Translocation form of Wolf-Hirschhorn syndrome – assessment of recurrence rate probability

*Panasiuk B[1], Leśniewicz R[1], Spółczyńska A[1], Myśliwiec M[1], de Die Smulders Ch[2], Sawicka A[1], Midro AT[1]**

[1] Department of Clinical Genetics, Medical University of Białystok, Poland
[2] Department of Molecular Cell Biology and Genetics, Maastricht University, The Netherlands

Abstract

Purpose: The families experienced by occurrence of child with Wolf-Hirschhorn syndrome (WHS: OMIM # 194190) and by other unfavourable pregnancy outcomes (miscarriages or stillbirths/early deaths and partial trisomy 4p imbalance leading to intellectual disability in live born progeny) are asking for genetic counseling. In order to obtain the recurrence probability rates for the particular forms of unfavourable pregnancy we collected the empirical data and evaluated pedigrees of reciprocal chromosome translocations (RCT) carriers involving 4p. Results were applied to family of carrier of t(4;11)(p16.1;q23.3) ascertained by four miscarriages, in which latter the girl with WHS was born.

Material and methods: Total empirical data about 170 pregnancies of 46 carriers were collected from 25 pedigrees RCT at risk for single segment imbalance. Classification was based mostly on cytogenetic methods. The probability rates of particular type of pathology related to total number of pregnancies after ascertainment correction have been calculated according to the method of Stengel-Rutkowski and Stene.

Results: The risk figures for unbalanced offspring after 2:2 disjunction and adjacent-1 segregation for whole group of pedigrees were calculated as 15.2±3.5% (16/105), for unbalanced fetuses at second trimester of prenatal diagnosis as 50±13.4% (7/14), for miscarriages about 19±3.8% (20/105) and for stillbirths/early death as 15.2±3.5% (16/105). The higher probability rate for RCT carriers at risk for distal 4p – shorter segment imbalance (28.6±12%, 4/14) in comparison to the rate for proximal (medium) one as 15.4±4.5% (10/65) and to more proximal (longer) one as 7.7±5.2% (2/26) were found.

Conclusions: Our results confirm that the recurrence probability rates are different for particular categories of unfavourable pregnancy outcomes and dependent on size and genetic content of unbalanced 4p segments.

Key words: chromosome 4p, partial monosomy 4p, partial trisomy 4p, reciprocal chromosome translocation (RCT), Wolf-Hirschhorn syndrome (WHS).

Introduction

Monosomy of the short arm of chromosome 4 has a strong effect on phenotype resulting as a rule in the phenotype of Wolf-Hirschhorn syndrome (WHS) with characteristic facial appearance, microsomy, several malformations, neurological changes, motor developmental delay, and distinct developmental profile [1]. Phenotype WHS is known since mid-1960' as a result of simple deletion. However, phenotype of WHS may be associated with complex unbalanced chromosome rearrangements, involving both 4p and another chromosome as the result of meiotic malsegregation of a parental chromosome translocation [2,3]. In such cases families with balanced reciprocal chromosome translocations (RCT) should be referred to genetic counseling to get informed about their probability for unbalanced offspring at birth and at prenatal diagnosis or other types of unfavourable pregnancy outcomes (miscarriages, stillbirths/early deaths of newborn) [4-6]. Those estimates can be done on the basis of clinical and cytogenetical data following by segregation analysis of pedigrees [4,7,8]. We collected empirical data of the particular forms of unfavourable pregnancy outcomes in families with RCT with breakpoint positions at 4p (RCT4p) to obtain the risk figures for single segment imbalances.

* CORRESPONDING AUTHOR:
Department of Clinical Genetics, Medical University of Białystok
ul. Waszyngtona 13
15-089 Białystok 8, PO Box 22, Poland
Tel: +48 85 7485980; Fax: +48 85 7485416
e-mail: midro@amb.edu.pl (Alina T. Midro)

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Table 1. **References for familial reciprocal chromosome translocations leading to single segment imbalance considered for the genetic risk assessment**

