Enlarged Satellites as a Familial Chromosome Marker

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RECENT ADVANCES in the techniques of cytogenetics have made possible the detailed examination of human chromosomes, both in normal and abnormal individuals. Initial efforts were directed toward establishing the major identifying features of the normal human chromosome complement, and toward investigating various disease syndromes related to gross chromosomal aberrations. (For reviews see Hirschhorn and Cooper, 1961-a; Miller, Cooper, and Hirschhorn, 1961.) Recently, technical improvements have made possible a more detailed examination of less obvious chromosomal details. Such details are the satellite bodies, secondary constrictions, chromosome associations, and possible population polymorphisms with respect to length and arm ratios of homologous chromosomes. This paper will present some observations on the small satellite bodies extending from the short arms of the acrocentric autosomes, a normal feature of the human chromosome set (Fig. 1).

Satellited chromosomes are well known to cytologists working with other organisms, and it is believed that the satellite body arises because of a secondary constriction of the chromosome near its end (Heitz, 1931). Theoretically, any length of chromosome distal to a secondary constriction may be considered to be a satellite body, but for the purposes of this paper, we shall consider only those secondary constrictions of the short arms of the acrocentric chromosomes which pinch off a tiny length of the chromosome, seldom longer than it is wide. The region of the chromosome near the secondary constriction has been shown, in plants, to be the nucleolar organizing portion of the chromosome (Heitz, 1931), and it has been suggested that the satellite regions of human chromosomes have a similar function (Chu and Giles, 1959; Ohno, Trujillo, Kaplan, and Kinosita, 1961).

Early workers in this field identified two pairs of satellited chromosomes (Tjio and Puck, 1958-a; Chu and Giles, 1959), but at the time of this writing almost all investigators agree that all five pairs of acrocentric chromosomes are capable of bearing satellites, or do in fact carry them at all times. Our studies have led us to the conclusion that the number of observable satellited chro-

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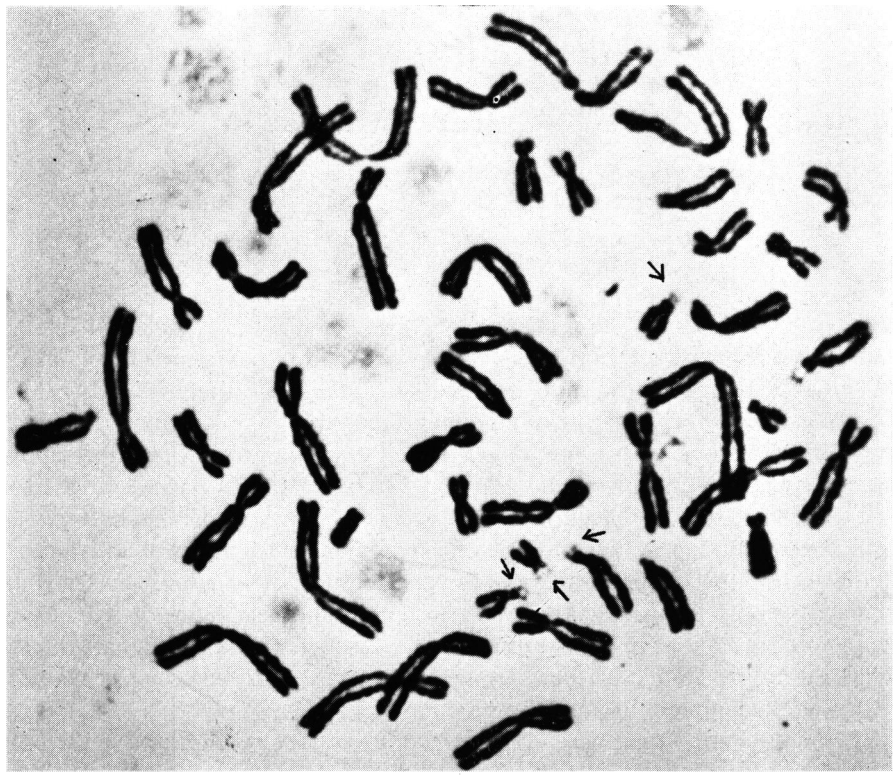


FIG. 1. Metaphase chromosomes from peripheral blood leukocyte culture of normal subject. Note satellite bodies on several acrocentric chromosomes (shown by arrows). X-1200.

mosomes is quite constant among different cells of the same individual but may differ markedly and consistently among different individuals. This observation has been made by others (Miller, 1961). Superimposed upon this variability between individuals are technical variations. At present our techniques are barely adequate to permit visualization of the tiniest satellites, and in those subjects who show a consistent pattern of satellited and nonsatellited acrocentric chromosomes, the nonsatellited ones may actually bear satellites whose size is below our power of resolution. Our microscopic observations have suggested that this is so, and that it is probable that all the acrocentric autosomes are always satellited, although sometimes undemonstrably so. Unfortunately, photographic demonstration of this fact has not been feasible to date, and we therefore offer this information as an impression only.

Attention was drawn to the human chromosomal satellites when Tjio, Puck and Robinson (1960) reported two patients with Marfan's syndrome in whom there was asymmetry of the satellites on one pair of chromosomes. One member of the pair had satellites which were much larger than those of its homologous partner. In one case the enlarged satellite was carried on a chromosome in the 13 to 15 group; in the other patient it was carried on a chromosome of the 21 to 22 group. It was suggested that the presence of Marfan's syndrome in

the two patients might be due to the abnormal enlargement of the satellite bodies. Other workers have noted enlarged satellites in subjects with various abnormalities (Buckton and Harnden, 1961), but no distinct relationship has been established between the presence of such enlarged satellites and any particular pathologic entity. In the case of Marfan's syndrome, other patients with this clinical condition have been studied and there does not seem to be any constant relationship between the presence of that syndrome and satellite enlargement (Ford, 1960; Hirschhorn and Cooper, 1961-b). That satellite asymmetry is compatible with normal development was suggested by Tjio and Puck (1958-b) when they reported such asymmetry in two normal individuals. We have briefly reported two families in whom markedly enlarged satellites were present on a single chromosome in several members of each family (Cooper and Hirschhorn, 1961). The present report is a more detailed description of the findings in these two families.

More recently, Ellis and Penrose (1961) have reported enlarged satellites and multiple malformations in the same pedigree. In a kindred of sixty-six individuals in three generations, three out of five members studied chromosomally had enlarged satellites. While many other members of the pedigree showed varying central nervous system abnormalities, the bearers of the enlarged satellites were all normal with the exception of one who apparently had an acquired type of blindness.

