European Journal of Human Genetics (2009) 17, 897 – 903

www.nature.com/ejhg

ARTICLE

Incidence of non-age-dependent chromosomal abnormalities: a population-based study on 88965 amniocenteses

Antonino Forabosco*[,1], Antonio Percesepe[1] and Sandra Santucci[1]

[1]*Department of Medical Genetics, University of Modena, Modena, Italy*

Current knowledge about the incidence of chromosomal abnormalities in the general population comes from studies in newborns carried out in the 70s, before the era of widespread prenatal diagnosis. In the following years, data on frequency of chromosomal abnormalities in the second trimester of pregnancy have been used in conjunction with the data on the natural history of chromosomally abnormal fetuses to infer maternal age-specific rates of cytogenetic abnormalities in live-born infants. Starting from the data gathered in 1995–1996 from all Italian cytogenetic laboratories (with 92% compliance to the study), we have compared the frequency of chromosomal abnormalities at amniocentesis in cases with maternal age of $\geq$35 years (51 758 individuals) and cases with maternal age of $<$35 years (37 207 cases). The comparison confirmed the age-dependency of aneuploidies, whereas none of the structural abnormalities showed age-related differences. Furthermore, among the mosaic aneuploidies, trisomy 21 and 45,X/46,XX were found with a significantly higher incidence in older women. Chromosomal abnormalities that showed no significant difference between the two groups were summed for the overall national cohort, providing a general estimate of the incidence in the second trimester of pregnancy. The data provide critical background information for prenatal genetic counseling and for the planning of health care policy.
European Journal of Human Genetics (2009) **17,** 897–903; doi:10.1038/ejhg.2008.265; published online 21 January 2009

Keywords: chromosomal abnormalities incidence; non-age dependent chromosomal abnormalities; cytogenetic epidemiology; cytogenetic population-based survey

Introduction

Estimates of the incidence of chromosomal abnormalities at birth are derived largely from studies in newborns carried out in the 70s, before the widespread use of prenatal diagnosis and pregnancy intervention. In 1977, Hook and Hamerton[1] reported on 56 902 newborns and subsequently Benn and Hsu[2] looked at 68 159 cases collected in the same years to infer the frequencies of the major chromosomal abnormalities. These data have not been further updated and because the early studies had technical and methodological limits in detecting some structural abnormalities and mosaicisms, our knowledge of the frequencies of those abnormalities in the general population has remained scanty. Data on 52 965 amniocenteses have been used to calculate the frequencies of specific abnormalities in the second trimester of pregnancy in cases with maternal age $>$35 years, estimating the age-dependent risks for the major aneuploidies;[3] moreover, Hook *et al*[4] showed that maternal age-specific rates of clinically significant cytogenetic abnormalities may be used in conjunction with the data on the natural history of chromosomally abnormal fetuses to infer maternal age-specific rates of cytogenetic abnormalities in live-born infants. Therefore, from the information gathered at the second trimester of pregnancy, it is possible

*Correspondence: Professor A Forabosco, Department of Medical Genetics, University of Modena, Via del Pozzo, 71, 41100 Modena, Italy.
Tel: +39 059 422 4826; Fax: +39 059 422 4840;
E-mail: antonino.forabosco@unimore.it
Received 1 August 2008; revised 18 November 2008; accepted 10 December 2008; published online 21 January 2009

also to establish the overall incidence of the chromosomal abnormalities in live-born infants.

Recently, the increasing reliability of non-invasive techniques has facilitated far more first trimester screening for the major aneuploidies[5] and in the European cities genetic counseling has led to more judicious use of amniocentesis for prenatal diagnosis.[6] However, the selection of cases for cytogenetic analysis creates a considerable ascertainment bias for estimates of the frequency of many chromosomal abnormalities in newborns in the general population.

