

No evidence of increased risk for schizophrenia or bipolar affective disorder in persons with aneuploidies of the sex chromosomes

[Original Articles]

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## ABSTRACT

**Background.** Several case reports and reviews have suggested an increased incidence of schizophrenia or bipolar disorder among persons with sex chromosome aneuploidies, but this observation may have been caused by biased sampling.

**Methods.** The 1122 individuals with sex chromosome aneuploidies registered in the Danish Cytogenetic Central Register were screened in the Danish Psychiatric Central Register for admissions with schizophrenia or bipolar affective disorder. Both registers are population based and have existed since 1968 and 1969 respectively. Relative risks were calculated for schizophrenia, bipolar affective disorder and either schizophrenia or bipolar disorder combined as one phenotype. Since hospitalization for a

psychiatric disorder increases the probability that a cytogenetic examination is performed, the relative risks could be inflated, and they were therefore adjusted accordingly.

**Results.** Aneuploidies of the X or Y chromosomes were not associated with an increased risk of schizophrenia or bipolar disorder. The occurrence of the combined phenotype including both schizophrenia and bipolar disorder was significantly reduced among persons with Turner's syndrome and significantly increased among individuals with the 47, XYY karyotype.

**Conclusions.** This population-based study did not find evidence supporting the presence of risk alleles for schizophrenia or bipolar disorder on the X chromosome or the pseudoautosomal region on the Y chromosome. The findings of an increased risk for the combined phenotype to XYY males and the reduced risk for persons with Turner's syndrome are interesting but difficult to explain with present neurobiological knowledge and inconsistent with the other findings of the study.

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## INTRODUCTION

The involvement of the sex chromosomes in the pathogenesis of schizophrenia has been suggested for a number of reasons. First of all, several case reports and reviews have been published ([DeLisi et al. 1994](#)) that suggest an increased incidence of sex chromosome abnormalities in persons with schizophrenia. However, these studies did not have sufficient power or appropriate design and the findings could be the result of biased sampling or publication bias. Secondly, the observation that siblings affected with schizophrenia more often than expected by chance tend to be of the same sex, has led to the hypothesis of a susceptibility gene in the pseudoautosomal region of the sex chromosomes ([Crow, 1988](#)). The validity of this finding has also been questioned because of the possibility of biased sampling and one large, epidemiological study did not find evidence of an increased sex concordance among sibs affected with schizophrenia ([Lichterman et al. 1998](#)). Furthermore, most linkage studies have not suggested susceptibility loci for schizophrenia in the sex chromosomes ([Paterson et al. 1999](#)).

An increased rate of bipolar disorder has been suggested but not to the same degree in aneuploidies of the sex chromosomes ([Craddock & Owen, 1994](#)), however, several case reports have been published ([Bekaroglu et al. 1997](#)). The possibility of a gene for bipolar affective disorder on the X chromosome has attracted attention for several decades ([Ewald, 2000](#)). The studies have been inconsistent but a susceptibility gene may be present at Xq in some rare families ([Pekkarinen et al. 1995](#)). Still, a recessive X-linked risk gene, not in the pseudoautosomal region, could increase the risk for the specific psychiatric disorder in individuals with the 47, XYY and 45, XO karyotype and a dominant gene in cases with 47, XXX and 47, XXY karyotype compared to persons with a normal karyotype.

Empirical evidence has suggested that schizophrenia and bipolar disorder may share some susceptibility genes ([Crow, 1995](#); Maier, 1999) and it would therefore be of interest to investigate the occurrence of both schizophrenia or bipolar disorder among individuals with sex chromosome aneuploidies.

The purpose of this study was to use two population-based registers to estimate the frequency of schizophrenia or bipolar affective disorder among individuals with sex chromosome abnormalities.

## METHOD

The Danish Cytogenetic Central Register (DCCR) was established in December 1968 ([Nielsen, 1980](#)). It contains data from all seven cytogenetic laboratories in Denmark covering the total population of 5.2 million inhabitants. It includes all individuals who have been referred to a cytogenetic examination, thus comprising individuals with chromosome abnormalities, relatives of probands with chromosome abnormalities and individuals with normal karyotype. It is fully computerized and comprised at the time of the register linkage 51828 persons, 27308 males and 24520 females. 9205 individuals had an abnormal karyotype, 4810 males and 4395 females.

The standard technique used throughout most of the period was metaphase examinations of approximately 10 cells stained with Giemsa (or similar methods: orcein, acridine-orange, quinacrine - giving the same degree of resolution). In recent years newer techniques such as fluorescence in situ hybridization (FISH) were used also.

