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The prevalence of translocations in parents of children with regular trisomy 21: a possible interchromosomal effect?

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SUMMARY It has been suggested that translocations, and perhaps other chromosome rearrangements, disturb meiotic disjunction of uninvolved chromosome pairs and predispose to trisomic offspring. If so, then one would expect an excess of translocations not involving chromosome 21 among the parents of regular trisomic Down's syndrome patients. Such translocations have been reported, but mostly as anecdotal single case reports or very small series. In an attempt to collect a larger series, a collaborative study of regular Down's syndrome families was made in southern England. This was retrospective, and covered periods of 7 to 10 years since 1970. The number of regular trisomy families investigated was 1454.

Only 945 of the 2908 parents were karyotyped, and 10 balanced reciprocal translocations not involving chromosome 21 were identified, together with one Robertsonian (13q14q). Expressing these as percentages of the parents tested (945), prevalences are as follows: reciprocals 1·06%, Robertsonians 0·11%, and all translocations 1·16%. Expressed as percentages of the total parents (2908), tested and untested, the prevalences are 0·34%, 0·03%, and 0·37% respectively. The 'true' prevalences, that is what would have been found had all parents been tested, must lie between these two sets of figures. The prevalence of reciprocal translocations exceeds that found for consecutive banded newborn infants, which is 0·16%, and this excess may reflect a real interchromosomal effect. Robertsonian translocations in the banded newborn series are at a frequency of 0·11%, identical to that found in the tested parents of regular trisomics. Interpretation of these figures is critically dependent upon the real prevalence of translocations among the newborn, estimates of which increase as technical methods are improving.

'Interchromosomal effect' implies an interactive disturbance of meiosis, whereby a structural chromosome rearrangement upsets disjunction or distribution of chromosome pairs not involved directly in the rearrangement and results in unbalanced or aneuploid gametes and offspring. Such an effect has been observed in *Drosophila* and in mouse translocations, and has been claimed to occur also in man.[1–3] Reports have been of single cases or very small series, and these reports are of little value in documenting this effect, which in man remains unproven.[4–7] Aurias *et al*[8] documented five Down's syndrome families with a balanced reciprocal translocation not involving chromosome 21 from a total of 10 000 karyotypes in their department. Stoll[6] claims 'interchromosomal effect' in four of the 40 reciprocal translocations reported from his laboratory.

The observation of four families with a regular trisomy 21 child and a parent with a balanced reciprocal translocation not involving chromosome 21, detected within the Oxford region during a decade,[9] led to estimates of 0·68% (3/439) as the minimum prevalence of reciprocal translocations in Down's syndrome with regular trisomy, and 0·91% (4/439) as the minimum prevalence of reciprocal translocations in the mothers of such Down's

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syndrome cases. Exclusion of families in which the Down's syndrome proband was not karyotyped made the prevalence of balanced reciprocal translocations 1·24% in parents tested, or 0·52% per total parents, tested and untested. These figures greatly exceeded the then current estimate of 0·078% (1/1280) for the prevalence of balanced reciprocal translocations in the general population,[4] and prompted extension of the Oxford study to regions immediately adjacent. Chromosome banding methods were employed during the greater part of the Oxford study period and the study periods within the neighbouring regions. This collaborative and retrospective study was set up expressly to examine prevalence of reciprocal translocations in parents of regular trisomics, but prevalence of Robertsonian translocations is also reported.

Material and methods

The initial Oxford study covered the years 1970 to 1980, during which 416 cases of Down's syndrome were karyotyped. Of these, 384 had regular trisomy 21 or mosaicism for 46/47,+21 and were included in the analysis. The study was extended by examination of families karyotyped at Salisbury General Hospital, Salisbury, at Southmead Hospital, Bristol, and at East Birmingham Hospital, Birmingham, over approximately the same time period. All cases of regular trisomy 21 identified as routine service work within these regional cytogenetic laboratories within the periods quoted were included. Mosaics with a 46,normal/47,+21 karyotype were also included, as were other mosaics with a 47,+21 cell line and a case of 48,XYY,+21. In this way a further 1070 families were added to the analysis, making a total of 1454 (table 1).