FAMILY ONE

Both of the families to be discussed here came to our attention because of an abnormal child. The pedigree of the first family is shown in Fig 2. The propositus was an 18 year old male, born in Puerto Rico. He was the first child of this marriage, although his mother had borne a normal child by a previous marriage. At the time of his birth the mother was 27 years old and the father 45. The pregnancy and birth were uncom-

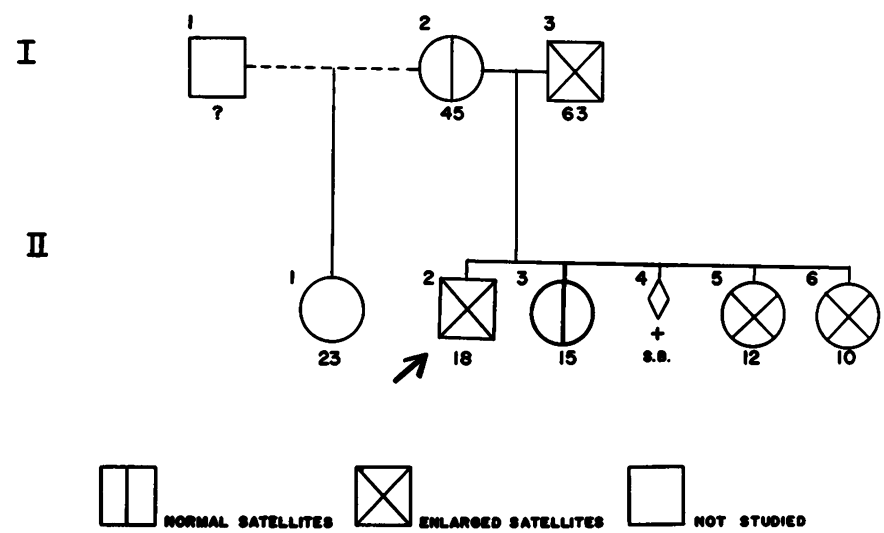


FIG. 2. Pedigree of family one. Figures beneath symbols indicate ages at time of study. S. B. - stillbirth.

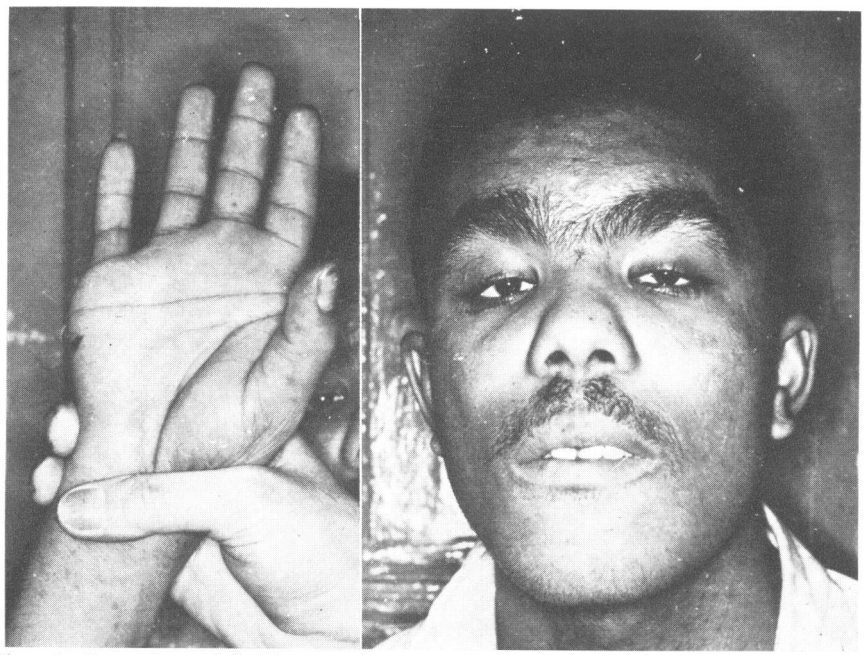
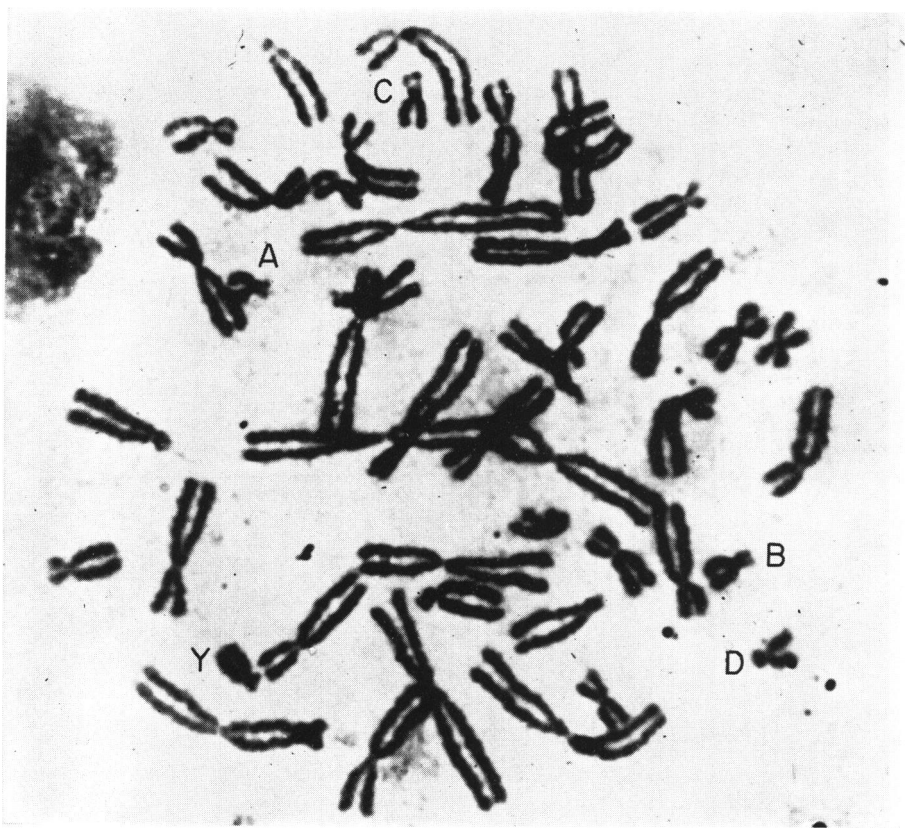


FIG. 3. Propositus of family one. Note transverse palmar crease, epicanthal folds.



plicated. The propositus developed normally at first but never learned to speak, although he understood commands. For 9 months before his admission to Bellevue Hospital he had complained (by signs) of abdominal distress. During a clinic visit for investigation of that complaint he had a convulsive seizure and was hospitalized.

On examination, he had a mongoloid appearance (Fig. 3) with mild bilateral eyelid ptosis. Definite epicanthal folds were present bilaterally, and there was flattening of the bridge of the nose. There was a unilateral simian palmar crease. The patient was unable to articulate clearly, his vocalization consisting of grunts. No other abnormalities were found on physical examination. Roentgenographic examination of the upper gastrointestinal tract showed abnormal filling of the duodenal bulb but no specific pathologic condition. All routine laboratory tests were normal. While under observation it was felt that his convulsive "seizures" were probably of psychiatric origin rather than due to any central nervous system pathology. His dysarthria, however, was thought to be on an organic basis.

The mother and father were both healthy, with no history of familial illnesses. The mother had had one stillborn child (II-4, Fig. 2) but no information could be obtained about it. Of the three younger sisters, the oldest and youngest (II-3 and II-6) were completely normal. The third sister (II-5) had rheumatic fever in early childhood and had evidence of mitral valvular disease, probably stenosis and insufficiency. She was otherwise normal, although she was said to be slow in school.

