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Sex Chromosome Anomalies in Childhood Onset Schizophrenia: an Update

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Schizophrenia is a debilitating brain disorder characterized by hallucinations, delusions, disordered thinking, diminished emotion, and cognitive impairment. Age of onset of schizophrenia is typically in late adolescence and early adulthood. Given a worldwide prevalence of approximately 1%, schizophrenia is the fourth leading cause of disability and major public health burden. Family, twin and adoption studies have demonstrated a large genetic component, with estimates of heritability around 81%.(1)

Childhood onset schizophrenia is rare, with the prevalence estimated to be approximately 1/300th the rate of the more typical adult onset form. As has been the case for other complex disorders such as breast cancer and Alzheimer's disease, the study of extreme early onset cases might facilitate the discovery of disease genes.(2) Since 1990, we have recruited and rigorously characterized 92 patients with COS.(3) None of these patients had notable dysmorphologies indicative of an obvious chromosomal anomaly. However, there was an increased rate of early pre-psychotic neurodevelopmental disorders relative to that seen in adult onset patients.(4) Such disorders are seen in many genetic syndromes of pediatric onset;(5) the mean IQ of this group was 80, somewhat lower than that of adult onset patients. Follow-up every 2 years for reevaluation confirms the stability of the diagnosis of schizophrenia and has shown continuity with the more common adult onset form of the disorder (AOS).(3, 6) Previously we reported that high resolution karyotyping and fluorescent *in situ* hybridization (FISH) revealed 4 cases with the typical 3 Mb 22q11 deletion,(7) 1 case with atypical Turner's syndrome (46,X,del(X)(q24-ter),(8) and 1 case with an inherited 1;7 balanced translocation.(9) The rate of 4 out of 92 cases for 22q11 deletion is significantly higher than that seen in samples of unselected patients with AOS.(7) In addition, one case with 5q32-ter segmental uniparental isodisomy (35 Mb) was observed through loss of heterozygosity (LOH) on the Affymetrix NspI 250K SNP array and confirmed with genotyping of microsatellite markers.(10)

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Numerous case reports for Turner syndrome and trisomy X provide evidence for the increased risk of psychotic disorders and relevant psychopathological manifestations among adults with X-chromosome anomalies.(11–13) Unrelated studies report rates of atypical Turner syndrome in the general and adult psychiatric population to be 0.2% and 0.17%, respectively.(13, 14) Women with Turner syndrome also show impairments in emotional and visual-spatial processing, decreased full-scale IQ, and share similarities with schizophrenia patients in structural and functional brain abnormalities.(15, 16) Less is known about the association between trisomy X and psychosis; however DeLisi et al. reported the prevalence of trisomy X to be 0.63% in studies of adult onset schizophrenia compared to the 0.39% in the general population.(12, 17)

Here we report 2 additional cases with X chromosome anomalies in the NIMH COS cohort: one mosaic Turner syndrome (46,X,i(X)(q10)(22%)/45,X(78%)), and one trisomy X (47, XXX), bringing the total prevalence to 3/38 (7.9%) among the females in this cohort. The prevalence of these X chromosome anomalies in the NIMH COS population is significantly greater than the reported rates in either the general population (0.2%) or adult onset schizophrenic populations (0.4%, p=0.001) (Table I).

Further, in accordance with Kaplan & Cotton's (1968) hypothesis of "the possibility that other and more subtle genetic instabilities may be associated with the schizophrenic disorders," we hypothesized that X-chromosome anomalies may be associated with previously unidentified micro-deletions and/or duplications that predispose to schizophrenia.(18) To test this hypothesis, we completed whole genome high density SNP and CGH arrays to ascertain novel structural variants (see details in Walsh et al 2008).(19) Briefly, Affymetrix Mapping 500K SNP arrays and Agilent 185K/244K oligo arrayCGH were completed according to manufacturer protocols (www.affymetrix.com, www.agilent.com) and only variants that were identified through both methods were considered for analysis. Results did not reveal any further *de novo* chromosomal events among the probands with X-chromosome anomalies that could be implicated in the etiology of schizophrenia. Nor did these cases tend to have a higher rate of rare structural variants as compared to karyotypically normal female COS probands (results not shown). However, the one case with atypical Turner syndrome who was missing part of one Xq arm was found to have also a 17 Mb duplication of chromosome 16q22.2-ter. Spectral karyotyping revealed that the extra copy of this segment of chromosome 16 was attached to the missing arm of the X chromosome. The duplicated region of chromosome 16 contains approximately 100 known genes, but presents an interesting case since it is not clear what the functionality of the derived chromosome X;16 would be. It is conceivable that the entire chromosome would be subject to X-inactivation, though functional studies would be warranted for this case.

To summarize, this report confirms that subsyndromal sex chromosome anomalies in COS are significantly higher than that found in the community or in AOS. The role of these anomalies in schizophrenia is unclear, though dysregulation of emotional processing may be one component. While we had hypothesized that these cases may have other, more subtle submicroscopic structural variants that could be involved in schizophrenia etiology, this was not confirmed. To date, the overall rate of rate of large chromosomal abnormalities and 22q11 deletions among this COS cohort is 10%.

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Table 1

Rates of specific sex chromosome anomalies in childhood onset schizophrenia (COS), adult onset schizophrenia (AOS), and general population samples

		Rates in Schizophrenia			
Sex chromosome anomaly	**Rates in General Population**	**AOS**	**COS**	**Odds Ratio (95% C.I.) COS vs. AOS**	**Fisher's exact test**
45,X Atypical/Mosaic	432/200000 (0.2%) (Stockholm et al 2006)	11/6483 (0.17%) (Prior et al 2000)	2/38 (5.3%)	32.7 (7.9–137.2)	p=0.002
47,XXX	20/19173 (0.1%) (Bhasin 2005)	22/8837 (0.25%) (DeLisi et al 1994)	1/38 (2.6%)	10.8 (1.8–65.1)	p=0.094
total	452/219173 (0.2%)	67/15320 (0.4%)	3/38 (7.9%)	39.7 (12.4–127.8)	p<0.001