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Chromosome X Aneuploidy in Brazilian Schizophrenic Patients

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Abstract. *The identification of cytogenetic abnormalities in schizophrenic patients may provide clues to the genes involved in this disease. For this reason, a chromosomal analysis of samples from 62 schizophrenics and 70 controls was performed with trypsin-Giemsa banding and fluorescence in situ hybridization of the X chromosome. A clonal pericentric inversion on chromosome 9 was detected in one male patient, and we also discovered mosaicism associated with X chromosome aneuploidy in female patients, primarily detected in schizophrenic and normal female controls over 40 years old. When compared with age-matched female controls, the frequency of X chromosome loss was not significantly different between schizophrenics and controls, except for the 40- to 49-year-old age group. Our findings suggest that the X chromosome loss seen in schizophrenic patients is inherent to the normal cellular aging process. However, our data also suggest that X chromosome gain may be correlated with schizophrenia in this Brazilian population.*

Schizophrenia is a common psychiatric disease with a genetic basis. However, to date, specific mutations associated with the disorder have not been identified. Current views on the genetics of schizophrenia are mainly based on a large set of linkage and cytogenetic studies suggesting that almost all human chromosomes may be involved in schizophrenia pathogenesis (1). In addition to some cases that show specific chromosomal translocations and deletions related to psychoses (2-5), sex chromosome anomalies (6-9) and pericentric inversions of chromosome 9 [inv(9)] (9-11) have also been reported in schizophrenic patients.

In the present study, we report the chromosomal analysis of peripheral blood lymphocytes isolated from 62 schizophrenic patients and 70 controls, as well as an assessment of the relationship between the abnormalities found and disease subtype, gender, age at disease onset and family history. To evaluate the incidence of X chromosome mosaicism in the control group, sex and age-matched Brazilian controls were also studied. Although several studies have reported the systematic cytogenetic screening of schizophrenic individuals, few have performed fluorescence *in situ* hybridization (FISH) analysis. Furthermore, to our knowledge, this is the first study to evaluate chromosomal alterations in Brazilian schizophrenic patients.

Patients and Methods

Patients and controls. A total of 62 unrelated schizophrenic patients (33 males and 29 females) representing a cross section of the population were selected from Gaspar Viana Psychiatric Clinics Hospital (city of Belém, Pará State, Northern Brazil) from July 2005 to June 2007. A consensus diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for schizophrenia (12) was made for each patient by at least two psychiatrists using unstructured clinical interviews and all available information from medical records. The patients' age ranged from 18 to 71 years. The mean (SD) age was 42.63 (±13.80) years, and the mean (SD) age of disease onset (first appearance of florid psychotic symptoms) was 27.37 (±7.40) years. Twenty-one (34%) patients had at least one first-degree relative with schizophrenia, and all patients had a history of at least one admission to a psychiatric hospital.

All participants were of a mixed population comprising three main ethnic groups: Amerindian, African and European (13). Patients were divided into the following subcategories of schizophrenia: paranoid (n=30), disorganized (n=8), catatonic (n=6), undifferentiated (n=4), residual (n=13) and schizophreniform disorder (n=1).

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Seventy sex- and age group-matched controls from the same geographical area were analyzed using conventional cytogenetic and FISH assays. These controls were recruited from 'healthy' individuals in the clinical section of Gaspar Viana Clinics Hospital and did not have any history of mental disorders or cancer. All patients and controls signed an informed consent form approved by Gaspar Viana Clinics Hospital Institutional Review Board.

Cytogenetic examination. A blood sample was drawn from each schizophrenic patient and control. Short-term lymphocyte cultures were carried out according to a standard protocol (14). Metaphase chromosomes were G-banded using trypsin Giemsa (GTG) staining. Karyotyping was performed on 30 metaphase spreads per individual. Metaphase chromosomes were analyzed using Bandview EXPO 3.0.1 software (Applied Spectral Imaging, CA, USA), and the description of the chromosome aberrations was based on the International System for Human Cytogenetic Nomenclature (15).

