

## Microarray comparative genomic hybridization analysis of 59 patients with schizophrenia

Takeshi Mizuguchi · Ryota Hashimoto · Masanari Itokawa · Akira Sano · Osamu Shimokawa · Yukiko Yoshimura · Naoki Harada · Noriko Miyake · Akira Nishimura · Hiroto Saito · Nadiya Sosonkina · Norio Niikawa · Hiroshi Kunugi · Naomichi Matsumoto

Received: 18 April 2008 / Accepted: 8 July 2008 / Published online: 7 August 2008  
© The Japan Society of Human Genetics and Springer 2008

**Abstract** Schizophrenia is a common psychiatric disorder with a strong genetic contribution. Disease-associated chromosomal abnormalities in this condition may provide important clues, such as *DISC1*. In this study, 59 schizophrenia patients were analyzed by microarray comparative genomic hybridization (CGH) using custom bacterial artificial chromosome (BAC) microarray (4,219 BACs with 0.7-Mb resolution). Chromosomal abnormalities were found in six patients (10%): 46,XY,der(13)t(12;13)(p12.1;p11).ish del(5)(p11p12); 46,XY, ish del(17)(p12p12); 46,XX.ish dup(11)(p13p13); and 46,X, idic(Y)(q11.2); and in two cases, mos 45,X/46XX. Autosomal abnormalities in three cases are likely to be pathogenic, and sex chromosome abnormalities in three follow previous findings. It is noteworthy that 10% of patients with schizophrenia have (sub)microscopic chromosomal abnormalities, indicating

that genome-wide copy number survey should be considered in genetic studies of schizophrenia.

**Keywords** Schizophrenia · Chromosomal abnormality · Array comparative genomic hybridization · Copy number variation

### Introduction

Schizophrenia is a common psychiatric disorder involving approximately 1% of the population worldwide. Family, twin, and adoption studies suggest genetic factors contribute to this illness (Lang et al. 2007; McGuffin et al. 1995). Meta-analysis including 18 genome scans revealed strong evidence at chromosomal regions 22q, 8p, and 13q

T. Mizuguchi · Y. Yoshimura · A. Nishimura · H. Saito · N. Matsumoto (✉)  
Department of Human Genetics, Yokohama City University Graduate School of Medicine, Fukuura 3-9, Kanazawa-ku, Yokohama 236-0004, Japan  
e-mail: naomat@yokohama-cu.ac.jp

R. Hashimoto · H. Kunugi  
Department of Mental Disorder Research, National Center of Neurology and Psychiatry, Kodaira, Japan

R. Hashimoto  
Department of Psychiatry, Osaka University Graduate School of Medicine, Suita, Japan

M. Itokawa  
Schizophrenia Research Team, Schizophrenia Project, Tokyo Institute of Psychiatry, Tokyo, Japan

A. Sano  
Department of Psychiatry, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan

O. Shimokawa · N. Harada  
Department of Molecular Cytogenetics, Kyushu Medical Science, Inc., Nagasaki, Japan

N. Miyake  
Department of Medicine (Genetics), Children's Hospital Boston, Boston, MA, USA

N. Miyake  
Department of Neurology, Harvard Medical School, Boston, MA, USA

N. Sosonkina · N. Niikawa  
The Research Institute of Personalized Health Sciences, Health Sciences University of Hokkaido, Tobetsu-cho, Ishikari-gun, Japan

as the susceptibility loci (Badner and Gershon 2002), and another meta-analysis of 20 genome-wide scans suggested regions of chromosomes 2q, 5q, 3p, 11q, 6p, 1q, 22q, 8p, 20q, and 14p as the significant loci (Lewis et al. 2003). Chromosomal abnormalities in patients with schizophrenia may provide useful information regarding the susceptible loci (Bassett et al. 2000). Disrupted in schizophrenia 1 (*DISC1*) gene isolated from a large Scottish family with t(1;11)(q42.1;q14.3) and high risk of schizophrenia in velo-cardio-facial syndrome (VCFS) with a 22q11 deletion are good examples (Arinami 2006; Millar et al. 2000; Murphy 2002). Some linkage and association studies support that schizophrenia could be associated with *DISC1* and genes at 22q11 (Chubb et al. 2008; Liu et al. 2002; O'Donovan et al. 2003; Shifman et al. 2002).

