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Reciprocal chromosome translocations involving short arm of chromosome 9 as a risk factor of unfavorable pregnancy outcomes after meiotic malsegregation 2:2

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ABSTRACT

Purpose: Genetic counseling of carriers with individual chromosome translocation requires information on how balanced reciprocal chromosome translocations (RCT) will segregate, what possible form of unbalanced embryo/fetus/child can occur, and the survival rates that have been observed in the particular families. We collected new empirical data and evaluated pedigrees of RCT carriers involving 9p in order to improve risk figures.

Material and Methods: Empirical data on 241 pregnancies of 70 carriers were collected from 32 pedigrees of carriers of RCT at risk for a single 9p segment imbalance (RCT9p) from the literature and unpublished data. The probability rates of particular types of pathology have been calculated according to the method of Stengel-Rutkowski and Stene. Cytogenetic interpretation was based on GTG, RBG and FISH techniques.

Results: The probability rate for unbalanced offspring at birth for the whole group of pedigrees was calculated as 17.8±3% (33/185) (high risk). Considering the size of the imbalanced segment of 9p, the probability rates for RCT carriers with a breakpoint position at 9p22 at 9p13 and at 9p11.2 were estimated separately, and were found as 21.2±4.4% (18/85), 25±8.8% (6/24) and 11.8±3.7% (9/76), respectively. For unbalanced fetuses at 2nd prenatal diagnosis, we found the risk value as 57.9±11.3 % (11/19). The risk value for unkaryotyped stillbirths/early deaths of newborns and miscarriages were 5.4±1.7% (10/185) (medium risk) and 13±2.8% (rate 24/185) (high risk) respectively.

Conclusions: Our results showed that the recurrence probability rates are different for particular categories of unfavorable pregnancy outcomes. How much they are dependent on the size of 9p chromosome segments taking part in the imbalance needs further studies based on a larger number of observations.

Key words: chromosome 9p, genetic counseling, partial monosomy 9p, partial trisomy 9p, reciprocal chromosome translocation (RCT)

INTRODUCTION

Reciprocal chromosome translocations (RCT) represent one of the most common chromosomal structural aberrations in man [1-3]. The clinical effects of the RCT carrier state on progeny are due to an unbalanced karyotype, which is produced by meiotic malsegregation of the chromosomes involved in chromosome translocation. Depending on the survival rate of the unbalanced embryo/fetus/child, different forms of clinical effects such as miscarriages, stillbirths, malformed offspring at birth and at prenatal diagnosis, and early newborn deaths have been observed [1-3]. Parent carriers of RCT are asking for genetic counseling, within which the probability rates of particular forms of pathology in progeny should be estimated. The prediction of how a balanced rearrangement will segregate requires providing information about the form of unbalanced

Table 1. **Material of 32 familial reciprocal chromosome translocations leading to single segment imbalance.**