The Danish Psychiatric Central Register (DPCR) was established as fully computerized in 1969 ([Munk-Jørgensen & Mortensen, 1997](#)). It is nationwide covering all psychiatric departments in Denmark. Each patient is registered with all admissions as an in-patient and since 1995 as an out-patient also with a main diagnosis and up to three subsidiary diagnoses at each admission or contact. The system of classification has been the International Classification of Diseases, 8th revision (ICD-8) from 1969 until 31 December, 1993. Since 1 January, 1994 ICD-10 has been used. The diagnoses are the clinical diagnoses reported by the individual psychiatric departments at discharge. At the time of the register linkage (1 October, 1998) 425928 persons, 195439 males and 230489 females had been registered at least once.

Of these, 33512 persons were registered with schizophrenia, 18756 males and 14756 females. Schizophrenia was defined as a main diagnosis of ICD-8; 295 or ICD-10 F20, F21 or F25 at least at one admission or out-patient contact.

A total of 15585 individuals were registered with a diagnosis of bipolar affective disorder, 5980 males and 9605 females. Bipolar affective disorder was defined as a main diagnosis of ICD-8 296.10, 296.39 or ICD-10 F30, F31 at least at one admission or out-patient contact. Furthermore, these individuals must not ever have been registered with a main diagnosis of schizophrenia as defined above.

#### Identification of cases

The individuals registered in the DCCR with aneuploidies of the sex chromosomes were re-identified in the DPCR if they had been registered with schizophrenia or bipolar affective disorder as defined above. Persons with mosaics or other complex aberrations of the sex chromosomes possibly involving the autosomes also, were not included, because the interpretation of the biological effect of these abnormalities would be even more difficult.

The relative risks of schizophrenia or bipolar disorder were calculated as the observed/expected number of individuals with the specific cytogenetic abnormality (XXY; XYY; XO; XXX), who had ever been registered with a main diagnosis of schizophrenia or bipolar affective disorder during the period April 1969 to 1 October, 1998.

The overall expected number was calculated as the sum of  $(C(i)/N(i)) \times P(i)$ , where  $C(i)$  is the number of persons diagnosed with the specific cytogenetic abnormality born in year (i),  $N(i)$  is the number of people born in year (i) and  $P(i)$  is the number of persons registered with a diagnosis of schizophrenia or bipolar affective disorder during the observation period, born in year (i). The relative risk estimates were

thus indirectly standardized for year of birth.

Since hospitalization for a psychiatric disorder could increase the probability that a cytogenetic examination is performed, the relative risks could be inflated. The expected number was therefore multiplied by the following ratio: proportion of individuals with cytogenetic examinations in the DPCR/proportion of individuals with cytogenetic examinations in the general population in year (i). The ratio was calculated separately for males and females. The P values were calculated as exact P values assuming the observed number of cases to be Poisson distributed.

We assessed the statistical power in the following way: since the overall expected number of cases was known for each chromosome abnormality and each specific psychiatric disorder, the observed number of cases that would have resulted in a P value of  $\leq 0.05$  in the Poisson distribution, was calculated. The minimal detectable relative risk for the data set was then calculated as this observed number divided by the expected number.

The study was approved by the Central Scientific Ethical Committee of Denmark and the Danish Data Protection Agency. The Ethical Committee did not allow personal contact with the individuals in the investigation, because the dataset was retrieved through registers.

## RESULTS

During the study period approximately 2000 post-natal cytogenetic examinations were performed each year and of those approximately 300 were abnormal. A total of 1122 individuals had a sex chromosome aneuploidy.

Four hundred and eighty-nine individuals with schizophrenia (1.5%) had a cytogenetic examination performed, there were 383 males and 106 females. One hundred and thirty-nine individuals with bipolar affective disorder (0.89%) had a cytogenetic examination performed, there were 88 males and 51 females.

The frequencies and relative risks of schizophrenia for the different sex chromosome abnormalities are shown in [Table 1](#), and the frequencies and relative risks of bipolar affective disorder for the different sex chromosome abnormalities are shown in [Table 2](#).

| Karyotype | <i>N</i> * | <i>n</i> † | Expected‡ | RR   | <i>P</i> |
|-----------|------------|------------|-----------|------|----------|
| 45, X     | 313        | 0          | 2.89      | —    | 0.13     |
| 47, XXX   | 57         | 0          | 0.53      | —    | 1.00     |
| 47, XXY   | 641        | 13         | 13.99     | 0.93 | 1.00     |
| 47, XYY   | 111        | 5          | 2.42      | 2.10 | 0.10     |

\* Total number of individuals with the sex chromosome abnormality detected from the general population.

† The observed numbers of cases admitted at least once with schizophrenia.

‡ The expected numbers of cases admitted at least once with schizophrenia.