Patients and controls were analyzed by FISH. FISH was performed on cells fixed in methanol/acetic acid, according to a modified protocol (16). Interphase/metaphase cells were hybridized with an X chromosome α-satellite DNA probe (corresponding to the chromosome region Xq11.1-q11.1) labeled with spectrum-green, DZX1 (Cytocell Technologies Ltd., UK). Nuclei were counterstained with diamidino phenylindole (DAPI)/antifade. The molecular cytogenetic analysis was carried out using an Olympus BX41 fluorescence microscope with a double FITC/TRICT filter (Olympus, Japan) and an Applied Spectral Imaging image analysis system (ASI Ldt., Israel). For each case, 200 interphase nuclei were analyzed. Positive chromosome signals appeared as green spots in the nucleus and were scored using the criteria of Hopman *et al*. (17). Mosaicism was defined as the presence of a minor cell population, greater than 5% of the total cells. All statistical analyses were conducted using the chi-square test (Bioestat 5.0, PA, Brazil), and a 5% significance level was set.

Results

Fifteen out of the sixty-two schizophrenic patients (24.2%) showed karyotypic abnormalities. The clinical details and full karyotypes of these 15 patients are shown in Table I.

In 5 out of the 15 patients (33.3%), random chromosome aberrations were detected, and these aberrations, which occurred in only one cell in each patient sample, included a case of trisomy 21, a loss of the Y chromosome, a marker chromosome and a triradial figure.

When samples were divided into the five subtypes of schizophrenic disorders based on the DSM-IV criteria, no statistically significant difference was seen between disease subtypes with regard to chromosomal abnormalities. Neither having an affected first-degree relative nor a history of admission was correlated with the incidence of karyotype abnormalities ($p>0.05$).

A clonal pericentric inversion on chromosome 9, probably occurring between bands p11 and q13, was found in one male patient (case no. 10) (1.6%), (Table I). Given the 5% cut-off level for GTG-banding, no mosaic aneuploidy of sex chromosomes was seen in the male patients.

Mosaicism associated with X chromosome aneuploidy was the most frequent chromosomal change found in schizophrenic patients (Table I) (Figure 1). It was detected only in female patients, 9 out of 29 (31%), using GTG-banding and FISH. For this reason, we decide to compose the control group for FISH analyses only by females (age ranged from 12 to 77 years). Twenty-four out of the seventy female controls (34.3%) showed mosaicism with X chromosome aneuploidy (Table II). Neither the control nor the schizophrenic group had individuals that showed only X gain mosaicism: all patients with X gain also had X loss. Table III shows the frequency of cells with X chromosome hypodiploidy (45,X) and hyperdiploidy (47,XXX and 48,XXXX) in schizophrenic and normal female controls with chromosome X mosaicism, as detected using FISH.

X chromosome mosaicism was primarily detected in female patients over 40 years of age in both the schizophrenic and control groups. Table IV shows the relationship between X chromosome mosaicism and age in female patients and controls as determined using FISH analysis.

A chi-square test showed that the frequency of X chromosome loss was not significantly different between the schizophrenics and controls ($p>0.05$). However, when the frequency of X chromosome loss was compared between the schizophrenic and control females in age-matched groups, chromosome X loss in the 40- to 49-years-old age group was significantly higher in schizophrenics than in normal females ($p<0.001$). In other age-matched groups, no significant differences ($p>0.05$) were found.

In schizophrenic females, the frequency of X chromosome loss was significantly lower ($p=0.0312$) in females below the age of 50 compared with older schizophrenics. Likewise, in female controls, the incidence of X chromosome loss increased with age ($p<0.001$). Interestingly, X chromosome gain was detected more frequently in female schizophrenics than in controls ($p<0.001$). In both groups, the incidence of X chromosome gain increased with aging.

Discussion

In the present study, Brazilian schizophrenic patients showed two types of clonal chromosomal aberration: inv(9)(p11q13) and X chromosome aneuploidy. These chromosome findings corroborate those of previous studies (7, 9, 11, 18). Other chromosome aberrations reported in schizophrenic patients, such as trisomy 8 or 21, translocations such as (1;7) and t(18;21), inversions of chromosome 4 or deletions at 1q, 5q, 7q, 11q and 22q (4, 5, 18-23) were not found in lymphocytes of the study patients, probably due to classic cytogenetic limitations. Conventional cytogenetic analysis is one of the simplest and therefore one of the most popular assays. However, this analysis is restricted to the study of metaphase cells and moderate cell scoring potential (1).