Breakpoint	Nº	Translocation	References
4p16	1.	t(4;15)(p16;p13)	De Die Smulders (Maastricht), 2003, (unpublished data)
4p16. 1	2.	t(4;21)(p16.1;q22.3)	Narahara et al., Jpn J Hum Genet, 1984; 29: 403-13
4p15	3.	t(4;18)(p15.2;q23)	Petit et al., Genet Couns, 1990; 38(2): 179-84
	4.	t(4;22)(p15;p11)	Lurie et al., 1980, Clin Genet, 1980: 17(6): 375-84
	5.	t(1;4)(q44;p15)	Stengel-Rutkowski et al., DFG, München 1992
4p14	6.	t(1;4)(p36;p14)	[4]
	7.	t(4;6)(p14;p25)	[4]
	8.	t(4;9)(p14;p24)	Crane et al., Am J Med Genet, 1979; 4(3): 219-29
	9.	t(4;10)(p14;q26)	[4]
	10.	t(4;11)(p14;p15)	[4]
	11.	t(4;12)(p14;p13)	Mortimer et al., Hum Hered, 1978; 28(2): 132-40
	12.	t(4;15)(p14;p12)	Schröcksnadel et al., Humangenetik, 1975; 29: 329-35
	13.	t(4;17)(p14;p13)	Yardin et al., Ann Genet, 1997; 40(4): 232-4
	14.	t(4;17)(p14;q25)	del Mazo et al., Hum Genet, 1984; 66: 370
	15.	t(4;18)(p14;p11)	[4]
	16.	t(4;18)(p14;qter)	Schinzel et al., Humangenetik, 1972;15(2):163-71
	17.	t(4;20)(p14;q13)	[4]
	18.	t(4;21)(p?14;p11)	Owen et al., J Med Genet, 1974; 11(3): 291-5
	19.	t(4;22)(p 14;p12)	Dallapiccola et al., Clin Genet, 1977; 12(6): 344-56
	20.	t(4;22)(p14;p11)	Schwanitz et al., Ann Genet, 1973; 16(4): 263-6
	21.	t(4;22)(p14;q13)	Sartori et al., Acta Pediatr Scand, 1974; 63: 631-5.
4p13	22.	t(4;10)(p13;q26)	Hedner et al., Clin Genet. 1977; 12(2): 101-3.
4p12	23.	t(4;7)(p12;qter)	Andrle et al., Hum Genet, 1976, 33: 155-60
	24.	t(4;16)(p12;p13)	Bauknecht et al., Hum Genet, 1976, 34: 227-30.
	25.	t(4;21)(p11;p12)	Darmady et al., J Med Genet, 1975; 12: 408-11.

Material and methods

Based on the cytogenetic interpretation performed on chromosomes from lymphocyte cultures of peripheral blood according to standard procedures using GTG, RBG banding techniques or exceptionally fluorescence *in situ* hybridisation technique (FISH), we selected 25 pedigrees of carriers of RCT at risk for a single 4p segment imbalance (RCT4p) in progeny from total available data of 137 RCT [9]. Empirical data of 170 pregnancies of 46 carriers of RCT 4p were evaluated (*Tab. 1*). The probability rates of the unbalanced progeny at birth and at second trimester of prenatal diagnosis as well as of unkaryotyped miscarriages and stillbirths/early deaths of newborn for RCT carriers related to total number of pregnancies after ascertainment correction have been calculated according to the method of Stengel-Rutkowski et al. [4,5].

Results

Probability estimation for different categories of unfavourable pregnancy outcomes and ascertainment correction

Totally forty-three unbalanced offspring at birth and seven unbalanced foetuses at second trimester of prenatal diagnosis were found among 170 pregnancies of 46 carriers. Twenty--seven children that were single index cases, three stillbirths/ /early deaths and ten miscarriages and one malformed child belonging to index siblings were omitted due to ascertainment correction. Finally, 16 unbalanced live born children out of 105 pregnancies, 7 unbalanced foetuses out of 14 pregnancies observed at prenatal diagnosis, 16 stillbirths/early deaths out of 105 pregnancies and 20 miscarriages out of 105 pregnancies were accepted for risk estimation. Results are presented in *Tab. 2* and *Fig. 1*.

Application of risk assessment in families at risk for double segment imbalances

A family was ascertained by four miscarriages and a balanced chromosomal translocation t(4;11)(p16.1;q23.3)GTG, RBG, FISH (III;2) was found (*Fig. 2a*), in which later a child with WHS was born. However, numerous members with normal karyotype make the pedigree not informative for risk estimation by direct analysis (*Fig. 2b)*. Based on data described above (*Tab. 2, Fig. 1*) the probability rates estimated and proposed for the family were 3.45% (low risk) for unbalanced progeny at birth and about 30% for miscarriages (*Fig. 2c, d*).

