Cytogenetic and epidemiological findings in Down syndrome, England and Wales 1989 to 1993

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Abstract

Data from the National Down Syndrome Cytogenetic Register is used to describe the cytogenetics and epidemiology of registered cases. The register comprises notifications from cytogenetics laboratories in England and Wales. This report is of 5737 cases registered between 1989 and 1993: 2169 prenatal and 3436 postnatal diagnoses, and 132 spontaneous abortions. Eighty eight registrations were from multiple pregnancies.

Ninety five percent had regular trisomy 21. In 4% there was a translocation, mostly Robertsonian t(14;21) or t(21;21). One percent were mosaics with one normal cell line. Mean maternal age was raised in free trisomy 21, but not in translocations. Where families had been investigated, about a third of translocations were inherited, six to seven times more often from the mother than the father. Associations between free trisomy 21 and structural chromosomal defects in the births were no more common than expected from newborn series.

The overall sex ratio was raised (male to female: 1.23 to 1), and there was an excess of associated male sex chromosomal aneuploidy. However, in mosaics with one normal cell line the male to female ratio was 0.8 to 1, and in twins discordant for trisomy 21 there was also a female excess.

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Key words: Down syndrome; national sample; karyotypes; prenatal diagnosis.

The National Down Syndrome Cytogenetic Register¹ receives reports of cases found to have a karyotype characteristic of phenotypic Down syndrome from all clinical cytogenetic laboratories in England and Wales. It is estimated that it comprises reports relating to about 94% of Down syndrome (DS) births in England and Wales, and data on nearly all DS terminations.² This report relates to 5737 cases registered in the calendar years 1989 to 1993, including 3516 livebirths, which are derived from a cohort of about 3.5 million live births.

The size and representative nature of this data set make it possible to present extensive descriptive data on the different karyotypic sub-

groups which contribute to the Down syndrome phenotype, including parental age, sex ratio, and pregnancy outcome.

Methods

DATA COLLECTION

The methods of data collection and processing have been described previously.¹⁻³ Since 1.1.89, with the support of the Association of Clinical Cytogeneticists (ACC) and its members, a form completed by the laboratory is received for each DS karyotype. This includes questions on the cytogenetic findings, indication for referral, diagnostic test performed and date, maternal age or date of birth, and outcome of the pregnancy and date.

For a majority of cases the referring physician receives a copy of the form with a request to supply any missing information. Checks and corrections are made for possible duplication of records because of confirmatory studies, some at a second laboratory. Additional information and leads to the small number of unregistered cases are found by exchanging information with the Office of Population Censuses and Surveys (OPCS). They receive notifications within 10 days from local Health Authorities of births with congenital anomalies.⁴ Up to mid-1994 an additional check was made using the Chromosome Abnormality Database at Oxford (funded by the MRC and managed under the auspices of the Association of Clinical Cytogeneticists). All sets of data are anonymous but have sufficient identifying details to allow case matching.

TYPE OF REFERRAL

Cases include those referred for prenatal diagnosis (2169), postnatal diagnosis (3436), or investigations after a spontaneous embryonic or early fetal loss (miscarriage) (132). Postnatal diagnoses and miscarriages are registered in the calendar year of occurrence and all prenatal specimens in the calendar year in which the first diagnostic sample was received by the laboratory.

LABORATORY TECHNIQUES

The types of samples received by the laboratories have ranged from amniotic fluid to chorionic villus or placental biopsy, to fetal blood, skin, or cord. Practice has varied over time,

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particularly the use of chorionic villus samples, where there was a relative decline in first trimester sampling (85% of all CVS in 1989, 65% in 1993) following reports of risk of fetal limb anomalies.⁵ Second trimester tests on placental samples represented 7% of all cytogenetic diagnoses in 1993.

No details are available of the cytogenetic techniques used but it is assumed that standard current practices apply, including the identification of chromosomes at moderate banding levels. In only two cases reported was banding unsuccessful, diagnosis resting on the presence of an additional small acrocentric chromosome.

Both amniotic fluid and chorionic villus samples are susceptible to pseudomosaicism from maternal contamination or confined placental mosaicism. To our knowledge the techniques used usually involve multiple analyses with results derived from two or more cultures and, if mosaic, a repeat sample if time permits. Laboratory standards are monitored through the United Kingdom National External Quality Assessment Scheme in Clinical Cytogenetics (NEQAS).

