Chapter 6

Resolving Paradoxes of Robertsonian Translocations

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Additional information is available at the end of the chapter

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Abstract

Since Robertsonian translocations (ROB) are essential in the etiology of congenital malformations and reproductive disorders, it is natural to assume that they represent a thoroughly studied subject. However, on closer inspection, there are poorly studied areas within this field. The aim of this report is to present results of a comprehensive analysis of available data collected by researchers worldwide that allows a new look at the problems mentioned above. There were determined rates and spectrums of ROB in the general population and in patients with reproductive disorders. The comprehension of a female-based sex ratio (male-to-female ratio) among newborn carriers of balanced nonhomologous ROB in the general population leads to a conclusion on the mechanism of sex-specific correction of translocation trisomy, which might explain both inexplicably low occurrence of rob-associated uniparental disomy and phenomenon of "non-Mendelian-inheritance." The data obtained indicate that female ROB carriers are at a much higher risk of uniparental disomy compared to male ROB carriers. In the majority of asymptomatic male carriers of homologous translocation/isochromosome (HT), spermatogenesis is not impaired. An analysis of sex ratio among ill-defined HT carriers showed a difference between patients with Prader-Willi syndrome and Angelman syndrome, indicating different mechanisms of HT formation.

Keywords: Robertsonian translocations, isochromosomes, sex ratio, uniparental disomy, non-Mendelian inheritance, reproductive disorders, Prader-Willi syndrome, Angelman syndrome

1. Introduction

Robertsonian translocations (ROBs) are common structural chromosome rearrangement in humans. Since they are central in the etiology of congenital malformations and reproductive disorders, it is natural to assume that they represent a thoroughly studied subject. However, on closer inspection, there are poorly studied areas within this field. Surprisingly, exact rates of ROB carriers were determined neither among consecutive newborns nor among patients with reproductive disorders. The literature reiterates the information on tenfold, or even more than tenfold, increase in the rate of ROB carriers among patients with reproductive disorders compared to the general population. In addition, the quoted rates among newborns vary depending on the source that the authors cite [1–3]. Another omission in the area under consideration is the lack of systematic comparative analysis of the ROB spectrum in various carrier groups. The phenomenon of exceptional rarity of some nonhomologous rearrangements was not given due attention. There are some enigmatic problems in the field not yet resolved. One of them, unusual segregation of maternally transmitted translocations, has been discussed for the last five decades [4–6]. Another, established more recently, is the unexpectedly low incidence of ROB-associated uniparental disomy among carriers of balanced rearrangement [7]. The epidemiology of Robertsonian homologous translocations (HTs)/isochromosomes, due to their rarity, has largely not been investigated. The aim of this report is to present results of a comprehensive analysis of available data collected by researchers worldwide that allows a new look at the problems mentioned above.

2. Materials and methods

Study groups: newborns, prenatal diagnoses for indications other than familial rearrangement (the main indication for prenatal testing was advanced maternal age, and the transmitting parent was defined following detection of a rearrangement in the fetus), spontaneous abortuses with regular and translocation trisomy for chromosome 13 and chromosome 14, carriers of *rob* (13;14)-associated maternal uniparental disomy for chromosome 14, couples with reproductive disorders, patients with male infertility, and ill-defined carriers of homologous translocation/isochromosome (listed in Additional files S1–S8: Tables S1–S10; Additional file 11: Supplemental References, available either on request or from https://www.researchgate.net/profile/Natalia_Kovaleva/contributions).Methods:meta-analysis of data retrieved from published studies. Only reports on ROB carriers of known sex were selected for the study. The data were analyzed using two packages of statistical programs: one of which utilized procedures of traditional approach and the other one utilized procedures of a modern Bayes approach. Guided by modern recommendations for the statistical analysis, we did not limit ourselves to the null hypothesis significance testing based on the p-values but also calculated the 95% confidence intervals (CIs) for proportions and their ratios. StatXact, the world's most expansive toolkit for exact nonparametric inference StatXact-8 (Cytel Co., USA), was used. To construct CIs for the proportion ratios, the method of variance estimates recovery (MOVER) algorithm implemented in the program MOVER-R.xls (http://medicine.cf.ac.uk/primary-care-public-health/resources/) was used.

