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Review

Trisomy 14 Mosaicism Including Concomitant Uniparental Disomy: Population Frequency, Cytogenetic Profile, Sex Ratio, Maternal Age and Obstetric History

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Abstract

Mosaicism for trisomy of chromosome 14 (T14) is a very rare chromosomal disease in liveborn patients. Since the 1970s, when the first patients with mosaicism for T14 were reported, a number of studies on the clinical manifestations of this abnormality have been published. No information on epidemiological parameters was known except for the rarity of the disease and its predominance among female carriers. This was the first systematic review of published cases of mosaic T14 that addressed some epidemiological aspects of this abnormality. We conducted a literature review and collected information on 194 cases of regular T14 and only two cases of mosaic T14 among 21,082 tested spontaneous abortuses. Thus, the rates of nonmosaic T14 and mosaic T14 were 0.9% and 0.09‰, respectively. Additionally, we identified 76 carriers of mosaic T14, diagnosed prenatally and postnatally. Among them, there were 50 carriers of mosaicism for regular T14, 21 carriers of mosaicism due to unbalanced homologous translocation/isochromosome, and five carriers of mosaicism for unbalanced non-homologous Robertsonian translocation involving chromosome 14. The most significant findings were as follows. i) The unexplained fourfold

predominance of the carriers of homologous rearrangement relative to non-homologous translocations, but the occurrence of exceptionally rare homologous rearrangements compared to non-homologous translocations in human populations; also, the ratio between these two types of rearrangements (21 and 28, respectively) differed from that in the carriers of non-mosaic UPD(14) ($p < 0.005$). ii) Female patients were predominant in all studied groups, irrespective of the type of the trisomic line and parental origin of the euploid cell line; there were 19 male and 57 female cases reported. iii) The differences in the maternal age between carriers of mosaicism for regular T14 with and without maternal uniparental disomy were statistically significant (average age of 35.4 and 29.8 years, respectively; $p < 0.05$). This is intriguing because of the common mechanism of the formation of biparental and uniparental disomy. Additionally, a complicated reproductive history was noted in 25% of the families.

Keywords
Mosaicism for trisomy 14; uniparental disomy for trisomy 14; sex ratio; maternal age; miscarriage

1. Introduction

Trisomy for chromosome 14 is lethal; individuals only with the mosaic form can survive. The first patient with this chromosomal abnormality was described in 1970 [1]. Mosaicism for trisomy of chromosome 14 (mosT14) is not characterized epidemiologically due to its rarity. Therefore, we conducted a systematic review of published cases to address the epidemiological aspects of this abnormality. The data were retrieved from various resources, including PubMed, Research Gate, and the ChromosOmics UPD Database [2]. We also conducted a comparative analysis of the parameters in spontaneous abortions and carriers of uniparental disomy (UPD) of chromosome 14 caused by non-mosaic rearrangements.

For a comprehensive analysis of the cytogenetic profile and other parameters under consideration, describing the mechanism of mosT14 formation is important. Mosaicism for regular trisomy might arise due to meiotic nondisjunction followed by mitotic loss of the trisomic chromosome, also known as “trisomy correction” or “trisomy rescue”. This mechanism leads to the restoration of biparental inheritance (BD, biparental disomy) in two-thirds of the cases and uniparental disomy (UPD) in one-third of the cases. This may lead to the expression of clinical features of both mosT14 and UPD(14). Few cases of mixed mosaic trisomy in the same individual have been described, where a cell line with BD coexists with a cell line with UPD; the first case was reported by McCaskill et al. in 1995 [3]. Complete trisomy rescue leads to a non-mosaic euploid condition, with or without biparentally derived homologs or (rarely) with mosaicism for UPD, as mentioned above. In a few cases, mosT14 results from postzygotic mitotic nondisjunction.

