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Satellite Association and Translocation Mongolism*

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Cytogeneticists before 1960 recognized only two pairs of satellited chromosomes in man: a large acrocentric pair of the D group and a small acrocentric pair of the G group. In 1960 another pair of the D chromosomes was found to be satellited, and in 1961 Ferguson-Smith and Handmaker presented conclusive evidence of all 10 acrocentric autosomes having satellites, though usual staining methods rarely show all of them in a single metaphase plate. Better visibility of satellites is obtained in our laboratory by staining the chromosomes with Giemsa.

By careful inspection of many karyograms we noticed that the satellited ends of two or more chromosomes lay closely together more often than expected if random distribution of the chromosomes was assumed. This phenomenon is called satellite association (S.A.). Its occurrence in human karyograms was first described in 1961 (Ferguson-Smith and Handmaker, 1961; Harnden, 1961; Ohno, Trujillo, Kaplan, and Kinosita, 1961). A schematic drawing of S.A. as it may appear in mitotic metaphase is shown in the Figure. S.A. is known to occur in meiosis as well as in mitosis (Ferguson-Smith, 1964). It has been related to the presence of persistent nucleolar RNA located near the nucleolar organizers which are proximal to the satellited ends of the acrocentric chromosomes. This material has lately been detected by special cytochemical methods, though it is not visible in ordinary karyogram preparations (Hsu, Arrighi, Klevecz, and Brinkley, 1965). It is somewhat sticky and has, particularly if present in abundance, a tendency to keep the associated chromosomes together through later phases of meiosis or mitosis. The respective chromosomes (meiosis) or chromatids (mitosis) may fail to disjoin and aneuploid karyotypes result. Thus S.A. may represent a cause of aneuploidy.

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Furthermore, the heterochromatic site of the nucleolar organizers is prone to chromosomal breakage. Thus fragments of acrocentric chromosomes arise which tend to fuse in various combinations, whereby translocations may be formed (Ohno *et al.*, 1961). This explains why translocations between acrocentric chromosomes are far more frequent than translocations between other non-acrocentric chromosomes of the groups A, B, C, E, and F. As a working hypothesis it can be assumed that non-disjunction and translocations may occur more often if there is (a) increased stickiness of some of the satellited chromosomes, or (b) if the number of S.A. is increased. The first part of this hypothesis cannot be tested in our laboratory, but there are methods available to check its second part: the number of S.A. In a previous study evidence was presented that increased S.A. may be transmitted as an inherited trait (Abbo, Zellweger, and Cuany, 1966). In this paper studies concerning S.A. in our cases of translocation mongolism and their parents will be presented.

Material and Method

Two, three, or more satellited chromosomes may participate in the formation of S.A., and one can speak of double, triple, and multiple configurations. Double S.A. is found with greater frequency than triple and quadruple S.A. Double S.A. between two D chromosomes is more frequent than S.A. between two G chromosomes and less frequent than S.A. between a D and a G chromosome. These differences are not surprising, since 10 chromosomes are available to form a D-G association; 6 to form a D-D association; and only 4 to form a G-G association. The satellited ends of acrocentric chromosomes may be contiguous or at a distance which is measured conveniently in multiples of the width of one chromatid. Ferguson-Smith and Handmaker (1961) used the terms satellite associations and satellite adjacencies, and assumed that the degree of separation of the associated ends could be influenced by the technical processing of the leucocyte cultures, particularly the addition of hypotonic solution. In this study we differentiate between satellite association (S.A.) and close and loose satellite approximations

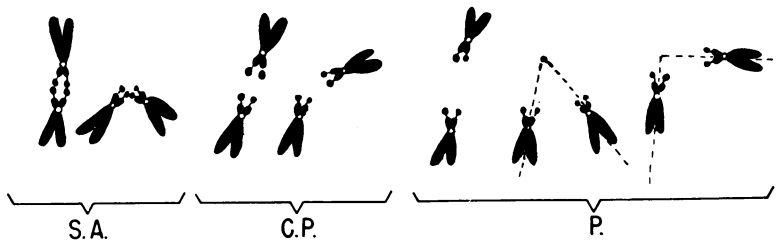

FIG. Schematic drawing of satellite association (S.A.), close satellite approximation (C.P.), and loose satellite approximation (P.).

