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Chromosomal Aberrations and Schizophrenia
Autosomes

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Chromosomal aberrations associated with schizophrenic disorders may suggest regions in which to focus a search for genes predisposing to schizophrenia by a linkage strategy. As for other genetic illnesses, chromosomal abnormalities may also provide useful tools for subsequent physical mapping, fine localisation, and isolation of important susceptibility genes. Identification of several chromosomal aberrations may be especially important, given the unknown pathophysiology, the paucity of known brain genes, and the probable genetic heterogeneity of schizophrenia and manic-depression. However, because psychiatric disorders are common and inherited in a complex manner, researchers must use caution when drawing inferences about associations with chromosomal aberrations. Reported abnormalities involving autosomes (chromosomes 1–22) associated with psychotic disorders are reviewed. Their relevance to linkage studies localising genes for schizophrenia was estimated by standardised criteria for specificity, diagnosis, family history, and overall weight of evidence. Four 'possibly relevant' chromosomal regions were identified: 5q, 11q, 18q, and 19p. This paper outlines strategies for future studies to detect new chromosomal aberrations associated with major psychotic disorders that may be relevant to isolating the genes for schizophrenia.

There is strong evidence from family, twin, and adoption studies that a genetic vulnerability underlies schizophrenia (Gottesman & Shields, 1982; Lowing *et al*, 1983; Kendler *et al*, 1985). The principal challenge now is to locate and identify major genes that may predispose to this vulnerability. To this end, genetic linkage studies are underway around the world. However, many difficulties face researchers in this area, both in the initial search and in confirmatory studies (Bassett, 1989). There is a single positive report of linkage to date, linking schizophrenia to DNA markers from chromosome 5q (Sherrington *et al*, 1988). Researchers studying other families (e.g. Kennedy *et al*, 1988; St Clair *et al*, 1989) have not replicated this result. Given the likelihood that several major genes predispose to schizophrenia, a method to help maximise the probability of finding such genes would be valuable.

One approach to investigating specific genetic involvement in psychiatric disorders is to identify associated chromosomal abnormalities. Chromosomal aberrations associated with psychiatric disorders may suggest regions in which to focus the initial search for disease-causing genes by a genetic linkage strategy. As for other illnesses, such as neurofibromatosis, chromosomal abnormalities may also provide useful tools for subsequent physical mapping, fine localisation, and isolation of important susceptibility genes. Identification of several chromosomal aberrations may be especially important given the unknown pathophysiology, the paucity of known brain genes, and the probable genetic heterogeneity of major psychotic illnesses.

Chromosomal abnormalities associated with various genetic disorders have proven valuable for localising and isolating causative genes (Table 1). The fortuitous observation of these rare events has substantially aided in, for example, the physical mapping and subsequent cloning of the gene causing Duchenne muscular dystrophy (DMD) (Ray *et al*, 1985). In addition, associations of specific diseases with chromosomal aberrations have suggested candidate regions for linkage studies. A complex unbalanced translocation involving a partial trisomy of the long arm of chromosome 11, observed in a neonate with cardiac rhabdomyoma (Clark *et al*, 1988), focused the search for a tuberous sclerosis (TS) gene on the 11q23 region, although positive linkage to the ABO locus on chromosome 9 had already been found in some families (Fryer *et al*, 1987). Researchers subsequently reported significant linkage of TS to markers from 11q22-11q23 (Smith *et al*, 1990).

Chromosomal abnormalities have also provided important clues to the genetic cause of behavioural disorders. Many patients with Prader-Willi syndrome (PWS), a hypothalamic disorder leading to behavioural disturbances, with onset in adolescence, have small deletions of the long arm of chromosome 15 (Mattei *et al*, 1984). PWS is more complex than this, however, as the Prader-Willi deletion chromosome is almost always paternally inherited, and similar deletions when maternally inherited cause Angelman

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Table 1
Examples of chromosomal abnormalities aiding gene localisation

Disorder	Clinical observations	Chromosomal location[1]	Uses		References
			Candidate region for linkage studies	Physical mapping	
Tuberous sclerosis	Neonate with unbalanced translocation	11q23	+		Clark *et al*, 1988 Smith *et al*, 1990
Retinoblastoma	Associated deletions	13q14	+	+	Yunis & Ramsay, 1978 Friend *et al*, 1986
Neurofibromatosis (NF1)	Associated balanced translocations	17q11.2		+	Wallace *et al*, 1990
Familial Alzheimer's disease (FAD)	Signs of AD in older Down's syndrome (trisomy 21) patients	21q21	+		Oliver & Holland, 1986 St George-Hyslop *et al*, 1987
Duchenne muscular dystrophy	Rare affected females with translocation	Xp21		+	Ray *et al*, 1985
Fragile X mental retardation	Many affected males with fragile sites	Xq27.3		+	Krawczun *et al*, 1985 Verkerk *et al*, 1991

1. p = short arm of chromosome; q = long arm of chromosome.

syndrome (Knoll *et al*, 1989). This suggests that genetic imprinting may be an important phenomenon in some chromosomal abnormalities. Imprinting may also be important in disorders lacking a clear pattern of inheritance (Hall, 1990).