Microarray technologies have now become practical tools for detection of submicroscopic copy number changes. Using custom bacterial artificial chromosome (BAC) microarray (4,219 BACs at 0.7-Mb resolution), we analyzed 59 patients with schizophrenia. Chromosomal abnormalities found in this study are presented.

## Materials and methods

### Subjects

A total of 59 subjects (31 men and 28 women) with schizophrenia were recruited in this study. Forty-one had family history. Diagnosis was made for each patient according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria on the basis of unstructured interviews and information from medical records. Participants were excluded if they had organic brain diseases, including head injury and infection, or if they met criteria for alcohol/drug dependence. After written informed consent, genomic deoxyribonucleic acid (DNA) from lymphoblastoid cell line (LCL) of all patients was isolated using DNA isolation systems [Quick Gene-800 (Fujifilm, Tokyo, Japan) and/or NA-3000 (Kurabo, Osaka, Japan)]. Microarray comparative genomic hybridization (CGH) and fluorescence in situ hybridization (FISH) analysis were performed using materials from LCL. Peripheral blood lymphocytes were reevaluated in ID394, MZ102, and MZ127, but could not be obtained for reexamination in ID67, ID345, or ID391. Only parents of ID345 subjects were available for familial analysis. Other parents or sibs could not be evaluated. Experimental protocols were approved by the Committee for Ethical Issues at Yokohama City University School of Medicine.

### Microarray CGH analysis

Comparative genomic hybridization analysis was performed using our custom BAC microarray containing 4,219 BAC clones, as previously described (Saitsu et al. 2008). In brief, after complete digestion using *DpnII*, subject's DNA was labeled with Cy-5 dCTP (Amersham Biosciences, Piscataway, NJ), and reference DNA was labeled with Cy-3 deoxycytidine triphosphate (dCTP) (Amersham Biosciences) using the DNA random primer Kit (Invitrogen). Prehybridization, probe hybridization, washing, and drying steps for arrays were performed on a Tecan hybridization station HS400 (Tecan Japan, Kawasaki, Japan). Arrays were scanned by GenePix 4000B (Axon Instruments, Union City, CA, USA) and analyzed using GenePix Pro 6.0 (Axon Instruments). The signal intensity ratio between patient and control DNA was calculated from the data of the single-slide experiment using the ratio of means formula (F635 mean – B635 median/F532 mean – B532 median) according to GenePix Pro. 6.0. The standard deviation was calculated from the data of all clones. We regarded the signal ratio as abnormal if it ranged out of  $\pm 3$  standard deviations (SD). Clones showing abnormal copy number were checked to see whether they were in the position of previously registered copy number variations using the Human Genome Variation Database (<http://www.hgvbase.org/>) (Iafate et al. 2004). Unregistered changes were considered for further confirmation. Genome position was based on the UCSC genome browser Human Mar. 2006 (hg18) assembly.

### Fluorescence in situ hybridization

To confirm status of clones with a possibly abnormal copy number, FISH was performed, as previously described (Shimokawa et al. 2005). BAC DNA was labeled with SpectrumGreen<sup>TM</sup>-11-deoxyuridine triphosphate (dUTP) or SpectrumOrange<sup>TM</sup>-11-dUTP (Vysis, Downers Grove, IL, USA) by nick translation and denatured at 70°C for 10 min. Probe-hybridization mixtures (15  $\mu$ l) were applied on chromosomes, incubated at 37°C for 16–72 h, then washed and mounted in antifade solution (Vector, Burlingame, CA, USA) containing 4'-6'-diamidino-2-phenylindole (DAPI). Photographs were taken on an AxioCam MR CCD fitted to Axioplan2 fluorescence microscope (Carl Zeiss, Oberkochen, Germany). In ID394 and MZ102, we counted 100 interphase nuclei to validate the number of cells with X aneuploidy, as well as 30 metaphases.

