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Chromosomal Abnormalities and Schizophrenia

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Abstract

Schizophrenia is a common and serious psychiatric illness with strong evidence for genetic causation, but no specific loci yet identified. Chromosomal abnormalities associated with schizophrenia may help to understand the genetic complexity of the illness. This paper reviews the evidence for associations between chromosomal abnormalities and schizophrenia and related disorders. The results indicate that 22q11.2 microdeletions detected by fluorescence in-situ hybridization (FISH) are significantly associated with schizophrenia. Sex chromosome abnormalities seem to be increased in schizophrenia but insufficient data are available to indicate whether schizophrenia or related disorders are increased in patients with sex chromosome aneuploidies. Other reports of chromosomal abnormalities associated with schizophrenia have the potential to be important adjuncts to linkage studies in gene localization. Advances in molecular cytogenetic techniques (i.e., FISH) have produced significant increases in rates of identified abnormalities in schizophrenia, particularly in patients with very early age at onset, learning difficulties or mental retardation, or dysmorphic features. The results emphasize the importance of considering behavioral phenotypes, including adult onset psychiatric illnesses, in genetic syndromes and the need for clinicians to actively consider identifying chromosomal abnormalities and genetic syndromes in selected psychiatric patients.

Keywords

schizophrenia; chromosomal aberrations; 22q11 deletion syndrome; velocardiofacial syndrome; sex chromosomes

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INTRODUCTION

Schizophrenia is a common and serious psychiatric illness with peak age at onset in early adulthood, but with some evidence of minor developmental changes in infancy and childhood [Done et al., 1994]. Family, twin, and adoption studies provide strong evidence for genetic etiologies [McGuffin et al., 1995], although transmission patterns are complex and genetic heterogeneity likely. Variable expression of a schizophrenic phenotype may include related disorders such as schizoaffective disorder and other psychotic conditions [McGuffin et al., 1995]. There are now linkage findings achieving significance, including one replicated localization to a 5 cM region on chromosome 13 [Brzustowicz et al., 1999], but no specific loci have yet been identified to cause schizophrenia. Chromosomal abnormalities associated with schizophrenia provide a possible means to help localize causative genes and help understand the genetic complexity of the illness.

There are few reports of chromosomal abnormalities associated with major psychiatric disorders [Bassett, 1992; Craddock and Owen, 1994; DeLisi et al., 1994], likely due to the fact that geneticists usually consult on pediatric cases, with rare follow-up to adolescence/adulthood when psychiatric disorders onset, and psychiatrists generally have a low index of suspicion for genetic syndromes in psychiatric patients. Establishing criteria for meaningful associations between chromosomal abnormalities and schizophrenia may assist clinicians in identifying patients who could benefit from further investigations, and researchers in identifying regions of interest for gene localization [Bassett, 1992; Karayiorgou et al., 1996]. A meaningful association would be present if: 1) for the few chromosomal or molecular cytogenetic abnormalities that are relatively prevalent in the general population such as 22q11.2 microdeletions, increased rates of schizophrenia are present in individuals with the abnormality and patients with the abnormality have increased rates of schizophrenia; or 2) in the more usual case of rare chromosomal abnormalities, there is co-occurrence with schizophrenia in the presence of other supportive data, such as linkage. Recent findings suggest that there is a genetic subtype of schizophrenia associated with chromosome 22q11.2 deletions that meets the first of these criteria [Propping et al., 1995; Karayiorgou et al., 1996; Bassett et al., 1998].

This paper considers the evidence for associations between various chromosomal abnormalities and schizophrenia and related disorders. The findings update those outlined in previous reviews [Bassett, 1992; DeLisi et al., 1994], and demonstrate the significant contributions made by advances in molecular cytogenetic techniques, in particular, fluorescence in-situ hybridization (FISH). The findings also emphasize the importance of considering behavioral phenotypes, including adult onset psychiatric illnesses, in genetic syndromes and the need for clinicians to actively consider identifying chromosomal abnormalities and genetic syndromes in selected psychiatric patients.