Table I. *Clinical and karyotypic information on schizophrenic probands and their families displaying chromosome alterations.*

Case no. (Proband n=62)	Age (years)	Age of onset (years)	Gender	Family history[a]	Diagnosis by DSM-IV	Karyotype[b]
Chromosome mosaicism						
01	44	25	F	+	Paranoid	mos 45,X[3]/46,XX[27]
02	49	27	F	–	Paranoid	mos 45,X[3]/47,XXX[2]/46,XX[25]
03	57	17	F	–	Paranoid	mos 45,X[5]/47,XXX[2]/46, XX [23]
04	59	29	F	–	Paranoid	mos 45,X[6]/47,XXX[2]/48,XXXX[2]/46XX[20]
05	59	37	F	–	Catatonic	mos 45,X[6]/47,XXX[3]/48,XXXX[3]/46,XX[18]
06	65	32	F	–	Residual	mos 45, X[9]/47,XXX[3]/46,XX[18]
07	67	29	F	+	Disorganized	mos 45, X[8]/47,XXX[2]/46,XX[20]
08	70	20	F	+	Residual	mos 45,X[10]/46,XX[20]
09	71	23	F	–	Paranoid	mos 45,X[9]/46,XX[21]
10	57	48	M	+	Paranoid	46, XY, inv[9](p11q13)[3]/46XY[27]
Random chromosome aberrations						
11	42	23	M	–	Residual	triradial figure[1]/46, XY[29]
12	44	28	M	+	Paranoid	45, X[1]/46, XY[29]
13	56	34	F	–	Paranoid	47, XX, + mar [1]/46, XX[29]
14	57	36	M	–	Disorganized	47, XY, +21[1]/46, XY[29]
15	62	40	M	–	Paranoid	45, X[1]/46, XY[29]

[a]At least one first-degree relative with schizophrenia; [b]the numbers in square brackets shows the number of cells with the indicated karyotype.

Except for inv(9), no other clonal abnormalities were found in the autosomes. Previous studies have suggested that the pericentric region of chromosome 9 may be etiologically linked to schizophrenia (9, 24). However, as this is the most common chromosome variation in the general population, it is not associated with a specific phenotype; furthermore, it is generally considered to be a normal variant rather than an abnormal karyotype in schizophrenia (25, 26).

Gorwood *et al*. (27), who investigated 25 familial schizophrenics, and DeLisi *et al*. (7), who studied 46 male schizophrenics, did not report any affected individual with the inv(9) abnormality. The results of the present study do not support an increased incidence of inv(9) among Brazilian schizophrenics.

X chromosome aneuploidies in schizophrenia. In our study, 31% of the female patients presented aneuploidy of the X chromosome, as identified using classic cytogenetics (Table I) and FISH (Table III and IV). The FISH assay is considered a useful method for numerical chromosome aberrations analysis. It can be applied to interphase cells and it can be very useful in the study of several conditions as it does not require high-quality chromosome preparations and allows for the analysis of a greater number of cells than classic cytogenetics (28).

In the present study, we found a higher frequency of X chromosome gain in schizophrenic female patients than in normal controls, and this gain increased with age. Moon *et al*. (29) also reported that gain of the partial fragment Xq23 was the most frequently detected change in lymphocytes from 30 schizophrenic patients (52%) analyzed using array comparative genomic hybridization (CGH), an approach with higher resolution that allows for the direct mapping of aberrations to a genomic sequence. The Xq23 region showed both loss and gain in the arrayCGH, and this location showed the highest overall frequency of aberrations. Moon *et al*. have suggested this to be a candidate region relating to the pathogenesis of schizophrenia, and our findings corroborate theirs.

Most of the genes along the X chromosome are expressed in the brain. Quantitative alterations in any of these genes hinder normal brain development and function and, therefore, are potential causes of schizophrenia (18). Warwick *et al*. (30) and Crow (31) have suggested that schizophrenia may be attributable to an abnormality in cerebral lateralization, possibly involving abnormal expression of a cerebral dominance gene on the X chromosome. Yurov *et al*. (32), in a preliminary FISH study, showed trisomy of the X chromosome in two out of six schizophrenic brain samples (3-4% of neurons analyzed), suggesting a possible involvement of mosaic X aneuploidy in the pathogenesis of this illness. Furthermore, Iourov *et al*. (33) demonstrated that while in normal human brain analyses approximately 10% of neurons and glial cells are aneuploid, an increased aneuploidy rate is a feature of the diseased brain. Neuronal and glial dysfunction caused by genetic instability (aneuploidy) may lead to abnormal behavior in adulthood. Therefore, genetic instabilities mediated by