## Results and discussion

Six patients showed chromosomal abnormalities (10%, 6/59) (Table 1). As we could not obtain materials from most

**Table 1** Summary of six patients with (sub)microscopic chromosomal rearrangements

Patient	Gender	FH	Karyotype	Size of imbalance
ID67	M	No	46,XY,der(13)t(12;13)(p12.1; p11).ish del(5)(p11p12)	1.7 Mb deletion (chr.5) 23.1 Mb gain (chr.12)
MZ127	F	Yes	46,XX.ish dup(11)(p13p13)	430 bp (?) gain (chr.11)
ID345	M	No	46,XY, ish del(17)(p12p12)	1.3 Mb deletion (chr.17)
MZ102	F	Yes	Mos45,X/46,XX	Whole X loss (mosaic)
ID394	F	Yes	Mos45,X/46,XX	Whole X loss (mosaic)
ID391	M	Yes	46,X,idi(Y)(q11.2)	Yq12-qter deletion Yq11.23-Yq12 gain

FH family history of schizophrenia and/or other psychiatric disorders

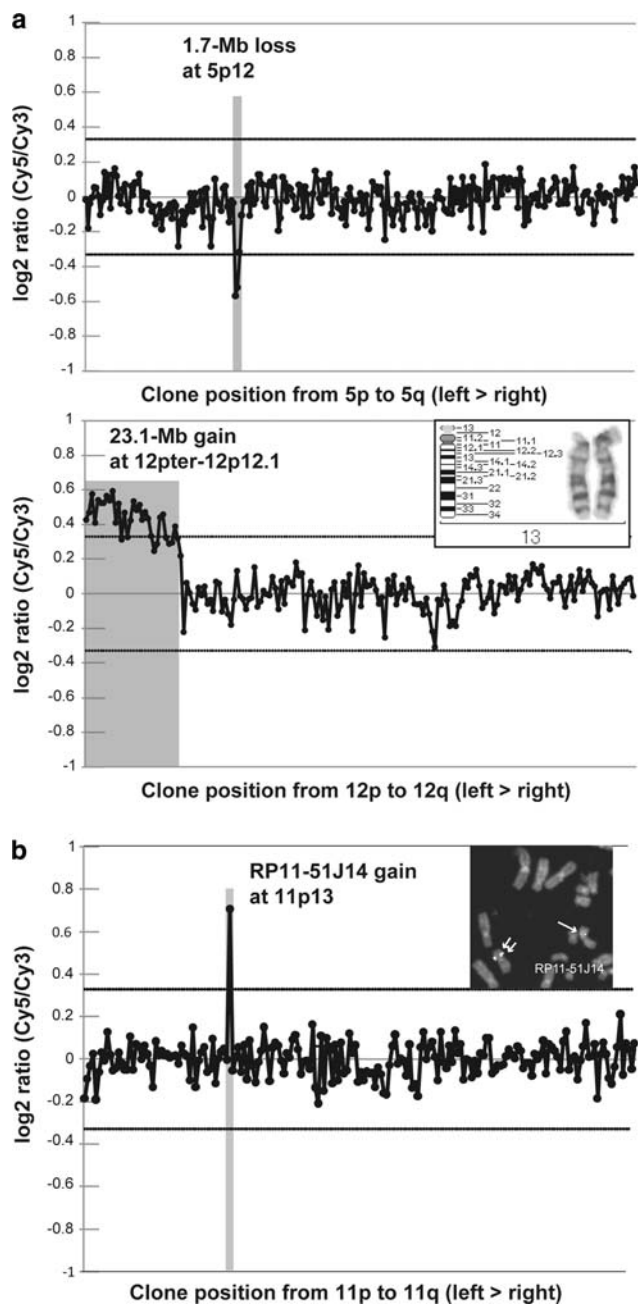
of their parents and sibs, heritability of the abnormalities could not fully be investigated. According to our experiences of microarray CGH analysis of more than 200 Japanese patients associated with mental-retardation-related disorders, all chromosomal abnormalities described here were never detected. Thus, it is less likely that the changes are polymorphisms.

