Association of D/D translocations with fetal wastage and aneuploidy

A report of four families

PAUL M. FERNHOFF, D. N. SINGH, JAMES HANSON, SUZANNE TRUSLER,
CHERYL R. DUMONT, and ANDREW T. L. CHEN

Cellular Genetics Laboratory, Pathology Division, Bureau of Laboratories, Center for Disease Control, Public Health Service, Department of Health, Education, and Welfare, Atlanta, Ga. 30333, Division of Cytogenetics, Department of Pediatrics, Meharry Medical College, Nashville, Tenn. 37208, Birth Defects Branch, Cancer and Birth Defects Division, Bureau of Epidemiology, Center for Disease Control, Atlanta, Ga. 30333, USA

Summary. Four families are described with a $t(13q14q)$ segregating. Two of them were identified through index cases with Down's syndrome; their karyotypes revealed the unusual $46,XY,-13,-14,+t(13q14q),+21$. The other two families were identified through a chromosomal study of parents with repeated spontaneous abortions.

Analysis of data on 3 of these 4 families and on 7 others from the published reports showed no evidence of increased fetal wastage among 13/14 carriers. However, the risk of producing offspring with various types of aneuploidy may be greater among carriers than among persons with a normal chromosome pattern. *Qualitative and quantitative* differences in D/D translocations may account for the observed variation in clinical findings. These differences add to the problem of determining genetic risks from an analysis of grouped data.

Although D/D translocations are now recognized as one of the most common autosomal structural rearrangements in man, with an incidence of about 1 per 1500 live births (Jacobs, 1972), the clinical significance of this translocation remains unclear. If genetic counselling is to be provided to D/D heterozygotes, the answers to two general questions must be documented: first, are these heterozygotes at greater risk of infertility and fetal wastage than is the general population; and second, are they at greater risk of producing offspring with aneuploidy? We report four additional 13/14 families, two identified through an index case with phenotypic Down's syndrome and two through a chromosome study of parents with repeated spontaneous abortions.

Case reports

Family 1. The index patient, a 3.09 kg white male, was born to a 39-year-old gravida 11, para 10, ab. 1,

after an uncomplicated 38-week gestation. Shortly after delivery, the infant was noted to have features of Down's syndrome, and a chromosomal analysis was performed.

When the infant was 16 months of age (Fig. 1), his weight was 9.0 kg (third centile); height, 74 cm (third centile), and head circumference, 45.0 cm (third centile). He showed most of the features of Down's syndrome. No cardiac abnormalities were noted. His dermatoglyphic patterns showed bilateral single transverse palmar creases, 10 ulnar loops, a right *atd* angle of 50.5° , bilateral third interdigital loops, and bilateral small loops in the hallucal areas. His Walker index was 1.4 (overlap area), and a Reed dermatogram showed an overlap pattern.

The family pedigree is shown in Fig. 2. The father, a $45,XY,13/14$ translocation carrier, is clinically normal. Though his left index finger had been amputated previously, his dermatoglyphic patterns were within the normal range. Walker and Reed indices could not be calculated.

Family 2. The mother of the proband, a 32-year-old white woman, gravida 2, para 1, came to the Medical University of South Carolina for an amniocentesis. Her

FIG. 1

FIG. 2

first child, by a previous marriage, had the clinical stigmata of Down's syndrome. Previous cytogenetic analysis had shown her to be a carrier of a balanced translocation. Analysis of the amniotic fluid cell culture showed the fetus to be normal 46,XY. As shown by dermatoglyphic studies, the proband had bilateral single transverse palmar creases, eight ulnar loops, and two arches, with total ridge counts of 70, *atd* angles $\leq 90^\circ$,

FIG. 3

loop patterns on the hypothenar regions of both hands, an interdigital loop between the third and fourth digits of the right hand, and an interdigital loop between the fourth and fifth digits of the left hand. Dermatoglyphs of the mother of the proband were normal.

Families 3 and 4. Families 3 and 4 were found through a study designed to analyse the chromosomal pattern of parents with 2 or more spontaneous abortions; this study was initiated at the Medical College of Virginia in 1973 by one of us (A.T.L.C.). The details of this work will be published elsewhere. In family 3, the propositus (the husband) was clinically normal. His wife had experienced 3 spontaneous abortions, and had given birth to a normal female and a hydrocephalic female who died in infancy. In family 4, the propositus (the wife), who was clinically normal, had 2 normal sons and 3 early spontaneous abortions. The pedigrees of these 2 families are seen in Fig. 3.