Mosaicism for trisomy 14 caused by unbalanced non-homologous Robertsonian translocation, either inherited (in most cases) or *de novo*, typically arises due to rescue as well. The main mechanism of mosaicism associated with homologous translocation/isochromosome is mitotic, caused by the formation of an isochromosome and trisomy rescue. Euploid zygotes with non-

mosaic homologous translocations/isochromosomes may also be formed by "gametic complementation", which is the fusion of two abnormal gametes, nullisomic for a specific chromosome and gamete with translocation disomy occurring in the same chromosome [4]. Additionally, monosomy rescue might occur in the first zygotic cleavage (perizygotic error) [5]. As first observed by Robinson et al. [6], all homologous rearrangements with UPD are isochromosomes.

2. Population Frequency

The frequency of liveborn carriers of mosT14 in the population showing clinical manifestation cannot be accurately calculated because they are extremely rare. The only data available for analysis are surveys on the spontaneous loss of pregnancy. From published studies, we selected 61 reports where the cytogenetic profile was clearly described (data available on request). Overall, 194 cases of regular T14 and two cases of mosaic T14 among 21,082 tested spontaneous abortuses (0.9% and 0.09‰, respectively) were identified. The two cases of mosaic T14 were identified by conventional cytogenetic testing; one was identified among 259 products of conception (POC) after 6–12 weeks of gestation [7], while the other one was identified among 543 POC after 7–34 weeks of gestation [8]. The rarity of mosaic cases might be due to underdiagnosis.

However, data from a cytogenetic survey on 10,730 recurrent pregnancy losses (not included in the above-mentioned list of 61 reports), where non-mosaic T14 was detected in about 6% of full aneuploidies, supported the conclusion regarding the low frequency of mosaic T14. The study did not report any case of mosaicism for T14, although mosaic trisomies of chromosomes 16, 13, 2, and 22 were identified in 0.35%, 0.35%, 0.28%, and 0.21% of aneuploid POC [9]. This observation was intriguing since mosaics are more viable than full trisomy carriers. Alternatively, it might be possible that almost all mosaic T14 infants survive to term.

3. Cytogenetic Profile of Mosaicism

Among 76 carriers of mosaicism for trisomy 14, 50 carriers showed mosaicism for regular MT14 (10 prenatal and 40 postnatal), 21 carriers showed mosaicism for unbalanced homologous translocation/isochromosome 14 (three prenatal, one stillborn, and 17 postnatal), and five carriers showed mosaicism for unbalanced non-homologous Robertsonian translocation involving chromosome 14 (one prenatal, one miscarriage, and three postnatal). The cytogenetic profile of trisomy 14 was not significantly different between prenatal (n = 16) and postnatal (n = 60) diagnoses; 63% were carriers of regular trisomy, 25% were carriers of homologous unbalanced translocation/isochromosome, and 12% were carriers of unbalanced non-homologous translocation among prenatally detected individuals, while 67%, 28%, and 5% were carriers among postnatally diagnosed individuals, respectively (Table 1, Table 2 and Table 3 [10-77]).

Table 1 Mosaicism for regular trisomy 14.

Source	Karyotype	Patient's age at examination	Maternal age	Paternal age	Proportion of cell line with trisomy 14	Maternal reproductive history	Parental origin of disomy
Prenatal diagnosis							
Burns et al., 2001 [10]	46,XX/47,XX,+14	prenatal	ns	ns	?% AF, 5% BL, 40% placenta	ns	not studied
Keitges et al., 1993 [11]	46,XY/47,XY,+14	prenatal	35	ns	22% AF, 12.5% long-term CVS, 0% SF	ns	not studied
Phelan et al., 2020 [12]	46,XX/47,XX,+14	prenatal	40	ns	NIPT, ns % AF	ns	maternal UPD
Ralph et al., 1999 [13]	46,XX/47,XX,+14	11 wg	42	ns	42% CVS, 6% AF, 0–100% placenta, 5% amnion	G4P3	maternal MII ND; maternal isodisomy with segmental heterodisomy
Sanlaville et al., 2000 [14]	46,XX/47,XX,+14	11 wg	41	ns	100% cytotrophoblast, 21% mesemchymal stroma, 0% AF, 0% BL	ns	rescue of initial trisomy; maternal heterodisomy

