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Cytogenetic survey in couples with recurrent fetal wastage

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Summary. Cytogenetic studies have been performed in 1068 couples with antecedent fetal wastage, i.e., at least two spontaneous first trimester abortions or one spontaneous first trimester abortion and one late fetal death, particularly with multiple congenital malformations.

Three major types: 33 reciprocal translocations (3.09%), 20 Robertsonian translocations (1.87%) and six other chromosomal abnormalities (0.56%) were found, bringing the total number of chromosomal abnormalities to 59 (5.5%) in 1068 couples under investigation.

In contrast to couples with reciprocal translocations, a high excess of female over male carriers was found in the group of Robertsonian translocations.

In the evaluation of chromosomal polymorphisms, only variants with particularly large paracentromeric constitutive heterochromatin blocks were taken into account, and their low frequency in the present study is therefore not comparable with that in a general population.

The impact of further extensive familial investigation on genetic counseling and the follow-up of prenatal diagnosis are discussed.

Introduction

During the past few years, the importance of cytogenetic investigations in couples with recurrent abortions and/or reproductive failure has generally been acknowledged (Kajii and Ferrier 1978; Turleau et al. 1979; Boué and Boué 1981; Tsenghi et al. 1981; Davis et al. 1982; Michels et al. 1982; Osztovics et al. 1982; Lippman-Hand and Vekemans 1983; Lyberatou-Moraitou et al. 1983).

In the present study, the cytogenetic data of 1068 couples, who were examined in our center for this indication, are given. The aim of this study was: (1) to investigate the frequency of different types of chromosome aberrations in these couples; (2) to further evaluate the impact of more extensive familial cytogenetic investigations and genetic counseling; (3) to discuss the follow-up of prenatal diagnosis.

Materials and methods

In the period 1972–1982 cytogenetic studies were performed in 1068 couples with antecedent fetal wastage (after exclusion of any other etiology): (1) with at least two spontaneous first trimester abortions; (2) one spontaneous first trimester abortion and one late fetal death, particularly with multiple congenital malformations. Besides routine orceine staining technique in all patients, at least G- and R-banding techniques were routinely applied. After detection of the chromosomal abnormality additional banding techniques (Q-, C-, NOR-staining) were used, if they were necessary for further identification of the translocation type and the respective breakpoints.

In the evaluation of chromosomal polymorphism, only variants with particularly large paracentromeric constitutive heterochromatin blocks were taken into account. According to these criteria only extremely large 1qh+ and 9qh+ variants as well as evident cases of inv(9) were collected and confirmed by C-banding.

Results

The general results are summarized in Table 1, and more extensively described in the Addendum. The specific data on

Table 1. Cytogenetic data in 1068 couples with repetitive fetal loss

Type of abnormalities		Sex distribution		Percentage in 76	Percentage in 1068
		Male	Female		
Reciprocal translocations	33	15	18	43.4	3.09
Robertsonian translocations	20	5	15	26.3	1.87
Other chromosomal abnormalities	6	2	4	7.9	0.56
Variants	17	7	8+2[a]	22.3	1.59
Total	76	–	–	100%	–

[a] Variants found in both parents

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Table 2. The breakpoints found in 33 couples with reciprocal translocations

Male carriers	Female carriers
1. 46,XY,t(1;2)(p36;q37)	1. 46,XX,t(1;2)(p36;q13)
2. 46,XY,t(1;4)(q32;q31)	2. 46,XX,t(1;3)(p22;p27)
3. 46,XY,t(1;6)(p34;q16)	3. 46,XX,t(1;4)(q44;q22)
4. 46,XY,t(2;3)(p13;p14)	4. 46,XX,t(1;10)(q12;q26)
5. 46,XY,t(2;6)(q33;q27)	5. 46,XX,t(1;14)(q25;q13)
6. 46,XY,t(2;7)(p24;p21)	6. 46,XX,t(2;5)(p14;p15)
7. 46,XY,t(2;14)(q11;q24)	7. 46,XX,t(2;7)(p25;q11)
8. 46,XY,t(4;6)(p15;q24)	8. 46,XX,t(2;8)(q23;p11)
9. 46,XY,t(4;10)(p16;q26)	9. 46,XX,t(2;9)(q23;p24)
10. 46,XY,t(6;11)(q21;q25)	10. 46,XX,t(3;15)(p21;q25)
11. 46,XY,t(6;12)(q27;p11)	11. 46,XX,t(5;7)(q35;q11)
12. 46,XY,t(7;5)(p12;q35)	12. 46,XX,t(6;10)(q15;q22)
13. 46,XY,t(7;18)(p13;q23)	13. 46,XX,t(6;18)(q23;p11)
14. 46,XY,t(8;22)(q24;q12)	14. 46,XX,t(7;8)(q36;p12)
15. 46,XY,t(11;22)(q23;q13)	15. 46,XX,t(7;12)(p15;p13)
	16. 46,XX,t(9;18)(p24;q21)
	17. 46,XX,t(18;19)(q12;q13)
	18. 46,XX,t(X;9)(p11;q13)
Total: 15	Total: 18

three major types of chromosomal abnormalities and variants, i.e.:

1) reciprocal translocations
2) Robertsonian translocations
3) other chromosomal abnormalities
4) chromosome polymorphic variants

are now briefly described with special reference to the results of further familial investigations.

1. Reciprocal translocations

Of 33 couples the reciprocal translocation was found in 18 females (54.5%) and 15 males (45.5%). One of these translocations was an X autosome translocation 46,XX,t(X;9)(p11;q13). The breakpoints in these translocations are given in Tables 2 and 2a.

After the diagnosis of the reciprocal translocation further family studies were performed whenever possible. Including the 33 index patients, a total number of 203 family members could be investigated and an identical translocation was found in 90 (49 females and 41 males). (As the index patient in this study we took into account this spouse from each couple, who was a translocation carrier.)

In none of the index patients was the reciprocal translocation found to be de novo: it proved to be familial in nine, and could not be investigated in 24 index patients.

In the 33 families anamnestic data of 114 spontaneous abortions with early fetal wastage were obtained. The chromosomal study was successful in seven, as seen in Table 3.

In three fetuses unbalanced karyotypes were diagnosed (8p trisomy, 4p trisomy and 8p monosomy, respectively). In four others, apparently reciprocal translocations, identical to those present in the parents, were found. They were all of maternal origin.

A total number of 35 pregnancies were prenatally monitored by amniocentesis as summarized in Table 4.

Table 2a. The comparison of the exactly stated breakpoints in present and previous studies

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	X	Y
	2p25					7p21																	Not involved
1p36	2p24[a,d]	3p27				7p15																	
1p34	2p14	3p21	4p16[a,b]			7p13	8p12[a,c]	*9p24*[a,b,c]			12p13[a]						18p11					Xp11	
1p22[a,c]	2p13	3p14	4p15[a,c,c,c]	5p15		7p12[a]	8p11	9p11			12p11[a]												
																					Not involved		
1q12	2q11		4q22	*5q35*	6q15	7q11[a]	8q24		10q22[a,b,c]	11q23			14q13[a]					18q12	19q13			22q12	
1q25[a]	2q13		4q31		6q16	7q36[a,c]			*10q26*	11q25			14q24	15q25				18q21[a,b,c,c]				22q13	
1q32[a,b]	*2q23*				6q21													18q23					
1q44	2q33[a,c]				6q23[a]																		
					6q24																		
					6q27[a]																		

Underlined these breakpoints which repeated in this study
[a] Breakpoints found in complex chromosomal rearrangements (Kleczkowska et al. 1982)
[b] Breakpoints found also by Jacobs et al. (1974)
[c] Breakpoints found also by Aurias et al. (1978)
[d] Breakpoints found also by Stoll (1980)

Table 3. Available karyotypic data on aborted fetuses

Type of chromosomal aberration in parents	Total number of aborted fetuses	Type of chromosomal aberration in aborted fetuses	
Rcp t	7	1. 46,XY,t(5;7)(q35;q11)	Addendum 1 – F. 15
		2. 46,XX,t(7;12)(p15;p13)	Addendum 1 – F. 18
		3. 46,XX,t(7;8)(q36;p12)	
		4. 46,XX,t(7;8)(q36;p12)	
		5. 46,XX,der(7),t(7;8)(q36;p12) partial trisomy 8p12→8pter	Addendum 1 – F. 27
		6. 46,XX,del(8),(p12→pter) partial monosomy 8p12–8pter	
		7. 46,XX,der(10),t(4;10)(p16;q26) partial trisomy 4p16→4pter	Addendum 1 – F. 17
Rob t	2	1. 45,XX,–13,–15,+t(13q;15q)	Addendum 2 – F. 14
		2. 45,XX,–13,–15,+t(13q;15q)	
Other chromosomal aberrations	–	–	
Chromosomal variants	1	1. 46,XX,9qh+	Addendum 4 – F. 5

In 14 fetuses normal karyotypes were found, whereas in 17 reciprocal translocations were diagnosed. All were liveborn and did not present visible congenital malformations. In three fetuses unbalanced translocations were detected: a partial trisomy (partial trisomy 7q11→qter and partial trisomy 12p11→pter) in two and a partial 18q monosomy (18q21→qter) in one. In addition to the balanced parental translocation t(4;20)(p16;q26)mat, one fetus presented a de novo inversion of chromosome 6. No termination was done and the pregnancy is progressing normally.

