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Mosaic Trisomy 1q Due to a *de novo* Translocation in a Foetus with Early Developmental Abnormalities (Karyotype 46,XY,der(14),t(1;14)(p11;p11.2)/46,XY) Delineation of Parent and Cell Stage of Origin

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KEYWORDS Mosaic trisomy 1q; de-novo translocation 1/14; paternal origin of structural aberration; combination of meiotic and postzygotic aberration

ABSTRACT Pure trisomies of the whole long arm of chromosome 1 are extremely rare and have been reported only once in association with mosaicism. We report on a malformed foetus with mosaic trisomy 1p11 to 1qter whose clinical features were partially in accordance with those of previously described trisomy 1q patients. An additional long arm of chromosome 1 was translocated onto 14p11.2 (karyotype: mos46,XY,der(14)t(1;14)(p11;p11.2)/46,XY). Mosaic formation of the partial trisomy 1 was investigated in seven different somatic tissues of first and second trimester pregnancy. The distribution of the pathologic cells was unequal, ranging from 4 to 93%. The duplicated region was paternal in origin. We were able to delineate two possible complex formation mechanisms involving paternal meiosis and postzygotic mitoses.

INTRODUCTION

The increasing number of cytogenetic and molecular genetic techniques allows the identification of rare chromosome aberrations and the corresponding phenotypes. In cases involving mosaicism, a combination of conventional karyotype analysis and interphase FISH are currently the only way to detect and delineate an often unequal mosaic distribution in different somatic tissues of a patient.

Mosaicism in unbalanced rearrangements is rare and arises *de-novo*. Interestingly, it is often associated with an unequal distribution of normal and aberrant cell lines in different somatic tissues. In tissues with high mitotic activity, the aberrant cell line often already declines during the prenatal period and thus cannot be detected in the newborn.

The foetus reported here exhibited mosaicism for an unbalanced de novo 1;14 translocation resulting in a partial trisomy of the whole long arm of chromosome 1. Trisomies of whole 1q have rarely been reported while trisomies of regions 1q32qter and 1q42qter are more frequent (for review: Kimya et al. 2002; Scheuerle et al. 2005; Utine et al. 2007). To date, 8 cases of partial trisomy 1q deriving from a translocation have been reported, among them one foetus with a 1/14 translocation (Pettenati et al. 2001; for review: Scheuerle et al. 2005).

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Case report

The 42-year-old mother (paternal age was 41 years) underwent chorionic villous biopsy for chromosome examination during the 12th week of her second pregnancy. The first child is a healthy two-year-old girl. The family did not reveal any genetic or exogenous risk factors.

The indication for CVS (chorionic villous

sampling) was increased maternal age and pathologic ultrasound findings at GA 12+2 (gestational age): abdominal sonography with a

A TL HDI 5000 scanner had revealed an increased nuchal translucency, omphalocele and intrauterine growth retardation. The nasal bone was not visible (Tables 1 and 2).

Ultrasound investigation at GA 14+3 showed mild ventriculomegaly, wide sutures, bilateral cleft lip and palate, microphthalmy, small mandible, low set ears, long trunk, short femur, ascites, hypoplastic thumb on the right side and triphalangeal on the left side (Acuson Sequoia and GE Voluson 730 expert (3D/4D), transabdominal sonography) (Fig. 1, Table 1). This detailed documentation of a high number of abnormalities in the foetus by 3D/4D ultrasound is in good accordance with findings from the literature (Picone et al. 2008).

Based on the ultrasonographic and cytogenetic findings, the parents chose to terminate the pregnancy after nondirective genetic counselling.

Pathoanatomic Findings after Therapeutic Abortion

Dysproportion of the *body*; increased neurocranium, elongation of the neck, long trunk with short extremities.

Craniofacial dysmorphisms included pseudoturricephalia with flattened occiput, cranial asymmetry, a high and prominent forehead, normal size of orbitae but with extreme microphthalmia, hypertelorism, temporal narrowing, short palpebral fissures, downslanting eyes, broad nasal bridge, anteverted nostrils, bilateral cleft lip and palate including uvula bipartita, small mouth, dysmorphic low set ears with bilateral atresia of auditory canal, missing porus acusticus externus. The skull showed an enlarged fontanella magna (3.0 x 1.5 cm) as well as an enlargement of the other sutures. Reduced ossification of calvaria bones and increased fossa cranii posterior were observed. Differentiation of the brain (25.5 g) corresponded to the pregnancy week.

The *limbs* displayed several malformations: a triphalangeal thumb with narrowing of the tips and nail hypoplasia and hypoplasia of metacarpale I right, aplasia of thumb and metacarpale I left, incomplete syndactylia of toes (III-IV right and III-IV left side) and an enlarged gap between the first and the second toe. Contractions of the elbows and the knees were diagnosed.

Organs: Both kidneys were malrotated with a dorsomedian origin of the ureter. The testes were small for the gestational age. In addition, pleural effusion, ascites, skin edema, and nuchal thickening were noted.

The *placental* development corresponded to the gestational week; the umbilical cord contained three vessels.

The clinical features of the foetus were in good accordance with findings from the literature (Table 2).