Chromosome preparations were made by our modification (Hastings, Freedman, Rendon, Cooper, and Hirschhorn, 1961) of the standard peripheral blood leukocyte culture

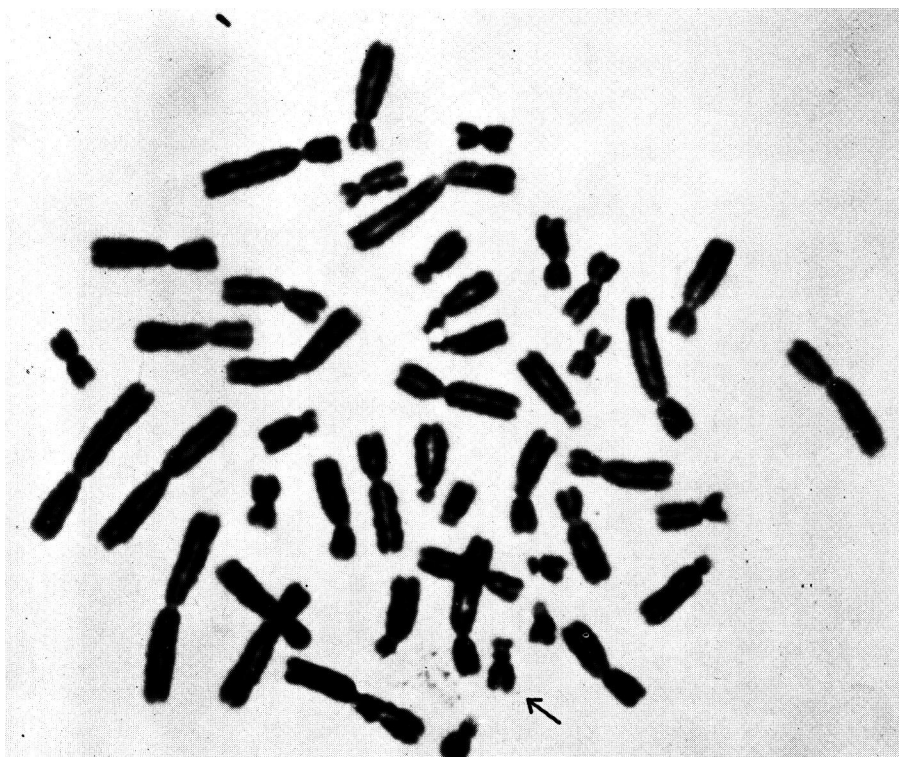


FIG. 4. Metaphase chromosomes of propositus of family one: a. *(left)* Chromosomes marked A and B show normal-sized satellites. Chromosome marked C shows enlarged satellites. Chromosome marked D shows no demonstrable satellites. Y chromosome is also indicated. X 1200. b. *(above)* Chromosome with enlarged satellites is indicated by arrow. X 1200.

method of Moorhead *et al.* (1960). Examination of such preparations from the propositus (Fig. 4) revealed a chromosome number of forty-six. It can be seen that two of the small acrocentric chromosomes of group 21 to 22 have satellites which are of normal size. A third has markedly enlarged satellites, while the fourth does not show any satellites in this preparation. The karotype of the patient (Fig. 5) is normal in every other respect. We have identified the chromosome with enlarged satellites as number 22, although this cannot be decided with certainty. Our basis for this identification is the consistent finding in group 21 to 22 of two morphologically similar chromosomes with easily discernible satellites, another of slightly differing morphology with no or poorly visible tiny satellites, and finally the chromosome bearing the enlarged satellites. It is likely that there are two members each of pairs 21 and 22. The size, arm ratio, and satellite morphology of the chromosome pair bearing normal sized satellites suggests that this is the number 21 pair, the chromosome with poorly visible satellites being one member of the number 22 pair. The chromosome carrying the enlarged satellites, by exclusion, appears to be the other member of pair 22. The validity of these criteria for distinguishing chromosome number 21 from number 22 is, however, still open to question.

Chromosome examination was performed on other members of the family. In Fig. 6 are shown the small acrocentric chromosomes of the members of the family. The patient's father and two sibs have similarly enlarged satellites on one of the chromosomes in this group. His mother and another sib have normal satellites. The parents and sibs were healthy, except for one sister with rheumatic heart disease. None of the other family members exhibited any of the features of mongolism shown by the propositus.

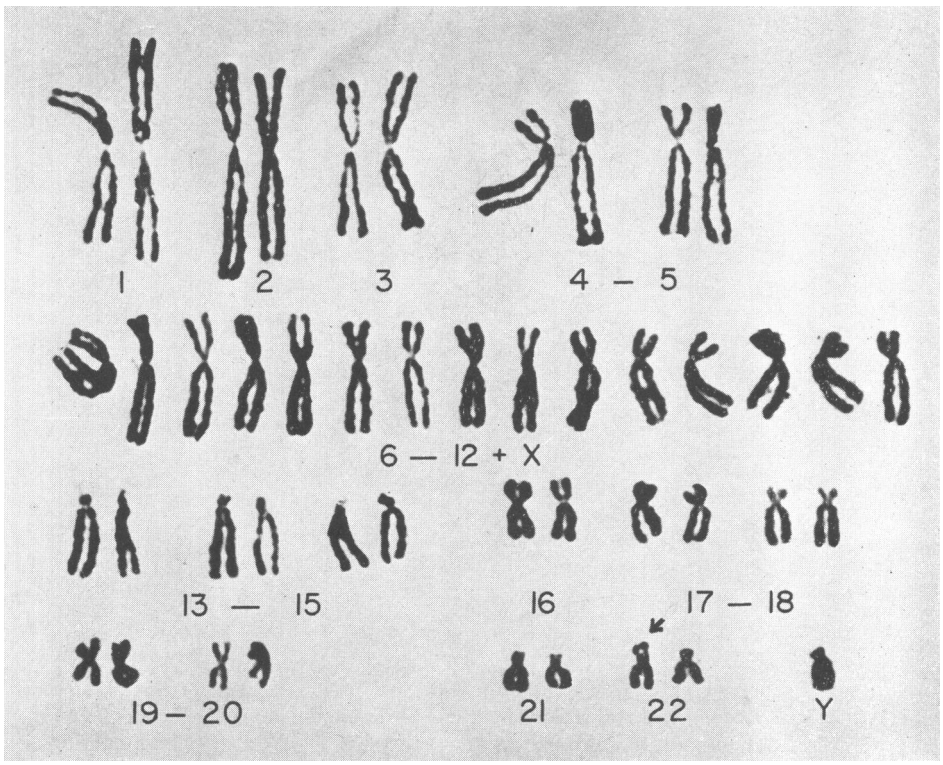


FIG. 5. Karyotype of propositus of family one.

It must be noted that an occasional cell may be found in any peripheral blood culture preparation where satellite asymmetry appears to exist. This is usually not a constant finding and can be attributed to technical variation. However, in the preparations from all individuals reported in this paper as carrying a chromosome with enlarged satellites, at least twenty-five to fifty cells were carefully examined, and in those subjects in whom it was present, satellite asymmetry could be observed in the majority of the cells studied (over 80 per cent).

