXY begin to accumulate scar tissue early in life, a process that accelerates during puberty, leaving the vast majority of affected males infertile. Testosterone levels in adulthood tend to be low or within low range of normal and are likely related to several of the characteristic elements of Klinefelter's, such as eunuchoid body habitus, low energy, metabolic abnormalities, and osteoporosis. The degree to which the prenatal and postnatal testosterone surges are affected is more controversial, with some studies reporting decreased testosterone levels during this period, whereas others do not [Ross et al., 2005; Aksglaede et al., 2006, 2007a; Bastida et al., 2007].

A handful of magnetic resonance imaging (MRI) studies have examined the impact of an additional X chromosome in males (see Table 1). Warwick et al. [1999] followed up a cohort of individuals who had been identified prospectively during the Edinburgh study of growth and development of children [Ratcliffe et al., 1982] as having SCAs (10 XXY, 12 XXX, 10 XYY; findings relating to the other SCAs are described in the pertinent sections below). Individuals with SCAs were compared with healthy controls matched on age, parental socioeconomic status, and height (13 females, 26 males). Participants were between 16 and 28 years of age. The subjects in this study had been found in a previous investigation to have significantly lower IQ (47,XXY: mean NART IQ 86.1, SD 15.8; controls 105.1, SD

7.6, $P < .001$) and higher levels of schizoid/ schizotypal personality traits, although none met criteria for a major psychiatric disorder [Gotz 1996;Gotz et al., 1999]. The investigators therefore also included a structured psychiatric interview (the Structured Interview for Schizotype, SIS) [Kendler et al., 1989] to assess if these traits were related to brain structural differences. MRI regions of interest were manually delineated, including volumes of whole brain, right- and left-prefrontal lobes, temporal lobes, basal ganglia, amygdalo-hippocampal complex, and ventricles.

Brain imaging findings for the 47,XXY individuals in this cohort included significantly smaller whole brain volume and increased volume of the ventricles. White matter hyperintensities 2 mm or greater in diameter were seen in five of the 47,XXY males but in none of the controls.

Ten of the 13 47,XXY males who had been identified as part of the Denver cohort were studied with MRI when they were between 24 and 32 years of age (mean age 27.3, SD 3.0 years) [Patwardhan et al., 2000]. In the Denver study, an unselected cohort of 40,000 consecutive newborns were screened for SCAs in Denver between 1964 and 1974 and followed from birth to adulthood [Bender et al., 1993b]. Full-scale IQ had been obtained on these subjects during childhood and found to be slightly below average (mean IQ 91.30, SD 13.86) [Bender et al., 1993a]. Subjects undergoing MRI were individually matched on age and sex with 10 healthy controls (mean age 26.81, SD 3.28 years). Half of the XXY males had been given testosterone supplementation (XXY + T) and half had not (XXY − T), allowing a post hoc comparison of the effects of testosterone on brain structure. Gray and white matter segmentation and measurement of lobar, subcortical, and ventricular volumes were performed using automated methods [Reiss, 1999], whereas manual tracing was used to delineate the volume of the superior temporal gyrus (STG). Measurements of cognitive function included IQ and verbal fluency.

In this cohort, overall gray and white matter volumes were similar between XXY males and controls. Smaller temporal lobe volumes and STG volumes were found in the XXY group, although this did not persist after adjustment for total brain volume. However, when XXY individuals with and without testosterone supplementation were compared, it was found that the XXY individuals without testosterone supplementation had smaller temporal and STG volumes than did both XXY individuals who had received testosterone and healthy controls. The difference with controls survived covarying for total brain volume, although the difference with XXY + T did not. The KS − T group also had diminished scores in verbal fluency compared with the KS + T group. A limitation here is that when the overall cohort was identified prospectively, the groups who had chosen to take testosterone supplementation were self-selected, raising the question of whether there may have been functional differences before treatment in those individuals who sought out testosterone supplementation. Some support for baseline similarity between the KS + T and KS − T group was that both groups had similar IQ findings before the initiation of testosterone.

A separate analysis of amygdala and hippocampal volumes obtained by manual tracing in these same MRIs [Patwardhan et al., 2002] found that the volume of the amygdala was significantly decreased in XXY males, but hippocampal volumes were preserved. Effects of testosterone exposure were not reported in this analysis.

