Structure and inheritance of some heterozygous Robertsonian translocations in man

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Summary. Banding studies in 25 Robertsonian translocations showed that *all* could be interpreted as stable dicentrics. The mechanism for their stability is likely to be the proximity of their centromeres but centromeric suppression could also have a role. In many of these dicentric translocations, discontinuous centromeric suppression, as indicated by chromatid separation at one of the centromeric regions, was observed in C-banded preparations. A further observation of undefined relation to the first was that the ratio of the two constitutive centromeric heterochromatin (CCH) regions from the component chromosomes of the translocations was variable in the same translocation type, e.g. t(13;14). It is proposed that this ratio may influence the segregation ratio. Abnormal spermatogenesis is suggested as the likely mechanism for the difference in the proportion of aneuploid offspring in the progeny of maternal and paternal heterozygotes. Neither of the t dic(21;21)s could be interpreted as isochromosomes. It is proposed that Robertsonian fusion translocations be defined as stable, dicentric, whole-arm translocations, with both centromeres in a median position and resulting in the loss of a small acentric fragment during their formation. It is suggested that they occur at high frequency between telocentric or, as in man, certain acrocentric chromosomes because of some intrinsic property of those chromosomes not possessed by metacentric chromosomes and mediated by interphase association of centromeres.

Whole-arm translocations were first proposed by Robertson in 1916, to correlate changes in chromosome morphology with certain taxonomic relations in insects. The concept developed to mean the translocation of acrocentric or telocentric chromosomes with the inclusion of two entire long arms in the major translocation product. If the translocation was dispersed then individuals bearing the stabilized homozygous form would eventually appear. The generally accepted model for Robertsonian translocation has been breakage immediately adjacent but on opposite sides of the centromere in the two chromosomes involved and the exclusion of one centromere from the major translocation product (White, 1961; Hirschhorn and Cohen, 1969), i.e. unequal reciprocal translocation. That the centromeres fuse, or that neither is lost, appearing as a single centromere under light microscopy,

has been proposed by Hsu and Mead (1969). A not necessarily exclusive alternative has been suggested by Ferguson-Smith (1967, 1971), i.e. that an abnormal recombination event occurs between homologous regions, e.g. the repeated 18 and 28s ribosomal cistrons in man resulting in a dicentric translocation product, the regions often being on non-homologous chromosomes. Isochromosome formation has been considered as a possible model for some specific Robertsonian translocations, e.g. t(21;21) in man (Fraccaro; Kaijser, and Lindsten, 1960).

Electron microscopy studies on a human t(D;G) (Barnicot, Ellis, and Penrose, 1963), and on some mammalian metacentric chromosomes (Comings and Okada, 1970), have provided support for the concept that both centromeric regions are included in Robertsonian translocations. Also C-banded Robertsonian translocations in the mouse often appear to have 4 heterochromatin masses instead of

the usual 2 seen in the telocentric chromosomes (Chen and Ruddle, 1971). This quadripartite structure in some metacentrics can also be seen in heterochromatin stained karyotypes of *Mus poschiavinus*. In man, Niebuhr (1972c) studied 5 balanced Robertsonian translocations. Heterochromatin staining showed 4 masses in all of the translocations except 1, a t(15;21) where 6 masses were seen and it was likely that the satellites of the chromosome 21 were incorporated. This suggests that many Robertsonian translocations are dicentric, but before any real distinction can be made between the possible mechanism of origin, the regular breakpoints will have to be determined. In man, many studies on Robertsonian translocations are being published with Q- and/or G-banding but without heterochromatin staining and, therefore, the dicentric nature or otherwise of various Robertsonian translocations has not been commented upon.

In this study the structure of the region surrounding the centromeres was examined by C-, G, and Q-banding in as many Robertsonian translocations as were available from the New South Wales Registry of Chromosomal Abnormalities to indicate whether: (a) Robertsonian translocations commonly had their breakpoints in their short arm, and if so, what is the likely mechanism, and (b) whether

the structure of the centromeric region influenced the segregation of the chromosomes.

