Fertility in Balanced Heterozygotes for a Familial Centric Fusion Translocation, t(DqDq)

J. A. WILSON

From the Nuffield Unit of Medical Genetics, Department of Medicine, University of Liverpool, Liverpool

Centric fusion translocations of the t(DqDq) type are now recognized to be the commonest structural chromosomal variation in human populations, having a frequency of approximately 1/1000 adults according to Court Brown (1967). The translocations are commonly transmitted by heterozygotes.

Almost all the known families have been ascertained in the investigation of conditions in which various chromosomal abnormalities might have been expected. For example, 8 of 26 families recorded by Hamerton (1968) were found in the investigation of the birth of an infant with Down's syndrome, either of the regular or translocation type. Only 3 of the 26 families were ascertained because of the birth of a child with the Patau syndrome which probably occurs in less than 1% of the offspring of t(DqDq) heterozygotes.

Studies of normal populations may well be the major source of such families in the future. Ratcliffe and her associates (1970) found 3 balanced t(DqDq) heterozygotes and one 46,XY,D-, t(DqDq)+ individual with the signs of the Patau syndrome in their series of 3500 consecutive, newborn, male infants.

Hamerton (1968) found virtually no increase in the frequency of spontaneous abortion in families with three types of centric fusion translocation, t(DqDq), t(21q22q), t(DqGq), and suggested that the increased incidence of abortion recorded by Court Brown in a number of pedigrees (35.3% among the progeny of male heterozygotes and 43.1% in the progeny of female heterozygotes) might be due to selection artefact in a limited series. It was agreed, however, that the conceptual histories of these families might be more complete than those of the larger series. Ford and Clegg (1969) in an extensive review of all types of reciprocal

translocation in man, found only a slightly excessive frequency of spontaneous abortion in heterozygotes as compared with normal individuals. They stressed the need for further, full, unbiased pedigrees of translocation families, including the progenies of normal subjects as well as of heterozygotes, and of males as well as of females. Further details are therefore presented of a family ascertained during a study of habitual abortion (Wilson, 1969).

Methods

Chromosome preparations were made from the leucocytes of peripheral blood by various modifications of the method of Moorhead *et al* (1960). A minimum of 30 metaphases was counted for each individual.

Autoradiographic studies were carried out on the heterozygote II.6, tritiated thymidine being added to the cultures to give a final concentration of 0.2 μ Ci/ml 6 hours before fixation. Air-dried slides were stained with 0.25% acetic orcein and about 20 good metaphases were photographed using phase contrast. Kodak stripping film, AR.10 was then applied to the slides, exposed for 7 days and developed. Suitably labelled metaphases were rephotographed without phase contrast.

The Family

The probanda, III.9, presented with a history of 3 spontaneous abortions, each of which had occurred at the end of the first trimester of the respective pregnancy. The usual gynaecological investigation had been negative and her karyotype was found to be 45,XX,D-,D-, t(DqDq)+. She was then pregnant and was delivered of a normal 46,XY, male infant at 41 weeks, but has since had one further spontaneous abortion at 12 weeks. No aborted material was available for study. The probanda is presumed to have inherited the translocation from her deceased father, II.8, 3 of whose brothers were found to be balanced heterozygotes. The alternative possibility of a familial tendency to develop t(DqDq) translocations *de novo* seems unlikely and there is no direct evidence of this having occurred. Similarly, I.5

FIG. 1. Family pedigree.

and I.7 are presumed to have been heterozygotes as is their brother I.10. Both these sisters had heterozygote offspring, and their husbands were not related to each other or to other members of the family.

No abnormal children have been born in the family and the majority of the translocation heterozygotes have normal reproductive histories. All were questioned specifically about abortion. Apart from the proposita, no heterozygote was aware of having had any spontaneous abortion, nor was there any history of spontaneous abortion in the wife of any male heterozygote. The marriages of 2 male heterozygotes and of 1 female heterozygote had been totally infertile. The infertility was involuntary in all cases, contraception had not been practised, and gynaecological examination of the affected women had been normal. Seminal investigation of the men had been carried out, but details were no longer available and further examination of semen or testicular material was not permitted as infertility was no longer a pressing problem in any individual. One male heterozygote, II.12, and his wife were relatively infertile, having been married for 15 years before the birth of their only child, and similar investigation had been carried out with negative results. One other man, II.4, now dead and of unknown karyotype, also had a totally infertile marriage and examination of the wife had been negative. II.25 died of multiple sclerosis shortly after her marriage and no conclusions can be drawn regarding her fertility. No individual of known normal karyotype was infertile in this family, and the admitted incidence of spontaneous abortion in all known pregnancies of generations II and III (6 in 49) is less than the supposed frequency of 15% in the general population (WHO, 1966). No abortions

FIG. 2. Autoradiography. Labelling pattern of chromosomes 3, the D group chromosomes, and the translocation chromosome (T) from two representative metaphases of the translocation heterozygote II.6.

were known of in generation I but it is considered that the history at that length of time is probably unreliable.

