

Evidence for a Sex Chromosome Locus for Schizophrenia

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Abstract

The sex chromosomes are strong candidates for a genetic locus for schizophrenia and the affective psychoses. Gender differences in the clinical expression of illness and familial risks, concordance for gender and illness in relatives, and an association of X chromosome anomalies with psychosis suggest an X chromosome locus. The presence of male-to-male transmission in some families, in the face of a lack of strong evidence for heterogeneity, specifically focuses the search within the pseudoautosomal region of the X and Y chromosomes where sequence homology and recombination takes place.

Segregation analyses performed on data from major large family studies have not defined a specific pattern for the inheritance of schizophrenia, or even distinguished a single major gene from polygene inheritance (reviewed in Kendler 1988). Despite the failure to demonstrate clear Mendelian transmission, the presence of clusters of ill individuals within families has stimulated further searches for a single major gene by linkage and chromosomal mapping techniques.

Recent attempts to locate a gene for psychosis reveal discrepant findings. A report of linkage of manic-depressive illness to a locus on the short arm of chromosome 11 (Egeland et al. 1987) was not confirmed in at least two other studies (Detera-Wadleigh et al. 1987; Hodkinson et al. 1987). A claim of linkage of schizophrenia to a locus on the long arm of chromosome 5 (Sherrington et al. 1988) is not supported in a single large pedigree that includes members with this disease (Kennedy et al. 1988) and in other studies of smaller families

(Gershon et al. 1988; Kaufmann et al. 1989; St. Clair et al. 1989) and two independent reports of X-chromosome linkage in affective disorder (Baron et al. 1987; Mendlewicz et al. 1987) have also not been substantiated. Even before the advent of molecular studies, affective disorders were observed to be sometimes sex-linked and sometimes autosomal (reviewed in Goldin et al. 1983).

However, the conclusion that there is heterogeneity (Lander 1988) may be premature. Even the Kraepelinian binary concept—that manic-depressive insanity and schizophrenia (dementia praecox) are distinct entities—which has dominated psychiatric classification for 80 years may be challenged. Kraepelin himself (1920/1974) developed doubts about the validity of such a separation; such doubts are reinforced by studies of phenomenology (Kendell and Gourlay 1970) and the distribution of different types of psychotic illness within families (Ødegård 1963; Angst et al. 1983; Gershon et al. 1988). The alternative concept (Crow 1986) is that psychotic illness is distributed along a continuum that extends from unipolar depression through bipolar (manic-depressive) and schizoaffective psychosis to schizophrenia with increasing severities of defect state. Such a concept implies a single genetic locus at which significant variation occurs. How might apparent sex linkage (as sometimes reported in affective illness) and autosomal transmission (as gener-

For definitions of technical terms, see glossary on p. 366.

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ally seen in affective illness and schizophrenia) be compatible with inheritance at a single locus? One possibility is that the locus is within the pseudoautosomal region of the sex chromosomes (see below). Such a locus might be relevant to a number of influences of gender on psychosis: (1) Sex differences in clinical characteristics of the illness; (2) concordance for gender and illness in relatives; and (3) an association of X-chromosome anomalies with schizophrenic psychosis. In addition, there are other reasons for interest in the sex chromosomes in relation to psychosis: (1) the apparent linkage to Xq in some families with affective psychoses, and (2) the mapping of a few genes to the X chromosome that may be candidates for a "psychosis gene."

Gender Differences in the Clinical Presentation of Schizophrenia

Several studies report gender differences in the age of onset, clinical spectrum of symptoms, and course of illness, with males having a significantly earlier onset and more severe course than females (reviewed in Lewine 1988; DeLisi et al. 1989).