Size of segment	No	Translocation	References
9p23→pter	1.	t(9;13)(p23;p12)	Õunap et al., Am J Med Genet A. 2004;130A(4):415-23.
	2.	t(9;20)(p23;pter)	Hoo et al., Ann Genet. 1982;25(4):249-52.
9p22→pter	3.	t(1;9)(q44;p22)	Stengel-Rutkowski in Kovač (Ed). Early prenatal diagnostics, Verlag, 1995;187-94. Heidelberg 08317.
	4.	t(3;9)(p26;p22)	Potruli et al., Cytogenet Cell Genet. 1996;74:300-12.
	5.	t(6;9)(q27;p22)	E 1981 Sheffield [6].
	6.	t(8;9)(q24;p22)	Polish Collection of RCT, P-205 - Białystok
	7.	t(9;11)(p22;q25)	E1981 Bruxelles [6].
	8.	t(9;12)(p22;p13)	Midro et al., Ann Genet. 1992;35(1):33-40.
	9.	t(9;14)(p22;q32)	Centerwall et al., J Med. Genet. 1976;13:57-61.
	10.	t(9;15)(p22;q26)	Orye et al., Clin Genet. 1975;8:349-57.
	11.	t(9;15)(p22;q25)	Canki et al., Zdraw Vestn 1982;51:303-7.
	12.	t(9;16)(p22;q24)	Alfi et al., Ann Genet. 1976;19:11-6.
	13.	t(9;17)(p22;q25)	Junge et al., Med Genetik 1993;1:119.
9p21→pter	14.	t(4;9)(q35;p21/13)	E1981, Mitcham 1464 [6].
	15.	t(9;10)(p21;pter)	Ulm 13147 [6].
9p13→pter	16.	t(5;9)(p15;p13)	Mata et al., Rev Cubana Pediatr. 1989;61(1):120-8.
	17.	t(7;9)(p22;p13)	Tolksdorf et al., Eur J Pediatr. 1977;23:13-27.
	18.	t(7;9)(p22;p13)	Wajntal et al., Am J Med Genet. 1985;20:265-9.
	19.	t(9,10)(p13;p15)	Polish Collection of RCT, P-55 - Łódź.
	20.	t(9;17)(p13;q25)	Cruz-Mendez et al., Respyn 2006;5:CG04.
	21.	t(9;21)(p13;p11)	Sutherland et al., Hum Genet. 1976;32:217-20.
	22.	t(9;21)(p13;q22)	Mulcahy and Jenkyn, Clin Genet. 1975;8:199-204.
	23.	t(9;21)(p13;q22)	Byelorussian Collection of RCT, collected by Lurie.
9p12→pter	24.	t(7;9)(q36,p12)	Byelorussian Collection of RCT, collected by Lurie.
	25.	t(8;9)(p23;p12)	Mulcahy and Jenkyn, Clin Genet. 1975; 8:199-204.
	26.	(9;15)(p12;p12)	Pränatale diagnostik an chorionzotten. Informationsblatt, 1989;5. Lubeck 04277.
9p11→pter	27.	t(9;18)(p12;p11)	Rodewald et al, Clin Genet. 1979;16:405-41.
	28.	t(9;22)(p12;p11)	Lurie et al., Hum Genet. 1976;32:23-33.
	29.	t(9,22)(p12;p11)	Guven et al., Genet Couns. 2002;13(1):41-8.
	30.	t(1;9)(q44;p11.2)	Meschede et al., Hum Reprod. 1997;12(9):1913-4.
	31.	t(9;12)(p11.2;p13.3)	Chen et al., Prenat Diagn. 2002;2:1063-6.
	32.	t(9;18)(p11.2;p11.3)	Valkova et al., Folia Med. 1993;35:3-4.

embryo/fetus/child and the survival rate observed in the particular families of carriers with individual chromosome translocation. In spite of the great number of pedigrees (1120 pedigrees) elaborated by Stengel-Rutkowski *et al.* [4], specific empiric data are not available so far for all reciprocal translocations. Therefore empirical, clinical and cytogenetical data should be collected and evaluated further [4-6].

We collected all available empiric data from pedigrees of RCT carriers involving the short arm of chromosome 9 (9p) from our own observations and descriptions in the literature until 2008. RCT at risk for single segment imbalance, i.e. RCT with one breakpoint position at the interstitial region of 9p and a second breakpoint position in the terminal region of the partner chromosome, have been selected for re-evaluation. Using updated data, we estimated the improved figures for a different category of progeny (viable unbalanced progeny at birth and at prenatal diagnosis at 2nd trimester and other unfavorable pregnancy outcomes: miscarriages, stillbirths/ early newborn deaths). Risk figures for each category of progeny have been estimated separately (part I). As an example of how to practically apply the obtained risk figures for genetic counseling of an individual family, we use them for a family with t(3;9)(q22;p23) carriership and present it here in details (part II).