Subjects and methods

Patients comprised every available Robertsonian translocation from the New South Wales Registry of Chromosomal Abnormalities at the Prince of Wales Hospital, Sydney, N.S.W. 2031, Australia.

Routine chromosome preparations were flame spread from cells stored in fixative for Cases 10 and 14 who were not available for restudy. All other cases were banded from air dried preparations. G-bands (0.1% trypsin in DPB) and C-bands (0.07N NaOH followed by 18 hours $2 \times$ SSC) were photographed using Copex Pan Rapid (Agfa Gaever—ASA 20). Q-bands (0.005% quinacrine mustard in phosphate buffer pH 7.0) were photographed with Pan F (Ilford—ASA 50) using a HBO200W lamp and BG12 excitor and 530 μ m barrier filters. Development for both PanF and Copex was in Ilford FF 20% for 2 minutes at 20°C.

Ten metaphase plates of each banding type were examined in each study for G-, C-, and Q-banding. Q-banding was only applied to those translocations involving a chromosome 13.

Results

The results are summarized in the Table. The translocation chromosomes from each case both in

TABLE

Case No.	Translocation	Sporadic or Familial	*Chromosome Registry No.	Banding Studies on	Proband	Translocation Chromosome with 2 Regions of CCH
1	(14;21)	F	0101	III.2	Down's IV.2	+
2	(14;21)	F	0144	II.1	Down's III.1	+
3	(14;21)	F	0293	II.1	Down's III.4	+
4	(14;21)	F	0796	II.2	Down's III.1	+
5	(14;21)	F	0705	II.7	Down's III.6	+
6	(14;21)	F	0797	III.2	Down's IV.3	+
7	(14;21)	S	0291	Proband	Down's	+
8	(14;21)	S	0186	Proband	Down's	+
9	(14;21)	S	0270	Proband	Down's	+
10	(14;21)	S	0367	Proband	Down's	+
11	(14;21)	S	0345	Proband	Down's	+
12	(14;21)	S	0372	Proband	Down's	+
13	(13;21)	F	0502	II.3	Down's III.1	+
14	(13;21)	F	0045	II.2	Down's III.3	+
15	(13;21)	F	0794	II.1	Down's III.2	+
16	(15;21)	F	0795	II.6	Down's III.3	+
17	(13;22)	F	0168	I.1, II.1, II.2	Patau's II.1	Merged CCH
18	(14;22)	F	0555	II.2, III.1, IV.1	Down's IV.1 primary trisomy	Merged CCH
19	Primary trisomy 21 (21;21)	S	0299	Proband	Down's	+
20	(21;21)	S	0322	Proband	Down's	+
21	(13;14)	F	0861	Proband and mother (carrier)	Fetus (carrier) screened for increased maternal age	+
22	(13;14)	F	0550	Proband	Retarded bone growth not seg. with t(13;14)	+
23	(13;14)	?	0881	Proband	Infertile adult male (carrier)	+
24	(13;14)	F	0691	Proband and mother (carrier)	First born with Patau's; (no M/C's)	+
25	(13;14)	?	0573	Proband	Two early M/C's; no full-term offspring	+

* N.S.W. Chromosome Abnormalities Registry No.

FIG. 1. Cases 1 to 6 are from balanced carriers of familial $t(14;21)$'s; Cases 7 to 9 are from probands with mutant $t(14;21)$'s; G-banded (left) and C-banded (right) translocation chromosome from each case.

FIG. 2. Cases 10 to 12 are from probands with mutant $t(14;21)$'s; Cases 13 to 15 are from balanced carriers of familial $t(13;21)$'s; Case 16 is from a balanced carrier of a $t(15;21)$; Case 17 is from a balanced carrier of a $t(13;22)$; Case 18 is from a balanced carrier of a $t(14;22)$; Cases 19 to 20 are from probands with mutant $t(21;21)$'s; G-banded (left) and C-banded (right) translocation chromosome from each case.

C- and G-bands are shown in Fig. 1 to 3. The pedigrees of Cases 1 to 6 are shown in Fig. 4 and those of Cases 13 to 18 in Fig. 5. Q-banding in Cases 13 to 15 showed that the intensely quinacrine

fluorescent band of the 13 centromeric region was present in the translocation chromosome.