3. Results and discussion

3.1. Determination of exact rates and spectrums of ROB in the general population and in patients with reproductive disorders

The rates, spectrum, and parental origin of major nonmosaic balanced rearrangements in the general population are presented in the Additional files, Tables S1–S4. Statistical analysis showed distributions of nonhomologous ROBs from all studied groups to be homogenous in all combinations; therefore, both control groups were aggregated for further analysis. In the aggregated control (**Table 1**), the results seem to be in accordance with current views on the spectrum of individual ROBs, with the overwhelming majority of rob(13;14) 71%, followed by rob(14;21) 12%; the remaining translocations are rare or exceptionally rare; rob(15;21) and rob (13;21) were detected once each (0.4%). The total frequency of all translocations, calculated for newborns, is 1.06‰ with 95% CI from 0.8 to 1.3‰.

Data on patients with reproductive disorders are presented in Additional files S1–S3: Tables S1–S3. The distribution of translocations in couples with reproductive disorders (**Table 2**) is generally similar to that observed in the aggregated control group. However, the proportion of rob(13;14) is much less in couples with habitual abortion (139/245 = 57%, with 95% CI of 51–63%), while the proportion of homologous translocations is high (24/245 = 10%, with CI of 7–14%). The overall rate of ROB carriers among couples with infertility is 3.6‰ (95% CI of 2.8–4.1‰), and 4.8‰ (95% CI of 4.2–5.5‰) among couples with multiple miscarriages**.** These values, as can be seen, do not exceed ten times the value in general population. A high incidence of ROB was found among patients with male infertility, 7.1‰ (95% CI of 6.2–8.2‰). Among couples with miscarriages, there is a difference between males and females by proportions of carriers of rob(14;15) (1 and 6%, correspondingly) and carriers of rob(14;21) (5 and 14%, correspondingly). There is a difference between couples with habitual abortion and couples with infertility in involving of chromosome 22 into nonhomologous rearrangements (32/245 = 14% with 95% CI of 9–18% vs. 4/110 = 4.2% with 95% CI of 1.5–9%), as well as with patients with male infertility (2/201 = 1.3% with CI 0.3–3.5%). In addition, among HT patients with habitual miscarriages, most are carriers of translocations/isochromosomes 22 (7 of 24).

Of note is the extremely low frequency of *rob*(13;21); no carriers of this translocation were found in the newborn population, while among patients with habitual miscarriage, with a fourfold concentration of translocation carriers, only one carrier of *rob*(13;21) was found. This suggests one possible mechanism, a negative selection against certain types of translocations.

This hypothesis is consistent with the data of British authors [9] who reported the discovery of three constitutional *rob*(15;21) carriers among 95 children with acute lymphoblastic leukemia. It was proposed that the mechanism of triggering the neoplastic process is chromotrypsis. The authors concluded that in carriers of this rearrangement, the risk of the disease is 2700 times higher than in the general population. Interestingly, their assumption of a population frequency of *rob*(15;21) of about 1 per 100,000 newborns is very close to the real value presented in this paper.

Indeed, *rob*(15;21) appeared to be a very rare rearrangement, which is clearly not supported by natural selection: in the normal population, only one carrier of a *rob*(15;21) was detected (sex

Studied group	Gender	Number of tested patients	Number of ROB carriers	Nonhomologous rearrangements										Homologous rearrangements				
				13;14	13;15	13;21	13;22	14;15	14;21	14;22	15;21	15;22	21;22	13;13	14;14	15;15	21;21	22;22
Newborns (Table S1)	♂♂	33,371	24 (25)[a]	18	0	0	0	2	1	1	0	1	1	0	0	0	0	0
	♀♀	31,534	38 (39)[b]	33	0	0	1	0	4	0	0	0	0	0	0	0	0	0
	ns	28,811	34[c]	26	0	0	0	0	6	0	1	1	0	0	0	0	0	0
	Total	93,716	96 (98)[a,b]	77	0	0	1	2	11	1	1	2	1	0	0	0	0	0
Prenatal diagnoses (Table S3)	♂♂		56	35	4	0	1	0	12	3	0	1	0	0	0	0	0	0
	♀♀		86	55	5	1	3	4	6	5	0	2	3	1	0	1	0	0
	Total		142 (143)[c]	90	10[c]	1	4	3	18	8	0	3	3	1	0	1	0	0
Total			238 (241)	164	9	1	5	5	28	8	1	5	4	1	0	1	0	0

[a]Including carrier of 45,XY,tdic(D;D).
[b]Including carrier of 45,XX,t(D;D).
[c]In a part of this study (Nielsen, Wohlert, 1991), gender was reported (Nielsen, Sillesen, 1975); see Additional file 11: Supplemental references.

