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Balanced rearrangements of the autosomes: results of a longitudinal study of a newborn survey population

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SUMMARY Thirty-six infants were identified by cytogenetic screening at birth as having balanced rearrangements of their autosomes, and 30 of them took part in a longitudinal study of their development, together with four of their affected sibs. With the exception of one child with a de novo reciprocal translocation who died, all children attended normal schools. Congenital malformations and short stature were present in only one child who had a de novo reciprocal translocation. The IQ scores of the 10 children with de novo translocations were significantly lower than those of the 20 children with familial translocations, but there were children in the de novo group of above average intelligence. Children with familial reciprocal translocations had significantly higher IQ scores than both the Robertsonian translocations and the controls, but the numbers in each category were small and a variety of different chromosomes were involved.

The effect of an abnormal karyotype on human brain development and subsequent cognitive ability is critical for antenatal counselling and for accurate prognosis in the liveborn. However, the available information on the effect of balanced rearrangements of the autosomes on cognitive and physical development is heavily biased by selective ascertainment in abnormal persons or environments.

In 1972, Breg *et al*[1] suggested that there might be an increased incidence of balanced reciprocal translocations among the seriously mentally retarded population, having identified four cases among 1000 such subjects. In 1974, Jacobs[2] described results from Edinburgh of chromosome analysis on 33 533 persons, 12 of whom were found to have de novo translocations. When the source of ascertainment was examined it was found that a significantly greater proportion came from the mentally retarded institutions that had been surveyed than from the 12 295 newborns examined. These results suggested that the possession of a de novo structural euploid rearrangement of the autosomes was, in some cases, associated with severe mental retardation, and Jacobs commented that the newborn survey follow-up data would be required to give a precise prognosis.

Numerous cytogenetic surveys of mentally retarded populations have been undertaken, mainly at institutions. The study of Speed *et al*[3] was unique in that it aimed at surveying a complete population of mentally subnormal patients at home or in hospital. Despite examining 2770 persons, none was found with a balanced autosomal rearrangement, although the incidence of other types of chromosome abnormalities was similar to that found in other surveys. The authors comment that there may have been underascertainment of high grade defectives in rural areas, and in fact the number certified was considerably less than the 10 000 expected in the population of 500 000 at a 2% mental subnormality rate; this may be partly accounted for by early deaths.

In a survey of a Child Psychiatric and Mental Retardation Clinic, Funderburk *et al*[4] found seven 'balanced' autosomal rearrangements among 455 mentally retarded children compared with four among 1679 psychiatric patients. Reciprocal translocations and pericentric inversions only were identified. Review of published reports covering chromosome analysis in 5048 mentally retarded persons confirmed an excess of de novo translocations, specifically of the non-Robertsonian type. This finding was confirmed by Jacobs *et al*[5] in a survey in Hawaii and by Fryns and van der Berghe.[6]

As regards the association of congenital malformations with balanced autosomal rearrangements, the

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original reports of the newborn cytogenetic surveys did not reveal any increased incidence, despite the fact that there had been numerous reports of cases of de novo balanced translocations identified on account of multiple congenital malformations.[7]

The effect of balanced rearrangements, familial or de novo, on development will be determined definitively when there is sufficient information on large numbers of cases who have been identified by newborn screening and compared with adequate controls from the same population. In their paper dealing mainly with the inheritance and cytogenetics of translocations, Evans *et al*[8] also presented follow-up information on 24 infants with balanced autosomal rearrangements from the newborn survey of 14 069 infants in Winnipeg. It was not possible to state with certainty whether any of the children had de novo rearrangements owing to incomplete family studies. Only minor physical differences (upward slanting palpebral fissures and dermatoglyphic patterns) were noted on examination. Six of the 24 children were old enough for psychometric assessment and their mean IQ score was not significantly different from that of a small control group.

Nielsen and Krag-Olsen[9] reported follow-up of the 32 children with autosomal translocations found among 11 148 consecutive newborn infants in Denmark based on a parent or teacher report or both. All five de novo translocations were described as having normal mental development, while three abnormalities were reported among the 27 familial translocations: one case each of psychiatric referral, mental retardation, and early death. While generally reassuring, the report lacks any psychometric assessment of probands and controls.

In this communication we present the results from the Edinburgh newborn survey of a longitudinal study on 30 of the 36 children identified as having balanced autosomal rearrangements, and on four of their affected sibs, comparing their results with a large control group from the same population.