Discussion

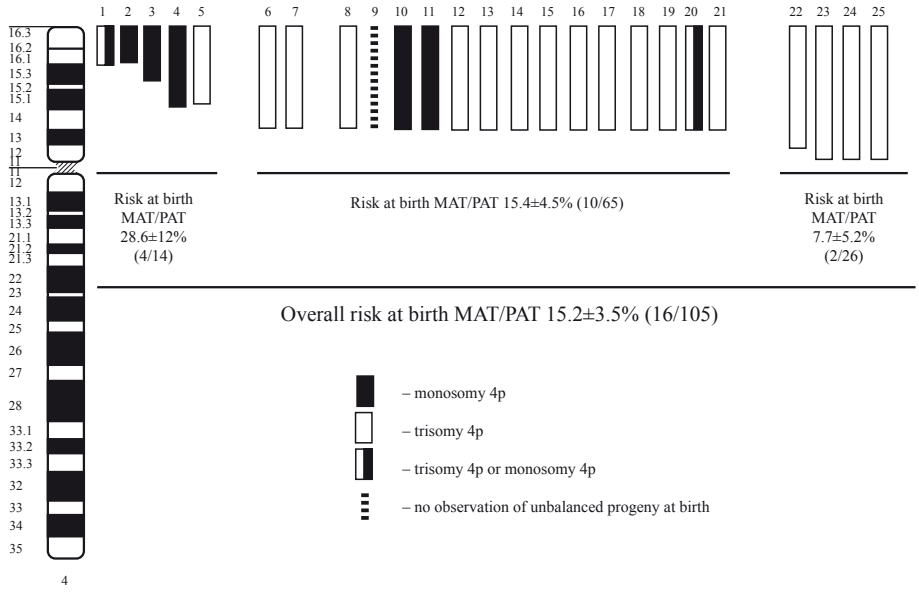
We found that there is a high risk (about 15%) for occurrence of translocation form of WHS. In general, this correspond to a previously published rate about 17% (high risk) by Sten-

***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 sex RCT rarriers with different breakpoint position (bp) in the short arm at the chromoseme 4 related to total pregnascies after ascertainment correction**

Type of progeny	Parental sex	Segment 4p…pter						Total	
		distal bp		proximal bp					
		segment 4p15→pter		segment 4p14→pter		segment 4p11→pter			
		rate	risk	rate	risk	rate	risk	rate	risk
Unbalanced – at birth	MAT	1/7		1/19		2/10		4/36	11±3.1%
	PAT	3/5		8/36		0/16		11/57	19.3±5.2%
	MAT?PAT?	0/2		1/10		-		1/12	8.3±7.9%
	Total rate	4/14	28.6±12%	10/65	15.4±4.5%	2/26	7.7±5.2%	16/105	15.2±3.5%
– at 2nd trimestr	MAT	2/3		1/4		-		3/7	
	PAT	1/1		3/6		-		4/7	
	MAT?PAT?	-		-		-		-	
	Total rate	3/4	?	4/10	40±15.5%	-	-	7/14	50±13.4%
Unkaryotyped – miscarriages	MAT	4/7		3/19		-/10		8/40	20±6.3%
	PAT	-/5		8/36		4/16		12/57	21.1±5.5%
	MAT?PAT?	-/2		1/10		-		1/12	8.3±7.9%
	Total rate	4/12	33.3±13.6%	12/65	18.5±4.8%	4/26	15.4±7.1%	20/105	19±3.8%
– stillbirths/ /early deaths	MAT	-/7		1/19		4/10		5/36	13.9±3.4%
	PAT	-/5		4/36		6/16		10/57	17.5±5%
	MAT?PAT	1/2		-/10		-		1/12	8.3±7.9%
	Total rate	1/14	7.1±6.9%	5/65	7.7±3.3%	10/26	38.5±9.5%	16/105	15.2±3.5%

Legend: MAT – maternal carrier; PAT – paternal carrier; MAT? PAT? – unknown sex of carrier; "-" no observations; 0 – obtained after ascertainment corrections; ? – not enough data

***Figure 1*. Synopsis of cytogenetic data of 25 reciprocal chromosome translocations involving short arm of chromosome 4 and probability rates for single – segment imbalance (trisomy/monosomy)**