Progeny IV.3 and IV.6 in Case 1, IV.4 in Case 6, III.4 in Case 14 and II.2 in Case 17 were prenatally screened, and IV.3, the only aneuploid fetus, was therapeutically aborted. The twin abortuses conceived following III.1 in Case 14 spontaneously aborted after prenatal diagnosis was undertaken. The single specimen of amniotic fluid obtained at amniocentesis (the twinning was unrecognized) grew secondary trisomy 21 clones. Tissue cultures of the aborted dizygotic twins showed one was a secondary 21 trisomic while the other had normal chromosomes.

All of the Robertsonian translocations contained two regions of centromeric heterochromatin (CCH). In Cases 16 and 17 these two regions have largely merged into a CCH mass which is larger than that in the homologue of either component.

FIG. 3. Cases 21 to 25 are from balanced carriers of $t(13;14)$'s; G-banded (left) and two C-banded (right) translocation chromosomes from each case.

FIG. 4. Pedigree of Cases 1 to 6.

Two preliminary observations can be made about the position and size of these two CCH regions:

(a) Chromatid separation at one of the regions occurred in many cells of a number of the translocations, e.g. the C-banded translocation chromosome of cells used to illustrate Cases 1, 2, 5, 7, 10, 18, and 19 (Fig. 1 and 2). In Case 21 (Fig. 3) the C-banded translocation chromosome on the left exhibits chromatid separation at the 14 CCH region while that on the right at the 13 CCH region. In Cases 22 and 24 (Fig. 3) the C-banded translocation chromosome on the left in each exhibits chromatid separation at the 13 centromere.

(b) A second observation is that the relative amounts of the two CCH regions in the translocation chromosomes varies between translocations, e.g. in the $t(14;21)$'s Cases 5 and 6 alone have more CCH at the 14 region than at the 21 region. Similarly of the $t(13;21)$'s only Case 13 had more CCH

at the 21 region than at the 13 region. In Cases 21 to 25 there is a graduation from Case 21 with the 13 derived CCH < 14 CCH to Case 25 with the 14 derived CCH < 13 CCH.

Discussion

Dicentric nature of Robertsonian translocations

It was evident that all of the Robertsonian translocations clearly contained the centromeric constitutive heterochromatic regions (CCH) from both contributing chromosomes. This is also likely to mean that both centromeres were present because:

(1) The amounts of CCH in the translocation chromosomes were such to suggest that there was no loss of CCH.

(2) There was some separation between the CCH region in the translocation chromosomes, suggesting

FIG. 5. Pedigree of Cases 13 to 18.

that the breakpoints were often in the nucleolar organizing constrictions.

(3) The G- and C-banding patterns were consistent with two contributions of CCH rather than CCH and chromosome satellites from one chromosome and neither from the other, e.g. some chromosome satellites are G-band positive or negative and C-negative or positive but there was a quadripartite structure, longitudinally bipartite structure, or two large merging CCH regions always present in the C-banded translocation chromosomes. Hsu *et al* (1973) have reported a presumptive Robertsonian translocation that was confirmed as a monocentric. The proposita, with partial Patau's syndrome, had the karyotype; 46,XX,-13+t(13;13) (p12;q13). A balanced carrier for a translocation such as this, would have another sizeable *centric* element presumably satellited on both ends and as such this would be a true reciprocal translocation.

Cases 19 and 20 were both $t(21;21)$ (Fig. 2) with different amounts of CCH at the two centric regions in the translocation chromosomes and so could not be interpreted as isochromosomes.

It follows that a short arm event in human acrocentric chromosomes is likely to be responsible for

Robertsonian translocation. Centric fusion is a somewhat unsatisfactory descriptive term because of the intercentric gaps in many of the Robertsonian translocations. However, the terms Robertsonian fusion and Robertsonian fission translocation, referring to the chromosomes not the centromeres, are suitable to describe the formation of dicentric from telocentrics and the reverse concept.

