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Translocations of D Chromosomes in Two Families: t(13q14q) and t(13q14q)+(13p14p)

CATHERINE G. PALMER, PATRICK M. CONNEALLY, and JOE C. CHRISTIAN

From the Department of Medical Genetics, Indiana University Medical Center, Indianapolis, Indiana, U.S.A.

Translocations involving two members of the D group of chromosomes appear to be a relatively common chromosomal polymorphism. Several of these translocations are familial (Chaptal, Jean, and Emberger, 1965; Dekaban, 1966; Dill and Miller, 1963; de Grouchy *et al.*, 1963, 1964; Hamerton, Giannelli, and Carter, 1963; Hamerton, 1966; D. Hayman, unpublished, cited by Hamerton, 1966; Hustinx, 1963; Jacobsen *et al.*, 1966; Jagiello, 1963; Marsden *et al.*, 1966; Nuzzo, Marini, and Flauto, 1966; Oikawa *et al.*, 1962; Orye and Delire, 1967; Pitt, Ferguson, and Baikie, 1964; Richards and Stewart, 1965; Stahl *et al.*, 1966; Walker and Harris, 1962; Zergollern *et al.*, 1964; J. Wahrman, unpublished, cited by Hamerton, 1966), and a number are sporadic (Antonuis *et al.*, 1965; Bühler *et al.*, 1963; Cohen, Takagi, and Harrod, 1968; Conen, Erkman, and Metaxoutou, 1966; Cooper and Hirschhorn, 1961; Court Brown, Jacobs, and Brunton, 1965; Ferguson and Pitt, 1962; Haas and Lewis, 1965; Court Brown *et al.*, 1966; Hemet *et al.*, 1967; Jacobs *et al.*, 1968; Jongbloet *et al.*, 1964; Kjessler, 1964; Pinkerton and Cohen, 1967; Summitt and Atnip, 1966; Therman *et al.*, 1962; Tiepolo *et al.*, 1967; Tolksdorf *et al.*, 1965; Van Hemel and Van Braink, 1966; Yarema *et al.*, 1965; Ying, 1966; Yunis *et al.*, 1964). Such translocations have been encountered in surveys of the normal population (Court Brown *et al.*, 1965; Court Brown, 1967; Jacobs, 1964), in individuals with trisomy-D syndrome (Cohen *et al.*, 1968; Conen *et al.*, 1966; Dill and Miller, 1963; de Grouchy *et al.*, 1963; Haas and Lewis, 1965; Jacobsen *et al.*, 1966; Jongbloet *et al.*, 1964; Oikawa *et al.*, 1962; Summitt and Atnip, 1966; Therman *et al.*, 1962; Tolksdorf *et al.*, 1965; Yunis *et al.*, 1964), and in families of patients with other aneuploidies (Chaptal *et al.*, 1965; Hamerton *et al.*, 1963; Hustinx, 1963; Marsden *et al.*, 1966; Orye and Delire, 1967; Stahl *et al.*, 1966; Tiepolo *et al.*, 1967; Yunis *et al.*, 1964; Zergollern *et al.* (1964). It is of interest to note that of the D trisomies with a t(DqDq)* only 4 of 18 reported occur in families bearing the translocation (Dill and Miller, 1963; de Grouchy *et al.*, 1963; Jacobsen *et al.*, 1966; Oikawa *et al.*, 1962). The other 14 cases represent sporadically occurring translocations with trisomy-D.

In the past year we have seen two separate families bearing D–D–,t(DqDq) in multiple individuals. In each case the family was ascertained through a propositus with Down's syndrome. One of the families carried the reciprocal t(DpDp) as well as t(DqDq). Transmission of the translocations has been studied in both families, and autoradiographic studies indicate that both translocations involve chromosomes 13 and 14.