2. Robertsonian translocations

In 20 couples, a Robertsonian type of translocation was found (Table 5). Apart from four males with 13/14 Robertsonian translocations and one with 13/15 translocation, all others were diagnosed in the females. Ten were D/D translocations, four were D/G translocations and one a G/G translocation (for further identification see Table 5).

After the diagnosis of Robertsonian translocation further family studies were performed and including the 20 index patients, a total number of 89 family members could be investigated. Robertsonian translocations were then found in 45 family members: 30 females and 15 males. One of the males had Klinefelter syndrome, together with 13/14 translocation (Addendum 2, family 1).

In the 20 families, 64 spontaneous abortions could be identified and chromosomal investigation was successful in two of them: in both fetuses an identical 45,XX,–13,–15,+t(13q;15q) translocation was detected, similar to that in the carrier mother. In none of the aborted fetuses was there any evidence for 21 or 13 trisomy.

Chromosomal analysis after amniocentesis has been performed in 13 pregnancies. In seven fetuses normal karyotypes were found and in the other six balanced Robertsonian translocations were detected.

3. Other chromosomal abnormalities

In six couples (two males and four females) other chromosomal abnormalities were found (Table 6).

A large paracentric inversion was present in two patients and a small marker chromosome was found in two others. One female presented an Xp deletion [del(X)(p2101)] and had already been reported elsewhere (Fryns et al. 1982a). Her phenotype and menstruation cycles were normal, but she was karyotyped because of her two previous spontaneous abortions.

In another female a ring chromosome 21 was found. The ring chromosome was present in all 100 lymphocytes analysed, without visible translocation of the deleted fragments to another autosome. She was physically and mentally normal. The ring chromosome 21 in her karyotype originated de novo.

There were no karyotypic data on a total of 13 spontaneous abortions in this group.

The only one from eight prenatally diagnosed fetuses had a karyotype 47,XX,+M and the remaining seven had normal karyotypes (Table 4).

4. Chromosomal variants

Besides 9qh+ and inv(9) polymorphisms, which were detected in ten patients, in one female and also one male, the lqh+ variants were found. In two females a deletion of the short arm of chromosome 13 was found and documented with G-, Q-, C- and R-banding. In one of these patients, who had four spontaneous abortions, family history was negative with regard to congenital malformations, recurrent abortions or mental retardation. Chromosomal examination in other family members has not yet been performed. In the second patient-carrier of the 13p deletion with familial occurrence of this variant, the first child with an apparently identical 13p deletion presented mental retardation, dwarfism and dysmorphism, and three other pregnancies ended with premature fetal wastage.

Finally, in one couple a chromosomal variant was present in both spouses; a 9qh+ variant in the male and an inv(9)(p11;q12) in the female. In the other couple the husband was an inv(9)(p11;q13) carrier and the wife had a lqh+ variant.

In this group we found 41 spontaneous abortions but only one of the aborted fetuses had been karyotyped. This fetus had 46,XX,9qh+ karyotype and originated from parents which both had variants of chromosome 9 (Table 7).

Table 4. Karyotypes found in 58 P.D. in 76 families with chromosomal aberrations

Type of chromosomal aberrations in parents	Number of P.D.	Carriers		Chromosomal aberrations		Normal	
I. Rcp. t.	35	1. 46,XY,t(2;5)(p14;p15)	Add. 1-F. 1	1. 46,XX,der(2),t(2;7)(p25;q11) partial trisomy 7q11→7qter	Add. 1-F. 12	1. 46,XY	Add. 1-F. 1
		2. 46,XX,t(1;4)(q44;q22)	Add. 1-F. 2	2. 46,XY,inv(6),t(4;10)(p16;q26)	Add. 1-F. 17	2. 46,XY	
		3. 46,XX,t(1;4)(q44;q22)		3. 46,XX,der(6),t(6;12)(q27;p11) partial trisomy 12p11→12pter	Add. 1-F. 25	3. 46,XX	
		4. 46,XY,t(1;4)(q44;q22)		4. 46,XY,del(18)(q21→qter) partial monosomy 18q21→18qter	Add. 1-F. 26	4. 46,XX	Add. 1-F. 2
		5. 46,XX,t(1;10)(q12;q26)	Add. 1-F. 8			5. 46,XY	
		6. 46,XY,t(3;15)(p21;q25)	Add. 1-F. 10			6. 46,XX	Add. 1-F. 5
		7. 46,XX,t(7;5)(p12;q35)	Add. 1-F. 16			7. 46,XX	Add. 1-F. 11
		8. 46,XY,t(7;12)(p15;p13)	Add. 1-F. 18			8. 46,XY	Add. 1-F. 13
		9. 46,XX,t(6;11)(q21;q25)	Add. 1-F. 19			9. 46,XY	Add. 1-F. 15
		10. 46,XX,t(7;18)(p13;q23)	Add. 1-F. 21			10. 46,XX	
		11. 46,XX,t(6;12)(q27;p11)	Add. 1-F. 25			11. 46,XY	Add. 1-F. 17
		12. 46,XX,t(6;12)(q27;p11)				12. 46,XY	Add. 1-F. 28
		13. 46,XY,t(9;18)(p24;q21)	Add. 1-F. 26			13. 46,XY	Add. 1-F. 30
		14. 46,XY,t(7;8)(q36;p12)	Add. 1-F. 27			14. 46,XX	Add. 1-F. 33
		15. 46,XX,t(7;8)(q36;p12)					
		16. 46,XY,t(X;9)(p11;q13)	Add. 1-F. 30				
		17. 46,XY,t(1;6)(p34;q16)	Add. 1-F. 3				
II. Rob. t.	13	1. 45,XY,−13,−14,+t(13q;14q)	Add. 2-F. 7			1. 46,XY	Add. 2-F. 2
		2. 45,XY,−13,−14,+t(13q;14q)				2. 46,XY	Add. 2-F. 3
		3. 45,XX,−13,−15,+t(13q;15q)	Add. 2-F. 14			3. 46,XY	Add. 2-F 5
		4. 45,XX,−14,−21,+t(14q;21q)	Add. 2-F. 15			4. 46,XY	Add. 2-F. 6
		5. 45,XX,−14,−22,+t(14q;22q)	Add. 2-F. 17			5. 46,XY	Add. 2-F. 14
		6. 45,XY,−15,−22,+t(15q;22q)	Add. 2-F. 18			6. 46,XY	Add. 2-F. 15
						7. 46,XY	Add. 2-F. 18
III. Other chromosomal aberrations	8	1. 47,XX,+M	Add. 3-F. 4			1. 46,XY	Add. 3-F. 1
						2. 46,XX	Add. 3-F. 2
						3. 46,XX	
						4. 46,XY	Add. 3-F. 3
						5. 46,XX	Add. 3-F. 4
						6. 46,XY	Add. 3-F. 5
						7. 46,XY	
IV. Variants	2	1. 46,XX,1qh+	Add. 4-F. 8			1. 46,XY	Add. 4-F. 4

P.D. Prenatal diagnosis

Table 5. Robertsonian translocation carriers found in 20 couples

Male carriers	Number	Female carriers	Number
45,XY,−13,−14,+t(13q;14q)	4	45,XX,−13,−14,+t(13q;14q)	8
45,XY,−13,−15,+t(13q;15q)	1	45,XX,−13,−15,+(13q;15q)	1
		45,XX,−D,−D,+t(Dq;Dq)	1
		45,XX,−14,−21,+t(14q;21q)	2
		45,XX,−14,−22,+t(14q;22q)	1
		45,XX,−15,−22,+t(15q;22q)	1
		45,XX,−21,−22,+t(21q;22q)	1
Total	5	Total	15

Table 6. Carriers of other chromosomal aberrations (six couples)

Male	Number	Female	Number
46,XY/47,XY,+M	1	46,XX/46,XX,inv(2)(q13;q24)	1
46,XY,inv(3)(p13;p25)	1	46,X,del(X)(p2101)	1
		46,XX/47,XX,+M	1
		46,XX,r(21)	1
Total	2	Total	4

Table 7. Carriers of chromosomal variants in 17 couples (19 patients)

Male	Number	Female	Number
46,XY,9qh+	2	46,XX,9qh+	4
46,XY,inv(9)(p11;q13)	2	46,XX,inv(9)(p11;q13)	2
46,XYq−	2	46,XX,13p−	2
46,XY,1qh+	1		
Total	7	Total	8
	[a] 46,XY,inv(9)(p11;q12)+46,XX,9qh+		2
	[a] 46,XY,inv(9)(p11;q13)+46,XX,1qh+		

[a] Both parents with chromosomal variants

Discussion

The present study summarized the cytogenetic findings in a consecutive series of 1068 couples examined because of recurrent fetal loss. The majority of couples under investigation had at least two early first trimester abortions but those in whom one spontaneous abortion and one stillborn child had occurred, particularly with multiple congenital malformations, were also taken into account.