Sirchia et al., 1994 [15]	46,XX/47,XX,+14	15 wg and 19 wg	36	ns	10% AF, 10% fetal BL	ns	maternal MI ND; maternal iso-and heterodisomy
Suzumori et al., 2015 [16]	46,XX/47,XX,+14	26 wg	38	ns	20% AF, 23% umbilical vein BL, 17% neonatal BL	G2P1	postzygotic duplication of paternal chromosome, BD
Towner et al., 2001 [17]	46,XX/47,XX,+14	prenatal	40	ns	100% placenta, 0% BL	ns	maternal isodisomy
Wegner et al., 1988 [18]	46,XX/47,XX,+14	11 wg	41	ns	88% short-term CVS, 100% long-term CVS; induced abortion: 0% long-term CVS, 7% umbilical cord, 2% SF	one liveborn, four abortions	materna MI ND, BD
Witters et al., 2004 [19]	46,XY/47,XY,+14	14 wg	ns	ns	60% AF	ns	BD
Postnatal diagnosis							
Balbeur et al., 2016 and personal communication, 2018 [20]	46,XX/47,XX,+14	15 yr	35	37	31% BL, 2.5% hyperpigmented SF, 2% normal SF, 42% urine, 49% saliva	Previous four healthy children	maternal iso- and heterosomy

Becerra-Solano et al., 2008 [21]	45,X/47,XX,+14	26 yr	25	23	10% T14 BL	1st pregnancy; two healthy younger sons, and 3 mid trimester miscarriages	not studied
Cheung et al., 2007 (patient 6) [22]	46,XX/47,XX,+14	ns	ns	ns	6.5% BL (B-lymphocytes)	ns	not studied
Cheung et al., 2007 (patient 8) [22]	46,XY/47,XY,+14	ns	ns	ns	12% whole BL (array CGS), 15% FISH; 0% T-lymphocytes, 0% SF (CGH)	ns	not studied
Choi et al., 2012 [23]	46,XX/47,XX,+14	2 weeks	30	ns	?% BL	ns	not studied
Conlin et al., 2010 (patient 11) [24]	46,XX/47,XX,+14	ns	ns	ns	50% BL, 5% SF by array	ns	BD
Conlin et al., 2010 (patient 15) [24]	46,XX/47,XX,+14	ns	ns	ns	10% BL; 20% BL by array	ns	paternal MII ND, paternal isodisomy

Cox et al., 2004 [25]	46,XX/47,XX,+14	5 yr	ns	ns	a low level of mosaicism for trisomy 14 not detectable by conventional cytogenetic techniques	ns	maternal heterodisomy
Dallapiccola et al., 1984 [26]	46,XY/47,XY,+14	6 mo	33	32	70% BL, 0.5% SF	the only child	not studied
Eventov-Friedman et al., 2015 [27]	46,XX/47,XX,+14	newborn	28	ns	0% cultured BL, 50% by microarray analysis; 15% cultured BL by FISH, 39% uncultured BL	four healthy children, two miscarriages	not studied
Fujimoto et al., 1992 (patient 1) [28]	46,XY/47,XY,+14	newborn	29	30	9% BL	G4P3	not studied
Fujimoto et al., 1992 (patient 2) [28]	46,XX/47,XX,+14	15 mo	26	33	4% BL	one full-sib died shortly after the birth of an unknown cause, one	not studied