Material and methods

The methodology of the original cytogenetic surveys has been described in detail elsewhere.[10 11] Of 15 673 infants who had full chromosome analysis shortly after birth, 36 were found to have balanced autosomal rearrangements. Children with inversion of chromosome 9 were considered to have a normal variant. Parents were informed of their child's chromosome constitution and in the majority of cases parental karyotypes were also obtained. With parental permission the children were enrolled in the Edinburgh Longitudinal Study of Growth and Development, along with 67 children with sex chromosome abnormalities and the controls. Details of the assessment protocol have been published.[12] The controls used in this study were children with normal karyotypes from the same newborn population. The social class distribution in this group was similar to that of the probands, social class being categorised by the father's occupation at the time of the child's birth (social class 1, professional, to social class 5, unskilled).

Cognitive ability was assessed by a psychologist unaware of the child's karyotype using, in general, the McCarthy Scale of Children's Abilities (MSCA)[13] for children under the age of 7 years (range 4·4 to 5·9 years) and the Wechsler Intelligence Scale for Children (WISC)[14] for those over that age (range 6·1 to 7·7 years).

Z scores of the IQ were calculated from the formula

$$Z = \frac{\text{IQ score for proband} - \text{mean IQ score for controls}}{\text{Standard deviation of the mean IQ score for controls.}}$$

Group comparisons were made using Student's t test for samples of unequal variance, except when the nature of the data dictated the use of Fisher's exact test. A level of significance where $p < 0.05$ (two tailed) was used throughout unless otherwise stated.

Results

CONTROLS

In 128 children (66 boys and 62 girls) under the age of 7 the mean MSCA score was 110·2 SD 14·0. For the 92 children (48 boys and 44 girls) over the age of 7 a higher score of 118·3 SD 13·7 was obtained using the WISC. (The explanation for this apparent disparity lies in the fact that the WISC was standardised in 1949, and the population mean score is influenced by secular changes. Flynn[15] has calculated that a rise of 0·3 IQ points occurs annually in the mean population score, requiring restandardisation of IQ tests at intervals. Since this study was started the revised form WISC-R has been introduced to overcome this problem but results from the WISC cannot be transposed directly. To facilitate comparisons, test results have been converted into Z scores.)

DE NOVO TRANSLOCATIONS

The results of the IQ tests and details of the karyotype are given in table 1 and show a wide range from less than 50 up to 136. It should be noted that all surviving children attended normal schools, although two required remedial teaching and one speech therapy. Clinical data are presented in table 2, illustrating that phenotypic abnormalities were present only in case 8. The mean age of the mothers

TABLE 1 *De novo translocations: intelligence quotients and karyotypes.*

ID No	*Social class*	*IQ*	*IQ Z score*	*Karyotype*
1	1	136	+1·84	46,XX,t(4;9)(p12;q32)
2	2	122	+0·84	46,XX,t(11;15)(p15;q15)
3	3	122	+0·84	45,XX,t(13q;14q)
4	2	109	−0·68	45,XX,t(13;14)(p11;q11)
5	2	101	−1·26	45,XX,t(14q;21q)
6	4	101	−1·26	46,XX,t(1;15)(q2;q15 or 21 or 22)
7	1	96*	−0·27	46,XY,t(6;9)(q25;p13)
8	2	95	−1·70	46,XY,t(6;7)(q23;q22)
9	3	84	−2·50	46,XX,t(2;10)(q11;q22)
10	3	<50	−3·00	46,XY,t(5;11)(p11;p15)

*WISC-R: see acknowledgements.

(28·8 years) and fathers (31·9 years) of these children was slightly, but not significantly, greater than that of the control mothers (27·4 years) and fathers (29·2 years).

The mean Z score for IQ of this group was −0·72±1·47. While one of the children would almost certainly have required institutional care had he survived, there were three children in this group with above average cognitive ability, and one child was in the superior range. As a group, their mean IQ score was not significantly lower than that of the control group, but it was significantly lower than that of all the familial rearrangements ($p<0·01$ one tailed) and of the combined familial reciprocal and Robertsonian translocations ($p<0·025$ one tailed). In view of the chromosomal heterogeneity of this small group, it is more meaningful to consider their results individually rather than to amalgamate their widely differing scores.

FAMILIAL REARRANGEMENTS

Robertsonian translocations

The IQ scores and karyotypes for the seven children in this group, together with results for two of their sibs, are given in table 3 and the clinical information in table 4. The mean Z score for cognitive ability in this group was −0·10±0·94 and was not significantly different from that of the controls. Phenotypically, three children had minor malformations but all were healthy and attended normal schools.