The incidence of cytogenetic abnormalities in the present study, excluding chromosome variants, is 5.5%. This is in good agreement with the 4.78% found by Osztovics et al. (1982) in a large series of 418 couples with recurrent fetal wastage.

During the past few years, other investigators have published their experience in this field. In most reviews the number of couples studied was smaller than 200 and the frequency of cytogenetic abnormalities varied greatly from 0% to 4.7% (Tsenghi et al. 1976; Breuker et al. 1978; Duca et al. 1979; Neu et al. 1979; Pescia et al. 1979; Kardon et al. 1980; Ward et al. 1980; Adžić et al. 1981; Sant-Cassia and Cooke 1981; Simpson et al. 1981; Stoll 1981; Blumberg et al. 1982; Husslein et al. 1982; Lippman-Hand and Vekemans 1983; Lyberatou-Moraitou et al. 1983). This discrepancy is probably due to differences in selection and referral of patients for cytogenetic examination. The higher discrepancy on subjects obtained from the other studies (Rosenmann et al. 1977; Stenchever et al. 1977; Heritage et al. 1978; Mennuti et al. 1978; Hahn and Kim 1981; Nordenson 1981) may also be due to the small number of couples investigated, to the inclusion of polymorphic variants into chromosomal aberrations or finally to the probable exposure of patients investigated to different mutagens.

Some studies indicated that the frequency of chromosomal aberrations increased with a higher number of early abortions (more than three) and/or in couples with late fetal wastage associated with multiple congenital malformations (Tho et al. 1979; Tsenghi et al. 1981), but this was not confirmed by others nor in the present study.

The present study indicated that the frequency of chromosome abnormalities in couples with recurrent fetal loss, at least, with the available cytogenetic techniques at this moment, is 5–6%. It is therefore indicated that cytogenetic investigations be performed in all couples confronted with this problem.

In the present study 33 reciprocal translocations were found in the 1068 couples (3.09%). Davis et al. (1982) collected the data of different authors and showed a rate of 6.2% trans-

locations, i.e., 82 balanced translocations (reciprocal + Robertsonian) in 1331 couples with reproductive failure. These data are therefore not comparable with our findings because we discuss Robertsonian translocations as a separate group. The 33 reciprocal translocations in the present study were found in 18 females and 15 males. There was no evident prevalence of female carriers over males either in the present study or in the latest on this subject (Lippman-Hand and Vekemans 1983).

In other studies on smaller numbers of couples, a similar prevalence has been noted (Tho et al. 1979; Bortotto et al. 1980; Sant-Cassia et al. 1981; Stoll 1981; Davis et al. 1982; Husslein et al. 1982; Michels et al. 1982). Except for one X-autosome translocation, all others were autosomal reciprocal translocations.

Comparing the breakpoints in previous studies on reciprocal translocations (Aurias et al. 1978; Stoll 1980) and those found in complex chromosomal rearrangements (Kleczkowska et al. 1982), it is seen that some of them repeated also in the present study (see Table 2a). The repeating breakpoints were located at: 1q32; 2q33 and 2q37; 3p27; 4p15 and 4p16; 7q36; 9p24; 10q22 and 18q21.

The diagnosis of the reciprocal translocation in the 33 patients led to the detection of a total of 90 family members (49 females and 41 males) who were translocation carriers from 203 persons examined (44.3%).

The detection of a reciprocal translocation in the first patient therefore means that almost three times as many individuals and couples can receive information and genetic counselling.

In the 33 families, anamnestic data on 114 spontaneous abortions were obtained but chromosomal investigation was successful only in seven of them; in four a balanced karyotype was found and in the remaining three unbalanced karyotypes were detected (see Table 3). Prenatal diagnosis in 35 pregnancies revealed 17 balanced reciprocal translocation fetuses and three other fetuses with unbalanced karyotypes (Table 4).

The 8.6% chromosomally abnormal fetuses in this study does not statistically differ from the previous finding of Boué et al. (1981). This frequency is much lower than the 25% chromosomally abnormal fetuses detected with amniocentesis after the birth of a previous child with multiple congenital malformations and unbalanced karyotype.

Of the three chromosomally abnormal fetuses in the present study, it is probable that without prenatal diagnosis at least two of them would have been delivered at term.

In this study Robertsonian translocations were found in 20 couples (1.87% of all couples studied). In contrast to the findings in reciprocal translocations, a large excess of female carriers was found. Of the 20 couples only five spouses were males. Familial investigation of these 20 couples revealed 25 other translocation carriers. Thus, the total number of family members investigated in this group was 89, and a total number of Robertsonian translocation carriers was 45 with an evident prevalence of female (30) over the male (15) carriers.

It is very improbable that the difference in sex distribution in this large group of patients is fortuitous. One possible explanation could be that the lower detection rate in male carriers of Robertsonian translocation might be due to their lower risk of chromosomally abnormal fetuses resulting from the decreased possibility of fertilization with chromosomally unbalanced spermatozoa. On the other hand, it is known that Robertsonian translocations may lead to sterility in the male by spermatogenic arrest (Kjessler 1964; Fraccaro et al. 1973; Plymate et al. 1976; Fraccaro 1980; Marmor et al. 1980; Mićić et al. 1980; Chandley 1981).

Prenatal diagnosis was performed in 13 pregnancies, and normal karyotypes were detected in seven fetuses, whereas Robertsonian translocations identical with those in parents were found in the six others. No unbalanced fetal karyotype was detected in this series. Thus, the risk of liveborn trisomy 13 and 21 children is relatively low, estimated as being no higher than 2% for each of these trisomies (Dutrillaux and Lejeune 1970).

In six couples other chromosomal aberrations were present, and they are listed in Table 6. The occurrence of recurrent abortions in patients with large paracentric inversions (two patients in this study) and with small marker chromosomes (also two patients in this study) is well known (Fryns and Van den Berghe 1980; Fryns et al. 1982b).

One female had an Xp deletion [del(X)(p2101)] without any effect on her phenotype or on menstrual cycle. It is probable that the two early abortions in this patient were related to her Xp monosomy, which predisposes to early fetal loss.

A ring chromosome 21 has been detected in one phenotypically normal female. The phenotypic effect of ring chromosomes is known to be variable (Funderburk et al. 1979). Extensive banding techniques did not show evidence of translocation of the deleted part of the chromosome 21 to other chromosome, as had been demonstrated in another report on ring chromosomes (Fryns et al. 1978). Transmission of a ring chromosome through different generations has been rarely observed, and depends on the number and kind of crossover events between the ring and its homologue. Recently Stoll and Roth (1983) reported on a family in which the ring chromosome 22 had been segregating in three generations.

A number of reports have documented an excess of chromosomal variants, especially of chromosome 9 with inv(9) and 9qh+ in couples with reproductive failure (de la Chapelle et al. 1974; Holbek et al. 1974; Nielsen et al. 1974; Boué et al. 1975; Tsenghi et al. 1976; Rosenmann et al. 1977; Pescia et al. 1979; Karetnikova et al. 1980; Tejada et al. 1980; Kędzia et al. 1981; Milani-Comparetti et al. 1981; Tibiletti et al. 1981; Ford et al. 1982). In contrary to these findings, some authors did not find any significant differences in the frequency of such polymorphic variants when comparing control group with reproductive failure couples (Hemming and Burns 1979; Blumberg et al. 1982). Thus, according to their opinion, chromosomal polymorphic variants do not play an important role in the etiology of recurrent fetal wastage.

In the present study, we took into account only chromosomal variants which showed particularly large paracentromeric constitutive heterochromatin blocks, i.e., large 1qh and 9qh variants and inv(9) confirmed with C-banding. According to these criteria we found carriers of chromosomal variants in only 17 couples. In two couples, in both spouses, a chromosomal variant was found, bringing the total number of patients with chromosomal polymorphisms to 19 (Table 7). This is a low frequency, not comparable to that found in a general population.

In two females a 46,XX,13p– karyotype was observed. In one woman this chromosomal variant was found to be familial and was also present in a previous child with multiple congenital malformations. Whether any karyotype-phenotype correlation exists for this chromosomal polymorphism, it is difficult to determine with the available data. Chromosomal variants in general, however, do not seem to play a major role in the etiology and understanding of early fetal wastage.