						normal half-sib	
He et al., 2014 (twin B) [29]	46,XX/47,XX,+14	neonate	22	ns	40% BL	G2P0	BD
Hur et al., 2012 [30]	46,XX/47,XX,+14	17 mo	37	ns	44% BL	G1P1	not studied
Iglesias et al., 1997 [31]	46,XY/47,XY,+14	6 mo	28	ns	14% BL, 8% SF	G2P2	BD
Jenkins et al., 2009 [32]	46,XY/47,XY,+14	12 mo	ns	ns	10% BL (G-banding), 60% BL (interphase FISH), 18% buccal smears	ns	maternal heterodisomy
Johnson et al., 1979 [33]	46,XX/47,XX,+14	13 yr	16	22	41% BL	healthy four maternal half sibling	not studied
Kaplan et al., 1986 [34]	46,XY/47,XY,+14	newborn	20	ns	24% BL	normal previous child	not studied
Kryukova et al., 2005 [35]	46,XX/47,XX,+14	2 yr 4 mo	ns	ns	90% BL	G1P1	not studied

Lindgren et al., 2021 [36], Liehr, 2022 [2]	46,XX/47,XX,+14	3 mo	35	29	3% BL by FISH	G2P1	maternal MI ND, maternal heterodisomy
Lipson, 1987 [37]	46,XX/47,XX,+14	infant	29	33	23% BL, 4% SF	two previous healthy daughters	not studied
Lynch et al., 2004 [38]	46,XX/47,XX,+14	infant	28	ns	23% BL, 0% SF	G9P7	BD
Martin et al., 1977 [39]	46,XX/47,XX,+14	8 mo	26	32	12.5% BL, 3% SF	two previous pregnancies resulted in healthy children	not studied
Massara et al., 2019 [40]	47,XXX/47,XX,+14	newborn	33	38	30% BL	ectopic previous pregnancy	not studied
McGaughran et al., 2009 [41]	46,XY/47,XY,+14	6 wk	ns	ns	0% BL, 7% SF	ns	maternal UPD could not be clearly demonstrated
Merrit, Natarajan, 2007 [42]	46,XX/47,XX,+14	newborn	43	43	15% BL, 3% and 12% SF	G4P2, two normal children, one spontaneo	BD

						us abortion	
Mucha-Le et al., 2010 (patient 2) [43]	46,XX/47,XX,+14	postnatal	ns	ns	20–25% BL by array SNP, confirmed by chromosome analysis	ns	paternal UPD
Murken et al., 1970 [1]	46,XX/47,XX,+14	2 yr 6 mo	37	40	93% BL	normal older child	not studied
Petersen et al., 1986 [44]; Fagerberg et al., 2012 [45]	46,XX/47,XX,+14	2 yr 2 mo; 27 yo	18	25	6% BL, 16% SF at 2.2 yo; 6% light skin and 0.01% dark skin	normal older child	paternal MII or mitotic ND; BD
Rethore et al., 1975 [46]	46,XX/47,XX,+14	newborn	31	41	9.5% BL, 9% SF	two normal children	not studied
Rodriguez et al., 2016 [47]	46,XY/47,XY,+14	19 days	25	29	4% BL	2nd pregnancy, previous first trimester miscarriage	not studied (parents not available)
Salas-Labadia et al., 2014 [48]	46,XX/47,XX,+14/ 47,XX,+del(14)(q11.2)	15 yr	ns	ns	10%/45% BL, 0%/47% light SF, 0%/46% dark SF	2nd child, one previous	BD

						miscarriage	
Sepulveda et al., 1998 (twin A) [49]	46,XY/47,XY,+14	neonate, dead on day 36	38	ns	12% BL	G4P2, one spontaneous abortion	not studied
Shinawi et al., 2008 (patient 1, twin A) [50]	46,XY/47,XY,+14	3 yr	40	40	12% by aCGH BL, 15% by FISH on stimulated T-lymphocytes, 18% by FISH on BL smears, 0% by aCGH on T lymphocytes and on SF	G5P1–2, twins born after three attempts of IVF; normal twin B and 2 yo sister	maternal origin of trisomy, BD
Shinawi et al., 2008 (case 3) [50]	46,XX/47,XX,+14	6 yr 6 mo	ns	ns	6.5% B-stimulated culture, 17% by aCGH, 2% by FISH on stimulated T-lymphocytes, 9.5% by FISH on BL smears	ns	maternal origin of trisomy, BD
Stalman et al., 2015 (patient A)	female	2 yr 8 mo	ns	ns	low level	ns	maternal UPD