In ID67, arr cgh 5p12p12(RP11-1037A10 → RP11-929P16) × 1, 12pterp12.1(GS-124K20 → RP11-12D15) × 3 was found. A 23.2-Mb copy number gain from 12pter to 12p12.1 (chr12: 0–23,176,547 bp) was detected (Fig. 1a). G-banded chromosomal analysis revealed that 12pter-12p12.1 was translocated to 13p11 (Fig. 1a). The 12p12.1 translocation breakpoint was localized between two BAC clones, RP11-35A22 and RP11-349E13, by FISH (chr12: 23,176,547–23,861,227 bp) (data not shown). Additionally, a 1.7-Mb submicroscopic deletion at 5p12 from RP11-1037A10 to centromeric sequence gap (chr5: 44,778 009–46,437 323 bp) was also found in this patient (Fig. 1a). The 12p trisomy is recognized as multiple congenital anomalies/mental retardation (MCA/MR) syndrome characterized by dysmorphic face, heavy birth weight, foot deformities, hypotonia, and mental retardation (Allen et al. 1996). A previous study suggested that partial duplication of 12pter-p13.2 is sufficient for recognizable phenotype of 12p trisomy (Rauch et al. 1996). The 23.1-Mb duplicated region contained at least 229 genes. Dysmorphic facial features of 12p trisomy (Rauch et al. 1996) were not recognized in this patient. It is interesting that ID67 also had a 1.7-Mb deletion at 5p12, containing two genes, *MRPS30* (the mitochondrial ribosomal protein S30 gene) and *HCNI* (the hyperpolarization-activated cyclic nucleotide-gated potassium channel 1 gene). It is worth noting linkage findings within the vicinity of this region in Costa Rican schizophrenia samples (Cooper-Casey et al. 2005). *HCNI* is an intriguing candidate gene. The general *Hcn1* loss in mice led to a defect in the learning of motor tasks, and specific deletion of the gene in forebrain neurons resulted in an unexpected enhancement of spatial learning and memory (Herrmann et al. 2007; Nolan

et al. 2003). ID67 (a 72-year-old male) developed psychotic symptoms (delusions, hallucinations, and psychomotor excitement) at age 20 years. He had received electroconvulsive therapy many times and continuous sleep therapy until antipsychotic medication (chlorpromazine) was introduced at age 23 years. Since the onset of the illness, he has spent most of his life in psychiatric hospitals because of exacerbations of psychotic episodes and marked deterioration of social functions. Intelligent quotient (IQ) at 72 years was 72. He had no family history of major psychosis within the first-degree relatives.

In MZ127, arr cgh 11p13p13(RP11-51J14) × 3 was recognized. Duplication of RP11-51J14 at 11p13 (chr11: 33,302,231–33,302,660 bp) was confirmed by FISH using LCL and peripheral blood lymphocytes (Fig. 1b). According to the genome browser, the size of RP11-51J14 is 430 bp, indicating that the reference sequence is somehow odd and may contain a deletion overlapping with RP11-51J14 as FISH signals of RP11-51J14 are strong enough to detect on a microscope, suggesting that its size is at least >10 kb. *HIPK3* (the homeodomain interactive protein kinase 3 gene) was corresponding to this clone. *HIPK3* is a Fas-associated death-domain (FADD)-interacting kinase involved in apoptosis (Curtin and Cotter 2003), remaining unknown in relation to schizophrenia. MZ127 (42-year-old woman) presented with epilepsy at age 12 years and has had recurrent depression and slight mania since age 29 years. She began to exhibit auditory hallucination, not synchronizing with mood swing, and was diagnosed as schizophrenia at 40 years. Her mother and sister suffered from major depression and schizophrenia, respectively. Her father committed suicide induced by depression.

In ID345, arr cgh 17p12p12(RP11-78J16 → RP11-103P10) × 1 was found, as previously described (Ozeki et al. 2008). The deletion from RP11-246F16 to RP11-103P10 (chr17: 14,061,460–15,374,745 bp) is 1.4 Mb, compatible with the common deletion found in approximately 85% of hereditary neuropathy with liability to pressure palsies (HNPP; OMIM #162500) (Stogbauer et al.