PREGNANCY OUTCOME

The laboratories report any information they have on pregnancy outcome but for prenatally diagnosed cases the notification of the karyotype is often received before the outcome of pregnancy is known. In about half of the cases, information about outcome is sent to the register by the referring clinician, and in the remainder, the data managers of the register follow up prenatal diagnoses to determine the outcome. At the time of the preparation of the present report this was missing for nearly 8% of prenatal diagnoses reported (168/2169).

INCLUSIONS AND EXCLUSIONS

The present account includes information on all eligible cases pre- and postnatally diagnosed

in England and Wales entered on the database by mid May 1995. Diagnoses relating to a small minority of mothers resident outside England and Wales (for example, the Channel Islands, British Forces overseas) are excluded. In contrast to previous reports using this data set, this account also includes registrations of early embryonic losses or fetal deaths (miscarriages) with diagnosed trisomy 21. The legal gestational limit of late fetal deaths (stillbirths) changed during the life of the register from a baby without any sign of life born after 28 completed weeks of gestation to one born after 24 completed weeks. Registration practices changed accordingly.

QUALITY AND COMPLETENESS OF DATA

The collaboration with the Chromosome Abnormality Database showed only a small number of mosaics and translocations which were missed from initial registrations. For livebirths only, a "capture-recapture" comparison⁶ with the independently ascertained cases notified anonymously on a national scale to the Office of Population Censuses and Surveys within 10 days of birth suggests that the National Down Syndrome Cytogenetic Register is about 94% complete.

Ninety four percent of the postnatal referrals were within 10 days of birth, but the oldest child was referred at the age of 3 years. The ascertainment of affected embryonic or fetal deaths is known to be incomplete. There are almost certainly selection biases in this group, which may have been referred for reasons such as the presence of clinical signs, a "positive family history", or a history of recurrent miscarriages.

Parental age was known for 96.4% of mothers but only 36.6% of fathers. The survey team are continuing to collect missing data so that information is most complete for 1990, the second year of the register where less than 2% of maternal ages are missing, and least complete for 1993 where 8% are still missing.

Table 1 Karyotype groups and subgroups

Karyotype group	No	%
Free trisomy	5451	95.0
Regular + variants*	5411	94.3
Translocations of chromosomes other than 21†	15	0.3
Double aneuploidy‡	25	0.4
Contributory translocations	220	3.8
Robertsonian§	214	3.7
t(13;21)	9	0.2
t(14;21)	100	1.7
t(15;21)	8	0.1
t(21;21)	90	1.6
t(21;22)	3	<0.1
Other rea(21) leading to trisomy	4	<0.1
Reciprocal	6	0.1
t(A;21) (6)¶	6	0.1
Mosaics (normal/free trisomy)	66	1.2
All	5737	100

* Regular free trisomy with or without chromosome variants including inversion (9) or (Y).

† Free trisomy 21 associated with reciprocal or Robertsonian translocations (appendix cases 1–15).

‡ Includes four mosaics (appendix cases 16–40).

§ Includes three mosaics and one double translocation (appendix cases 41–44) and one case with an additional structural anomaly: 46,Y,inv(X)(p11.2q26),-14,+t(14q21q).

|| Appendix cases 45–48.

¶ Appendix cases 49–54. Includes two sibs: unbalanced t(6;21)mat.

TREND IN DIAGNOSES

Over the five complete years which are registered here (1989–1993), the numbers of diagnoses rose from 1103 in 1989 to 1188 in 1993, with a marked increase in prenatally diagnosed cases, the proportion of which rose from 29% in 1989 to 47% in 1993.² The increase in diagnoses is in part because of the expansion of prenatal screening, but is also related to the population shift towards older maternal ages, from a mean of 27.3 years in 1989 to 28.1 years in 1993.⁷ A report of the estimated maternal age specific rates over these years, in the absence of prenatal diagnosis, is in preparation.

GROUPING OF KARYOTYPES

Although the majority of karyotypes reported to this register were regular trisomy 21, there were also a number of mosaics and translocations. These were grouped into three main

Table 2 Time of diagnosis and outcome by karyotype group, number (%)