References

Adžić S, Marković S, Mijin K, Stolević E, Šulociv V, Vidaković B (1981) Les recherches cytogénétiques chez les sujets ayant des échecs de la reproduction. J Gyn Obst Biol Rep 10 : 371–374

Aurias A, Prieur M, Dutrillaux B, Lejeune J (1978) Systematic analysis of 95 reciprocal translocations of autosomes. Hum Genet 45 : 259–282

Blumberg BD, Shulkin JD, Rotter J, Mohandas T, Kaback MM (1982) Minor chromosomal variants and major chromosomal anomalies in couples with recurrent abortion. Am J Hum Genet 34 : 948–960

Bortotto L, Baccichetti C, Lenzini E, Tenconi R, Delendi N, Caufin D (1980) Cytogenetic survey of couples with habitual abortion and other reproductive wastage. Clin Genet 17 : 56–57

Boué A, Boué J (1981) Chromosome structural rearrangements and reproductive failure. Chromosomes-today 7 : 281–290

Boué J, Taillemite JL, Hazael-Massieux P, Leonard C, Boué A (1975) Association of pericentric inversion of chromosome 9 and reproductive failure in ten unrelated families. Hum Genet 30 : 217–224

Boué J, Barichard F, Deluchat C (1981) Diagnostic prénatal des anomalies de la structure chromosomique. Nouv Presse Med 10 : 3299–3302

Breuker KH, Winkhaus-Schindl I, Citoler P (1978) Chromosomenanomalien bei Ehepaaren mit wiederholten Aborten. Geburtsh u Frauenheilk 38 : 11–17

Chandley AC (1981) The origin of chromosomal aberrations in man and their potential for survival and reproduction in the adult human population. Ann Genet 24 : 5–11

Chapelle A de la, Schröder J, Stenstrand K, Fellman J, Herva R, Saarni M, Anttolainen J, Tallila J, Tervilä L, Husa L, Tallqvist G, Robson EB, Cook PJL, Sanger R (1974) Pericentric inversions of human chromosomes 9 and 10. Am J Hum Genet 26 : 746–766

Davis JR, Weinstein L, Veomett JC, Shenker L, Giles HR, Hauck L (1982) Balanced translocation karyotypes in patients with repetitive abortion. Am J Obstet Gynecol 144 : 229–233

Duca D, Cioltei A, Ioan D, Maximilian C (1979) The importance of cytogenetic investigation of the couples with multiple spontaneous abortions and malformed offsprings. Endocrinology 17 : 17–22

Dutrillaux B, Lejeune J (1970) Etude de la descendance des individus porteurs d'une translocation t(Dq;Dq). Ann Génét 13 : 11–18

Ford JH, Callen DF, Jahnke B, Roberts CG (1982) Within pair differences of human chromosome 9C-bands associated with reproductive loss. Hum Genet 61 : 360–363

Fraccaro M (1980) Cytogenetics of human male infertility. Clin Genet 17 : 65–66

Fraccaro M, Maraschio P, Pasquali F, Tiepolo L, Zuffardi O, Giarola A (1973) Male infertility and 13/14 translocation. Lancet 1 : 488

Fryns JP, De Boeck K, Jaeken J, Van den Berghe H (1978) Malformative syndrome associated with a ring 10 chromosome and a translocated 10q/19 chromosome. Hum Genet 43 : 239–244

Fryns JP, Kleczkowska A, Petit P, Van den Berghe H (1982a) Fertility in patients with X chromosome deletions. Clin Genet 22 : 76–79

Fryns JP, Kleczkowska A, Van den Berghe H (1982b) Small accessory chromosomes (SAC) and their genotype-phenotype correlation. J Génét Hum 30 : 199–214

Fryns JP, Van den Berghe H (1980) Paracentric inversion in man: Personal experience and review of the literature. Hum Genet 54 : 413–416

Fryns JP, Van den Berghe H, Van Herck G, Cassiman JJ (1974) Trisomy 12q due to familial t(12p–,6q+) translocation. Hum Genet 24 : 247–253

Fryns JP, Van der Hauwaert L, Dumoulin M, Van den Berghe H (1979) New chromosomal syndrome. Acta Paediatr Belg 32 : 217–219

Funderburk SJ, Sparkes RS, Klisak I (1979) Phenotypic variation in two patients with a ring chromosome 22. Clin Genet 16 : 305–310

Hahn S, Kim DS (1981) Cytogenetic studies of the leukocytes of couples with habitual abortions. Yonsei Med J 22 : 59–70

Hemming L, Burns C (1979) Heterochromatic polymorphism in spontaneous abortions. J Med Genet 16 : 358–362

Heritage DW, English SC, Young RB, Chen ATL (1978) Cytogenetics of recurrent abortions. Fertil Steril 29 : 414–417

Holbek S, Friedrich U, Lauritsen JG, Therkelsen AJ (1974) Marker chromosomes in parents of spontaneous abortuses. Hum Genet 25 : 61–64

Husslein P, Huber J, Wagenbichler P, Schnedl W (1982) Chromosome abnormalities in 150 couples with multiple spontaneous abortions. Fertil Steril 37 : 372–383

Jacobs PA, Buckton KE, Cunningham C, Newton M (1974) An analysis of the breakpoints of structural rearrangements in man. J Med Genet 11 : 50–64

Kajii T, Ferrier A (1978) Cytogenetics of aborters and abortuses. Am J Obstet Gynecol 131 : 33–38

Kardon NB, Davis JG, Berger AL, Broekman A (1980) Incidence of chromosomal rearrangements in couples with reproductive loss. Hum Genet 53 : 161–164

Karetnikova NA, Rozovsky IS, Muravieva MV (1980) Geneticzeskije isledovanja pri privycznom nievynaszivanii bieremiennosti. Akusz Ginekolog 4 : 42–46

Kędzia H, Pisarski T, Klejewski A (1981) Badania cytogenetyczne u małżeństw z niepowodzeniami położniczymi. Gin Pol 52 : 801–804

Kjessler B (1964) Meiosis in a man with a D/D translocation and clinical sterility. Lancet 1 : 1421–1423

Kleczkowska A, Fryns JP, Van den Berghe H (1982) Complex chromosomal rearrangements (CCR) and their genetic consequences. J Génét Hum 30 : 199–214

Lippman-Hand A, Vekemans M (1983) Balanced translocations among couples with two or more spontaneous abortions: are males and females equally likely to be carriers? Hum Genet 63 : 252–257

Lyberatou-Moraitou E, Grigori-Kostaraki P, Retzepopoulou Z, Kosmaidou-Aravidou Z (1983) Cytogenetics of recurrent abortions. Clin Genet 23 : 294–297

Marmor D, Taillemite JL, Van den Akker J, Portnoi MF, Le Porrier N, Joye N, Delafontaine D, Raix C (1980) Semen analysis in subfertile balanced-translocation carriers. Fertil Steril 34 : 496–502

Mennuti MT, Jingeleski FS, Schwarz RH, Mellman FW (1978) An evaluation of cytogenetic analysis as a primary tool in the assessment of recurrent pregnancy wastage. Obstet Gynecol 52 : 308–313

Michels VV, Medrano C, Venne VL, Riccardi VM (1982) Chromosome translocations in couples with multiple spontaneous abortions. Am J Hum Genet 34 : 507–513

Mićić MD, Nicolis JG, Mićić R (1980) 13/14 translocation in a man with reproductive failure. Hum Genet 55 : 137–139

Milani-Comparetti M, Catena Q, Donati D, Magistrelli R, Saccucci F (1981) Incidenza della variante 9qh+ in soggetti professionalmente radioesposti ed in casi di patologia riproduttiva. Boll Soc Ital Biol Sper 57 : 351–354

Neu RL, Entes K, Bannerman RM (1979) Chromosome analysis in cases with repeated spontaneous abortions. Obstet Gynecol 53 : 373–375

Nielsen J, Friedrich U, Hreidarsson AB, Zeuthen E (1974) Frequency of 9qh+ and risk of chromosome aberrations in the progeny of individuals with 9qh+. Hum Genet 21 : 211–216

Nordenson J (1981) Increased frequencies of chromosomal abnormalities in families with a history of fetal wastage. Clin Genet 19 : 168–173

Osztovics MK, Tóth SP, Wessely JA (1982) Cytogenetic investigations in 418 couples with recurrent fetal wastage. Ann Génét 25 : 232–236

Pescia G, Jotterand M, Gaide A-C (1979) Fausses-couches précoces itératives et caryotype. Etude cytogénétique de 80 couples consécutifs. J Gyn Obst Biol Rep 8 : 35–38

Plymate SR, Bremner WJ, Paulsen CA (1976) The association of D-group chromosomal translocations and defective spermatogenesis. Fertil Steril 27 : 139–144

Rosenmann A, Segal S, Palti Z, Cohen MM (1977) Chromosomes in familial primary sterility and in couples with recurrent abortions and stillbirth. Isr J Med Sci 13 : 1131–1132

Sant-Cassia LJ, Cooke P (1981) Chromosomal analysis of couples with repeated spontaneous abortions. Br J Obst Gynaecol 88 : 52–58

Simpson JL, Elias S, Martin AO (1981) Parental chromosomal rearrangements associated with repetitive spontaneous abortions. Fertil Steril 36 : 584–590

Stenchever MA, Parks KJ, Daines TL, Allen MA, Stenchever MR (1977) Cytogenetics of habitual abortion and other reproductive wastage. Am J Obstet Gynecol 127 : 143–150

Stoll C (1980) Nonrandom distribution of exchange points in patients with reciprocal translocations. Hum Genet 56 : 89–93