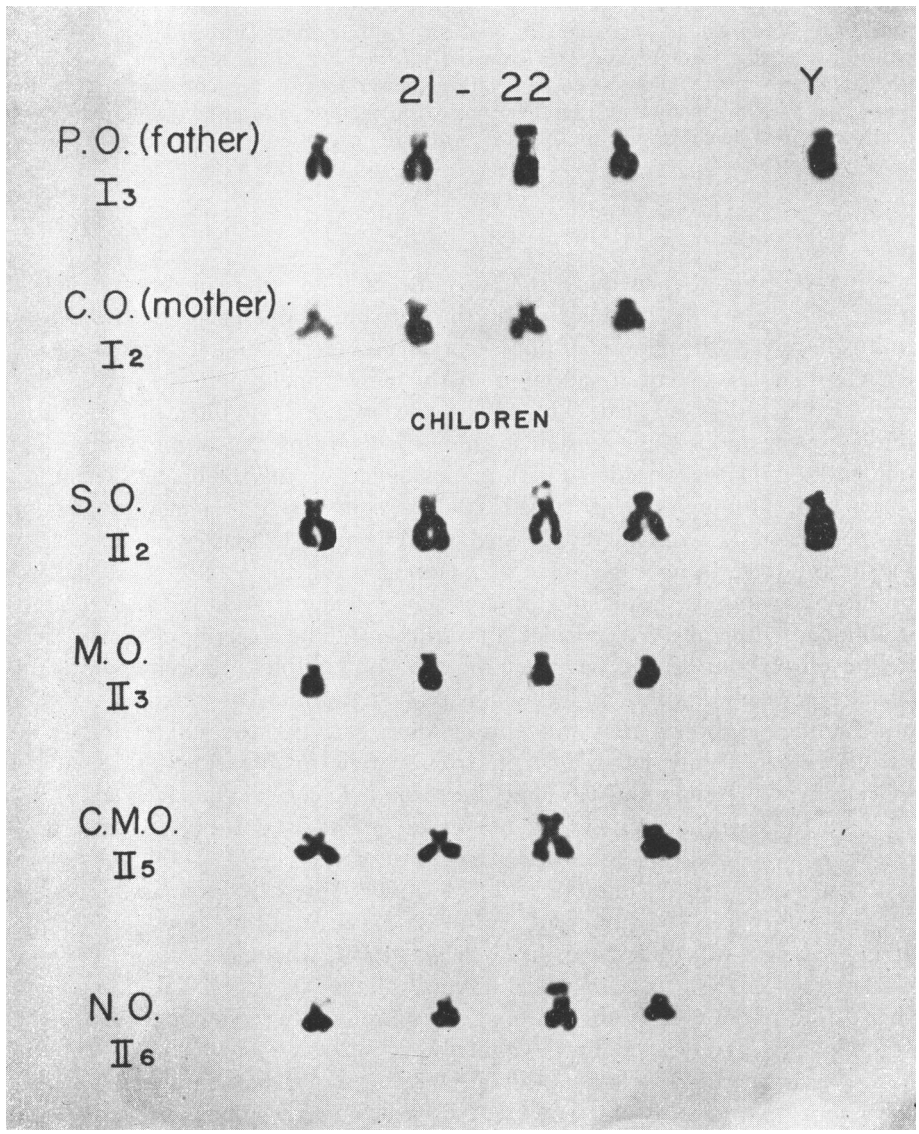


FIG. 6. Small acrocentric chromosomes of all members of family one available for study. Note enlarged satellites on one chromosome of this group in subjects I-3, II-2, II-5, and II-6. No satellite enlargement in subjects I-2 and II-3.

FAMILY TWO

In the second family (Fig. 7), the propositus was an 18 year old boy with clinical mongolism (Fig 8). He was observed when he developed acute lymphoblastic leukemia. This patient has been described in detail elsewhere (Hirschhorn, Cooper, Sklarin, Rendon, and Meyers, 1961). Chromosome examination (Figs. 9 and 10) revealed forty-six chromosomes with evidence of a translocation and fusion involving two small acrocentrics. There was also an enlarged satellite on one member of the 13 to 15 group of long acrocentrics. On morphologic grounds, we have tentatively identified this chromosome as a number 13. Here, as previously, there is still doubt as to the validity of such morphologic identifications. Chromosome examination of the other members of this family (Fig. 11), all of whom were mentally and physically normal, revealed that several of them also carried a chromosome with enlarged satellites. It can be seen that the patient's father and two sisters show satellite enlargement on one of the chromosomes in this group. The patient's mother and brother showed no satellite enlargement. The karyotypes of all examined members of the family, with the exception of the propositus, were otherwise normal.

DISCUSSION

It is of interest that in the first family the satellite enlargement consisted of an increase primarily in the size of the satellite body itself. In the second family, however, the length of the secondary constriction has been increased to a considerable extent in addition to the enlargement of the satellite body itself, which is less marked. This makes the enlarged satellites in the second family appear to lie some distance from the body of the chromosome. The grandchild indicated in Fig. 11 shows evidence of this elongated secondary constriction, although the enlarged satellite body itself is not very evident. This, however, is a photographic artifact. The mitotic figures obtained from this subject were in an early stage of metaphase and the satellite material was not heavily condensed, making photographic demonstration of the enlarged satellite body difficult. We consider this child also to be a carrier of the enlarged satellite chromosome. The fact that the type of satellite enlargement remains constant in each family, and the apparent segregation of this character in both families, suggests that the chromosome carrying the enlarged satellite is transmitted in Mendelian fashion from parent to offspring, and that the replication of the satellite body and the secondary constriction is exact.

The actual mechanism of satellite enlargement is entirely speculative at present. One possibility is that the enlargement of the satellite body and secondary constriction region do not represent any quantitative change in genetic material but reflect alterations of coiling and condensation due to unknown but nevertheless hereditary causes. Such alterations might not affect the information stored in the genetic material but only change its superficial morphology. During interphase, when the chromosomes are in their extended state, this morphologic difference might be obliterated; however, some functional difference between this and other normally satellited chromosomes might persist with respect to nucleolus organization, chromosome replication, or disjunctional behavior. On this basis a hypothesis may be constructed to explain how the enlarged satellite carried by the father of family two may have resulted in a gamete carrying an attached pair of group 21-22 chromosomes. The hypothesis

