Occurrence of a Presumptive C/B Translocation Carrier [46,XY,t (? Cp-; Bp+)] in a Family of D/G Translocation Carriers [45,D-,G-,t (DqGq)+]*

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Though there have been many reported instances in which two or more sibs have been found to have an abnormal karyotype variation such as reported by Penrose, Ellis, and Delhanty (1960), and by Walker and Harris (1962), only rarely do the chromosomal

aberrations differ in the affected members of the same kindred, e.g. Marsden *et al.* (1966), Summitt and Atnip (1966).

The present report describes such a family in which a t(DqGq) abnormality has been transmitted through at least four generations, associated in one sibship with a rare type of translocation involving a group B and probably a group C chromosome.

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FIG. 1. Pedigree of family containing both a t(DqGq) and a t(?Cp-;Bp+) chromosomal abnormality.

Family History

The proband (IV.5) was a 1-year-old Caucasian male with the characteristic features of Down's syndrome. He was the only child of his mother (III.12) and father (III.11) who were 23 and 26 years of age at the time of his birth. There was no history of the occurrence of Down's syndrome or other familial defects in the immediate family. It was noted, however, that the father's maternal aunt's sixth child was diagnosed as having Down's syndrome (III.6). Chromosome studies, however, were not performed. The first child (IV.6) of a cousin of the mother of the proband also had Down's syndrome. Chromosome studies carried out elsewhere indicated that this child had 47 chromosomes with G trisomy (47,XY,G+).

The proband's mother (III.12) was the first of two phenotypically normal sibs. Six additional pregnancies of the maternal grandmother and her second husband resulted in two early abortions and four phenotypically normal children (Fig. 1).

Methods

Chromosome studies were performed on the leucocytes from peripheral blood by a modification of the method of Moorhead *et al.* (1960). In addition to a microscopical examination of the chromosomes of at least 20 cells, several karyotypes were prepared from photographic enlargements for each person included in this study.

Results

The chromosomal studies of the proband (IV.5) showed that he had an unbalanced translocation resulting in an excess of G group chromosome material [46,XY,D-,t(DqGq)+]. The same translocation in the balanced form was found in the proband's mother (III.12) and grandmother (II.9) (Fig. 2). The same balanced translocation was also found in the mother's sister (III.13), two of her three half sisters (III.15, III.16), and a maternal uncle (II.7).

FIG. 2. Karyotype of the t(DqGq) carrier mother (II.9) of the t(?Cp-;Bp+) son (III.19).

In contrast to the above findings, a half brother (III.19) of the proband's mother was found to have a consistent abnormality resulting from a probable translocation of a portion of the short arm of a C group (6-12+X) chromosome to the short arm of a group B chromosome. This resulted in a chromosome which could not be distinguished from the No. 2 pair of chromosomes in the A group (Fig. 3). This phenotypically normal child was the youngest member of his family, his mother being 39 years of age at the time of his birth; while his father was 40 years of age. Chromosome studies of the father of this child (II.10) were normal, while the mother was a t(DqGq) carrier. The chromosomal findings are summarized in Table I.

While no specific evidence for an inherited defect

could be found, it was noted that there were various random abnormalities in addition to the t(DqGq) translocation in the leucocytes of his mother (Fig. 4). There was also, in two cells, an extra chromosome of group C size and structure. The cells with these additional chromosome findings accounted for 5.3% of the 151 leucocytes studied from two blood samples obtained on separate occasions. It is of interest, in view of these chromosomal findings, that her dermatoglyphic patterns included such unusual findings as nine ulnar loops, a distal triradius on each hand, and a simian crease on one hand (Table II).

Blood group typing was done on this family for antigens A, B, D, C, c, E, e, M, N, S, s, P₁, K, k, Kp^a, Kp^b, Jk^a, Lu^a, Lu^b, Le^a, Le^b, and Sf^a

FIG. 3. Karyotype of the t(?Cp-;Bp+) carrier offspring (III.19) of the t(DqGq) carrier mother (II.9).

TABLE I
SUMMARY OF CHROMOSOMAL STUDIES*

Subject	Chromosome Counts					Total	Karyotype Analyses
	< 44	44	45	46	47		
I.1	—	—	7†	23	—	30	46,XX
II.7	—	3	24	—	—	27	45,XY,D-,G-, t(DqGq)+
II.9	8	6	95	2	—	111	‡45,XX,D-,G-, t(DqGq)+
II.10	1	1	2	28	—	32	46,XY
III.11	—	—	1	19	—	20	46,XY
III.12	—	3	34	1	—	38	45,XX,D-,G-, t(DqDq)+
III.13	—	2	24	—	—	26	45,XX,D-,G-, t(DqGq)+
III.15	1	3	22	—	—	26	45,XX,D-,G-, t(DqGq)+
III.16	1	2	21	—	—	24	45,XX,D-,G-, t(DqGq)+
III.17	1	—	—	22	—	23	46,XX
III.19	1	—	3	46	—	49	46,XY,t(?Cp-,Bp+)
IV.5	1	1	—	29	—	31	46,XY,D-,t(DqGq)+

* Chicago Conference (1966).
† Random losses.
‡ See also Fig. 4.

