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De Novo Balanced Chromosome Rearrangements and Extra Marker Chromosomes Identified at Prenatal Diagnosis: Clinical Significance and Distribution of Breakpoints

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Summary

A questionnaire sent to major cytogenetics laboratories in the United States and Canada over a 10-year period collected data on the frequency and outcome of cases with either apparently balanced de novo rearrangements or de novo supernumerary marker chromosomes detected at amniocentesis. Of 377,357 reported amniocenteses, approximately 1/2,000 had a de novo reciprocal translocation, 1/9,000 a Robertsonian translocation, 1/10,000 a de novo inversion, and 1/2,500 an extra structurally abnormal chromosome of unidentifiable origin. The risk of a serious congenital anomaly was estimated to be 6.1% (n = 163) for de novo reciprocal translocations, 3.7% (n = 51) for Robertsonian translocations, and 9.4% (n = 32) for inversions. The combined risk for reciprocal translocations and inversions was 6.7% (95% confidence limits 3.1%–10.3%). The risk of abnormality for extra nonsatellited marker chromosomes was 14.7% (n = 68), and that for satellited marker chromosomes was 10.9% (n = 55). In non-Robertsonian rearrangements, distribution of breakpoints among chromosomes was not as would be expected strictly on the basis of length. Most breaks were stated to occur within G-negative bands, but there was little evidence of particular hot spots among these bands. Nevertheless, there did appear to be a correlation between those bands in which breakage was observed most often and those bands where common or rare fragile sites have been described.

Introduction

Very limited data are available concerning the prognosis for fetuses diagnosed prenatally as having either an apparently balanced de novo chromosome rearrangement or a supernumerary marker chromosome of unknown origin. Series of cases derived from routine postnatal cytogenetic studies (e.g., see Buckton et al. 1985; Fryns et al. 1986) cannot be used to derive risk estimates, because of their usual ascertainment via some kind of abnormality in either the proband or a relative. Since 1980 I have been collecting data on the frequency and outcome of these types of abnormality when found at prenatal diagnosis, through a questionnaire sent to cytogenetics laboratories in the United States and Canada. Preliminary reports have been published (Warburton 1984, 1987), and there have been reports of other small series of prenatal patients with these cytogenetic findings (Benn and Hsu 1984; Mohandas et al. 1985; Wolff et al. 1986; Sachs et al. 1987; MacGregor et al. 1989; Wassman et al. 1989; Cheung et al. 1990). The present paper summarizes the results of 10 years of my mail survey.

De novo rearrangements found at prenatal diagnosis also provide the most satisfactory material for investigating the randomness of human constitutional chromosomal breakpoints. Previously analyzed data have included familial as well as de novo cases and have been derived either from surveys of the literature or from mostly postnatal cases studied in clinical laboratories (Jacobs et al. 1974; Aurias et al. 1978; Boue and Gallano 1984; Hecht and Hecht 1984*a*, 1984*b*; Fryns et al. 1986; Koduru and Chaganti 1988). These are subject to biases of ascertainment, because of the relative viabilities or frequencies of unbalanced segre-

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gants (Daniel et al. 1986) leading to infertility, congenital malformation, or reproductive loss. On the other hand, the great majority of cases of de novo balanced rearrangements are clinically normal, and ascertainment at the time of prenatal diagnosis eliminates biases concerned with reproductive fitness. The present paper analyzes the distribution of chromosomal breakpoints in these de novo rearrangements and compares them with known nonrandom breakpoints in human chromosomes.

Material and Methods

Questionnaires were sent to major cytogenetic laboratories in the United States and Canada at approximately 2-year intervals. Information requested included the reason for the prenatal diagnosis, a detailed karyotype description, and all available information on the outcome of the pregnancy. Only cases where both parental karyotypes were known to be normal were included. Cases were excluded if the amniocentesis was done because of fetal abnormalities seen on ultrasound, because this would introduce biased ascertainment via an anomaly. This occurred more frequently in later years.

The sample reported here includes cases presented elsewhere (Warburton 1984, 1987). However, some of the outcome data may have changed because of further information. For example, a case that had a satellited marker chromosome and that in 1984 was reported as abnormal because of microcephaly is now reported as normal because, in spite of continued microcephaly, at age 4 years the subject was reported to have an IQ of 125. A spontaneous abortion previously included as abnormal is now included as probably normal, on the basis of a review of the autopsy report.

Rearrangements were classified as Robertsonian translocations, reciprocal translocations, insertions, and inversions. Cases of true mosaicism but not pseudomosaicism were included, using the standard criteria for true mosaicism (level III, as defined by Gardner and Sutherland [1989, p. 193]). Information requested on supernumerary markers included additional staining techniques that had been used to try to define the chromosome. These cases were subdivided into those which were satellited and nonsatellited and those which were mosaic and nonmosaic. Marker chromosomes with a positive AgNOR stain were classified as "satellited" even if they were not stated to have visible satellites, since their derivation from acrocentric short arms was inferred. Although other information on these markers (e.g., size, DAPI staining properties, and C-banding) was sometimes provided, the number of cases with known outcome was too small to make most further subdivisions useful for prognostic purposes. Extra chromosomes of identifiable origin, e.g., i(18p), i(12p), were not included among "markers," with the exception of those described as inv dup(15).

Information on outcome of pregnancies terminated by induced or spontaneous abortion was included only if information was available from either a fetal pathology report or personal examination by a dysmorphologist. In some fetal cases the only abnormalities described were facial features which could be interpreted as normal in a 20-wk fetus (e.g., low-set ears, broad nasal bridge, and epicanthal folds). These cases were

Table 1

Frequency of De Novo Rearrangements and Supernumerary Markers in Amniotic Fluid Cultures

Series	No. (%) of Cases with					Total No. of Amniocenteses
	Translocations		Inversions	Supernumerary Markers		
	Reciprocal	Robertsonian		Satellited	Nonsatellited	
Before 1983	41 (.042)	11 (.011)	6 (.005)	17 (.017)	26 (.022)	98,745
1983–85	39 (.055)	3 (.004)	7 (.010)	17 (.024)	16 (.024)	70,501
1985–87	47 (.053)	16 (.018)	13 (.015)	15 (.017)	13 (.015)	88,624
1987–89	49 (.041)	12 (.010)	7 (.006)	28 (.023)	30 (.025)	119,487
Total	176 (.047)	42 (.011)	33 (.009)	77 (.020)	85 (.023)	377,357
Van Dyke et al. 1983	4 (.049)	2 (.025)	1 (.012)			8,158
Wassman et al. 1989	13 (.055)	6 (.026)				23,495
Hook et al. 1987*b*	31 (.051)	17 (.028)	7 (.011)			61,166
Hook et al. 1987*a*					26 (.034)	75,924

not scored as abnormal. In all questionable or abnormal cases laboratories were recontacted in an attempt to obtain more information. Often no more information was available, and I had to make a subjective judgment, based on incomplete information, as to how to score a case. The available descriptions of all cases classified as abnormal have been included in the present paper.