Materials and Methods

Chromosome studies were carried out on peripheral blood cultures of all available members of both families. Leucocytes were grown in spinner medium (BME-suspension medium without calcium, 2X vitamins and amino acids) and laboratory prepared phytohaemagglutinin. At 71 hours of growth, colcemid (0·025 μg./ml.) was added to the cultures which were then fixed one hour later. Hypotonic treatment in 0·95% sodium citrate for 30 minutes preceded fixation in 1:1 methanol acetic acid. Air-dry preparations were made and stained with acetic acid, and others were stained with aceto orcein. For autoradiographic studies, tritiated thymidine (Schwartz Bioresearch, specific activity 1·9 Ci/mM) was added 4½ to 5 hours before fixation. The final concentration of labelled thymidine was 1 μCi/ml. The cells were fixed as above, and the prepared slides were dipped in Kodak NTB2 emulsion. The slides were exposed for 10 days, developed, and stained with Giemsa. After photographing suitably labelled cells, the grain and emulsion were removed (Bianchi, Lima-De-Faria, and Jaworska, 1964); the slides were restained with orcein and rephotographed.

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Family History and Chromosome Findings

Family 926 was ascertained through a 6-week-old male infant with Down's syndrome. The father was 44 years old and the mother 37. There were 4 normal sibs in the family, and the mother had had 10 additional pregnancies ending in early abortions. This fact and the occurrence of 4 abortions in her sister made us consider the possibility that the patient might be a translocation mongol.

Leucocyte cultures showed that the propositus had a (46,XX,D−D−,t(DqDq)+,21+) chromosome complement, and that the mother was a translocation heterozygote (45,XX,D−D−,t(DqDq)+) (Fig. 1). Among other members of the mother's family who were studied, the sister (who had 4 miscarriages), 3 of her children, 1 brother, and the father were also translocation heterozygotes (Table I). The pedigree is shown in Fig. 2. Thus the translocation is present in 9 members in 3 generations, and is transmitted by males and females. The family shows multiple instances of spontaneous abortion.

Family 1156 was ascertained through an 18-month-old boy with the diagnosis of Down's syndrome and severe congenital heart defect who died before chromosome cultures could be obtained. The mother was 21 years of age at the child's birth.

Leucocyte cultures were established from peripheral blood of the mother, and proved to have cells with a translocation involving two D chromosomes (45,XX, D−D−,t(DqDq)+). Thereafter, only maternal sibs and relatives were studied. Her mother and one brother had normal chromosomes. The second brother had 46 chromosomes with four D's, a large metacentric, and a small metacentric bearing satellites on both ends (46,XY,D−D−,t(DqDq)+,t(DpDp)+) (Fig. 3). This was interpreted to be the reciprocal translocation involving the two short arms of the translocated chromosomes. The family pedigree is shown in Fig. 4.

Subsequently cells were cultured from peripheral blood of the grandfather and 4 additional half-sibs of the mother (see Fig. 4). The grandfather had two populations of cells 45,XY,D−D−,t(DqDq)+/46, XY,D−D−,t(DqDq)+,t(DpDp)+. Two of the half-brothers had normal chromosomes and one half-brother and one half-sister also carried the balanced translocation in mosaic form. Thus, of 6 translocation heterozygotes found in this family, 4 individuals have been shown to carry both parts of the reciprocal translocation involving two D chromosomes in at least part of their peripheral blood cells. Three of the four had loss of the short arm translocation in some cells, and thus were