In another study, Itti compared brain volumes and measures of cognitive functioning between a group of 18, XXY adult males (18 to 63 years of age) and 20 controls matched on age and handedness [Itti, 2006]. The XXY males in this study were not identified prospectively, but were identified from a clinic for hypogonadism rather than for having any specific behavioral or cognitive abnormalities. Volumes of total brain volume, cerebellar

volume, gray matter lobar volumes, and the hippocampus were drawn manually. Findings included decreased volume in the left temporal lobe and increased volume of the lateral ventricles. Results were not different between the subgroup of 47,XXY who had received testosterone supplementation versus those who had not.

DeLisi used both structural imaging and diffusion tensor imaging (DTI) in a self-referred group of 11 47,XXY adults and age-matched controls [DeLisi et al., 2005]; this study is the only one to date reporting DTI data. Five of the 11 subjects in this group had some type of mosaicism. Although XXY males did not have lower IQ levels than control subjects, they had worse scores on several measures of verbal performance and executive functioning. Notable in this group was the high degree of psychopathology; nine of the 11 met criteria for a primary psychiatric diagnosis, including one with schizoaffective disorder and three with affective disorders with psychotic features. The brain imaging data showed decreased total brain volumes, with specific decreases in the frontal and temporal lobes and posterior STG; there were no significant differences in the anterior STG, amygdala/ hippocampus complex, or ventricles. Rightward asymmetry in the STG was decreased in the XXY males at a trend level.

Four regions showed decreased fractional anisotropy (FA) in the XXY males: one in the left posterior internal capsule, one in the left arcuate bundle, and areas in both the right and left anterior cingulate. Neither structural nor DTI data showed significant correlations with behavioral measures in the XXY males.

Psychotic disorders such as schizophrenia have been associated with both language impairment and decreased hemispheric asymmetry [Crow, 2000]. The association of an additional X chromosome with both of these cognitive features raised the question of whether there may be a dose-response relationship of the X chromosome and cerebral asymmetry. This group further explored this hypothesis by measuring cerebral torque (a combination of rightward frontal and leftward occipital asymmetry) in 10 of these 47,XXY males and matched controls together with data from a group of 45,XO women and female controls [Rezaie et al., 2009]. Cerebral torque was not significantly different in either patient group. However, the 47,XXY males had decreased asymmetry in the frontal lobes compared with male controls, whereas 45,XO women had increased leftward asymmetry compared with matched healthy female controls, suggesting that X chromosome dosage may affect the development of brain asymmetry in ways besides affecting torque.

The only quantitative neuroimaging studies published thus far in children and adolescents with 49,XXY have been from the Sex Chromosome Variations Study being carried out within the National Institute of Mental Health [Giedd et al., 2007]. Forty-two nonmosaic 49,XXY subjects were recruited nationally with assistance of parental advocacy and support groups and compared with an age and sex matched group of 87 healthy controls. All 49,XXY boys over the age of 14 were receiving testosterone supplementation, none of the group under 12 years were receiving testosterone supplementation, and of the remainder half were receiving testosterone supplementation, and half were not receiving testosterone supplementation. IQ was significantly lower in the 49,XXY group (95.2 ± 17.1 vs. 120.3 ± 11.3, $P < 0.0001$), although still within the normal range of intelligence, whereas the control group was higher than expected for population norms. Nonverbal IQ was less impaired than verbal IQ.

Structural imaging measurement of brain volumes including total gray and white matter, lobar measures, caudate volume, cross-sectional area of the corpus callosum, and cortical thickness were obtained using an automated pipeline [Zijdenbos et al., 2002; Lerch and Evans, 2005]. Overall brain volume and regional volumes for both gray and white matter

were significantly decreased in the 49,XXY group, with the exception of the parietal white matter. This was not different than controls, possibly in keeping with the relative sparing of nonverbal function. The area of the corpus callosum was also not affected. All brain volume differences survived covarying for IQ differences except for frontal white matter, which was no longer significant. The caudate was approximately 10% smaller in the 49,XXY group and was still significantly smaller after controlling for overall changes in brain volume. Measures of brain asymmetry were not reported.

Broad areas of the cortex were significantly thinner in the 49,XXY males (see Fig. 1). The most strongly affected regions were in the motor strip, temporal, inferior parietal, and inferior left frontal regions, whereas cortical thickness was preserved in the superior parietal regions.

An innovative automated voxel based volumetric analysis method was applied to MRI data from a subgroup of the same subjects (32 47,XXY males and 62 matched controls) [Shen et al., 2004]. Whole brain volumes were again smaller in the 47,XXY subjects. Decreased volumes were also seen in a variety of gray matter regions, including areas containing the amygdala, hippocampus, cingulate, insula, and temporal and occipital gyri. White matter volumes were not different with the exception of a region in the right parietal lobe. Although the differences in methodology and number of subjects make direct comparison between the two studies difficult, both analyses found decreased brain volume and that temporal lobes structures appear to be strongly affected, consistent with the language difficulties reported by a majority (30/42) of the subjects in the study.