To circumvent the ascertainment bias, we have focused on data from 1995–1996. In that era the impact of the first trimester screening strategies was still negligible, and we assess here the incidence of non-age-dependent chromosomal abnormalities in the second trimester of pregnancy. In Italy national genetic data, including the number of cytogenetic analyses carried out in each laboratory, have been collected since 1987.[7] For 1995–1996, data also included the results of cytogenetic analyses, grouping diagnoses into three categories: women $\geq$35 years, women $<$35 years and women who underwent amniocentesis based on familial, ultrasonographic or biochemical indications.[8]

We have compared the frequencies of the chromosomal abnormalities in 51 758 women $\geq$35 years with those in 37 207 women $<$35 years, and have then evaluated the age-dependency of single chromosomal abnormalities. For the non-age-dependent abnormalities, frequencies in the second trimester of pregnancy were established across the entire study cohort.

Materials and methods

Data accrual

Supported by the Italian National Institute of Health (Istituto Superiore di Sanità), a retrospective study was carried out by accessing the results of cytogenetic analyses of amniotic fluid performed in Italy during the period 1 January 1995–31 December 1996. Data were collected from the records of the public and private laboratories performing prenatal cytogenetic diagnosis in Italy. The laboratories had been earlier identified by the Italian Association of Medical Cytogenetics (AICM) and adhered to the AICM guidelines,[9] requiring banded chromosomes (G or Q banding) with a resolution above the 320-band stage and a minimum cell count, according to Hsu *et al*.[10] A form was distributed to each laboratory to record the following data: the initials of the proband, age of the mother ($<$ or $>$35 years, calculated at the time of amniocentesis), the result of the karyotype analysis (described according to the International System for Human Cytogenetics Nomenclature – ISCN-1985[11]) and the indication for undergoing the examination.

Of the 106 laboratories operating in 1995 in Italy, according to the AICM guidelines, 98 (92%) participated in the study. Two laboratories did not specify items in the standard form and were thus excluded from the analysis; six laboratories did not respond.

A total of 98 118 amniocenteses were accessed: among them, 2025 cases were excluded because of poor/incomplete reports or because amniotic fluid analysis was carried out after the finding of an abnormality in chorionic villi analysis and 7128 cases were excluded from the analysis because there was a biochemical, ultrasonographic or familial indication for the analysis. In the latter exclusion group, those women undergoing amniocentesis with maternal age $\geq$35 years and a clinical, biochemical or familial indication were also included.

All the chromosomal abnormalities detected by karyotype analysis, including the mosaics, were classified into the following categories: (a) autosomal aneuploidies, (b) sex chromosomal abnormalities in males, (c) sex chromosomal abnormalities in females, (d) polyploidies (e) balanced autosomal rearrangements and (f) unbalanced autosomal rearrangements.

The cytogenetic nomenclature adopted for the definition of abnormal karyotype was classified according to the criteria reported in ISCN 1995.[12] All chromosomal variants, defined following the ISCN 1995, were excluded.

Data analysis

Rates of sex chromosomal abnormalities were calculated for the affected sex, assuming equal numbers of males and females in the prenatal series. Statistical analyses were carried out by comparing the frequencies of chromosomal abnormalities at amniocentesis, using χ^2 analysis. Owing to the large number of comparisons carried out, to reduce the risk of a Type 1 statistical error, significance was set at $P<0.01$.

Results

This study thus reports the results of 88 965 amniocenteses with a total of 1607 chromosomal abnormalities, including 224 mosaic. The frequencies of chromosomal abnormalities observed in second trimester amniocenteses for women $\geq$35 years were compared with the frequencies in women $<$35 years of age (Table 1). The trisomies 21 and 18 and the 47,XXX and 47,XXY karyotypes were largely age-related ($P<0.001$); trisomy 13 showed a significant age-dependency ($P<0.01$), whereas the 47,XYY, 45,X and triploid karyotypes showed a borderline significance ($P=0.01$). On the other hand, among the autosomal mosaic aneuploidies, trisomy 21 showed a significant age-related increase ($P<0.01$), suggesting that the incidence of the mosaicisms, with the exception of trisomy 21, is not significantly influenced by the age of the mother.