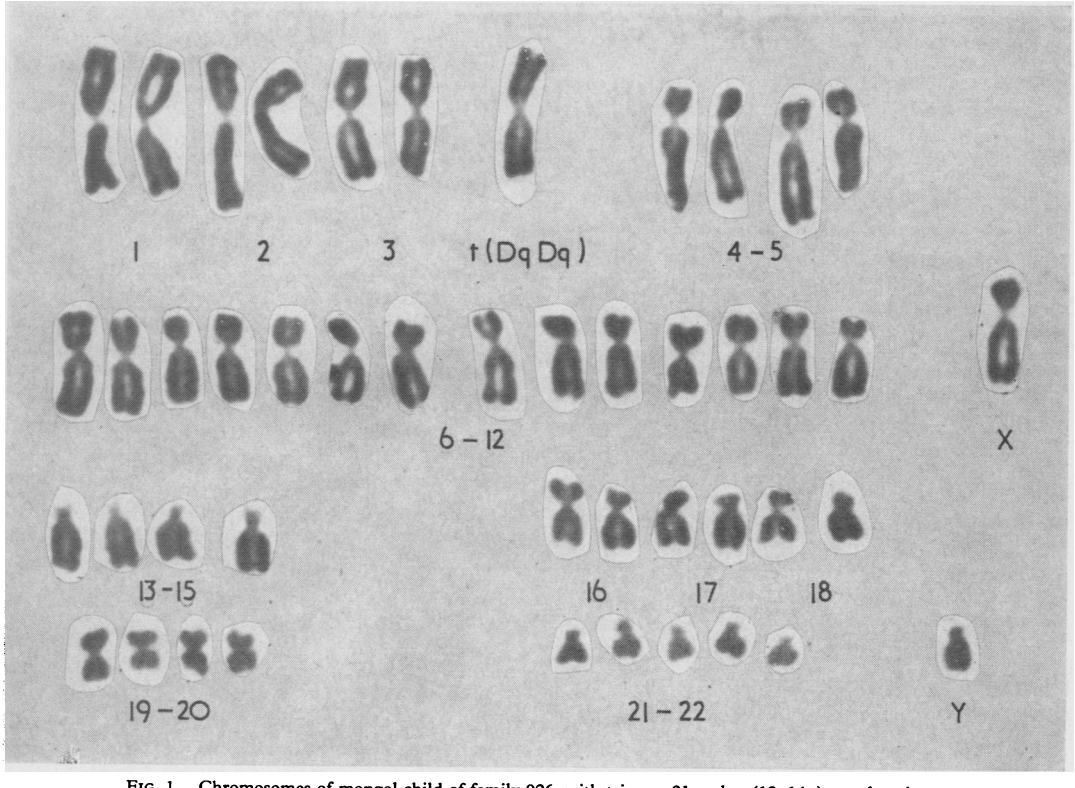

FIG. 1. Chromosomes of mongol child of family 926, with trisomy 21 and a t(13q14q) translocation.

45/46 chromosome mosaics. The chromosome counts and karyotypic findings are summarized in Table I.

Autoradiography

When tritiated thymidine is added approximately 4½ hours before fixation it is possible to differentiate among the D chromosomes by the pattern of termination of DNA synthesis.

Giannelli and Howlett (1966) have established the following replication pattern among the D chromosomes; one pair which completes its replication early is also the shortest and may be identified as chromosome 15 (D_3); one pair, No. 13 (D_1), continues synthesis relatively late in the distal segments of the long arms; one pair, No. 14 (D_2), continues synthesis relatively late in the area proximal to the centromere.

Autoradiographic studies of cells of five translocation carriers of family 926 were carried out. In 34 informatively labelled cells one pair of D chromosomes was unlabelled. Of the two remaining D chromosomes, 26 cells showed, in addition, one proximally and one distally labelled chromosome. Of the three chromosomes resembling chromosome 3, two differ in their labelling pattern from the third which is labelled proximally in one arm and distally in the other. Thus, the data indicate that in this family chromosomes 13 and 14 are most likely involved in the translocation.

In family 1156, 33 cells from four translocation carriers were informatively labelled. Of these cells, 30 had two unlabelled early-replicating chromosomes appearing in the D group, and, of these, 17 also showed differential labelling in the remaining two D's, one labelling proximally, the other distally. This then suggests the involvement of the homologues of 13 and 14 in the translocation present in this family.

Both families, therefore, appear to carry translocations of chromosomes 13 and 14, t(13q14q) (Fig. 5).