Two studies to date have looked at the effects of an additional X chromosome on brain activity in males. In addition to the structural imaging study described earlier, Itti et al. had used single photon emission computed tomography (SPECT) imaging to measure regional cerebral blood flow (rCBF) in nine self-selected adult right-handed 47,XXY males (average age 27.8 ± 6.6) and nine controls matched on age and handedness [Itti et al., 2003]. Cognitive performance was significantly lower in the 47,XXY males than controls, particularly in the verbal domain. The 47,XXY subjects did not show the expected leftward perfusion asymmetries demonstrated in the control subjects, with the exceptions of the a few regions (precentral gyrus, transverse temporal gyrus, and cerebellum). Instead, significant rCBF increase was observed in the 47,XXY subjects in the right hemisphere regions including the prefrontal motor area, parietal associative regions, and temporal language areas. Subcortical areas such as the hippocampi and cerebellum had decreased rCBF. There appeared to be some association between increased right-sided flow and cognitive scores, for example, the increase in rCBF in several right-sided temporal gyri was associated with lower verbal scores, as was lower CBF in the left hippocampus.

Functional magnetic resonance imaging (fMRI) was used to study language lateralization in 15 self-referred right-handed 47,XXY adult males (average age 36.9, SD 11.8; mean IQ 94.5, 95% CI 86.9 to 102.1) and 14 controls matched on age, handedness, and years of education (average age 35.5, SD 9.5, IQ not provided) [van Rijn et al., 2008]. Fourteen of the 47,XXY males were on testosterone supplementation (mean age of testosterone initiation 23.9, SD 7.1 years). Although none of the subjects met the criteria for a psychiatric disorder, an earlier analysis of a larger group of which the subjects in the present study was a subset had found higher scores on measures sensitive to schizophrenia-spectrum pathology [van Rijn et al., 2006]. The investigators therefore also explored the relationship of brain activation to scores on the Schizotypal Personality Questionnaire (SPQ) [Raine, 1991] and the Positive and Negative Symptoms Scale (PANSS) [Kay et al., 1987].

The fMRI task included three different tasks shown to activate language-related areas in the brain: a paced verb-generation task, an antonym-generation task, and a semantic decision task. Five regions of interests (ROIs) in language-related areas were studied in addition to whole brain measures. A lateralization index was computed for each of these regions by taking the difference between the number of active voxels on the left and right and dividing by the sum of all active voxels.

Although the 47,XXY group performed as well as controls, they were found to have a lower mean lateralization index across all the ROIs, driven primarily by differences in the STG and supramarginal gyrus. Similar to the SPECT results mentioned earlier, the loss of lateralization was due to increased language-related activity in the right hemisphere compared with controls. Examination of the relationship of measures of psychopathology with the brain activation data found that a higher total PANSS score correlated with decreased lateralization, and that evidence of more disorganized thoughts on the SPQ correlated with decreased functional lateralization in the STG.

In summary, the presence of an additional X chromosome in males has significant effects on both brain structure and function, in at least a subset of individuals. Several brain regions appear to be affected, with differences in frontal and temporal lobe structures reported by several of the existing studies using different patient groups and methods, and some suggestion of relative preservation of parietal regions. Microstructural white matter abnormalities are suggested by decreased FA and a high prevalence of white matter hyperintensities. Although the evidence of significant abnormalities in structural asymmetry is equivocal, both SPECT and fMRI functional imaging studies found decreased lateralization in 47,XXY subjects compared with controls, primarily due to increased activity in the right hemisphere.

The uncertain role of ascertainment bias is a significant limitation in being able to extend the results of most of the studies here to the broader population of males with an additional X chromosome. Although two of the studies were of subjects who had been prospectively ascertained, both of these had small numbers, a general problem among most of the studies.

It is not clear whether the differences associated with the additional X chromosome are due to hypogonadism or more direct dosage effects of genes on the X chromosome. Of the two studies which were able to compare subjects based on whether they had received testosterone supplementation, one suggested that gray matter was less diminished in the group that had additional testosterone, whereas the other found no difference. Another means of investigating this is to look at the impact of an additional X chromosome in 47,XXX females, who typically have normal pubertal development and fertility.