Table 1. Spectrum of Robertsonian translocations in consecutive newborns and in prenatal diagnoses for indications other than familial translocation (updated from [8]).

Patients		Number of tested patients	Number of detected carriers	Nonhomologous rearrangements										Homologous rearrangements				
				13;14	13;15	13;21	13;22	14;15	14;21	14;22	15;21	15;22	21;22	13;13	14;14	15;15	21;21	22;22
Couples with infertility (Table S5)	♂♂	15,432	91	68	5	0	0	5	11	1	0	0	1	0	0	0	0	0
	♀♀	15,468	20	12	2	0	1	1	2	0	0	1	0	1	0	0	0	0
	Total	30,900	111	80	6	0	1	6	13	1	0	1	1	1	0	0	0	0
Couples with habitual abortion (Table S6)	♂♂	25,577	86 (87)[a]	56	3	0	2[c]	1	4	4	1	5	1	2	1	2	1	3
	♀♀	25,676	159 (160)[b]	83	2	1	4[d]	9[d]	22	6	7	5	5	5	4	1	1	4
	Total	51,253	245 (248)[e]		139	1	6	10	26	10	8	10	6	7	5	3	2	7
Patients with male infertility (Table S7)	♂♂	28,112	201	140[f]	11	1	0	9	27	1	5	0	1	2[g]	2	1	0	1

[a]Including 45,XY,t(D;G) carrier.
[b]Including 45,XX,t(D;D) carrier.
[c]Including carrier of 45,XY,t(13;22), inv.(6) (Valkova, 1986).
[d]Including a carrier of 44,XX,t(13;22),t(14;15) (Sugiura-Ogasawara et al., 2008).
[e]Including carrier of t(13;14) of unknown gender.
[f]Including two patients with 45,XY,inv.(5) (Dul et al., 2012; Tuerlings et al., 1998).
[g]Carrier of 45,XY,der(13;13)/46,XY,der(13;13),der(13;13) (Tuerlings et al., 1998); see Additional file S11: Supplemental references.

Table 2. Spectrum of Robertsonian translocations in patients with reproductive disorders (updated from [8]).

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not specified), while among about a twofold smaller group of patients with habitual miscarriage, eight carriers of this translocation were diagnosed. Five carriers of *rob*(15;21) were identified among patients with male factor of infertility. These observations are of significance for medical genetic counseling of the carriers. Firstly, it is necessary to find out whether the risk of leukemia varies among the carriers depending on whether this translocation is inherited or occurred de novo. Currently, such data are not available.

Based on this data review, it is evident that it is necessary to continue accumulating survey data of couples with reproductive disorders to establish the existence or absence of differences in the range of ROB both between the patient groups and the population.

3.2. The phenomenon of female predominance among carriers of ROB in the general population has promoted comprehension of both low incidence of ROB-associated uniparental disomy and transmission ratio distortion in offspring of female ROB carriers

3.2.1. The parental origin of ROB and the sex ratio among carriers in the general population and in prenatal diagnosis

The sex ratios (SR) and parental origin of major nonmosaic balanced rearrangements in the general population are presented in the Additional files, Tables S2 and S4. The observed sex ratio was 1.06 (95% CI 1.04–1.07) which correlates with population ratios worldwide (Table S2).

The majority of both RECs and ROBs detected among consecutive newborns (but not inversions) occurred de novo. Interestingly, the proportions of mutant REC and mutant ROB in newborns were similar (9/50 = 18% and 7/52 = 13%, correspondingly), despite different parental origins: RECs arise predominantly in spermatogenesis [10, 11], while ROBs arise predominantly in oogenesis [12, 13].

Some female prevalence among transmitting parents was in concordance with reported data on REC carriers (23mat/18pat), but not on carriers of ROB (24mat/21pat), since according to common conception, a twofold female predominance should be expected in this group due to reduced male fertility of ROB heterozygotes [14].