TABLE I

SUMMARY OF CHROMOSOME FINDINGS IN FAMILIES 926 AND 1156

Pedigree No.	No. of Cells Counted		Karyotypic Findings*
	45	46	
Family 926			
II.5	28		45,XX,13–14–,t(13q14q)+
III.14		24	46,XY,13–14–,t(13q14q),21+
III.10		10	46,XY
III.11		10	46,XX
III.12	10		45,XY,13–14–,t(13q14q)+
III.13		10	46,XY
III.15		25	46,XX
I.2	10		45,XY,13–14–,t(13q14q)+
I.3		11	46,XX
II.2		11	46,XX
II.3		10	46,XY
II.8		26	45,XX,13–14–,t(13q14q)+
III.17		10	46,XY
III.18	10		45,XX,13–14–,t(13q14q)+
III.19	10		45,XX,13–14–,t(13q14q)+
III.20	10		45,XY,13–14–,t(13q14q)+
II.10		10	46,XX
II.11	10		45,XY,13–14–,t(13q14q)+
III.24		11	46,XY
Family 1156			
I.2	6	13	45,XY,13–14–,t(13q14q)+/46,XY, 13–14–,t(13q14q)+,13p14p)+
II.6	31		45,XX,13–14–,t(13q14q)+
II.8	25		45,XX,13–14–,t(13q14q)+
II.9		26	46,XY,13–14–,t(13q14q)+t(13p14p)+
II.1		9	46,XY
II.2	7	14	45,XX,13–14–,t(13q14q)+/46,XX,13–14–, t(13q14q)+t(13p14p)+
II.3		18	46,XY
II.4	12	10	45,XY,13–14–,t(13q14q)+/46,XX,13–14–, t(13q14q)+t(13p14p)+
I.3		28	46,XX
II.10		11	46,XY

* Nomenclature recommended by the Chicago Conference on Standardization in Human Cytogenetics, 1966.

Linkage Data

A summary of blood group, Gm, Inv, haptoglobin, phosphoglucomutase, and acid phosphatase markers in these families is given in the Appendix.

Discussion

There have been frequent reports of t(DqDq) translocations, but none have reported the reciprocal translocation t(DpDp) as seen in family 1156.

The unusual occurrence of the t(DpDp) reciprocal in this family might be indicative of its recent origin. The t(13p14p) chromosome is transmitted less frequently than the t(13q14q) chromosome (see Table III), and is subject to frequent loss in the

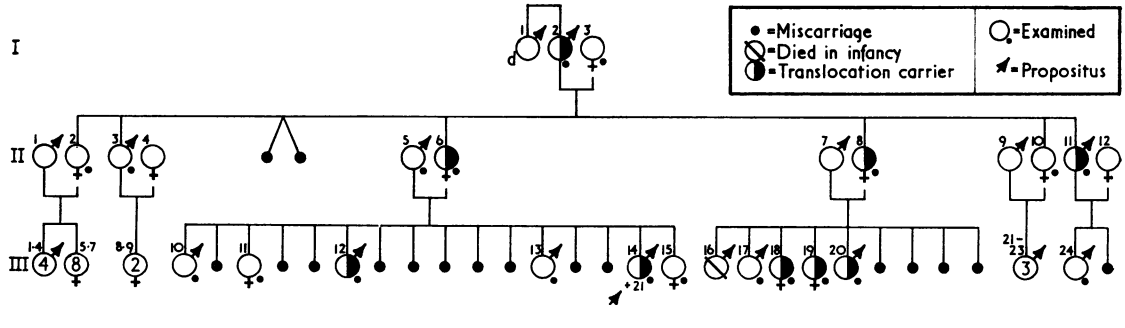

FIG. 2. Pedigree chart of family 926.

FIG. 3. Chromosomes of male member of family 1156 bearing the reciprocal translocation of two D chromosomes 46,XY,13–14–t(13q14q)+,t(13p14p)+.

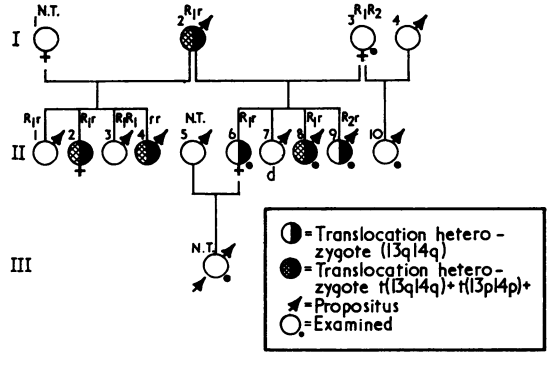

FIG. 4. Pedigree chart for family 1156 showing blood group data for Rh locus.

cells of carriers of this chromosome (Table I). The t(13q14q) chromosome is transmitted equally by males and females.