Excluded from the study were all families in which the diagnosis of Down's syndrome was a purely clinical one and not confirmed by karyotyping, although in some cases one or both parents did have chromosome examination. (There were, for example, combining Oxford and Birmingham figures, 94 mothers and 54 fathers of such untested Down's syndrome patients, all these parents having normal karyotypes but being excluded from analysis.) The study was set up to examine the prevalence of reciprocal translocations in the parents of regular trisomics, and where a reciprocal translocation was found in the Down's syndrome child, but the parents were not tested, the family was also excluded. Cases of reciprocal or Robertsonian translocations originally identified outside the study periods, but re-examined during these periods, would create obvious bias and were excluded. All cases with structural rearrangements involving chromosome 21, such as reciprocal or Robertsonian translocations involving this chromosome, inversions of 21, or a ring, were excluded; although not further subjected to analysis, such exclusions are listed. Inversions involving chromosomes other than 21 were not analysed, as we feared incomplete ascertainment, and the true population frequency of such inversions has perhaps been underestimated.[10] Parental cases of sex chromosome aneuploidy were identified, but are not listed. For further information on exclusions see table 1 and the appendix.

TABLE 1 *Numbers of cases studied by regions.*

Lab/region	*Period*	*Total Down's syndrome*	*Down's syndrome with rob/rcp/inv/r(21)*	*Other Down's syndrome*
Birmingham	1974–1980	190	12	178
Bristol	1974–1981	400	19	381
Oxford	1970–1980	416	32	384
Salisbury	1971–1980	534	21	513
Total		1540	84	1456

The total of 1456 Down's syndrome without rob/rcp/inv/r(21) includes two families with pairs of affected sibs, so there are only 1454 parental pairs for study.

Results

The results of the survey are listed, analysed, and compared in tables 2, 3, and 4, and the details of individual translocation families and the manner of ascertainment are shown in the appendix.

The initial Oxford study covered 384 families with regular trisomy 21; 323 parents were tested, among

TABLE 2 *Numbers of parents tested and number of translocations found, excluding t(21).*

	Tested	*Not tested*	*Total*	*No of rcp*	*No of rob*
Mothers	545	909	1454	7	0
Fathers	400	1054	1454	3	1
Total parents	945	1963	2908	10	1

Mothers: rcp included 1;7, 1;17, 1;20, 2;4, 6;22, 7;11, 9;18.
Fathers: rep included 3;8, 11;22, 18;20, rob(13q14q).

TABLE 3 *Prevalence of translocations in tested parents and total parents.*

(a) The prevalence of rcp and rob in tested parents is as follows:		
Tested mothers	rcp 7/545=1·28%	rob 0/545=0%
Tested fathers	rcp 3/400=0·75%	rob 1/400=0·25%
Tested parents	rcp 10/945=1·06%	rob 1/945=0·11%
(b) Prevalance expressed as per total parents, tested and untested, is as follows:		
Total mothers	rcp 7/1454=0·48%	rob 0/1454=0%
Total fathers	rcp 3/1454=0·21%	rob 1/1454=0·07%
Total parents	rcp 10/2908=0·34%	rob 1/2908=0·03%

TABLE 4 *Balanced structural rearrangements (rcp, rob) in neonatal and amniocentesis surveys, and in parents of regular trisomy 21.*