47,XXX (TRISOMY X)

Although prospective studies have shown that 47,XXX is also quite common (1/1,000 female births) [Nielsen and Wohlert, 1990; Ratcliffe, 1994], it is even more rarely recognized than 47,XXY, likely due to the mildness of the physical phenotypic characteristics. Similar to 47,XXY males, 47,XXX females also show increases in height beginning before puberty, and may have many of the same mild skeletal malformations such as clinodactyly and radio-ulnar synostosis. Behavioral characteristics commonly include increased risk for anxiety and impairment in executive function, such as impulsivity and difficulties with sustained attention and planning [Tennes et al., 1975]. The Denver prospective longitudinal study found that functional outcome in 47,XXX females was highly dependent on having strong social or familial support structures [Bender et al., 1999].

Two studies of neuroimaging findings in 47,XXX females are currently available, both of adult subjects who had been identified as part of birth cohort studies (for details see description under 47,XXY studies in previous section). Imaging data were acquired from 12 47,XXX females (mean age 21.6 years, SD 3.1 years) who had participated in the Edinburgh birth cohort [Warwick et al., 1999]. The 47,XXX women had significantly lower IQ than controls (47,XXX: mean NART IQ 82.5, SD 7.7; controls 102.8, SD 7.0, $P < .0001$), and significantly increased scores in three domains of the SIS: introversion, magical thinking, and impulsivity. Whole brain volumes were significantly smaller in the 47,XXX women, as were several regional volumes, although the latter were no longer statistically significant after differences in total brain volume were taken into account. There were also no systematic volumetric asymmetries found between the groups. White matter hyperintensities were found in three of the 47,XXX subjects and none of the healthy controls. There were no correlations between SIS scores and brain volumes, or between IQ and brain volumes within diagnostic groups, although there was a correlation between measures of IQ and total brain volume across females as a whole.

The second study compared whole brain, amygdala, and hippocampus volumes of subjects identified from the Denver birth cohort study in 10 47,XXX females (mean age 29.1, SD 2.1 years) with 10 healthy controls individually matched on age (mean age 28.5 years, SD 3.21 years) [Patwardhan et al., 2002]. IQ in the 47,XXX group had been measured when the subjects were children and was 81.73 (SD 15.84) [Bender et al., 1993a]. MRI results showed that total brain volume was significantly smaller in the 47,XXX group; although there was a trend toward smaller volume of the amygdala, it did not reach significance, and hippocampal volume was not different.

Although both of these studies are limited by small sample sizes, each found 47,XXX to be associated with significantly decreased overall brain size. Data on whether this was primarily due to gray or white matter differences were not available, although the presence of white matter abnormalities in several of the participants suggests white matter is affected. This would be further supported by a case study of a 6 year female who showed extensive white matter hyperintensities on T2 weighted and FLAIR images [Garcia-Cazorla et al., 2004]. The amygdala did not appear to be as significantly affected by the presence of an additional X chromosome in females compared with males, suggesting that at least part of the reduction in amygdala volumes seen in 47,XXY males is due to the additional influence of an abnormal hormonal milieu.

47,XYY

47,XYY is also not uncommon, estimated at 1/1,000 male births [Nielsen and Wohlert, 1990; Ratcliffe, 1994]. It was the object of intense interest in the 1970s, when studies appeared to find a higher number of individuals with 47,XYY in penal and psychiatric institutions than expected [Hook, 1973]. Although these studies were later recognized as having significant methodological flaws [Theilgaard, 1984; Gotz et al., 1999; Ike, 2000; [Weigmann, 2005], the idea that an additional Y chromosome will result in violent criminal behavior unfortunately continues to live on in popular perception [Ike, 2000]. 47,XYY does appear to be associated with an increased risk of behavioral and cognitive problems, including language and motor delay, disruptive behavior, impulsivity and poor attention, and impairment in social interaction, found in individuals diagnosed prenatally as well as those identified as part of postnatal evaluations [Bender et al., 1984b; Nielsen and Wohlert, 1990; Ratcliffe, 1999]. An increased risk of pervasive developmental disorders in 47,XYY males has also been identified [Bender et al., 1984b; Ratcliffe et al., 1990; Nicolson et al., 1998]. The most common somatic phenotypic trait is increased size, beginning before puberty, and extending into a larger pubertal growth spurt. Evidence regarding head circumference is

mixed, with some studies reporting no differences from controls despite the increase in height [Ratcliffe et al., 1994], and others an increased head circumference [Nicolson et al., 1998; Geerts et al., 2003].