However, the most intriguing finding is the SR variability in newborns depending on the type of rearrangement (**Table 3**); there were equal numbers of REC carriers of both sexes (31 M/31F; for rates of 0.93 and 0.98‰, correspondingly) and a notable female predominance among carriers of ROB (27 M/41F, for rates of 0.77 and 1.24‰, correspondingly). The difference between the SR among carriers of ROB (0.61 with 95% CI of 0.27–1.00) and the SR among tested newborns (1.06 with CI of 1.04-1.07) was statistically significant (Bayes approach).

Analysis of the SR according to the parental origin of rearrangements showed female preponderance among ROB carriers in either maternal or paternal origin or de novo origin: 11 M/13F, 7 M/14F, and 2 M/5F, correspondingly. Among carriers identified prenatally for indications other than familial rearrangement, female-based SR was found for both maternally and paternally transmitted rearrangements: 26 M/43F and 23 M/35F, correspondingly.

Collectively, among carriers of ROB with known parental origin, there were 67 males and 105 females (SR = 0.64), a difference from the expected ratio of 1:1 was determined to be significant

Studied group	Reciprocal translocations				Robertsonian translocations				Inversions			
	Maternal origin		Paternal origin		Maternal origin		Paternal origin		Maternal origin		Paternal origin	
	♂♂	♀♀	♂♂	♀♀	♂♂	♀♀	♂♂	♀♀	♂♂	♀♀	♂♂	♀♀
Newborns (Table S4)	15	8	8	9	11	13	7	14	2	6	0	3
	23 M/17F, SR = 1.35				18 M/27F, SR = 0.67				2 M/9F			
Prenatal diagnoses (Table S5)	51	43	52	36	26	43	23	35	45	49	54	47
	103 M/79F, SR = 1.3				49 M/78F, SR = 0.63				99 M/96F, SR = 0.96			
Total	126 M/96F, SR = 1.31				67 M/104F, SR = 0.64[a]				101 M/105F, SR = 0.96			
Sex ratio with 95% CI	$_{0.92}1.22_{1.62}$				$_{0.50}0.68_{0.93}$[b]				$_{0.77}1.03_{1.39}$			

[a]Difference with the expected ratio of 1:1 is statistically significant at $p = 0.0033$ (binomial test).
[b]Difference with the expected population ratio of 1.06 is statistically significant (Bayes approach).

Table 3. Sex ratio among carriers of balanced rearrangements according to parental origin (updated from [19]).

statistically by both traditional statistics (p = 0.0033, binomial test) and by a Bayes approach (**Table 3**). Among offspring of REC carriers and carriers of inversion, SR was not different statistically from the expected ratio of 1:1. (126 M/96F, SR = 1.31 and 102 M/105F, SR = 0.96, correspondingly).

Among ROBs identified in newborns, the vast majority of the cases constitute translocations between chromosomes 13 and 14 (50 of 61). It is these rearrangements that determine unusual SR among ROB carriers: out of 50 carriers of der(13;14), 18 were males and 32 were females (SR = 0.56). A similar ratio was observed among fetuses with der(13;14): 32 male carriers and 53 female carriers (SR = 0.60). In total, SR among carriers of der(13;14) was 0.59 (50 M/85F), which is statistically significant from the expected 1:1 ratio both when using standard statistics (p = 0.001) and when using Bayes approach.

Thus, there is currently unexplained mechanism for maintaining female-biased sex ratio in carriers of ROB. A biased SR among offspring of male ROB carriers would have been explained by some meiotic process providing preferable production of X-bearing gametes with ROB. However, for female carriers, such a mechanism cannot be considered, since women produce X-bearing gametes only, and the offspring's gender is determined by male gametes. For an explanation of the discussed phenomenon, the author suggests application of the concept of sex-specific correction of initial trisomy mostly in female embryos [15, 16]. In relation to ROBs, that means the loss of the odd chromosome is not involved to the translocation. If it is true, among carriers of balanced rearrangements, female-biased SR is expected, along with male preponderance among carriers of unbalanced translocations.

3.2.2. Sex ratio among abortuses with unbalanced translocation 13 and among abortuses with unbalanced translocation 14

Carriers of an unbalanced 46,+13,der(13;14) rearrangement are rarely found among liveborns. In the population of 64,905 newborns, translocation T13 was detected in four instances; among

them only 1 was identified as der(13;14). Similarly, they are rarely found at amniocentesis in the second trimester: 2 instances only among 52,965 and 31,194 tested fetuses [17, 18]. Carriers of the other unbalanced derivative of rob(13;14), i.e., translocation trisomy for chromosome 14, 46,+14,der(13;14), are unlikely to survive to a long gestation age. Therefore, aiming to obtain data on SR among carriers of T13 and/or T14, the author analyzed studies on chromosomal constitution in spontaneous abortions.