**Fig. 1** Results of microarray comparative genomic hybridization (CGH) in ID67 (a) and MZ127 (b). Chromosomes 5 (upper) and 12 (lower) are displayed (a). The karyotype is arr cgh 5p12p12(RP11-1037A10 → RP11-929P16) × 1, 12pterp12.1(GS-124K20 → RP11-12D15) × 3. Partial karyotype clearly shows a 12pter-p12.1 segment is translocated to 13p11. Chromosome 11 is presented (b). The karyotype is arr cgh 11p13p13(RP11-51J14) × 3. RP11-51J14 at 11p13 is duplicated

2000). The deletion was also identified in his father’s chromosomes from peripheral blood lymphocytes. He suffered from auditory hallucination and delusion of persecution and received antipsychotic treatment at age 19. Neurological examination did not reveal any manifestations

of HNPP (Ozeki et al. 2008). Pareyson et al. (1996) reported that about 25% of individuals with HNPP deletion are asymptomatic. The peripheral myelin protein 22 gene (PMP22) may be a candidate that is not only expressed in the peripheral nervous system but also in the central nervous system (Ohsawa et al. 2006), this being supported by linkage studies of psychotic bipolar disorder (Park et al. 2004) and schizophrenia (Owen et al. 2004). No family history regarding psychiatric disorders was observed in ID345.

Entire X chromosome copy number aberration was suspected in two patients, ID394 and MZ102 (data not shown). FISH analysis using RP11-65B15 at Xq23 revealed mosaic monosomy of chromosome X: mos45,X[41]/46,XX[59] in ID394 and mos45,X[84]/46,XX[16] in MZ102. X aneuploidy is well known to be seen in elderly normal females (Stone and Sandberg 1995). ID394 and MZ102 were 67 and 38 years old, respectively. The fraction of cells with X monosomy was very high (84% and 41%) in lymphoblastoid cell lines of these patients. Reevaluation of peripheral blood lymphocytes showed mos 45,X[7]/46,XX[98] in ID394 and mos 45,X[4]/46,XX[96] in MZ102. These findings may support involvement of X-chromosomal abnormalities in schizophrenia (Kumra et al. 1998; Kunugi et al. 1999), but mosaic X monosomy is also found in age-matched normal controls (Toyota et al. 2001). ID394 (a 67-year-old woman) developed psychotic symptoms (paranoid delusion and hallucinations) at age 31 years when she delivered her second child. Since then, she had been admitted to a psychiatric hospital three times (each for a few months). She quit her job as a pharmacist after the onset of the illness and has lived as a housewife. She has been managed by antipsychotic medications without major exacerbation for the past decade. The second child developed schizophrenia-like symptoms, including social withdrawal and lack of volition. MZ102 (a 38-year-old woman) exhibited psychomotor excitement and was diagnosed as having schizophrenia at age 23 years. Her father showed psychotic disorder, and her uncle had schizophrenia. In ID391, arr cgh Ypterq11.23(GS-98C4 → RP11-214M24) × 3, Yq11.23qter(RP11-263C17 → RP11-80F8) × 1 was identified. FISH analysis using BACs, RP11-74L17 at PAR1, RP11-375P13 at Yp11.2, RP11-655E20 at Yq11.2, and RP11-80F8 at Yq12 revealed the isodicentric Y chromosome [46,X, idic(Y)(q11.2)] (data not shown). Previously, two cases of idic(Yp) were reported in schizophrenia, although idic(Yp) is one of the most common rearrangements in the Y chromosome (Nanko et al. 1993; Yoshitsugu et al. 2003). ID391 (a 29-year-old man) developed hallucinations and abnormal sense of self at age 21 years, when he was admitted to a psychiatric hospital for 3 months. Since then, his illness has been well controlled by antipsychotic medication. He quit university after the onset

of illness and has not obtained a job, suggesting deterioration of functioning. His younger sister (apparently without the Y chromosome) has schizophrenia. Thus, contribution of sex chromosomal abnormalities found in this study is less likely.

Four microarray CGH studies of schizophrenia were reported: 1,440 BAC microarray for 30 patients, 2,460 BAC microarray for 35 patients, a tiling-path microarray consisting of ~36,000 BACs for 93 patients, and high-resolution microarrays (85,000–2,100,000 oligos) for 150 patients (Kirov et al. 2008; Moon et al. 2006; Walsh et al. 2008; Wilson et al. 2006). We could not replicate any similar abnormalities, though microarray platforms were all different in terms of clones and genome coverage. In this study, (sub)microscopic rearrangements were detected in 10% of patients. Similarly, 15% of patients analyzed by high-resolution microarrays were found to possess submicroscopic chromosomal changes (Walsh et al. 2008). Various kinds of recurrent and unique submicroscopic changes were found in 10–17% of idiopathic mental retardation and 7% of autism by microarray CGH analysis (Miyake et al. 2006; Sebat et al. 2007; Zahir and Friedman 2007). Importantly, a 22q13 deletion (in autism) involving Sh3 and multiple ankyrin repeat domains 3 (*SHANK3*), whose point mutation was related to autism (Durand et al. 2007), strongly supports this approach as one of the most powerful and straightforward strategies in neuropsychiatric disorders.