All chromosome breakpoints in translocations and inversions were plotted against a karyotype diagram at the 400-band level. These were compared with the number of breakpoints that would be expected on the basis of the relative length of each chromosome. For G-negative bands, the number of bands with a given number of breaks was compared with that expected from a Poisson distribution. The proportion of G-negative bands classified as either fragile sites or nonrandom cancer breakpoints, as listed in Human Gene Mapping 10 (Sutherland and Ledbetter 1989; Trent et al. 1989), was compared in those bands with the highest and lowest number of constitutional breakpoints.

Results

Apparently Balanced De Novo Chromosome Rearrangements

Frequency.—Reports of 218 de novo reciprocal translocations, 73 Robertsonian translocations, one insertion, and 43 inversions were received by December 1990. Two reciprocal translocations were mosaic with a normal cell line, and one patient had two de novo translocations.

Laboratories were asked for their total number of amniotic fluid diagnoses in each period. From those responding to this question the frequency of de novo balanced rearrangements was estimated. As shown in table 1, the frequency of de novo rearrangements was quite stable over the course of the study. Approximately 1/2,000 cases had a de novo balanced reciprocal translocation, and 1/10,000 had either a de novo balanced Robertsonian translocation or a de novo inversion. These figures are similar both to those found in earlier studies by Van Dyke et al. (1983) and Wassman et al. (1989) and to those for cases reported, by Hook and Cross (1987*a*), from the New York State Chromosome Registry. However, the frequency of Robertsonian translocations appears to be underestimated in my series. This might be due to underreporting, if some laboratories thought the questions pertained only to balanced reciprocal rearrangements.

Outcome of pregnancy.—Table 2 summarizes the data

Table 2

Outcome of De Novo Balanced Rearrangements

Rearrangement	No. of													
	Live Births			Elective Abortions			Stillbirths/ Spontaneous Abortions			Unknown Outcomes	Total with Known Outcomes			
	Normal	Abnormal	?	Normal	Abnormal	?	Normal	Abnormal	?		Normal	Abnormal	% (95% confidence limits)	
Reciprocal translocation[a]	134	8	7	16	2	30	3	0	0	18	153	10	6.1 (2.3–9.9)	
Inversion[b]	28	1	0	1	1	4	0	1	0	5	29	3	9.4 (0–19.6)	
Subtotal	162	9	7	17	3	34	3	1	0	23	182	13	6.7 (3.1–10.3)	
Robertsonian translocation	48	2	5	1	0	0	0	0	0	8	52	2	3.7 (0–9.3)	

[a] Includes one insertional translocation.
[b] Omits two inv(Y)—one normal and one with hydronephrosis.

Table 3

Abnormalities Described in Cases with De Novo Balanced Rearrangements

Karyotype	Type of Outcome	Site[a]	Abnormal Findings
46,XX,t(2;8)(q11;q24).....	Elective termination	1	Bilateral renal agenesis
46,XX,t(5;6)(q13;p23).....	Elective termination	2	Hypertelorism, epicanthus, simian crease, pes calcaneus, dilation of ureter, and incomplete lobulation of lung
46,XX,t(6;7)(q13;p14).....	Live birth	3	Hypoplastic left heart, low-set ears, redundant neck folds, hypotelorism, and epicanthus; died at 5 d of age
46,XX,t(2p;10q).....	Live birth	4	Delayed development at 21 mo
46,XX,t(2;7)(q31;q36).....	Live birth	5	Hypotonia, seizures, strabismus, and severe to profound mental retardation at 30 mo
46,Xt(X;4)(p21;q35)	Live birth	5	Duchenne muscular dystrophy (Bodrug et al. 1990)
46,XY,t(7;22)(q32;q11)	Live birth	6	Spondylocostal dysplasia; died at 2 years of age
46,XX,t(3;9)(q24;p22).....	Live birth	5	Megalocornea, corneal clouding, aplastic skin lesions on abdomen and legs; blind at 1 year of age but mental development apparently normal; and possible intrauterine infection
46,XX,t(7;16)(p22;q24)	Live birth	5	Ultrasonography showed duodenal atresia and situs inversus; died at 5 d of age; at autopsy, volvulus obstruction of duodenum, patent ductus arteriosus, abnormal carotid artery origin, absent lung lobulation, and annular pancreas
46,XX,t(2;6)(q33.1;p12.1).....	Live birth	7	Aniridia, developmental delay at 6 mo of age, and increased tone in upper extremities
46,XX,t(3;4)(q28;p14).....	Elective termination	8	Amniocentesis done because of omphalocele seen on ultrasound; twin pregnancy (other twin with same karyotype was normal); not in table 2
46,XY,t(9;18)(q22.3;q11).....	Elective termination	6	Amniocentesis done because of multiple anomalies seen on ultrasound; no fetal limbs, no evidence of spine, cystic area in caudal region, and abnormal head shape; not in table 2
46,XY,t(5;6)(q33;q25).....	Live birth	9	Amniocentesis done because of bilateral hydronephrosis on ultrasound; at birth, ventricular septal defect, hydronephrosis, and diaphragmatic hernia; not in table 2
46,XX,t(2;10)(q21.1;q24.3).....	Live birth	9	Amniocentesis done because of intrauterine growth retardation; baby died soon after birth and had club hands, club feet, and pectus excavatum; not in table 2
46,XY,t(14;22)(q24;q11.2).....	Elective termination	9	Amniocentesis done because of possible abnormalities seen at ultrasound; fetal autopsy showed two-chambered heart and other abnormalities; not in table 2
46,XX, inv(8)(p23,q11)	Elective termination	10	Facial clefting
46,XX, inv(16)(p13q11).....	Live birth	11	Intrauterine growth retardation, cardiac defects, seizures, and severe mental retardation at 6 years of age
46,X,inv(X)(q22q28)	Spontaneous abortion	12	Intrauterine growth retardation and oligohydramnios on ultrasound at 20 wk; fetal demise at 25 wk
46,XX,inv(5)(p13q15).....	Live birth	13	Amniocentesis done because of omphalocele on ultrasound (omphalocele repaired at birth); said by mother to be otherwise normal; not in table 2
45,XY,t(13q14q)	Live birth	14	Hypospadius; no follow-up since birth
45,XX,t(13q14q)	Live birth	15	Mild developmental delay and seizures at 5 years of age (mother also has seizures and is "slow")

[a] 1 = University of California at San Francisco; 2 = Erlangen, Germany, via Dr. Stengel-Rutkowski, Munich; 3 = NMG Genetic Services, New York; 4 = McMaster University Medical Center, Hamilton, Ontario; 5 = Henry Ford Hospital, Detroit; 6 = Prenatal Diagnosis Laboratory of New York, New York; 7 = Case Western Reserve, Cleveland; 8 = Johns Hopkins University, Baltimore; 9 = Vivigen, Santa Fe; 10 = Albany Medical College, Albany; 11 = University of California at Los Angeles, Los Angeles; 12 = Yale University School of Medicine, New Haven, CT; 13 = University of Tennessee, Memphis; 14 = Danbury Hospital, Danbury CT; and 15 = Reproductive Genetics Center, Denver.