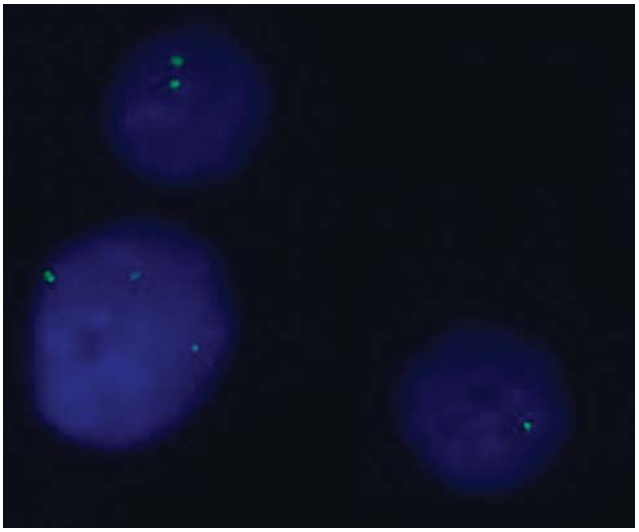

Figure 1. *Aneuploidy of the X chromosome. Interphase nuclei from a female schizophrenic patient presenting one, two and three X chromosomes (green X chromosome probe), as detected using FISH.*

Table II. *Age and karyotype of control females with chromosome alterations.*

Control no. (Proband n=70)	Age (years)	Karyotype[a]
Chromosome mosaicism		
01	40	mos 47,XXX[3]/45,X[1]/ 46,XX[26]
02	45	mos 45,X[3]/47,XXX[2]/46,XX[27]
03	45	mos 45,X[3]/46, XX [27]
04	54	mos 45,X[3]/47,XXX[2]/ 46XX[27]
05	57	mos 45,X[4]/46,XX[26]
06	58	mos 45,X[3]/46,XX[27]
07	59	mos 45,X[5]/46,XX[25]
08	60	mos 45,X[6]/46,XX[24]
09	63	mos 45,X[4]/47,XXX[2]/46,XX[24]
10	63	mos 45,X[5]/46,XX[25]
11	65	mos 45,X[5]/47,XXX[2]/46,XX[23]
12	66	mos 45,X[6]/46,XX[24]
13	68	mos 45,X[6]/46,XX[24]
14	69	mos 45, X[7]/46,XX[23]
15	70	mos 45,X[7]/47,XXX[2]/46,XX[21]
16	71	mos 45,X[7]/46,XX[23]
17	71	mos 45,X[8]/46,XX[22]
18	73	mos 45,X[5]/46,XX[25]
19	74	mos 45,X[7]/46,XX[23]
20	74	mos 45,X[8]/46,XX[22]
21	75	mos 45,X[7]/46,XX[23]
22	77	mos 45,X[9]/46,XX[21]
23	79	mos 45,X[7]/46,XX[23]
24	79	mos 45,X[8]/46,XX[22]

[a]The number in square brackets shows the number of cells with the specified karyotype.

Table III. *Age at examination and X chromosome signal number in female individuals with chromosome X mosaicism as analyzed by FISH.*

Case	Age (years)	Nuclei exhibiting chromosome X signals, no. (%) out of 200			
		1	2	3	4
Schizophrenia					
01	44	20 (10)	180 (90)	0	0
02	49	18 (9)	162 (81)	22 (10)	0
03	57	17 (8.5)	160 (80)	23 (11.5)	0
04	59	26 (13)	139 (69.5)	19 (9.5)	16 (8)
05	59	24 (12)	130 (65)	24 (12)	22 (11)
06	65	19 (9.5)	154 (77)	27 (13.5)	0
07	67	16 (8)	155 (77.5)	29 (14.5)	0
08	70	17 (8.5)	183 (91.5)	0	0
09	71	32 (16)	168 (84)	0	0
Control					
01	40	08 (4)	181 (90.5)	11 (5.5)	0
02	45	09 (4.5)	179 (89.5)	12 (6)	0
03	45	12 (6)	188 (94)	0	0
04	54	26 (13)	162 (81)	12 (6)	0
05	57	28 (14)	165 (82.5)	7 (3.5)	0
06	58	26 (13)	168 (84)	6 (3)	0
07	59	33 (16.5)	159 (79.5)	8 (4)	0
08	60	31 (15.5)	165 (82.5)	4 (2)	0
09	63	20 (10)	164 (82)	16 (8)	0
10	63	28 (14)	169 (84.5)	3 (1.5)	0
11	65	25 (12.5)	161 (80.5)	14 (7)	0
12	66	10 (5)	188 (94)	2 (1)	0
13	68	26 (13)	170 (85)	4 (2)	0
14	69	23 (11.5)	176 (88)	1 (0.5)	0
15	70	28 (14)	160 (80)	12 (6)	0
16	71	20 (10)	177 (88.5)	3 (1.5)	0
17	71	25 (12.5)	174 (87)	1 (0.5)	0
18	73	26 (13)	173 (86.5)	1 (0.5)	0
19	74	22 (11)	176 (88)	2 (1)	0
20	74	30 (15)	170 (85)	0	0
21	75	27 (13.5)	170 (85)	3 (1.5)	0
22	77	22 (11)	178 (89)	0	0
23	79	29 (14.5)	171 (85.5)	0	0
24	79	30 (15)	170 (85)	0	0