In conclusion, microarray technologies could provide good opportunity to identify chromosomal copy number changes in relation to mental and psychiatric disorders, and genome-wide copy number survey should be considered in genetic studies of these disorders.

**Acknowledgments** We thank all patients for their participation in this study. This work was supported by Research Grants from the Ministry of Health, Labour and Welfare (HK and NM), and Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Culture, Sports, Science and Technology of Japan (RH and NM).

## References

- Allen TL, Brothman AR, Carey JC, Chance PF (1996) Cytogenetic and molecular analysis in trisomy 12p. *Am J Med Genet* 63:250–256
- Arinami T (2006) Analyses of the associations between the genes of 22q11 deletion syndrome and schizophrenia. *J Hum Genet* 51:1037–1045
- Badner JA, Gershon ES (2002) Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. *Mol Psychiatry* 7:405–411
- Bassett AS, Chow EW, Weksberg R (2000) Chromosomal abnormalities and schizophrenia. *Am J Med Genet* 97:45–51
- Chubb JE, Bradshaw NJ, Soares DC, Porteous DJ, Millar JK (2008) The DISC locus in psychiatric illness. *Mol Psychiatry* 13:36–64

- Cooper-Casey K, Mesen-Fainardi A, Galke-Rollins B, Llach M, Laprade B, Rodriguez C, Riondet S, Bertheau A, Byerley W (2005) Suggestive linkage of schizophrenia to 5p13 in Costa Rica. *Mol Psychiatry* 10:651–656
- Curtin JF, Cotter TG (2003) Live and let die: regulatory mechanisms in Fas-mediated apoptosis. *Cell Signal* 15:983–992
- Durand CM, Betancur C, Boeckers TM, Bockmann J, Chaste P, Fauchereau F, Nygren G, Rastam M, Gillberg IC, Anckarsater H, Sponheim E, Goubran-Botros H, Delorme R, Chabane N, Mouren-Simeoni MC, de Mas P, Bieth E, Roge B, Heron D, Burglen L, Gillberg C, Leboyer M, Bourgeron T (2007) Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. *Nat Genet* 39:25–27
- Herrmann S, Stieber J, Ludwig A (2007) Pathophysiology of HCN channels. *Pflugers Arch* 454:517–522
- Iafrate AJ, Feuk L, Rivera MN, Listewnik ML, Donahoe PK, Qi Y, Scherer SW, Lee C (2004) Detection of large-scale variation in the human genome. *Nat Genet* 36:949–951
- Kirov G, Gumus D, Chen W, Norton N, Georgieva L, Sari M, O'Donovan MC, Erdogan F, Owen MJ, Ropers HH, Ullmann R (2008) Comparative genome hybridization suggests a role for NRXN1 and APBA2 in schizophrenia. *Hum Mol Genet* 17:458–465
- Kumra S, Wiggs E, Krasnewich D, Meck J, Smith AC, Bedwell J, Fernandez T, Jacobsen LK, Lenane M, Rapoport JL (1998) Brief report: association of sex chromosome anomalies with childhood-onset psychotic disorders. *J Am Acad Child Adolesc Psychiatry* 37:292–296
- Kunugi H, Lee KB, Nanko S (1999) 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
- Lang UE, Puls I, Muller DJ, Strutz-Seeborn N, Gallinat J (2007) Molecular mechanisms of Schizophrenia. *Cell Physiol Biochem* 20:687–702
- Lewis CM, Levinson DF, Wise LH, DeLisi LE, Straub RE, Hovatta I, Williams NM, Schwab SG, Pulver AE, Faraone SV, Brzustowicz LM, Kaufmann CA, Garver DL, Gurling HM, Lindholm E, Coon H, Moises HW, Byerley W, Shaw SH, Mesen A, Sherrington R, O'Neill FA, Walsh D, Kendler KS, Ekelund J, Paunio T, Lonnqvist J, Peltonen L, O'Donovan MC, Owen MJ, Wildenauer DB, Maier W, Nestadt G, Blouin JL, Antonarakis SE, Mowry BJ, Silverman JM, Crowe RR, Cloninger CR, Tsuang MT, Malaspina D, Harkavy-Friedman JM, Svrakic DM, Bassett AS, Holcomb J, Kalsi G, McQuillin A, Brynjolfson J, Sigmundsson T, Petursson H, Jazin E, Zoega T, Helgason T (2003) Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: schizophrenia. *Am J Hum Genet* 73:34–48
- Liu H, Heath SC, Sobin C, Roos JL, Galke BL, Blundell ML, Lenane M, Robertson B, Wijsman EM, Rapoport JL, Gogos JA, Karayiorgou M (2002) Genetic variation at the 22q11 PRODH2/DGCR6 locus presents an unusual pattern and increases susceptibility to schizophrenia. *Proc Natl Acad Sci USA* 99:3717–3722
- McGuffin P, Owen MJ, Farmer AE (1995) Genetic basis of schizophrenia. *Lancet* 346:678–682
- Millar JK, Wilson-Annan JC, Anderson S, Christie S, Taylor MS, Semple CA, Devon RS, Clair DM, Muir WJ, Blackwood DH, Porteous DJ (2000) Disruption of two novel genes by a translocation co-segregating with schizophrenia. *Hum Mol Genet* 9:1415–1423
- Miyake N, Shimokawa O, Harada N, Sosonkina N, Okubo A, Kawara H, Okamoto N, Kurosawa K, Kawame H, Iwakoshi M, Kosho T, Fukushima Y, Makita Y, Yokoyama Y, Yamagata T, Kato M, Hiraki Y, Nomura M, Yoshiura K, Kishino T, Ohta T, Mizuguchi