Table 4 summarizes the data from 26 surveys that detected cases of regular and/or translocation trisomy (T) of either chromosome 13 or 14 (see Additional file: Table S8). Analysis showed that among abortuses with regular T13, there were some predominance of male carriers, 75 M/63F (SR = 1.2), not statistically different from the population ratio of 1.06. In contrast, an unusual increase in the proportion of male carriers was observed among carriers of translocation T13 (17 M/3F) which might be interpreted as evidence supporting female-specific correction of translocation trisomy. Increased SR among carriers of translocation T14 in comparison with carriers of regular T14 was observed as well, with 15 M/9F (SR = 1.7) vs. 25 M/39F (SR = 0.6), correspondingly. It is quite possible that elimination of male embryos trisomic for chromosome 14 occurred at earlier stages of embryo development.

3.2.3. Sex ratio among carriers of balanced translocation 45,der(13;14), upd(14) resulted from correction of initial translocation trisomy 14

To evaluate whether a correction of translocation T14 occurs predominantly in female carriers, one may study the SR among individuals with uniparental disomy 14, upd(14). Unlike upd (13), upd(14) carriers demonstrate clinical manifestations depending on the sex of the transmitting parent and have therefore undergone cytogenetic and molecular testing. Analysis of published cases with reported sex of the carriers of upd(14) showed that of 16 patients with 45, der(13;14),upd(14), 12 were females, including 8 carriers of upd(14)mat [20–27] and 4 carriers of upd(14)pat [28–31]; the remaining 4 male patients had upd(14)mat [32–35].

It was logical to assume that in this group, incomplete correction of initial translocation trisomy 14 may take place as the result of postzygotic events, i.e., mosaicism can be found. Moreover, carriers of mosaicism were expected to be females. Accordingly, mosaicism 45,XX, der(13;14)/46,XX,der(13;14),+14 was detected in two female patients [20–21].

References[a]	**Regular trisomy**				**Translocation trisomy**			
	Chromosome 13		**Chromosome 14**		**46,+13,der(13;14)**		**46,+14,der(13;14)**	
	♂♂	♀♀	♂♂	♀♀	♂♂	♀♀	♂♂	♀♀
Additional file: Table S8	73	63	27	39	17	3	15	9
Sex ratio with 95% CIs	$_{0.8}$ 1.2 $_{1.6}$		$_{0.43}$ 0.7 $_{1.13}$		$_{1.8}$ 4.8[b] $_{17.4}$		$_{0.7}$ 1.7 $_{3.7}$	

[a]Only studies where trisomy for either chromosome 13 or chromosome 14 were detected.
[b]Different statistically from the expected ratio of 1.06, P (Bayes approach).

Table 4. Sex ratio in spontaneous abortions with nonmosaic regular and translocation trisomy 13 or 14 (updated from [19]).

Among carriers of other translocations with upd(14)mat, there was also a female predominance, with four females out of five patients [25, 36–39]. This observation supports the suggestion that the trisomy correction phenomenon might not be restricted to unbalanced translocation (13;14). The data obtained is of clinical significance, indicating that female ROB carriers are at a much higher risk of uniparental disomy than male ROB carriers.

3.2.4. Preferential loss of a maternal extra chromosome in female embryos as a correction mechanism leading to biparental disomy

The data obtained, while presenting evidence for sex-specific correction of trisomy as a reason for female predominance among carriers of balanced ROB, are in apparent contradiction with the data on low incidence of uniparental disomy carriers among both prenatally tested fetuses and abortuses with familial translocations. According to collective data, the incidence of translocation trisomy correction causing uniparental disomy does not exceed 1% [7]. It is understandable that so rare an event cannot cause the observed bias in the sex ratio. In turn, the low incidence of uniparental disomy due to trisomy correction is in contradiction with the data on a very high incidence of self-correction found in preimplantation embryos [40, 41].