REVIEW

22q11.2 Microdeletions

Chromosome 22q11.2 microdeletions provide the most convincing evidence of an association between a molecular cytogenetic abnormality and schizophrenia. Chromosome

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22q11 deletion syndrome (22qDS) encompasses the syndromes velocardiofacial syndrome (VCFS), DiGeorge syndrome, and conotruncal anomaly face syndrome generally associated with 22q11.2 deletions [Demczuk et al., 1995]. The deletion is usually detected using a commercially available 22q11.2 probe (D22S75) and FISH, that has revolutionized the detection of microdeletion syndromes [Turk et al., 1995]. The variable phenotype of 22qDS includes learning difficulties (LD), mental retardation (MR), characteristic physiognomy, palate anomalies, cardiac defects, and later-onset psychiatric illnesses such as schizophrenia [Pulver et al., 1994; Bassett et al., 1998]. Mood, anxiety, attention deficit, autistic, and substance use disorders are also reported [Pulver et al., 1994; Bassett et al., 1998].

The prevalence of psychiatric illnesses is high in 22qDS. A review of 22qDS in adults [Cohen et al., 1999] found that psychiatric disorders were reported in 53% of cases that were not ascertained from psychiatric sources. An early study reported 4 (31%) of 13 adult VCFS patients had schizophrenia or schizoaffective disorder [Shprintzen et al., 1992], and a recent study found that 13 (26%) of 50 adults with 22q11.2 microdeletions had schizophrenia or schizoaffective disorder, 6 (12%) had major depression, and one had bipolar disorder [Murphy et al., 1999]. These figures suggest that schizophrenia may be the most prominent adult psychiatric phenotype associated with 22q11.2 deletions, occurring at up to 25 times the general population rate of 1/100.

The few studies using FISH and a chromosome 22q11.2 probe to screen for 22q11.2 deletions in schizophrenia have demonstrated that 22q11.2 deletions are present in some patients [Karayiorgou et al., 1995; Gothelf et al., 1997; Murphy et al., 1998; Bassett et al., 1999; Nicolson et al., 1999], confirming an association between the psychiatric illness and this chromosomal anomaly. 22q11.2 deletions were found in two (2%) of 100 patients with schizophrenia [Karayiorgou et al., 1995] and in three (6%) of 47 patients with rare childhood onset (<12 years of age) schizophrenia [Nicolson et al., 1999], none of whom had mental retardation. Selecting adult schizophrenic samples with other 22qDS features increases the prior probability of identifying patients with 22q11.2 deletions [Gothelf et al., 1997]. Nine per cent of 22 patients with mild mental retardation and schizophrenia [Murphy et al., 1998], and 32% of 28 referred patients who met two or more proposed clinical screening criteria (including learning difficulties, characteristic physiognomy, hypernasal speech), had 22q11.2 deletions [Bassett et al., 1999]. These preliminary results indicate the rate of 22q11.2 deletions in schizophrenia may be approximately 80 times that of conservative estimates of the general population prevalence (1/4,500) [du Montcel et al., 1996; Devriendt et al., 1998].

Increased rates of schizophrenia in patients with 22q11.2 deletions and of these deletions in patients with schizophrenia support the likelihood that a meaningful association exists between this chromosomal anomaly and schizophrenia [Propping et al., 1995; Karayiorgou et al., 1996; Bassett et al., 1999]. The nature of this association is as yet unknown. There are some positive linkage findings to markers from 22q11.2, but most studies of schizophrenia have found linkage to a more distal region (22q12–13), suggesting there may be two or more loci on chromosome 22 [Schwab et al., 1999], and association studies report mostly negative results using a 22q11.2 candidate gene, catechol-*O*-methyltransferase [Karayiorgou et al.,

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1998]. Genes located in the 22q11.2 deletion region may therefore be involved in causing schizophrenia in a small proportion of cases.