An hypothesis suggesting a short arm event to account for Robertsonian translocations in man has been proposed by Ferguson-Smith (1967, 1971). This hypothesis argues that an abnormal recombination event mediated by true synapsis within centromere localized ribosomal cistrons could occur between different acrocentric chromosomes resulting in polymorphisms or dicentric translocation. It is quite probable in man that the D and G short arm localized 18 and 28s ribosomal cistrons (Henderson, Warburton, and Atwood, 1972) are involved but there are no non-nucleolar organizing acrocentrics in man. In the mouse, which also has a high frequency of Robertsonian translocation, the ribosomal cistrons are localized to the mid long arms of only three autosomes (Henderson *et al*, 1974). However, as in man an interphase association of

non-homologous centromeres is often observed (Ohno, Christian, and Stenius, 1963; Hsu *et al*, 1971; Spence-Campbell, Forsythe, and Nesbitt, 1972), and other molecular interchanges may be involved in Robertsonian translocation formation in the mouse.

Centromeric suppression

The stability of each of these dicentric translocations may be the result of two factors; the closeness of the centromeres and the suppression at times of one or the other of them. This phenomenon of centromeric suppression was first described in *Triticum* (Sears and Camara, 1952) in which one of the centromeres is active in meiosis, the other in mitosis. In human cytogenetics, there is a growing body of evidence for this concept. Relatively stable dicentrics have been described in marker Y chromosomes (Angell, Gianelli, and Polani, 1970); in a t(5;13) (Niebuhr, 1972a); in a telomeric fusion of two X chromosomes (Distèche *et al*, 1972), and in a tandem translocation mosaic, 46,XY/45,XY,tan(14;15) (q32;q26) (Koulischer and Lambotte, 1974).

We have a further case in a proposita with Turner's syndrome, who was a mosaic; 45,X/46,X,mar. Y. The marker Y possessed two CCH regions and had the proximal G-band of the normal Y long arm at its centre with the centromere and short arm of a Y chromosome on either side of the central band. However, in 80% of orcein stained cells, it appeared as a submetacentric chromosome. In the remainder it appears as a pair of parallel chromatids or two constrictions were evident.

Centromeric suppression is indicated then by chromatid separation at the suppressed centromere while on C-banding the CCH is still present in each chromatid. Suppression is unlikely to be continuous but may occur at critical times.

In Robertsonian translocations, centromeric suppression has been described at a 13 centromere in a t(13;14) by Niebuhr (1972b). On quinacrine staining, the intensely fluorescent duplex spots of the 13 CCH region were widely spaced. In a further case, Niebuhr (1972c), a t(13;13), the duplex spots of one of the contributing 13 chromosomes, were widely spaced in 20% of the cells. Chromatid separation at one centromere in this series of Robertsonian translocations, was observed in many cells of a number of the translocations (see results).

A further observation of undefined relation to the first is that the ratio of the two CCH regions varies between individual translocations of the same

translocation type (see results). The amount of centromeric heterochromatin at the centromere in routine C-banded preparations is often 15 region > 13 > 14. On the assumption that this is reflected in the Robertsonian translocated chromosomes then the usual t dic(13;14) would have the 13 CCH region > 14 region, resembling Cases 21 to 22 rather than cases 23 to 25 (Fig. 3). Both of the former cases were ascertained accidentally with no relevant clinical history, while the latter cases with the opposite CCH ratio had a more suggestive clinical history. This preliminary observation suggests that a working hypothesis in the examination of t(13;14) may be that the segregation ratio is influenced by the relative amounts of the two CCH regions in the translocation.