The only case-control study of the effects of an additional Y chromosome on brain development is from neuroimaging data obtained on the subjects identified as part of the previously described Edinburgh cohort study [Warwick et al., 1999]. Ten 47,XYY males were included (mean age 21.8, SD 3.2 years). The subjects were significantly taller than the control subjects (188.2 cm, SD 4.7 vs. 183.2, SD 4.8, $P < .005$), and had significantly lower IQ (mean NART IQ 90.4, SD 9.3 vs. 105.1, SD 7.8, $P < .001$). The 47,XYY group scored significantly higher on the antisocial traits component of the SIS. Brain imaging results showed no significant differences in brain volumes between 47,XYY and controls, although white matter hyperintensities were found in one of the 47,XYY subjects and no controls. There was no correlation between behavioral or cognitive indices and brain size in the XYY group, although antisocial traits did have a negative correlation with brain size in the healthy male controls.

Other data on brain development in 47,XYY subjects had been limited to case reports. Abnormalities were reported on ultrasound examination of two 47,XYY fetuses. One was done as part of a workup of an abnormal midgestational serum marker screening test, and identified agenesis of the corpus callosum. The second was evaluated as part of evaluation of increased nuchal translucency; increased size of the cisterna magna and cerebellar vermal deficiencies were seen, consistent with Dandy-Walker syndrome [Maymon et al., 2002]. A separate report of a postmortem examination of a 47,XXY infant found abnormal gyral formation in the frontal lobes [Austin and Sparkes, 1980].

48,XXYY

The incidence of 48,XXYY is estimated at between 1/18,000 and 1/ 50,000 [Muldal et al., 1962; Sorensen et al., 1978; Nielsen and Wohlert, 1990]. Approximately 2.3% of individuals with the clinical signs of Klinefelter's syndrome have the 48,XXYY karyotype [Hasle et al., 1995]. Although frequently classified with 47,XXY due to shared characteristics such as hypogonadism, it has been recognized that 47,XXYY varies in medical, cognitive, and behavioral characteristics [Visootsak et al., 2007; Tartaglia et al., 2008]. It is generally associated with more pronounced phenotypic abnormalities, including mild craniofacial dysmorphism; skeletal anomalies such as radio-ulnar synostosis and clinodactyly; lower IQ, typically between 70 and 80; significant developmental delays; a higher risk of behavioral symptoms such as inattentiveness, hyperactivity, mood instability, and poor social function, and medical problems including neurological symptoms such as intention tremor; poor dentition, and reactive airway disease [Visootsak et al., 2007; Tartaglia et al., 2008]. Physical height is increased to a greater extent than in 47,XXY [Linden et al., 1995]. Individual case studies of clinical MRI findings in individuals with 48,XXYY have reported white matter hyperintensities in a 48,XXYY male with autism [Jha et al., 2007], and in a 9-year-old with premature puberty [Garcia-Cazorla et al., 2004]; and frontoparietal cortical atrophy on CT scan in a 22-month-old toddler with multiple developmental delays [Demirhan, 2003].

The largest clinical MRI series available was obtained from subjects participating in a multicenter study of clinical features in 48,XXYY males [Tartaglia et al., 2008]. Thirty-five of the 95 subjects had received a clinical MRI as part of evaluating conditions such as cognitive or behavioral problems, developmental delay, hypotonia, or seizures. The most common finding was nonspecific white matter abnormalities of varying extent, reported in 16/ 35 of the scans. Other findings were enlarged ventricles (8/35), agenesis of the corpus

callosum (2/35), corpus callosum lipoma (3/35), cortical dysplasia (3/35), and pituitary adenoma (1/35).

SCAs with More Than One Additional X or Y Chromosome

Syndromes associated with more than one additional X chromosome are much less common, and thus have not been present in enough numbers in any of the published prospective studies to provide a description of the phenotype free of potential referral bias. The cases that have been reported are generally associated with more severe developmental delays and physical manifestations, most frequently affecting the skeletal, cardiac, and genital systems. Although individuals with two additional X chromosomes are typically taller than normal, this begins to reverse with three additional chromosomes, such that females with pentasomy X (49,XXXXX) and 49,XXXXY males are often below average height [Linden et al., 1995; Visootsak et al., 2007].

Individuals with more than one additional Y chromosome (48,XYYY or 49,XYYYY) are even more rarely reported. The available cases consistently describe delayed development, intellectual disability, and mild skeletal anomalies. Although additional Y-chromosomes also results in more severe cognitive and manifestations, it has been suggested that they may not have as severe an impact as additional X chromosomes [Linden et al., 1995].

Information about the impact of tetrasomy or pentasomy on brain development is sparse. In addition to the increasingly severe impact on cognitive function of each additional chromosome, head size tends to be significantly decreased, suggesting that, brain volumes are likely to be significantly smaller [Linden et al., 1995; Visootsak et al., 2007].