Table 2. **The probability rates for unbalanced offspring after 2:2 disjunction and adjacent-1 segregation at birth and at 2nd trimester of pregnancy (prenatal diagnosis) and for unkaryotyped pregnancy outcomes (miscarriages, stillbirths/early deaths) of maternal, paternal and unknown gender RCT carriers with different breakpoint position (bp) in the short arm at the chromosome 9 related to total pregnancies after ascertainment correction.**

Type of progeny	Gender	Segment 9p…pter						Total	
		distal bp		proximal bp					
		segment 9p22→pter		segment 9p13→pter		segment 9p11.2→pter			
		rate	risk (%)	rate	risk (%)	rate	risk (%)	rate	risk (%)
Unbalanced - at birth	MAT	9/33	27.3±7.8	4/15	26.7±11.4	9/64	14.1±4.3	22/112	19.6±3.8
	PAT	6/33	18.2±6.7	2/6	?	0/2	?	8/41	19.5±6.2
	MAT?PAT?	3/19	15.8±8.4	-/3	?	0/10	?	3/32	9.4±5.2
	Total	18/85	21.2±4.4	6/24	25±8.8	9/76	11.8±3.7	33/185	17.8±2.8
- stillbirth/ early death	MAT	-/33	<1.5	-/15	<2.8	7/64	11±3.9	7/112	6.2±2.3
	PAT	2/33	6.1±4.2	1/6	?	-/2	?	3/41	7.3±4.1
	MAT?PAT?	-/19	<2.5	-/3	?	-/10	?	-/32	<1.5
	Total	2/85	2.4±1.6	1/24	4.2±4.1	7/76	9.2±3.3	10/185	5.4±1.7
Unkaryotyped -miscarriages	MAT	7/33	21.2±7.1	2/15	13.3±4.3	12/64	18.8±4.9	21/112	18.8±3.7
	PAT	3/33	9.1±5	-/6	?	-/2	?	3/41	7.3±4.1
	MAT?PAT?	-/19	<2.5	-/3	?	-/10	?	-/32	<1.5
	Total	10/85	11.8±3.5	2/24	8.3±5.6	12/76	15.8±4.2	24/185	13±2.8
Foetus with unbalanced karyotype in prenatal diagnosis	MAT	4/6	?	1/3	?	1/2	?	6/11	54.5±18.3
	PAT	3/4	?	1/2	?	1/2	?	5/8	?
	MAT?PAT	-	?	-	-	-	-	-	-
	Total	7/10	70±14.5	2/5	?	2/4	?	11/19	57.9±11.3

Legend: MAT - maternal carrier; PAT - paternal carrier; MAT? PAT? - unknown gender of carrier; 0 – obtained after ascertainment corrections; ? – not enough data

MATERIALS AND METHODS

198 RCT, involving any segment of the short arm of chromosome 9, have been found in total. Among them, 32 pedigrees of RCT carriers at risk for a single 9p segment imbalance (RCT9p) were selected on the basis of breakpoint position identification (*Tab. 1*). Chromosome karyotyping was performed by GTG (G-bands, Trypsin, Giemsa) and/or RBG (R-bands, BrdU, Giemsa) banding techniques. In some cases, Fluorescence In-Situ Hybridization (FISH) using arm specific and YAC (yeast artificial chromosome) probes, which spanned the specified region, was additionally applied. Empirical data on 241 pregnancies of 70 RCT9p carriers were evaluated. The material has been grouped taking into consideration the genetic content of the involved 9p segments (determined by breakpoint position), carrier gender, and the category of unfavorable pregnancy outcomes. The probability rates of unbalanced progeny at birth and at second trimester of prenatal diagnosis, as well as of unkaryotyped miscarriages and stillbirths/early newborn deaths for RCT carriers related to the total number of pregnancies, after ascertainment correction, have been calculated according to the method of Stengel-Rutkowski *et al*. [4]. Ascertainment correction, according to Stene and Stengel-Rutkowski [7], was performed by elimination of probands (or index sibships) and carriers with a proband in the direct line of descent. Probability rate estimates for unfavorable pregnancies were presented as:

$$p = \frac{a}{n} \qquad S = \sqrt{\frac{a(n-a)}{n^3}}$$

p – risk value

a – number of unfavorable pregnancies after ascertainment correction

n - number of all pregnancies after ascertainment correction

s – standard deviation

If the number of abnormal pregnancies after ascertainment correction is 0, then the maximum risk estimate *m*, corresponding to the upper limit of the risk interval, has been calculated by the formula:

$$m = 1 - e^{-\frac{1}{2n}}$$

m – maximum risk

where e=2.71828 is the base number for natural logarithms

The empirical data for each category of pregnancy outcomes have been considered separately.