Unlike simple Mendelian conditions such as DMD and TS, the major psychotic disorders, schizophrenia and manic–depression, are complex genetic conditions. Like hypertension or diabetes mellitus, major psychotic disorders may have several important genetic and non-genetic factors that predispose to the illness, either individually or in an interactive fashion (Risch, 1990). The pathophysiology of schizophrenia and manic–depression is unknown, and researchers have identified relatively few of the up to 100 000 brain-related genes which, in a broad sense, could all be considered candidate genes. These problems make linkage analysis of psychiatric illness challenging, and a complementary strategy for finding major susceptibility genes more important.

There are few reviews of chromosomal abnormalities and psychiatric disorders in the literature. Chromosomal abnormalities may involve either the sex chromosomes (X and Y) or the autosomes (chromosomes 1–22). Propping (1983) tabulated three chromosomal abnormalities associated with possible schizophrenia-like psychoses: XXY, XXX, and 18q- or ring 18. More recently, in the context of their own cytogenetic survey of 46 men with schizophrenia, DeLisi & Lovett (1990) summarised 15 X chromosome studies and four reports of autosomal abnormalities associated with psychoses. Crow (1988) has also examined sex chromosomes and psychotic disorders, an important area with numerous reports dating back to 1962, deserving its own critical review. The focus in the current paper, however, is restricted to autosomal abnormality associations, which have been less discussed than the sex chromosomal anomalies. The present review updates and extends the references catalogued in the Propping (1983) and DeLisi & Lovett (1990) articles, and critically reviews the evidence for reported associations of autosomal abnormalities and psychiatric illness. The relevance of these associations for genetic linkage studies was estimated with standardised criteria for specificity, diagnosis, family history, and overall weight of evidence. The results of this critical review suggest strategies for future studies to detect new chromosomal aberrations associated with major psychotic disorders that may be relevant to isolating a gene for schizophrenia.

Background: cytogenetic techniques

A chromosomal aberration is an abnormality detectable by standard cytogenetic techniques (Gardner & Sutherland, 1989). Cell samples (e.g. blood lymphocytes) are cultured, and then cell division is arrested during metaphase or prophase when chromosomes have condensed and are therefore visible under the light microscope. Prophase samples provide the longest chromosomes and therefore the highest resolution, but are also the most fragile and difficult to handle; thus, metaphase samples are the standard technique in service laboratories. Staining of chromosomes, usually with trypsin-giemsa, provides the light and dark banding pattern (G-banding) that assists in identifying and localising structural

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abnormalities. Photomicrographs of a spread of stained chromosome pairs from a single cell are cut out and arranged in order of size (largest (chromosome 1) to smallest (chromosome 22)) with the sex chromosomes (XX female or XY male) last. This is called the karyotype.

In recent years, improved cytogenetic techniques have resulted in the detection of a much greater number of chromosomal aberrations. In a sample of 85 mentally retarded patients, most with previously reported normal chromosomes, Tengström & Autio (1987) found 15 chromosomal abnormalities by high-resolution analysis. Resolution is usually described by the number of bands visible under the light microscope (1000 × enlargement). A standard metaphase spread reveals 300–550 bands, whereas a pro-metaphase high-resolution spread has 550–800 or even 1200 or more bands. Greater resolution allows finer localisation of abnormalities and identification of smaller deletions and duplications, such as those found in retinoblastoma (Yunis & Ramsay, 1978) and Prader-Willi syndrome (Ledbetter *et al*, 1981). Abnormalities as small as 1–5 million base pairs, which would usually involve many genes, may be visible with high-resolution analyses. The technique remains limited, however, by the light microscope and the difficulties involved in handling fragile long chromosomes. Fluorescent *in situ* hybridisation is a technique now being applied in clinical cytogenetics laboratories for better identification of structural rearrangements (Pinkel *et al*, 1986). Electron microscopic examinations hold some promise for finer resolution of chromosomal abnormalities in the future (Drouin *et al*, 1988). Another advancing research tool is the use of molecular genetic techniques to detect structural mutations as small as a few kilobases in size.