Autoradiography distinguishes the translocation chromosome from chromosomes 3 and shows it to be late labelling proximally in one of its arms and distally in the other (Fig. 2). The translocation is, therefore, $t(13q14q)$ according to the D chromosome replication pattern established by Giannelli and Howlett (1966). This appears to be the most common of the three theoretically possible D combinations when autoradiographic evidence is available (Palmer, Conneally, and Christian, 1969).

Blood group examination of available individuals (Appendix I) does not indicate any linkage with the translocation chromosome in this family.

Discussion

Infertility has been fairly frequently recorded in balanced $t(DqDq)$ heterozygotes (eg, Walker and Harris, 1962; Kjessler, 1964; Yunis *et al.*, 1964). Many of the earlier cases, however, were ascertained in studies of infertile individuals, and infertility has been less frequently noted by more recent authors. Kjessler (1964), finding a low sperm count and many abnormal sperms in the semen of an infertile male heterozygote, assumed that unbalanced spermatids are incapable of developing into normally functioning spermatozoa, and that the infertility was a result of the dilution of normal forms. If this is so, the existence of fertile male heterozygotes implies that it must be only a relative effect. Infertility in female heterozygotes and the occasional finding of unbalanced fetuses indicate that additional factors must be involved.

Post-zygotic infertility owing to very early abortion of unbalanced zygotes has also been suggested. In this case total infertility would not be expected assuming that segregation at meiosis is random. If the zygotes ensuing from adjacent segregations were equally lethal in early pregnancy, 2 viable zygotes would be expected from 4 conceptions. Hamerton (1966), noting the low frequency of malformed offspring in the progeny of D/D and 21/22 translocation heterozygotes, concludes that preferential alternate segregation, in fact, occurs at meiosis in these conditions. His finding of an excess of balanced heterozygotes over normal individuals in the offspring of male heterozygotes would not support the hypothesis that normal women usually reject $t(DqDq)$ heterozygous embryos. Even if such rejection occurs in some women, and with random meiotic segregation, there should be a 1 in 4 possibility of a normal pregnancy.

Such rates of embryonic loss, particularly if the

loss occurred at or before the time of the first menstrual period expected after conception, might well be compatible with apparently normal fertility in an otherwise healthy couple. The pregnancy intervals in the larger sibships of this family would probably be adequate to conceal similar rates of early loss (Appendix II).

The disparity of fertility among apparently balanced heterozygotes, in this and other $t(DqDq)$ families, remains unexplained. No evidence was found to suggest that the fertile individuals had a less abnormal karyotype than those who were infertile. No individual had the rarely found reciprocal translocation, $t(DpDp)$ and deficiency of the D short arm chromatin is usually considered to be without significance.

The differences in fertility may be completely fortuitous, but it is also possible that other factors, perhaps genetic, can modify potentially deleterious effects of the heterozygous state. Such modifying factors may also explain the tendency for one heterozygote to have recurrent abortions whereas another appears not to become pregnant.

There remains a need for further studies of semen and meiosis in $t(DqDq)$ heterozygotes, also for karyotyping the aborted fetuses of heterozygote marriages. These fetuses are usually assumed to be chromosomally unbalanced but there is as yet very little evidence that this is always so, or of the karyotype abnormalities to be expected.

Summary

Further details are presented of a family, ascertained during a study of habitual abortion, in which a $t(DqDq)$ centric fusion translocation was transmitted. Autoradiographic studies show the translocation to be $t(13q14q)$.

Habitual abortion had occurred in the marriage of no heterozygote, other than the proposita, but the marriages of 3 heterozygotes, 2 males and 1 female, were totally infertile. One male heterozygote was relatively infertile and one male of unknown karyotype had a totally infertile marriage. No individual of known normal karyotype was shown to be infertile. The marriages of other heterozygotes were normally fertile.

The observed variability in fertility of $t(DqDq)$ heterozygotes is discussed.

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APPENDIX I

BLOOD GROUP DATA

(Only cases IV.5, IV.6, and IV.7 were tested against anti-s.)

