

would lead to failure of suppression of HOXB-8 expression in the anterior limb field. Ectopic expression of HOXB-8 would then specify cells in the anterior limb field as ZPA, leading to partial or complete duplication of zeugopod, autopod, and stylopod.

There are no reports of zeugopod (humerus/femur) duplication in Laurin-Sandrow syndrome, which would argue against the above hypothesis. To my knowledge, however, no author has to date thoroughly examined the humeri and femora of Laurin-Sandrow patients for any evidence of abnormal patterning.<sup>7-11</sup> Further delineation of the Laurin-Sandrow phenotype, especially with regard to more proximal skeletal elements, would be most helpful in the search for candidate genes for this intriguing syndrome.

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## A study of brothers with Klinefelter syndrome

Klinefelter *et al*<sup>1</sup> described males with infertility, hypogonadism, and gynecomastia in 1942. The other clinical features of Klinefelter syndrome are now well delineated but not present in all affected subjects.<sup>2</sup> The live birth prevalence of Klinefelter syndrome is approximately 1 in 1000.<sup>3</sup> The diagnosis is made and confirmed by the cytogenetic finding of 47,XXY. Klinefelter syndrome is considered to be a sporadic disorder resulting from non-disjunction. This is maternal in one half of cases and paternal in the remainder.<sup>4,5</sup> The empirical recurrence risk is negligible as the condition occurs sporadically, with the recurrence risk equal to the birth prevalence, that is, 1 in 1000. Given this, it is not surprising that Klinefelter syndrome is very rarely

reported to recur within a family. There are limited reports of sibs with Klinefelter syndrome<sup>6,7</sup> or of twins.<sup>8,9</sup> Therefore we wish to document our clinical, cytogenetic, and molecular findings of a family in which brothers had Klinefelter syndrome.

The older boy was diagnosed as having Klinefelter syndrome at the age of 5 years. He had reduced left elbow supination and radiography showed radioulnar synostosis. Diagnosis was made in the younger sib at the age of 3 years because of undescended testes and a "willowy appearance" similar to his older affected brother. Both had heights approximately on the 50th centile, weights on the 3rd centile, and reduced upper to lower body segment ratios of 0.87 and 0.85. The older sib is at Tanner stage 1 of sexual development at 11 years. Both are otherwise normal on examination, of normal intellectual ability, and neither has any behavioural problems.

Both parents were healthy, normal on examination, and aged 24 years at the time of birth of their first child with Klinefelter syndrome. The couple had no difficulty in conceiving and no recognised pregnancy losses. They are first cousins from the Punjab and are themselves products of first cousin marriages (fig 1). There are no other family members known to have chromosome anomalies, infertility, or frequent miscarriages.

Chromosome analysis of peripheral blood lymphocytes was performed on nuclear family members, 50 cells being examined in each case. The brothers with Klinefelter syndrome were non-mosaic 47,XXY, other family members having normal results. X chromosome haplotype analysis was performed using an Applied Biosystems 373 DNA Sequencer and Genescan 672 software. The microsatellite present in intron 13 of the factor VIII C gene at Xq28 was informative, but nine microsatellites from the dystrophin gene were uninformative.<sup>10</sup> The results are shown in fig 1; both boys with Klinefelter syndrome had

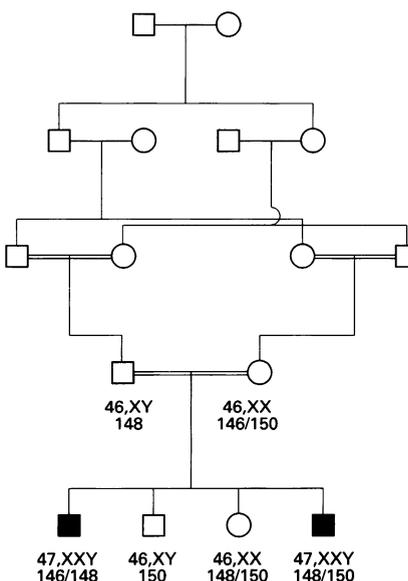


Figure 1 Pedigree with the males with Klinefelter syndrome shown as filled squares. Cytogenetic analyses and X chromosome genotype results are shown for the nuclear family. The latter were generated using the microsatellite present in intron 13 of the factor VIII C gene. The results are given as the polymerase chain reaction products measured in base pairs.

apparently inherited an X chromosome from their father.

These sibs with Klinefelter syndrome had typical clinical features, non-mosaic 47,XXY, and their additional X chromosome was the result of a paternal meiosis I error. Possible explanations for this situation are chance, that the father is a Klinefelter syndrome mosaic which seems unlikely, or that the father has an autosomal recessive disorder affecting meiosis. We have been unable to investigate the family further by single sperm analysis and because no other relative is known to have had a child with aneuploidy.

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