Reciprocal translocations

The IQ scores and karyotypes for the seven children

TABLE 3 *Familial Robertsonian translocations: intelligence quotients and karyotypes.*

ID No	*Social class*	*IQ*	*IQ Z score*	*Karyotype*	*Origin*
11	2	138	+1·44	45,XY,t(14q;22q)	Paternal
12	1	132	+1·00	45,XX,t(13q;22q)	Paternal
13	3	117	−0·09	45,XX,t(13q;14q)	Paternal
14	3	109	−0·09	45,XY,t(13q;14q)	Maternal
15	3	109	−0·68	45,XX,t(13q;14q)	Paternal
16	3	105	−0·97	45,XY,t(14q;22q)	Paternal
17	2	100	−1·34	45,XY,t(13q;14q)	Paternal
18*	1	127		45,XY,t(13q;22q)	Paternal
19†	3	125		45,XY,t(13q;14q)	Paternal

*Sib of case 12.
†Sib of case 15.

TABLE 2 *Clinical information on children with de novo translocations.*

ID No	*Parental age*		*Pregnancy and delivery*	*Birth weight (kg)*	*Congenital malformations*	*Height centile*	*Progress*
	Mother	*Father*					
1	26	29	PET Normal delivery	3·02	None	75	Infantile eczema (familial), otherwise healthy
2	24	32	Normal	3·40	None	50	Healthy child
3	27	36	Normal pregnancy Breech delivery	3·21	None		Healthy child
4	26	27	Normal	2·69	None	25	Healthy child
5	34	42	Normal	3·50	Dislocatable R hip at birth	3	Myoclonic epilepsy aged 3 weeks. Normal EEG. Complete recovery in 3 weeks. Normal child
6	24	27	Normal pregnancy Caesarian section	3·06	Partially dislocatable hips at birth	50	Healthy child
7	27	30	Normal	3·17	None	25	Healthy child
8	30	33	PET Normal delivery (at 37 weeks)	1·94	Abnormal facies, hypospadias, and chordee	−3·0 SD	Marked delay of speech development. Normal school, remedial teaching. Speech therapy
9	23	25	Normal	3·88	None	50	Healthy child. Remedial teaching at normal school
10	41	40	Antepartum haemorrhage Normal delivery	3·62	None		Age 9 weeks, development delayed, onset of screaming fits, then myoclonic epilepsy. EEG abnormal, spike and wave complexes. Progressive deterioration with grand mal epilepsy until death at age 3 years 11 months. No necropsy

PET = pre-eclamptic toxaemia.

TABLE 4 *Familial Robertsonian translocations: clinical information.*

ID No	*Pregnancy and delivery*	*Birth weight (kg)*	*Congenital malformations*	*Height centile*	*Progress*
11	Mild PET Forceps delivery	3·36	None	75	Healthy child
12	PET SVD	3·28	None	3	Healthy child
13	Normal	3·35	None	90	Healthy child
14	Normal	3·60	Hypospadias	10	Healthy child
15	Normal pregnancy Forceps delivery	4·36	None	75	Healthy child
16	PET SVD	3·57	None	75	Healthy child
17	Normal	3·02	Syndactyly of 2nd and 3rd toes on both feet (familial)	25	Healthy child
18	Normal	3·68	Minor degree of hypospadias	10	Healthy child Daytime wetting up to 8 years
19	Normal	3·78	None	25	Surviving twin, other was fetus papyraceous

SVD = spontaneous vertex delivery.

TABLE 5 *Familial reciprocal translocations: intelligence quotients and karyotypes.*

ID No	*Social class*	*IQ*	*IQ Z score*	*Karyotype*	*Origin*
20	4	131	+0·93	46,XY,t(1;14)(q42;q23)	Maternal
21	3	131	+0·93	46,XX,t(3;13)(q12 or 13;q31)	Maternal
22	5	130	+1·41	46,XX,t(11q−;13q+)	Maternal
23	5	127	+0·64	46,XY,t(11q−;13q+)	Maternal
24	3	125	+0·49	46,XX,t(3;7)(p14;p22)	Maternal
25	3	124	+0·99	46,XX,t(7;11)(p22;q23)	Maternal
26	3	117	−0·09	46,XY,t(11;19)(q14;q13)	Maternal

in this group are shown in table 5 and the clinical information in table 6. Here the mean Z score for cognitive ability of $0·76 \pm 0·44$ was significantly higher than that of the controls ($p < 0·05$) and of the familial Robertsonian translocations ($p < 0·05$). Only one child had a score marginally below the mean for the control group. The mean social class of this group at $3·43 \pm 0·73$ was significantly lower than that of the Robertsonian group at $2·43 \pm 0·73$. While the numbers are small this further accentuates the higher ability of the reciprocal translocation group. The health and growth of these children was unremarkable and there were no congenital malformations.