Author	Date	Survey size	rep		rob	
			No	%	No	%
Consecutive newborn surveys						
Hamerton *et al*[11]*	up to 1975	46 150	36	0·08%	42	0·09%
Hamerton *et al*[11]	1970–1973	14 069	11	0·08%	13	0·09%
Nielsen and Sillesen[12]	1971–1974	6099	7	0·11%	9	0·15%
Buckton *et al*[13]	1976–1977	3993	3	0·08%	3	0·08%
Hansteen *et al*[14]	1978–1979	1830	5	0·27%	4	0·22%
Maternal age amniocenteses						
van Dyke *et al*[10]	1978–1981	8158	14	0·17%	9	0·11%
95% confidence limits banded newborn[10]			0·01–0·19%		0·00–0·13%	
Parents of regular trisomy 21, this study 1970–1981						
Parents: all/tested		2908/945	10	0·34–1·06%	1	0·03–0·11%
Mothers: all/tested		1454/545	7	0·48–1·28%	0	0%
Fathers: all/tested		1454/400	3	0·21–0·75%	1	0·07–0·25%
This study, excluding Oxford data						
Parents: all/tested		2140/622	6	0·28–0·96%	1	0·05–0·16%
Mothers: all/tested		1070/364	3	0·28–0·82%	0	0%
Fathers: all/tested		1070/258	3	0·28–1·16%	1	0·09–0·38%
Corrected prevalences–see Discussion†						
Parents: all			0·41–0·55%		0·10%	

*Pooled data from earlier surveys, reported in Hamerton,[11]
†Adjusted to allow for the probable presence of translocations in some of the untested parents.

whom four balanced reciprocal translocation carriers were identified. Expressed per parents tested the prevalence of reciprocal translocations was 1·24%. Expressed per total parents, tested and untested, the prevalence was 0·52% (4/2×384).

Extension of the study to the neighbouring regions added a further 1070 families. Among these were identified a further six balanced reciprocal translocations and a single Robertsonian (13q14q). Expressing these additional findings per parents tested the prevalence of reciprocal translocations was 0·96%. Expressed per total parents, tested and untested, the prevalence was 0·28%. The prevalence of Robertsonian translocations not involving chromosome 21 was 0·16% per parents tested, or 0·05% per total parents.

Combining Oxford and subsequent data, reciprocal translocation prevalence was 1·06% per tested parents, or 0·34% per total parents. Prevalence of Robertsonian translocations not involving chromosome 21 was 0·11% per tested parents or 0·03% per total parents.

Discussion

Observation of the high figures for the Oxford region was the reason for extension of the study. Exclusion of the Oxford results (table 4) shows the initial high frequency of balanced reciprocal translocations to be confirmed in a study of the adjacent regions.

As not all the 2908 parents were karyotyped the true figure for prevalence of reciprocal translocations must lie between the prevalence in tested parents and the prevalence in all parents, tested and untested (table 3).

In cases 1, 7, and 10 (appendix), although a reciprocal translocation was present in a parent, it had not been passed to the trisomic offspring. Since these three cases appeared among the 939 tested parents, we might expect to find among the 1963 untested parents a further six reciprocal translocations (that is, 1969 × 3/939), making the true prevalence 16/2908, or 0·55% for all parents, mothers and fathers combined. Alternatively, if we argue that the untested parents carry balanced reciprocal translocations at the frequency found in the earlier newborn surveys (about 0·1%), the untested 1963 parents would carry just a further two translocations, making the count of balanced reciprocals 12/2908, a frequency of 0·41%. These 'corrected prevalences' are shown in table 4, which also shows prevalence estimates for balanced reciprocal and balanced Robertsonian translocations, as made from consecutive newborn surveys. These figures are compared with frequencies found in maternal age amniocenteses,[10] with the findings in parents of regular trisomy 21, and the estimated 'corrected prevalences', as described above. Balanced reciprocal translocations appear to be over-represented in the Down's syndrome families (tables 3 and 4). Even the lower figures, as given in table 3(b) and in the left hand of the paired figures in the lower lines of table 4, obtained by disregarding the possibility of untested parents being translocation carriers, lie above the 95% confidence limits of van Dyke *et al*,[10] and are several-fold above those quoted in all newborn surveys except that of Hansteen *et al*.[14] Crucial to any arguments about a possible interchromosomal effect are reliable figures for prevalence of translocations in the general population. It may yet prove that currently accepted figures considerably underestimate this incidence. The earlier newborn surveys were made without the benefit of banding. The later studies[10 14] have suggested slightly higher figures, particularly for reciprocal translocations.