[51]

Ushijima et al., 2018 and personal communication [52]	46,XX/47,XX,+14	3 yr	40	37	12% BL, 47% BL by FISH, 0.6% buccal cells by FISH	G4P2, one child without genetic abnormalities, no info were SA or not	trisomy rescue, maternal iso- and heterodisomy
Vachvanichsanong et al., 1991 [53]	46,XY/47,XY,+14	5 yr 6 mo	28	26	26% BL		not studied
Yakoreva et al., 2018 [54]	46,XX/47,XX,+14	prenatal at 20 wg, 6 yr	32	ns	0% AF, 4% BL, 0% SF normal, 0.7% SF hyperpigmented	2nd child	maternal heterodisomy
Zhang et al., 2016 [55]	46,XY/47,XY,+14	10 yr	35	36	1% BL, 10–20% BL by SNP array, 10–20% hyperpigmented SF, 0% normal SF, 11% BL by interphase FISH	G2P2	maternal iso- and heterodisomy

Abbreviations: AF amniotic fluid cells, BD biparental disomy, BL blood sample, CVS chorionic villus sample, MI 1st meiotic division, MII 2nd meiotic division, ND nondisjunction, NIPT non-invasive prenatal testing, SF skin fibroblasts, UPD uniparental disomy

Table 2 Mosaicism for trisomy 14 due to unbalanced homologous translocation/isochromosome.

Source	Mosaic trisomy 14	Patient's age at examination	Maternal age	Paternal age	Proportion of cell line(s) with chromosome abnormality	Maternal reproductive history	Parental origin of euploid cell line
Prenatal diagnosis							
Chen et al., 2013 [56]	46,XX/46,XX,der(14;14)	prenatal 17 wk	39	38	23.5% AF, 0% SF, 0% umbilical cord culture, 75% culture liver cells	G2P1	BD
Hsu et al., 1996 (patient IIb-3) [57]	46,XY/46,XY,t(14;14) or i(14)	prenatal	ns	ns	4% AF, 0% BL and placenta	ns	not studied
Lambert et al., 1994 [58]	46,XX/46,XX,dic(14)	prenatal, 17 wk	35	37	71% and 60% AF, 4% kidney, 32% ovary, 13% SF	history of infertility, with one miscarriage and no living children	not studied
Wang et al., 2007 [59]	46,XX,del(14)(p11.1)/46,XX,idic(14)(p11.1)	Stillborn, 23 wk	26		33% AF, 8% SF, 30% fetal lung, 22% kidney	G1P0	BD
Postnatal diagnosis							
Cantu et al., 1989 [60]	46,XX/46,XX,i(14)/46,XX,r(14)/45,XX,-14	8 yr	22	25	76%/19%/4% BL; 19%/78/1% dark SF; 8%/82%/7% light SF	first-born child	not studied
Cheung et al., 1988 [61]	46,XX/46,XX,i(14)	newborn	38	ns	0% AF, 37% BL, 0% SF	primigravida	not studied