Table 4

Length of Follow-up in Normal Cases with De Novo Rearrangements

Age at Last Follow-up (mo)	No. of Cases with				
	Translocations			Supernumerary Markers	
	Reciprocal	Robertsonian	Inversions	Satellited	Nonsatellited
≤1	57	29	11	17	20
2–5	13	3	6	4	2
6–8	13	6	1	1	2
9–11	2	1	4	0	1
≥12	42	9	10	9	11
≥24	24	4	2	5	5

on outcome. In some cases no information at all was available. Since most patients received counseling which advised them of an increased risk for abnormalities in pregnancies with de novo rearrangements, many pregnancies were electively terminated. The rate of termination was highest for reciprocal translocations (24%) and was lowest for Robertsonian translocations (2%), in keeping with the general perception of the relative risks for these rearrangements. Of the 291 pregnancies known to have continued, only 4 (1.4%) ended in either spontaneous abortion or stillbirth. This is not higher than the rate expected after 16 wk of pregnancy and a normal amniocentesis.

The frequency of abnormality was 6.1% for reciprocal translocations, 3.7% for Robertsonian translocations, and 9.4% for inversions. Since no control sample is available, these figures are best compared with the usual estimate of congenital malformations at birth, i.e., 2%–3%. The 95% confidence limits of each estimate include 3%. It is logical to group reciprocal translocations and inversions, since both involve two chromosomal breakpoints; the combined risk for detected abnormality is then 6.7%, with 95% confidence limits 3.1%–10.3%.

Table 3 lists the specific abnormalities among the cases in table 2. No attempt has been made to assess whether the abnormalities were the result of the rearrangement; the risk is close enough to the background rate of abnormality that one has to assume that most are, in fact, unrelated. There are five abnormal cases with a balanced reciprocal translocation and one case with an inversion which are listed in table 3 but not included in table 2. These are cases which represent biased ascertainment, because the amniocentesis was done because of an abnormality discovered at ultrasound. However, in institutions where both ultrasonography in early pregnancy and amniocentesis are common obstetrical practices, omission of these cases may underestimate the risk, since many abnormalities would be detected and then excluded. If the six abnormal cases omitted from table 2 were included, the risk would be 8.9% for reciprocal translocations and 12.1% for inversions, for a combined risk of 9.5% (95% confidence limits 5.5%–13.5%).

Tables 2 and 3 include many cases which were either elective terminations with autopsies or live births followed for only a brief time after birth. Thus many types of problems will not have been detected, and the estimated risk applies chiefly to congenital abnormalities obvious at birth or at fetal autopsy. Table 4 provides data on the age at last follow-up in normal cases. There was no case in which a live birth originally reported as normal was later classified as abnormal after longer follow-up. In fact, the opposite tended to occur: several cases described as having neonatal problems were later described as completely normal. Forty-two cases of reciprocal translocations, 10 cases of inversions, and nine cases of Robertsonian translocations are known to have been free of abnormalities at 1 year of age or later.

Supernumerary Marker Chromosomes

Frequency.—As shown in table 1, de novo supernumerary markers were found in about 1/2,500 amniocenteses. This does not include extra chromosomes of identified origin, with the exception of cases classified as inv dup(15). Markers that had recognizable satellites or were AgNOR positive occurred at a frequency approximately equal to that for markers lacking these features. Mosaicism with a normal cell line was found in 70% of cases with nonsatellited markers and in 39% of cases with satellited markers. Two cases had a cell line with two or three copies of a marker chromosome.

Table 5

Frequency of Abnormality in De Novo Supernumerary Markers

Type of Marker	No. of Live Births			Elective Abortions		Stillbirths/ Spontaneous Abortions			Unknown Outcomes	Total with Known Outcomes		
	Normal	Abnormal	?	Normal	Abnormal	?	Normal	Abnormal	?	Normal	Abnormal	% (95% confidence limits)
Nonsatellited, or Ag-NOR negative:												
Mosaic	29	3	5	10	4	10	0	0	0	39	7	15.2 (4.6–25.8)
Nonmosaic	9	1	1	7	2	1	3	0	0	19	3	13.6 (0–28.2)
Subtotal	38	4	6	17	6	11	3	0	0	58	10	14.7 (6.1–23.3)
Satellited, or Ag-NOR positive:												
Mosaic	11	1	3	5	1	6	1	0	0	17	2	10.5 (0–22.7)
Nonmosaic	20	2	1	12	2	8	0	0	0	32	4	11.1 (0.7–21.5)
Subtotal	31	3	4	17	3	14	1	0	0	49	6	10.9 (2.5–19.3)
Total	69	7	10	34	9	25	4	0	0	107	16	13.0 (6.9–19.1)

Outcome of pregnancy.—Table 5 summarizes the outcome of these cases. Almost half of those pregnancies with extra de novo marker chromosomes were electively terminated, reflecting the perception of medical geneticists that the risk of abnormalities is high in such cases. Four of 86 pregnancies known to have been continued ended in either stillbirth or spontaneous abortion, which does not suggest a greatly increased risk for these outcomes.

There is no evidence of a different risk of abnormality for mosaic versus nonmosaic cases. While the risk for nonsatellited markers (14.7%) is somewhat greater than that for satellited markers (10.9%), these two risks are not significantly different, and both have broad 95% confidence limits. The lower limit for satellited markers is close to the rate of congenital abnormalities that is expected for all births. When both types of markers are combined, the overall risk of an abnormality is 13.0%, with confidence limits 6.9%–19.1%.

The types of abnormalities observed are listed in table 6, along with any available descriptive data on the marker chromosome involved. It should be noted that the proportion of information that comes from fetal autopsy data is much higher in these cases than in the cases of the de novo balanced translocations. Table 6 also includes three abnormal cases which were excluded from table 5 because of ascertainment bias; if these three cases are included, the risk becomes 15.9% for nonsatellited markers, 14.0% for satellited markers, and 15.1% (confidence limits 8.7%–21.5%) for all markers combined.