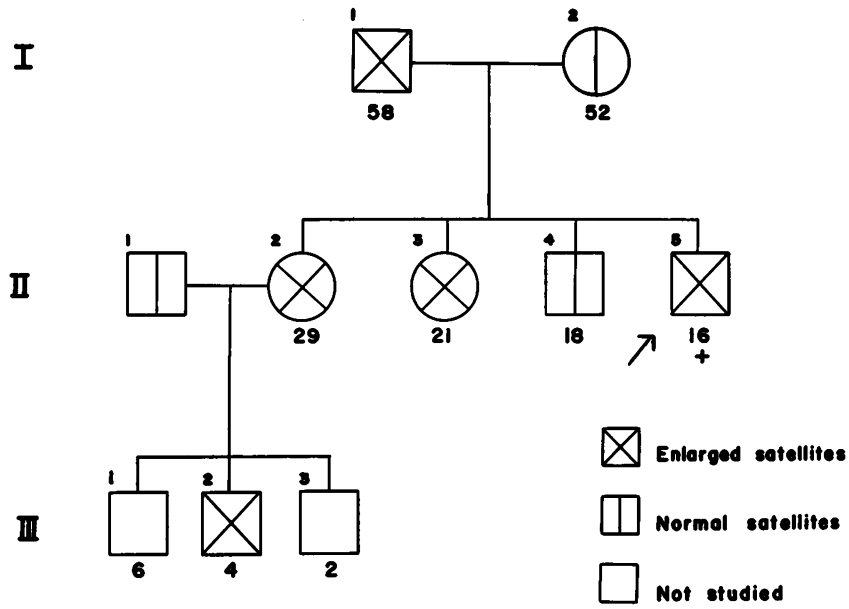


FIG. 7. Pedigree of family two.

requires that two small acrocentric chromosomes and the enlarged satellite chromosome participated in the organization of one nucleolus. Some abnormality in function of the enlarged satellite chromosome might have been conducive to simultaneous breakage of both small acrocentric chromosomes, and subsequently they may have fused to form a double-21 (or 21/22) chromosome. This cell might then have gone on to form a spermatozoon carrying both the translocation chromosome and the enlarged satellite chromosome, and on fertilizing a normal ovum, produced the propositus of family two.

Other possible causes of satellite enlargement are duplications of localized chromosome segments and inversions. We are inclined to doubt the possibility of inversion as the cause in the two families under discussion, since a pericentric inversion would be expected to result in a secondary constriction in the long arms, which was not found. Similarly, a paracentric inversion of the short arms would not account for the apparent absolute increase of chromosomal material on the short arm side of the centromere of the involved chromosome in family one (as shown in Fig. 6). Neither does it account for the elongated secondary constriction region in family two. About the possibility of duplication of a short segment of genetic material we can say little except that if satellite enlargement is caused by such a duplication, the increase in genetic material appears to be relatively innocuous in these families.

Another alternative exists, especially with regard to the first family described. It is possible that in this family the enlarged satellites are actually translocated pieces of another chromosome. While the translocated piece would be detectable as an enlarged satellite, the chromosome from which the piece came might well escape detection with our present techniques. As illustrated in

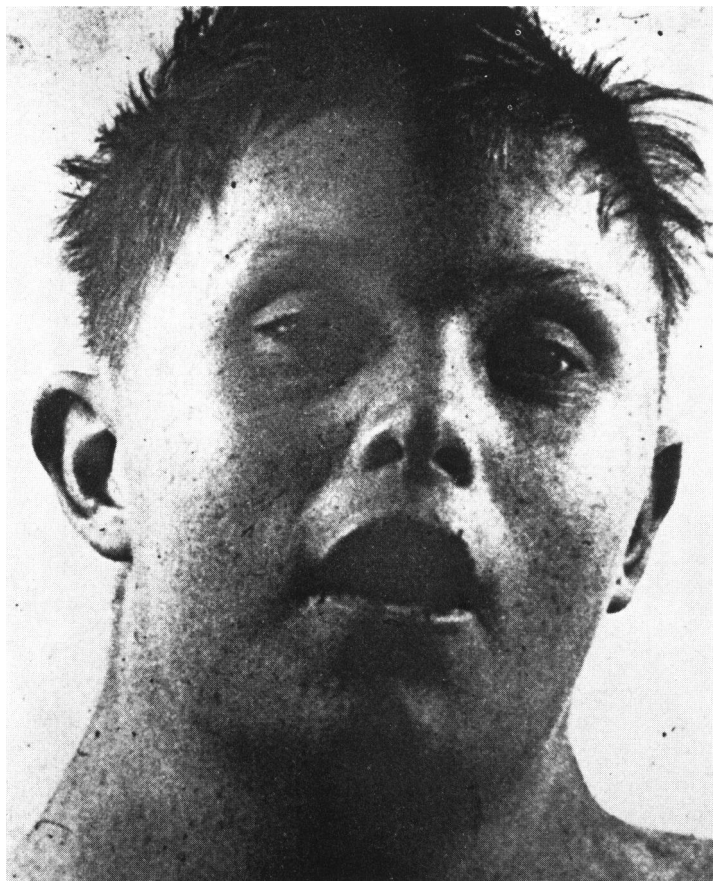


FIG. 8. Propositus of family two. Note mongoloid facies.

Fig. 12, there may have been a translocation between two of the small acrocentrics. If meiosis occurs after such a translocation, four types of gametes are possible. One type is completely normal. Another has an excess of genetic material, appearing as an enlarged satellite. A third type has the normal quantity of genetic material, since the portion missing from one chromosome is carried on the other as an enlarged satellite. This is the so-called balanced translocation heterozygote. Still a fourth type, missing a portion of one chromosome, is possible. Types one and three (Fig. 12), on fertilization, should produce normal individuals, unless there is a position effect in type three. Types two and four may or may not be abnormal, since type two will be partially trisomic for a portion of genetic material, and type four is partially monosomic for the same portion. It is possible that in the first family described the normal father and two daughters who carried the enlarged satellites were all of type three. The abnormal propositus may have been of type two and his abnormalities might be due to partial trisomy for chromosome 21. The stillborn child in family one Fig. 2, (II-4) may have represented one of the unbalanced zygote types. However, it seems more likely that erythroblastosis may have

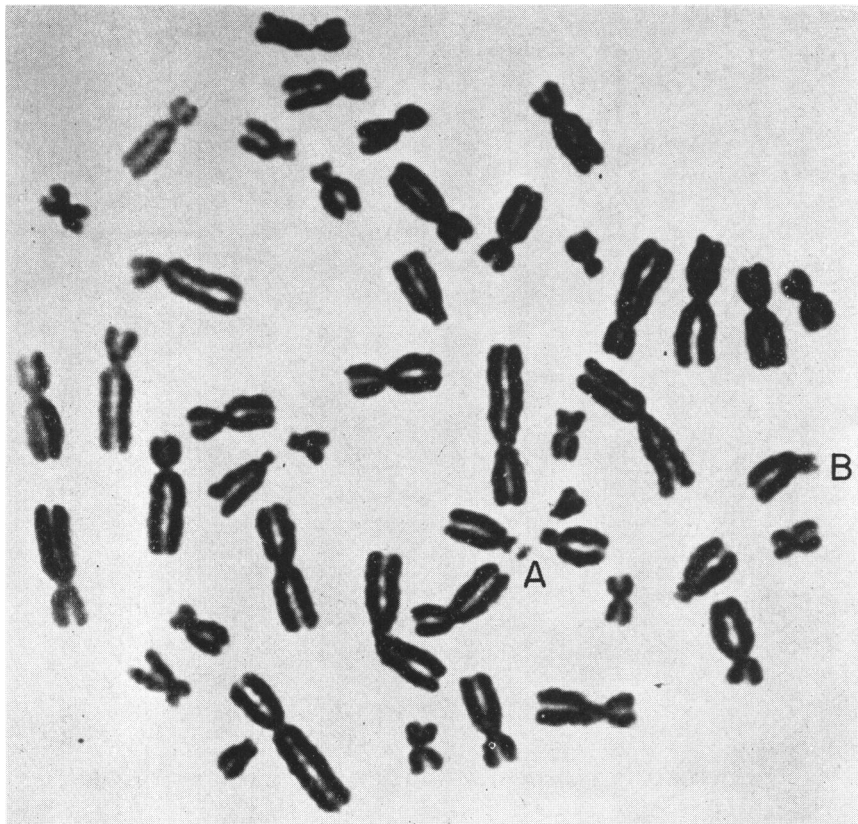


FIG. 9. Metaphase chromosomes of propositus of family two. Enlarged satellite is indicated at A; normal satellite is indicated at B. X-1200.