Table 1 Comparison between the frequency of chromosomal abnormalities at the second trimester amniocentesis in women aged ≥35 and <35 years

Chromosomal abnormality	*Maternal age ≥35 years (N = 51 758)*	*Frequency (1/X)*	*Maternal age <35 years (N = 37 207)*	*Frequency (1/X)*	χ^2	P-*value*
Autosomal aneuplodies						
47, +21	517	100	63	591	210.00	<0.0001
mos 47, +21	20	2588	2	18 604	8.92	0.0028
47, +18	114	454	13	2862	47.80	<0.0001
mos 47, +18	3	17 253	1	37 207	0.46	0.49
47, +13	36	1438	8	4651	0.38	0.0027
mos 47, +13	3	17 253	1	37 207	0.46	0.49
47, +22	3	17 253	—	—	—	—
Other trisomies (2, 8, 12)	3	17 253	—	—	—	—
mos 47, +20	11	4705	6	6201	0.29	0.58
Other trisomies (2, 6, 7, 8, 15, 17), mosaic	5	10 352	4	9302	0.22	0.63
Double abnormality	8	6470	2	18 604	1.95	0.16
Sex chromosomes, males						
47,XYY	19	1362	6	3101	2.77	0.01
mos 47,XYY	4	6470	3	6201	0.00	0.90
47,XXY	62	417	17	1094	11.62	0.0007
mos 47,XXY	13	1991	9	2067	0.00	0.95
mos45,X/46,XY	13	1991	10	1860	0.02	0.87
chi46,XX/46,XY	4	6470	1	18 604	0.97	0.32
t(X;Y)	2	12 940	1	18 604	0.09	0.76
idic(Y), including mosaics	5	5176	1	18 604	1.56	0.21
Sex chromosome, females						
45,X	26	995	6	3101	6.19	0.01
45,X/46,XX	32	809	6	3101	10.59	0.001
45,X/47,XXX	4	6470	2	9302	0.17	0.67
47,XXX	46	563	10	1860	11.75	0.0006
mos 47,XXX	3	8626	2	9302	0.01	0.93
X rearrangements, including eight mosaics	13	1991	7	2658	0.38	0.53
Polyploidies						
Triploidy	13	3981	4	9302	1.99	0.01
Tetraploidy, mosaic	1	51 758	—	—		
Balanced autosomal rearrangements						
Robertsonian	46	1125	29	1283	0.70	0.40
Reciprocal, including five mosaics	93	557	65	572	0.03	0.86
Inversions	50	1035	29	1283	0.32	0.04
Unbalanced autosomal rearrangements						
Robertsonian	11	4705	4	9302	1.16	0.02
Deletions	7	7394	4	9302	0.77	0.40
Ring chromosomes	2	25 879	2	18 604	0.11	0.74
Duplications	6	8626	2	18 604	0.78	0.38
Derivatives	11	4705	2	18 604	3.36	0.067
Supernumerary						
Isochromosomes	5	10 352	3	12 402	0.06	0.80
Markers	25	2070	13	2862	0.90	0.34
Markers, mosaic	20	2588	10	3721	0.88	0.35

In the category of mos 45,X, all the sex chromosome complements in male fetuses were evenly distributed in women aged above and <35 years, including the 45,X/46,XY and idic(Y) karyotypes. On the contrary, the 45,X/46,XX karyotype was significantly more frequent in the group of women >35 years of age, whereas the 45,X/47,XXX karyotype was not influenced by the age of the mother. Also chi 46XX/46XY did not show any age-dependency.

The autosomal trisomies, involving chromosomes 2, 8, 12, 22 and mosaic tetraploidy, detected in women with advanced matemal age (equal or older than 35 years) could not be compared, not being present in the group of women <35 years of age.