Segregation

Of all the translocations (Table), 18 out of 25 were t(D;G) and the ascertainment was Down's syndrome in 19 out of all the cases. However, there was an excess of t dic(14;21) in the t(D;G) group, there being only 3 t dic(13;21) and one t dic(15;21). This excess was also observed by Cohen (1971) and Jacobs *et al* (1974) in larger samples. There were clear object lessons from Case 18, who on banding was found to have a primary trisomy 21 and a balanced t dic(14;22) and also from Case 17, where the proposita had Patau's syndrome caused by an unbalanced t dic(13;22). When the t(D;21)'s are pooled (see results) then there were more chromosomally unbalanced progeny born to maternal than to paternal carriers. In either case there was equivalence with the number of spontaneously aborted progeny in the first trimester. Initial evidence that segregation ratios in the offspring of male and female translocation carriers may be quite different was shown by Hamerton *et al* (1961). Equations applicable to the segregation ratios in t(D;21) have been developed by Stene (1970a, b), and Stene (1970c) has calculated the risk rate for mongolism for female carriers as 0.10085 ± 0.01825 . Because the segregation ratio for male carriers varies in the different family studies published (Stene, 1970c), the probability of a male carrier having a mongol child could not be calculated but was estimated as very small. With only 6 families with t(14;21), 3 with t(13;21), and 1 with t(15;21) there were insufficient data in this study for a comparison of segregation ratios in the different translocations. Only in Cases 17, a t(13;22) and in 24, a t(13;14) was there a proband with Patau's syndrome. In 33 families with t(Dq;Gq) (Hamerton, 1971) ascertainment was by a proband or probands with Down's syndrome,

none by Patau's syndrome. This dearth of Patau's probands may be accounted for by the following:

(a) The relative infrequency of $t(13;21)$ or $t(13;14)$.

(b) Differential viability of embryos with Down's or Patau's syndromes.

(c) Other mechanisms, e.g. centromeric dominance or suppression.

In these data there were 6 $t(14;21)$'s to 3 $t(13;21)$'s, which, if reflected in the (unbanded) published cases means a significant proportion of $t(13;21)$. Also the $t(13;14)$ group is by no means uncommon and yet the risk in many individual translocations of this group is zero with no increased abortion rate or infertility, suggesting that mechanisms other than (a) or (b) are influential.

If centromeric suppression influences segregation in $t\ dic(D;G)$ s and $t\ dic(D;D)$ s, then it may help to explain the absence of Patau's progeny, e.g. if in a particular $t\ dic(13;21)$ the 21 centromere was often suppressed, then adjacent I segregation would result in 21 trisomic and 21 monosomic gametes, while adjacent II segregation would result in 13 trisomic and 13 monosomic gametes. Conversely, if the 13 centromere was suppressed, then 13 trisomic and monosomic gametes would be produced. However, adjacent II segregation will be very rare in translocations that regularly form chain trivalents as $t(D;G)$ s and $t(D;D)$ s do in man (Hamerton, 1971). Considering only adjacent I segregation and excluding the presumably lethal monosomies, then 21 centromere suppression will result in 21 trisomic gametes and 13 centromere suppression in 13 trisomic gametes. With the same argument in the $t\ dic(13;14)$'s then 14 centromeric suppression will result in 14 trisomic gametes and 13 centromeric suppression in 13 trisomic gametes.

The finding that female heterozygotes more readily produce abnormal offspring in $t(Dq;Gq)$ as well as in human reciprocal translocations generally suggests that the female is less able to eliminate chromosome imbalance during meiosis or by means of genetic selection than is the male (Hamerton, 1971).

The distinction between these two areas is unlikely to be made experimentally in man, but Gropp, Giers, and Kolbus (1974) have designed an elegant system to examine autosomal trisomy in the mouse which provides some comparative data concerning these mechanisms. They examined the proportion of aneuploid gametes at male M2 and back-crossed male and female metacentric heterozygotes of Robertsonian translocations to elucidate fetal wastage and aneuploid embryogenesis. They

found a similar difference in the proportion of aneuploid back-crossed progeny between male and female Robertsonian translocation heterozygotes and attributed this to augmented aneuploid segregation in the females. However, on comparing their data on the proportion of aneuploid gametes at M2 in the males, there is little difference between the Robertsonian translocation heterozygotes and the stabilized Robertsonian translocation homozygotes. It follows that a reduction in the proportion of aneuploid gametes is likely to have already occurred in the heterozygote males, possibly between M1 and M2. The pairing difficulty—abnormal spermatogenesis hypothesis of Peacock and Miklos (1973) and Miklos (1974)—could be invoked to provide a mechanism. In human Robertsonian translocations, the high incidence of chain trivalents (Hamerton, 1971), the chains indicating somewhat unsaturated pairing, is also compatible with the above hypothesis.

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