Some studies suggest that symptoms are differentially distributed, with females having a tendency toward more affective illness and paranoia, and males more frequently being characterized as having an "amotivational" syndrome (Seeman 1982; Lewine 1985; Goldstein 1988). The peak age of onset of schizophrenia is significantly later for females, even when current diagnostic criteria are employed (Lewine et al. 1981; Loranger 1984; Seeman 1985; Sartorius et al. 1986). Lewine (1988)

recently summarized six major epidemiological studies defining age of onset. For males the peak age of onset is 26 years, while in females it is approximately 30 (the mean for men ranging from 21.4 to 29.5 years and for women from 26.0 to 36.4 years across all studies). When patients are subgrouped by age, the incidence ratio for males versus females at age 15–25 is 2:1, at age 25–35 it is approximately equal, while at age 40 it is at least 1:2 (Forrest and Hay 1971; Loranger 1984). This finding is consistent whether one examines age at first treatment, age at first hospitalization, or age when the family first noted psychotic symptoms, thus suggesting that sex differences cannot be explained by better toleration of families for illness in females and less pressure to seek treatment or hospitalization (Lewine 1980; Lewine et al. 1981; Angermeyer and Kuhn 1988).

Outcome studies also indicate that females have a significantly less severe course to their illness than males (Sartorius et al. 1978; Salokangas 1983; Watt et al. 1983; Seeman 1986). Whether this is a consequence of later age of onset, an effect of misdiagnosis of women, or better response to neuroleptic medication is unclear.

While gender differences in the expression of illness may be the consequence of hormonal fluctuation or a variety of nongenetic or nonsex-linked genetic mechanisms and are known to be present in some autosomally inherited diseases, they also could arise from inheritance on the sex chromosomes. A defect on the X chromosome, when present in females (having two X chromosomes), may be expressed as a milder form of illness, or alter-

natively, when present in males, may be modified by a factor on the Y chromosome that contributes to earlier onset and increased severity.

Gender Differences in Familial Patterns of Illness

Some gender-related differences are also present in analyses of family data. At least four groups (Reed et al. 1973; Macciardi et al. 1987; Shimizu et al. 1987; M.T. Tsuang et al., unpublished data from the Iowa-500) have shown that the risk for psychotic illness among relatives of schizophrenic females is significantly greater than for relatives of males. Rosenthal (1962), in reviewing early studies, found that pairs of first-degree relatives with psychosis were more apt to be of the same sex than of opposite sex, with an overall preponderance of female/female pairs; and in parent-child pairs, the mother was more likely to be affected than the father.

Studies of siblings with schizophrenia show higher concordance than discordance for gender (Schulz 1932; Zehnder 1941; Penrose 1945; Tsuang 1967; DeLisi et al. 1987). Similarly, twin studies show higher concordance rates in same-sex than opposite-sex pairs, and female twins have higher concordance rates than males (Rosanoff et al. 1934–35; Kallmann 1946; Slater 1953; Kringlen 1968).

Cytogenetic Evidence

A summary of studies of sex chromosome aneuploidies (table 1) suggests that there is a modest excess of XXY males and (table 2) XXX females among psychiatric hospital patients, although these aberrations account for no more than a small proportion of cases of psychosis. There are case reports of schizophrenic-like illnesses in

Table 1. XXY (Klinefelter's syndrome) in psychiatric hospital patients¹

| Study | Cases of XXY | Male population studied | |
|-----------------------------|--------------|-------------------------|-------------------------|
| | | Sample# | Diagnosis |
| Cowie et al. (1960) | 0 | 22 | Schizophrenia |
| Tedeschi & Freeman (1962) | 2 | 248 | Schizophrenia |
| Raphael & Shaw (1963) | 1 | 105 | Schizophrenia |
| Judd & Brandkamp (1967) | 0 | 22 | Schizophrenia |
| Anders et al. (1968) | 6 | 529 | Chronic psychosis |
| MacLean et al. (1968) | 11 | 2895 | Schizophrenia |
| Sperber et al. (1972) | 4 | 350 | Childhood schizophrenia |
| Dasgupta et al. (1973) | 2 | 500 | Schizophrenia |
| Trixler et al. (1976) | 0 | 39 | Schizophrenia |
| Axelsson & Wahlstrom (1984) | 2 | 134 | Paranoid psychosis |
| Nanko (1985) | 14 | 3226 | Schizophrenia |
| DeLisi et al. (1988) | 0 | 46 | Schizophrenia |
| Totals | 42 | 8116 | (0.52%) |