Pedigree No.	ABO	Rhesus	MNS	Duffy (Fya)	Kell	Kidd (Jka)	P
I.8	O	CcDee	MMss	-	-	-	-
II.6	O	ccdee	MMss	+	+	-	-
II.9	O	CcDee	MMS	+	-	+	+
II.10	AI	CCDee	MMss	-	-	+	+
II.12	AI	CcDee	MMss	-	-	+	+
II.15	O	CcDee	MMss	-	-	-	+
II.16	O	CcDee	MMss	-	-	-	+
II.33	O	CcDee	MNss	+	-	-	+
III.5	O	ccDee	MMss	-	-	+	-
III.7	AI	ccDee	MMS	+	-	+	-
III.9	AI	CCDee	MMS	-	-	+	-
III.10	O	CcDee	MMss	+	-	+	+
III.11	AI	CcDee	MMss	-	-	-	-
IV.5	O	ccDEE	MNss	-	-	-	+
IV.6	O	CcDee	MNss	-	-	+	+
IV.7	O	CcDee	MNss	-	-	+	+

APPENDIX II

DATES OF BIRTH/SPONTANEOUS ABORTION FOR THE OFFSPRING OF TRANSLOCATION HETEROZYGOTES AND OF NORMAL MEMBERS OF THE FAMILY

Pedigree No.	Parents' Pedigree No.	Date of Birth	Chromosome Complement
I.1		1876	Not known
I.3		1878	Not known
I.5		1880	Not known
I.7		1882	Not known
I.8		1886	46,XY
I.10		1890	45,XY,D-,D-,t(DqDq)+
I.12		1896	Not known
II.4	I.4 I.5	1900	Not known
II.6	I.4 I.5	1902	45,XY,D-,D-,t(DqDq)+
II.8	I.4 I.5	1904	Not known
II.10	I.4 I.5	1906	45,XY,D-,D-,t(DqDq)+
II.12	I.4 I.5	1908	45,XY,D-,D-,t(DqDq)+
II.15	I.6 I.7	1909	45,XX,D-,D-,t(DqDq)+
II.16	I.6 I.7	1919	45,XY,D-,D-,t(DqDq)+
II.18	I.6 I.7	1924	46,XY
II.20	I.8 I.9	1912	Not known
II.22	I.8 I.9	1915	Not known
II.23	I.8 I.9	1920	Not known
II.25	I.10 I.11	1922	Not known
II.27	I.10 I.11	1923	Not known
II.29	I.10 I.11	1926	Not known
II.31	I.10 I.11	1928	Not known
II.33	I.10 I.11	1930	46,XX
II.34	I.10 I.11	1933	Not known
II.36	I.10 I.11	1935	Not known
II.37	I.12 I.13	1920	Not known
II.39	I.12 I.13	1921	Not known
III.3	II.8 II.9	1930	46,XY
III.5	II.8 II.9	1932	45,XY,D-,D-,t(DqDq)+
III.7	II.8 II.9	1936	45,XY,D-,D-,t(DqDq)+
III.9	II.8 II.9	1940	45,XX,D-,D-,t(DqDq)+
III.10	II.8 II.9	1946	45,XX,D-,D-,t(DqDq)+
III.11	II.12 II.13	1948	46,XX
III.12	II.16 II.17	1953	Not known
III.13	II.16 II.17	1955	Not known
III.14	II.16 II.17	1958	Not known
III.15	II.16 II.17	1960	Not known
III.16	II.18 II.19	1951	Not known
Abortion	II.18 II.19	1954	Not known
III.17	II.18 II.19	1956	Not known
III.18	II.20 II.21	1937	Not known
III.29	II.32 II.33	1957	Not known
III.30	II.32 II.33	1959	Not known
III.31	II.32 II.33	1960	Not known
III.32	II.32 II.33	1964	Not known
Abortion	II.32 II.33	1965	Not known
IV.2	III.3 III.4	1959	46,XY
IV.3	III.3 III.4	1961	46,XY
IV.4	III.3 III.4	1962	46,XY
IV.5	III.5 III.6	1955	46,XX
IV.6	III.5 III.6	1957	46,XY
IV.7	III.5 III.6	1960	45,XX,D-,D-,t(DqDq)+
Abortion	III.8 III.9	1962	Not known
Abortion	III.8 III.9	1962	Not known
Abortion	III.8 III.9	1964	Not known
IV.8	III.8 III.9	1966	46,XY
Abortion	III.8 III.9	1967	Not known