Our own study failed to confirm the rise of serum FSH with age. Instead, we found a negative correlation between serum FSH and testicular volume irrespective of age.

J HASEN
25 Lake Street,
White Plains,
New York 10603,
USA.

Reference

- ¹ Hasen J, Boyar MR, Shapiro RL. Gonadal function in trisomy 21. *Horm Res* 1980;12:345-50.

Interstitial duplication/deletion owing to unequal crossing-over in association with pericentric inversion

SIR,

Einfeld and Smith¹ reported two brothers, aged 4½ and 2½, with similar clinical features, namely developmental delay, short stature, and small delicate facies. They were quite different from the other unaffected family members. A pericentric inversion of chromosome 11, inv(11) (p15q14), was found in the younger retarded boy and in the father, whereas the karyotypes of the older retarded boy, the mother, and the two unaffected sibs were normal. Although it was obvious that the clinical features of the two brothers had a similar aetiology, it was not explicable on the grounds of cytogenetic findings. Unknown environmental factors, sex linked mental retardation, or an autosomal recessive condition were considered as possible causes of the abnormal clinical features.

Based on the following personal observation, I would suggest that the clinical features of the two boys may still be explained cytogenetically. Recently, an apparently balanced paracentric inversion of the proximal part of 7q, inv(7) (q11q22), was found in a girl with multiple congenital anomalies and in her phenotypically normal mother. Further examination of high resolution chromosomes revealed an additional tiny dark band on the inverted chromosome 7 of the girl, but not on the inverted chromosome 7 of the mother. It was therefore assumed that an unequal crossing-over had occurred at the base of a meiotic loop of the chromosomes 7 in the mother, which resulted in a tiny interstitial duplication in the girl. A detailed account of this case is published elsewhere.²

As suggested in fig 1, the events of unequal crossing-over occurring in the spermatogenesis of the father, in the two directions shown, would result in identical duplications or deletions either associated

FIG 1 Diagrams illustrating the occurrence and results of unequal crossing-over in the spermatogenesis of the father. (a) Chromosome 11 and its inverted homologue as diagnosed by Einfeld and Smith. The interrupted line denotes the short arm of chromosome 11. (b) Formation of meiotic loops as a consequence of the pericentric inversion. The dotted lines denote the directions of unequal crossing-over. The zigzag lines denote the duplicated or deleted chromosome segment. (c) Various products of unequal crossing-over. Dup = duplication, Del = deletion, Inv = inversion.

with pericentric inversion or not. The older retarded boy could have one of the non-inverted recombinants, and the younger retarded boy one of the inverted recombinants. By performing high resolution chromosome study, the authors may be lucky enough to detect a tiny duplication or deletion in both retarded boys. Nevertheless, the duplicated or deleted chromosome segment might be so tiny that it could not be seen under a microscope.

Unequal crossing-over is a well known event occurring in meiosis. Results of unequal crossing-over occurring in the course of evolution are best demonstrated in the anatomy of haemoglobin genes.³ For example, the genes for beta, delta, and pseudo-beta, which are immediately adjacent to each other within the short arm of chromosome 11, differ only slightly in their base sequences. Haemoglobinopathies such as haemoglobin Lepore with gene

FIG 2 Assuming that the gene omega (Ω) and the adjacent pseudogene pseudo-omega ($\Psi\Omega$) display significant homology, winding and coiling at the base of a loop would facilitate the occurrence of sliding meiotic pairing. An unequal crossing-over as indicated by the dotted line would result in deletion or duplication of omega in the two recombinants.

deletion and haemoglobin anti-Lepore with gene duplication are other examples of unequal crossing-over.

Winding and coiling of chromatids at the base of a meiotic loop in association with a pericentric or paracentric inversion may increase the possibility of an unequal crossing-over, and the presence of repetitive genes at the base of a loop, as shown in fig 2, may further enhance this tendency.

Should the above assumption prove to be correct in the future, it will have two important consequences.

- (1) An apparently balanced inversion or a normal chromosome diagnosed antenatally in conjunction with a parental balanced inversion does not rule out the possibility of the presence of a tiny duplication or deletion owing to unequal crossing-over.
- (2) Cytogenetic study should also be done on the parents of a child with a suspected chromosomal anomaly, even though the karyotype of the child appears to be normal. A tiny, microscopically undetectable duplication or deletion in an apparently normal chromosome could result from an unequal crossing-over of a balanced pericentric or paracentric inversion in one parent.

JOE J HOO

Department of Pediatrics,
University of Calgary,
3330 Hospital Drive, Calgary,
Alberta T2N 4N1, Canada.

References

- ¹ Einfeld SL, Smith A. Pericentric inversion of chromosome 11 in one of two similar retarded brothers. *J Med Genet* 1982;**19**:312.
- ² Hoo JJ, Lorenz R, Fischer A, Fuhrmann W. Tiny interstitial duplication of proximal 7q in association with a maternal paracentric inversion. *Hum Genet* (in press).
- ³ Antonarakis SE, Phillips JA, Kazazian HH. Genetic diseases: diagnosis by restriction endonuclease analysis. *J Pediatr* 1982;**100**:845-56.