Note.—Cases of XY/XXY mosaicism (frequency in newborns = 0.02%) and schizophrenia have also been reported (e.g., Judd and Brandkamp 1967: 1 case in 40 examined; Axelsson and Wahlstrom 1984: 1 case in 134; Nanko 1985: 1 case in 3,326; and MacLean et al. 1968: 3 cases in 2,895). Akesson (1983) compared a group of 36 males admitted to mental hospitals with supernumerary X chromosomes (XXY, XY/XXY, XXXY) with other patients and found an excess of schizophreniform psychoses among the former.

¹XXY = 0.09–0.15% live male births (Hamerton et al. 1975; Ratcliffe et al. 1986).

Table 2. XXX in female psychiatric hospital patients¹

| Study | Cases of XXX | Female population studied | |
|------------------------------|--------------|---------------------------|-------------------------------------|
| | | Sample# | Diagnosis |
| Cowie et al. (1960) | 0 | 20 | Schizophrenia |
| Raphael & Shaw (1963) | 1 | 105 | Schizophrenia |
| Asaka et al. (1967) | 2 | 424 | Schizophrenia |
| Judd & Brandkamp (1967) | 0 | 18 | Schizophrenia |
| Anders et al. (1968) | 1 | 445 | Chronic psychosis |
| MacLean et al. (1968) | 7 | 2017 | Schizophrenia |
| Filippov (1970) ² | 9 | 2431 | Schizophrenia |
| Kaplan (1970) | 4 | 1061 | Schizophrenia |
| Tsuang (1974) | 2 | 614 | Psychiatric inpatients. |
| | | | Probable schizophrenia in XXX cases |
| Nanko (1985) | 6 | 2343 | Schizophrenia |
| Totals | 32 | 9478 | (0.34%) |

Note.—In addition, Money and Hirsch (1963) found that 2 of 5 mentally defective patients with XXX syndrome also suffered from schizophrenia. A number of further cases of XXX syndrome and schizophrenia are recorded (noted in Asaka et al. 1967). In 20 cases of females with supernumerary X chromosomes identified in a mental hospital, Olanders (1974) found an excess with delusions and paranoid reactions by comparison with mental hospital controls. In his series Kaplan (1970) also reports 8 cases of XX/XO mosaicism (frequency in newborn = 0.0006%). Nanko (1985) reports 1 XX/XO case and 2 other mosaicisms (XX/XXX and X/XXX).

¹XXX = 0.07–0.11% in live female births (Hamerton et al. 1975; Ratcliffe et al. 1986).

²As cited by Vartanian and Gindilis 1972.

patients with known Klinefelter (XXY), triple X syndromes (reviewed in Money and Hirsch 1963; Polani 1969; Forssman 1970; Sorensen and Nielsen 1977b), and XYY (Dorus et al. 1977; Sorensen and Nielsen 1977a), although no study has yet reported the prevalence of psychosis in these patients. Why should an extra dose of genes on the X chromosome lead to psychosis, particularly if the extra X is inactivated? One answer is that the location of the gene is within the pseudoautosomal region of the X chromosome, where inactivation does not take place.