Cheung et al., 2007 (patient 7) [22]	46,XX/46,XX,der(14;14)	ns	ns	ns	3% BL	ns	not studied
Jenkins et al., 1981 [62]	46,XX/45,XX,t(14;15)/46,XX,i(14),+14	17 mo	30	ns	10% BL, 6.6% SF	G4P3, three normal children	BD
Katahira et al., 2002 [63]	45,XY,der(14;14)/46,XY,der(14;14)+14	21 mo; 20 yr	ns	ns	6% BL; 0.8% BL	normal younger brother	maternal heterodisomy, isodisomy for 14q21-q24
Kolotiy et al., 2020 [64]	46,XX/46,XX,i(14)(q10)	3 yr	29	26	5% BL	G2P2	BD
Ozawa et al., 1984 [65]	46,XY/46,XY,i(14)(q10)	infant	28	30	29% BL	3 yo healthy sibling	not studied
Pangalos et al., 1984 [66]	46,XY/46,XY,r(14)/46,XY,t(14q14q)	7 mo	22	29	74%/5%	2nd of two children	not studied
Shinawi et al., 2008 (patient 2) [50]	46,XX/46,XX,der(14;14),+14	neonate	40	ns	3% BL, 1% SF, 21% by aCGH, 3% by FISH on stimulated lymphocytes, 17.5% by FISH on BL smears	G6P4, sibling with trisomy 21, a prior spontaneous abortion	not studied
Shinawi et al., 2008 (patient 4) [50]	46,XX/46,XX,der(14;14),+14	3 days	32	36	7.3% in T lymphocytes culture, 77% by aCGH, 42% by FISH on stimulated T lymphocytes	G3P2	not studied
Shinavi et al.,2008 (patient 5) [50]	45,XX,der(14;22)/46,XX,der(14;14),+14	neonate	25	ns	82.5%/17.5%	G2P0–1, a prior spontaneous	BD

						abortion	
Smith et al., 2014 [67]	45,XX,t(14;14)/46,XX,t(14;14),+14	postnatal	ns	ns	ns	ns	maternal UPD
Thomas et al., 1989 (patient 1) [68]	46,XX/46,XX,r(14)/45,XX,-14/46,XX,rob(14;14)	7 yr	22	25	22%/19%/57% BL, 79%/1%/18% dark SF, 83%/7%/7% light SF	first-born child	not studied
Tunca et al., 2000 [69]	46,XX/psu dic dup(14)	1 day	17	23	0% BL, 32% SF	ns	not studied
Turleau et al., 1980 [70]	46,XY/46,XY,i(14)	newborn	26	24	25% BL	ectopic pregnancy and 2 SA	not studied
Velissariou et al., 2020 [71]	46,XX/46,XX,der(14;14)+14/47,XX,+ mar	12 yr	33	45	3%/0% BL; 0%/1005	G2P0	BD
von Sneidern, Lacassie, 2008 [72]	46,XX/46,XX,i(14)	16 mo	23	29	0% BL, 4% SF	I - early miscarriage, II and III -healthy daughters, IV - proband	not studied

Table 3 Mosaicism for trisomy 14 due to unbalanced non-homologous translocation.

Source	Karyotype	Patient's age at examination	Maternal age	Paternal age	Proportion of abnormal cell line(s)	Maternal reproductive history	Parental origin of euploid line
Prenatal diagnosis							
Taucher et al., 2014 [73]	46,XX/46,XX,add(13)(p11)/46,XX,der(13;14)(q10;q10),+14	miscarriage	ns	ns	ns	ns	not studied
Wu et al., 2017 [74]	45,XX,der(14;21)mat/46,XX,der(14;21)mat+14	prenatal	30 yr	ns	30% CVS with partial upd, 18% AF, 0% cord BL	nulliparous woman	BD
Postnatal diagnosis							
Antonarakis et al., 1993 [75]	45,XX,t(13;14)/46,XX,t(13;14)+14	9 yr	ns	ns	5% BL, 0% SF	ns	proximal isodisomy and distal heterodisomy maternal isodisomy
Barton et al., 1996 [76]	45,XX,t(13;14)/46,XX,t(13;14)+14	1 yr	ns	ns	10% BL	ns	
Fujimoto et al., 1985 [77]	45,XX,t(14;15)mat/46,XX,t(14;15)mat,+14	2.3 yr	32	32	20% and 32% BL, 0% and 2% SF	G2P1, normal 46,XX child	BD

Our finding that mosaicism for regular T14 dominates mosaicism due to unbalanced translocation/isochromosome was similar to the findings of other studies, which reported that full trisomies predominate visible chromosomal abnormalities. In contrast, homologous translocations predominate nonhomologous translocations. This observation is interesting since nonhomologous translocations are very common chromosome rearrangements found both in consecutive newborns and in prenatal diagnosis, whereas homologous translocations are extremely rare. Among 93,716 tested newborns, 96 carriers of non-homologous translocation were diagnosed, and no carriers of homologous translocations were identified. Among 221 prenatally detected carriers of Robertsonian translocation, only two females were reported as carriers of a homologous translocation: 45, XX, t(13;13) and 45, XX, t(15;15) (see review [78]).