The vertical bar indicates the actual unbalanced 4p 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 (4p15→pter, 4p14→pter, 4p11→pter) for 2:2 disjunction and adjacent –1 segregation and overall probability rate at birth (down frame) with indication of sex of parental carrier. Each translocation is numbered on the bottom from 1 to 25 according following references (see *Tab. 1*): **1** – Maastricht (C. De Die Smulders), 2003; **2** – Narahara et al., 1984; **3** – Petit et al., 1990; **4** – Lurie et al., 1980**; 5** – DFG, 1992**; 6, 7, 9, 10, 15, 17** – Stengel-Rutkowski et al., 1988; **8** – Crane et al., 1979; **11** – Mortimer et al.; **12** – Schröcksnadel et al., 1975; **13** – Yardin et al., 1997; **14 –** del Mazo et al., 1984; **16 –** Schinzel et al., 1972; **18** – Owen et al., 1974; **19** – Dallapicola et al., 1977; **20** – Schwanitz et al., 1973; **21** – Sartori et al., 1974; **22** – Hedner et al., 1977; **23** – Andrle et al., 1976; **24** – Bauknecht et al., 1976; **25** – Darmady et al., 1975

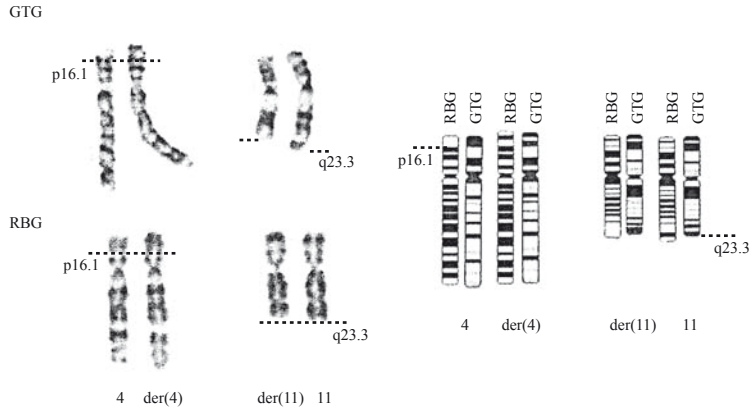
***Figure 2*. Risk chart of the t(4;11)(p16.1;q23.3) carrier family**

LOW RISK (<5%)

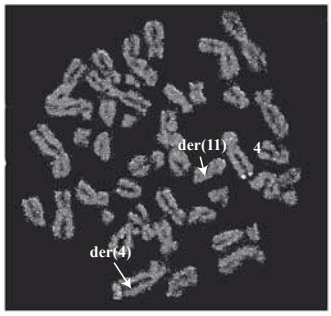
t(4;11)(p16.1;q23.2)

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 with probe for critical region of WHS