	Free trisomy			Contributory translocation (incl rea(21))		Mosaic	Total
	Regular	Translocation non-contrib	Double aneuploid	Robertsonian	Reciprocal		
<i>Prenatal diagnoses*</i>							
Termination	1753 (32.4)	9 (60)	5 (20)	37 (17.3)	3 (50)	22 (33.3)	1829 (31.9)
Livebirth/neonatal death	103 (1.9)	—	1 (4)	2 (0.93)	—	2 (3.0)	108 (1.9)
Late fetal death	22 (0.4)	—	—	—	—	—	22 (0.4)
Early fetal death	39 (0.7)	—	—	2 (0.93)	—	1 (1.5)	42 (0.7)
Outcome not known	161 (3.0)	1 (7)	3 (12)	1 (4.6)	—	2 (3.0)	168 (2.9)
Subtotal	2078 (38.4)	10 (67)	9 (36)	42 (19.6)	3 (50)	27 (40.8)	2169 (37.8)
<i>Postnatal diagnoses</i>							
Livebirth and neonatal death	3190 (59)	4 (27)	10 (40)	163 (76.2)	3 (50)	35 (53)	3405 (59.4)
Late fetal death (stillbirth)	29 (0.5)	—	—	1 (0.5)	—	1 (1.6)	31 (0.5)
Subtotal	3219 (59.5)	4 (27)	10 (40)	164 (76.6)	3 (50)	36 (54.5)	3436 (59.9)
<i>Spontaneous early fetal death (miscarriage)</i>							
	114 (2.1)	1 (7)	6 (24)	8 (3.7)	—	3 (4.5)	132 (2.3)
Total [row %]	5411 (100) [94.3]	15 (100) [0.3]	25 (100) [0.4]	214 (100) [3.7]	6 (100) [0.1]	66 (100) [1.1]	5737 (100) [100]

* Includes late diagnoses by fetal blood or placental biopsy after abnormal ultrasound findings.

classes as shown in table 1. We refer to structural changes not involving chromosome 21 as “non-contributory” and those involving 21 as “contributory”. The appendix provides a list of the exceptional karyotypes other than regular trisomy 21 or Robertsonian translocations and indicates the group to which they have been allocated.

Results

OUTCOME OF PREGNANCY BY KARYOTYPE GROUP

Table 2 shows how stage at diagnosis differed between the main karyotype classes. In those with regular trisomy, 38.4% were prenatally diagnosed and 2.1% were spontaneous early fetal losses. However, in the small subgroup of cases of double aneuploidy, 24% were spontaneous fetal losses. Of the 220 contributory translocations, 19.6% were prenatally diagnosed and 3.7% were spontaneous early fetal deaths, and among the mosaics 40.8% were prenatally diagnosed and 4.5% were found in spontaneous early fetal deaths.

FREE TRISOMY AND ASSOCIATED CHROMOSOMAL ANOMALIES

The 5451 cases with free trisomy included 15 cases of associated structural anomalies of other

chromosomes (eight with reciprocal and seven with Robertsonian translocations), and 25 doubly aneuploid, four being mosaic for the other aneuploidy. When subdivided by pregnancy outcome the associations with the 3308 affected livebirths (including 104 prenatally diagnosed cases) were two reciprocal and two Robertsonian translocations and 11 double aneuploids. Associated with the 2022 terminations, fetal deaths, or outcome unknown were six reciprocal and four Robertsonian translocations and eight other aneuploids. The 121 cases that had miscarried spontaneously before diagnosis included one translocation and six double aneuploidies.

PARENTAL AGE DISTRIBUTION

As would be expected, given that raised maternal age, alone or in combination with serum tests, is an indication of level of risk, the mean age of mothers who received prenatal diagnosis was raised, 36.2 years compared with 30.3 years in those whose babies had first been diagnosed postnatally, and 35.1 years in those who had miscarried. Table 3 shows mean maternal ages in the different outcome and karyotype groups, and separately for the pregnancies referred for diagnosis and those which had miscarried spontaneously. In each karyotype

Table 3 Mean maternal age (SD) by time of diagnosis and karyotype group

	Free trisomy			Contributory translocation (incl rea(21))		Mosaic	Total
	Regular	Translocation non-contrib	Double aneuploid	Robertsonian	Reciprocal		
<i>Prenatal diagnoses</i>							
All	36.3 (5.6) n = 2072	37.6 (4.1) n = 10	42.1 (3.8) n = 9	28.5 (7.2) n = 42	33.7 (2.5) n = 3	35.2 (6.2) n = 27	36.2 (5.7) n = 2163
<i>Postnatal diagnoses</i>							
All	30.5 (6.3) n = 3052	32.5 (7.6) n = 4	30.2 (7.1) n = 9	26.6 (5.2) n = 158	26.3 (4.0) n = 3	28.9 (4.7) n = 32	30.3 (6.3) n = 3258
<i>Pre- and postnatal diagnoses</i>							
All	32.8 (6.7) n = 5124	36.1 (5.5) n = 14	36.2 (8.2) n = 18	27.0 (5.7) n = 200	30.0 (5.0) n = 6	31.8 (6.2) n = 59	32.6 (6.8) n = 5421
<i>Spontaneous early fetal death (miscarriage)</i>							
All	34.8 (6.6) n = 100	43 (—) n = 1	42.4 (1.7) n = 5	31.9 (7.5) n = 7	—	39.7 (2.5) n = 3	35.1 (6.7) n = 116
Total	32.9 (6.7) n = 5224*	36.6 (5.6) n = 15	37.5 (7.7) n = 23	27.1 (5.8) n = 207	30.0 (5.0) n = 6	32.2 (6.3) n = 62	32.7 (6.8) n = 5537