The proportion of homologous translocations/isochromosomes in the studied mosaic group (21 of 26) was significantly different than that in the carriers of non-mosaic UPD(14) associated with balanced translocations (Table 4 [6, 79-113]), with the prevalence of non-homologous translocations (29 of 50; $p = 0.0029$) (Chi-squared test; Yates-corrected). Overall, these observations supported a preferential mitotic mechanism of homologous translocation/isochromosome formation [114]. The relatively higher proportion of homologous translocations in non-mosaic UPD(14) carriers needs further investigation.

Table 4 Non-mosaic Robertsonian translocations/isochromosomes with UPD(14) based on parental origin and the gender of the carriers.

Parental origin of disomy	Type of rearrangement						Sex ratio	*P*-value (chi-square, Yates-corrected)
	Nonhomologous translocation, n = 29			Homologous translocation or isochromosome, n = 21				
	males	females	Total	males	females	Total		
Maternal UPD	7 [79-85]	11 [81, 82, 86-94]	18	6 [6, 86, 95-98]	5 [2, 99-102]	11	13 males/16 females	0.2819
Paternal UPD	1 [103]	10 [104-109]	11	2 [107, 110]	8 [99, 107, 111- 113]	10	3 males/18 females*	0.0000 **

Difference in sex ratio between individuals with paternal UPD is significant, $p = 0.0479$; ** difference with population value of 1.06 is highly significant

In the group of mosaic unbalanced homologous translocation/isochromosome 14, there were a number of carriers with a cell line containing a ring chromosome (3 of 19). Several studies have reported the association of ring chromosomes with homologous translocations, including chromosomes 13 [115], 15 [116], 21 [117], and 18 [118]. Stetten et al. suggested that a homologous translocation was necessary for the formation of ring chromosomes [115].

The parental origin of the diploid cell line was examined in 39 individuals; among them, 17 were diagnosed with maternal UPD(14), two had paternal UPD(14), and the remaining 20 demonstrated biparental inheritance. Theoretically, only one-third of the cases with mosaics for regular T14 might be expected to be UPD carriers. However, the observed ratio of UPD(14) to BD of 15:12 differed from the expected ratio, probably because of publication bias (i.e., the tendency to publish more "interesting" cases of uniparental disomy). The ratio of paternal UPD to maternal UPD (2 of 15) of 2:13 might occur because of more frequent chromosome nondisjunction during oogenesis.

4. Sex Ratio (Male-to-Female Ratio)

Most mosT14 patients were females in all studied groups irrespective of whether the trisomic line was regular or caused due to an unbalanced rearrangement and independent of the parental origin of the euploid line. Data reviewed from 26 published reports (Table 5 [7, 119-144]) on 45 males and 65 females showed that male cases were not predominant among abortuses with T14 (sex ratio of 0.70, in contrast to trisomies 13 and 21 with a sex ratio of 1.1 and 1.4, respectively). Therefore, a female-biased sex ratio in the studied groups cannot be explained by high intrauterine male mortality.

Table 5 The sex ratio of spontaneous abortuses with regular trisomy of chromosomes 13, 14, and 21.