genetic and environmental factors may provide clues to understanding the molecular mechanisms underlying major psychiatric disorders (1).

In our samples, none of the male patients showed mosaicism using conventional cytogenetic analysis. However, Kunugi *et al.* (9) reported the occurrence of XXY in 1.6% of 122 males. Additionally, Warwick *et al.* (30) described abnormal cerebral asymmetry in a patient with Klinefelter's syndrome (XXY). These results provide additional evidence for cytogenetic heterogeneity in schizophrenic patients.

Sex chromosome aneuploidy is known to increase with age in peripheral lymphocyte cultures, and hypodiploidy is more common than hyperdiploidy in cultured cells (34). In the present

Table IV. *Comparison of the relationship between X chromosome mosaicism and age in schizophrenic and control females.*

Age at examination (years)	No. of females examined	No. of cells exhibiting X mosaicism[a] / No. of total cells examined (%)[b]	
		X loss	X gain
Schizophrenia			
10-19	01	0/200 (0)	0/200 (0)
20-28	04	0/800 (0)	0/800 (0)
30-39	06	0/1,200 (0)	0/1,200 (0)
40-49	09	38/1,800 (2.1)*	22/1,800 (1.2)
50-59	05	67/1,000 (6.7)	104/1,000 (10.4)
60-69	02	35/400 (8.8)	56/400 (14)
70-71	02	49/400 (12.5)	0/400 (0)
Total	29	189/5,800 (3.3)	182/5,800 (3.2)
Control			
10-19	10	0/2,000 (0)	0/2,000 (0)
20-29	10	0/2,000 (0)	0/2,000 (0)
30-39	10	0/2,000 (0)	0/2,000 (0)
40-49	10	12/2,000 (0.6)	23/2,000 (1.2)
50-59	10	113/2,000 (5.7)	12/2,000 (0.6)
60-69	10	163/2,000 (6.8)	30/2,000 (1.5)
70-77	10	259/2,000 (13)	12/2,000 (0.6)
Total	70	547/14,000 (3.9)	77/14,000 (0.6)

[a]Considering a 5% cut-off level for interphase FISH; [b]the ratio of cells with X loss or gain against the total number of cells analyzed from all individuals of the same age group; *$p<0.001$ compared to corresponding control group.

study, FISH analysis of the X chromosome of female schizophrenics was compared with age-matched controls. Although the 40- to 49-year-old age group showed a significant difference between schizophrenics and normal females, other age-matched groups showed that the incidence of X chromosome loss with age does not differ between schizophrenic and control samples. Toyota *et al*. (11) also demonstrated that the age-stratified incidence of X chromosome loss in females was not significantly different between schizophrenic and control samples. Therefore, the results of our study corroborate this finding, suggesting that X chromosome loss is not related to schizophrenic disease, specifically above the age of 50 year.

Guttenbach *et al*. (35) analyzed 1,000 leukocyte interphase nuclei from 90 healthy Caucasian females using FISH to evaluate the frequency of X chromosome loss and its age dependence. They observed a correlation between X chromosome loss and age in females aged 52–91 years. In our samples, we found that X chromosome loss occured after the age of 40 in schizophrenic patients and in normal controls. In normal female controls, a gradual increase of X chromosome loss after the age of 40 years was observed. Therefore, our findings are consistent with those of Guttenbach *et al*., suggesting that an increased rate of X chromosome loss is associated with the aging process.