An attempt was made to look at marker chromosomes subdivided into groups defined by more than just the presence or absence of satellites. These data are shown in table 7. In risk of abnormality, markers described as bisatellited did not seem to differ from other satellited markers. Nonsatellited markers described as "minute" or "dot-like" appeared to have a better prognosis, although the number of cases is small. Only one of 23 such cases with known outcome had evidence of abnormality at birth. This was a very unusual and difficult-to-interpret case: culture of fetal skin showed trisomy 21, and there were fetal features compatible with Down syndrome. There were six cases identified as inv dup(15p) on the basis of DAPI staining, two C-bands, and satellites on both ends. Of the two which went to term, one appears to be perfectly normal at 17 mo, and the other is neurologically abnormal, with mild developmental delay and features suggesting Prader-Willi syndrome. Of the four

terminations, autopsy information is available on only one case, which was grossly normal; this is uninformative with respect to Prader-Willi syndrome.

Among the cases that had "identified" markers and that are not included in tables 5 and 6, there were four cases described as having an extra chromosome that was probably i(18p). All of these cases were terminated, and all were described as being grossly normal fetuses with a few minor anomalies noted, such as clinodactyly and abnormal flexion creases. This is compatible with the phenotype recently described for postnatally ascertained cases (Callen et al. 1990). There were also three cases with an additional chromosome identified as an i(12p). One of these cases had amniocentesis because of a diaphragmatic hernia diagnosed at ultrasound and therefore represented biased ascertainment. Diaphragmatic hernia and hypoplastic lungs were found at autopsy in one other case, and the third case was described as grossly normal. These features are compatible with those seen in Pallister-Killian syndrome.

Although the survey did not ask for information on familial marker chromosomes, several laboratories reported this information. Information was available on outcome in 14 live-born cases, all of which were reported to be phenotypically normal. Among these cases, five had a marker described as inv dup(15). Familial transmission of such a marker with normal phenotype has been described elsewhere (Knight et al. 1984).

Table 4 gives the age, at last follow-up, for normal live births with a de novo supernumerary marker. This information was very unsatisfactory, since only nine cases with satellited markers and only 11 cases with nonsatellited markers had been followed for at least 1 year.

Distribution of Breakpoints among Balanced De Novo Rearrangements

The distribution of chromosomes involved in de novo Robertsonian translocations is shown in table 8. There is a predominance of 13/14 translocations, with 14/21 being next in frequency and with the rest all being rare. This is very similar to the distribution of Robertsonian translocation types in series which include both familial and de novo rearrangements (Therman et al. 1989). Thus the nonrandom distribution of Robertsonian translocation types reflects their relative frequencies of origin as de novo events and does not reflect selection which favors one kind over another.

All breakpoints which were reported as associated with apparently balanced reciprocal translocations or inversions were plotted on chromosome banding diagrams and are listed in the Appendix (table A1). The distribution of these breakpoints, by chromosome, is shown in figure 1, together with the distribution that would be expected solely on the basis of relative chromosome length. The χ^2 for goodness of fit of the autosomal breakpoints is 38.9 ($P = .01$), indicating that the number of breaks is not strictly proportional to the length. Chromosomes 10, 11, 15, and 22 have substantially more breaks than expected, while chromosomes 4, 5, 13, and 14 have fewer. Only three de novo non-Robertsonian rearrangements were reported more than once. There were two cases each of t(11;22)(q23;q11) and t(18;21)(p11;q11) and three cases of inv(2)(p11q13). The first of these is well known as the most frequent familial reciprocal translocation leading to unbalanced segregants and a defined syndrome (Fraccaro et al. 1980). The inv(2) is a common familial inversion. Thus these rearrangements are probably common because they occur with a high frequency as mutations, rather than because of selective factors.

There was a marked tendency for breaks to be designated in Giemsa-negative bands; 84% of breakpoints were in G-negative regions. However, it is unclear whether this is a real phenomenon or an artifact of looking at G-banded preparations when deciding on breakpoints. This same predominance of G-negative breakpoints is found both for the fragile sites on human chromosomes and for breakpoints in rearrangements found in neoplasia. If not taken into account, this can lead to artifactual associations in any analysis of breakpoints (Sutherland and Simmers 1988).

To explore whether there were significant hot spots for chromosome breakage within chromosomes, the distribution of the number of breakpoints per G-negative chromosome band was compared with that expected under a Poisson distribution. For this purpose a "band" was considered to be the band designation with two digits and no decimal subband. This low level of resolution was chosen because the difficulties of assigning breakpoints made it likely that many of the finer distinctions between bands were not accurate. As shown in table 9, there was a good fit to the Poisson distribution, although there was some tendency for bands with more than four breakpoints to

Table 6

Abnormalities Described in Cases with Supernumerary Markers

Karyotype	Type of Outcome	Site[a]	Abnormal findings
mos 46 XY/47,XY, + mar (1/3 size of 22)	Elective termination	1	"Fetal malformations seen" (pathology report)
47,XY, + mar (very small fragment).....	Elective termination (due to maternal toxemia)	2	47,XY, + 21 in cultures from fetal blood and skin and features of Down syndrome
47,XX, + mar (metacentric, G-size).....	Elective termination	3	Abnormal appearing fetus with single umbilical artery, micrognathia, abnormal facies, low-set ears, rockerbottom feet, and simian creases
46,XY, + mar (metacentric, <G).....	Live birth	4	Hypospadius, persistent bilirubinemia noted at birth, hypertonia and cortical thumbs noted at 2-1/2 mos. At 18 mos. milestones normal, but persistent hypertonia and hyperbilirubinemia with discoloration of skin
mos 46,XX/48,XX, + 2mar (<G).....	Live birth	5	"Multiple anomalies"; died soon after birth
mos 46,XX/47,XX, + mar (submetacentric, G-size)	Elective termination	6	Malformed low-set ears, simian creases, imperforate anus, and abnormal facies
mos 46,XX/47,XX, + mar (small ring).....	Elective termination	7	No gross abnormalities but focal aberrant neuronal migration in cerebrum
mos 46,XY/47,XY, + mar (G-negative metacentric).....	Live birth	8	Sonogram in second trimester showed urinary tract obstruction; "kidney abnormality" at birth (chromosomally normal sib had the same kidney problem: recessive?); no follow-up after 1 mo of age
mos 46,XY/47,XY, + mar (G-negative band)...	Elective termination	5	"Abnormalities of face and hands"
mos 46,XY/47,XY, + mar (>G, G and DAPI negative).....	Live birth	9	Cleft palate, bilateral preauricular pits, possible metopic and lamboidal synostosis, and cryptorchidism; no follow-up after 1 mo of age
47,XY, + marS (G-size)	Elective termination	3	Omphalocele and low-set ears
mos 46,XX/47,XX, + marBS (metacentric, NOR positive on both ends).....	Live birth	10	Cleft palate at 2 wk of age; no recent follow-up

(*continued*)

be more frequent than expected. There is thus little evidence that the breakpoints in these constitutional chromosome anomalies are nonrandom, or "hot spots" for breakage exist.