(Stoltzfus). The immunoglobulins Gm 1, 2, 3, 5, 6, 12, 13, and 14 were typed by the agglutination inhibition method of Steinberg and Wilson (1963). Haptoglobin (Hp), transferrin (Tf), and group-specific component (Gc) were separated by vertical polyacrylamide gel electrophoresis, as by Bias and Migeon (1967), and their types determined.

It is assumed that a loss of all or a portion of the short arms of the D and G group chromosomes involved in the interchange occurred. Heterozygosity of any marker locus rules out the possibility of that locus being on the deleted regions. At least one carrier of the translocation is heterozygous for the following loci: Rh, MNS, Fy, Lu, Hp, and Gc (Table III).

The likelihood of the pedigree phenotypes, if a particular locus lies on the relevant D or G long arm, was calculated with the assistance of the standard computer linkage programme of Renwick and Schulze (1961). Each likelihood, applying to a particular recombination fraction, was then combined with the initial probability of this recombination fraction over a range (0.4 for G and 0.5 for D) restricted by the map length of the chromosome arm. The sum of these final probabilities over this range is the final probability of assignment. For all loci tested, the probability of assignment is small, the highest being 0.04 that Rh lies on the long arm of a D chromosome against an initial probability of 0.03. The lod scores will be included in a subsequent publication (J. H. Renwick, 1970, in preparation).

Discussion

The most unusual aspect of this family is the birth to a t(DqGq) carrier female, of a child with a

FIG. 4. Chromosomal abnormalities found in six separate leucocyte metaphase cells from a t(DqGq) carrier (II.9). These include the following: 4A, exchange figure; 4B, endoreduplication; 4C, two large acentric fragments; 4D, large acentric fragment; 4E, isochromatid break; 4F, chromatid break.

TABLE II
DERMATOGLYPHIC FEATURES OF FAMILY MEMBERS

Generation	IV	III	III	III	III	III	III	III	II	II
Member	5	12	13	15	16	17	19	11	7	9
Side	L R	L R	L R	L R	L R	L R	L R	L R	L R	L R
<i>Digits</i>										
1	L ^u L ^u	L ^u L ^u	L ^u L ^u	W L ^u	L ^u L ^u	L ^u L ^u	W W	L ^u W	L ^u W	L ^u L ^u
2	L ^u L ^u	L ^u L ^u	L ^u L ^u	W L ^u	W L ^u	W L ^u	W W	L ^u L ^r	W L ^u	L ^u L ^u
3	L ^u L ^u	L ^u L ^u	L ^u L ^u	L ^u L ^u	L ^u L ^u	L ^u L ^u	L ^u W	L ^u L ^u	L ^u L ^u	L ^u W
4	L ^u L ^u	L ^u L ^u	L ^u L ^u	L ^u W	L ^u W	L ^u W	L ^u W	L ^u W	L ^u W	L ^u W
5	W W	L ^u L ^u	L ^u L ^u	L ^u L ^u	L ^u L ^u	L ^u L ^u	L ^u L ^u	L ^u W	L ^u L ^u	L ^u L ^u
Triradius	abs t	t t	t t	t' t'	t' t'	t t'	t t'	t t	t t'	t' t'
Hypothenar	V O	L ^r L ^r	L ^r L ^r	O O	O O	L ^c L ^r	O O	O O	O O	O O
<i>Interdigital</i>										
1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
2	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 L ^v	0 0
3	0 L	0 L	0 0	0 L	L L	0 L	0 L ^v	0 L	L ^v L ^v	0 L
4	0 0	0 0	W ^v L	L 0	W ^v 0	0 0	L 0	L 0	L L	L 0
Simian crease	abs +	abs abs	abs abs	abs abs	abs abs	abs abs	abs abs	abs abs	abs abs	abs +
Flexion creases 5th finger	2 1	2 2	2 2	2 2	2 2	2 2	2 2	2 2	2 2	2 2
Hallucal	A ^t A ^t	L ^d L ^d	L ^d L ^d	W W	W W	W W	W W	L ^d L ^d	W ^v W ^v	W L ^d
Great toe	W W	L ^f L ^f	L ^f L ^f	L ^f L ^f	L ^f L ^f	L ^f W	L ^f L ^f	L ^f L ^f	W W	L ^f L ^f

W = whorl, W^v = whorl vestige, A^t = arch tibial, V = vestige, L = loop, L^u = loop ulnar, L^r = loop radical, L^c = loop carpal, L^v = loop vestige, L^d = loop distal, L^f = loop fibular, O = no pattern.

translocation involving two different autosomes. In this child the chromosomal findings are interpreted as a probable translocation of a portion of the short arm of a C group chromosome to the short arm of a B group chromosome, resulting in a chromosome with the appearance of a submetacentric member of the A group. It should be noted, however, that in any single cell it was cytologically impossible to show conclusively the origin of the extra chromosomal material which appears to be translocated on to the B chromosome. It was, however, quite difficult in most of the karyotypes to locate the proper number of the larger C group chromosomes while an extra chromosome resembling smaller members of this group was encountered. In view of the normal phenotype of this child it is

believed that this karyotype abnormality represents a nearly balanced translocation.