The three major categories of chromosomal aberrations are imbalances, rearrangements, and fragile sites. Imbalances, or aneuploidies, may be more than the normal amount of chromosomal material, e.g. trisomies or duplications, or less than the normal amount, e.g. monosomies or deletions. These can occur in all cells or in a percentage of cells in a 'mosaic'. Rearrangements may be in the form of translocations, involving the breakage and rejoining of chromosomes in different locations. These can be either balanced, i.e. containing the normal total amount of chromosomal material in a rearranged format, or unbalanced. Unbalanced translocations involve duplications or deletions. Other types of chromosomal rearrangements include inversions (breaks at two points on a chromosome and the segment inverted when rejoined) and rings (usually breaks at two distal points on a chromosome, forming a ring when rejoined, with some loss of chromosomal material from either end). Fragile sites are areas of narrowing seen when cells are cultured under special conditions, e.g. in folate or thymidine-deprived medium. Their aetiology and function remain unknown. However, researchers have recently sequenced a gene at the fragile X site that contains an unusual CGG nucleotide repeat sequence (Verkerk *et al*, 1991).

Chromosomal aberrations may arise *de novo*, usually during meiosis in germ cell lines, or may be inherited from a parent who carries an abnormality. Determination of segregation of abnormalities is important in deciding whether an abnormality is truly associated with a particular phenotype, for example, a specific psychiatric disorder.

Method

The literature on chromosomal abnormalities associated with schizophrenia or psychotic disorders was reviewed through multiple sources. References to autosomal abnormalities in Schmid & Nielsen (1981), Propping (1983), and DeLisi & Lovett (1990) served as a starting point. As an update of these studies, a Medline search was done for the years 1966–1990 by using the search strategy: "Schizophrenia" or "Mental disorders", and "Chromosomal abnormalities" or "Chromosomal aberrations". Textbooks cataloguing chromosomal aberrations (Schinzel, 1984; Borgaonkar, 1989; McKusick, 1990) were also examined for references to psychiatric illness. A broad search strategy was employed in order to pick up any signs and symptoms suggesting schizophrenia, psychosis, and schizophrenia-spectrum disorders in adolescents and adults. References for autism or true childhood disorders were omitted. One citation for a man with homosexuality and no psychiatric disorder was also excluded. Each reference was reviewed for psychiatric diagnosis. Since the boundaries of schizophrenic syndromes are unknown, and because many references recorded just "psychosis" or symptoms such as aggressiveness, any symptoms suggestive of major psychiatric disturbance were included. The presence of mental retardation, a common indication for chromosomal studies, was noted.

Information about the chromosomal abnormality and cytogenetic techniques used was recorded. The type of study and, when possible, the indication for karyotyping were also noted. Chromosomal aberrations initially believed by cytogeneticists to be abnormalities, but more recently determined to be normal variants of no clinical significance, were excluded. These were mostly chromosomal variants of heterochromatin (h), e.g. 1qh+ (long variant of chromosome 1 long arm), which behave like normal chromosomes (Gardner & Sutherland, 1989). Reports of "possible" abnormalities (e.g. 2p;12p translocation in Dasgupta *et al* (1973)), or acentric chromosomal fragments which are of uncertain significance, were also excluded.

The segregation pattern of the chromosomal abnormality and pertinent family history of psychiatric illness were recorded. Each reported chromosomal abnormality was

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then assessed for relevance to localising major genes for schizophrenia by standardised criteria arbitrarily developed for each of four areas: diagnosis, family history, specificity, and overall weight of evidence, with a scoring system from 0 to 3 for each. These criteria are outlined in Table 2. Given the maximum score of 12, four categories were arbitrarily created: "probably no or low relevance" (0–3), "possible modest relevance" (4–5), "possible relevance" (6–9), and "probably high relevance" (10–12).

Results

There were 26 reports of psychiatric illness or suggestive symptoms associated with 21 different autosomal abnormalities (Table 3). Most of these were identified since 1976, coinciding with improvements in cytogenetic techniques. However, no high-resolution studies were done. Four cytogenetic surveys of psychiatric patient populations reported nine of the autosomal abnormalities (Nielsen *et al*, 1973; Price *et al*, 1976; Escobar, 1976; Axelsson & Wahlström, 1984). All 17 remaining references were case reports of individuals or families. Few of these recorded the original indication for karyotyping.

The relevancy rating system sorted the reported associations reviewed ($n=26$) into three of the four created relevance categories. Results of the relevancy rating assignments are presented in Table 4. Eighteen (69%) of the reported associations had low relevance scores of 3 or less, and a further three (13%) had modest scores of 4 or 5. Five of the associations achieved relevancy scores of 6 or above: partial trisomy 5q11.2-5q13.3 (Bassett *et al*, 1988), fragile site 19p13 (Chodirker *et al*, 1987), balanced translocation 2q21;18q23 (Genest *et al*, 1976), balanced translocation 6q14.2;11q25 (Holland & Gosden, 1990), and balanced translocation 1q43;11q21 (St Clair *et al*, 1990). Each of these were autosomal abnormalities associated with one or more cases of schizophrenia, although the last two also had significant cosegregation of mood disorders. No report scored higher than 8 out of 12.