- T, Niikawa N, Matsumoto N (2006) BAC array CGH reveals genomic aberrations in idiopathic mental retardation. *Am J Med Genet A* 140:205–211
- Moon HJ, Yim SV, Lee WK, Jeon YW, Kim YH, Ko YJ, Lee KS, Lee KH, Han SI, Rha HK (2006) Identification of DNA copy-number aberrations by array-comparative genomic hybridization in patients with schizophrenia. *Biochem Biophys Res Commun* 344:531–539
- Murphy KC (2002) Schizophrenia and velo-cardio-facial syndrome. *Lancet* 359:426–430
- Nanko S, Konishi T, Satoh S, Ikeda H (1993) A case of schizophrenia with a dicentric Y chromosome. *Jpn J Hum Genet* 38:229–232
- Nolan MF, Malleret G, Lee KH, Gibbs E, Dudman JT, Santoro B, Yin D, Thompson RF, Siegelbaum SA, Kandel ER, Morozov A (2003) The hyperpolarization-activated HCN1 channel is important for motor learning and neuronal integration by cerebellar Purkinje cells. *Cell* 115:551–564
- O'Donovan MC, Williams NM, Owen MJ (2003) Recent advances in the genetics of schizophrenia. *Hum Mol Genet* 12 Spec No 2: R125–133
- Ohsawa Y, Murakami T, Miyazaki Y, Shirabe T, Sunada Y (2006) Peripheral myelin protein 22 is expressed in human central nervous system. *J Neurol Sci* 247:11–15
- Owen MJ, Williams NM, O'Donovan MC (2004) The molecular genetics of schizophrenia: new findings promise new insights. *Mol Psychiatry* 9:14–27
- Ozeki Y, Mizuguchi T, Hirabayashi N, Ogawa M, Ohmura N, Moriuchi M, Harada N, Matsumoto N, Kunugi H (2008) A case of schizophrenia with chromosomal microdeletion of 17p11.2 containing a myelin-related gene PMP22. *Open Psychiatry J* 2:1–4
- Pareyson D, Scaioni V, Taroni F, Botti S, Lorenzetti D, Solari A, Ciano C, Sghirlanzoni A (1996) Phenotypic heterogeneity in hereditary neuropathy with liability to pressure palsies associated with chromosome 17p11.2-12 deletion. *Neurology* 46:1133–1137
- Park N, Juo SH, Cheng R, Liu J, Loth JE, Lilliston B, Nee J, Grunn A, Kanyas K, Lerer B, Endicott J, Gilliam TC, Baron M (2004) Linkage analysis of psychosis in bipolar pedigrees suggests novel putative loci for bipolar disorder and shared susceptibility with schizophrenia. *Mol Psychiatry* 9:1091–1099
- Rauch A, Trautmann U, Pfeiffer RA (1996) Clinical and molecular cytogenetic observations in three cases of “trisomy 12p syndrome”. *Am J Med Genet* 63:243–249
- Saitsu H, Kato M, Mizuguchi T, Hamada K, Osaka H, Tohyama J, Uruno K, Kumada S, Nishiyama K, Nishimura A, Okada I, Yoshimura Y, Hirai SI, Kumada T, Hayasaka K, Fukuda A, Ogata K, Matsumoto N (2008) De novo mutations in the gene encoding STXBP1 (MUNC18-1) cause early infantile epileptic encephalopathy. *Nat Genet* 40(6):782–788