Three possible combinations of D chromosomes in the translocations 13–14, 13–15, and 14–15 may be expected. Identification of the chromosomes involved has been made by measurements of relative lengths of the chromosomes and, more recently, by autoradiography. Earlier workers, using the measuring technique, identified all the expected translocations (Table II). However, those using autoradiography have identified the translocations only of 13 and 14. In one instance (Cohen *et al.*, 1968), the patient had both 13–14 and 13–15 translocations.

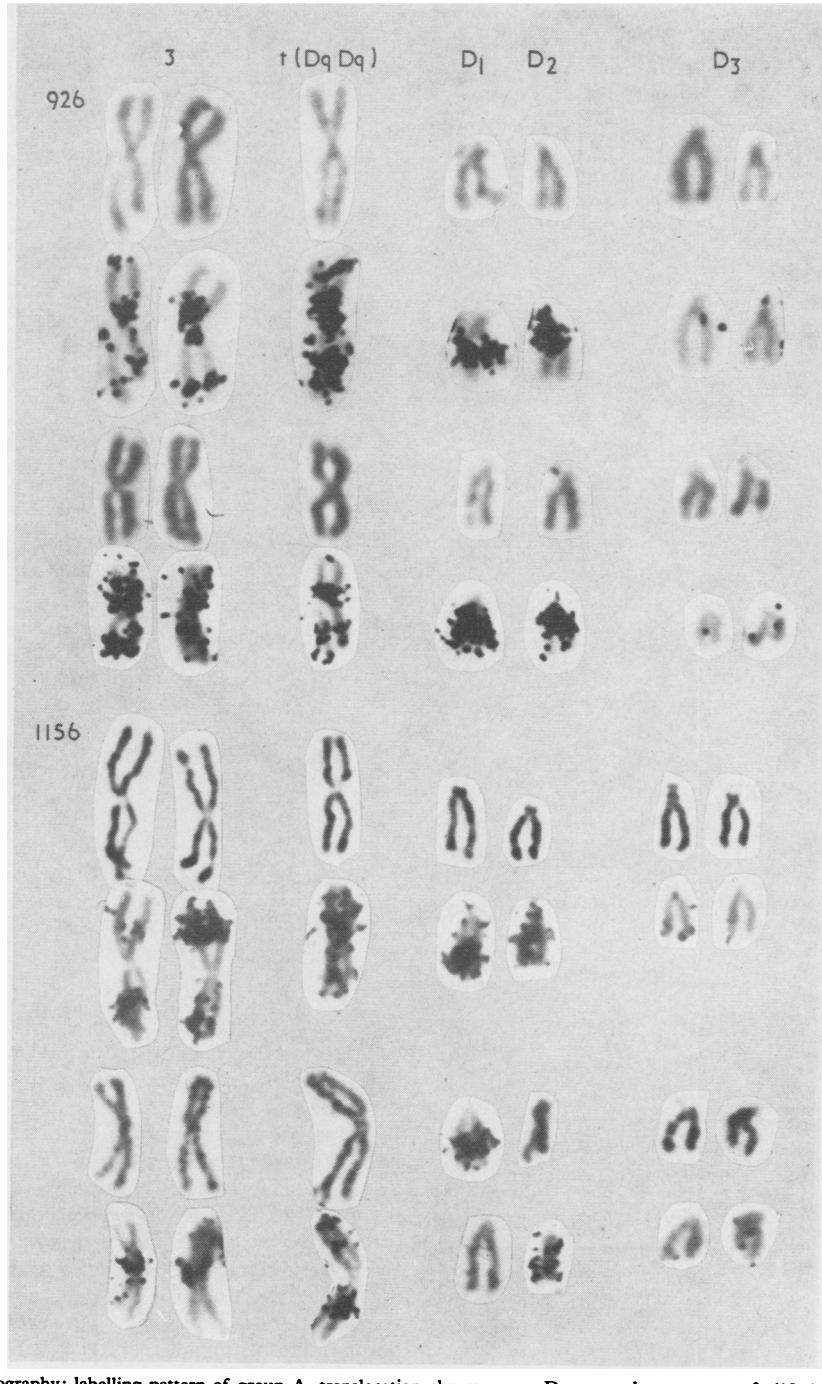

FIG. 5. Autoradiography: labelling pattern of group A, translocation chromosome, D group chromosomes of t(13q14q)+ translocation heterozygotes of families 926 and 1156.