RESULTS

Probability estimation for different categories of unfavorable pregnancy outcome of RCT carriers (part I)

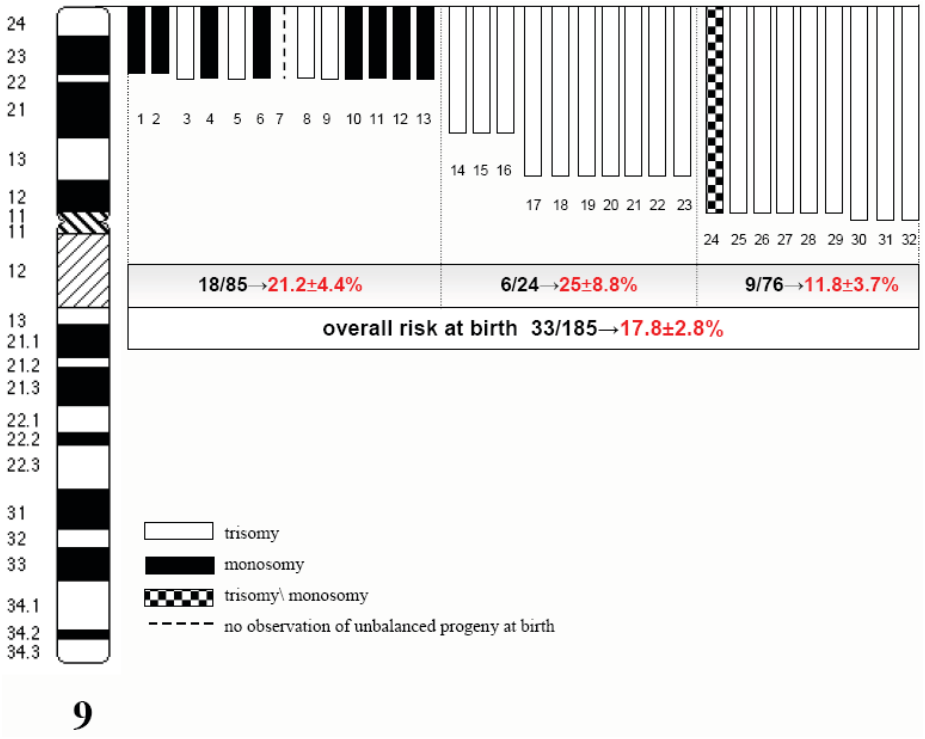
Ascertainment correction

A total of 68 unbalanced offspring at birth (with monosomy or trisomy 9p) and 11 unbalanced fetuses at second trimester of prenatal diagnosis were found among 241 pregnancies of 70

Figure 1. **Synopsis of cytogenetic data of 32 reciprocal chromosome translocations involving short arm of chromosome 9 and probability rates for single – segment imbalance (trisomy/ monosomy).**