Table 2 Non-age-dependent chromosomal abnormalities in the overall study population

Chromosomal abnormality	*Total number* N = *88 965*	*Frequency (%)*	*Frequency (1/X)*
Autosomal aneuploidies			
47, +22	3	0.003	29 655
Other trisomies (2, 8, 12)	3	0.003	29 655
mos 47, +9	3	0.003	29 655
mos 47, +13	4	0.004	22 241
mos 47, +18	4	0.004	22 241
mos 47, +20	17	0.019	5233
Other trisomies (2, 6, 7, 8, 15, 17), mosaic, total	6	0.007	14 828
Sex chromosome, males			
mos 47,XYY	7	0.016	6355
mos 47,XXY	22	0.049	2022
45,X/46,XY	23	0.052	1934
chi 46,XX/46,XY	5	0.011	8897
t(X;Y)	3	0.007	14 828
idic(Y), including mosaics	6	0.013	7414
Sex chromosome, females			
mos 47,XXX	5	0.011	6355
45,X/47,XXX	6	0.013	7414
X rearrangements, including mosaics	20	0.045	1934
Balanced autosomal rearrangements			
Robertsonian	75	0.084	1186
Reciprocal	158	0.178	563
Inversions	79	0.089	1126
Unbalanced autosomal rearrangements			
Robertsonian	15	0.017	5931
Derivatives[a]	14	0.016	6355
Deletions			
del(4p)	4	0.004	22 241
del(4q34-qter)	2	0.002	44 483
del(5p)	2	0.002	44 483
del(18p11)	2	0.002	44 483
Other deletions	3	0.003	29 655
Duplications	8	0.009	11 121
Ring chromosomes (r(5), r(13), r(15), r(22)	4	0.004	22 241
Supernumerary			
Isochromosomes:			
i(20q)	3	0.003	29 655
i(18p)	2	0.002	44 483
i(9p)	2	0.002	44 483
i(12p)	1	0.001	88 965
Markers	38	0.043	2341
Markers, mosaic	30	0.034	2966

[a]One mosaic included.
Frequencies are expressed both as percentages and as its inverse (1/X).

Both balanced and unbalanced structural rearrangements showed no significant differences between the two age groups, suggesting that the incidence of these anomalies is not significantly influenced by the age of the mother.

For specific chromosomal abnormalities that showed no significant difference with age, frequencies were calculated for the entire cohort (Table 2). Non-age-dependent mosaic autosomal and sex chromosome aneuploidies occurred in 1 out of 2600 and 1 out of 1000 amniocenteses, respectively. Trisomy 20 mosaicism and 45X/46XY karyotypes were particularly frequent, being found in 1 out of 5200 and in 1 out of 1900 amniocenteses. The frequency of chimeras is around 1 out of 18 000 amniocenteses. The total incidence of balanced autosomal rearrangements ranged from 1 out of 560 for reciprocal translocations to 1 out of 1100–1200 for inversions and robertsonian translocations, respectively. The incidence of unbalanced rearrangements was considerably lower, 1 out of 5900 for robertsonian and 1 out of 6300–6800 for derivatives and deletions (the most frequent of the latter being the terminal deletion of the short arm of chromosome 4, more frequent than 5p deletion). Ring chromosomes showed an incidence of about 1 out of 22 000, whereas supernumerary markers were scored in 1 out of 1200 cases.

Table 3 Comparison between our results and those reported by Ferguson-Smith and Yates, 1984

	Present study		*Ferguson-Smith and Yates, 1984*			
Chromosomal abnormality	*Maternal age ≥35 years (N = 51 758)*	*Frequency (%)*	*Maternal age ≥35 years (N = 52 965)*	*Frequency (%)*	χ^2	P-*value*
Autosomal aneuplodies						
47, +21	517	1.00	613	1.16	6.16	0.013
47, +18	114	0.22	121	0.23	0.07	0.77
47, +13	36	0.07	39	0.07	0.06	0.80
Aneuploidies, mosaic	56	0.11	16	0.03	23.17	<0.001
Sex chromosome, males						
47,XYY	19	0.07	18	0.03	0.004	0.9
47,XXY	62	0.24	87	0.16	2.12	0.14
Sex chromosome, females						
45,X	26	0.10	24	0.05	0.13	0.71
47,XXX	46	0.18	65	0.12	2.83	0.09
Balanced autosomal rearrangements						
Rob(13q14q)[a]	37	0.07	28	0.05	1.46	0.22
Reciprocal	91	0.18	94	0.18	0.04	0.94
Unbalanced autosomal rearrangements						
Supernumerary markers	25	0.05	31	0.06	0.51	0.47
Robertsonian	11	0.02	6	0.01	1.58	0.20
Others	25	0.05	15	0.03	2.73	0.10

[a]For comparison with the data from Ferguson-Smith and Yates (1984), among the robertsonian translocations, only the 13q14q were considered. Data are limited to second trimester amniocentesis for maternal age >35 year.