* Missing maternal age in 200 cases.

Table 4 Maternal age distribution by karyotype and mean parental ages

Karyotype class	Maternal age									All known*	Mean mat age (SD)	Mean pat age (SD)
	<20	20-24	25-29	30-34	35-39	40-44	45-49	>49	Missing			
Free trisomy	154	539	947	1148	1546	833	51	6	187	5224	32.9	34.4
Regular + variants	—	1	—	4	4	6	—	—	—	(1970)	(6.7)	(7.7)
"Non-contributory" translocation	—	2	2	1	7	8	3	—	2	15	36.6	39.1
Double aneuploid	—	—	—	—	—	—	—	—	—	(7)	(5.6)	(10.5)
										23	37.5	40.7
										(9)	(7.7)	(6.6)
Contributory Robertsonian translocation	—	2	5	—	1	—	—	—	1	8	27.5	27.3
t(13;21)	—	—	—	—	—	—	—	—	—	(4)	(4.3)	(2.2)
t(14;21)	12	33	31	12	9	2	—	—	1	99	26.1	27.9
	—	1	3	4	—	—	—	—	—	(57)	(5.9)	(5.6)
t(15;21)	—	—	—	—	—	—	—	—	—	8	28.1	30.8
	—	—	—	—	—	—	—	—	—	(5)	(3.8)	(1.3)
t(21;21)	6	20	21	25	13	1	—	—	4	86	28.3	31.2
	—	—	—	—	—	—	—	—	—	(45)	(5.9)	(6.8)
t(21;22)	—	—	2	1	—	—	—	—	—	3	28.0	31.3
	—	—	—	—	—	—	—	—	—	(3)	(2.0)	(1.2)
Other rea(21)†	1	1	1	—	—	—	—	—	1	3	22.7	22.0
	—	—	—	—	—	—	—	—	—	(1)	(6.0)	(—)
Contributory reciprocal translocation t(A;21)	—	1	1	3	1	—	—	—	—	6	30.0	19.0
	—	—	—	—	—	—	—	—	—	(1)	(5.0)	(—)
Mosaic:normal/trisomy	1	7	16	12	16	9	—	—	4	62	32.2	34.5
	—	—	—	—	—	—	—	—	—	(24)	(6.3)	(7.9)
All	174	607	1030	1210	1597	859	54	6	200	5537	32.7	34.2
	—	—	—	—	—	—	—	—	—	(2126)	(6.8)	(7.7)
England & Wales livebirths 1989-1993‡	256 462	854 017	1 224 885	800 743	270 488	47 063	2259	286	—	3 456 205	27.7	—

* Number with known father's age in brackets. † See table 1. ‡ OPCS birth data, England and Wales.

group, the mean age of mothers who had miscarried spontaneously was higher than that of all diagnoses.

The distribution by maternal age groups and mean parental ages for each of the karyotypic subgroups are given in table 4 and compared with the England and Wales livebirth data.^{8,9} However, the latter is not precisely comparable and relates only to livebirths in the calendar years 1989 to 1993.

The highest maternal ages are in the groups where there is a free trisomy, with or without associated cytogenetic anomalies. The groups with a contributory translocation have lower maternal ages, particularly the subgroup t(14;21) and the few cases of structural change

in chromosome 21 leading to partial trisomy (appendix). Although the difference is not statistically significant, 12% of the t(14;21) group are born to mothers under the age of 20, compared with 7% in population births, and the mean maternal age is just lower than the population mean. It is because of their low maternal age that DS pregnancies with possible translocations are least likely to be ascertained prenatally.

Mean paternal ages, where known, are on average 1.5 years greater than those of the mothers, and their pattern follows that of mean maternal ages. However, paternal age data are not complete enough to warrant further analyses.