been the cause of the stillbirth. Table 1 shows that the mother of family one is Rh negative, her husband is Rh positive, she had at least one Rh positive child (the propositus), and the unstudied child of the first marriage may have been another. It may be significant that the remaining healthy children are all of the rare Rh positive type, $R^u_o r$ (ccD^uee), where the antigen gives a very weak reaction with anti-Rh_o (anti-D) serum.

The translocation hypothesis may well be the explanation of the satellite enlargement and the abnormal propositus of family one, but such an explanation will not suffice for the second family. There the propositus apparently had complete trisomy for the genetic material of chromosome 21, an abnormality sufficient to account for his pathologic condition. The enlarged satellites seem to have played no direct part in producing this clinical picture, although, as indicated earlier, it cannot be determined at this time whether the presence of enlarged satellites in the patient's father may have in some way affected spermatogenesis and increased the probability of trisomy for chromosome 21.

Although these and other hypotheses may be advanced relating the abnormality of the propositi to the presence of enlarged satellites, we have no definite evidence either supporting or refuting them.

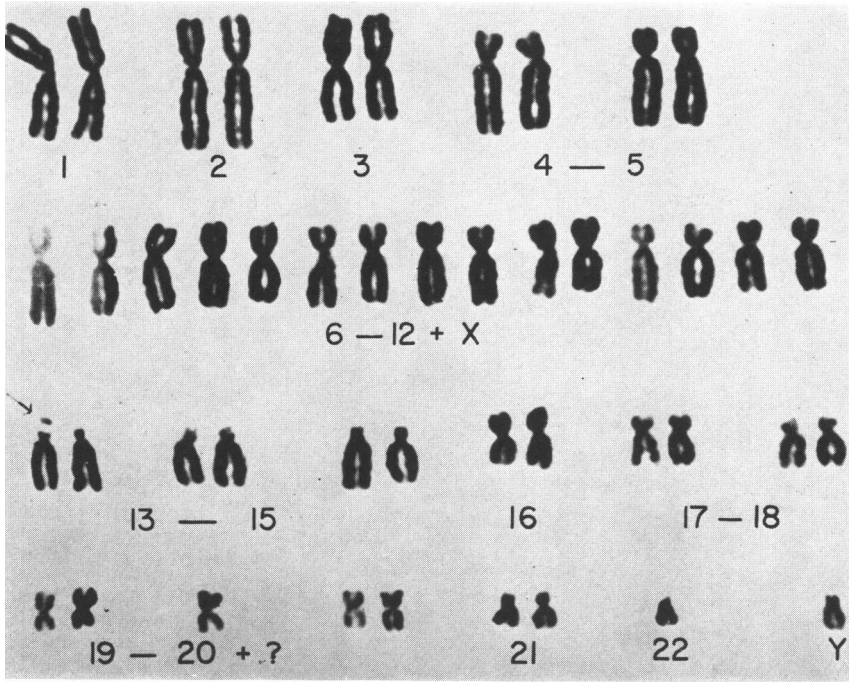


FIG. 10. Karyotype of propositus of family two.

The occurrence of a patient with physical abnormalities possibly due to a chromosomal aberration in each of these families should not be considered as evidence that the possession of enlarged satellites is conducive to such anomalies, since the abnormal family member was the propositus in each case. The fact that all other carriers of enlarged satellites in both families were normal demonstrates that satellite enlargement is compatible with normal development, and casts doubt on any direct causal relationship between the enlarged satellites and the abnormalities found in the propositi, except perhaps in the case of the translocation hypothesis for family one.

There is still a strong possibility that the finding of enlarged satellites in these propositi was fortuitous and reflects a relatively high frequency of such satellite enlargement among all persons. The question to be resolved is whether or not such satellite enlargement exists, and is transmitted in familial fashion among the general population, in families not ascertained through an abnormal member. Preliminary studies conducted at this laboratory indicate that such is the case, and further work is being done to verify this observation. At the present time, it seems justifiable to say that satellite size and length of secondary constriction are both subject to considerable variation within the general population, although they remain relatively constant within the individual. This constancy seems to be hereditary.

Whatever the cause, and whatever the pathologic potentialities for offspring, it appears that there exist within the general population phenotypically normal individuals who have morphologically detectable chromosome variants. Such