Table 2
Criteria used to assess relevance of reported chromosomal abnormality associations with schizophrenia

	Criteria	Score
Psychiatric diagnosis	Standard diagnostic criteria for psychiatric illness named and used (e.g. DSM-III, ICD, RDC) *and* no mental retardation associated	3
	Clinical psychiatric diagnosis given without using criteria or noting its use (e.g. schizophrenia, depression) *and/or* mild mental retardation associated	2
	Symptoms reported suggestive of a psychotic illness or schizophrenia-spectrum disorder *and/or* moderate to severe mental retardation associated with most of the diagnosed psychiatric illness	1
	Non-specific psychiatric symptoms only reported	0
Family history of psychiatric illness (schizophrenia)	Complete family history reported *and* no schizophrenia or related illness segregating without chromosomal abnormality	3
	Negative family history reported but without details *or* only different (i.e. not schizophrenia) psychiatric illness or minor symptoms segregating without chromosomal abnormality	2
	Family history of occasional schizophrenia or related illness not associated with chromosomal abnormality *or* chromosomal analysis not available for relatives with psychiatric illness	1
	Significant family history of schizophrenia or related illness segregating in branches of family without chromosomal abnormality *or* family history of psychiatric illness not reported	0
Specificity of chromosomal abnormality to schizophrenia	All family members with chromosomal abnormality are cosegregating psychiatric illness (schizophrenia and schizophrenia-spectrum disorders)	3
	Occasional (<50%) family members with psychiatric illness and no chromosomal abnormality *or* occasional (<50%) family members with chromosomal abnormality but no psychiatric illness	2
	Many (≥50%) family members with psychiatric illness and no chromosomal abnormality *and/or* with chromosomal abnormality and no psychiatric illness; *or* in family segregating the chromosomal abnormality, the majority of psychiatric diagnoses are neither schizophrenia nor schizophrenia-spectrum disorders	1
	Many family members neither tested nor obligate carriers for chromosomal abnormality *or* no information reported about chromosomal abnormality in most family members	0
Weight of evidence	All or most reports of the same chromosomal abnormality are associated with very similar psychiatric symptoms/illness (in age at risk)	3
	Several (three or more) reports of the same chromosomal abnormality have similar psychiatric illness or a spectrum of psychiatric illnesses (in age at risk) *or* other evidence points to the same chromosomal area as potentially important to schizophrenia (e.g. candidate gene location association study)	2
	One or two reports of proximate or similar chromosomal abnormality associated with a psychiatric illness	1
	No reports of the same chromosomal abnormality note any psychiatric illness or symptoms (in age at risk) *or* the rate of schizophrenia found with the chromosomal abnormality is at a rate less than or equal to the rate of schizophrenia found in the general population *or* the association of chromosomal abnormality with schizophrenia was ascertained in a survey of patients with schizophrenia to be at a rate less than or equal to the rate of the chromosomal abnormality in a general population sample	0

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Table 3
Autosomal aberrations associated with schizophrenia and related disorders

Site	Details	Diagnoses[1]	Comments	References[2]
1q32.3	See 5q11.2–5q13.3			
1q43	See 11q21–11q22			
2p11–2q13	Two inverted segments: inv 2(p11q13) and inv 5(p13q13)	Psychopath (M-proband) Alcoholism; violent (father)	Family history of manic-depression and alcoholism with normal chromosomes. Other family members with just one inversion (of chromosome 2 or 5) and no illness.	Romain *et al*, 1982 (1)
2q21	See 18q23			
3p21	Fragile site	Schizophrenia (6 sib pairs + 2 others) NA (mother of 1 sib pair)	Fragile site common in general population. Most parents neither tested nor diagnosed.	Rudduck & Franzén, 1983 (2)
5p13(-5pter)	Balanced translocation (5p13;6q15)	Paranoid psychosis ($n = 1$)	From survey of 134 male patients in a psychiatric hospital. No physical abnormalities reported. No family history available.	Axelsson & Wahlström, 1984 (3)
5p13–5q13	See 2p11–2q13			
5q11.2–5q13.3	Translocated segment into 1q32.3; unbalanced translocation (partial trisomy 5q) Balanced translocation (1q32.3;5q11.2–13.3)	Schizophrenia (M-proband) Schizophrenia (maternal uncle) NA (mother)	Multiple physical abnormalities with partial trisomy, not with balanced translocation. No other family history of schizophrenia.	Bassett *et al*, 1988 (4)
6q14.2	See 11q25			
6q15	See 5p13			
7p12(-7pter)	Balanced translocation (7p12;8p23)	Schizophrenia, antisocial (M-proband) NA (other family members)	From survey of 611 male patients in maximum security hospitals. No physical abnormalities reported. Family history unknown.	Price *et al*, 1976 (5)
8	Trisomy (mosaic)	(a) Schizophrenia and 'organic brain syndrome' (F-proband)	(a) Multiple physical abnormalities. Strong maternal family history of depression. Paternal cousin with MR. Family members not karyotyped.	(a) Sperber, 1975 (6)
		(b) 'Immature personality'	(b) Multiple physical abnormalities. No family history available. Review of mosaic trisomy 8; most children with MR but no psychiatric diagnoses (Berry *et al*, 1978). Report of 'normal personality' and mild physical abnormalities in an adult (Chandley *et al*, 1980).	(b) Theilgaard *et al*, 1977 (7)
8p23	See 7p12			
9p11–9q11 or 9p11–9q12 or 9p11–9q13	Inverted segments	Paranoid psychosis ($n = 13$)	See comments for 5p13. Frequent inversions in general population (Kaiser, 1984).	Axelsson & Wahlström, 1984 (3)
9p13	Fragile site	Paranoid psychosis ($n = 1$)	See comments for 5p13.	Axelsson & Wahlström, 1984 (3)
9p22	See 11q22.3			