In order to test whether the most common breakpoints for the constitutional rearrangements were similar either to the known fragile sites on human chromosomes or to breakpoints found nonrandomly in tumors, the 31 Giemsa-negative bands where four or more breakpoints had occurred were compared with the 51 Giemsa-negative bands where zero or one break had occurred. Table 10 shows the results of this analysis. The bands with four or more breakpoints are listed at the bottom of the table. There is a statistically significant tendency for both rare and common fragile sites to coincide with the bands found most commonly in constitutional de novo rearrangements. For bands found as breakpoints in neoplasia there was no significant tendency in this direction.

Discussion

Prognosis for Prenatally Diagnosed De Novo Structural Rearrangements

Data supporting an increased risk for mental retardation or congenital anomalies in apparently balanced translocation carriers were first presented by Breg et al. (1972) and Jacobs (1974) and have been supported by other studies showing that presumptive balanced de novo rearrangements in populations of the mentally retarded occur more frequently than expected (Funderburk et al. 1977; Warburton 1982). The rate was six-to-sevenfold higher in the populations of the re-

Table 6 (continued)

Karyotype	Type of Outcome	Site[a]	Abnormal findings
47,XY, + marS (G-size, NOR positive, DAPI negative)	Live birth	11	SGA; at birth, prominent occiput, malformed ears, long philtrum, broad nasal tip, anal dimple, and bilateral simian creases; no follow-up after birth
47,XX, + marBS (G-size, C-bands on both ends)	Elective termination	12	Dysmorphic facies, clinodactyly, cervical ribs, complex congenital heart disease with hypoplastic right side of heart, and ovarian hypoplasia
mos 46,XX/47,XX, + marBS (<G, DAPI negative)	Elective termination	12	Preauricular tags, agenesis of 12th rib, malrotation of gut, and dolicocephaly
47,XY, + inv dup(15p) (acrocentric, DAPI positive, satellites both ends)	Live birth	13	Moderate developmental delay at 13 mo, abnormal neurological exam, originally poor feeding but now voracious eater, and possible Prader-Willi syndrome
47,XY, + i(15p) (metacentric, DAPI positive satellites both ends)	Live birth	14	Amniocentesis done because of omphalocele on ultrasound; seizure disorder at 10 mo; not in table 5
mos 46,XY/47,XY, + r (small)	Elective termination	15	Amniocentesis done because of ventral wall defect on ultrasound; ectopia cordis; not in table 5
47,XX, + marS (<G, metacentric, satellites on one end)	Live birth	15	Amniocentesis done because of possible hydrocephalus on ultrasound; hydrocephalus at birth and severe developmental delay; not in table 5

[a] 1 = Reproductive Genetics Center, Denver; 2 = Long Island Jewish Medical Center, New York; 3 = Letchworth Village Developmental Center, Thiells, NY; 4 = University of Texas Medical School at Houston, Houston; 5 = University of California at Los Angeles, Los Angeles; 6 = Yale University School of Medicine, New Haven, CT; 7 = Danbury Hospital, Danbury, CT; 8 = Georgetown University Hospital, Washington, DC; 9 = University of Washington, Seattle; 10 = Kapiolani Childrens Medical Center, Honolulu; 11 = Greenwood Genetics Center, Greenwood, SC; 12 = Prenatal Diagnosis Laboratory of New York, New York; 13 = Stanford University, Palo Alto, CA; 14 = Cytogenetics Brigham and Women's Hospital, Boston; and 15 = Vivigen, Santa Fe.

Table 7

Outcome for Special Classes of Marker Chromosomes

	No. of											
	Live Births			Elective Abortions			Still births/Spontaneous Abortions			Total		
Type of Marker	Normal	Abnormal	?	Normal	Abnormal	?	Normal	Abnormal	?	Normal	Abnormal	%
Minute, nonsatellited	16	0	3	4	1	4	1	0	0	22	1	4.3
Bisatellited	20	2	4	10	2	9	1	0	0	31	4	11.4
inv dup(15)	1	1	0	1	0	3	0	0	0	2	1	33.3
i(12p)	0	0	0	1	2	0	0	0	0	1	2	66.7
i(18p)	0	0	0	4	0	0	0	0	0	4	0	
Familial	14	0	6	0	0	2	0	0	0	14	0	

Table 8

Frequency of De Novo Robertsonian Translocation Types

Type of Robertsonian Translocation	No. (% of total)
13/14	51 (69.9)
14/21	12 (16.4)
13/15	2 (2.7)
14/15	3 (4.1)
15/15	1 (1.4)
13/21	1 (1.4)
14/22	1 (1.4)
21/21	1 (1.4)
22/22	1 (1.4)[a]

[a] Mosaic with a normal cell line.

Table 9

Distribution of G-negative Bands That Possess Given Number of Breakpoints

No. of Breakpoints/Band	No. of Bands	
	Observed	Expected[a]
0	15	16.6
1	36	36.2
2	38	39.5
3	27	28.7
4	13	15.6
5	10	6.8
≥6	8	3.5

[a] Based on Poisson distribution, with $m = 2.18$ and $n = 147$; $\chi^2 = 6.55$, df = 5, $.20 < P < .30$.

tarded, when compared with the rate of such rearrangements in series of random newborns. However, this is likely to overestimate the increase, because these newborn surveys were done prior to the introduction of chromosome banding.