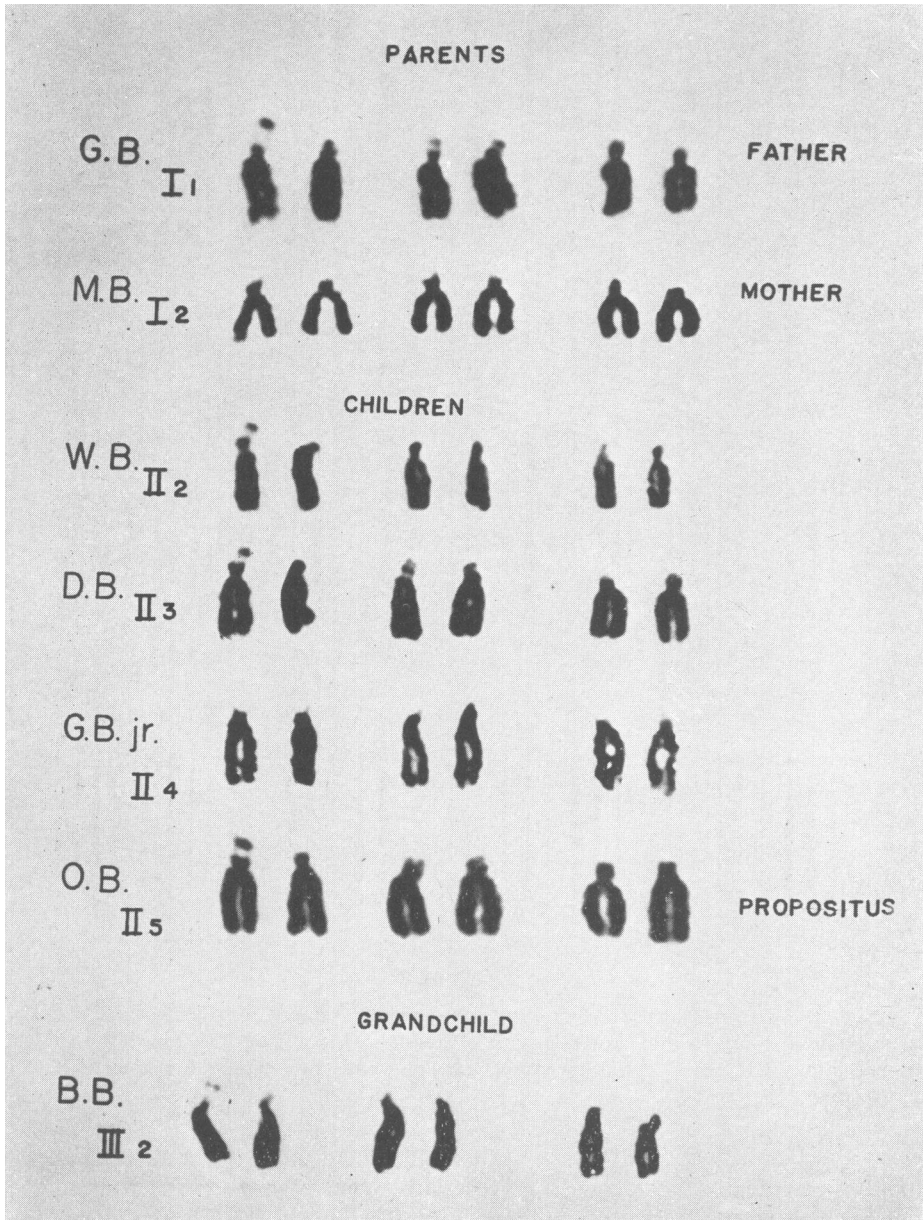


FIG. 11. Long acrocentric chromosomes of all members of family two available for study. Note enlarged satellites on one chromosome of this group in subjects I-1, II-2, II-3, and II-5. No satellite enlargement in subjects I-2 and II-4. Subject III-2 shows elongated secondary constriction. (See text.)

individuals are exemplified by the normal carriers of a giant-satellited chromosome in the two families discussed in this paper.

The finding of such variability in chromosomes from normal subjects sug-

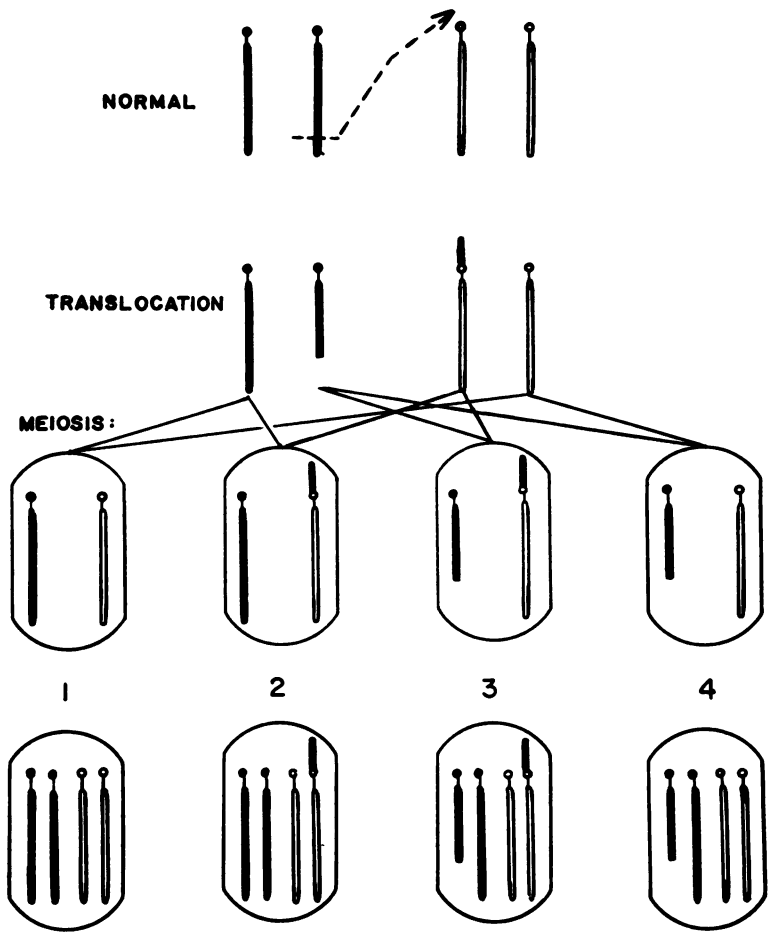


FIG. 12. Diagram illustrating satellite enlargement produced by translocation of a part of one chromosome to the satellite region of another chromosome. Meiosis following this translocation will produce four types of gametes, and four types of zygotes following fertilization. (See text.)

gests that great care be exercised in interpretation of chromosomal abnormalities, especially those classed as deletions, translocations, and other smaller morphologic variants. Family studies must be done in such cases to rule out the possibility of variation within the range of normal. Any attempt to correlate satellite variants with specific disease syndromes is particularly hazardous in the absence of multiple examples of the same syndrome.

LINKAGE STUDIES

The straightforward transmission of a chromosome with a recognizable characteristic now enables us to attempt to perform linkage studies with the

TABLE 1. BLOOD GROUP AND SERUM FACTOR STUDIES IN TWO FAMILIES

Family	Pedigree No.	Satellite enlarged	Blood groups: ABO	Rh	MN S	P	Fy^a	Hp	Gm: a	Gm: b	Gm: x	Gm: c	Gc (Group specific)
1	I-1	.....	.....	....	....	....	....	....	....	....	....	....	....
	I-2	—	0	rr	NN	+	+	1-1	+	+	—	—	2-1
	I-3	+ (22)	0	$R_0R_0^{u*}$	MM	+	+	2-1	+	—	+	—	1-1
	II-1	.....	.....	....	....	....	....	....	....	....	....	....	....
	II-2	+ (22)	0	R_0r	MN	—	+	1-1	+	+	—	—	1-1
	II-3	—	0	R_0^ur	MN	+	—	2-1	+	+	—	—	1-1
	II-4	.....	.....	....	....	....	....	....	....	....	....	....	....
	II-5	+ (22)	0	R_0^ur	MN	+	+	2-1	+	—	—	—	2-1
	II-6	+ (22)	0	R_0^ur	MN	+	+	2-1	+	—	—	—	2-1
2	I-1	+ (13)	A_10	rr	NN ss	+	+	2-1	—	+	—	—	2-1
	I-2	—	A_20	R_1r	MN ss	+	+	2-2	+	+	—	—	1-1
	II-1	—	A_2A_2 or A_20	R_2r or R_2R_0	MM Ss	+	....	2-2	+	—	+	—	1-1
	II-2	+ (13)	A_10 or A_1A_2	R_1r	MN ss	+	....	2-2	—	+	—	—	2-1
	II-3	+ (13)	0	rr	MN ss	+	+	2-1	—	+	—	—	2-1
	II-4	—	A_20	rr	NN ss	+	+	2-1	—	+	—	—	2-1
	II-5	+ (13)	....	.....	....	....	....	....	....	....	....	....	....
	III-1	.....	A_1—	R_2r	MN Ss	+	....	2-2	+	+	—	—	1-1
	III-2	+ (13)	A_2—	R_2r	MN Ss	+	....	2-2	+	+	—	—	2-1
	III-3	.....	A_1	R_1R_2	MN Ss	+	....	2-2	+	+	+	—	1-1

Transferrins: all CC. All Lu^a negative.