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Table 3 (*cont.*)

Site	Details	Diagnoses[1]	Comments	References[2]
10p12–10q21	Inverted segment	Paranoid psychosis ($n = 1$)	See comments for 5p13. Fairly frequent inversion in general population.	Axelsson & Wahlström, 1984 (3)
11q21–22 (-11qter)	Balanced translocation (1q43;11q21)	Delinquent (M-proband) Depression ($n = 7$); Schizophrenia ($n = 3$); Schizoaffective ($n = 2$); Adolescent conduct disorder ($n = 3$); Anxiety ($n = 2$); NA ($n = 18$)	Extended family. Six members with other (13;14) translocation. Five members with minor disorders and normal karyotypes. No physical abnormalities. Total $n = 77$ karyotyped.	St Clair *et al*, 1990 (8)
11q22.3(-11qter)	Balanced translocation (9p22;11q22.3)	Bipolar disorder ($n = 5$) NA ($n = 2$)	Extended family. Identified through unbalanced translocation with multiple physical abnormalities. Location of D_2 dopamine receptor is 11q22–23 (Grandy *et al*, 1989). 11q23 is very frequent translocation site.	Smith *et al*, 1989 (9)
11q25(-11qter)	Balanced translocation (6q14.2;11q25)	Schizoaffective disorder and mild MR (M-proband) Schizophrenia (mother); Alcohol, violent (Maternal GF); Suicide (sister); Depression (niece); NA (maternal aunt, uncle and niece)	No physical abnormalities. Family history of depression with normal chromosomes (maternal uncle) and MR (maternal GM).	Holland & Gosden, 1990 (10)
13	Balanced translocation (13;14) ('Robertsonian' translocation)	(a) Schizophrenia and borderline MR (F-proband)	(a) From survey of 30 child psychiatry in-patients. Bilateral coloboma of iris. Cousin with MR. Other family members not karyotyped.	(a) Escobar, 1976 (11)
		(b) Schizophrenia; antisocial (M-proband) NA (other family members)	(b) From survey of 611 maximum security hospital patients. No physical abnormality. Family history unknown.	(b) Price *et al*, 1976 (5)
		(c) Depression (M-proband)	(c) From survey of 1208 male psychiatric in-patients. No physical abnormalities. Family history of manic-depression. (t13;14) most common translocation in general population. See also 11q21–q22 entry.	(c) Nielsen *et al*, 1973 (12)
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; violence (F-proband) MR; psychosis (mother); MR (brother); NA (brother)	MR in two family members with normal chromosomes. Family history of violence and low intelligence.	Roberts *et al*, 1986 (13)
17p12	Fragile site	Paranoid psychosis ($n = 4$)	See comments for 5p13. Known heritable fragile site.	Axelsson & Wahlström, 1984 (3)
18p	Deleted segment	MR; catatonic schizophrenia (F-proband)	Multiple physical abnormalities, deafness. Family history unknown. Second most frequent autosomal deletion syndrome.	Ayraud *et al*, 1969 (14)

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Table 3 (*cont.*)