Brain imaging studies in these groups are limited to a few case reports, and we were unable to find any published data on females with tetrasomy or pentasomy X. A young 49,XXXXY male who had significant developmental delays and began to have generalized tonic-clonic seizures at approximately age 6 underwent an MRI when he was 12 years old. It showed enlarged ventricles, particularly in the occipital horn of the left hemisphere, and generalized cortical atrophy, again most severe on the left [Galasso et al., 2003]. MRI results from a 4-year-old boy also showed global volume loss and scattered areas of white matter hyperintensity. A 3-year-old male with a history of speech and motor delays was found to have enlarged ventricles, general decreased volume of the cerebral cortex, and hypoplasia of the corpus callosum [Haeusler et al., 1992]. A T2-weighted and FLAIR image from a 1-year-old 49,XXXXY male showed extensive white matter hyperintensities [Garcia-Cazorla et al., 2004].

Linden et al. reported imaging results from three subjects with 49,XXXXY: the first was a 21-year-old male with an IQ estimated at 39, little speech, and a history of a seizure disorder, who was found to have mild hydrocephaly and diffuse atrophy of the cerebrum and cerebellum on CT performed at the age of 12. The second male had an IQ of 58 and was found on CT to have mildly enlarged ventricles. The third was a 15-year-old male with an IQ of approximately 40 whose head size was at the 25th percentile, but whose CT was otherwise read as normal [Linden et al., 1995].

The largest 49,XXXXY imaging case series to date included three individuals studied at different ages [Hoffman et al., 2008]. One subject who underwent MRI for significant developmental delay was scanned at 14 months of age and again at 20 months. Both exams were significant for decreased brain volume, increased ventricular volume, and decreased width of the corpus callosum. T2 images also showed widespread bilateral patchy and confluent areas of abnormal high signal intensity, particularly in the periventricular and deep white matter of the parietal and frontal lobes. The second subject was scanned at 7 years of

age. He also had volume loss, enlarged ventricles, and thinning of the corpus callosum. Periventricular and subcortical white matter showed several puncate foci of increased signal intensity. The third case was an adult of 39 years, who underwent MRI following the development of generalized tonic-clonic seizures. Findings included volume loss and atrophy in both cerebrum and cerebellum, associated with increased ventricular volume and thinning of the corpus cal-losum. The greatest volume loss was seen in the parietal lobes. Multiple foci of increased signal intensity throughout white matter of the periventricular, deep, and subcortical areas were present, much more than would be expected for an individual of his age.

There are a few case reports of brain imaging results of individuals with more than two Y-chromosomes. CT scan results were reported in a 22-year-old nonmosaic 49,XYYYY male who appeared to be having moderate to severe intellectual disability. Although he had normal head size in the 75th centile, CT scan results showed bilateral ventricular enlargement and diffuse cortical atrophy [Shanske et al., 1998]. A postmortem report from a 28-week-old 49,XYYYY fetus also found abnormalities, including a hypoplastic corpus callosum and a small cerebellum with a large cyst [Frey-Mahn et al., 2003]. By contrast, CT scans in other young 49,XYYYY males, including a 14 month old [Sirota et al., 1986] and a 28 month old [DesGroseilliers et al., 2002], were reported as normal.

SUMMARY

Some common patterns in effects from an additional X or Y chromosome are suggested by the available data. The addition of an additional X chromosome in either males or females is associated with a decrease in total brain volume which affects both white and gray matter and becomes progressively more severe with additional supernumerary chromosomes. There appears to be a particularly strong effect in temporal lobe regions, perhaps related to the abnormalities in language development that are frequently found in these individuals. Studies specifically addressing whether the language impairments and increased risk for psychotic symptoms associated with 47,XXY also were associated with differences in brain symmetry did not find strong structural differences, but both SPECT and fMRI studies did observe brain activation to be more symmetrical in the 47,XXY group. This appeared to be due to increased activation in the right hemisphere rather than decrease on the left. Although decreased volume in white matter was not as commonly found as in gray matter, the thinner corpus callosum in 49,XXXXY, decreased FA in 47,XXY, and X-chromosome dosage-related increases in white matter hyperintensities suggest supernumerary X-chromosomes have a significant impact on white matter development as well. This appears severe enough in individuals with pentasomy or tetrasomy that it has been suggested these disorders be included in the differential diagnosis for leukoencephalopathy [Garcia-Cazorla et al., 2004; Hoffman et al., 2008].