Stoll C (1981) Cytogenetic findings in 122 couples with recurrent abortions. Hum Genet 57 : 101–103

Stoll C, Roth MP (1983) Segregation of a 22 ring chromosome in three generations. Hum Genet 63 : 294–296

Tejada J, Soler A, Salami C, Cararach J, Fortuny A (1980) Chromosomal polymorphic variants in couples with recurrent spontaneous abortions. Clin Genet 17 : 90

Tho PT, Byrd JR, Donough PGC Mc (1979) Etiologies and subsequent reproductive performance of 100 couples with recurrent abortion. Fertil Steril 32 : 389–395

Tibiletti MG, Simoni G, Terzoli GL, Romitti L, Fedele L, Candiani GB (1981) Pericentric inversion of chromosome 9 in couples with repeated spontaneous abortion. Acta Eur Fertil 12 : 245–248

Tsenghi Ch, Metaxotou C, Kalpini-Mavrou A, Strataki-Benetou M, Matsaniotis N (1981) Parental chromosome translocations and fetal loss. Obstet Gynecol 58 : 456–458

Tsenghi Ch, Metaxotou-Stavridaki C, Strataki-Benetou M, Kalpini-Mavrou A, Matsaniotis N (1976) Chromosome studies in couples with repeated spontaneous abortions. Obstet Gynecol 47 : 463–468

Turleau C, Chavin-Colin F, Grouchy J de (1979) Cytogenetic investigation in 413 couples with spontaneous abortions. Eur J Obstet Gynaecol Rep Biol 9 : 65–74

Ward BE, Henry GP, Robinson A (1980) Cytogenetic studies in 100 couples with recurrent spontaneous abortions. Am J Hum Genet 32 : 349–554

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Addendum 1. Reciprocal translocations

Family	Family member	Indication for karyotyping	Phenotype	Number of S.A. and other reproductive failure	Karyotype and origin of chromosomal aberration	Remarks
1	1. Proband	S.A.	N	3	46,XX,t(2;5)(p14;p15)pat	
	2. Husband of 1	Familial investigation	N	–	46,XY	
	3. Aborted fetus of 1				No karyotype was available	
	4. P.D. in 1				46,XY	N boy was born from this pregnancy
	5. P.D. in 1				46,XY	N boy was born from this pregnancy
	6. Father of 1	Familial investigation	N	–	46,XY,t(2;5)(p14;p15)	
	7. Mother of 1	Familial investigation	N	–	46,XX	
	8. Sister of 1	Familial investigation	N	–	46,XX,t(2;5)(p14;p15)	
	9. Brother of 1	Familial investigation	N	–	46,XY,t(2;5)(p14;p15)	
	10, 11 and 12 sibs of 1	Familial investigation	N		Karyotypically normal	
	13. Paternal aunt of 1	N	Familial investigation		46,XX,t(2;5)(p14;p15)	
	14. Paternal aunt of 1	Familial investigation	Borderline intelligence		47,XXX	
	15. Paternal uncle of 1	Familial investigation	N	–	46,XY,t(2;5)(p14;p15)	He has two sons: one of them with subfertility
	16. Paternal cousin of 1	Familial investigation	N		46,XY,t(2;5)(p14;p15)	
	17. Cousin of 1	Familial investigation	N		46,XX,t(2;5)(p14;p15)	
	18. P.D. in 17				46,XY,t(2;5)(p14;p15)	Phenotypically N boy was born from this pregnancy
	19. P.D. in 17				46,XX	
	20. Cousin of 1		N		46,XY,t(2;5)(p14;p15)	
	21–26: the remaining relatives of 1		N		Karyotypically normal	
2	1. Proband	R.F.	N	One S.A., one child with M.C.M.	46,XX,t(1;4)(q44;q22)mat	
	2. Husband of 1	Familial investigation	N		46,XY	
	3. First child of 1	M.C.M.	Stillborn, small for dates, microcephaly, holoprosencephaly, cleft lip and palate, hemivertebras, absent kidneys and testes		46,XY,der(1),t(1;4)(q44;q22) (partial tris 4q22→4qter)	

Addendum 1 (continued)

Family	Family member	Indication for karyotyping	Phenotype	Number of S.A. and other reproductive failure	Karyotype and origin of chromosomal aberration	Remarks
	4. P.D. in 1				46,XX	N girl was born from this pregnancy
	5. Aborted fetus of 1				No karyotype was available	
	6. Father of 1	Familial investigation	N		46,XY	
	7. Mother of 1	Familial investigation	N	Two S.A. but 9 living children	46,XX,t(1;4)(q44;q22)	
	8. Sister of 1	Familial investigation	Primary subfertility		46,XX,t(1;4)(q44;q22)	
	9. Husband of 8	Familial investigation	N		46,XY	
	10. P.D. in 8				46,XX,t(1;4)(q44;q22)	No further data were available about this child
	11. Sister of 1 and 8	Familial investigation	N	Unmarried	46,XX,t(1;4)(q44;q22)	
	12. Sister of 1, 8 and 11	Familial investigation	N	Unmarried	46,XX,t(1;4)(q44;q22)	
	13. Sister of 1, 8, 11, 12	Familial investigation	N		46,XX,t(1;4)(q44;q22)	
	14. Husband of 13	Familial investigation	N		46,XY	
	15. P.D. in 12				46,XY	N boy was born from this pregnancy
	16. P.D. in 12				46,XX,t(1;4)(q44;q22)	N girl was born from this pregnancy
	17. P.D. in 12				46,XY,t(1;4)(q44;q22)	N boy was born from this pregnancy
	18. Brother of 1, 8, 11, 12, 13	Familial investigation	N	Two children: both t carriers	46,XY,t(1;4)(q44;q22)	
	19. Son of 18	Familial investigation	N		46,XY,t(1;4)(q44;q22)	
	20. Daughter of 18	Familial investigation	N		46,XX,t(1;4)(q44;q22)	
	21, 22, 23: the relatives of 1	Familial investigation	N		Karyotypically normal	
3	1. Proband	S.A.	N	2	46,XX	
	2. Husband of 1	Familial investigation	N		46,XY,t(1;6)(p34;q16)pat	
	3. P.D. in 1				46,XY,t(1;6)(p34;q16)	
	4. Father of 2	Familial investigation	N		46,XY,t(1;6)(p34;q16)	
	5. Mother of 2	Familial investigation	N		46,XX	No data about S.A. in this woman were available
4	1. Proband	S.A.	N	2	46,XX	
	2. Husband of 1	Familial investigation	N		46,XY,t(2;3)(p13;p14) unknown origin	
	3. Sister of 2	Familial investigation	N	One healthy child, no S.A.	46,XX	
5	1. Proband	S.A.	N	3	46,XX,t(1;2)(p36;q13) unknown origin	Two of her sibs died in early infancy
	2. Husband of 1	Familial investigation	N		46,XY	
	3. P.D. in 1				46,XX	
	4. Brother of 1	Familial investigation	N		46,XY	
6	1. Proband	S.A.	N	3	46,XX	
	2. Husband of 1	Familial investigation	N		46,XY,t(2;14)(q11;q24) unknown origin	
7	1. Proband	S.A.	N	2	46,XX	
	2. Husband of 1	Familial investigation	N		46,XY,t(1;2)(p36;q37) unknown origin	His mother had no S.A.

Addendum 1 (continued)

Family	Family member	Indication for karyotyping	Phenotype	Number of S.A. and other reproductive failure	Karyotype and origin of chromosomal aberration	Remarks
8	1. Proband	S.A.	N	3	46,XX,t(1;10)(q12;q26) unknown origin	Her mother had one S.A.
	2. Husband of 1	Familial investigation	N		46,XY	
	3. P.D. in 1				46,XX,t(1;10)(q12;q26)	
9	1. Proband	S.A.	N	Four S.A., no living children	46,XX,t(1;3)(p22;p27) unknown origin	
	2. Husband of 1	Familial investigation	N		46,XY	
10	1. Proband	S.A.	N	Three S.A., one healthy daughter	46,XX,t(3;15)(p21;q25) unknown origin	
	2. Husband of 1	Familial investigation	N		46,XY	
	3. P.D. in 1				46,XY,t(3;15)(p21;q25)	
11	1. Proband	S.A.	N	Two S.A. no living child	46,XX,t(2;9)(q23;p24) unknown origin	
	2. Husband of 1	Familial investigation	N		46,XY	
	3. P.D. in 1				46,XX	
12	1. Proband	M.C.M.		Hydrocephalus, low set ears, micro and rethrognathia, broad nasal bridge, died within 5 days		46,XY
	2. Mother of 1	Familial investigation	N	One S.A., one boy with M.C.M., one healthy boy	46,XX,t(2;7)(p25;p11)mat	
	3. Father of 1	Familial investigation	N		46,XY	
	4. Brother of 1	Familial investigation	N		46,XY	
	5. P.D. in 2				46,XX,der(2),t(2;7)(p25;q11) partial tris 7q11→7qter	Therapeutic abortion at 18½ weeks
	6. Maternal grandmother of 1	Familial investigation	N	3	46,XX,t(2;7)(p25;q11)	
	7. Maternal grandfather of 1	Familial investigation	N		46,XY	
	8. Maternal uncle of 1	Familial investigation	N, except oligoteratozoospermia	Two children but after artificial insemination	46,XY,t(2;7)(p25;q11)	
	9. Maternal uncle of 1	Familial investigation	N		46,XY,t(2;7)(p25;q11)	
	10–13: relatives of 1	Familial investigation			Karyotypically normal	
13	1. Proband	S.A.	N	2	46,XX	Two N sons
	2. Husband of 1	Familial investigation	N		46,XY,t(8;22)(q24;q12) unknown origin	
	3. P.D. in 1				46,XY	N boy was born from this pregnancy
	4 and 5: Twins, sons of 1	Familial investigation			Karyotypically normal	
14	1. Proband	S.A.	N	Two S.A., no living child	46,XX,t(2;8)(q23;p11) unknown origin	Proband's mother had one handicapped child, who died shortly after delivery
	2. Husband of 1	Familial investigation	N		No karyotype	
	3. Brother of 1	Familial investigation	N		46,XY	
15	1. Proband	R.F.	N	One intrauterine death, one premature delivery, two normal children	46,XX,t(5;7)(q35;q11) unknown origin	