1. Õunap et al., Am J Med Genet A. 2004;130A(4):415-23; **2.** Hoo et al., Ann Genet. 1982;25(4):249-52; **3.** Stengel-Rutkowski in Kovač (Ed). Early prenatal diagnostics, Verlag, 1995;187-94. Heidelberg 08317; **4.** Potruli et al., Cytogenet Cell Genet. 1996;74:300-12; **5.** E 1981 Sheffield [6]; **6.** Polish Collection of RCT, P-205 - Białystok; **7.** E1981 Bruxelles [6]; **8.** Midro et al., Ann Genet. 1992;35(1):33-40; **9.** Centerwall et al., J Med. Genet. 1976;13:57-61; **10.** Orye et al , Clin Genet. 1975;8:349-57; **11.** Canki et al., Zdraw Vestn. 1982;51:303-7; **12.** Alfi et al., Ann Genet. 1976;19:11-6; **13.** Junge et al., Med Genetik, 1993;1:119; **14.** E1981, Mitcham 1464 [6]; **15.** Ulm 13147 [6]; **16.** Mata et al., Rev Cubana Pediatr. 1989;61(1):120-8; **17.** Tolksdorf et al., Eur J Pediatr. 1977;23:13-27; **18.** Wajntal et al., Am J Med Genet. 1985;20:265-9; **19.** Polish Collection of RCT, P-55 - Łódź; **20.** Cruz-Mendez et al., Respyn 2006;5:CG04; **21.** Sutherland et al., Hum Genet. 1976;32:217-20; **22**. Mulcahy and Jenkyn, Clin Genet. 1975;8:199-204; **23.** Byelorussian Collection of RCT collected by Lurie; **24.** Byelorussian Collection of RCT, collected by Lurie; **25.** Mulcahy and Jenkyn, Clin Genet. 1975;8:199-204; **26.** Pränatale diagnostik an chorionzotten. Informationsblatt, 1989; 5. Lubeck 04277; **27.** Rodewald et al., Clin Genet. 1979;16:405-41; **28.** Lurie et al., Hum Genet. 1976;32:23-33; **29.** Guven et al., Genet Couns. 2002;13(1): 41-8; **30.** Meschede et al., Hum Reprod. 1997;12(9):1913-4; **31.** Chen et al., Prenat Diagn. 2002;22:1063-6; **32.** Valkova et al., Folia Med. 1993;35:3-4.

The vertical bar indicates the actual unbalanced 9p segment observed in live born child with the identification of breakpoint position. There are shown probability rates at birth dependent on size of involved segments (9p22→pter, 9p13→pter, 9p11.2→pter) for 2:2 disjunction and adjacent –1 segregation and overall probability rate at birth (down frame). Each translocation is numbered on the bottom from 1 to 32 according following references (*Tab. 1*).



carriers. Twenty seven children that were single index cases were omitted because of ascertainment correction. Finally, 33 unbalanced live-born children out of 185 pregnancies, 11 unbalanced fetuses out of 19 pregnancies observed at prenatal diagnosis, 9 stillbirths/early deaths out of 185 pregnancies, and 24 miscarriages out of 185 pregnancies were accepted for risk estimation.

The probability rate for unbalanced offspring at birth

For all of the RCT9p carriers, 33 unbalanced progeny related to a total of 185 pregnancies, after ascertainment correction, was observed, giving a risk estimation of 17.8±2.8%. This represents a high recurrence probability of unbalanced offspring at birth. The probability rate for paternal carriers was similar (19.6±6.2%, rate 8/41) to the probability rate for maternal carriers (19.6±3.8%, rate (22/112), and both are higher than for unknown carrier gender (9.4±5.2%, rate 3/32). Considering the imbalance segment size of 9p, the probability rate for RCT carriers with a breakpoint position at 9p22 and at 9p13 (more than half of 9p) was similar, i.e. 21.2±4.4% (18/185) and 25±8.8% 6/24, respectively. If the breakpoint position was at 9p11.2 (proximal region), the probability rate was reduced to 11.8±3.7% (9/76) *(Tab. 2; Fig. 1).*

The probability rate for unbalanced fetuses at second trimester of prenatal diagnosis

The overall probability rate for unbalanced fetuses in the whole subgroup was estimated as 57.9±11.3% (11/19). The number of observations in the single subgroup was not large enough for a separate estimation *(Tab. 2).*

The probability rate for stillbirths/early newborn deaths

The risk of unkaryotyped stillbirths/early newborn deaths for all carriers of RCT9p was 5.4±1.7% (10/185). This represents a medium risk of recurrence. For maternal and paternal carriers, the risk values were similar, i.e. 6.2±2.3% (rate 7/112) and 7.3±4.1% (rate 4/41) respectively. Considering different segment lengths of 9p, the risk for RCT carriers with a breakpoint position at 9p22 was low (2.4±1.6, rate 2/85), but for a breakpoint position at 9p13 and at 9p11.2 (proximal segments) was higher, i.e 4.2±4.1% (1/24) and 9.2±3.3% (7/76) respectively *(Tab. 2)*.