Site	Details	Diagnoses[1]	Comments	References[2]
18p11;18q23	Ring chromosome 18; approximate breakpoints with deleted segments: 18pter–p11 and 18q23-qter	(a) MR; Manic-depressive psychosis (F-proband) (b) MR; Manic-depressive psychosis (mother)	(a) Family history of schizophrenia (father). (b) Other reported ring 18 cases, many with multiple physical anomalies, some with hyperactivity, aggressiveness, "psychosis".	(a) Christensen *et al*, 1970 (15) (b) Krag-Olsen *et al*, 1981 (16)
18q23(18qter)	Balanced translocation (2q21;18q23)	Schizophrenia; alcoholism (M-proband); "Behavioural disturbance" (daughter)	Family history unknown. No physical abnormalities. Wife and three other children normal.	Genest *et al*, 1976 (17)
19p13	Fragile site	MR and autism (M-proband) Schizophrenia (MZ twin); Schizophrenia (brother); NA (brother)	Other reports of fragile site 19p13 with neither MR nor psychiatric diagnosis. Site of C3 complement gene implicated in association studies of schizophrenia (Rudduck *et al*, 1985).	Chodirker *et al*, 1987 (18)
21	Trisomy or partial trisomy (karyotype surmised from diagnosis of Down's syndrome (DS))	Paranoid schizophrenia and mild MR (M-proband)	Report of 32-year-old DS ("mongoloid") case before cytogenetic studies available. Rare cases of paranoid psychoses with trisomy 21 have older age of onset and dementia (Reid *et al*, 1978), probably of Alzheimer type.	Neville, 1959 (19)
21	Trisomy	MR and bipolar disorder, manic with mood-congruent psychotic features (M-proband)	Report of 23-year-old man with DS. No family history of psychiatric illness. Prevalence of manic-depression in DS possibly less than in general population (Turner, 1989).	Cook & Leventhal, 1987 (20)
21pcen–21pter	Deleted segment	Manic-depressive (F-proband) Manic-depressive (mother)	Family history unknown. Hirsutism associated. No cytogenetic studies of other family members. Short arm of chromosome 21 may appear absent with low-resolution techniques (Gardner & Sutherland, 1989).	El-Badramany *et al*, 1989 (21)

1. Psychiatric diagnosis of individuals with autosomal abnormality.
2. Numbers in parentheses following references refer to reference column in Table 4.
M-proband: male proband; F-proband: female proband; NA: no psychiatric abnormality; MR: mental retardation; GF: grandfather; GM: Grandmother.

Discussion

This review suggests that four broad chromosomal regions meet sufficient, arbitrarily defined relevance criteria to appear promising for localising susceptibility genes for schizophrenia and related disorders: proximal 5q, distal 11q, distal 18q, and distal 19p. The chromosomal areas suggested in this review are consistent with those indicated by other authors (Byerley *et al*, 1989; DeLisi & Lovett, 1990; Diehl & Kendler, 1989) as of potential interest for schizophrenia. Published results of linkage studies of schizophrenia have focused on chromosome 5. Other candidate regions invite exploration, and new candidate chromosomal regions need to be found to complement linkage analysis efforts.

Although every attempt was made to obtain pertinent citations, the list of reports from which these conclusions are drawn may be incomplete,

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Table 4
Relevancy ratings of reported chromosomal abnormalities associated with psychiatric disturbances

Reference[1]	Chromosomal site	Total score	Diagnosis	Family history	Specificity	Weight of evidence
1	2p11-2q13	2	0	1	1	0
2	3p21	2	2	0	0	0
3	5p13	1	1	0	0	0
4	5q11.2-5q13.3	8	3	2	3	0
5	7p12	2	2	0	0	0
6	8	3	2	0	0	1
7	8	1	0	0	0	1
3	9p11-9q11/12/13	1	1	0	0	0
3	9p13	1	1	0	0	0
3	10p12-10q21	1	1	0	0	0
8	11q21/22	7	3	1	2	1
9	11q22.3	5	2	0	2	1
10	11q25	7	3	1	2	1
11	13	4	2	1	0	1
5	13	3	2	0	0	1
12	13	4	2	1	1	0
13	13q31-13q32	2	0	1	1	0
3	17p21	1	1	0	0	0
14	18p	1	1	0	0	0
15	18p11;18q23	3	1	0	1	1
16	18p11;18q23	2	1	0	0	1
17	18q23	6	2	0	3	1
18	19p13	7	2	1	2	2
19	21	2	2	0	0	0
20	21	3	1	2	0	0
21	21pcen-21pter	3	3	0	0	0

1. See Table 3.

especially for the non-English literature. The relevance criteria used offer a tentative approach to reported associations of chromosomal anomalies and schizophrenia. There may be many imperfections in these criteria, and interested readers may wish to draw their own conclusions from the reports tabulated. For example, while the distal 18q area achieved a moderate relevance score, one may alternatively consider the chromosome 2q region of the balanced translocation (Genest *et al*, 1976) as potentially important.

Strategies for future studies

This review is meant as a starting point for critically considering the potential importance of chromosomal abnormalities to schizophrenia and other psychiatric illnesses. However, because psychiatric disorders are common and complex genetic conditions, researchers must use extra caution when drawing inferences about associations with chromosomal aberrations. Probably the most striking finding of the review is the overall paucity of reported abnormalities associated with psychiatric illness. This may seem surprising, considering how common psychiatric disorders are in the general population. However, there are several possible explanations for the relatively few reports.