Table 1. Relative risks for schizophrenia among cases with sex chromosome abnormalities (mosaicisms excluded)

| Karyotype | <i>N</i> * | <i>n</i> † | Expected‡ | RR   | <i>P</i> |
|-----------|------------|------------|-----------|------|----------|
| 45, X     | 313        | 0          | 1.88      | —    | 0.28     |
| 47, XXX   | 57         | 0          | 0.34      | —    | 1.00     |
| 47, XXY   | 641        | 7          | 4.46      | 1.57 | 0.23     |
| 47, XYY   | 111        | 2          | 0.77      | 2.59 | 0.18     |

\* Total number of individuals with the sex chromosome abnormality detected from the general population.

† The observed numbers of cases admitted at least once with bipolar affective disorder.

‡ The expected numbers of cases admitted at least once with bipolar affective disorder.

Table 2. Relative risks for bipolar affective disorder among cases with sex chromosome abnormalities (mosaicisms excluded)

Three hundred and thirteen individuals had Turner's syndrome with the 45, X karyotype. The study had the power to detect a relative risk of  $> 2.4$  for schizophrenia and  $2.7$  for bipolar disorder. Of the cases 17 had been registered with any psychiatric illness, but none with schizophrenia or bipolar affective disorder.

Fifty-seven individuals were found with the 47, XXX karyotype. The minimal detectable relative risk was  $5.7$  for schizophrenia and  $5.9$  for bipolar disorder. Six individuals had been registered with any psychiatric illness, none with schizophrenia or bipolar affective disorder.

Six hundred and forty-one males had Klinefelter's syndrome with the 47, XXY karyotype. The minimal detectable relative risk was  $< 0.4$  or  $> 1.6$  for schizophrenia and  $> 2.0$  for bipolar disorder. One hundred and forty-two individuals had been registered with any psychiatric illness, 13 with schizophrenia and seven with bipolar affective disorder.

One hundred and eleven males were identified with the 47, XYY-syndrome. The minimal detectable relative risk was  $> 2.5$  for schizophrenia and  $3.9$  for bipolar disorder. Forty-three had been registered with any psychiatric diagnosis, five with schizophrenia and two with bipolar affective disorder.

In [Table 3](#) the relative risks are reported when schizophrenia and bipolar affective disorder are counted as one phenotype.

| Karyotype | <i>N</i> * | <i>n</i> † | Expected‡ | RR   | <i>P</i> |
|-----------|------------|------------|-----------|------|----------|
| 45, X     | 313        | 0          | 4.77      | —    | 0.02     |
| 47, XXX   | 57         | 0          | 0.87      | —    | 1.00     |
| 47, XXY   | 641        | 20         | 18.45     | 1.08 | 0.64     |
| 47, XYY   | 111        | 7          | 3.19      | 2.19 | 0.04     |

\* Total number of individuals with the sex chromosome abnormality detected from the general population.

† The observed numbers of cases admitted at least once with bipolar affective disorder or schizophrenia.

‡ The expected numbers of cases admitted at least once with bipolar affective disorder or schizophrenia.

Table 3. Relative risks for bipolar affective disorder and schizophrenia counted as one phenotype among individuals with sex chromosome abnormalities (mosaicisms excluded)

## DISCUSSION †

Persons with mosaics of the sex chromosomes were excluded, because they are a very heterogeneous

group with varying degrees of mosaicism and because the abnormal cell line can be present in varying degrees in different tissue including the brain. It is thus an advantage, that only fully comparable individuals with exactly the same abnormalities are included in the present study.

In Denmark the incidence of the different sex aneuploidies are, when mosaicisms are excluded: Klinefelter's syndrome 1.12:1000, XYY-syndrome 1.06:1000, Triple-X syndrome 1.06:1000 and Turner's syndrome 0.06:1000 ([Nielsen & Wohler, 1991](#)). These figures are calculated on the basis of full ascertainment in a representative district of Denmark. The detection rate is much smaller in the general population and only a minor fraction of individuals with the XXX, XXY or XYY karyotypes have been identified in the population. This is a common problem for all epidemiological studies of sex chromosome abnormalities, but we have included all individuals diagnosed in the population, since no other cytogenetic facilities exist in Denmark. It is a possible limitation that the karyotypes have not been checked by independent review. However, review of the cytogenetic diagnosis would probably not change the results significantly, since the detection of an extra sex chromosome is not so difficult as, for example, the band location in an inversion or translocation.

It may be considered a problem that ICD-8 diagnoses were used and that the patients were not diagnosed with the addition of a semistructured interview. However, in ICD-8 schizophrenia is defined by prototypic descriptions of symptoms such as bizarre delusions, delusions of control, abnormal affect, autism and disorganized thinking, whereas in the Diagnostic and Statistical Manual of Mental Disorders and ICD-10 most of the same symptoms have been transformed into explicit criteria, operationally defined. In Denmark the ICD-8 schizophrenia diagnosis was applied in a conservative manner. Furthermore, in a sample of 53 patients with schizophrenia as defined by ICD-8, 91% also met the criteria for DSM-III-R, suggesting that the majority of persons identified by us would meet newer criteria for schizophrenia ([Munk-Jørgensen, 1995](#)).