The Pseudoautosomal Region of the Sex Chromosomes

The hypothesis that there is a locus for psychosis within the pseudoautosomal region on the short arm of the sex chromosomes, the segment within which there is sequence homology between X and Y chromosomes and recombination in male meiosis (Burgoyne 1982), can explain how X-linkage is compatible with male-to-male transmission in the absence of heterogeneity (Crow 1987, 1988; Crow et al., in press *a*, in press *b*). Transmission of genes in this region may appear X-linked in some families but autosomal, with male-to-male transmission, in others. The defining characteristic of pseudoautosomal transmission is a tendency for affected individuals within a family to be more often than would be expected of the same sex: This arises because such a gene is transmitted from an affected father either on his Y chromosome to sons or on his X chromosome to daughters. Such a tendency has been noted in schizophrenia as mentioned above; it is also present in

affective illness (Crow 1988). If such concordance were pseudoautosomal in origin, an association with paternal rather than maternal inheritance would be predicted. We recently found this to be the case for schizophrenia in a study of 120 pairs of affected siblings (Crow et al., in press *a*, in press *b*).

Siblings concordant for schizophrenia were collected from two sources: (1) a series ($n = 79$ sibships from 78 families) collected across the United States with the help of the National Alliance for the Mentally Ill and under the auspices of the Clinical Neurogenetics Branch of the National Institute of Mental Health (Dr. E.S. Gershon, Chief) and at the State University of New York at Stony Brook, and (2) a population-based series ($n = 41$ families) collected under the auspices of the U.K. Medical Research Council at Northwick Park Hospital in northwest London. All identified sets of affected siblings met the criteria for a diagnosis of chronic schizophrenia or schizoaffective disorder by Research Diagnostic criteria (RDC; Spitzer et al. 1978) (series 1) or fulfilled the Saint Louis criteria for schizophrenia (Feighner et al. 1972), or on Present State Examination (Wing et al. 1974) were placed in one of the CATEGO categories of schizophrenia (series 2). In each series, other family members who suffered from major psychiatric illness were identified by interviews with multiple informants. Families were classified according to whether there was a history of illness on the maternal or paternal sides according to three separate systems of classification (Crow et al., in press *b*) that take into account different major diagnoses in relatives, as well as the category of affected relative. In a number of sibships, more than two

individuals were affected; thus, analysis by sex was carried out both sibshipwise and pairwise.

There is an excess of same-sex over opposite-sex pairs in the paternally derived sibships (16:5) that is significantly greater in paternally than maternally derived pairs by sibshipwise analysis ($p = 0.01$, Fisher's exact test) and pairwise analysis ($p = 0.009$) modified to take into account pairs originating from the same family (weighted pairs correction of Suarez and van Eerdewegh 1984). (See tables 3*a* and 3*b*.) This pattern was present when parental inheritance was defined as illness in the categories schizophrenic, psychosis unspecified, and affective disorder in any relative, and with two other methods of classifying parental origin of illness, taking into account the closeness of the relation and category of illness. These data are compatible with transmission of a gene within the pseudoautosomal region.

Other Candidate X Chromosome Locations

Monoamine oxidase (MAO) at one time was thought to be an enzyme marker for schizophrenia on the basis of reports of decreased platelet MAO in numerous patient samples and both members of pairs of illness-discordant monozygotic twins (reviewed in DeLisi et al. 1982). Although a neuroleptic effect on low MAO activity in platelets has hindered the pursuit of decreased MAO as a genetic vulnerability marker, the cloning and mapping of this gene to the proximal portion of Xp (Bach et al. 1988; Ozelius et al. 1988) makes the direct determination of linkage to this gene now possible.

The gene for Alport syndrome

Table 3a. Sibshipwise analysis of concordance by sex in maternal vs. paternal inheritance families¹

| Sibships (n = 120) | Parental origin | | | |
|-----------------------|-----------------|----------|------|---------|
| | Paternal | Maternal | Both | Neither |
| All male | 12 | 9 | 11 | 12 |
| All female | 3 | 3 | 5 | 8 |
| Mixed sex | 5 | 20 | 12 | 20 |

¹p = 0.02, Fisher's exact test, for same-sex vs. opposite-sex in paternal vs. maternal origin families