Cytogenetic studies

All chromosome studies were carried out in lymphocyte cultures of peripheral blood by standard methods. More than 30 cells were counted and at least five suitable metaphase spreads were photographed and karyotyped in all the patients studied. G and Q bandings were done when indicated (Lin, Uchida, and Byrnes, 1971; Seabright, 1971).

Family 1. The karyotype of the propositus showed 46 chromosomes. G and Q bandings indicated an extra 21 chromosome, while one chromosome was missing from each of the 13 and 14 pairs. The two missing chromosomes were found to result in a Robertsonian translocation (Fig. 4). The patient's chromosome constitution was 46,XY,-13,-14,+t(13q14q),+21. Chromosome analyses of the parents showed that the mother was normal, and the father was a balanced translocation carrier, i.e. 45,XY,-13,-14,+t(13q14q) (Fig. 4). Since Q banding failed to show marker chromosomes from either the propositus or his parents, we could not

FIG. 4

establish in which parent the nondisjunction occurred. The propositus had 9 living sibs—7 brothers and 2 sisters. Six of the brothers were available for studies, and 2 of them were carriers. One of the 2 sisters was also a carrier. The paternal grandparents are dead, and the father's sibs are unavailable for studies. Therefore, it is not possible to determine whether the 13/14 translocation in the father was transmitted or arose *de novo* during gametogenesis of either paternal grandparent.

Family 2. Cytogenetic studies of the propositus showed 46 chromosomes. Q banding showed that the patient had trisomy 21 and a balanced translocation of the arms of chromosomes 13 and 14, i.e. 46,XY,-13,-14,+t(13q14q). Two of the three 21 chromosomes had brightly fluorescent satellites. The biological father was not available for chromosome analysis. The mother, however, was found to be a balanced translocation carrier, i.e. her chromosome constitution was 45,XX,-13,-14,+t(13q14q). One of her 21 chromosomes was also brightly satellited.

Family 3. The propositus had a chromosome complement of 45. G and Q bandings showed that chromosomes 13 and 14 were missing, and an extra metacentric chromosome was present as the result of a Robertsonian translocation between the long arms of the missing 13 and 14 chromosomes. The patient was thus 45,XY,-13,-14,+t(13q14q). His mother was also a 13/14 heterozygote, as were his brother and sister. The brother had been married twice, and he had a 13/14 carrier daughter from each marriage. The patient's sister had a son who also was a 13/14 heterozygote.

Family 4. The propositus had 3 spontaneous abortions. Her chromosome constitution was 45,XX,-13,

-14,+t(13q14q). One of her 2 living sons was found to be a 13/14 translocation carrier.

Discussion

Genetic counselling in the absence of statistically supported evidence is difficult. The increasing demand for cytogenetic counselling services makes imperative the gathering of accurate information about the less well-defined abnormal chromosome patterns, e.g. D/D translocations. These 'centric fusion' translocations are not uncommon, and they have been extensively analysed (Hamerton, 1970, 1971; Levine, 1971). However, these analyses are, by necessity, retrospective and contain grouped data from all D/D translocations. The disadvantages of this type of group analysis have been reviewed by Shaw (1962).

Most individuals with any type of D/D translocation are normal (Hamerton, 1971; Levine, 1971; Zeuthen and Neilsen, 1973). However, a few abnormal individuals have been found with this translocation (Levine, 1971; Crandall *et al*, 1972; Escobar, 1973). Since no consistent clinical patterns have been identified, it is doubtful that the translocation is causally related to the abnormalities in most cases.

Whether these translocations are responsible for decreased fertility or increased fetal wastage is not clear. The frequent finding of D/D heterozygote parents in studies of recurrent abortions has caused

TABLE
t(13q;14q): SIBSHIP SIZE AND FREQUENCY OF
SPONTANEOUS ABORTIONS*

Sex of Heterozygote	Male	Female	Com- bined
No. of sibships	18	14	32
Recorded conceptions	81	67	148
Recorded number of spontaneous abortions	4	18	22
Abortions as % total conceptions	4.9	26.8	14.9
Estimated incidence of spontaneous abortions in general population†			15.0

* t(13q;14q) Ten families: Crandall *et al* (1972); Kohno and Makino (1969); Palmer *et al* (1973); Sparkes and De Chieri (1970); Wilson (1971); Zeuthen and Nielsen (1973); and present report (families 1, 2, and 3).

