Pericentric inversion of chromosome 1: frequency and possible association with cancer

N.B.		Atkin
M.C.		Baker

Department of Cancer Research, Mount Vernon Hospital, Northwood, Middlesex

Request reprints from: Dr. N.B. Atkin, Department of Cancer Research, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN (England).

Paired unstained spheres are frequently, though not constantly, seen at the centromeres of human chromosomes (Lubs and Blitman, 1967), and they may indeed represent these structures or their associated proteins (Evans and Ross, 1974). In a recent study it was found that heteromorphism for the size of the C-bands of the No. 1 chromosomes was significantly more common in patients with malignant disease than in controls (Atkin, 1977); further cases have now been studied and, in all, 41 out of 76 (54 %) malignant cases show the heteromorphism, as compared with 22 out of 68 (32 %) controls. In the course of this study it has been noted that, where the heteromorphism is present, part of the C-band of the No. 1 chromosome with the greater amount of hetero-chromatin sometimes extends onto the short arm, suggesting that a pericentric inversion is present. This observation is based on the presence of unstained spheres at the centromere region.

The present report is concerned with the frequency of pericentric inversions of the No. 1 chromosomes and includes evidence for such an inversion in one of the No. 1 chromosomes of six patients with malignant disease and one with a nonmalignant condition who are *not* heteromorphic for C-band size. Four of the six patients have carcinoma of the ovary, and the presence of this phenomenon in three of these has been briefly reported (Atkin and Pickthall, 1977); the other two have Hodgkin's disease.

Supported by a grant from the Cancer Research Campaign.

Brief Report

181

Chromosome preparations were made from normal cells (mostly cultured lymphocytes) as previously described (Atkin, 1977) and were C-banded by the BSG technique (Sumner, 1972). Observations were made with a Zeiss Photomicroscope (planapochromat X100 1.4 NA objective); 144 individuals, including 76 cancer patients, were available for study.

Cases were assessed for the presence of an inversion wherever there were at least 10 "suitable" metaphases; the latter were defined as those in which the No. 1 chromosomes were not too contracted (at least 7 μm in length) or angled at the centromere, and either one or two spheres were visible at the centromeric region of each chromosome. On the chromosome with the inversion, the sphere or spheres were situated along the C-band at a distance of at least 1/3rd of its length from either end, usually opposite an indentation. Generally, consistent results were obtained on each case; in those that were considered positive for a pericentric inversion,

observations on all suitable metaphases (from 10 to 30 per case) were compatible with the presence of such an inversion in one of the No. 1 chromosomes.

As shown in table I, six patients who were heteromorphous for C-band size had an inversion in the No. 1 chromosome with the larger C-band. These were: three with carcinoma of the ovary (aged 56, 65, and 55), the last having been included in the previous report (Atkin and Pick-thall, 1977); one with seminoma (aged 31); one with carcinoma of the breast (aged 64); and one with lymphosarcoma (male, aged 65). Also, six patients without the heteromorphism for size had an inversion (see fig. 1): four with carcinoma of the ovary (two aged 70 and one aged

Table I. Presence of a pericentric inversion and heteromorphism for size of the C-bands of the No. 1 chromosomes in 76 patients with malignant disease and

68 controls.

C-band size heteromorphism Pericentric inversion

Patients with malignant disease Present Absent Not determined Total

Present **6a** 19 16 41

Absent **6** 13 16 35

Total 12 32 32 76

Controls

Present **2a** **8** 12 22

Absent **1** 20 25 46

Total 3 28 37 68

a Inversion present in the chromosome with the larger C-band.

182 Brief Report

Fig. 1. No. 1 chromosomes from three patients with an inversion who are not heteromorphous for C-band size. The chromosome with the inversion is on the right of each pair. C-banded preparations of lymphocytes from blood or (Hodgkin's disease) lymph-node cultures. Top row: carcinoma of ovary (aged 70), all from the same slide preparation. Bottom row: left and center, Hodgkin's disease (male, aged 38); right, carcinoma of ovary (aged 70). The patients with carcinoma of the ovary are respectively the same as cases 8 and 7 in Atkin and Pickthall (1977). 21 who were included in the previous report [Atkin and Pickthall, 1977] and one aged 44), and two with Hodgkin's disease (both male, aged 22 and 38). Two controls with the heteromorphism had an inversion: both female, aged 49 (suspected glomerulonephritis) and 59 (fracture of the tibia). One control without the heteromorphism had an inversion: female, aged 55 (cholecystitis). A total of 69 cases (32 malignant cases and 37 controls) were not assessed because insufficient suitable metaphases were found.