The probability rate for unkaryotyped miscarriages

The risk value for unkaryotyped miscarriages for carriers of the whole group was 13±2.8% (rate 24/185), which is a high risk. It was higher for maternal carriers (18.8±3.7%, rate 21/112) compared to paternal carriers (7.3±4.1%, rate 3/41) and with carriers of unknown carrier gender (<1.5%, rate -/32). The risk values for different segments of 9p were similar *(Tab. 2)*.

Application of risk assessment in family at risk for double segment imbalances (part II).

A family was ascertained by two miscarriages and a balanced chromosomal translocation t(3;9)(q22;p23) was found in the female carrier using GTG and RBG banding techniques (*Fig. 2a, 2b)*. In addition, these results were confirmed by the FISH method using arm specific (3q, 9p) and YAC probes. Based on these methods, it was shown that both breakpoint positions are intermediate, and hence, the RCT carrier is at risk of a double-segment imbalance *(Fig. 2a)*. Further evaluation and karyotyping of family members allow us to construct a large pedigree *(Fig. 2b)*. Results of pedigree segregation analysis were used to estimate the probability rates for unfavorable pregnancy outcomes using two methods, namely direct and indirect. Furthermore, our original data obtained in part I were used to predict the risk figures using the indirect method *(Fig. 2d*) and to compare the effectiveness of both methods.

Genetic risk estimation using the direct method

Any unbalanced live-born out of the total 14 pregnancies, one stillbirth/early newborn death and two miscarriages were accepted to make a risk estimate after ascertainment correction. A low probability rate for unbalanced progeny at birth was obtained as -/14 (risk: <2.7% i.e about 1.3%). The risk for stillbirths/early newborn deaths was 7.1±6.9% (rate 1/14), and for miscarriages 14.3±9.3% (rate 2/14) *(Fig. 2d)*.

Genetic risk estimation using the indirect method

The analysis of the possible form of imbalance produced by meiotic malsegregation of the parental chromosomes observed at birth showed that only trisomy 3q22→qter and monosomy 9p23→pter have been viable. Therefore, we can only predict an imbalance in live-born offspring after 2:2 disjunctions and adjacent-1 segregation *(Fig. 2c)*. For the calculation of the total probability rate, the recommendation by Stengel-Rutkowski [4] was taken into account. First, the probability rate for each segment imbalance should be obtained independently and then compared. Next, the half value of the lower probability rate is considered. For the translocation t(3;9)(q22;p23), using information about the risk value for each segment imbalance separately, we can consider the risk figure for segment 9p23→pter (21.2±4.4%) (18/85) *(Tab. 2; Fig. 1)* (see part I of our investigation), and for segment 3q22→qter (0.9%, -/27) [4]. As the risk for segment 3q22→qter is a lower value, so overall risk for double segment imbalance is simply halving, i.e. as 0.45% (low risk) for viable imbalance. Using the factors proposed by Stene and Stengel-Rutkowski for low risk progeny, the risk figures of about 30% for miscarriages and about 4.5% for prenatal diagnosis at 2nd trimester of pregnancy *(Fig. 2d)* have been proposed [4].