(Fig.). We speak of S.A. if the distance between the two short arms (with or without distinct satellites) of two or more acrocentric chromosomes does not exceed the width of one chromatid and if the prolongations of the axes of the respective chromosomes meet each other in the interspace ahead of or between their satellited ends. We speak of close satellite approximation (C.P.) when the satellited ends of the acrocentric chromosomes point toward each other and the distance between them is between one and two chromatid widths. We speak of loose satellite approximation (P.) when the satellited ends approach each other and their distance is between two and five chromatid widths. For the results presented in this study, we counted the number of metaphase plates with S.A. (regardless of whether there was one or more S.A. configuration per plate) and expressed the S.A.-carrying metaphases as a percentage of the total number of metaphase plates examined for the respective individual. Metaphase plates showing only C.P. and P. and no S.A. were included in the non-S.A. fraction of the total. On our worksheets we listed satellite approximations as well for technical reasons which will be presented in detail elsewhere The normal range of S.A. established by examining 1161 metaphase plates of 22 controls ranged from 2 to 27% with a mean of 13·3%.

Two cases of sporadic D/G, one case of sporadic G/G, and one case of familial D/G translocation mongolism and the parents of these four patients were available for study. One or several samples of peripheral blood were processed for chromosomal analysis following a modification of the method of Arakaki and Sparkes (1963). Black and white, 24 × 36 mm., films were taken of every metaphase plate which showed a good spread of chromosomes. These films were checked for S.A. and other configurations by several team members in joint sessions. Only plates with a modal number ±1 were counted. Plates in which the number of chromosomes varied from the modal number by more than one were not included in the study.

Results

The results of this investigation are listed in the Table. The 3 mongoloid children of families A, B, and D had S.A. in 33%, 31%, and 33% of their metaphase plates. These values are above the normal range, which is between 2% and 27%. Likewise, increased S.A. was found in one parent of each of these 3 mongoloids: the mother in family A had 38·5%; the mother in family B had 33%; and the father in family D had 60% S.A. Altogether

TABLE

SATELLITE ASSOCIATION (S.A.) AND TRANSLOCATION

	Chromosomal Complement	Number of Cells Examined	Percentage of Cells with S.A.
Family A (Bo)			
Father	46 normal	28	0
Mother	45 balanced D/G translocation	26	38·5
Mongoloid girl	46 with D/G translocation	24	33·3
Family B (Sc)			
Father	46 normal	31	19
Mother	46 normal	30	33
Mongoloid girl	46 with D/G translocation	29	31
Family C (Om)			
Father	46 normal	31	16
Mother	46 normal	38	21·1
Mongoloid boy	46 with D/G translocation	30	16·7
Family D (Gr)			
Father	46 normal	30	60
Mother	46 normal	30	20
Mongoloid boy	46 with G/G translocation	30	33·3
Control Group			
Males (11)	46 normal	617	12·4
Females (11)	46 normal	544	14·7

170 metaphase plates of these 6 individuals were examined and S.A. was found in 65 plates, i.e. 38% of all plates. The other parent of each of these 3 mongoloids as well as all 3 members of family C, father, mother, and mongoloid child, had between 0 and 21% S.A., all values being below the upper limit of the normal range. Six people of the second group had S.A. in 38, i.e. 15·6% of 188 analysed metaphase plates. The difference between these percentages is statistically significant at the 0·01 level of confidence. We conclude, therefore, that 3 of our translocation mongoloids and one parent of each of them had increased S.A.

