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22q11 deletion syndrome in childhood onset schizophrenia: an update

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SIR – The 22q11 deletion syndrome (22q11DS) is a relatively common (population rate 0.01%)[1] genetic anomaly associated with congenital physical defects and psychosis. To date, 22q11DS rates in adult onset schizophrenia (AOS) are reported as: two out of 100,[1] one out of 300,[3] one out of 329 cases of adult onset, and none among 141 cases of 'juvenile onset' (<18 years old, mean age = 15.6) (Table 1).[4] Thus, combined rate of 22q11DS in AOS samples is 4/870 (0.46%).

Childhood onset schizophrenia (COS) is a rare but severe form of the illness hypothesized to have high genetic loading. In COS, a high rate of several cytogenetic abnormalities including 22q11DS has been reported previously.[5] Here, we provide an update on the rate and neurobiological characteristics of 22q11DS in COS and compare the rate with that in AOS.

The NIMH COS sample consists of 75 nationally recruited children and adolescents, meeting the DSM-IIIR/IV criteria for schizophrenia with the onset of psychosis before the 13th birthday (mean age of onset 10.4 years). The diagnosis of COS was carried out by structured interviews and medication-free inpatient observation. Significant medical or neurological illnesses or premorbid IQ below 70 were exclusionary. Clinical and neurobiological measures including anatomical MRI scans were obtained at admission and 2-year follow-up visits. The rate of total gray matter reduction was calculated for patients with two or more scans (defined as follow-up scan value minus first scan value divided by time elapsed between scans).

Cytogenetic testing for the 22q11 deletion was carried out using fluorescence *in situ* hybridization (FISH) with the cosmid probe D22S75. In addition, all cases were tested with multiplex ligation-dependent probe amplification (MLPA)[6] using MLPA test kit for DiGeorge/VCFS syndrome to confirm 22q11 deletion. The probe mixture contained 11 probes for the 22q11 region as well as probes for 4q, 8p23, 10p12–23, and 10q. Parental origins of the deletions were established by genotyping probands and parents for four polymorphic dinucleotide repeat markers (D22S941, D22S944, D22S264, and D 22S311) using techniques described elsewhere.[7] All cases of 22q11DS were checked for paternity.

The rate of VCFS in the NIMH COS sample was compared with reported rates across three independent AOS samples (total number 870) using Fisher's exact test. Phenotypic and biological measures were compared for COS subjects with and without 22q11DS and to 22q11DS cases without schizophrenia reported elsewhere.

Out of 75 COS patients, four (5.3%) were found to have a spontaneous 3 Mb deletion at 22q11, which is significantly higher than the 0.46% found for AOS cases ($P = 0.002$). All cases identified by FISH were confirmed by MLPA and no new deletions were identified in 22q11or any of the other regions covered by MLPA probes. All four cases had subtle craniofacial and body dysmorphic characteristics that had not been noticed previously. Three of the four 22q11 deletions were from maternal chromosomes.

The 22q11DS cases did not differ from the other COS patients in the age of onset, IQ, premorbid functioning, or severity of psychosis, but had fewer negative symptoms as measured by Scale for the Assessment of Negative Symptoms (30.5 ± 26.3 *vs* 70.1 ± 26.9; $P = 0.006$). All four had good clinical response to atypical neuroleptics (clozapine, olanzapine, or quetiapine); however, three developed epileptiform EEG changes/seizures.

There were no significant differences in total cerebral, total gray mater, lateral ventricle volumes, or progressive reduction of gray matter (all *P*-values >0.25). The rate of progressive gray matter reduction in 22q11DS cases (-18.7 ± 12.3 ml/year) was similar to that reported in a cross-sectional study of nine VCFS cases (age = 12.1 ± 2.9) without psychosis with maternal origin of 22q11 deletion (−12.5 ml/year) (A Reiss, personal communication).

This report confirms that the rate of 22q11DS in COS is significantly higher than that in the commu-

Table 1 Rates of 22q11 deletion syndrome in childhood onset schizophrenia and adult onset schizophrenia samples

	AOS	*COS*	*Fisher's exact test*
4/870 (0.46%)	1/300 (0.33%) (Arinami *et al*[3]) 1/470 (0.21%)[4] (Ivanov *et al*[4]) 2/100 (2%) (Karayiorgou *et al*[2])	4/75 (5.3%)	$P = 0.002$

nity and in AOS. Since 22q11DS is associated with learning and developmental problems,[8] its rate may be even higher in children with psychosis and IQ below 70.

The role of 22q11 deletion in schizophrenia is unclear. Possibly one or more important genes implicated in schizophrenia lie within the deleted region. However, for the COS sample high-density mapping of the 22q11 region indicate this not to be the case.[9] Alternatively, a general chromosomal instability may account for 22q11DS and other cytogenetic abnormalities, which appear more salient for early-onset disorder. A more general screening for microdeletions in COS is underway.

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1 Tezenas Du Montcel S, Mendizabai H, Ayme S, Levy A, Philip N. *J Med Genet* 1996; **33**: 719.
2 Karayiorgou M, Morris MA, Morrow B, Shprintzen RJ, Goldberg R, Borrow J *et al. Proc Natl Acad Sci USA* 1995; **92**: 7612–7616.
3 Arinami T, Ohtsuki T, Takase K, Shimizu H, Yoshikawa T, Horigome H *et al. Schizophr Res* 2001; **52**: 167–170.
4 Ivanov D, Kirov G, Norton N, Williams HJ, Williams NM, Nikolov I *et al. Br J Psychiatry* 2003; **183**: 409–413.
5 Nicolson R, Giedd JN, Lenane M, Hamburger S, Singaracharlu S, Bedwell J *et al. Am J Psychiatry* 1999; **156**: 1575–1579.
6 Schouten JP, McElgunn CJ, Waaijer R, Zwijnenburg D, Diepvens F, Pals G. *Nucleic Acids Res* 2002; **30**: e57.
7 Eliez S, Antonarakis SE, Morris MA, Dahoun SP, Reiss AL. *Arch Gen Psychiatry* 2001; **58**: 64–68.
8 Bassett AS, Chow EW, Weksberg R. *Am J Med Genet* 2000; **97**: 45–51.
9 Liu H, Abecasis GR, Heath SC, Knowles A, Demars S, Chen Y J. *Proc Natl Acad Sci USA* 2002; **99**: 16859–16864.