Separating out brain structural changes due to low testosterone levels from those due to dosage effects of other genes cannot be done with the existing data, but the possibility that insufficient testosterone is contributing to smaller gray matter volumes is supported both by the observation of more pronounced gray matter decreases in 47,XXY males than in 47,XXX females [Patwardhan et al., 2002], and by the finding in one study that gray matter deficits were less pronounced in males who had testosterone supplementation than those who did not [Patwardhan et al., 2000].

The effect of additional Y chromosomes is less clear. Although cases have been reported in which ultrasound and postmortem data linked additional Y chromosomes with brain malformations, several of the available case studies did not detect any differences. There is some controversy regarding whether head size is significantly larger in 47,XYY. This

appears particularly interesting given the increased risk for pervasive developmental disorders such as Autism, which are also associated with increased brain size [Nicolson et al., 1998; Courchesne et al., 2007].

The commonalities across types of brain structural and functional abnormalities are also seen in the behavioral domain, where there is an intriguing suggestion of dosage effects on common domains of cognitive and behavioral abnormalities across the X chromosome SCAs. For example, individuals with Turner's syndrome who have haploin-sufficiency of the X chromosome tend to have impaired visuospatial cognition in the presence of intact language capabilities [Bender et al., 1984a; Haberecht et al., 2001; Ross et al., 2006]. Conversely, as described earlier, the most common cognitive abnormality in either males or females with an extra X chromosome is delayed or impaired language development, whereas in XXY males visuospatial abilities are relatively preserved.

By contrast, XYY shows a distinct pattern of behavioral features. Given the role of the Y chromosome in creating male-specific sexual differentiation, it is interesting that the behavioral phenotypes associated with Y chromosome polynomial also tend to be among those generally more common in males, such as hyperactivity with impulsivity, aggression, and pervasive developmental disorders. The reason for the increased risk of disorders such as autism in males is not known, although it has been hypothesized to be an exaggeration of male-typical characteristics, perhaps as a result of high levels of prenatal testosterone exposure [Auyeung et al., 2009]. As additional Y chromosomes do not appear to be associated with abnormalities in testosterone production [Aksglaede et al., 2007b], the findings suggest that in addition to hormonal factors, another route to increased risk in males for these disorders is through direct effects of Y chromosome genes.

The identification of the SHOX (short stature homeobox) gene in the pseudoautosomal region (PAR) of the X and Y chromosomes was a significant advance in linking dosage effects with specific genetic factors [Clement-Jones et al., 2000]. The SHOX gene is a transcription factor whose decreased expression in 46,XO was demonstrated through deletion studies as being at least partially responsible for the characteristic short stature and skeletal abnormalities. It is thought that excessive copies of the SHOX gene may be responsible for the increased height characteristic of SCAs with additional chromosomes [Kanaka-Gantenbein et al., 2004; Aksglaede et al., 2007b]. Although some of the increased height in 47,XXY may be related to hypogonadism delaying the closure of the epiphyseal growth plates, the observations that taller stature is present well before puberty and is also present in SCAs not associated with hypogonadism such as 47,XXX and 47,XYY suggests genetic dosage effects likely also contribute.

Although the effects of additional X and Y chromosomes tend to occur within characteristic domains, one of the most striking aspects of the SCAs is the heterogeneity in the degree to which the phenotypes are expressed. For example, while IQ may be depressed on average within males or females with an additional X chromosome, some individuals may be very high functioning and have an above average IQ, while others may have severe cognitive impairments [Ratcliffe, 1994; Linden and Bender, 2002]. Some of this is likely related to mosaicism, which may decrease the impact of sex chromosome aneuploidy. Males who are 47/ XXY; 46/XY mosaic may have more functional testicular tissue, which would decrease the severity of hypogonadism. The source of the supernumerary chromosomes (maternal or paternal) or the degree of skewing of X chromosome inactivation may also have an impact, although the evidence for these playing a significant role is mixed [Iitsuka et al., 2001; Zinn et al., 2005; Wikstrom et al., 2006; Zeger et al., 2008].

The other genetic factor thus far identified as most clearly contributing to outcome is the androgen receptor (AR), which contains a highly polymorphic CAG repeat region. A study in 47,XXY boys found that increased length of this region was inversely correlated with penile length, indicating less effective early androgen action [Zinn et al., 2005]. It is also possible that specific allelic variation of genes on the sex chromosomes may add to variation, although there is little data available looking at this specifically.

Exploring the sources of heterogeneity in SCAs will be an important next step in better understanding how specific genes contribute to dosage effects of the X and Y chromosomes, and thus the potential roles these genes may play both in healthy sexual differentiation and as risk factors for neuro-developmental disorders that are differentially expressed in males and females.