TABLE II

IDENTIFICATION OF D CHROMOSOMES IN TRANSLOCATIONS D–D–,t(DqDq)

Chromosomes Involved	Criteria for Identification	Reference
13/15	Chromosome lengths	Walker and Harris (1962)
13/15	'Arm ratio'	Kjessler (1964)
13/14	Chromosome length	Oikawa *et al.* (1962)
13/15	,,	Hamerton *et al.* (1963)
14/15	,,	Zergollern *et al.* (1964)
D_1/D_2	Autoradiography	Yunis *et al.* (1964)
D_1/D_2	,,	Dekaban (1966)
D_1/D_2	,,	Giannelli and Howlett (1966)
D_1/D_2	,,	Van Hemel and Van Braink (1966)
D_1/D_2,D_1/D_3	,,	Cohen *et al.* (1968)
D_1/D_2	,,	Jacobsen *et al.* (1966)
D_1/D_2 probably	,,	Tiepolo *et al.* (1967)
13/14	,,	L. Reisman (personal communication)
13/14	,,	This paper
13/14	,,	This paper

TABLE III

TRANSMISSION OF D TRANSLOCATIONS

	Sex of Heterozygous Parents	Total Children	Carrier Children	Percentage
Family 926				
(13q14q)	2 Males	7	4	60
	2 Females	10	5	50
Family 1156				
(13q14q)	1 Male	8	5	62
(13p14p)	1 Male	8	3	38

The frequent occurrence of t(13q14q) translocation may result from similarity of replication time. Both 13 and 14 chromosomes have regions continuing to replicate relatively late in the cycle, while 15 completes its replication at an earlier period. Hence breakage and reunion occurring during replication might occur more frequently between 13 and 14.

Chromosomes 13 and 14, but not 15, have also been shown to have induced secondary constrictions after treatment with 5-bromodeoxyuridine (BUdR) (Palmer and Funderburk, 1965; unpublished data). Since secondary constrictions show greater breakability to a variety of agents (Engel, Krone, and Wolf, 1967), there may be a relation of these constrictions to the involvement of 13 and 14 chromosomes on translocation. Non-randomness of translocations involving a D chromosome has also been reported in t(DqGq) translocations, where 14 occurs in the translocation more frequently than 15. Chromosome 13 was not involved in any case (Hecht *et al.*, 1968). In this case the difference in frequency of chromosomes 13 and 14 might be related to the positioning of the constriction close to the centromere in 14, and medial in 13.

The association of aneuploidy of chromosomes other than D's in families with t(DqDq) translocations has been noted (Hamerton *et al.*, 1963; Yunis *et al.*, 1964). Some investigators (Grell and Valencia, 1964; Grell, 1967; Hamerton *et al.*, 1963; Yunis *et al.*, 1964) have considered the possibility that 'distributive pairing' brings about the non-disjunction of autosomes other than those involved in the translocation in such families. However, the similar frequencies of the DqDq translocations in the general population, 1:1000 (Hamerton, 1968), and in unselected surveys of mongols, 1:900 (Richards and Stewart, 1965), argue against the functioning of this mechanism of non-disjunction in DqDq translocation heterozygotes.

In considering the possibility of linkage of serum proteins or erythrocyte enzymes and blood groups, all translocation heterozygotes in the two families were tested for the possibility of a deleted gene. No evidence for such a deletion was found in the systems studied (Appendix). Furthermore, the possibility of linkage of a marker gene with the translocated chromosome segments t(13q14q) or t(13p14p) was examined. All informative matings (translocation heterozygote parent heterozygous for a known marker) and their offspring were tested. No evidence for linkage was found, with the possible exception of Rh.

In family 1156 (Fig. 4), I.2 is a carrier of the reciprocal translocation (45,XY,13–14–,t(13q14q)+/46, XY,13–14–,t(13q14q)+,t(13p14p)+ and is heterozygous at Rh locus (R_1r). If we assume the r(cde) allele is on the t(13q14q) portion of the translocation, then among his 5 informative offspring no crossovers occurred. Since II.6 does not carry the t(13p14p) portion and is heterozygous R_1r, the gene cannot be on the short arm translocation (13p14p).