Our observations suggest that pericentric inversions involving the heterochromatic regions of the No. 1 chromosomes are relatively common, at least among individuals who develop cancer. A minimum of 12 out of the 76 patients with cancer (15%) had the inversion, as compared with 3 out of the 68 controls (4 %), i.e., a total incidence of 15 out of 144 (10%). In two previous population surveys (Müller et al., 1975; Buckton et al., 1976) the incidence of an inversion (regarded as present when at least 1/3rd of the C-band extended onto the short

Brief Report

183

arm) was estimated to be of the order of 1–2 %. Although our estimate is subject to some uncertainty owing to the number of cases that were not assessed, our data nevertheless suggest an incidence of at least 4 % (the incidence we found in the controls) and possibly 10 % or more.

An association with cancer seems possible from (but has not been proven by) our results. We may speculate that the heterochromatin polymorphism, the pericentric inversion, and the risk of cancer are each interrelated. First, there may be a relationship between the inversion and the polymorphism. Baimai (1977) has recently pointed out that in *Drosophila*, when one break point of a long inverted segment of a chromosome occurs in the vicinity of constitutive heterochromatin, it may exert an effect in eliciting the production of heterochromatic material in the same chromosome; he suggests that a similar phenomenon could account in part for heterochromatin polymorphisms in higher organisms, including man.

Second, there may be a direct relationship between the presence of an inversion or unequal amounts of heterochromatin, or both, on the No. 1 chromosomes and the risk of cancer. This might be a consequence of somatic pairing and crossing-over between these homologs, perhaps resulting in daughter chromosomes which have undergone deletions or duplications. Evidence for the occurrence of mitotic crossing-over in man has come from various sources, especially from the observation of chiasmata (Therman and Kuhn, 1977). Also, since mosaicism for C-band polymorphisms has been observed in man (Craig-Holmes et al., 1975), it has been suggested that the mosaicism is the consequence of the production of C-band variants through unequal crossovers following homologous pairing in somatic cells, and that this may occur more frequently in some families than in others.

Atkin, N.B.: Chromosome 1 heteromorphism in patients with malignant disease: a constitutional marker for a high risk group? *Br. med. J.* 1: 358 (1977).

Atkin, N.B. and Pickthall, V.J.: No. 1 chromosomes in 14 ovarian cancers: heterochromatin variants and structural changes. *Hum. Genet.* (1977, in press).

Baimai, V.: Chromosomal polymorphisms of constitutive heterochromatin and inversions in *Drosophila*. *Genetics* 85: 85–93 (1977).

Buckton, K.E.; O'Riordan, M.L.; Jacobs, P.A.; Robinson, J.A.; Hill, R., and Evans, H.J.: C- and Q-band polymorphisms in the chromosomes of three human populations. *Ann. hum. Genet.* 40: 99–112 (1976).

Craig-Holmes, A.P.; Moore, F.B., and Shaw, M.W.: Polymorphism of human C-band heterochromatin. II. Family studies with suggestive evidence for somatic crossing over. *Am. J. hum. Genet.* 27: 178–189 (1975).

184

Brief Report

Evans, H.J. and Ross, A.: Spotted centromeres in human chromosomes. *Nature, Lond.* 249: 861–862 (1974).

Lubs, H.A. and Blitman, S.L.: Observations on the centromere area of human chromosomes. *Experientia* 23: 1067–1069 (1967).

Müller, H.J.; Klinger, H.P., and Glasser, M.: Chromosome polymorphism in a human newborn population. II. Potentials of polymorphic chromosome variants for characterizing the idiogram of an individual. *Cytogenet. Cell Genet.* 15: 239–255 (1975).

Sumner, A.T.: A simple technique for demonstrating centromeric heterochromatin. *Exp. Cell Res.* 75: 304–306 (1972).