*R_0^u = factor reacting weakly with anti-D serum.

Hp= haptoglobins. Gm= Gm groups. Gc= Group-specific serum factor.

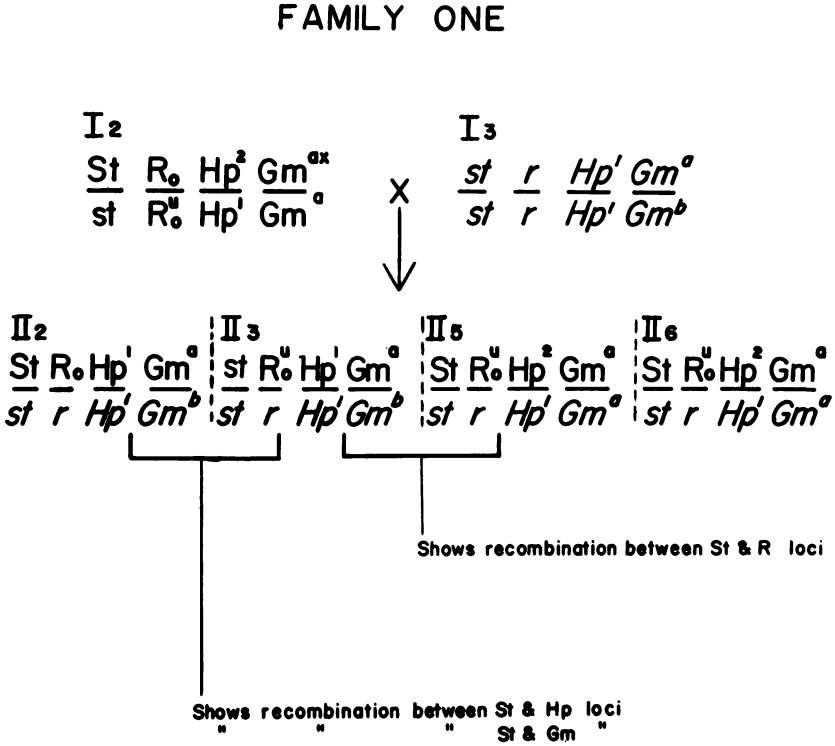


FIG. 13. Matings for factors studied in family one: St= enlarged satellite; st= normal-sized satellite. Hp= haptoglobin locus; Gm= Gm group locus (Steinberg *et al.*, 1961); R, r= Rh blood group loci. Paternally contributed factors shown in upright symbols; maternally contributed factors shown in slanted symbols.

purpose of localizing other known genes on this marked autosome. This represents a step toward the goal of establishing linkage maps of the human autosomes. To this end, both families presented here are being studied with regard to blood groups, transferrins, haptoglobins, Gm-groups and group-specific serum proteins. The information available to date is summarized in table 1. The data for family one provide linkage information regarding the *Rh* locus, the haptoglobin locus, and the *Gm* locus. For the remainder of the factors studied this is a noninformative mating. As shown in Fig. 13, there is evidence of recombination between each of these loci and the enlarged satellite. This is presumptive evidence that the *Rh, Hp* and *Gm* loci are either not carried on chromosome number 22 (or 21 if our identification is incorrect), or are carried at a sufficient distance from the satellited end of the chromosome to permit frequent recombination to occur.

The data for the second family provide linkage information regarding the A_1A_2BO locus, the haptoglobin locus and the group-specific serum protein locus (Hirschfeld, Jonsson and Rasmusson, 1960). No information is obtained regarding the other factors tested. Fig. 14 shows that recombination has occurred between each of these loci and the enlarged satellite. This is presumptive evidence that the A_1A_2BO, *Hp* and *Gc* loci are not carried on chromo-

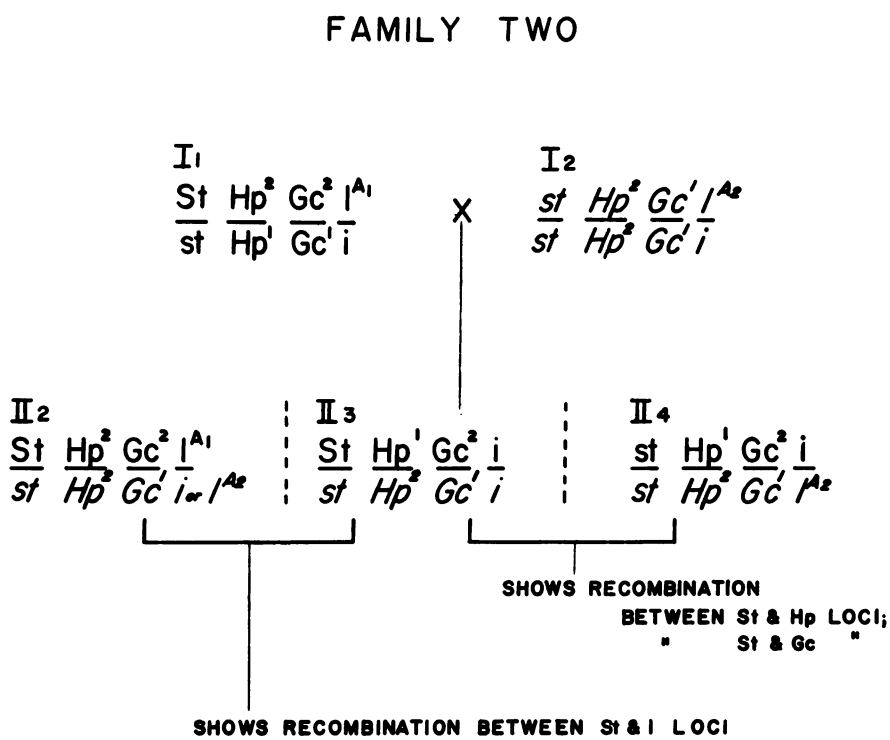


FIG. 14. Matings for factors studied in family two. Gc= group-specific serum factor; I, i= ABO blood group locus. Other symbols as in Fig. 13.

some 13, or at least are located at a considerable distance along the chromosome away from the satellite end.

No positive evidence was obtained of linkage between any factors tested and the enlarged satellite present in that family. This, of course, was not surprising, considering the small size of the sample examined. However, the study does demonstrate the usefulness of morphologic chromosome variants in linkage studies.

SUMMARY

This study indicates that a structural chromosomal variant, enlarged satellites, exists and is compatible with normal development. This structural variant is reproducibly transmitted from one generation to the next in mendelian fashion. Further study is required to determine the frequency of this and other structural variants in the general population and to use them as chromosomal markers in the mapping of human chromosomes. Linkage studies, using the enlarged satellites and various blood groups and serum factors, are described.

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