In contrast to the problem of determining the true prevalence of reciprocal translocations in a newborn or a parental population, the prevalence of Robertsonian translocations could be securely established even without banding. The general population prevalence of Robertsonian translocations lies close to 0·11%, of which no more than

one-fifth (0·02%) involve chromosome 21. Unless, as seems unlikely, the prevalence in parents of Down's syndrome children lies below the general population prevalence there would be approximately two further Robertsonian translocations not involving chromosome 21 among the 1963 untested parents, that is, a total of 3/2908 parents, which is 0·10%. Thus, the prevalence of Robertsonian translocations not involving chromosome 21 in parents of children with regular trisomy 21 lies close to the accepted general population mean.

The maternal age effect well recognised in Down's syndrome might be supposed to be absent when a parental reciprocal translocation contributed to the meiotic non-disjunction. Therefore, we might expect to find the reciprocal translocation group of parents younger, on average, than the other parents of regular trisomy 21 children. For the Oxford series of Down's syndrome (standard trisomy 21, excluding the reciprocal translocation families) the mean maternal age was 31·13 years (age recorded in 286 cases), and the mean paternal age was 32·60 years (age recorded in 164 cases). Table 5 lists the parental translocation carriers by age, together with the age of their spouses. Mean age of the maternal reciprocal translocation carriers was 28·07 years, and mean age of the paternal reciprocal translocation carriers was 28·5 years, figures which are well below the means for parents of Down's syndrome children (Oxford). The figure shows the ages of Oxford and other parental carriers of reciprocal translocations against a background of Oxford parents not carrying a reciprocal translocation, but with a Down's syndrome child, born within the region during the years 1970 to 1980. The mean age of the four Oxford mothers with a reciprocal translocation was 29·0 years (whole year ages corrected by adding 0·5 years). No parents with a reciprocal translocation appear in the long 'tail' of older parents.

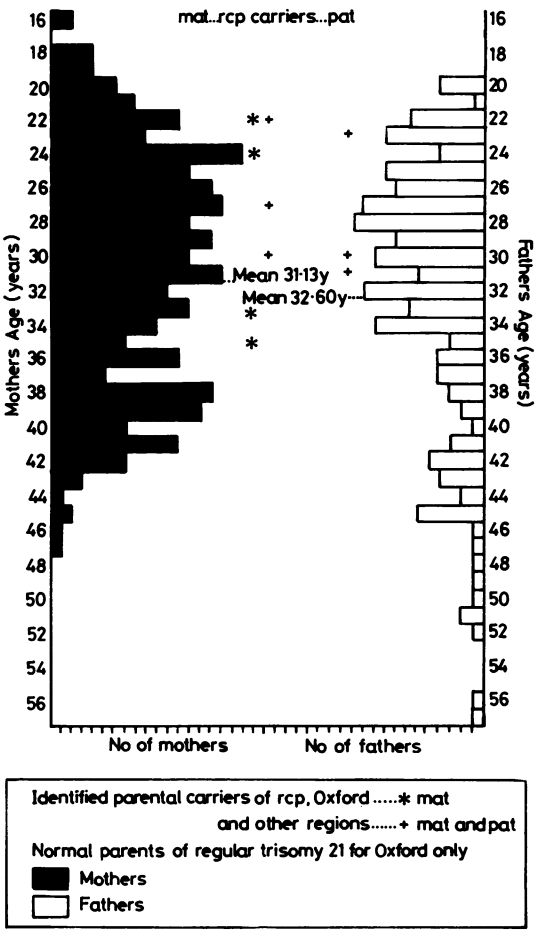

FIGURE *Histogram showing distribution of maternal age and paternal age, where recorded, for the parents of regular trisomy 21 DS (Oxford only), and the age of rcp carrier parents of regular DS for Oxford and other regions. Mean maternal age and mean paternal age shown for Oxford parents only (mean MA 31·13 y, n=286, SD=6·86; mean PA 32·60 y, n=164, SD=7·97).*

TABLE 5 *Age at birth of Down's syndrome child, parents carrying reciprocal translocation, and their spouses.*

Case No	*Mother's age*	*Father's age*
1 rcp	27*	29
2 rcp	32	30*
3 rcp	37	31*
4 rcp	25	23*
5 rcp	22*	23
6 rcp	35*	34
7 rcp	24*	26
8 rcp	33*	40
9 rcp	22*	24
10 rcp	30*	33
11 rob	?	?