Table 3b. Pairwise analysis of concordance by sex using a weighted pairs correction in families where there is either unilateral maternal or paternal inheritance¹

| Pairs | Parental origin | |
|----------------------|-----------------|----------|
| | Paternal | Maternal |
| Same sex | 18.66 | 17 |
| Mixed sex | 5.33 | 22 |
| Same/mixed sex ratio | 3.50 | 0.77 |

¹p = 0.009, Fisher's exact test

(hereditary nephritis), also recently mapped to the proximal long arm of the X chromosome (Atkin et al. 1988), has been of some interest. A family has been identified and is presently being evaluated with coexisting schizophrenia, schizophrenia spectrum disorder, and Alport syndrome (Pomeroy et al. 1989), and may provide clues for another potential region for further investigation.

A structural defect of the X chromosome that has gained recent attention is the fragile site mapped to X_{q27} (see figure 1). Its presence is now known to be associated with approximately 30–50 percent of all X-linked mental retardation in males (Turner et al. 1978) and 4–5 percent of all mental retardation in males (Rogers and Simensen 1987; Webb et al. 1987). This syndrome, first described by Martin and Bell (1943), is characterized phenotypically by mild dysmorphic facial

features (long narrow facies, large ears) and other physical anomalies, including macro-orchidism, and joint hyperextensibility. Fragile X males and females have also been reported with autistic and psychotic symptoms, and an excess of fragile X has been reported among children diagnosed with autism (Brown et al. 1986). Diagnostic studies of family members of fragile-X probands (Reiss et al. 1986, 1988) suggest that the female carriers of the fragile X site have an increased prevalence of schizoaffective disorder and schizophrenia spectrum personality disorders.

While a previous study failed to find evidence of the fragile X defect in random males with schizophrenia (DeLisi et al. 1988), this does not eliminate the possibility that a gene near the fragile site could be influenced by the structural alteration such that it would function abnormally and lead to

psychotic illness. This would imply that a gene for psychosis could be linked to this region independent of the presence or absence of fragility.

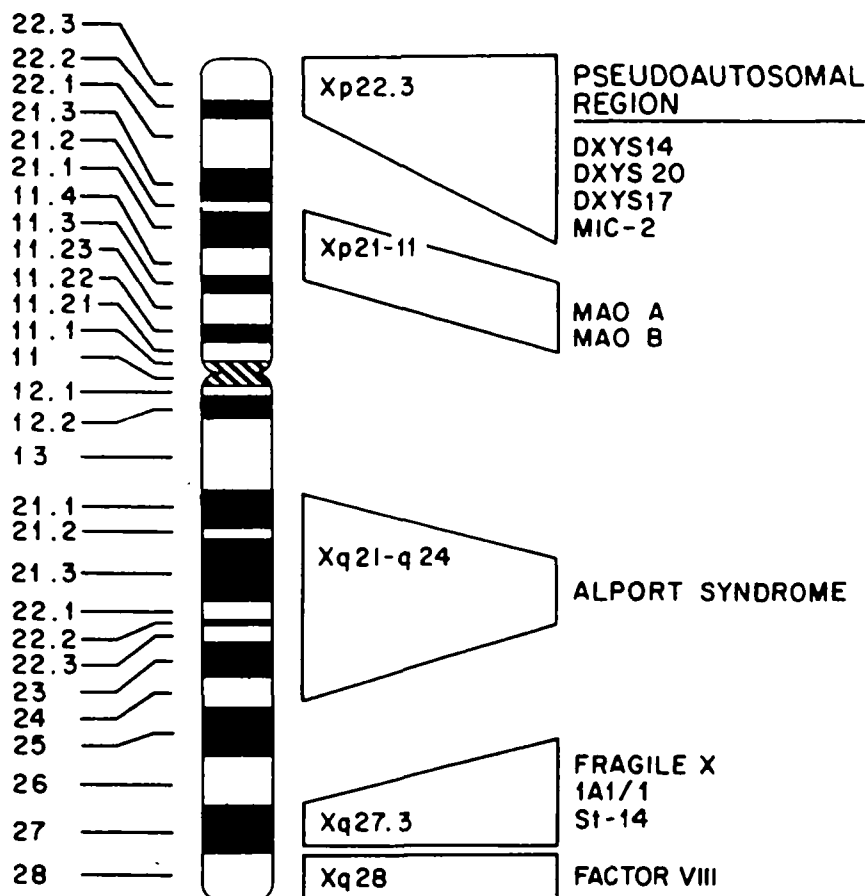
Linkage of affective disorder to this region has been reported by two independent groups using factor IX as a marker (Mendlewicz et al. 1987) and deutan color blindness as another marker (Baron et al. 1987). Others, however, have not found linkage to this region in different sets of families with manic-depressive disorder (Gershon et al. 1979; Leckman et al. 1979; Kidd et al. 1984).