Y;autosomal translocations and inversions

The IQ scores, karyotypes, and clinical information for these six children, together with that of two affected sibs, appear in tables 7 and 8. As there were

TABLE 7 *Y;15 translocations and inversions: intelligence quotients and karyotypes.*

ID No	*Social class*	*IQ*	*IQ Z score*	*Karyotype*	*Origin*
27	3	121	+0·20	46,XY,t(Y;15)(q12;p11)	Paternal
28	3	110	−0·61	46,XY,t(Y;15)(q12;p11)	Paternal
29	3	105*	−0·37	46,XY,t(Y;15)(q12;p11)	Paternal
30	1	133	+1·07	46,XX,inv(1)(p32;q42)	Maternal
31	2	125	+0·49	46,XX,inv(6)(p21;q21)	Paternal
32	3	121	+0·77	46,XX,inv(2)(p11;q13)	Paternal
33†	2	143		46,XY,inv(6)(p21;q21)	Paternal
34‡	3	117		46,XX,inv(2)(p11;q13)	Paternal

*WISC-R: see acknowledgements.
†Sib of case 31.
‡Sib of case 32.

TABLE 6 *Familial reciprocal translocations: clinical information.*

ID No	*Pregnancy and delivery*	*Birth weight (kg)*	*Congenital malformations*	*Height centile*	*Progress*
20	Normal	3·09	None	90	Healthy child
21	Normal	3·06	None	10	Healthy child
22	Maternal UTI Caesarian	3·71	None	75	Healthy child
23	Mild PET Caesarian	3·30	None	25	Healthy child
24	PET Normal delivery	4·70	None	50	Healthy child
25	Maternal UTI Normal delivery	2·98	None	90	Healthy child
26	Normal pregnancy Forceps delivery	3·78	None	50	Fractured clavicle at birth

UTI = urinary tract infection.
PET = pre-eclamptic toxaemia.

TABLE 8 *Y;15 translocations and inversions: clinical information.*

ID No	*Pregnancy and delivery*	*Birth weight (kg)*	*Congenital malformations*	*Height centile*	*Progress*
27	Normal	3·49	None	25	Maternal atypical tuberculosis treated during pregnancy. Child treated postnatally. Behaviour problems after maternal desertion
28	Normal	3·04	None	50	Healthy child
29	Threatened abortion at 25 weeks	3·62	None	90	Behaviour problems and learning difficulties. Poor visual-motor abilities. Psychiatric referral. Father (Y;15) had same problems in childhood
30	Normal	3·83	None	97	Healthy child
31	Normal	3·63	Haemangioma on left foot	75	Eczema and asthma (familial)
32	Normal	3·27	None	90	Healthy child
33	Normal pregnancy Forceps delivery	4·15	None	75	Eczema and asthma (familial) Neonatal jaundice requiring phototherapy
34	Normal	3·27	None	75	Healthy child

only three children in each group mean scores have not been calculated.

Behaviour problems were present in two of the Y; autosomal translocations, one probably being of environmental origin (case 27), while those present in case 29 may have had some association with the karyotype as the father was similarly affected.

The combined Z score for IQ for all 20 children in the group was $0{\cdot}31 \pm 0{\cdot}78$. The children with familial Robertsonian and reciprocal translocations had a mean Z score for IQ of $0{\cdot}33 \pm 0{\cdot}85$. Neither of these two groups was significantly different from the controls.

Comparison of the seven de novo reciprocal translocations with the seven familial reciprocal translocations does reveal a significant deficit in IQ score for the former group ($p < 0{\cdot}05$).

MISCELLANEOUS CASES WITH LIMITED INFORMATION

These cases are described in table 9.

ORIGIN OF THE FAMILIAL TRANSLOCATIONS

When the parental origin of the two main groups of familial translocations was examined, it was found that for the Robertsonian translocations six cases were of paternal origin, one was maternal, and no parental information was available for three children. All seven reciprocal translocations were of maternal origin. In this group two of the assessed children were sibs (cases 22 and 23) reducing the maternal origin to six, but as the origin of one of the translocations in the group of children with limited information was also maternal, there remain seven cases of maternal origin.