Our present findings suggest that X chromosome loss alterations seen in peripheral lymphocytes of schizophrenic patients are inherent to the cellular aging process. However, X chromosome gain may be related to schizophrenia in this Brazilian population.

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References

1 Yurov YB, Iourov IY, Vorsanova SG, Demidova IA, Kravetz VS, Beresheva AK, Kolotii AD, Monakchov VV, Uranova NA, Vostrikov VM, Soloviev IV and Liehr T: The schizophrenia brain exhibits low-level aneuploidy involving chromosome 1. Schizophr Res *98*: 139-147, 2008.

2 Berman DR, Couyoumjian CA, Treadwell MC and Barr M Jr: Familial 4;18 chromosome translocation resulting in trisomy 4p and monosomy 18p: affected individuals with discordant phenotype. Prenat Diagn *29*: 538-540, 2009.

3 Idol JR, Addington AM, Long RT, Rapoport JL and Green ED: Sequencing and analyzing the t(1;7) reciprocal translocation breakpoints associated with a case of childhood-onset schizophrenia/autistic disorder. J Autism Dev Disord *38*: 668-677, 2008.

4 Millar JK, Wilson-Annan JC, Anderson S, Christie S, Taylor MS, Semple CA, Devon RS, Clair DM, Muir WJ, Blackwood DH and Porteous DJ: Disruption of two novel genes by a translocation co-segregating with schizophrenia. Hum Mol Genet *9*: 1415-1423, 2000.

5 Arinami T, Ohtsuki T, Takase K, Shimizu H, Yoshikawa T, Horigome H, Nakayama J and Toru M: Screening for 22q11 deletions in a schizophrenia population. Schizophr Res *52*: 167-170, 2001.

6 van Rijn S, Aleman A, Swaab H and Kahn R: Klinefelter's syndrome (karyotype 47,XXY) and schizophrenia-spectrum pathology. Br J Psychiatry *189*: 459-460, 2006.

7 DeLisi LE, Reiss AL, White BJ and Gershon ES: Cytogenetic studies of males with schizophrenia. Screening for the fragile X chromosome and other chromosomal abnormalities. Schizophr Res *1*: 277-281, 1988.

8 Eckstrand K, Addington AM, Stromberg T, Merriman B, Miller R, Gochman P, Long R, Dutra A, Chen Z, Meltzer P, Nelson SF and Rapoport JL: Sex chromosome anomalies in childhood onset schizophrenia: an update. Mol Psychiatry *13*: 910-911, 2008.

9 Kunugi H, Lee KB and Nanko S: Cytogenetic findings in 250 schizophrenics: evidence confirming an excess of the X chromosome aneuploidies and pericentric inversion of chromosome 9. Schizophr Res *40*: 43-47, 1999.

10 Demirhan O, Pazarbasi A, Suleymanova-Karahan D, Tanriverdi N and Kilinc Y: Correlation of clinical phenotype with a pericentric inversion of chromosome 9 and genetic counseling. Saudi Med J *29*: 946-951, 2008.