Table 5 Translocations: chromosomes involved, inheritance, and mean parental age

	Inheritance of anomaly (No)				Mean parental ages* by inheritance group (SD)							
	Maternal	Paternal	De novo	Not known	Maternal		Paternal		De novo		Not known	
					MMA	MPA	MMA	MPA	MMA	MPA	MMA	MPA
Non-contrib trans	5	5	—	5	36.4	41.0	33.2	39.7			40.2	36.5
					(3.4)	(4.2)	(7.5)	(17.7)			(3.6)	(0.7)
Contrib trans Robert	2	1	4	2	26.0	28.0	27.0	28	30.7		24.5	26.5
t(13;21)	—	—	—	—	(2.8)	(—)	(—)	(—)	(4.7)		(4.9)	(3.5)
t(14;21)	26	3	42	29	26.8	27.7	25.0	30.0	25.5	27.9	26.5	27.9
	—	—	—	—	(6.5)	(6.0)	(1.7)	(—)	(6.0)	(5.3)	(5.5)	(6.3)
t(15;21)	1	—	6	1	27.0	30.0			28.7	31.0	26	31
	—	—	—	—	(—)	(—)			(4.4)	(1.7)	(—)	(—)
t(21;21)	1	—	50	39	27.0	27.0			28.4	31.7	28.1	30.8
	—	—	—	—	(—)	(—)			(6.0)	(7.3)	(5.8)	(6.3)
t(21;22)	1	—	1	1	28.0	32.0			26.0	30.0	30.0	32.0
	—	—	—	—	(—)	(—)			(—)	(—)	(—)	(—)
Other rea(21)			3	1					25.5	22.0	17.0	
									(4.9)	(—)	(—)	
Reciprocal translocation t(A;21)	6	—	—	—	30.0	19.0						
	—	—	—	—	(5.0)	(—)						
Totals	42	9	106	78	28.4	28.8	29.8	34.5	27.3	29.7	28.1	29.9
	21 F	1 F	54 F	34 F	(6.3)	(6.7)	(6.7)	(12.5)	(6.0)	(6.4)	(6.5)	(6.1)
	21 M	8 M	52 M	44 M	42	22	9	6	103	59	74	36

* MMA = mean maternal age; MPA = mean paternal age.

Table 6 Sex ratio by stage of diagnosis, karyotype group, and mean maternal age: number (mean)*

	Prenatal			Postnatal			Spontaneous miscarriage			Total		
	Male	Female	Sex ratio	Male	Female	Sex ratio	Male	Female	Sex ratio	Male	Female	Sex ratio
Free trisomy	1162	916	1.27	1774	1445	1.23	63	51	1.24	2999	2412	1.24
Regular trisomy	(36.3)	(36.3)		(30.4)	(30.5)		(34.7)	(34.8)				
Non-contributory translocations	5	5	1.00	4	—	—	1	—	—	10	5	2.0
Double aneuploids	(38.2)	(37.0)		(32.5)			(43)					
(41.0)	5	4	1.25	8	2	4	2	4	0.5	15	10	1.5
(43.5)	18	24	0.75	(30.1)	(30.5)		(40)	(43)				
Contributory translocation	(30.1)	(27.4)		88	76	1.16	5	3	1.67	111	103	1.08
Robertsonian (incl reat(21))	2	1	2.0	(26.9)	(26.2)		(33.8)	(29.3)				
Reciprocal	(32.5)	(36)		2	1	2.0	—	—	—	4	2	2.0
(36.0)	6	21	0.29	(26.0)	(27)							
Mosaics	(32.5)	(36.0)		16	20	0.8	1	2	0.5	23	43	0.53
(30.1)	1198	971	1.23	(30.1)	(28.1)		(40)	(39.5)				
Totals	(36.2)	(36.2)		1892	1544	1.22	72	60	1.2	3162	2575	1.23
				(30.3)	(30.4)		(31.9)	(35.3)				

* Mean maternal age excluding those for which it is unknown.

INHERITANCE OF TRANSLOCATIONS

Cytogenetic results were available on both parents of 157 of the 235 cases with translocations. Of those investigated, the ratio of maternal: paternal:de novo was 42.9:106 (table 5).