Addendum 1 (continued)

Family	Family member	Indication for karyotyping	Phenotype	Number of S.A. and other reproductive failure	Karyotype and origin of chromosomal aberration	Remarks
	2. Fetus of 1		N fetus, born after 34 weeks of gestation		Not checked karyotypically	
	3. Husband of 1	Familial investigation	N		46,XY	
	4. Fetus of 1		N fetus, born at 16 weeks of pregnancy, died		46,XY,t(5;7)(q35;q11)	
	5. P.D. in 1				46,XY	N boy was born from this pregnancy
	6. P.D. in 1				46,XX	N girl was born
16	1. Proband	S.A.	N	3	46,XX	
	2. Husband of 1	Familial investigation	N		46,XY,t(7;5)(p12;q35) unknown origin	His mother had 4 S.A. and 1 boy who died early, sister of this man had 5 S.A. and 1 N boy
	3. P.D. in 1				46,XX,t(7;5)(p12;q35)	
17	1. Proband	S.A.	N	2	46,XX	
	2. Husband of 1	Familial investigation	N		46,XY,t(4;10)(p16;q26)mat	
	3. Father of 2	Familial investigation	N		46,XY	
	4. Mother of 2	Familial investigation	N	No S.A.	46,XX,t(4;10)(p16;q26)	She has 3 N children
	5. Sister of 2	Familial investigation	N	1	46,XX,t(4;10)(p16;q26)	
	6. Husband of 5	Familial investigation	N		46,XY	
	7. Aborted fetus of 5		?		46,XX,der(10),t(4;10)(p16;q26) partial tris 4p16→4pter	
	8. P.D. in 5				46,XY,inv(6),t(4;10)(p16;q26) inv(6)(p25;q21) de novo	
	9. Sister of 2 and 5	Familial investigation	N	Two S.A., one stillborn baby with probable trisomy 21	46,XX	
	10. P.D. in 9				46,XY	N boy was born from this pregnancy
	11, 12: Other family members	Familial investigation	N		Karyotypically normal	
18	1. Proband		Aborted fetus, apparently normal, decidua in a haemorrhagic necrosis		46,XX,t(7;12)(p15;p13)	
	2. Mother of 1	S.A.	N	S.A. with chromosomal abnormality	46,XX,t(7;12)(p15;p13) unknown origin	
	3. Father of 1	Familial investigation	N		46,XY	
	4. P.D. in 2				46,XY,t(7;12)(p15;p13)	N boy was born from this pregnancy
19	1. Proband	S.A.	N	2	46,XX	
	2. Husband of 1	Familial investigation	N		46,XY,t(6;11)(q21;q25) unknown origin	
	3. P.D. in 1				46,XX,t(6;11)(q21;q25)	
20	1. Proband	S.A.	N	Three S.A., one pregnancy with hydatidiform mole	46,XX	
	2. Husband of 1	Familial investigation	N		46,XY,t(2;6)(q33;q27) pat? mat?	His mother and sibs had S.A.
	3. Daughter of 1	Familial investigation	N		46,XX	

Addendum 1 (continued)

Family	Family member	Indication for karyotyping	Phenotype	Number of S.A. and other reproductive failure	Karyotype and origin of chromosomal aberration	Remarks
	4. Sister of 2	Familial investigation	N		46,XX,t(2;6)(q33;q27)	
	5. Daughter of 4	Familial investigation	N		46,XX,t(2;6)(q33;q27)	
	6. Brother of 2	Familial investigation	N		46,XY,t(2;6)(q33;q27)	
	7. Wife of 6		N	3	No karyotype	
	8. Sister of 2, 4 and 6	Familial investigation	N		46,XX	
21	1. Proband	S.A.	N	2	46,XX	
	2. Husband of 1	Familial investigation	N		46,XY,t(7;18)(p13;q23) unknown origin	
	3. P.D. in 1				46,XX,t(7;18)(p13;q23)	
	4. Sister of 2	Familial investigation	N		46,XX	
22	1. Proband	S.A.	N	2	46,XX,t(6;18)(q23;p11) unknown origin	Her mother had one S.A.
	2. Husband of 1	Familial investigation	N		No karyotype	
23	1. Proband	S.A.	N	6	46,XX	3 N children
	2. Husband of 1	Familial investigation	N		46,XY,t(4;6)(p15;q24) unknown origin	
24	1. Proband	S.A.	N	3	46,XX,t(6;10)(q15;q22) unknown origin	Her mother had one S.A.
	2. Husband of 1	Familial investigation	N		46,XY	
	3 and 4, sisters of 1	Familial investigation	N		Karyotypically normal	
25	1. Proband	M.C.M.	Child described elsewhere (Fryns et al. 1974)	Threatening abortion during this pregnancy	46,XY,der(6),t(6;12)(q27;p11) partial tris 12p11→12pter	
	2. Father of 1	Familial investigation	N		46,XY,t(6;12)(q27;p11) unknown origin	His mother had two S.A. and one premature still-born baby
	3. Mother of 1	Familial investigation	N	One S.A., two polymalformed children	46,XX	
	4. P.D. in 3		M.C.M. fetus born after $4\frac{1}{2}$ months of gestation		46,XX,der(6),t(6;12)(q27;p11) partial tris 12p11→12pter	
	5. P.D. in 3				46,XX,t(6;12)(q27;p11)	N girl was born from this pregnancy
	6. P.D. in 3				46,XX,t(6;12)(q27;p11)	N girl was born from this pregnancy
	7. Brother of 1	Familial investigation	N		46,XY,t(6;12)(q27;p11)	
	8. Sister of 1	Familial investigation	N		46,XX	
26	1. Proband	ALL	N		46,XY,t(9;18)(p24;q21)	
	2. Mother of 1	Familial investigation	N	Two S.A., two children with chromosomal aberrations and M.C.M.	46,XX,t(9;18)(p24;q21) unknown origin	
	3. Father of 1	Familial investigation	N		46,XY	
	4. Brother of 1	M.C.M.	Child described elsewhere (Fryns et al. 1979)		46,XY,der(9),t(9;18)(p24;q21) partial tris 18q21→18qter	
	5. P.D. in 2		?		46,XY,del(18)(q21→qter)	
	6. P.D. in 2				46,XY,t(9;18)(p24;q21)	N boy was born from this pregnancy

Addendum 1 (continued)