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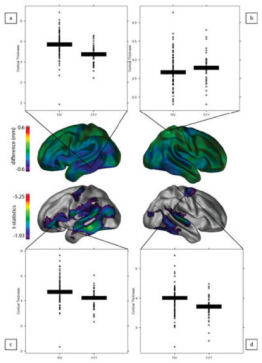

Fig. 1.

Maps of differences in cortical thickness between 42 47,XXY males (5.3 to 26.0 years) and 87 matched healthy controls. (a,b) Mean difference in cortical thickness. (c, d) Statistical significance of these differences. NV, normal volunteer. Figure from Giedd et al., [2007]. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Table 1

Case control Neuroimaging Studies of Sex Chromosome Aneuploidies

Study	Population (age, SD)	Imaging Parameters	Results (SCA Compared with NV)	Comments
47,XXY				
Warwick et al., 1999	10 47,XXY (21.8, 4.2)	1.0 T MRI, T1 weighted MP-RAGE	TBV ↓	Prospectively identified subjects
	13 46,XY (21.5, 1.3)	Manually drawn ROIs	Ventricular volume ↑	Study included several SCAs, see entries below
			WMH ↑	
Patwardhan et al., 2000, 2002	10 47,XXY (27.3, 3.0)	1.5 T MRI, 3D SPGR	Amygdala ↓	Prospectively identified subjects
	10 46,XY (26.81, 3.28)	Combination automated and manual drawn ROIs.	Temporal and STG ↓	Study also included 47,XXX (below)
Itti et al., 2003	9 47,XXY (27.8, 6.6)	SPECT	rCBF asymmetry ↓	Subset of Itti, 2006
	9 46, XY (matched)*			
Itti, 2006	18 47,XXY (35.8, 11.8)	1.5T MRI, T1 weighted DSE	Left temporal lobe ↓	
	20 46,XY (32.3, 11.3)	Manually drawn ROIs	Ventricular volume ↑	
DeLisi et al., 2005	11 47,XXY (34.6, 12.0)	1.5T MRI, T1 weighted MP-RAGE	TBV, frontal, temporal lobes ↓	Only study to date including DTI
Rezaie et al., 2009	11 46,XY (36.5, 13)	EPI DTI, six directions	Regions of FA ↓	
		Manually drawn ROIs	Frontal asymmetry ↓	
Shen et al., 2004	32 47,XXY (12.6, 4.3)	1.5T, T1 weighted 3D SPGR	Regional decreases in	Subset of sample from
	64 46,XY (12.9, 4.3)	Automated voxel based analysis	gray matter volume	Giedd 2007
Giedd et al., 2007	42 47,XXY (12.8, 5.0)	1.5T, T1 weighted 3D SPGR	TBV, caudate, all lobar volumes except parietal white matter ↓	Pediatric subjects
	87 46,XY (12.7, 5.0)	Automated measures of volumes and cortical thickness	Ventricular volume↓	
			Cortical thickness ↓	
van Rijn et al., 2008	15 47,XXY (36.9, 11.8)	1.5T T, 3D PRESTO fMRI sequence	Lateralization index during language related tasks ↓	
	14 46,XY (35.5, SD 9.5)			
47,XXX				
Warwick et al., 1999	12 47,XXX (21.6, SD 3.1)	see Warwick et al., 1999, above	TBV ↓	
	13 46,XX (21.5, SD 1.4)			
Patwardhan et al., 2002	10 47,XXX (29.1, SD 2.31)	see Patwardhan et al., 2002, above	TBV ↓	
	10 46,XX (28.5, SD 3.21)		Hippocampal volume ↓	
47,XYY				
Warwick et al., 1999	10 47,XYY (21.8, SD 3.2)	see Warwick et al., 1999, above	No significant differences	

Study	Population (age, SD)	Imaging Parameters	Results (SCA Compared with NV)	Comments
	13 46,XY (26.81, SD 3.28)			

DSE, dual spin echo; DTI, diffusion tensor imaging; EPI, echo planar imaging; FA, fractional inositropy; fMRI, functional magnetic resonance imaging; MP-RAGE, magnetization prepared rapid gradient echo; MRI, magnetic resonance imaging; NV, normal volunteer; PRESTO, principles of echo shifting with a train of observations; SPGR, spoiled gradient recalled acquisition; rCBF, regional cerebral blood flow; SCA, sex chromosome aneuploidy; SD, standard deviation; STG, superior temporal gyrus; TBV, total brain volume; WMH, white matter hyperintensities.

* Actual ages not provided by authors.