An assumption of a special correction mechanism leading to biparental disomy might explain this contradiction. Such a mechanism, a preferential loss of maternal chromosome (and, hence, reconstitution of biparental disomy) in female embryos, was suggested as an explanation of the twofold male predominance among patients with Prader-Willi syndrome due to maternal uniparental disomy [15] (for details, see Section 4.3.2).

Preferential loss of maternal extra chromosome in carriers of inherited unbalanced translocation may be explained "topographically": in the human zygote, maternal and paternal pronuclei are separated, and this condition is preserved during some mitotic divisions. In the case of translocation trisomy (which mostly have maternal origin), a competition for spindle attachment occurs. The vast majority of human ROBs are dicentric [12]. The dicentric structure allows for more spindle attachment sites and consequently for a "stronger" centromere [14], which provides preferential loss of maternal extra chromosome. At later postzygotic stages, while trisomy correction results in mosaicism for balanced translocation, preferable loss of maternal chromosome should not occur.

Sex-specific correction of transmitted translocation trisomy might explain either partly or entirely the phenomenon discussed since the 1960s, namely, transmission ratio distortion in offspring of female carriers of ROB [4–6]. Unfortunately, the precise mechanism of selective trisomy correction in female embryos is undefined.

3.3. Homologous Robertsonian translocations/isochromosomes: uneven involvement of acrocentric chromosomes, varying sex ratio, and no association with infertility

3.3.1. Rates and spectrum of HT in asymptomatic carriers

When groups of couples with reproductive disorders are compared (**Table 2**), tenfold difference is evident between them by both an incidence of HT carriers (0.03‰ in couples with

infertility and 0.4% in couples with habitual abortion) and a proportion among all detected ROB*s*: 0.9% (1/111) with 95% CI of 0.2–4.9% vs. 10% (24/245) with CI of 7–14%, the difference is significant at $p < 0.0013$. And since the only carrier of HT in the group with infertility was a woman, one can assume that her "infertility" was due to early undiagnosed pregnancy losses.

In patients with male factor of infertility, it was originally intended to combine them with males from couples with infertility, especially since these groups did not statistically significantly differ either in the frequency of the detected ROB carriers (0.36 and 0.21‰, respectively) or in the spectrum of translocations. However, it was taken into account that in the surveyed couples, about half of males were partners of females with a female factor, and therefore their aggregation into one group is unnecessary. Nevertheless, despite the fact that in this group, the majority of the patients had a proven male infertility factor, proportion of HT carriers was only 3% (6/201 = 3.3 with 95% CI of 1.4–6.4%), which is not statistically different from that in the males from couples with infertility (0/91 = 0.0% with CI of 0.0–4%) at p = 0.18. Of note is that one of the six patients presented mosaicism for balanced/unbalanced HT [42].

Seventy-one single cases of HT carriers, including 48 females, were identified from the literature (Additional file S7). Almost all female carriers, except for two, were tested cytogenetically for multiple miscarriage and/or abnormal offspring. Of 23 male carriers, only 2 were tested for infertility, 1 of whom had mosaicism for an unbalanced rearrangement.

Table 5 presents the data collation from single reports, systematic surveys of couples with reproductive disorders, and also the publication of the authors who summarized the results of the diagnostic laboratory without detailing the indications for the testing. The most frequent were the HT of chromosome 13 and chromosome 22. A somewhat smaller number of asymptomatic carriers of HT of chromosomes 14 and 15 might be explained by the presence of imprinted genes on these chromosomes, a proportion of both HT14 and HT15 carriers have clinical manifestations depending on which of the parents the HT is inherited from (see Section 3.4).

The sex ratio in carriers of HT of chromosomes 13–15 and 21 is female biased, varying from 0.21 to 0.54, with the overall figure of 0.34 (22 M/64F) with 95% CI of 0.21–0.56. The predominance of female individuals among carriers of chromosome rearrangements of this type is explained by the sex-specific instability of pericentromeric regions [15, 69]. In contrast, sex

Translocations	Couple with reproductive disorders (Tables S5, S6)		Single cases tested for various reasons (Table S9)		Consecutive patients from a genetic unit [44]		Total		Sex ratio
	♂♂	♀♀	♂♂	♀♀	♂♂	♀♀	♂♂	♀♀	
13;13	2	6	1	15	2	3	5	24	0.21
14;14	1	4	5	6	1	3	7	13	0.54
15;15	2	1	3	9	0	2	5	12	0.42
21;21	1	1	4	8	0	6	5	15	0.33
22;22	3	4	10	8	2	1	15	13	1.15