Cytogenetic Surveys and Sex Chromosome Aneuploidies

Although no other single chromosomal abnormality approaches the apparent prevalence of 22q11.2 deletions in schizophrenia, the few available surveys of cytogenetic anomalies in schizophrenic patients indicate that sex chromosome anomalies, reviewed extensively by DeLisi et al. [1994], may have an increased prevalence, and that other anomalies may also be detected. Rates of 47,XXY and 47,XXX in schizophrenia are about four to six times general population rates [DeLisi et al., 1994]. One group karyotyped 64 men and 49 women and found one 47,XXY and one 45,X/46,XX mosaic [DeLisi et al., 1994]. Another group found two autosomal abnormalities (see Table I) and one sex chromosome aneuploidy (47,XXX) in 29 patients with both schizophrenia and mild mental retardation [Doody et al., 1998]. Molecular cytogenetic surveys of childhood onset psychotic disorders have found sex chromosome aneuploidies in three (10%) of 28 patients (47,XXY; 47,XXY/46,XY mosaic; 47,XYY) [Kumra et al., 1998] and in one (2%) of 47 patients with childhood onset schizophrenia (45,X/46,XX mosaic with Xq24-qter deletion) [Nicolson et al., 1999]. The latter study also reported three subjects with 22q11.2 deletions and an autosomal abnormality (see Table I), thus abnormalities were found in 10% (5/47) of the sample. Other small studies of familial schizophrenia [Gorwood et al., 1991; Friedrich et al., 1996] or schizophrenia with IQ >85 and no physical anomalies [Casacchia et al., 1996] found no chromosomal abnormalities. Systematic testing for fragile X found none in childhood onset schizophrenia [Nicolson et al., 1999], but was not performed in other cytogenetic studies. There may be an association of fragile X with bipolar disorder, however, consistent with cosegregation with X-linked traits mapping to Xq28 [Craddock et al., 1994], including PPM-X, an X-linked mental retardation syndrome [Lindsay et al., 1996].

There is no consistent sex chromosome abnormality associated with schizophrenia. Systematic studies examining for the presence of schizophrenia in adults with sex chromosome aneuploidies are needed [DeLisi et al., 1994; Harmon et al., 1998] to determine whether increased rates of sex chromosome abnormalities in schizophrenia are due in part to selection biases. Studies of schizophrenia have neither excluded nor found suggestive linkage to X chromosome markers [DeLisi et al., 1994]. The significance of associations between schizophrenia and sex chromosome aneuploidies is therefore uncertain.

Other Autosomal Abnormalities

Case reports of rare associated abnormalities may provide important clues to gene localizations. Table I outlines findings from recent reports of chromosomal abnormalities associated with schizophrenia and related disorders, and summarizes previous findings. There are relatively few reports overall [Bassett, 1992; Craddock et al., 1994]. Cytogenetic studies were undertaken in most reported cases because of the presence of mental retardation or dysmorphic features in an individual with a psychotic illness, although one study was prompted by chromosome 18 linkage findings [Mors et al., 1997] and others were surveys for fragile sites [Garofalo et al., 1993; Fananas et al., 1997]. Some of these reports may be relevant to recent significant and suggestive linkage findings for schizophrenia and bipolar

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disorder, particularly those involving regions 5q22–q31 [Straub et al., 1997], 10p14–p11 [Faraone et al., 1998], 13q32 [Brzustowicz et al., 1999], 18p11 [Schwab et al., 1998], and 18q21–23 [Freimer et al., 1996]. Because most linkage studies now include a genome scan, however, a specific chromosomal abnormality could potentially help to localize minor schizophrenia susceptibility loci if coupled with even weakly positive linkage findings.

DISCUSSION

The results of this review indicate that 22q11.2 deletions are significantly associated with schizophrenia. Sex chromosome abnormalities seem to be increased in schizophrenia but insufficient data are available to indicate whether schizophrenia or related disorders are increased in patients with sex chromosome aneuploidies. Other rarer chromosomal abnormalities have the potential to be important adjuncts to linkage studies in gene localization.

Clinical Significance

Identifying a chromosomal abnormality in a patient with schizophrenia is of profound importance to the individual and their family. Diagnosis of a chromosomal abnormality can alter medical management and affect prognosis with respect to known associated conditions, such as hypocalcemia in 22qDS, and has important genetic counseling implications. In addition, receiving a genetic diagnosis may relieve parents of guilt or inappropriate blame for causing behavioral manifestations of the condition [Turk et al., 1995].

Genetic Studies

Chromosomal abnormalities may cooccur with schizophrenia due to chance. Alternatively, they may represent linkage to a susceptibility locus, be involved with causing schizophrenia by disrupting an important locus [Bassett, 1992], or provide a permissive genetic environment for mutations elsewhere in the genome to become expressed as psychotic illness. The genetic complexity of schizophrenia makes it more difficult to draw conclusions in this regard than it is for a single gene disorder. Associated chromosomal anomalies may be worth investigating, however, especially if there are positive linkage results in the region, because fine localization using linkage methods may be problematic in complex disorders. A mechanism that could encompass several chromosomal associations is disruption of transcription factors that interact with genes important in brain development. Retinoic acid signaling could be involved in such a process, because it seems to play an important role in forebrain, limb, face, and cardiac development [LaMantia, 1999], the development and functioning of the dopamine system [Goodman, 1998], and neural crest cell migration that may be involved in pathogenesis of 22qDS.