Discussion

Major efforts are now targeted to reduce the incidence of the major aneuploidies through prenatal diagnosis, but the incidence and the impact of other abnormalities are generally more obscure. Important data have been collected on the risk for structural rearrangements, marker chromosomes, mosaicisms, etc; however, those data customarily come from selected series (ie, cases at risk for a specific abnormality)[13] and can not be used to calculate the true incidence of the single rare abnormality.

On the other hand, data on incidence are vital not only for genetic counseling, but also for informed discussions of the possible desirability of focusing only on the major aneuploidies by adopting faster and cheaper new techniques of prenatal diagnosis, like QF-PCR.[14] They are also important to establish a standard reference incidence to compare increased risks in procedures like *in vitro* fertilization.[15]

Our study can contribute to valid estimates of the frequency of the chromosomal abnormalities because it is based on 88 965 amniocenteses, with high compliance (92%) in Italian laboratories and uniform coverage of the population over a two-year period (1995–1996). To our knowledge, similar data are not available for other countries.

The comparison of our data with the series published by Ferguson-Smith *et al*[3] confirms the earlier estimates for the main categories of abnormalities with surprising accuracy, reinforcing the validity of the inferences (Table 3). As shown there, apart from the overall rate of mosaic abnormalities ($P<0.001$), trisomy 21 was the only category that showed some indication of a difference (borderline *P*-value of 0.013). In addition to the data about the women >35 years of age, our study also reports the results for younger women undergoing amniocentesis. By comparing the frequencies in the two groups (< and >35 years) we could detect some age-dependency of the abnormalities. Our results confirm the age-dependency of the common autosomal and sex chromosomal aneuplodies, show a borderline significance of the age-dependency of 47,XYY, 45,X and triploidy and, surprisingly, show a significant age-dependency of the mosaicisms of trisomy 21, substantiating the hypothesis that a meiotic non-disjunction mechanism followed by rescue of trisomy could account for some of the mosaic cases.[16]

Our study shows that the incidence of the 45,X/46,XX karyotype is significantly age-related, whereas the 45,X/47,XXX is not. This new finding can be explained with the evidence that the 45,X/47,XXX cases are derived from a mitotic non-disjunction in a normal disomic cell line, whereas the majority of the 45,X/46,XX cases almost always result from the loss of a chromosome from a normal disomic fertilization.[16] Therefore, it can be hypothesized that the 45,X/46,XX karyotype originates from an anaphase lag of the X chromosome in XX zygotes because of the aging of the oocyte.

On the other hand, our results show the absence of an effect of the maternal age on the frequency of the 45,X/46,XY karyotype. Molecular studies of 45,X karyotypes show that the single X chromosome is maternally derived in about 80% of the cases, probably due to a higher risk of mispairing between the X and Y chromosomes during male meiosis, as well as a greater tendency to mitotic loss of a Y chromosome compared with an X chromosome.[17] Therefore, the postzygotic loss of the Y chromosome as a mechanism of the 45,X/46,XY may well explain why this karyotype is not influenced by the age of the mother.

The level of reciprocal balanced translocations, about 1 out of 560, is consistent with other estimates from prenatal diagnosis.[18] The frequency we find is about double of that observed in studies of live-born children in the 1970's,[2] but is in agreement with the frequency found by Jacobs *et al*[19] in an unselected series of newborns using moderate levels of banding.

After excluding variant forms, inversions (not scored for peri- *vs* para-centric) were found in about 1 out of 1100 cases, a level similar to the upper limit reported by Van Dyke *et al*,[18] but significantly higher than the 1 out of 5200 reported by Benn and Hsu[2] from historical data. By contrast, we observe a frequency of robertsonian translocations very comparable to the earlier estimate (1 out of 1186 *vs* 1 out of 1099 in the newborns studied by Benn and Hsu).