Though the data are suggestive of linkage of Rh with 13q or 14q in our family 1156, Dekaban has also reported a family with a t(13q14q) translocation, informative for Rh, in which no evidence for linkage could be demonstrated. Further studies of this system in t(DqDq) translocation-bearing families, in which definitive chromosome identification has been made, are needed to resolve this question.

Summary

Two families with D–,D–,t(DqDq) translocations in multiple individuals are described. Members of one family also carried the reciprocal translocation t(DpDp). Transmission of the translocations has been studied in both families. Autoradiographic studies indicate that the translocations in both families involve chromosomes 13 and 14.

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APPENDIX

GENOTYPING DATA

Pedigree No.	ABO	Rhesus	MNS	Duffy	Kidd	Kell	P	Hp*	P G M†	A P‡	Gm	Inv
	Family 1156										a b f	
I.2	O	R_1r	MNs	−	NT	−	NT	2–2	1–1	BA	+ + +	−
I.3	A_1B	R_1R_2	MSs	+	NT	−	NT	1–1	2–2	BA	+ + +	−
II.1	O	R_1r	MNs	+	NT	−	NT	2–1	2–1	AA	− + +	+
II.2	O	R_1r	NSs	+	NT	−	NT	2–1	2–1	BA	− + +	+
II.3	O	R_1R_1	NSs	+	NT	−	NT	2–1	2–1	BA	+ + +	+
II.4	O	rr	MNSs	+	NT	−	NT	2–2	2–1	BA	− + +	+
II.6	B	R_1r	MSs	+	NT	−	NT	2–1	2–1	BB	+ − −	−
II.8	B	R_1r	Ms	+	NT	−	NT	2–1	2–2	BA	+ + +	−
II.9	B	R_2r	MNs	+	NT	−	NT	2–1	2–2	BA	+ ? +	?
	Family 926											
I.2	O	rr	Ns	−	−	−	+	2–2	2–1	BB	− + +	−
I.3	O	R_2r	MS	+	−	−	+	2–1	1–1	BA	+ + +	−
II.2	O	R_2r	MNSs	−	−	−	+	2–2	2–1	BB	− + +	−
II.3	O	R_2r	MNSs	−	−	−	+	2–1	2–1	BB	+ + +	−
II.5	A_1	R_1R_2	MNS	+	+	−	+	2–2	2–1	BB	− + +	−
II.6	O	rr	MNSs	−	−	−	+	2–1	2–1	BA	− + +	−
II.7	B	R_1R_1	Ns	−	+	−	+	2–2	2–1	BA		
II.8	O	rr	MNSs	−	−	−	+	2–1	2–1	BB	+ + +	−
II.10	O	rr	MNSs	−	−	−	+	2–1	2–1	BB	+ + +	−
II.11	O	rr	MNSs	+	−	−	+	2–2	1–1	BA	+ ? +	?
II.12	B	rr	MSs	+	+	−	+	2–1	2–1	BB	+ + +	−
III.10	O	R_2r	MNSs	−	+	−	+	2–2	2–1	BB	− + +	−
III.11	O	R_2r	MNSs	+	−	−	+	2–2	2–1	BA	− + +	−
III.12	O	R_2r	NSs	−	+	−	+	2–1	2–1	BA	− + +	−
III.13	A_1	R_2r	MNS	−	−	−	+	2–2	2–1	BA	− + +	−
III.14	A_1	R_2r	NSs	+	−	−	−	2–1	2–2	BA	− + +	−
III.15	A_1	R_1r	MNSs	+	NT	−	NT	2–1	2–1	BB	− + +	−
III.17	O	R_1r	MNSs	−	+	−	−	2–1	2–1	BB	+ + +	−
III.18	O	R_1r	MNSs	−	+	−	+	2–1	2–1	BB	− + +	−
III.19	B	R_1r	MNSs	−	+	−	+	2–2	2–1	BB	− + +	−
III.20	O	R_1r	MNSs	−	+	−	+	2–2	2–1	BB	+ + +	−
III.24	B	rr	MSs	+	+	−	+	2–1	1–1	BA	− + +	−

* Haptoglobin.
† Phosphoglucomutase.
‡ Red cell acid phosphatase.
? = Agglutinator.