*Denotes the parent carrying a balanced translocation.

Finding a high prevalence of reciprocal translocations in parents of standard trisomy 21 Down's syndrome does not necessarily imply that these translocations increase the likelihood of parental meiotic non-disjunction. Proof is still lacking that the parent carrying the reciprocal translocation was the parent in whom non-disjunction for chromosome 21 occurred, but it is planned to reinvestigate the reciprocal translocation families to decide this. The possibility of the reciprocal translocation inducing post-zygotic disjunctional errors cannot be excluded. One mosaic was identified among the 10

cases of reciprocal translocation plus trisomy 21 reported here.

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APPENDIX *Case reports.*

Case	*Lab*	*DS karyotype*	*Mat karyotype*	*Pat karyotype*	*MA*	*PA*	*Translocation*	*Notes*
1	BI	N+21	rcp	N	27	29	(1;17)(p21;q21)	Routine karyotype, parents of DS. 4/4 sibs of mother all with rcp.
2	BI	rcp+21	N	rcp	32	30	(3;8)(q13;q24)	Sister of DS karyotyped when pregnant. She was found to carry the rcp, as was her father, and the child (at amniocentesis). The DS child was karyotyped subsequently.
3	BR	rcp+21	N	rcp	37	31	(11;22)(q25;q13)	Found at amniocentesis for MA 37. rcp also present in 2 other paternal relatives.
4	BR	rcp+21	N	rcp	25	23	(18;20)(p11;q12)	Ascertained through DS child. Father appears to get rcp de novo.
5	OX	rcp/rcp+21	rcp	N	22	23	(1;7)(cen1;cen7)	School referred as possible DS mosaic. Mother declined family follow-up.
6	OX	rcp+21	rcp	N	35	34	(2;4)(q31;q12)	Parents referred and karyotyped because of 6 spontaneous abortions plus DS child.
7	OX	N+21	rcp	N	24	26	(6;22)(q13;q11)	Parents karyotyped at their own insistence. Mother apparently de novo carrier of rcp.
8	OX	rcp+21	rcp	N	33	40	(9;18)(q34;q23)	Mother karyotyped after birth of DS, but there were 3 spontaneous abortions before birth of DS and one after. Maternal relatives later found to have rcp.
9	SA	rcp+21	rcp	N	22	24	(1;20)(p32;q12·2)	Ascertained through DS child. rcp in mother and 5 other relatives.
10	SA	N+21	rcp	N	30	33	(7;11)(p15;p11)	rcp found in mother and sister of DS, karyotyped because of anxiety regarding possible recurrence.
11	BI	N+21	N	rob	?	?	rob(13q14q)	2 DS born to 2 sisters. Sister of one DS pregnant, tested, carried rob, as did her father, father of one of the DS. The 2 sisters, linking the 2 DS, both had normal karyotypes.
Excluded from survey because outside study period when originally ascertained								
	BR	rob+21	rob	?	24	?	rob(13q14q)	Referred in 1971.
	BR	rcp+21	N	rcp	?	42	(2;4)(p11;p16)	Referred in 1967; reassessed in 1975 as special case.
Excluded from survey because parents not tested								
	BR	rcp+21	?	?	?	?	(9;17)(p13 or 21;p12 or 11)	Parents not available.

MA, PA = maternal, paternal age at birth of DS.
BI, BR, OX, SA = Birmingham, Bristol, Oxford, Salisbury.
N = normal, or no rcp/rob.
rcp, rob = balanced rcp, rob.