References	Number of tested abortuses *	Trisomy 13		Trisomy 14		Trisomy 21	
		males	females	males	females	males	females
[7, 119-144]	11,026	89	80	48	66	122	84
Sex ratio		1.1		0.7		1.4	

* only those where trisomy 14 was detected

A comparison of the two datasets supported the hypothesis of very early mortality of T14 male carriers. In a large series (n = 534) of spontaneous miscarriages of 7–34 weeks of gestation, one male and 14 female carriers of mosaicism for autosomal trisomy (3%) were identified by conventional cytogenetics; among them, one was a female mosaic for T14 (46, XX/47, XX, +14) [145]. In a smaller sample (n = 60) of spontaneous abortions of 5–12 weeks of gestation, the results of the interphase FISH analysis revealed nine males and six females with mosaicism for autosomal trisomy (25%), one of them being a male mosaic for T14 [146].

If males are less tolerant to the presence of T14 cells, they are expected to have a lower frequency of trisomic cells than females. Since many patients, for various reasons, were not examined using modern techniques, we analyzed a proportion of trisomic cells from the blood

cultures of 11 male patients and 46 female patients. Male patients had a lower proportion of trisomic cells than female patients, with average frequencies of 16.3% (0%-70%) and 20.1% (0%-93%). Comparing the clinical manifestation of the mosaic T14 in male and female carriers was difficult because of few reported cases.

The observed four-fold female predominance among mosT14 (19 males/57 females) cannot be explained entirely by a male intolerance to the presence of T14 cells, since this pattern is also observed in the carriers of UPD(14) without mosaicism for T14 (16 males/34 females), particularly to paternal UPD(14) (3 males/18 females). We speculated that the observed female predominance might be explained by female-specific instabilities of pericentromeric regions [147], female-specific trisomy correction [148], and male-specific selection against abnormal cells [149].

5. Maternal Factors

5.1 Maternal Age

Data on maternal age was available for 38 postnatally diagnosed patients; their average age was 28.7 years, and 18% of the mothers were 35 years and above. The origin of the diploid cell line was determined in a subset of these patients; 11 were of biparental origin, and five had maternal uniparental disomy. The average maternal age in the BD group was 29.8 years (18–43 years), and 18% of the mothers were above 35 years. The average maternal age in the UPD group was 35.4 years (32–40 years), and 80% of the mothers were above 35 years. The difference between these groups was statistically significant ($p < 0.05$; Mann-Whitney U test).

Although the association of UPD with advanced maternal age is well-established [150], Mitter et al. [84] suggested that maternal age does not increase the risk of maternal UPD(14), unlike maternal UPD(15). Therefore, our finding is even more intriguing, especially considering the common mechanism of the formation of BP and UPD. As mentioned previously, the sample size was small and more studies on mosT14 need to be published.

5.2 Maternal Reproductive History

Unfortunately, information on maternal reproductive history is limited. After excluding primigravida women and carriers of non-homologous translocation, data on 44 mothers were available. Among them, even after we disregarded the low quality of the anamnesis description (for example, healthy child, first-born child, G2PO, etc.), there were 11 (or 25%) families with complicated reproductive history (including previous spontaneous abortion(s), infertility, etc.). The estimated rate of reproductive disorders in the population was approximately 12.5% for families [151].

Chromosomal mosaicism might not be transmitted. However, genetic predisposition to mitotic nondisjunction might occur; mosaicism for T21 in successive generations was reported in at least 12 of 80 families of gonadal mosaicism (see review [152]). Gonadal mosaicism may cause reproductive disorders and abnormalities in offspring. Further studies on such cases are required for accurately determining the complicated reproductive history as a risk factor for T14 mosaicism.

6. Conclusions

This was the first systematic review of published cases of mosaic trisomy 14 to address epidemiological aspects of this abnormality. The analysis of the data provided an initial epidemiological evaluation of this rare disorder. Conducting a more detailed analysis is challenging due to the under-reporting of cases. Even when cases are reported, limited data on parameters such as genetic testing, the karyotype and age of the patient, the age of the parents when the patient was born, and parental reproductive history have been reported, despite being readily available at the first examination of the patient. Developing consensus protocols for reporting cases to registries or public databases can benefit future studies.

Author Contributions

Both authors equally contributed to this paper.

Competing Interests

The authors have declared that no competing interests exist.

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