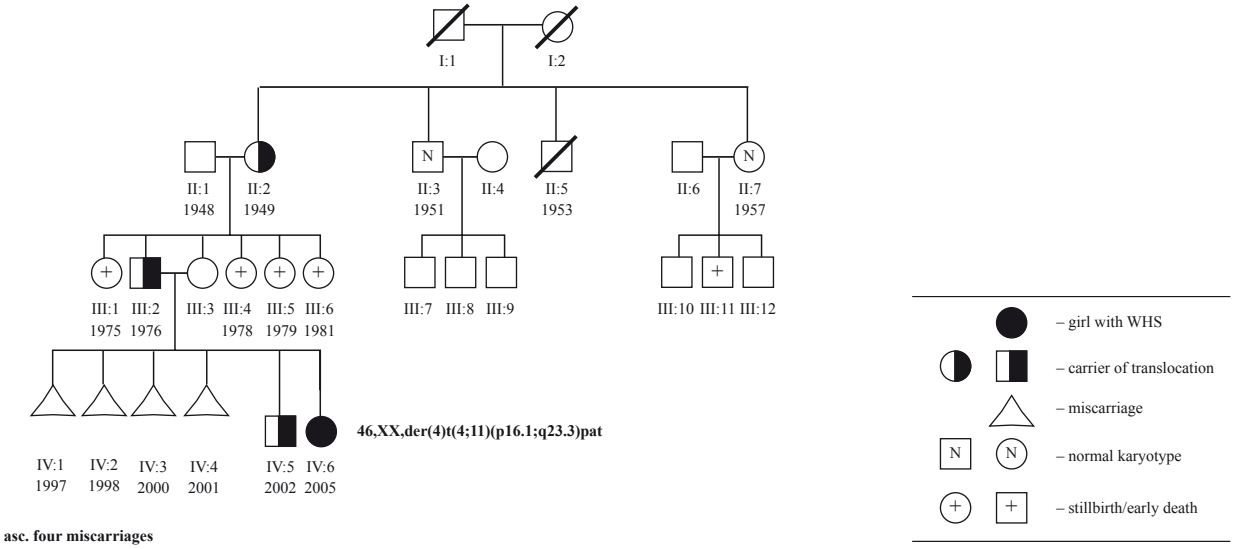


FISH-WHSCR probe



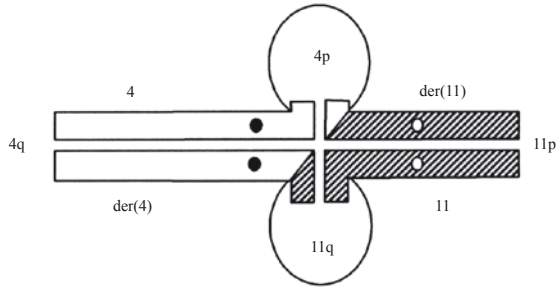
ish t(4;11)(p16.1;q23.2)(WHSCR-;WHSCR+)

B. Investigated pedigree with indication of ascertainment by arrow



asc. four miscarriages

C. Scheme of meiotic quadrivalent with visualisation 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

Risk for double segment imbalance
monosomy 4p16.1→pter and trisomy 11q23.3 →qter, or
trisomy 4p16.1 →pter and monosomy 11q23.3 →qter
after 2:2 disjunction and adjacent-1 segregation

segment: 4p16.1 →pter	segment 11q23.2 →qter
risk: 28.6±12% (4/14)*	risk: 6.9±3.8% (3/43) [4]

MAT/PAT: 6.9 : 2 ~3.45%

Probability for unbalanced offspring: MAT/PAT: 3.45% – low risk
Risk for miscarriages – about 30%

gel-Rutkowski et al. [4] evaluated this same methods. In this way we confirm, that the applied method is efficient and the way of collection of our data was proper to obtain risk figures. The probability rate for carriers RCT with distal breakpoint (segment 4p15→pter), is of higher risk compared to rates for unbalanced progeny of carriers of RCT with more proximal breakpoints leading to longer 4p imbalances (4p14→pter and 4p11→pter) (*Tab. 1* and *Fig. 1*). The similar results were obtained from the original data [4] and by others authors [7]. It confirm that risk is dependent on genetic content of imbalance. Our data were differentiated enough to test the probability rates for unbalanced progeny depending on parental origin of carrier: the risk value was higher for paternal carrier. It is worth to notice, that the number of male carriers having offspring with imbalance (29 male carriers) after 2:2 disjunction was higher than the corresponding of female carriers (18 carriers) in our collection. These differences can be explained by chromosome 4 segmental uniparental disomy Mat 4p16-15 [10]. Interestingly, the rate of unbalanced fetuses is about three times higher in comparison to the rate of unbalanced progeny at birth and can be explained by diminished survival rate for unbalanced fetuses leading to stillbirths, early death of newborns and miscarriages [7]. It is supported by our observation of a relatively high frequency of miscarriages and stillbirths/early deaths in total collective (*Tab. 2*). Worthy to notice, that probability rates obtained for families of RCT at risk for single segment imbalance may be useful for calculation the risk for double segment imbalances as demonstrated in the individual risk assessment in carriers t(4;11)(p16.1;q23.3) (*Fig. 2*). In that family empirical data were not enough statistically representative to make direct calculation of risk figures. Recently the precision of identification of breakpoint's position in the involved chromosomes is more advanced. It would be interesting to verify our conclusions in a new data collection with RCT carriers risk identified on basis of methods of higher resolution, e.g. FISH and/or using the different specific BAC and PAC probes for breakpoint identification with use of the same method of pedigree evaluation [11].

Conclusions

Our results confirm that the recurrence probability rates are different for particular categories of unfavourable pregnancy outcomes and dependent on size and genetic content of unbalanced 4p segments.

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