Examination of the distribution of parental origin of these two groups of translocations in those ten newborn surveys with reasonably complete data is shown in table 10, and suggests that the observed distributions in the Edinburgh study, while significant in both instances ($p < 0{\cdot}04$ Fisher's exact test), were probably chance findings.

TABLE 10 *Incidence and origin of balanced autosomal translocation from newborn survey.*

Reference	*Number*	*Robertsonian*				*Reciprocal*			
		DN	*mat*	*pat*	*Total*	*DN*	*mat*	*pat*	*Total*
16	2081	0	1	0	1	0	0	0	0
10	11 680	1	0	6	10*	4	6	0	10
11	3993	2	1	0	3	2	2	0	4
17	14 069	0	6	5	13*	1	2	6	11*
18	2500	0	1	0	1	2	0	0	2
19	4500	0	0	0	0	3	1	1	6*
20	5049	2	5	2	9	2	2	3	7
21	6099	0	5	3	8	1	1	5	7
22	2626	0	3	2	5	0	0	0	0
23	930	0	0	0	0	0	1	0	1
24	1830	1	0	3	4	0	3	2	5
Totals	55 354	6	22	21	54	15	18	17	53

*Includes cases of unknown origin.

TABLE 9 *Miscellaneous cases (limited information).*

ID No	*Social class*	*Karyotype*	*Origin*	*Progress*
35	1	45,XY,D−,D−,t(Dq;Dq)+	Unknown	Healthy child
36	3	45,XY,D−,D−,t(Dq;Dq)	Unknown	Emigrated, untraced
37	2	45,XY,tdic(D;D)(pl;pl)	Unknown	Infantile eczema. Normal school. Healthy child
38	2	46,XY,t(11;12)(q25;q13)	Maternal	Normal until 2·5 years, no further contact
39	3	46,XX,inv(8)(p23;q11)	Maternal	Eczema and asthma. Normal school
40	3	46,XX,inv(10)(p13;q22)	Maternal	Healthy child

Discussion

The principal conclusion that can be drawn from these results is that balanced autosomal rearrangements in the main are not as harmful as previous reports would imply. Adverse effects were restricted to three children in the de novo group. Of the 30 children examined, only one (case 10) could be categorised as mentally retarded. In addition, one other child (case 9) achieved an IQ score which was 2·5 SD below the mean for the control group and may therefore have been affected by the chromosome abnormality, although her mother is also of low normal intelligence. She is, however, coping within a normal school with remedial teaching for reading. A third child (case 8) had speech and learning difficulties together with markedly reduced stature. There was evidence of impaired intrauterine growth as well as congenital malformation of the genitalia. However, postnatal growth velocity was normal, and with the aid of intensive speech therapy and remedial teaching he is coping in a normal school. There were, however, three children in the de novo group of above average cognitive ability, one of whom is in the superior range.

The large variance in the results of the de novo group is to be expected in view of the differences in the chromosomes and the breakpoints involved but presents difficulties in genetic counselling of prospective parents when amniocentesis has revealed an affected fetus. The literature would imply that there is an appreciable risk of intellectual deficit, but until there are more extensive results on cases with unbiased assessment it remains difficult to quantify the risk.

The children with familial reciprocal translocations achieved IQ scores which were in the main above those of the controls. Bearing in mind the social class distribution already referred to, this is all the more impressive. In order to examine this finding in greater depth a further study comparing sibs carrying the familial reciprocal translocation with those having a normal karyotype is being undertaken.

Claims for increased cognitive ability in groups distinguishable on biological rather than socio-economic variables have been made previously. It has been suggested that persons with the adrenogenital syndrome[25] or retinoblastoma[26] may have increased cognitive ability. These claims are open to criticism of the controls used in the studies. Whereas the numbers involved in this study were small and a chance finding cannot be excluded, the appearance of translocations in evolutionary progress[27] would not conflict with the suggestion that those reciprocal translocations that survive and are reproduced may confer a small intellectual advantage rather than disadvantage.

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Addendum

We have subsequently appreciated that case 8 among the de novo translocations was identified during an interval when chromosome analysis was not being performed on every baby but only on those with congenital malformations, so there was selection in his identification. Consequently the Z score for the de novo translocations should be $-0{\cdot}61$ ($1{\cdot}51$). The comparison between the de novo and the familial translocations remains significant.