First, there are difficulties with ascertainment. Cytogenetic studies, if not pregnancy related (e.g. miscarriages or infertility), are performed for a few main indications, usually mental retardation and/or physical dysmorphisms. Because most congenital malformation syndromes are noted at or soon after birth and most mental handicap is recognised in early life, far more karyotyping is done in affected children than in adults. Most case reports of chromosomal abnormalities are therefore of infants and children. Unless these children are followed into adulthood, most geneticists and other clinicians would not be aware of adult onset psychiatric conditions. In addition, mental retardation may make diagnosis of comorbid psychiatric illness difficult. A further possibility is that psychiatrists have focused more on psychodynamics than genetics, while medical geneticists, most of whom are paediatricians, have focused on childhood disorder and well-defined adult conditions. Fortuitous discoveries of associated chromosomal abnormalities may be few because geneticists are rarely called in as consultants for psychiatric patients. With vastly improved reliability of psychiatric diagnoses and a resurgent interest in

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psychiatric genetics, perhaps there will be more productive cross-fertilisation between psychiatrists and geneticists in the future.

A second possible explanation for the few reported associations is pessimism arising from the low yields of larger-scale studies. Cytogenetic surveys of psychiatric populations have generally found little in the way of autosomal abnormalities, although there are few reported studies since cytogenetic techniques have improved in the last 10 to 15 years. None of the four cytogenetic surveys of psychiatric patients in the current review yielded a moderately relevant chromosomal area. Most were handicapped by inadequate diagnostic practices and little or no assessment (psychiatric or cytogenetic) of the proband's family. The most recent cytogenetic survey study (DeLisi & Lovett, 1990) reported no autosomal aberrations in 46 men with schizophrenia.

The probability of detecting a visible chromosomal aberration in patients with schizophrenia may be enhanced by selecting those who also have congenital physical abnormalities or dysmorphic features. A partial trisomy of chromosome 5 associated with schizophrenia was found because the two affected patients had several physical abnormalities (McGillivray *et al*, 1990), prompting a medical genetics consultation and subsequent karyotyping (Bassett *et al*, 1988). While many individuals in the general population have one or two minor anomalies, e.g. asymmetric length of toes, those with three or more frequently have accompanying major malformations, e.g. renal agenesis (Jones, 1988). A study of neonates revealed that 0.5% had three or more minor anomalies, and that 90% of these had one or more major defects as well (Marden *et al*, 1964). Recent studies have reported an increased prevalence of certain minor physical abnormalities in primarily male schizophrenic in-patients (Guy *et al*, 1983; Green *et al*, 1989), although no chromosomal analyses were performed. This indicates that patients with several minor dysmorphisms may be relatively prevalent in the schizophrenic population. One must, however, exercise caution when examining adults for minor physical abnormalities since many of these may be acquired rather than congenital, e.g. furrowed tongue secondary to medication-induced xerostomia. Other ways to increase the probability of finding cytogenetic abnormalities include selecting patients with mental retardation or lowered IQ (Schinzel, 1984); however, diagnosis of schizophrenia may be more difficult in these patients (Turner, 1989).

A third possible reason for the low number of reported associations is that schizophrenia may be more like neurofibromatosis and other adult onset conditions in that any causal chromosomal abnormalities are truly rare. One suspects that if a common association were present in the general population, researchers would have identified the chromosomal abnormality by now. However, if the chromosomal abnormality is subtle, only recently available cytogenetic techniques may detect it. In the 1970s chromosomal staining had poor resolution and relied on grouping chromosomes in twos or threes by size; for example, chromosomes 13, 14, and 15 are the 'D' group. Since about 1980, resolution of banding patterns has improved, and culture techniques revealing fragile sites have become more common, resulting in detection of more abnormalities, even in the same population previously examined by less sophisticated techniques (Tengström & Autio, 1987). However, high-resolution banding and fragile-site analyses are expensive. Only if a higher yield of abnormalities could be expected should these techniques be applied to psychiatric disorders. Such a yield is possible, given an improved understanding of how chromosomal abnormalities may be associated with psychiatric illness.

Mechanisms of association

There are two major types of true (non-chance) associations between a chromosomal aberration and schizophrenia: linkage and causal. Like any other genetic marker, a chromosomal abnormality 'linked' to schizophrenia is one that is so close to a schizophrenia susceptibility gene that the two cosegregate in a family. Possible examples include fragile sites and translocation or inversion breakpoints. A causal association implies that the chromosomal abnormality itself somehow involves a faulty gene or genetic mechanism that directly or indirectly leads to a schizophrenic illness.