- Sebat J, Lakshmi B, Malhotra D, Troge J, Lese-Martin C, Walsh T, Yamrom B, Yoon S, Krasnitz A, Kendall J, Leotta A, Pai D, Zhang R, Lee YH, Hicks J, Spence SJ, Lee AT, Puura K, Lehtimäki T, Ledbetter D, Gregersen PK, Bregman J, Sutcliffe JS, Jobanputra V, Chung W, Warburton D, King MC, Skuse D, Geschwind DH, Gilliam TC, Ye K, Wigler M (2007) Strong association of de novo copy number mutations with autism. *Science* 316:445–449
- Shifman S, Bronstein M, Sternfeld M, Pisante-Shalom A, Lev-Lehman E, Weizman A, Reznik I, Spivak B, Grisaru N, Karp L, Schiffer R, Kotler M, Strous RD, Swartz-Vanetik M, Knobler HY, Shinar E, Beckmann JS, Yakir B, Risch N, Zak NB, Darvasi A (2002) A highly significant association between a COMT haplotype and schizophrenia. *Am J Hum Genet* 71:1296–1302
- Shimokawa O, Miyake N, Yoshimura T, Sosonkina N, Harada N, Mizuguchi T, Kondoh S, Kishino T, Ohta T, Remco V, Takashima T, Kinoshita A, Yoshiura K, Niikawa N, Matsumoto N (2005) Molecular characterization of del(8)(p23.1p23.1) in a case of congenital diaphragmatic hernia. *Am J Med Genet A* 136:49–51
- Stogbauer F, Young P, Kuhlenbaumer G, De Jonghe P, Timmerman V (2000) Hereditary recurrent focal neuropathies: clinical and molecular features. *Neurology* 54:546–551
- Stone JF, Sandberg AA (1995) Sex chromosome aneuploidy and aging. *Mutat Res* 338:107–113
- Toyota T, Shimizu H, Yamada K, Yoshitsugu K, Meerabux J, Hattori E, Ichimiya T, Yoshikawa T (2001) 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
- Walsh T, McClellan JM, McCarthy SE, Addington AM, Pierce SB, Cooper GM, Nord AS, Kusenda M, Malhotra D, Bhandari A, Stray SM, Rippey CF, Roccanova P, Makarov V, Lakshmi B, Findling RL, Sikich L, Stromberg T, Merriman B, Gogtay N, Butler P, Eckstrand K, Noory L, Gochman P, Long R, Chen Z, Davis S, Baker C, Eichler EE, Meltzer PS, Nelson SF, Singleton AB, Lee MK, Rapoport JL, King MC, Sebat J (2008) Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science* 320:539–543
- Wilson GM, Flibotte S, Chopra V, Melnyk BL, Honer WG, Holt RA (2006) DNA copy-number analysis in bipolar disorder and schizophrenia reveals aberrations in genes involved in glutamate signaling. *Hum Mol Genet* 15:743–749
- Yoshitsugu K, Meerabux JM, Asai K, Yoshikawa T (2003) Fine mapping of an isodicentric Y chromosomal breakpoint from a schizophrenic patient. *Am J Med Genet B Neuropsychiatr Genet* 116:27–31
- Zahir F, Friedman JM (2007) The impact of array genomic hybridization on mental retardation research: a review of current technologies and their clinical utility. *Clin Genet* 72:271–287