Discussion

Several investigators (Ferguson-Smith and Handmaker, 1961; Harnden, 1961; Ohno *et al.*, 1961; Zellweger and Abbo, 1965) suggested that S.A. and, particularly, increased S.A. may be of significance for the causation of translocation in meiosis as well as in mitosis. Clinical evidence to prove this sequence of events is almost non-existent. Scanty reports are available indicating that increased S.A. in *mitosis* may produce mosaicism with translocation of various acrocentric chromosomes (Abbo *et al.*, 1966; Zellweger and Abbo, 1965). S.A. in meiosis as a cause of translocation in man has hitherto not been described. The observations of family B and family D reported here present the first clinical evidence that in man translocation may occur as a consequence of increased S.A. in meiosis. Family A does not qualify in this respect since the mother already had a balanced D/G translocation. That such chromosomal anomaly of a parent may lead to translocation mongolism in the offspring is well known and has been extensively discussed elsewhere (Zellweger, 1965). It suffices to recapitulate here that meiosis of a gonial cell with balanced D/G [15/21] translocation can lead to 3 different viable gametes. It is generally presumed nowadays that the D/G element and the two 'homologous' chromosomes D [15] and G [21] are unable to form a synaptic junction regularly in the prophase of meiosis I. They do not form normal bivalents and hence segregate independently from each other. Although 8 different gametes are theoretically conceivable, only 3 gametes have been found to be viable. After fertilization with a normal gamete of the opposite sex, they lead to zygotes with the following karyotypes: (a) zygote with normal complement; (b) zygote with balanced D/G translocation; and (c) zygote with unbalanced D/G translocation and partial trisomy G-21. The experience gained from a rather limited number of observations (Polani, Hamerton, Giannelli, and Carter, 1965) has shown that translocation mongolism occurs in about 20% of the offspring of mothers with balanced D/G translocation (or of the zygotes originating from ovogonia with balanced D/G translocation).

As to family B, one can conjecture that increased S.A. of the mother led to a D/G translocation in (some) ovogonial cells, perhaps pre-meiotically or during the early phases of meiosis I. It is likely to have been a *balanced* D/G translocation. The situation of meiosis for the ovogonial cells of the mother in family B (balanced D/G [15/21] translocation presumed) would be the same as for the mother in family A, i.e. the same 3 karyotypically different zygotes are possible, one of them with *unbalanced* D/G translocation and partial trisomy 21, as evidenced by the mongoloid child of this family. The sequence of events would then be: (a) increased S.A. of the mother; (b) formation of a balanced D/G translocation in one or more of her ovogonia; (c) irregular synapsis and independent segregation of the respective D and G chromosomes; (d) zygote with partial trisomy G; and (e) translocation mongoloid.

A similar assumption can be made for family D. The father in family D had an exceptional increase of S.A., which presumably was responsible for a spermatogonial G/G translocation in *balanced* form. If the translocation occurred between a 21 and a 22 chromosome three different types of viable zygotes could be expected, one with a normal karyotype, one with a balanced 21/22 translocation, and one with a partial trisomy 21, including the 21/22 translocation. If the G/G translocation occurred between the two 21 chromosomes only two types of zygotes are possible, one with monosomy 21 (not viable) and one with partial trisomy 21 including the 21/21 translocation, which would lead to mongolism.

These few observations suggest that increased S.A. in a parent may lead to offspring with translocation mongolism. Further observations are necessary to determine how often increased S.A. may cause translocation mongolism. However, increased S.A. cannot be the only cause of translocation mongolism, as evidenced by family C. Here all family members had normal S.A., which suggests another cause of translocation mongolism than parental S.A.

Increased S.A. was found not only in one parent of family A, B, and D, but also in the respective mongoloid child. In other words, increased S.A. was present in 2 consecutive generations of these families. This could indicate that the tendency toward increased S.A. may be transmitted as a

familial trait which seemingly follows an autosomal dominant pattern. Our limited data show that it is obviously neither a recessive nor a sex-linked trait. The observation of normal S.A. in family C does not contradict this assumption since nobody in this family showed increased S.A. The data presented here are too few to prove that increased S.A. is a heritable phenomenon. However, the data appear to be of sufficient interest to suggest further investigations in this field, especially since increased S.A. as a familial trait has also been observed in families with multiple cases of mosaicism (Abbo *et al.*, 1966).

Summary

Three families each with a case of sporadic translocation mongolism and one family with a familial translocation and translocation mongolism were studied with respect to satellite association (S.A.). Three mongoloids and one parent of each of them revealed increased S.A. The other parent of these 3 mongoloids and the fourth translocation mongoloid and both of his parents had normal S.A. The data suggest that increased S.A. may be one but not the only cause of translocation mongolism, and that the tendency toward increased S.A. may be transmitted as a familial, perhaps inherited, trait.

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