Determining the approximate probabilities of a chance association and these two categories of 'true' association is possible, given the availability of suitable families. Ideally, observations of a chromosomal abnormality and schizophrenia coexisting in patients and consistently cosegregating in families would greatly increase the likelihood of a true association. However, even with true associations such invariable correlations may not exist. With a linkage type of association, several mechanisms may lead to inconsistencies in the associations. Crossover events between the chromosomal abnormality and disease gene may, in a family where the two are segregating, lead to normal individuals carrying the abnormality or to patients exhibiting schizophrenia without the abnormality. As for any marker, the likelihood of these events is proportional to the distance between the aberration and disease gene; the closer together,

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the less likely a crossover will occur between them. Also, because the chromosomal abnormality and disease gene are merely linked, or proximate, the chromosomal abnormality could occur in other individuals or families in the population with no associated schizophrenic illness. A linkage association would be observed in families only where schizophrenia and the chromosomal abnormality are both segregating, emphasising the importance of both a careful family history of psychiatric illness and karyotyping other family members.

The fragile site at 19p13 is a possible example of a chromosomal abnormality acting as a linked marker to a susceptibility gene. In one family segregating schizophrenia (Chodirker *et al*, 1987), the fragile site may be linked to a schizophrenia susceptibility gene. In unrelated families, there is no schizophrenia segregating, and therefore no psychiatric illness is reported associated with the same fragile site (Tommerup *et al*, 1985). Interestingly, in the family reported by Chodirker *et al* (1987), there appears to have been a recombination, or crossover, event in one of the sons, who is asymptomatic and yet carries the fragile site. Reduced penetrance of a schizophrenia susceptibility gene or chance association are other possible explanations.

In contrast to linkage, a causally associated chromosomal aberration should result in schizophrenia in any individual who carries the abnormality, except in instances of reduced penetrance or variable expressivity. In families with the chromosomal abnormality, and where a true causal association exists, one should not observe schizophrenia without the cytogenetic abnormality, unless the schizophrenic illness is a (non-genetic) phenocopy or is caused by another gene. The finding of a partial trisomy of chromosome 5 and schizophrenia in two family members (Bassett *et al*, 1988) may be an example of a causally associated chromosomal aberration. This possibility would be strengthened by finding other individuals with a similar chromosomal abnormality who also had schizophrenia or a related disorder.

In both linkage and causal types of true association, there is the possibility that a schizophrenia-susceptibility gene may not be expressed as schizophrenia (reduced penetrance) or may cause a spectrum of psychiatric morbidity (variable expression). Any family where schizophrenia and a chromosomal aberration are truly cosegregating could therefore have individuals with the chromosomal abnormality but no associated schizophrenia. This is comparable to the situation with trisomy of chromosome 21 and the congenital heart defects of Down's syndrome (DS). A congenital heart defect may or may not be present in DS, and, if present, may manifest itself in a variety of forms (Jones, 1988). The genetic mechanisms underlying reduced penetrance and variable expressivity are as yet unknown.

Alternatively, a chromosomal abnormality may be acting as a non-specific potentiator of an underlying and separate susceptibility gene for schizophrenia. In this case, one may not expect the chromosomal abnormality to give any clue to the location of the susceptibility gene. However, the effect of the chromosomal abnormality may still be important in an interactive (epistatic) genetic mechanism. Risch (1990) has recently suggested that an epistatic mechanism may be likely for schizophrenia. Both the chromosomal abnormality site and the separate vulnerability gene could then be of interest for linkage studies.

Uses for associated chromosomal abnormalities

A strategy employing the candidate regions provided by chromosomal aberrations associated with psychiatric disorders may be a more efficient way to localise susceptibility genes for schizophrenia in a linkage study than undertaking a random search of the entire genome. The existence of a chromosomal abnormality associated with the disorder and an independent positive linkage finding to the same chromosomal region may strengthen the power of any finding. An associated chromosomal abnormality may also provide a means for developing new closely linked markers and for physically delineating the genetic area involved through the use of somatic cell hybrid cell lines. The individual with a chromosomal abnormality of interest can provide lymphocytes from which somatic cell hybrid cultures can be made. These may have broader molecular biological applications. For example, somatic cell hybrids made from a chromosome 5 balanced translocation cell line (Gilliam *et al*, 1989) were used to develop new markers that, while possibly useful for schizophrenia, have helped localise a spinal muscular atrophy gene in recent linkage studies (Brzustowicz *et al*, 1990).

Conclusion

This review identifies potential candidate regions for linkage analysis of schizophrenia on chromosomes 5q, 11q, 18q, and 19p, and suggests that more chromosomal investigations into schizophrenia and other major psychotic disorders are needed. Improved methods should maximise the likelihood of identifying significant chromosomal abnormalities, as in the following procedures or methods: (a) standardised psychiatric diagnoses, (b) reporting segregation

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patterns of both psychiatric illness and chromosomal abnormality, (c) cytogenetic surveys of dysmorphic or mentally handicapped psychiatric patients, (d) judicious use of high-resolution cytogenetic techniques, and (e) increased consultation between psychiatrists and geneticists. Identification of associated chromosomal aberrations may well be essential to the successful localisation and subsequent isolation of major genes for the complex psychiatric syndrome of schizophrenia.

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