The discovery of a second translocation within this family involving different chromosome members does, however, raise the question of the possible effect of chromosomal rearrangements on the remainder of the chromosomal constitution. One could attribute the occurrence of both the t(DqGq) and the t(?Cp-;Bp+) abnormalities in the same sibship to the chance association of two entirely independent events. It is, however, also reasonable to consider the possibility that the two abnormalities are related in a cause-effect manner, or are due to some common genetic or environmental factor.

The finding of cell breakage and aneuploidy in the t(DqGq) carrier mother of the child with the

TABLE III
BLOOD GROUPS AND SERUM TYPES

Individual	ABO	Rh	MNSs	P	Fy	Jk ^a	Lu	Le	Sf ^a	Hp	Gc	Gm	1	Inv
I.1	O	DCE/dce	MS/MS	+	(a+b+)	O	a-b+	(a-b-)	+	2-1	2-1	O	O	
II.7	O	DCE/DCe	MNSs	+	a+b+	+	a+b+	a-b-	O	2-2	1-1	+	O	
II.9	O	DCE/dce	MS/MS	O	a+b+	+	a-b+	a-b+	+	2-1	2-1	+	+	
II.10	A ₁	DCE/dce	MS/MS	+	a+b+	+	a-b+	a-b+	O	2-2	2-1	O	O	
III.12	O	DCE/DCe	MS/MS	+	a+b+	+	a-b+	a-b-	+	2-1	2-1	O	O	
III.13	O	DCE/dce	MS/MS	+	a+b+	+	a-b+	a-b+	O	2-2	1-1	O	O	
III.15	A ₁	DCE/DCe	MS/MS	+	a+b-	+	a-b+	a-b+	+	2-2	2-1	+	O	
III.16	O	DCE/DCe	MS/MS	+	a+b+	+	a-b+	a-b+	O	2-2	2-1	+	O	
III.17	A ₁	DCE/DCe	MS/MS	+	a-b+	+	a-b+	a-b+	O	2-2	2-1	O	O	
III.19	A ₁	DCE/dce	MS/MS	O	a-b+	+	a-b+	a-b+	+	2-1	2-1	O	O	
IV.5	O	DCE/DCe	MNSs	O	a+b+	+	a-b+	a-b-	O	—	—	O	O	

All individuals are Kp(a-b+), K(-), k(+), Mi(a-), Go(a-), Js(a-), Tf C, Gm(2-3+5+6-12+13+14+).

t(?Cp-;Bp+) abnormality suggests that these translocations are not coincidental. A suggestion that this occurrence of increased chromosomal breakage and rearrangement is of significance is found in the fact that similar genome instability has been noted earlier by German, De Mayo, and Bearn (1962) in another family with a t(DqGq) abnormality and more recently by Zuelzer, Thompson, and Mastrangelo (1968) in a family with an infant with a partial D trisomy due to a translocation. In the first family chromatid exchanges were found in the cells of the translocation-bearing mother and her karyotypically normal brother. In the second family chromatid exchanges usually accompanied by chromosome breakage, endoreduplications, and acentric fragments were found in the mother, her twin brother, and the grandmother of a child with a partial D trisomy due to a translocation.

There are, also, other published examples which suggest a possible influence of structurally altered chromosomes on the remainder of the genome. These include a case reported by Marsden *et al.* (1966) in which a familial t(DqDq) abnormality was found in association with a t(GqGq) abnormality and a case of D trisomy (due to a t(DqDq) abnormality or a D isochromosome) in association with a familial inherited D group chromosome which had long upper arms with alternating regions of negative and positive heteropyknosis, described by Summitt and Atnip (1966). More recently, Cohen, Takagi, and Harrod (1968) reported a sporadic case of D trisomy in which the patient possessed a modal number of 45 chromosomes and carried two t(DqDq) chromosomes.

At the present time, the relation, if any, between these multiple chromosomal abnormalities is unknown.

Summary

The family of a phenotypically normal male with a presumptive t(?Cp-;Bp+) chromosomal ab-

normality is described. This child was the last offspring of a mother who was found to be a t(DqGq) carrier. This mother also gave birth to four t(DqGq) carrier daughters, one of whom gave birth to a 46,XY,D-,t(DqGq)+ child with Down's syndrome. Blood group typing and linkage data for this family are also included in this report.

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