11 Toyota T, Shimizu H, Yamada K, Yoshitsugu K, Meerabux J, Hattori E, Ichimiya T and Yoshikawa T: Karyotype analysis of 161 unrelated schizophrenics: no increased rates of X chromosome mosaicism or inv(9), using ethnically matched and age-stratified controls. Schizophr Res *52*: 171-179, 2001.
12 American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Washington: American Psychiatric Association, 1994.
13 Batista dos Santos SE, Rodrigues JD, Ribeiro-dos-Santos AK and Zago MA: Differential contribution of indigenous men and women to the formation of an urban population in the Amazon region as revealed by mtDNA and Y-DNA. Am J Phys Anthropol *109*: 175-180, 1999.
14 Preston RJ, San Sebastian JR and McFee AF: The *in vitro* human lymphocyte assay for assessing the clastogenicity of chemical agents. Mutat Res *189*: 175-183, 1987.
15 ISCN: An International System for Human Cytogenetic Nomenclature. Switzerland: S. Karger AG, 2009.
16 Pinkel D, Straume T and Gray JW: Cytogenetic analysis using quantitative, high-sensitivity, fluorescence hybridization. Proc Natl Acad Sci USA *83*: 2934-2938, 1986.
17 Hopman AH, Ramaekers FC, Raap AK, Beck JL, Devilee P, van der Ploeg M and Vooijs GP: *In situ* hybridization as a tool to study numerical chromosome aberrations in solid bladder tumors. Histochemistry *89*: 307-316, 1988.
18 Demirhan O and Tastemir D: Chromosome aberrations in a schizophrenia population. Schizophr Res *65*: 1-7, 2003.
19 Mensah AK, De Luca V, Stachowiak B, Noor A, Windpassinger C, Lam ST, Kennedy JL, Scherer SW, Lo IF and Vincent JB: Molecular analysis of a chromosome 4 inversion segregating in a large schizophrenia kindred from Hong Kong. Schizophr Res *95*: 228-335, 2007.
20 Ong SH and Robertson JR: Schizophrenia with karyotype mosaic 47,XXY/48,XXY + 8. Psychiatr Genet *5*: 67-69, 1995.
21 Raedle J, Friedl W, Engels H, Koenig R, Trojan J and Zeuzem S: A *de novo* deletion of chromosome 5q causing familial adenomatous polyposis, dysmorphic features, and mild mental retardation. Am J Gastroenterol *96*: 3016-3020, 2001.
22 Hercher L and Bruenner G: Living with a child at risk for psychotic illness: the experience of parents coping with 22q11 deletion syndrome: an exploratory study. Am J Med Genet A *146A*: 2355-2360, 2008.
23 Bassett AS, Chow EW and Weksberg R: Chromosomal abnormalities and schizophrenia. Am J Med Genet *97*: 45-51, 2000.
24 Miyaoka T, Seno H, Itoga M and Ishino H: A case of small cerebral cyst and pericentric inversion of chromosome 9 that developed schizophrenia-like psychosis. Psychiatry Clin Neurosci *53*: 599-602, 1999.
25 Goumy C, Mihaescu M, Tchirkov A, Giollant M, Bonnet-Dupeyron MN, Jaffray JY, Geneix A, Perissel B, Francannet C, Boespflug-Tanguy O and Vago P: An unusual familial chromosome 9 "variant" with variable phenotype: characterization by CGH analysis. Morphologie *89*: 71-75, 2005.
26 Sharony R, Amiel A, Einy R and Fejgin M: Prenatal diagnosis of pericentric inversion in homologues of chromosome 9: a decision dilemma. Am J Perinatol *24*: 137-140, 2007.
27 Gorwood P, Leboyer M, Hillaire D, Jay M, Carteault F, Dugain AM, Berg S, Bois E and Feingold J: Cytogenetic studies of familial schizophrenics. Biol Psychiatry 29: 624-625, 1991.
28 Calcagno DQ, Leal MF, Taken SS, Assumpcao PP, Demachki S, Smith Mde A and Burbano RR: Aneuploidy of chromosome 8 and *C-MYC* amplification in individuals from Northern Brazil with gastric adenocarcinoma. Anticancer Res *25*: 4069-4074, 2005.
29 Moon HJ, Yim SV, Lee WK, Jeon YW, Kim YH, Ko YJ, Lee KS, Lee KH, Han SI and Rha HK: Identification of DNA copy-number aberrations by array-comparative genomic hybridization in patients with schizophrenia. Biochem Biophys Res Commun *344*: 531-539, 2006.
30 Warwick MM, Lawrie SM, Beveridge A and Johnstone EC: Abnormal cerebral asymmetry and schizophrenia in a subject with Klinefelter's syndrome (XXY). Biol Psychiatry *53*: 627-629, 2003.
31 Crow TJ: Temporal lobe asymmetries as the key to the etiology of schizophrenia. Schizophr Bull *16*: 433-443, 1990.
32 Yurov YB, Vostrikov VM, Vorsanova SG, Monakhov VV and Iourov IY: Multicolor fluorescent *in situ* hybridization on post-mortem brain in schizophrenia as an approach for identification of low-level chromosomal aneuploidy in neuropsychiatric diseases. Brain Dev *23*: S186-190, 2001.
33 Iourov IY, Liehr T, Vorsanova SG, Kolotii AD and Yurov YB: Visualization of interphase chromosomes in postmitotic cells of the human brain by multicolour banding (MCB). Chromosome Res *14*: 223-229, 2006.
34 Stone JF and Sandberg AA: Sex chromosome aneuploidy and aging. Mutat Res *338*: 107-113, 1995.
35 Guttenbach M, Koschorz B, Bernthaler U, Grimm T and Schmid M: Sex chromosome loss and aging: *in situ* hybridization studies on human interphase nuclei. Am J Hum Genet *57*: 1143-1150, 1995.

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