Table 5. Spectrum of homologous translocations and sex ratio among carriers, updated from [43].

ratio among carriers of HT22 is not female biased (15 males/13 females, with 95% CI of 0.56–2.45), which might indicate some different "circumstances" of the formation of HT22 and the other acrocentric chromosomes. It is known that HT may have either a meiotic or mitotic origin and may be mono- or dicentric and biparental or uniparental [45]. All the information that the authors reported on the origin of HT is included in Additional file: Table S9. However, its scarcity does not allow drawing any conclusions as to the possible differences in the mechanisms of the formation of certain HT.

3.3.2. Problems of reproduction in carriers of HT

The data of the previous study suggested that homologous translocations do not contribute to a disturbance of spermatogenesis [8]. The present study showed that in patients with a male factor of infertility, the percentage of HT is 3% of the identified ROBs, in contrast to 10.5% in partners of women with miscarriage (although in the latter group about half of the individuals are partners of women with a female factor for infertility). It was noted that of the 22 male HT carriers (Additional file: Table S9), only 2 have been evaluated for infertility, 1 of them having a cell line with an unbalanced HT [3]. In the analysis of a testicular biopsy of another carrier, the authors found no reason to link the presence of HT with the impairment of his spermatogenesis [46].

Thus, in the overwhelming majority of cases, male HT carriers produce gametes capable of fertilization. The absence of spermatogenesis disorders, typical to nonhomologous ROB carriers, is most likely due to the ability of chromosome arms of HT to conjugate, as previously reported [47]. The authors, examining a man whose wives had habitual miscarriages, found completely normal spermogram parameters and testicular histology, wherein conjugation between the long arms of the isochromosome 14 took place in such a way that the chromosome did not differ from the usual bivalent. It is obvious that such a configuration is fraught with the possibility for formation of a ring chromosome. Indeed, in the offspring of two carriers of HT, there were children with ring chromosomes, most likely formed from parental HT [48, 49]. There are multiple reports in the literature on patients with ring chromosomes accompanying homologous translocations but of postzygotic origin [50–53]. Stetten et al. [53] suggested that the presence of HT is a necessary precursor to the formation of ring chromosomes.

Despite the fact that carriers of nonmosaic HT produce only abnormal gametes, there are cases of the birth of healthy children with the same rearrangement [54–59]. These rare cases can be the result of one of two mechanisms: the syngamy of a gamete carrying HT with a gamete nullisomic for the same chromosome or correction of a trisomic zygote by losing a free extra chromosome. It is curious that out of seven of these cases, in four of them, HT22 was transmitted. Studies of the inheritance events of balanced HTs provided initial evidence that chromosomes 13, 21, and 22 did not bear imprinted gene.

Several cases of the birth of healthy children with normal chromosomes to apparently nonmosaic HT carriers were reported [60–64]. The birth of chromosomally normal children indicates the presence of a normal line in the gonads of the parents with HT. In addition, one can assume a rare event—sporadic dissociation of centromere. This phenomenon was shown both for ROB [65, 66] and for nonacrocentric chromosomes [67, 68]. Another possibility was

discussed as well, gonadal mosaicism in unbalanced HT (translocation trisomy), since gamete precursor cells with such a set of chromosomes are expected to produce 50% of daughter cells with normal karyotype [69].

It would seem that the feasibility of this possibility with respect to male patients is highly doubtful, since the presence of an additional chromosome induces spermatogenesis disorders. For example, it is well known that women with nonmosaic trisomy of chromosome 21 (Down's syndrome) are fertile, while men are mostly infertile, due to impaired spermatogenesis [70]. It is possible to assume that it is the presence of a cell line with unbalanced HT in the gonads as a result of incomplete correction of the original translocation trisomy that causes spermatogenesis disorders in carriers of apparently balanced HT.

Currently, infertility due to chromosomal abnormalities, with the corresponding pathologies of spermatogenesis, is overcome by reproductive technologies, and, paradoxically, it is possible that it is in male HT carriers with infertility that there is a chance to have a healthy offspring. For example, encouraging results were obtained using reproductive technologies for the production of healthy children from male carriers of trisomy 21 [71, 72].

