Klinefelter’s syndrome (karyotype 47,XXY) and schizophrenia-spectrum pathology

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Summary Klinefelter’s syndrome, characterised by a 47,XXY chromosomal pattern, has largely been associated with physical abnormalities. Here, we report high levels of schizophrenia-spectrum pathology in 32 men with this syndrome in comparison with 26 healthy controls. This may have implications for treatment of Klinefelter’s syndrome and suggests that the X chromosome may be involved in the aetiology of schizophrenia.

Declaration of interest None.

Klinefelter’s syndrome is the most common sex chromosome disorder, affecting approximately 1 in 1000 men. It is characterised by an additional X chromosome, leading to the 47,XXY karyotype. This aneuploidy results in a variety of phenotypes, including hypogonadism, androgen deficiency and infertility (Lanfranco et al., 2004). Although the primary focus in clinical research has been on the physical phenotypes of these men, there is an awareness of neuro-anatomical, cognitive and behavioural abnormalities (Lanfranco et al., 2004; Shen et al., 2004). Specific impairments in verbal skills, a high incidence of dyslexia and social dysfunctioning are among the most consistently reported behavioural phenotypes (Lanfranco et al., 2004). In a recent review Lanfranco et al. (2004) concluded that it remains unclear whether this syndrome can be associated with psychiatric disturbances; however, many of the abnormalities in Klinefelter’s syndrome resemble those in schizophrenia. For example, structural magnetic resonance imaging (MRI) studies have reported smaller whole-brain volumes, enlarged lateral ventricles and volume reductions of the superior temporal gyrus, amygdala, hippocampus, insula and cingulate in men with this syndrome (Shen et al., 2004). Support for the hypothesis that sex chromosomes may have a role in the development of schizophrenia is derived from studies showing that men are affected by the disease more often than women and at an earlier age (Aleman et al., 2003).

Case studies have been published describing patients with Klinefelter’s syndrome and schizophrenia, and reporting higher rates of Klinefelter’s syndrome among people with schizophrenia (DeLisi et al., 1994). Studies of psychiatric pathology in Klinefelter’s syndrome have been limited to psychiatric samples; there has been no systematic report of levels of schizophrenia psychopathology in a large sample of people with Klinefelter’s syndrome unselected for psychiatric disorders. Also, a biological–genetic vulnerability to schizophrenia may be investigated not only using dichotomous, diagnostic outcomes, but also using dimensional measures of schizophrenia-spectrum symptoms, which are more sensitive measures of vulnerability to schizophrenia. Schizophrenia-spectrum phenotypes share common cognitive, neuro-anatomical and genetic characteristics with the severe schizophrenia phenotype. Our study tested the hypothesis that increased levels of schizophrenia-spectrum pathology are present in people with Klinefelter’s syndrome.

METHOD

Thirty-two men with Klinefelter’s syndrome (mean age 38.8 years, s.d.=8.1) and 26 healthy controls (mean age 35.0 years, s.d.=9.0), matched for age, years of education and intellectual ability, participated in the study. The Klinefelter group was recruited from the Dutch Klinefelter Association and not selected for physiological or behavioural abnormalities; the psychiatry department was not mentioned during recruitment. Diagnosis of Klinefelter’s syndrome was confirmed by karyotyping using standard techniques. Analysis of 32 cells per individual indicated non-mosaicism in this group. Twenty-six of the men with this syndrome received testosterone supplementation. The mean age at onset of treatment was 27.8 years (s.d.=7.6). The control group was recruited by advertisement. None of the control group met criteria for an Axis I psychiatric disorder, as shown by screening with the MINI-Plus version of the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998).

RESULTS

In the Klinefelter group the mean level of schizotypal traits on the SPQ was significantly higher than in the control group (F(1.56)=36.67, P<0.0001). Scores on all individual sub-scales were significantly greater (see data supplement to the online version of this paper). Effect sizes were 1.43, 1.31 and 1.81 for the negative, positive and disorganised dimensions respectively. The importance of these findings is illustrated by comparing them with findings in schizophrenia: a study of 93 patients with schizophrenia and 172 healthy controls reported effect sizes (Cohen’s d) for mean total SPQ score of 1.95, for positive schizotypy 1.86, for negative schizotypy 1.83 and for disorganised schizotypy 1.45 (Rossi &
Daneluzzo, 2002). Similarly, PANSS scores showed increased levels of schizophrenia symptoms in the Klinefelter group ($t_{(48)} = 4.80, P < 0.0001$). All symptom categories contributed to this effect. Effect sizes of 1.60 were observed for negative symptoms, 1.45 for positive symptoms and 1.66 for general psychopathological symptoms. Results are shown in Fig. 1. No significant group difference was observed for IQ.

**DISCUSSION**

Our study shows that the 47,XXY karyotype is strongly associated with high levels of schizophrenia-spectrum pathology. This was evident in dimensional measures of schizotypal traits (SPQ) as well as schizophrenia symptoms (PANSS). Notably, the effect sizes of schizotypy levels approached those found in people with schizophrenia (Rossi & Daneluzzo, 2002; Vollema et al, 2002). Although healthy first-degree relatives of patients with schizophrenia also have elevated schizotypy scores, their schizotypy levels are substantially lower than those of the patients (Vollema et al, 2002). Thus, the liability to schizophrenia might be higher in Klinefelter’s syndrome than in relatives of people with schizophrenia. Treatment in Klinefelter’s syndrome is currently focused on medical problems, but our data suggest it is important to screen men with this syndrome for mental illness, in particular schizophrenia-spectrum disorders.

Furthermore, our findings suggest a link between a X chromosome abnormality and liability to schizophrenia. This might be useful in the search for the genetic aetiology of schizophrenia. A crucial role for X chromosome abnormalities in this context has been proposed by Lishman (1998). Specifically, it has been argued that reduced cerebral lateralisation may contribute to the development of schizophrenia, possibly involving abnormal expression of a gene on the X chromosome directing development of cerebral asymmetry (Crow, 2002). Interestingly, reduced cerebral asymmetry has also been reported in Klinefelter’s syndrome.

The prevalence of Klinefelter’s syndrome in the general population is 0.1–0.2% (Lanfranco et al, 2004), but two studies indicate that the prevalence among people with schizophrenia may be much higher (DeLisi et al, 1994; Kunugi et al, 1999), lending further support to a link between X chromosomal abnormalities and liability to schizophrenia. Also, our findings are consistent with a report of auditory hallucinations in 4 out of 11 men with Klinefelter’s syndrome (DeLisi et al, 2005). Research in Klinefelter’s syndrome may reveal specific genotype–phenotype associations. Endophenotypes in schizophrenia (i.e. expressions of a genetic predisposition at a neural or cognitive level) that are shared by Klinefelter’s syndrome and schizophrenia may be the result of an X chromosomal abnormality.

As many men with Klinefelter’s syndrome remain undiagnosed, our sample may not be completely representative. In spite of this, we believe that the effect sizes we report convincingly indicate a relationship between Klinefelter’s syndrome and schizophrenia-spectrum pathology, although the possibility that effect sizes might be attenuated in a representative sample from the general population cannot be excluded.

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**REFERENCES**