DISCUSSION

In the studied group of 32 pedigrees of 70 carriers with RCT9p, we found that the general probability rate of occurrence of having a child with a monosomy or trisomy 9p as a result of 2:2 segregation and adjacent - 1 segregation was 33/185 (about 17%). This value can be classified to the group of high probability (above 10%). In general, this corresponds to a previously published rate of about 12% (12/103) (high risk) by Stengel-Rutkowski *et al.* [4] obtained using the same method. In this way we confirmed that the applied method is efficient and the method of data collection was appropriate to obtain the risk figures. Furthermore, we obtained the probability rate taking into consideration three different-sized segments of 9p separately. In our investigation, the probability rate for carriers of RCT with distal (9p22→pter) and middle breakpoint (9p13→pter) were 21.2±4.4% (18/85) and 25±8.8% (6/24) respectively. These values were higher if compared to data obtained for carriers of RCT with more proximal breakpoints leading to a longer 9p imbalance (9p11.2→pter) i.e 11.8±3.7% (9/76) *(Tab. 1*; *Fig. 1)*. It is worth to notice that in our studies, the probability rate for RCT carriers with distal or middle breakpoints were similar. It is difficult to determine if this is due to not enough empirical and cytogenetic data, or if there are other reasons. As far as we know, the probability rate for unbalanced segment 9p22→pter has not been described so far. In the investigation by Stengel-Rutkowski *et al.* [4], the probability rates were obtained for two groups of RCT carriers, grouping for two segments (9p21→pter) and (9p11→pter). For two groups of carriers with chromosome translocation involved these segments separately we obtained following rates: 20.8±4.3% (19/91 and 14.9± 3.7% (14/94) respectively. The improved rates showed the same tendency, i.e. a higher probability rate for shorter segments and a lower probability rate for longer segment imbalance [4]. A similar trend was found in our previous data obtained for carriers of RCT involving 4p chromosome [8] and 16q chromosome [9].

***Figure 2*. Risk chart of the t(3;9)(q22;p23) carrier family.**

a. Cytogenetic results.

Left - Partial karyotype demonstrating the breakpoint position localization on chromosomes involved in translocation studied by GTG and RBG methods. Schematic representation of the breakpoint positions according to ISCN 2005.

Right - FISH YAC probes spanned the 3q region

b. Investigated pedigree with indication of ascertainment by arrow.

Legend:

- ◑ ◨ carrier of translocation
- △ miscarriage
- Ⓝ normal karyotype
- ⚲ ⚰ stillbirth/ early death

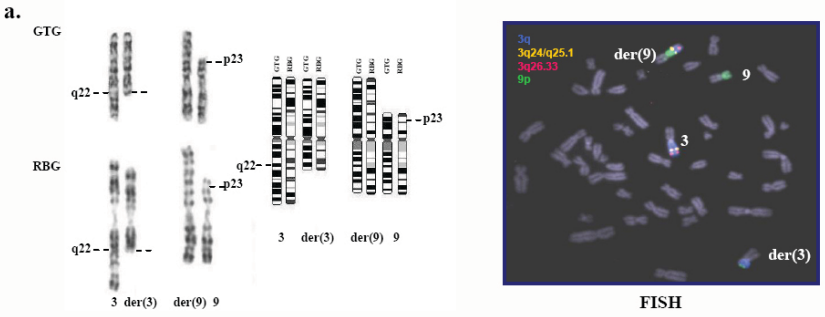
c. Scheme of meiotic quadrivalent with visualization of predicted form of imbalance compatible with survival from 2:2 disjunction and adjacent 1 segregation.

d. Predicted assessment for probability rate of unbalanced offspring at birth and for miscarriages: 1. Direct analysis; 2. Indirect analysis.

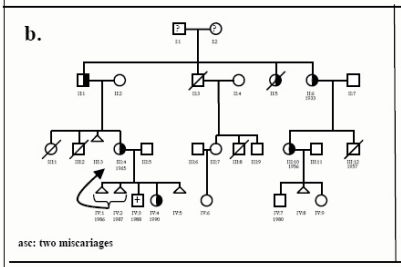
LOW RISK (<5%)

t(3;9)(q22;p23) Białystok

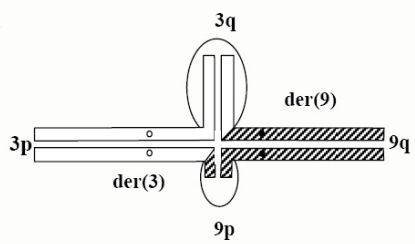
a.



b.



c.



d. Risk estimation

1. Direct analysis (see *Table*)

overall risk at birth: **<2.7% ~ 1.3% (-/14)**
for stillbirth/ early death: **7.1±6.9% (1/14)**
for miscarriages: **14.3±9.3% (2/14)**