Recommendations

Results from recent cytogenetic surveys suggest that selected populations of patients with schizophrenia, that is, those with mental retardation or childhood onset of psychosis, should routinely have molecular cytogenetic studies with FISH using a 22q11.2 probe. We recommend adding these chromosomal studies to standard assessment procedures because a significant proportion of patients in these subgroups will have 22q11.2 deletions or other

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chromosomal abnormalities [Kumra et al., 1998; Murphy et al., 1998; Nicolson et al., 1999]. Individual patients with schizophrenia and significant learning disabilities or dysmorphic and or other features (e.g., hypocalcemia) characteristic of 22qDS [Bassett et al., 1999], or compatible with other syndromes, should similarly have appropriate chromosomal studies. In all these cases, consultation with a medical geneticist would be valuable. Detection of chromosomal abnormalities, including 22qDS, has important clinical implications for the patient and their family, including monitoring for associated medical conditions, and providing genetic counseling specific to the condition [Bassett et al., 1999]. Adults with previously identified chromosomal anomalies and "behavioral disturbance" should be promptly assessed by a psychiatrist for early diagnosis and treatment of psychiatric illnesses, since these are usually amenable to treatment [Woodhouse et al., 1992]. This would also assist in determining which psychiatric illnesses may be part of the phenotype of a specific group of anomalies. In summary, identifying associations between chromosomal anomalies and schizophrenia is a clinically relevant endeavor, and there is a reasonable possibility that identifying more of these associations will assist in identifying susceptibility loci for this challenging illness.

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TABLE I

Chromosomal Abnormalities Associated With Schizophrenia and Related Disorders

Site	Details	Diagnoses[a]	Comments	References
1p22	Balanced translocation (1p22;7q22)	COSZ (M-proband), alcoholism (brother), language delay (father), NA (PGF)	Dysmorphic features in proband; survey of 47 COSZ patients	Gordon et al., 1994 Nicolson et al., 1999
1q21	Fragile site	SZ (7 of 19 patients screened)	Not observed in 10 controls	Fananas et al., 1997
1q32.3	See 5q11.2–5q13.3			
1q43	See 11q21–11q22			
2p11-2q13	Two inversions: inv 2(p11q13) and inv 5(p13q13)	Psychopath (M-proband), alcoholism violent (father)		*b*
2	See 11			
2q21	See 18q23			
3p21	Fragile site	SZ (6 sibpairs + 2 others), NA (mother of 1 sib pair)		*b*
4p15.2–4q21.3	Inversion	SZ and LD (M-proband), Schizotypal traits (mother)	Dysmorphic features in proband	Palmour et al., 1994
5p13(–5pter)	Balanced translocation (5p13;6q15)	Paranoid psychosis (n = 1 of 134 males screened)		*b*
5p13–5q13	See 2p11–2q13			
5p14(–5pter)	Translocated segment into 14q32.3; unbalanced translocation (partial trisomy 5p)	SZ (F-proband), severe MR and epilepsy (brother)	Identified through sibling with cri-du-chat syndrome	Malaspina et al., 1992
5q11.2–5q13.3	Translocated segment into 1q32.3; unbalanced translocation (partial trisomy 5q)	SZ (M-proband), SZ (maternal uncle)		*b*
5q22–5q23.3	Interstitial deletion	SZ and mild MR (F-proband)	Dysmorphic features in proband; no family history of MI	Bennett et al., 1997
6q14.2	See 11q25			
6q15	See 5p13			
7p12(–7pter)	Balanced translocation (7p12;8p23)	SZ and antisocial (M-proband), NA (other relatives)		*b*
7q22	See 1p22			
8	Trisomy (mosaic)	Two reports (SZ; immature)		*b*
8p23	See 7p12			
8q24	Fragile site	SZ (18 of 50 male patients screened)	Observed in 3 of 20 controls	Garofalo et al., 1993
9p11–9q13	Inversion	a) SZ and mild MR	Survey of 29 patients with SZ and MR; most common pericentric inversion	Doody et al., 1998
		b) SZ (4 of 120 patients screened)	0.26–0.80% in general population	Nanko et al., 1993
		c) SZ	Previous reports	*b*
9p21	Fragile site	SZ (41 of 50 male patients screened)	Observed in 4 of 20 controls	Garofalo et al., 1993
9p22	See 11q22.3			