In general, the reproductive prognosis for carriers of HT is pessimistic. But, given the nonzero chance of having gonadal mosaicism in them, we can recommend testing, the algorithm of which was published [69, 73]. In addition, another possibility of having a healthy child with the same rearrangement was discussed, that is, gamete donation from a carrier of the same balanced rearrangement, which does not carry imprinted genes [73].

3.4. Sex ratio in ill-defined carriers of homologous translocations/isochromosomes

A scrupulous search in available literature yielded 10 ill-defined carriers of HT14 and 28 carriers of HT15 (Additional file: S10). Although the number of published cases of HT with clinical manifestation of uniparental disomy is small, there are some observations of interest.

3.4.1. Sex ratio in patients with UPD(HT14)

Unlike asymptomatic individuals with biparental HT14, patients with UPD(HT14) demonstrate some male predominance (6 M/2F), while the majority of them (eight of ten) had maternally derived rearrangement. More cases are needed for solid conclusion on the SR in this group.

3.4.2. Sex ratio in patients with maternal UPD(HT15), Prader-Willi syndrome

Strong female predominance among patients with maternal UPD(HT15) was first reported in the discussion of the concept of trisomy correction due to parent-sex-specific loss [15]. In previous studies, a male predominance among patients with maternal non-ROB UPD (15) was suggested to be the result of either a bias of ascertainment due to milder phenotype in female UPD patients or difference in survival of early trisomy 15 conceptuses [74]. However, in contrast, Kovaleva noted that among patients with UPD(HT15), there was no male predominance, with five male and ten female carriers [15]. Mitchel et al. also suggested a possible

difference in the probability of trisomic zygote rescue depending on the sex [74]. However, the predominant rescue of trisomic male zygotes would result in a male predominance in mosaic cases, while no male predominance was reported in a collective sample of 50 fetuses with T15 mosaicism (SR = 0.67) [15]. Kovaleva suggested that the male prevalence among patients with non-ROB UPD(15) can be explained by female-specific loss of a maternal chromosome, causing biparental inheritance and therefore complete correction of trisomy in females (without UPD) [15]. For an explanation of the female predominance among carriers of UPD(HT15), parent-sex-specific loss should be considered, but in this case, a preferential loss of paternal extra chromosome from female trisomic zygotes with unbalanced HT is suggested.

3.4.3. Sex ratio in patients with paternal UPD(HT15), Angelman syndrome

Nine reported HT15 carriers with Angelman syndrome were males. All of eight tested for UPD patients had paternal isodisomy. Among homologous HT, the majority of them were established to be isochromosomes. Several mechanisms of isochromosomes formation were discussed, including gametic complementation, trisomy rescue, and monosomy rescue. It was suggested that they mainly should be formed postzygotically (see for review [73]). However, postzygotic formation of pericentromeric rearrangements is essentially female-specific [15, 69].

A strong male prevalence among patients with UPD(HT15) can be explained by meiotic event, nonhomologous co-orientation of the isochromosome with X chromosome during the first meiotic division in the spermatocyte. In such a case, X chromosome and isochromosome travel to the opposite poles, providing preferential segregation of isochromosome with Y chromosome. This mechanism, proven for *Drosophila* [75, 76], was proposed to explain male excess among carriers of paternally derived regular trisomy 21 [77], as well as male-biased SR in trisomic offspring fathered by carriers of dup(21) [78], and in trisomy 21 offspring inherited paternal noncontributing rearrangement [79].

4. Conclusion

It is interesting that very recently the epidemiology of Robertson translocations was suggested to this author as not worthy of any attention. Currently, in this field there are multiple unanswered questions. Further studies are required to elucidate the nature of female preponderance among carriers of Robertsonian translocation in newborns, as well as of other intriguing phenomena uncovered in this paper, such as a nonuniformity in the HT spectrum and difference in sex ratio between the carriers of the HT22 and the carriers of HT of the other acrocentric chromosomes. Moreover, chromosome 22 is rather mysterious in the context of the differences in the spectrum of nonhomologous translocations between groups of patients with reproductive disorders. There is no clear understanding of the role of HT in the etiology of male infertility and what factors determine the association of part of HT with impaired spermatogenesis. In addition, there are some aspects of ROB epidemiology not considered in this chapter, including interchromosomal effect and mosaicism.

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