Concerning bipolar affective disorder a study by [Kessing \(1998\)](#) revealed a very high concordance between clinical ICD-8 diagnoses and ICD-10 diagnoses based on the research criteria. The lifetime risk for bipolar affective disorder is assumed to be the same for males and females, but in the Psychiatric Case Register 62% of the cases with bipolar affective disorder are females. There is no known systematic selection bias and no cohort effects since there are a preponderance of females in all birth cohorts in the study. The lack of males could influence the power for detecting an association with Klinefelter's syndrome or the XYY-syndrome, but according to our power calculations the sensitivity of the study is reasonable. If schizophrenia, with an incidence of 1% and, for example, Klinefelter's syndrome were totally independent the expected risk of having Klinefelter's syndrome and schizophrenia would be about 1:100 000 if the two disorders co-occurred by chance only. An aetiological link, selection bias or confounding would change this estimate. The identification of XYY males among psychiatric patients are especially subject to detection bias since criminality and the XYY karyotype have been suspected to be associated ([Hook, 1973](#)). Males admitted as forensic cases will have an especially high probability of having a cytogenetic examination performed as a routine part of the investigation and the higher frequency of cytogenetic examinations among males with schizophrenia than females in our study may be a reflection of this.

The population-based ascertainment and the known frequency of cytogenetic examinations in the general population, as well as in the psychiatric population, makes it possible to correct the estimates of the relative risk for selection bias for each gender separately. The estimates are conservative due to this correction for Berkson's bias. No other studies have calculated relative risks in order to estimate the

association between the sex aneuploidies and schizophrenia or bipolar affective disorder. The study has the greatest statistical power for cases with Klinefelter's syndrome and least power for cases with Triple-X syndrome, where the genetic risk factor had to confer a relative risk of at least 5.7 for schizophrenia to be detected. The results must therefore be interpreted accordingly.

Schizophrenia and bipolar disorder in association with Turner's syndrome have rarely been reported, and a lack of association is indeed supported in our study. This can be stated with some confidence since according to the incidence figures, most individuals with Turner's syndrome have been ascertained and no cases were found.

Our results do not support an increased incidence of schizophrenia or bipolar disorder among cases with the sex aneuploidies XXX or XXY. The findings of previous studies may thus have been due to a biased sampling. The increased rate of schizophrenia among XYY males is not significant and the trend alone does not support the hypothesis of involvement of the pseudoautosomal region in the genesis of schizophrenia.

When schizophrenia and bipolar affective disorder are taken together as one phenotype the rate of either schizophrenia or bipolar affective disorder occurred significantly more often than expected in XYY males. The interpretation of this observation is difficult. If dominant genes in the pseudoautosomal region indeed were responsible, the finding is inconsistent with the observation of no increased risk in persons with Klinefelter's syndrome and in Triple-X syndrome but it is in accordance with the significantly reduced risk among individuals with Turner's syndrome. A dominant gene on the Y chromosome may act in an unspecific way since XYY males have an excess of other kinds of psychopathology such as mental retardation, which in itself is associated with an increase in the occurrence of schizophrenia ([David et al. 1997](#)). Alcoholism has also been reported with increased incidence ([Mors et al. 1998](#)) as well as a liability to antisocial behaviour ([Götz et al. 1999](#)). Conversely, a recessive gene in the pseudoautosomal region would lead to an increased risk among individuals with Turner's syndrome.

Both oestrogen and testosterone are psychoactive compounds ([Häfner et al. 1998](#); [Behl & Hoelsboer, 1999](#); [Yates, 2000](#)). Testosterone is a psychoactive compound similar to prednisone especially in susceptible individuals in supranormal dosages, but males with the XYY syndrome have a normal range of serum testosterone prenatally ([Ratcliffe et al. 1994](#)) and later in life ([Schiavi et al. 1988](#)), although it is significantly higher than in XXY males. Individuals with the XXY syndrome may thus be protected from an increased risk of susceptibility genes in the pseudoautosomal region by the relative lower level of testosterone and higher level of oestrogen. Individuals with Turner's syndrome have low oestrogen levels, but it has been common for several years in Denmark to induce puberty at a bone-age of 11 years and after completion of pubertal induction to continue with the oestrogen replacement therapy. Persons with Turner's syndrome will thus be exposed to the neuroprotective effects of oestrogen, at least from puberty onwards.

In summary, the main results of this population based study did not support the presence of risk alleles for schizophrenia or bipolar disorder on the X chromosome or the pseudoautosomal region on the Y chromosome. The findings of a positive association with a combined phenotype to XYY males and a reduced risk for persons with Turner's syndrome are inconsistent with the other findings of the study and difficult to explain with the present neurobiological knowledge.

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