No	Carrier	Gender	Unbalanced offspring at birth^		Stillbirth/ early died newborn#		Miscarriages^c		Pregnancies		Rate^	Rate#	Rate^c
			T	C	T	C	T	C	Tot	Cor			
1.	III,4	MAT	-	-	1	1	2	0	5	3	-/3	1/3	0/3
2.	III,7	MAT	-	-	-	-	1	1	3	3	-/3	-/3	1/3
3.	II,1	PAT	-	-	-	-	1	1	4	3	-/3	-/3	1/3
4.	II,5	MAT	-	-	-	-	-	-	2	2	-/2	-/2	-/2
5.	I,1, I,2	MAT/PAT ?	-	-	-	-	-	-	4	3	-/3	-/3	-/3
		Sum	-	-	1	1	4	2	18	14	-/14	1/14	2/14
		Risk									<2.7% about 1.3%	7.1±6.9%	14.3±9.3%

2. Indirect analysis (prediction)

- At birth

Risk for double segment imbalance
trisomy 3q22→qter and monosomy 9p23→pter or
monosomy 3q22→qter* and trisomy 9p23→pter
after 2:2 disjunction and adjacent -1 segregation

segment: 3q22→qter risk: 0.9% (-/ 27)	segment: 9p23→pter risk: 21.2±4.4% (18/85)

MAT/PAT: 0.45%

* - not observed at birth

OVERALL RISK

- **at birth**
  MAT/ PAT: 0.45%
- **risk for miscarriages: 30% [6]**
- **prenatal diagnosis at 2nd trimester of pregnancy: 4.5% [6]**

We found that the probability rate for unbalanced progeny at prenatal diagnosis was three times higher than the probability rate for unbalanced progeny at birth, 57% and 17%, respectively. This may be explained by a limited survival rate during pregnancy, and spontaneous loss of pregnancy with unbalanced fetuses. Indeed, we have observed a relatively high frequency of miscarriages (13±2.8%, rate 24/185) in our studied group.

In addition, we found that the probability rates for unbalanced progeny at birth were slightly different among paternal and maternal carriers This may represent the possible influence of UPD on the survival rate of progeny. However, it has been shown that, in general, the gender of parental carriers of any RCT has no impact on the probability rate of imbalance after 2:2 disjunction and adjacent - 1 segregation [4]. Moreover, no UPD for 9p chromosome was observed thus far [1].

Our data on improved probability rates obtained for families of RCT at risk for single segment imbalance were applied to genetic counseling of couples with carriership of t(3;9)(q22;p23) *(Fig. 2)*. Taking into consideration the breakpoint position, this translocation has been classified as a risk factor for double segment imbalanced karyotype in progeny. To better characterize the breakpoint position of t(3;9)(q22;p23), FISH experiments were performed with different YAC probes. Using the indirect method according to Stengel-Rutkowski *et al.* [4], we calculated a low probability rate for unbalanced progeny at birth (0.45%). Simultaneously, we also obtained a low probability rate of about 1.3% for viable imbalance, by preliminary direct calculation of individual probability rates. Despite no observation of a viable imbalance in the family, we could provide information based on published data about the survival rates for progeny with trisomy of 3q22→qter and monosomy 9p23→pter separately [10-12] with a low probability rate for unbalanced offspring at birth. A low probability rate for viable imbalance explains why we did not observe any unbalanced child in the constructed pedigree. For such a risk value, about 250 members should be evaluated according to statistical rules. Furthermore, the risk for stillbirths/early newborn deaths was medium (7%) and for miscarriages was high (14%).

The described example of pedigree data of t(3;9)(q22;p23) carriers demonstrates that in genetic counseling of RCT, the risk figures cannot be obtained based on the limited data from direct analysis of pedigree. However, our risk figures obtained for particular segments of chromosomes 9p are useful in predicting risk values using another indirect method. We can show that in the case of any family with RCT, the individual prediction of risk may be interpreted in light of what is otherwise known from the literature and databases now maintained online about viable imbalances and other category of progeny. It is particularly helpful in the case we cannot obtain enough data from observation within the same family.

CONCLUSIONS

Our results show that probability rates are different for particular categories of unfavorable pregnancy outcomes. How far they are dependent on the size of 9p chromosome segments taking part in the imbalance needs further studies based a larger number of observations.

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