Hook (1989) has recently provided data concerning the proportion of rearrangements estimated to have been undetected without banding. He calculated that, if banding had been carried out in the newborn surveys, the frequency of observed de novo structural rearrangements would have been 0.70/1,000 live births. This is in good agreement with both the frequency of 0.67/1,000 amniocenteses for all de novo rearrangements in the present survey (table 1) and the frequency of 0.90/1,000 amniocenteses reported by Hook and Cross (1987*b*). Comparison of the estimate of 2.4/1,000 de novo rearrangements among the mentally retarded (Warburton 1982, 1984) with the cor-

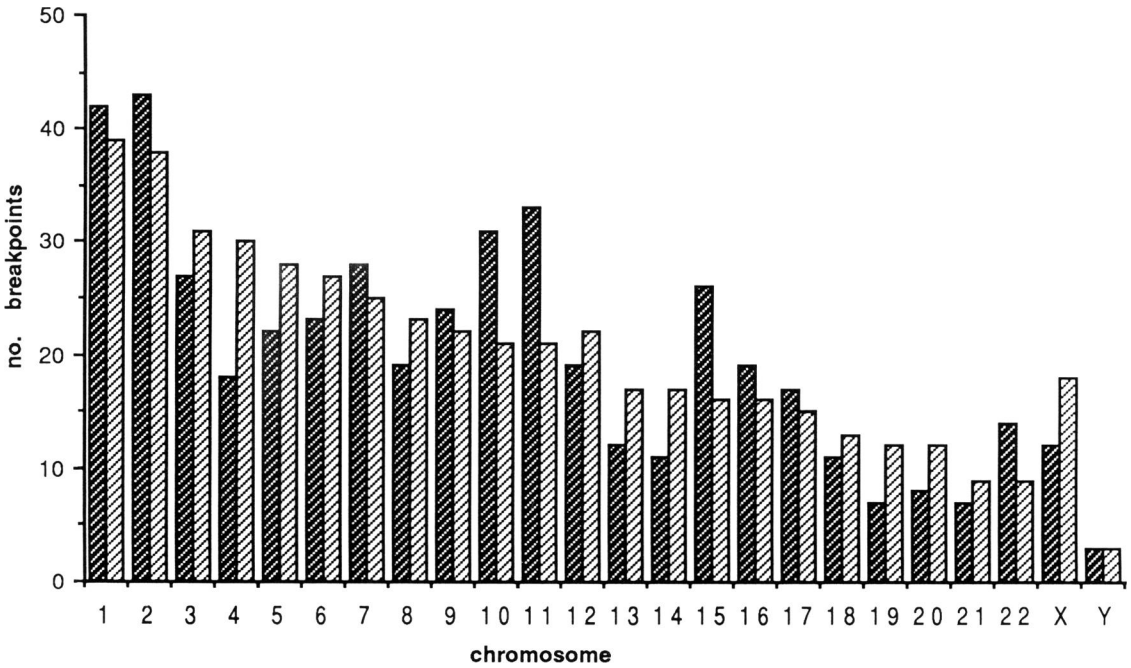

Figure 1 Chromosomal assignment of breakpoints in de novo reciprocal translocations and inversions. Shown are the observed (darker-hatched bars [▨]) and expected (lighter-hatched bars [▨]) numbers of breakpoints (expected numbers are based on relative chromosome length). Expected numbers for sex chromosomes were adjusted for the proportion of X and Y chromosomes involved.

Table 10

Association of Breakpoints with Fragile Sites and Nonrandom Rearrangements in Neoplasia

Type of Bands	No. (%) of G-negative Bands with	
	Four or More Breaks[a] (N = 31)	No Breaks or One Break (N = 51)
Containing rare fragile sites	7 (22.6)	3 (5.9)*
Containing common fragile sites	13 (41.9)	10 (19.6)*
Involved in neoplasia	23 (74.2)	29 (56.9)

[a] 1p36, 1p13, 1q21, and 1q42; 2p11, 2q11, 2q23, and 2q31; 3q25, and 3q27; 5q13; 6p25; 7q11; 8q22; 10q11.2 and 10q24; 11p15, 11p11, 11q23, and 11q25; 12q24; 13q12 and 13q22; 14q32; 15q11, 15q22, and 15q26; 16p13; 17q21; 18q21; and 22q11.

* $P < .05$ (one-tailed test).

rected newborn estimated still shows a two- to three-fold increase.

This increased risk can result from three different types of events at the DNA level: (1) The translocation is not truly "balanced," in that genetic material is missing or extra. An example of this situation was described by Puissant et al. (1988), who found a patient who had both the WAGR syndrome and an apparently balanced translocation involving band 11p13: at the molecular level a small deletion in 11p13 was detectable. (2) No material is missing, but a break has occurred within a gene, leading to abnormal or absent gene function. This situation has been documented in several females with Duchenne muscular dystrophy, including the subject included in the present survey, who has been described in detail by Bodrug et al. (1990). (3) No material is missing, but the new arrangement of genetic material leads to abnormal gene function. To my knowledge this has not been described for a constitutional rearrangement in man but is known to occur in somatic rearrangements leading to cancer. Those patients who have apparently balanced rearrangements as well as a defined genetic disease are extremely valuable for the localization and isolation of disease genes, having led, for example, to the identification of the genes for muscular dystrophy and neurofibromatosis. In this regard it is interesting that, in the series reported here, three of the abnormalities (Duchenne muscular dystrophy, spondylocostal dysplasia, and renal agenesis) found among patients with reciprocal translocations are known to occur as the result of single gene mutations. Thus follow-up of patients with de novo balanced rearrangements may lead to important information concerning known genetic disease.

The most direct way to measure the risk of abnormality in de novo rearrangements would be to follow cases ascertained either in newborn surveys or prenatally, to avoid the bias of ascertainment which invalidates data drawn from either older cases studied in cytogenetic laboratories (e.g., see Fryns et al. 1986; Philip et al. 1988; Kleczkowski et al. 1989) or single case reports. The very limited amount of unbiased data that is available from published reports is summarized in table 11. Although the numbers are very small, they do support the general findings of the present study in showing both a low risk of abnormality in balanced rearrangements and an increased risk for cases with extra marker chromosomes.

The outcome data presented in the present paper are very imperfect, because of both the lack of long-term follow-up and the questionable accuracy of diagnosis of abnormalities in terminated pregnancies. The latter is of concern because table 2 shows a trend for the rate of abnormalities to be higher in aborted fetuses than in pregnancies going to term. The frequency of diagnosed abnormalities in reciprocal translocations and inversions combined is 4/26 (15.4%) in fetuses, compared with 9/171 (5.3%) in term births. The same trend is shown for supernumerary markers (table 5), where the abnormality rate was 9/46 (21.7%) in fetuses and 7/76 (9.2%) in term births. The rates that are derived only from pregnancies which have been carried to term may be preferable as risk figures. Another problem is that only 15% of live-born cases of balanced rearrangements and only 11% of live-born cases of marker chromosomes have been followed to 2 years of age, so that little information is available on the incidence of either delayed development or neurological and other problems which could not be detected early in life. However, only 1/77 cases followed for as long as 1 year showed a problem not detectable

Table 11

Published Data on Prospectively Ascertained Cases of De Novo Rearrangements or De Novo Supernumerary Markers

	No. of Cases with					
	Robertsonian Translocations		Non-Robertsonian Rearrangements		Supernumerary Markers	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Cases found in surveys of newborns[a]	6	0	15	1	5	0
Prenatal detection[b]	3	0	21	0	11	3
Total	9	0	36	1	16	3

[a] Sources: references in Tierney et al. (1984) and Warburton (1984).