In a more recent study, we examined eight families with at least two members having an RDC diagnosis of chronic schizophrenia or schizoaffective disorder, and who did not appear to have father-to-son illness transmission (L.E. DeLisi, T.J. Crow, P. Davies, and J. Ott, unpublished data). DNA samples were prepared and screened for four markers distal to, but linked to the fragile site (St-14, Factor VIII, 1A1, and Dx13; see figure 1). Of the eight families, five were informative (mother heterozygous) for at least one of the probes. Multipoint analysis assuming a dominant gene and 30 percent penetrance ruled out linkage with the lowest lod score of -7.77 at 0 percent recombination. Thus, while an occasional family may have a schizophrenic illness linked to a gene on the distal long arm of the X chromosome, we have thus far failed to uncover any.

Conclusion

Recent claims and counterclaims for linkage of psychosis to loci on chromosomes 5, 11, and the X chromosome, as well as the observation that transmission of affective disorders is sometimes sex-linked and sometimes autosomal, have encour-

Figure 1. The X chromosome



aged the view that there is substantial heterogeneity and multiple genetic loci for the psychoses. The alternative view is that affective disorders and schizophrenia are related on a continuum of genetic variation occurring at a single locus.

In previous studies, a gene for psychosis on the sex chromosomes has been sought only in the affective disorders; the search in this case has focused on the region of the distal long arm of the X chromosome. A number of findings suggest that a broader diagnostic group ought to be surveyed and other areas of the sex chromosomes examined as well: (1) Psychoses are

seen more frequently than would be expected among individuals with extra X chromosomes (i.e., XXY males and XXX females); (2) gender influences age of onset and outcome in schizophrenia; (3) relatives of female probands with psychosis are at greater risk of illness than relatives of males; and (4) siblings with psychosis are more likely to be of the same sex than would be expected by chance.

Each of these findings suggests a greater influence of the sex chromosomes for both schizophrenia and affective disorder than has previously been thought. Points 1 and 4, in particular, can be explained on

the basis that the locus for psychosis is pseudoautosomal (i.e., located within that region of the short arms of both X and Y chromosomes where exchange of genetic material takes place in male meiosis). This region is not subject to X inactivation in the female. By contrast with other parts of the X chromosome, genes located here may be expressed in increased dosage in individuals with extra X chromosomes. A pseudoautosomal gene inherited from a father will be passed above chance expectation either on the X chromosome to daughters or on the Y chromosome to sons; thus, pairs of siblings will be more often of the same sex than of mixed sex. The pseudoautosomal hypothesis predicts that same-sex concordance will be seen in paternally rather than maternally derived cases; this has been tested in a series of 120 families including two or more siblings with psychosis. The prediction was confirmed at a probability of 0.01.

Thus, while other regions of the X chromosome have been suggested as a possible locus for a psychosis gene, a location on the short arms of the X and Y chromosomes within the pseudoautosomal region should be considered. Further examination of this region with RFLPs (restriction fragment length polymorphisms) are required to confirm the existence of a pseudoautosomal locus for psychosis, and to establish whether, as predicted by the continuum concept, this includes affective illness as well as schizophrenia.

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