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Site	Details	Diagnoses[a]	Comments	References
9q32–9q34.1	Interstitial deletion	SZ and mild MR	Dysmorphic features in proband; family history not recorded	Park et al., 1991
10p12–10q21	Inversion	Paranoid psychosis (n = 1 of 134 male patients screened)		[b]
10q24	Fragile site	SZ (27 of 50 male patients screened)	Observed in 9 of 20 controls	Garofalo et al., 1993
11	Balanced translocation (2;11) with inversion; no details of breakpoints	SZ and MR	Survey of 29 patients with SZ and MR; family history of SZ	Doody et al., 1998
11q21–22 (–11qter)	Balanced translocation (1q43;11q21)	Delinquent (M-proband), relatives with: depression (n = 7), SZ (n = 3), SZ (n = 2), conduct disorder (n = 3), anxiety (n = 2), NA (n = 18)		*b*
11q22.3 (–11qter)	Balanced translocation (9p22; 11q22.3)	Bipolar disorder (n = 5), NA (n = 2)		*b*
11q25 (–11qter)	Balanced translocation (6q14.2;11q25)	SA and mild MR (M-proband), SZ (mother), alcoholism and violence (MGF), suicide (sister), depression (niece), NA (n = 3)		*b*
13q21.2–21.3	See 13q31–13q32			
13q31–13q32	Translocated segment into 13q21.2–21.3; balanced intrachromosomal insertion 13(q31–q32;q21.2–q21.3)	MR, mood swings, and violence (F-proband), MR and psychosis (mother), MR (brother), NA (brother)		*b*
13	13;14 Robertsonian translocation	3 reports (SZ; SZ; depression)		*b*
14q32.3	See 5p14.1			
15pter–15q13.3	See 18q23			
17p12	Fragile site	Paranoid psychosis (4 of 134 males screened)		*b*
18p11.1	a) Unbalanced translocation 18p11.1–18pter deletion and 21p11.1–21pter partial trisomy	a) SZ and mild MR (F-proband)	Dysmorphic features in proband	Smith et al., 1996
	b) Balanced translocation (18p11.1;21p11.1)	b) SZ (brother), PNOS (mother), schizotypal traits (brother)		
18p11.3–18q21.2	Inversion	a) SZ, severe MR, NA in 3 siblings	Search for chromosome 18 anomalies using Scottish and Danish cytogenetic databases cross-linked with psychiatric registers	Mors et al., 1997
		b) Bipolar disorder, NA (sibling and father)		
18p11;18q23	Ring chromosome 18	Manic-depressive psychosis and MR (F-proband)		*b*
18q22.3 (–18qter)	Derivative translocation chromosome (15q13.3;18q22.3); partial trisomy 15q and 18q	Bipolar with psychosis (F-proband), SA (relative)	Breakpoints determined from 5 balanced translocation carriers	Calzolari et al., 1996
18q23 (18qter)	Balanced translocation (2q21;18q23)	SZ and alcoholism (M-proband), SZ (daughter), alcoholism (son), NA (daughter)	Updated data on family reported by Genest et al., 1976	Maziade et al., 1993
19p13	Fragile site	Autism and MR (M-proband), SZ (MZ-twin), SZ (brother), NA (brother)		*b*
21p11.1	See 18p11.1			

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Site	Details	Diagnoses[a]	Comments	References
22q11.2	Microdeletions	See text	See text	See text
Sex chromosomes	Aneuploidies	See text	See text	See text

[a]Psychiatric diagnoses of individuals with chromosomal abnormality. SZ, schizophrenia; COSZ, childhood onset schizophrenia; SA, schizoaffective disorder; LD, learning disability; MR, mental retardation; M, male; F, female; MI, mental illness; NA, not affected; MZ, monozygotic; MGF, maternal grandfather.

[b]Chromosomal abnormalities reported before 1992 for which original references and detailed comments are provided in a comparable table in the review by Bassett [1992].