[b] Sources: Benn and Hsu (1984), Bogart et al. (1986), Fryns et al. (1986), Miny et al. (1986), Wolff et al. (1986), Grass et al. (1987), Sachs et al. (1987), MacGregor et al. (1989), Wassman et al. (1989), Cheung et al. (1990). Two cases were omitted where amniocentesis was done because of an elevated serum α-fetoprotein and ultrasound evidence of neural tube defect, and one case was omitted where amniocentesis was done because of a diaphragmatic hernia and possible ventricular septal defect detected on ultrasound. One of the abnormalities was in a pregnancy with inv dup (15).

at birth (i.e., significant developmental delay), and several cases with problems reported in the newborn period (e.g., hypoglycemic episodes and heart murmurs) were later found to function normally. Thus, with longer follow-up, the estimate of the frequency of abnormality among balanced rearrangements actually decreased.

Since no control series is available with which to compare the frequencies of abnormalities observed in this series, one must use as a comparison the common estimate of the overall rate of congenital anomalies, i.e., 2%–3%. Although the 95% confidence limits include 3%, the data are consistent with no increase in risk for de novo Robertsonian translocations but a two- to threefold increase for de novo reciprocal rearrangements or inversions. This agrees well with the estimate derived above from surveys of the mentally retarded. The risk of a serious abnormality certainly does not seem to be as high as 10%, which has been a commonly used risk estimate for this type of cytogenetic finding. While it might be argued that one should increase the risk estimate because of the additional developmental and neurological problems which would be found with longer follow-up, one should then, in counseling, use a background comparison figure for congenital anomalies that is higher than the traditional 2%–3%. For example, the prevalence of mild mental retardation (excluding Down syndrome) among young adults has been consistently reported, in several settings, to be 2%–6% (Hansen et al. 1980). While longer follow-up and bigger series of cases are clearly necessary before a clear picture can emerge, it would seem that the risk of a serious congenital abnormality is not greatly increased for cases with de novo balanced rearrangements but is significantly increased for those with de novo supernumerary marker chromosomes. A study currently being carried out in the United Kingdom (Donnai 1989) should provide more information on these questions.

Since high-resolution ultrasonography usually is carried out when a potential problem is diagnosed prenatally, parents often wish to know how much reassurance a normal ultrasound scan provides. The small number of abnormal cases in my series does not provide an adequate sample for answering this question, but one can estimate from tables 3 and 6 that about one-third (9/31) of abnormal cases with de novo rearrangements or marker chromosomes would have had abnormal findings by ultrasonography.

Improved identification of "marker chromosomes" is now becoming possible through the application of either in situ hybridization or DNA analysis with chromosome-specific probes to cases with these abnormalities (for an example, see Callen et al. 1990). In itself this will not improve our ability to predict the outcome in cases ascertained at prenatal diagnosis, unless clinical information in a large series of such cases is obtained with as much accuracy as that attending the cytogenetic characterization of the marker. Appropriate attention must also be given to biases introduced by the way in which the cases are ascertained.

Randomness of Constitutional Chromosomal Breakpoints

The distribution of breakpoints among chromosomes has been previously analyzed in series of ran-

domly ascertained newborns, among parents coming for prenatal diagnosis, and among cases ascertained because of either congenital malformations or poor reproductive history. All these sources lead to possible selection bias, because of the clinical outcome: cases surviving to birth may be different from those which die in utero, and selection of balanced carriers on the basis of reproductive performance may also lead to overrepresentation of either those rearrangements which are relatively benign and familial or those which lead to surviving unbalanced offspring. The series of balanced de novo rearrangements presented here is relatively unbiased in terms of breakpoints, since (*a*) the only selection is for survival to the time of amniocentesis and (*b*) most are not associated with abnormalities. Since each rearrangement is a de novo event, the frequencies of the breakpoints represent the actual frequencies of chromosome breakage and rearrangement in viable germ cells.

Analysis of the breakpoints reported in the present survey indicated (*a*) that the distribution of breaks per chromosome did not strictly correspond to that expected on the basis of relative chromosome length and (*b*) that breaks tended to occur in G-negative bands. Among G-negative bands, the number of breaks per band correspond to that expected for a Poisson distribution, giving no evidence for particular "hot spots" among bands. However, in contradiction to this, there did seem to be a correlation between those chromosome bands where chromosome breaks were reported most often and the chromosome bands designated to contain fragile sites. This has been reported previously for constitutional breakpoints (Hecht and Hecht 1984*a*, 1984*b*; Koduru and Chaganti 1988), but these series either did not correct for the bias induced by the predominance of Giemsa-light bands or did not use only de novo rearrangements. There is thus some evidence that breakage in germ cells may cluster in particular chromosome regions with unusual properties. However, breakpoints were recorded at a low level of resolution, and the same band location for two breakpoints may represent positions 5 or more megabases apart in the genome. For example, molecular analysis has shown that the apparent similarity between the chromosome 11 and 22 breakpoints in the common constitutional rearrangement and in Ewing sarcoma is misleading, because the breakpoints are actually many megabases apart (Budarf et al. 1989). The apparent relationship between constitutional breakpoints and fragile sites which is suggested by the data in the present paper as well as by the results of other studies must therefore be regarded with skepticism until molecular analysis can be used to define the breakpoints.

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J. C. Baker and J. Tucker, West Virginia University Medical Center, Morgantown
N. Balkin, Children's Memorial Hospital, Chicago
L. Beauregard, Eastern Maine Medical Center, Bangor
R. Bernstein, University of California at Irvine Medical Center, Orange
D. S. Borgaonkar, The Medical Center of Delaware, Wilmington
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S. Soukup, Children's Hospital Medical Center, Cincinnati
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Appendix

Table A1

Breakpoints in Reciprocal Translocations and Inversions, by Chromosome Band

	Translocation	Breakpoints
XX	1;2	q43 p24
		q21 p11.2
XY	1;2	q42.1 p15
		p13 q32
XX	1;3	q21 q29
XY	1;4	p13 q12
		p22 q23
XY	1;6	q25 q27
		q42.1 q23.1
XY	1;7	p21 p21
		p36 q32
XX	1;8	q31 q13
XX	1;10	q36.1 p11.1
XX	1;11	q36.3 q13
		q11 p15
XX	1;12	p32 q12
		p32 q22
XX	1;13	p31.2 q22
XY	1;13	q21 q12
XX	1;14	q32 q26.1
XX	1;15	q42 q26
XY	1;15	p32 q26.1
		p36.3 q11
		q44 q21.3
XX	1;16	p22 p13
XY	1;16	p13.3 p13.3
XY	1;18	q42.2 q12.3

(*continued*)

Appendix

Table A1 (continued)