A mosaic abnormality was found in, approximately, 1 out of 400 amniocenteses. In particular, there were 34 non-age-dependent mosaic aneuploidies (approximately, 1 out of 2600 amniocenteses), with the most frequent being trisomy 20. The overall rate of mosaic abnormalities was significantly higher than the rate earlier reported by Ferguson-Smith *et al*,[3] consistent with the improvement in current diagnostic guidelines for mosaicism in prenatal diagnosis.[10] The finding of a high frequency of mosaic trisomies may be taken into account when considering the causes of unexplained phenotypes, as the chromosomal mosaicism could be involved in the pathogenesis of several disorders.[20]

The overall frequency of supernumerary markers, about 1 out of 1200, is close to the upper limit of the reported range in earlier studies.[4] No information was available to permit us to distinguish between *de novo* and familial markers, and this probably explains the absence of an effect of maternal age that has been reported in *de novo* cases.[13] A recent metanalysis of the frequency of small supernumerary marker chromosomes in prenatal and postnatal cases reported respective incidences of 0.075% (1 out of 1333, very close to ours) and 0.044% (1 out of 2270).[21]

The overall frequency of deletions that we observed (1 out of 6800) is similar to the earlier estimate by Benn and Hsu in a metanalysis of studies of newborns.[2] In both, the most frequent deletion is of terminal 4p, with a frequency of 1 out of 21 000 and only 4q34-qter, 5p and 18q11 deletions showed frequencies higher than 1 out of 50 000 – each reported in two cases. All other deletions were found only once in the entire cohort. The numbers are small, but it is of interest that the observed frequency of 4p abnormality is double of that reported in another study in which the cases were clinically ascertained,[22] whereas the 5p deletion (1 out of 44 000) falls into the reported frequency of 1 out of 20 000 to 1 out of 50 000.[23]

In agreement with an earlier study, duplications were detected less frequently than deletions, in about 1 out of 10 000 cases, even though both are suggested to be caused by the same mechanism of misalignment and unequal crossing over mediated by the presence of low-copy repeats.[24] However, because duplications are more difficult to see with conventional cytogenetic techniques, an ascertainment bias may artificially lower the apparent ratio of duplications to deletions.

In conclusion, by analyzing an unselected series from a country-wide population catchment, we have inferred the incidence of a range of chromosomal abnormalities at the second trimester of pregnancy. By having a large number of cases in both groups of pregnant women, $>$ and <35 years of age, we could determine the age-dependency of the chromosomal abnormalities, confirm most of the aneuploidies and identify some age-dependent categories like mosaic trisomy 21 and 45,X/46,XX that until now had escaped the identification. Moreover, on a series of 88 965 cases, we established the frequency of the non-age-dependent abnormalities. The data provide a reference standard for prenatal counseling and for discussions of choices for health care policy.

References

1 Hook EB, Hamerton JL: The frequency of chromosome abnormalities detected in consecutive newborn studies; difference between studies; results by sex and severity of phenotypic involvement; in Hook EB, Porter IH (eds): *Population Cytogenetics: Studies in Humans*. New York: Academic Press, 1977, pp 63–79.
2 Benn PA, Hsu LYF: Prenatal diagnosis of chromosomal abnormalities through amniocentesis; in Milunsky A (ed): *Genetic Disorders and the Fetus*, 5th edn. Baltimore: The Johns Hopkins University Press, 2004, pp 214–296.
3 Ferguson-Smith MA, Yates JR: Maternal age specific rates for chromosome aberrations and factors influencing them: report of a collaborative european study on 52 965 amniocenteses. *Prenat Diagn* 1984; **4** (Spec No): 5–44.
4 Hook EB, Cross PK, Schreinemachers DM: Chromosomal abnormality rates at amniocentesis and in live-born infants. *JAMA* 1983; **249**: 2034–2038.
5 Wapner R, Thom E, Simpson JL *et al*: First-trimester screening for trisomies 21 and 18. *N Engl J Med* 2003; **349**: 1405–1413.
6 Benn PA, Egan JF, Fang M, Smith-Bindman R: Changes in the utilization of prenatal diagnosis. *Obstet Gynecol* 2004; **103**: 1255–1260.
7 Dallapiccola B, Torrente I, Morena A, Dagna-Bricarelli F, Mingarelli1 R: Genetic testing in Italy, year 2004. *Eur J Hum Genet* 2006; **14**: 911–916.
8 Santucci S, Ranzi A, D'Ippolito C, Spagnolo A, Forabosco A: Indagine sulla diagnosi citogenetica prenatale in Italia: anni