† Court Brown (1967).

speculation that these translocations may increase fetal wastage. Hamerton (1970, 1971) concluded that decreased fertility was not a problem for D/D carriers. Using Hamerton's corrected method by which the proband is not included in the calculations, we analysed 10 kindreds with a t(13q14q) segregating which have been reported since 1970 (Table). Included in the 10 were the first three families in this report. Though Table shows differences in fetal wastage rates depending on the sex of the translocation carrier parent, the analysis fails to reveal evidence of more fetal wastage than in the general population, for the combined group of male and female 13/14 heterozygote parents. These discrepant results may arise from grouping dissimilar data and from inaccurate conceptual histories. One report (Bhasin, Foerster, and Fuhrmann, 1973) suggests that in Hamerton's case material conceptual histories were incomplete and that the correction factor might be too severe. In contrast, Court Brown's use of complete histories (1967) may have introduced a bias in the opposite direction. A prospective study is needed to compare the intrafamily rate of spontaneous abortions among heterozygotes with that among the chromosomally normal members of the kindred.

Although the spontaneous abortion rates for D/D heterozygotes and for the general population have not been shown to be significantly different in most past analyses, the chromosome patterns in the abortuses of each group were not reported. Carr (1970) estimated that nearly 40% of the spontaneous abortions that occur during the first 13 menstrual weeks are associated with chromosome abnormalities in the general population. In D/D heterozygotes it is possible that the majority of their spontaneous abortions are caused by D-group trisomy. The type of D-trisomy would depend on the specific chromosomes involved in the translocation, usually chromosomes 13 and 14 (Cohen, 1971). This sug-

gestion must await verification from chromosome studies of abortion material from such matings. Alternatively, meiotic studies of D/D translocation carriers would be helpful. Unfortunately, these studies are few (Kjessler, 1966; McIlree *et al*, 1966; Fraccaro *et al*, 1973).

It has been suggested on theoretical and clinical grounds that the offspring of D/D heterozygotes are at greater risk of aneuploidy than are offspring of the general population (Ridler *et al*, 1969; Hamerton, 1971). Theoretically the risk of 13 trisomy among the offspring of 13/14 or 13/15 heterozygotes is 33%, since 14 or 15 trisomy and all monosomies are probably non-viable. Hamerton (1971) reported that out of about 170 children from 24 kinships with a t(Dq;Dq) segregating, there were 5 children with Patau syndrome, 4 of whom were probands. Correction by eliminating the probands from calculations gives a frequency of 0.67% for the trisomy 13 syndrome. In comparison, estimated incidences of trisomy 13 in the general population vary between 0.005 and 0.02%, which suggests that the D/D heterozygote is at a greater risk of producing a child with trisomy 13 than is the general population.

The association of D/D translocations with Down's syndrome is less clear and has been thought by some authors to be fortuitous (Ridler *et al*, 1969; Hamerton, 1971). In addition to our two cases, the association of a D/D translocation and trisomy-21 has been reported in about 10 instances (Lundsteen, Vestermark, and Philip, 1974). These findings imply that this association might occur more frequently than the two individual events would occur by chance. In *Drosophila*, distributive pairing of non-homologous chromosomes may give rise to multiple aneuploidy (Grell, 1962). Furthermore, it can be inferred from the family reported by Weiss and Wolf (1968) that a balanced translocation might influence mitotic nondisjunction.

As we have mentioned, part of the confusion encountered in determining all genetic risks associated with any of the D/D translocations may be a result of the grouping of dissimilar data (Shaw, 1962). Autoradiographic labelling studies have shown the non-randomness of D/D translocations within the D group (Cohen, 1971) and have shown that the (13q;14q) translocation is most frequent. However, the (13q;14q) translocations may also not be a homogeneous group, since the origin of the centromere may be from either chromosome (Sparkes and De Chiere, 1970). Similarly, the location of break points may vary (Palmer *et al*, 1973) and as a result clinical effects might vary. Therefore, these translocations may represent true centric fusions, with equal components of each centromere present; or

FIG. 5

they may be translocations, with the centromere originating from either the 13th or 14th chromosome. A third group might have small fragments of the original short arm of the acrocentric chromosome present (Fig. 5). Thus possible heterogeneity of the (13q;14q) translocations might account for variable genetic risks. Further delineation of this heterogeneity should be possible by studying the finer morphology of these translocations and their break points. Spotted centromere staining technique (Eiberg, 1974), computer-assisted chromosome banding pattern analysis, and electron microscopical analysis of chromosome morphology may be helpful. Such refinements could help in further defining the genetic risks for the various types of D/D heterozygotes and other chromosomal patterns, and would thereby improve genetic counselling and diagnostic amniocentesis programmes.

We thank Dr William R. McLean for allowing us to study his patients in family 1; Dr Irene A. Uchida for the dermatoglyphic analysis in family 1; Ms Deborah Heritage and Ms Susan Englis for technical assistance; and Dr R. B. Young for the genetic counselling provided for families 3 and 4.