Family	Family member	Indication for karyotyping	Phenotype	Number of S.A. and other reproductive failure	Karyotype and origin of chromosomal aberration	Remarks
27	1. Proband	S.A.	N	2	46,XX,t(7;8)(q36;p12)pat	
	2. Husband of 1	Familial investigation	N		46,XY	
	3. Son of 1 and 2	Familial investigation	N		46,XY	
	4. P.D. in 1				46,XY,t(7;8)(q36;p12)	
	5. Father of 1	Familial investigation	N		46,XY,t(7;8)(q36;p12)	
	6. Mother of 1	Familial investigation	N		46,XX	
	7. Sister of 1	Familial investigation	N		46,XX,t(7;8)(q36;p12)	
	8. Husband of 7	Familial investigation	N		46,XY	
	9. Aborted fetus of 7	M.C.M.	Cleft lip and palate, vascular anomalies, hypoplastic left heart with atresic aorta, annular pancreas (neuroblastoma in situ)		46,XX,der(7),t(7;8)(q36;p12) partial tris 8p12→8pter	
	10. P.D. in 7				46,XX,t(7;8)(q36;p12)	N girl was born from this pregnancy
	11. Sister of 1 and 7	S.A.	N	4	46,XX,t(7;8)(q36;p12)	
	12. Husband of 11	Familial investigation	N		46,XY	
	13. Aborted fetus of 11				46,XX,t(7;8)(q36;p12)	
	14. Aborted fetus of 11				46,XX,del(8)(p12→pter)	
	15. Aborted fetus of 11				46,XX,t(7;8)(q36;p12)	
	16. Brother of 1, 7 and 11	Familial investigation	N		46,XY,t(7;8)(q36;p12)	
	17. Paternal uncle of 1	Familial investigation	N		46,XY,t(7;8)(q36;p12)	
	18. Paternal cousin of 1	Familial investigation	N	2	46,XX,t(7;8)(q36;p12)	
	19, 20, 21: Sibs of 1	Familial investigation	N		Karyotypically normal	
	22-30: Other family members of 1	Familial investigation	N		Karyotypically normal	
28	1. Proband	S.A.	N	2	46,XX	
	2. Husband of 1	Familial investigation	N		46,XY,t(2;7)(p24;p21)pat	
	3. P.D. in 1				46,XY	N boy was born from this pregnancy
	4. Father of 2	Familial investigation	N		46,XY,t(2;7)(p24;p21)	
	5. Mother of 2	Familial investigation	N		46,XX	
29	1. Proband	S.A.	N	3	46,XX	
	2. Husband of 1	Familial investigation	N		46,XY,t(11;22)(q23;q13) mat? pat?	
	3. Sister of 2	Familial investigation	N	1	46,XX,t(11;22)(q23;q13)	
	4. Sister of 2 and 3	Familial investigation	N	2	46,XX,t(11;22)(q23;q13)	
30	1. Proband	S.A.	N	2	46,XX,t(X;9)(p11;q13) unknown origin	
	2. Husband of 1	Familial investigation	N		46,XY	
	3. P.D. in 1		Slight psychomotor retardation		46,XY,t(X;9)(p11;q13)	
	4. P.D. in 1				46,XY	N boy was born from this pregnancy
31	1. Proband	S.A.	N	4	46,XX,t(1;14)(q25;q13) unknown origin	
	2. Husband of 1	Familial investigation	N		46,XY	
32	1. Proband	S.A.	N	3	46,XX	
	2. Husband of 1	Familial investigation	N		46,XY,t(1;4)(q32;q31) unknown origin	

Addendum 1 (continued)

Family	Family member	Indication for karyotyping	Phenotype	Number of S.A. and other reproductive failure	Karyotype and origin of chromosomal aberration	Remarks
33	1. Proband	S.A.	N	2	46,XX,t(18;19)(q12;q13) unknown origin	
	2. Husband of 1	Familial investigation	N		46,XY	
	3. P.D. in 1				46,XX	N girl was born from this pregnancy

S.A., spontaneous abortion; N, normal phenotype; P.D., prenatal diagnosis; R.F., reproductive failure; M.C.M., multiple congenital malformations; D.S., Down syndrome

Addendum 2. Robertsonian translocations

Family	Family member	Indication for karyotyping	Phenotype	Number of S.A. and other reproductive failure	Karyotype and origin of chromosomal aberration	Remarks
1	1. Proband	S.A.	N	3	45,XX,−13,−14,+t (13q;14q)mat	
	2. Husband of 1	Familial investigation	N		46,XY	
	3. Son of 1	Familial investigation	Klinefelter syndrome		46,XXY,−13,−14,+t(13q;14q)	
	4. Mother of 1	Familial investigation	N	1	45,XX,−13,−14,+t(13q;14q)	One child with M.C.M.
	5. Father of 1	Familial investigation	N		46,XY	
2	1. Proband	S.A.	N	3	46,XX	One healthy boy
	2. Husband of 1	Familial investigation	N		45,XY,−13,−14,+t(13q;14q) unknown origin	His mother had one S.A.
	3. P.D. in 1				46,XY	
3	1. Proband	S.A.	N	2	45,XX,−13,−14,+t(13q;14q) unknown origin	
	2. Husband of 1	Familial investigation	N		46,XY	
	3. P.D. in 1				46,XY	
4	1. Proband	S.A.	N	Two S.A., one premature delivery: female infant with spina bifida and hydrocephalus was born	46,XX	
	2. Husband of 1	Familial investigation	N		45,XY,−13,−14,+t(13q;14q) unknown origin	
5	1. Proband	S.A.	N	2	45,XX,−13,−14,+t(13q;14q) unknown origin	
	2. Husband of 1	Familial investigation	N		46,XY	
	3. P.D. in 1				46,XY	
6	1. Proband	S.A.	N	2	45,XX,−13,−14,+t(13q;14q) mat	
	2. Husband of 1	Familial investigation	N		46,XY	
	3. Mother of 1	Familial investigation	N	No spontaneous abortions	45,XX,−13,−14,+t(13q;14q)	
	4. Father of 1	Familial investigation	N		46,XY	
	5. P.D. in 1				46,XY	
	6, 7: sibs of 1	Familial investigation	N		Karyotypically normal	
7	1. Proband	S.A.	N	2	45,XX,−13,−14,+t(13q;14q) unknown origin	
	2. Husband of 1	Familial investigation	N		46,XY	
	3. P.D. in 1		N		45,XY,−13,−14,+t(13q;14q)	
	4. P.D. in 1		N		45,XY,−13,−14,+t(13q;14q)	

Addendum 2 (continued)

Family	Family member	Indication for karyotyping	Phenotype	Number of S.A. and other reproductive failure	Karyotype and origin of chromosomal aberration	Remarks
8	1. Proband	S.A.	N	3	45,XX,−13,−14,+t(13q;14q) unknown origin	
	2. Husband of 1	Familial investigation	N		46,XY	
9	1. Proband	S.A.	N	3	46,XX	
	2. Husband of 1	Familial investigation	N		45,XY,−13,−14,+t(13q;14q) unknown origin	
	3. Son of 1	Familial investigation	N		46,XY	
10	1. Proband	S.A.	N	Two S.A., no living child	45,XX,−13,−14,+t(13q;14q) mat	
	2. Husband of 1	Familial investigation	N		46,XY	
	3. Mother of 1	Familial investigation	N		45,XX,−13,−14,+t(13q;14q)	No data about her pregnancies
	4. Father of 1	Familial investigation	N		46,XY	
	5. Brother of 1	Familial investigation	N		45,XY,−13,−14,+t(13q;14q)	
11	1. Proband	S.A.	N	2	45,XX,−13,−14,+t(13q;14q) unknown origin	Her mother had also 3 S.A.
	2. Husband of 1	Familial investigation	N		46,XY	
12	1. Proband	S.A.	N	4	45,XX,t(Dq;Dq) unknown origin	
	2. Husband of 1	Familial investigation	N		46,XY	His sister had two S.A.
13	1. Proband	S.A.	N	2	46,XX	
	2. Husband of 1	Familial investigation	N		45,XY,−13,−14,+t(13q;14q) unknown origin	
14	1. Proband	R.F.	N	One S.A., one premature delivery	45,XX,−13,−15,+t(13q;15q) pat	
	2. Husband of 1	Familial investigation	N		46,XY	
	3. Aborted fetus of 1				45,XX,−13,−15,+t(13q;15q)	
	4. Aborted fetus of 1		Apparently N fetus		45,XX,−13,−15,+t(13q;15q)	
	5. P.D. in 1				46,XY	
	6. P.D. in 1				45,XX,−13,−15,+t(13q;15q)	
	7. Mother of 1	Familial investigation	N		46,XX	
	8. Father of 1	Familial investigation	N		45,XY,−13,−15,+t(13q;15q)	
	9. Brother of 1	Familial investigation	N		45,XY,−13,−15,+t(13q;15q)	
	10. Sister in law of 1	Familial investigation	N	3	46,XX	
15	1. Proband	AML-chromosome investigation	N	One daughter with D.S., one phenotypically normal son	45,XX,−14,−21,+t(14q;21q) mat An additional autosomal translocation was found in acute stage of AML t(8q−;21q+)	
	2. Husband of 1	Familial investigation	N		46,XY	
	3. Daughter of 1	Familial investigation	Down syndrome		46,XX,−14,+t(14q;21q)	
	4. Son of 1	Familial investigation	N		46,XY	
	5. Mother of 1	Familial investigation	N	Two S.A., one stillbirth	45,XX,−14,−21,+t(14q;21q)	
	6. Father of 1	Familial investigation	N		46,XY	
	7. Brother of 1	Familial investigation	N		45,XY,−14,−21,+t(14q;21q)	
	8. Sister in law of 1, wife of 7	Familial investigation	N		46,XX	
	9. P.D. in 1				45,XX,−14,−21,+t(14q;21q)	N girl was born
	10. P.D. in 1				46,XY	N boy was born

Addendum 2 (continued)