The largest groups were the 100 cases of t(14;21) and the 90 cases of t(21;21). The parents of 71 of the t(14;21) group had been studied for evidence of familial transmission. Of these, 26 (37%) had received the anomaly from the mother and three (4%) from the father. Of the 51 cases of t(21;21) investigated, only one case was found to be of maternal origin and 50 were described as de novo. Mode of inheritance was not related to parental age and the only cases of translocations in which this featured was in the small group with a non-contributory translocation and free trisomy 21. In these there was a raised mean maternal age regardless of whether or not the structural anomaly had been inherited (table 5).

SEX RATIO BY KARYOTYPE

Table 6 gives the sex ratio by karyotype. In all karyotype groups other than the mosaics there was a marked excess of males. The overall sex ratio was 1.23, but that of the reported mosaics was 0.53. This female excess in mosaics was most marked in those diagnosed prenatally with a ratio of 0.29. The female bias was seen also in liveborn mosaics with a ratio of 0.80. In affected twins discordant for Down syndrome the sex ratio was 0.47 (see below).

In the 12 cases of double aneuploidy which involved sex chromosomes, there were nine cases of 48,XXY, +21, one 48,XYX, +21, one 48,XXX, +21, and one mosaic with one cell line of 45,X. Among the nine translocations inherited from the father there were eight males and one female Down syndrome, while among the 42 of maternal origin there were equal numbers of males and females (table 5).

Two births on the register were reported with anomalous sex, one 47,XX, +21 with a male phenotype, the other a "female" with karyotype 46,XY,t(21;21). Further details on these are awaited.

MULTIPLE BIRTHS

Included in the 5737 cases described in this account were 66 twins with a normal co-twin,

45 females, 21 males (sex ratio 0.47), and nine twin pairs who were concordant for sex and trisomy 21, six male-male and three female-female pairs (sex ratio 2.0). In four cases the birth notified to the register was one of a set of triplets. The sex of the co-twin of those not concordant for DS was often not given, but of the discordant co-twins for whom sex was known, 13 were female and 18 male (sex ratio 1.38). The four affected triplets were all female.

The laboratories are not always informed if a referred case was one of a multiple birth, and the clinicians were not asked this question in the early years of the register. Multiple births may therefore be underascertained.

The crude rate per thousand of the twin maternities which included one or more registered cases is 1.5%, slightly raised compared with that of 1.2% in the newborn population.⁸ However, this comparison makes no allowance for the terminations carried out of affected twins, nor for the raised risk of both twinning and DS associated with increasing maternal age. Further studies into the multiple births are in progress.

Discussion

The data reported here represent the largest national consecutive series of trisomy 21 diagnoses known to us, and we comment below on features of particular interest.

KARYOTYPIC SUBGROUPS

The distribution of different anomalies associated with DS is very similar to that in earlier reports.¹⁰ Regular trisomy 21, without any associated chromosomal anomaly, is reported in 94% of all cases, and an unbalanced Robertsonian translocation involving chromosome 21 in 3.7%. The overall rate of translocation of 5% in the births (table 2) is a little lower than in previous reports (5.6%,¹¹ 5.2% in liveborn,¹² 6.8% in newborn¹³), but the actual level will depend on the maternal age distribution and the rate of, and indications for, prenatal diagnosis.

The present data gave an opportunity to ascertain whether the frequency of non-contributory translocations associated with free trisomy differs from that found in newborn series. Hook *et al*¹⁴ and Jacobs *et al*¹⁵ have revised

published estimates for such series allowing for the effect of the introduction of banding techniques. Many of the data on the frequency of chromosome anomalies are derived from population studies on newborn infants.¹⁶ Considering only livebirths with free trisomy, the frequency of associated balanced reciprocal and Robertsonian translocations in the register data was 0.121% (four in 3306) (excluding 11 with double aneuploidy). This is lower than the rate in newborn infants of reciprocal and Robertsonian translocations estimated by Jacobs *et al*¹⁵ (0.264%:0.242%) or that estimated by Hook *et al*¹⁴ (0.275%). The 2143 pregnancy outcomes with free trisomy, other than livebirths, included 11 with associated non-contributory translocations (0.513%), compared with the 0.367% described by Jacobs *et al*¹⁵ in cases referred for prenatal diagnosis.

MATERNAL AGE

As expected, the register data show marked differences between maternal ages in the different karyotype groups ranging from a mean of 27.2 years in 213 cases with translocations involving chromosome 21, to 32.2 years in the group with mosaicism, 32.9 years in regular trisomy 21, 36.6 in those with free trisomy 21 and a non-contributory translocation, and 37.5 years in the 23 cases of double aneuploidy of known maternal age (table 3).