	Translocation	Breakpoints
XX	1;22	q42 q11.2
XY	1;22	p22 q11.2
XX	2;5	q23 q31
XX	2;6	q11 p23
		q33.1 p12.1
		q24 q12
XX	2;7	q31 q36
		q11 p11
XX	2;8	q11 q24
XX	2;9	q12 p13
		q35 q22.1
XY	2;9	q31 p24
XX	2;10	q24.1 p11
XY	2;10	p11.2 p15
		q14 q22
		q31 q11.2
XY	2;11	p21 q22.1
XX	2;12	q33 q24
XY	2;12	2p12p 2q12q
XX	2;15	p15 q26
		q21 q24
XY	2;15	q21.2 q21.2
XX	2;16	q23 q21
XY	2;16	q13 q24
XX	2;17	q23 q23
		p25 q22
XY	2;17	p25.1 p11.1
		q37 q12
XY	3;4	q26.3 q15.2
XY	3;5	q25 q13
XX	3;6	p23 q15
XX	3;8	q11 p11
XX	3;9	q27 q21.2
		q24 p22
XY	3;9	q11 q11
XX	3;10	p21 p15
		q21 q26
		p11.2 q26.1
XY	3;11	p13 p15
XY	3;11	q25 q13
XX	3;12	p13 q21.2
XX	3;13	q28 q21
XY	3;13	p25 q12
		q26.2 q34
XX	3;14	q27 q24.3
XX	3;15	p14 q22
XY	3;15	q27 q21
		p26 q22
XX	3;17	q25.3 q11.2
XY	3;17	p21 q25
		q21 q23

(*continued*)

Appendix

Table A1 (continued)

	Translocation	Breakpoints
XX	4;5	q35 q13
XY	4;7	q21 q34
XX	4;8	p16 q22
XX	4;10	q13.2 q22.1
		q27 q11.2
XY	4;11	q13 p15
XX	4;12	p15 q24
XX	4;13	q23 q22
		q35 q12
XY	4;17	q11 q23
XX	4;21	q11 p11
XY	4;21	p15 q22
XX	5;6	q13 p23
XX	5;8	q13 p21
		q33 q13
XY	5;8	p13 p23
XX	5;9	p13 q21.2
		q22 p22
XX	5;11	q13 q25
XX	5;14	q34 q13
XY	5;14	p12 q22
XY	5;15	q12 q22
XX	5;16	p13 q24
XY	5;16	q13 p11
XY	5;18	p13 q11.2
		p15 q21
XX	5;19	q15 p13
XX	6;7	q13 p14
XY	6;8	p21 q22
		p12 q21
XX	6;9	p25 q22
XY	6;9	p21 p15.2
XX	6;10	q11 p11
XX	6;12	q26 q22
XY	6;14	q15 q32
XX	6;20	p25 q13.1
XX	6;22	p21 q13
XY	7;9	p21 q21
XX	7;10	q11 q24
XX	7;11	q11 p11
XY	7;11	p13 q25
		q11.2 p11.3
		q22 q23
XY	7;14	p15.2 q24
XX	7;16	p12 q12
		p22 q24
XY	7;16	q11.2 p13.1
XX	7;17	q11 q21.3
XY	7;17	p13 q25
XY	7;18	q11 q21

(*continued*)

Appendix

Table A1 (continued)

	Translocation	Breakpoints
XX	7;19	q22 q13
XY	7;22	q11.3 p11.1
		q31.2 q13
		q32 q11
XX	8;10	q11 p12
XY	8;10	q22 p13
		q23 p14
XX	8;12	q13 q11
XY	8;12	p12 q13
XY	8;18	q24 q12
XX	8;22	q23 q11
XY	9;10	q11 p15
XX	9;11	q21 q24
XX	9;12	q22.3 q24.3
		q33 q21.2
		q34 q24.3
XY	9;13	p13 q14.3
XY	9;14	q11 p11
XX	9;15	q12 p11
XY	9;15	p13 p13
		p23 q13
		q12 p11.2
XX	9;18	q32 q21
XX	9;19	9p19p 9q19q
XY	10;13	q24.3 q21.32
XX	10;14	q24 q32
XX	10;16	q26.3 p13.1
XX	10;18	q24 q23
XY	10;19	p11 p12
		p11.2 q13.4
XX	10;21	q11.2 q11.2
XY	11;12	q13 p13
XY	11;13	p15 q12
XY	11;14	q25 q22
XY	11;15	p11 q11
		q11 q21
XX	11;16	p11.2 p13.3
XY	11;17	q24 p11.2
XY	11;18	p14 q22
XY	11;21	q23.3 q21.2
XY	11;22	q23 q11
		q23 q11
XY	12;14	q22 q32
XX	12;15	q14 q21
XX	12;19	q15 q12
XY	12;20	q24 q11
XY	12;22	q13 q13.2
XX	13;14	q22 q13

(*continued*)

Appendix

Table A1 (continued)

	Translocation	Breakpoints
XX	13;15	q13 q24
XY	13;15	q22 q23
XY	14;15	q24.1 p11
XX	14;19	q32 p13
XX	14;20	q22 p11.2
XX	15;16	p11 q11
XX	15;17	q13 q21
		q22 p13
XX	16;19	q13 q13
XX	17;20	p13 q11.2
XY	17;20	q21 q13.1
XX	17;22	q22 q11
XY	17;22	q21 q11
XY	18;21	p11 q11
		p11 q11.2
X.....	X;1	q22 q23
X.....	X;2	q11 q28
		q21 p25
X.....	X;4	p21 q35
X.....	X;8	p21 q13
		q26 q22
X.....	X;12	q13 q24.3
X.....	X;20	q24 p13
X.....	Y;2	q12 q12
X.....	Y;4	p11 p16
X.....	Y;11	p11.1 q11.1
	Inversion	
XX	1	p31 q12
		p34 q21
		p36 q11
		p36 q21
XY	1	p35 q42
		q25 q44
XX	2	p11 q13
		p14 q11.2
		q23 q31
XY	2	p13 q31
		p11.2 q13
		p11.2 q13
XX	3	q21 q31
XY	3	p23 p25
XY	4	p14 q25
XY	5	q15 q31
		p13.1 q13.1
XX	6	p22 q21
		p25 q14
		p25 q21
XY	7	p12 p21
		q22 q36
XX	8	p23 q11
XY	9	q21.2 q34
XX	10	p11.2 q21
XY	10	q11 q25
		q11.2 q24
XX	11	p15.1 q11
		q12 q21
		q21 q23
XY	11	q21 q25
XX	16	p13 q11
		p13 q22
XY	18	p12.2 q11.2
XY	20	p13 q12
X.....	X	p11.2 q21
		q22 q28

(*continued*)

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