Family	Family member	Indication for karyotyping	Phenotype	Number of S.A. and other reproductive failure	Karyotype and origin of chromosomal aberration	Remarks
16	1. Proband	S.A.	N	2	45,XX,−14,−21,+t(14q;21q) unknown origin	
	2. Husband of 1	Familial investigation	N		46,XY	
17	1. Proband	S.A.	N	2	45,XX,−14,−22,+t(14q;22q) unknown origin	Dicentric t-chromosome
	2. Husband of 1	Familial investigation	N		46,XY	
	3. Son of 1	Familial investigation	N		46,XY	
	4. P.D. in 1				45,XX,−14,−22,+t(14q;22q)	N girl was born
	5. Sister of 1	Familial investigation	N		45,XX,−14,−22,+t(14q;22q)	No children
	6. Husband of 5	Familial investigation	N		46,XY	
18	1. Proband	S.A.	N	2	45,XX,−15,−22,+t(15q;22q) unknown origin	Her mother had 5 children and one S.A.
	2. Husband of 1	Familial investigation	N		46,XY	
	3. P.D. in 1				45,XY,−15,−22,+t(15q;22q)	
	4. Cousin of 1	Familial investigation	N	2	45,XX,−15,−22,+t(15q;22q)	No liveborn child
	5. Husband of 4	Familial investigation	N		46,XY	
	6. P.D. in 1				46,XY	
19	1. Proband	Down's syndrome	Down's syndrome		46,XY,−22,+t(21q;22q)	
	2. Mother of 1	Genetic counseling	N	3	45,XX,−21,−22,+t(21q;22q) pat	
	3. Father of 1	Genetic counseling	N		46,XY	
	4. Sister of 1	Familial investigation	N		45,XX,−21,−22,+t(21q;22q)	
	5. Maternal aunt of 1	Familial investigation	N	First pregnancy: girl with D.S. and 21/22 translocation	45,XX,−21,−22,+t(21q;22q)	
	6. Husband of 5	Familial investigation	N		46,XY	
	7. Maternal cousin of 1	Familial investigation	Down's syndrome		46,XX,−22,+t(21q;22q)	
	8. Maternal grandfather of 1	Familial investigation	N	45,XY,−21,−22,+t(21q;22q)		
	9. Maternal grandmother of 1	Familial investigation	N	No S.A.	46,XX	
	10. Maternal aunt of 1	Familial investigation	N	Unmarried	46,XX	
20	1. Proband	S.A.	N	3	46,XX	
	2. Husband of 1	Familial investigation	N		45,XY,−13,−15,+t(13q;15q) unknown origin	In his family 4 S.A.

Addendum 3. Other chromosomal abnormalities

Family	Family member	Indication for karyotyping	Phenotype	Number of S.A. and other reproductive failure	Karyotype and origin of chromosomal aberration	Remarks
1	1. Proband	S.A.	N	2	46,XX	
	2. Husband of 1	Familial investigation	N		46,XY,inv(3)(p13;p25)mat	
	3. P.D. in 1				46,XY	
	4. Father in law of 1	Familial investigation	N		46,XY	
	5. Mother in law of 1	Familial investigation	N		46,XX,inv(3)(p13;p25)	No data about reproductive failure
2	1. Proband	S.A.	N	2	46,XX/46,XX,inv(12)(q13;q24) unknown origin	
	2. Husband of 1	Familial investigation	N		45,XY	
	3. P.D. in 1				46,XX	
	4. P.D. in 1				46,XX	

Addendum 3 (continued)

Family	Family member	Indication for karyotyping	Phenotype	Number of S.A. and other reproductive failure	Karyotype and origin of chromosomal aberration	Remarks
3	1. Proband	S.A.	N	2	46,X,del(X)(p2101) unknown origin	
	2. Husband of 1	Familial investigation	N		46,XY	
	3. P.D. in 1				46,XY	
4	1. Proband	S.A.	N	2	46,XX/47,XX,+M unknown origin	2/3 cells have this marker
	2. Husband of 1	Familial investigation	N		46,XY	
	3. P.D. in 1				47,XX,+M,mat	
	4. P.D. in 1				46,XX	
	5. Father of 1	Familial investigation	N		46,XY	
	6. Mother of 1	Familial investigation	N		46,XX	
5	1. Proband	S.A.	N	3	46,XX	
	2. Husband of 1	Familial investigation	N		46,XY/47,XY,+M unknown origin	
	3. P.D. in 1				46,XY	N boy was born
	4. P.D. in 1				46,XY	
6	1. Proband	S.A.	N	2	46,XX,r(21), de novo	
	2. Husband of 1	Familial investigation	N		46,XY	
	3. Mother of 1	Familial investigation	N		46,XX	
	4. Father of 1	Familial investigation	N		46,XY	

Addendum 4. Chromosomal polymorphic variants

Family	Family member	Indication for karyotyping	Phenotype	Number of S.A. and other reproductive failure	Karyotype and origin of chromosomal variant	Remarks
1	1. Proband	S.A.	N	Three S.A. and one stillbirth	46,XX,9qh+ unknown origin	
	2. Husband of 1	Familial investigation	N		46,XY	
2	1. Proband	S.A.	N	2	46,XX,inv(9)(p11;q13) unknown origin	No living child
	2. Husband of 1	Familial investigation			46,XY	
3	1. Proband	Congenital malformations of genitalia and skull			46,XX,9qh+	
	2. Paternal cousin of 1	S.A.		3	46,XX,9qh+,pat	In her father's family four mentally retarded children
	3. Husband of 2	Familial investigation	N		46,XY	
	4. Mother of 2	Familial investigation	N	1	46,XX	
	5. Father of 2	Familial investigation	N		46,XY,9qh+	
4	1. Proband	R.F.	N	Two S.A., one daughter with anencephaly died shortly after birth	46,XX	
	2. Husband of 1	Familial investigation	N		46,XY,9qh+ unknown origin	
	3. P.D. in 1		Ultrasonography revealed normal development of CNS		No karyotype	
	4. P.D. in 1				46,XY	
5	1. Proband	S.A.	N	2	46,XX,9qh+	No living child

Addendum 4 (continued)

Family	Family member	Indication for karyotyping	Phenotype	Number of S.A. and other reproductive failure	Karyotype and origin of chromosomal variant	Remarks
	2. Husband of 1	Familial investigation	N		46,XY,inv(9)(p11;q12) unknown origin	
	3. Aborted fetus of 1				46,XX,9qh+	
6	1. Proband	S.A.	N	2	46,XX,9qh+ unknown origin	
	2. Husband of 1	Familial investigation	N		46,XY	
7	1. Proband	S.A.	N	4	46,XX,9qh+ unknown origin	No living child
	2. Husband of 1	Familial investigation	N		46,XY	
8	1. Proband	S.A.	N	2	46,XX	
	2. Husband of 1	Familial investigation	N		46,XY,1qh+ unknown origin	
	3. P.D. in 1				46,XX,1qh+	Phenotypically normal girl was born, but premature
9	1. Proband	S.A.	N	3	46,XX	No living child
	2. Husband of 1	Familial investigation	N		46,XY,inv(9)(p11;q13) unknown origin	
10	1. Proband	R.F.	N	One S.A., one macerated fetus (30 weeks) no living child	46,XX,inv(9)(p11;q13) unknown origin	
	2. Husband of 1	Familial investigation	N		46,XY	In his family two stillbirths and one premature delivery occurred
11	1. Proband	Congenital malformations	Arthrogryposis multiplex congenita, Peculiar head shape, low set ears, dysmaturity, hyperflexibility of fingers, cardiac defect		46,XX,inv(9)(p11;q13)1qh+	
	2. Mother of 1	Familial investigation	N	One S.A., one threatening abortion: from this pregnancy proband was born	46,XX,1qh+ unknown origin	
	3. Father of 1	Familial investigation	N		46,XY,inv(9)(p11;q13) unknown origin	
12	1. Proband	S.A.	Small stature, obesity, hypertension, partial Asherman syndrome	2	46,XX	No living child
	2. Husband of 1		N		46,XY,inv(9)(p11;q13) unknown origin	
13	1. Proband	Multiple congenital malformations	Mental retardation, dwarfism, dysmorphic features		46,XX,13p−	
	2. Mother of 1	Familial investigation	Small stature, slight hypertension	One S.A., two times mors in utero	46,XX,13p− unknown origin	In her family mental retardation and M.C.M. of limbs occurred
	3. Father of 1	Familial investigation	N		46,XY	
	4. Sister of 2	Familial investigation	N		46,XX,13p−	She has 11 children, two of them had M.C.M.

Addendum 4 (continued)

Family	Family member	Indication for karyotyping	Phenotype	Number of S.A. and other reproductive failure	Karyotype and origin of chromosomal variant	Remarks
	5. Brother of 2	Familial investigation	Hemiparesis after brain haemorrhage at the age of two years		46,XY,13p–	
	6, 7, 8: the remaining relatives of 1	Familial investigation	N		Karyotypically normal	
14	1. Proband	S.A.	N	4	46,XX,13p– unknown origin	
	2. Husband of 1	Familial investigation	N		46,XY	
15	1. Proband	S.A.	N, except cleft palate	3 S.A., one healthy daughter	46,XX	
	2. Husband of 1	Familial investigation			46,XY,9qh+ unknown origin	
16	1. Proband	S.A.	N	2	46,XX	
	2. Husband of 1	Familial investigation	N		46,XYq– unknown origin	
17	1. Proband	S.A.	N	3	46,XX	
	2. Husband of 1	Familial investigation	N		46,XYq– unknown origin	