Mean maternal age was low in all the contributory translocation groups, 27.5 in the t(13;21) group, and even lower, 26.1, in the t(14;21) group. These findings are in line with the observations of Pulliam and Huether,¹² who reported the exceptional mean maternal age of 21.6 years (SE 1.18 years) for 11 cases of t(D;21) and Richards¹⁷ who reported a mean maternal age of 26.3 years for 52 cases of D;G translocation and 28.1 years for 52 cases of G;G translocation collected from published reports.

In the current series the mean maternal age of spontaneously aborted fetuses with primary trisomy 21 is consistently raised above that of affected terminations or births with similar karyotypes (table 3), although the possibility of selection bias for diagnosis cannot be ruled out. An association between a raised maternal age and risk of spontaneous miscarriage of chromosomally normal fetuses is well known,¹⁸ and such an association with trisomy 21 fetuses has also been described.¹⁹

FAMILIAL AND DE NOVO TRANSLOCATIONS

Excluding the re(21;21), where the structural anomaly is not normally inherited, in families who had been investigated, the ratios of inheritance patterns "maternal:paternal:de novo" is 42:9:103. Of those with t(21;21) only one of 51 tested families was found to be inherited.

Mean maternal ages were low whether the translocation was familial (maternal or paternal) or de novo. This must be an important observation when considering the aetiology of this class of trisomies.

SEX RATIO

The anomalous sex ratio of Down syndrome patients has long been recognised.^{20,21} The live-born population in England and Wales has a sex ratio of 1.05 (male/female).⁸ The overall ratio in this series, similar to that previously reported for Down syndrome,²² was 1.23. However, in the present series this varied by karyotype, being 1.24 in regular trisomies, but falling to 1.08 in Robertsonian translocations and 0.53 in mosaics (0.29 in those diagnosed prenatally and 0.8 in those diagnosed postnatally) (table 6). There are few published reports on sex ratio in mosaics. Nielsen *et al*²³ reported an excess of females (sex ratio 0.82) in 146 cases of mosaicism and translocations, compared to 1.21 in 1931 cases of primary trisomy 21, and a review by Richards²⁴ on mosaicism listed 67 males and 75 females collected in a collaborative study. Assuming there was no selective bias, this would lead to a sex ratio of 0.89. We are not aware of any explanation for these findings.

The high sex ratio in regular trisomy is a well known phenomenon. Petersen *et al*²⁵ investigated the possibility that it is accounted for by cases of paternal origin. These researchers used DNA probes to study the error in 27 cases with confirmed paternal meiotic non-disjunction, and found that the sex ratio was 3.5 (21/6) with a mean maternal age of 28.1 compared with a mean of 31.8 years when the error had been maternal. The authors suggested this shift of sex ratio owing to the paternally derived aneuploids could be a factor in determining the male preponderance in Down syndrome.

If, in the present series, 5% of the 5411 regular trisomy 21 cases were the result of paternal error, and taking the extreme case that these were all male (not supported by the data of Petersen *et al*²⁵), they would contribute 270 males to the remaining 2633 males expected, assuming a 1.05 population sex ratio. This would still only lead to an overall sex ratio of 1.16 (2903/2508). Moreover, if the raised sex ratio were attributable to cases of paternal origin one would expect the maternal age of male cases with regular trisomy to be lower than that of female cases. Data in table 6 show that this is not the case, mean maternal age is the same for affected males and females (36.3 years for both in prenatally diagnosed, and 30.4 for males and 30.5 for females in postnatally diagnosed cases). It remains possible that some of the male excess is because of cases of paternal origin. Also marked is the male excess of associated anomalies involving the sex chromosomes, 10 XXY or XYY with only one XXX. This may be explained by a differential survival of these groups in utero, though the birth frequency of the sex chromosome anomalies, 47,XXY and 47,XXX, are very close (0.06 and 0.05/1000 livebirths).¹⁴ Moreover it is intriguing that in cases with inherited translocations of paternal origin there were eight males to one female offspring, while for the 42 of maternal origin the sex ratio was 1.0. In the 106 identified as de novo, there were 54 females and 52 males, a sex ratio of 0.96 (table 6).