1995–1996; in Dallapiccola B, Forabosco A, Mazzotti G, Spagnolo A (eds): *Rapporti ISTISAN 98/20* 1998, pp 37–57.
9 Associazione Italiana Citogenetica Medica (AICM): Diagnostica citogenetica – consensus 1995. *Analysis* 1995; **8**: 1–20.
10 Hsu LY, Kaffe S, Jenkins EC *et al*: Proposed guidelines for diagnosis of chromosome mosaicism in amniocytes based on data derived from chromosome mosaicism and pseudomosaicism studies. *Prenat Diagn* 1992; **12**: 555–573.
11 ISCN: Report of the Standing Committee on human cytogenetic nomenclature. *Birth Defects Orig Artic Ser* 1985; **21**: 1–117.
12 ISCN: An international system for human cytogenetic nomenclature (1995); Mitelman F (ed): Basel: S Karger, 1995.
13 Warburton D: *De novo* balanced chromosome rearrangements and extra marker chromosomes identified at prenatal diagnosis: clinical significance and distribution of breakpoints. *Am J Hum Genet* 1991; **49**: 995–1013.
14 Shaffer LG, Bui TH: Molecular cytogenetic and rapid aneuploidy detection methods in prenatal diagnosis. *Am J Med Genet C Semin Med Genet* 2007; **145**: 87–98.
15 Gosden R, Trasler J, Lucifero D, Faddy M: Rare congenital disorders, imprinted genes, and assisted reproductive technology. *Lancet* 2003; **361**: 1975–1977.
16 Robinson WP, Binkert F, Bernasconi F, Lorda-Sanchez I, Werder EA, Schinzel AA: Molecular studies of chromosomal mosaicism: relative frequency of chromosome gain or loss and possible role of cell selection. *Am J Hum Genet* 1995; **56**: 444–451.
17 Uematsu A, Yorifuji T, Muroi J *et al*: Parental origin of normal X chromosomes in Turner syndrome patients with various karyotypes: implications for the mechanism leading to generation of a 45,X karyotype. *Am J Med Genet* 2002; **111**: 134–139.
18 Van Dyke DL, Weiss L, Roberson JR, Babu VR: The frequency and mutation rate of balanced autosomal rearrangements in man estimated from prenatal genetic studies for advanced maternal age. *Am J Hum Genet* 1983; **35**: 301–308.
19 Jacobs PA, Browne C, Gregson N, Joyce C, White H: Estimates of the frequency of chromosome abnormalities detectable in unselected newborns using moderate levels of banding. *J Med Genet* 1992; **29**: 103–108.
20 Yurov YB, Vorsanova SG, Iourov IY *et al*: Unexplained autism is frequently associated with low-level mosaic aneuploidy. *J Med Genet* 2007; **44**: 521–525.
21 Liehr T, Weise A: Frequency of small supernumerary marker chromosomes in prenatal, newborn, developmentally retarded and infertility diagnostics. *Int J Mol Med* 2007; **19**: 719–731.
22 Shannon NL, Maltby EL, Rigby AS, Quarrell OW: An epidemiological study of Wolf-Hirschhorn syndrome: life expectancy and cause of mortality. *J Med Genet* 2001; **38**: 674–679.
23 Cerruti Mainardi P, Pastore G, Castronovo C *et al*: The natural history of Cri du Chat Syndrome. a report from the Italian Register. *Eur J Med Genet* 2006; **49**: 363–383.
24 Stankiewicz P, Lupski JR: Genome architecture, rearrangements and genomic disorders. *Trends Genet* 2002; **18**: 74–82.