REFERENCES

Bhasin, M. K., Foerster, W., and Fuhrmann, W. (1973). A cytogenetic study of recurrent abortion. *Humangenetik*, **18**, 139-148.

- Carr, D. H. (1970). Chromosome abnormalities and spontaneous abortions. In *Human Population Cytogenetics*, pp. 104-118. Ed. by P. A. Jacobs, W. H. Price, and P. Law. Edinburgh University Press, Edinburgh.
- Cohen, M. M. (1971). The chromosomal constitution of 165 human translocations involving D group chromosomes identified by autoradiography. *Annales de Génétique*, **14**, 87-96.
- Court Brown, W. M. (1967). *Human Population Cytogenetics*. North Holland, Amsterdam.
- Crandall, B. F., Francke, U., Campbell, A., and Sparkes, R. S. (1972). Inherited t(13q14q) in two retarded sisters. *American Journal of Human Genetics*, **24**, 416-424.
- Eiberg, H. (1974). New selective giemsa technique for human chromosomes, C₄ staining. *Nature*, **248**, 55.
- Escobar, J. I. (1973). G-banding patterns of children admitted to a psychiatric unit: a case of D/D translocation. *Lancet*, **2**, 973.
- Fracaro, M., Maraschio, P., Pasquali, F., Tiepolo, L., Zuffardi, O., and Giarola, A. (1973). Male infertility and 13/14 translocation. *Lancet*, **1**, 488.
- Grell, R. F. (1962). A new hypothesis on the nature and sequence of meiotic events in the female of *Drosophila melanogaster*. *Proceedings of the National Academy of Sciences*, **48**, 165-172.
- Hamerton, J. L. (1970). Robertsonian translocations: evidence on segregation from family studies. In *Human Population Cytogenetics*, pp. 64-75. Ed. by P. A. Jacobs, W. J. Price, and P. Law. Edinburgh University Press, Edinburgh.
- Hamerton, J. L. (1971). *Human Cytogenetics*, vol. 1. Academic Press, London and New York.
- Jacobs, P. A. (1972). Chromosome mutations: frequency at birth in humans. *Humangenetik*, **16**, 137-140.
- Kjessler, B. (1966). *Karyotype, Meiosis and Spermatogenesis in a Sample of Men Attending An Infertility Clinic*. Karger, Basle.
- Kohno, S. and Makino, S. (1969). An Autoradiographic investigation of the chromosomes showing a D/D translocation. *Proceedings of the Japan Academy*, **45**, 121-125.
- Levine, H. (1971). *Clinical Cytogenetics*. Little, Brown, Boston.
- Lin, C. C., Uchida, I. A., and Byrnes, E. (1971). A suggestion for the nomenclature of the fluorescent banding patterns in human metaphase chromosomes. *Canadian Journal of Genetics and Cytology*, **13**, 361.
- Lundsteen, C., Vestermark, S., and Philip, J. (1974). A familial, balanced 2/5 translocation associated with trisomy 21 in one individual. *Human Heredity*, **24**, 88-99.
- McIlree, M. E., Price, W. H., Court Brown, W. M., Tulloch, W. S., Newsam, J. E., and Maclean, N. (1966). Chromosome studies on testicular cells from 50 subfertile men. *Lancet*, **2**, 69-71.
- Palmer, C. G., Morris, J. L., Thompson, B. H., and Nance, W. E. (1973). Fertility and 13/14 translocation. *Lancet*, **1**, 728.
- Ridley, M. A. C., Pendrey, M. J., Fauch, J. A., and Berg, M. M. (1969). Association of D/D translocation with mongolism. *Journal of Mental Deficiency Research*, **13**, 89-98.
- Seabright, M. (1971). A rapid banding technique for human chromosomes. *Lancet*, **2**, 971-972.
- Shaw, M. W. (1962). Segregation ratios and linkage studies in a family with six translocation mongols. *Lancet*, **1**, 1407.
- Sparkes, R. S. and De Chiare, P. R. (1970). Inherited 13/14 chromosome translocation as a cause of human fetal wastage. *Obstetrics and Gynecology*, **35**, 601-607.
- Weiss, L. and Wolf, C. B. (1968). Familial C/G translocation causing mitotic nondisjunction. A cause of familial mosaic Down's syndrome. *American Journal of Diseases of Children*, **116**, 609-614.
- Wilson, J. A. (1971). Fertility in balanced heterozygotes for a familial centric fusion translocation, t(DqDq). *Journal of Medical Genetics*, **8**, 175-178.
- Zeuthen, E. and Nielsen, J. (1973). D/D translocations in males examined for military service. *Journal of Medical Genetics*, **10**, 356-361.