Appendix Exceptional karyotypes included in main groups: see footnotes to table 1

No	Case	Karyotype	Stage at diagnosis	Maternal age
Non-contributory reciprocal translation				
1	578	47,XY,+21,t(4;14)(p14p;q14q)mat	Pre	37
2	1037	47,XY,+21,t(5;18)(q15q21)pat	Post	33
3	4900	47,XY,+21,t(5;7)(q31.1;p15.1)	Pre	44
4	6812	47,XY,+21,t(1;14)(p36.11;p15.32)pat	Post	22
5	7101	47,XX,+21,t(9;16)(q34;p13)	Pre	40
6	8495	47,XX,+21,-8,der(8)t(4;8)(p15.3;p22)mat	Pre	34
7	8904	47,XY,+21,t(5;6)(q13;p23)pat	Pre	31
8	9200	47,XX,+21,t(1;7)mat	Pre	42
Non-contributory Robertsonian translocation				
9	692	46,XY,+21,t(13q14q)	Pre	39
10	2445	46,XY,+21,t(13q14q)	SA	43
11	4262	46,XY,+21,t(13q14q)	Post	35
12	4446	46,XY,+21,t(13q14q)pat	Pre	40
13	6818	46,XX,+21,t(13q14q)mat	Pre	35
14	8997	46,XY,+21,t(13q14q)pat	Post	40
15	8998	46,XX,+21,t(13q14q)mat	Pre	34
Double aneuploid				
16	270	48,XXY,+21	Post	38
17*	814	47,XY,+21/48,XXY,+21	Post	34
18	2324	48,XY,+21,+frag	Post	20
19	2332	48,XXY,+21	Post	27
20	2500	48,XXY,+21	Pre	45
21	2533	48,XXY,+21	Pre	41
22*	2748	47,XX,+21/48,XX,+18,+21	Pre	38
23	3095	48,XY,+21,+mar(mat)	Pre	42
24*	3106	47,XX,+21/48,XX,+8,+21	Post	26
25	4004	46,X,+21	Pre	41
26	4156	48,XXY,+21	Post	35
27	4623	48,XX,+21,+mar	Pre	49
28	4846	48,XXY,+21	Pre	38
29	5037	48,XXY,+21	Pre	39
30	5043	48,XX,+21,+21	SA	42
31	5117	48,XX,+16,+21	SA	42
32	5118	48,XY,+21,+22	SA	
33	5119	48,XX,+21,+22	SA	44
34*	6167	45,X/47,XX,+21 (20:80%) 10:40 cells	Post	35
35	6508	48,XXY,+21	Post	37
36	6697	48,XXY,+21	Post	
37	6790	48,XXY,+21	Post	20
38	7189	48,XX,+7,+21	SA	44
39	8026	48,XY,+14,+21	SA	40
40	8527	48,XXX,+21	Pre	46
Contributory Robertsonian translocation plus mosaicism or other rearrangement				
41	4368	46,XX/46,XX,-21,+i(21q)	Post	23
42	4642	46,XX,-21,+t(21q21q)/47,XX,-21,+t() +mar	Post	21
43	6390	46,XX/46,XX,-21,+i(21q)(92:8%)46:4 cell	Post	30
44	6118	46,XY,-21,+i(21q)t(4;18)(q27;p11.4)dn	Post	30
Other rearrangement (21)				
45	1116	46,XX,inv dup(21)dn	Post	
46	2070	46,XY,21p+ ,dn [probably dup21(q22.1-ter)]	Post	22†
47	3126	46,XX,dup(21)[q22.1→q22.13 or 22.2]	Post	17
48	6728	46,XX,-21,+rt(21;21)dn (ring)	Post	29
Contributory reciprocal translocation				
49	1057	46,XY,-6,+der(6)t(6;21)(p25q21)mat‡	Pre	31
50	2561	47,XY,-1,+der(1)+der(21)t(1;21)mat	Post	22
51	3123	46,XX,-6,+der(6)+der(21)t(6;21)mat	Post	27
52	3125	46,XY,-9,+der(9)t(9;21)(p24p21)mat	Post	30
53	8113	46,XY,-6,+der(6)t(6;21)mat‡	Pre	34
54	9187	47,XX,+der(21)t(10;21)(p11.2;q22)mat	Pre	36

Pre = prenatal diagnosis; Post = postnatal diagnosis; SA = miscarriage.

* Mosaic. † Clinically Down syndrome. ‡ Same mother.

Overall these analyses may provide some pointers for future studies on the variation in aetiology of trisomy 21. Unexpected findings have been the low sex ratio in mosaic cases, and the possibly raised maternal age in spontaneous early fetal losses compared with survivors with the same chromosome constitution. Much of the future work into the aetiology of Down syndrome will depend on the application of the DNA probes for chromosome 21, but only series of this size will generate enough cases of the rarer karyotypes to provide the type of descriptive epidemiology presented here.

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