Cytogenetic and Molecular Findings

Conventional GTG and QFQ banding on different tissues obtained in the 12th and the 15th weeks of pregnancy revealed mosaicism for an unbalanced translocation 1;14 resulting in a

Table 1: Fetal biometry
GA: 12+2/14+3 (GA gestational age: gestational week + day)
***Fetal measurements compared with normal mean values and 5th/95th percentile.**

Biometry	*GA 12+2*		*GA 14+3*	
	m m	*Percentile**	*m m*	*Percentile**
Crown-rump length (CRL)	50.0		87.0	
Biparietal diameter (BPD)	19.3		31.0	
Frontooccipital diameter (FOD)	21.7		38.5	
Head circumference (HC)	64.4		109.2	
Femur length (FL)	4.9		l. 14.5	
			r. 13.0	
Humerus length (HL)			14.7	
Ulna length (UL)			14.0	
Abdominal circumference (AC)	47.0		80.1	
Nuchal translucency (NT)	7.1			thickened
Nasal bone (NB)	not visible			visible

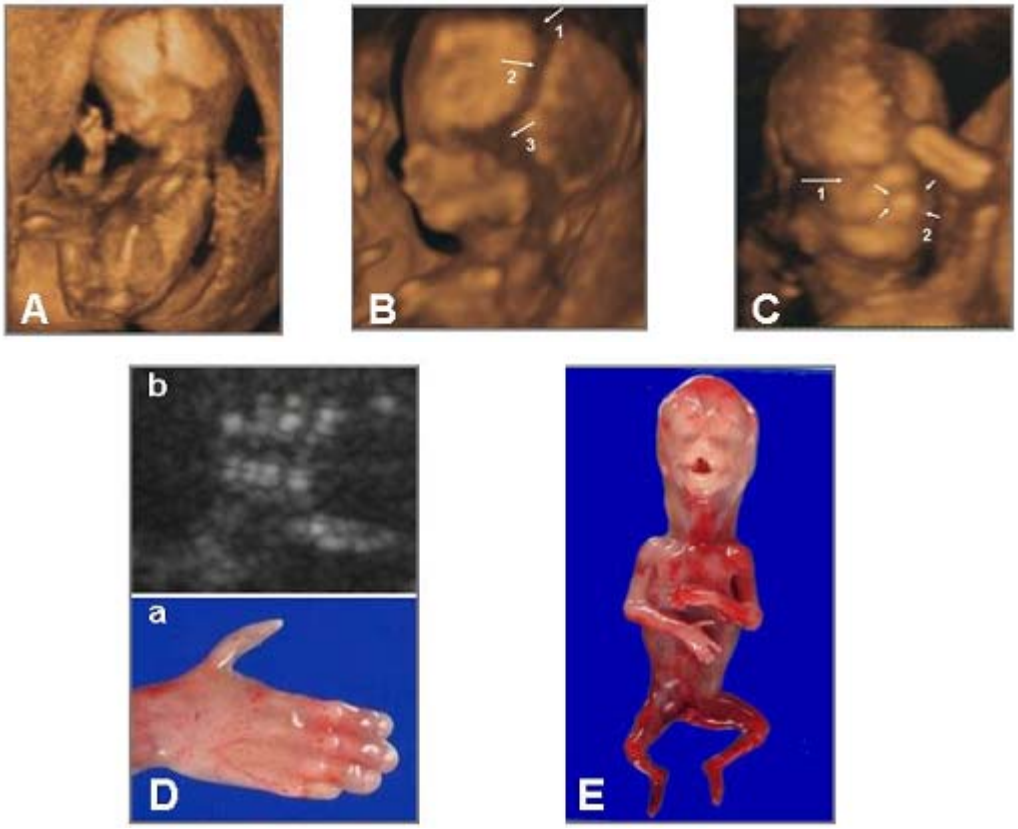

Fig. 1. Ultrasonographic and pathoanatomic findings in the fetus at GA 14+3 and 15+2 with mosaic duplication 1q (transabdominal 3D/4D sonography).
A. Fetus shows wide coronal sutures, micropthalmia, microgenia, enlarged neurocranium, long trunk and short femur.
B. Profile of the fetus, with wide coronal suture (2), frontal (1) and sphenoidal (3) fontanelles.
C. Frontal view of the face, with extreme microphthalmia (1) and bilateral cleft lip and palate (2).
D. Right hand of the fetus. Triphalangeal thumb and hypoplastic nails. a) Pathologic finding after termination of pregnancy; b) Ultrasound.
E. Fetus after termination of the pregnancy.

trisomy 1q (Fig. 2). Seven different somatic tissues were analysed. A very unequal distribution of the mosaic was found, with the proportion of aberrant cells ranging from 4% in chorionic villi cells to 93% in the lungs. An in vitro selection in favour of the normal cell line was excluded based on the range of cultivation times. These extended from 7 to 14 days, showing the smallest number of normal cells after the shortest cultivation in the CVS sample. Furthermore, significant differences in mosaic distribution were found in tissues which were all cultivated for 14 days (Table 3). Mosaic investigation was based on metaphase analyses.

The banding pattern of the marker showed a dicentric structure and the karyotype was defined as mos46,XY,der(14)t(1;14)(p11;p11.2)/46,XY,GTG,QFQ,NOR, resulting in a trisomy of the long arm of 1q. The translocation chromosome was dicentric and had an inactive chromosome 1 centromere. Both parental karyotypes were normal.

To confirm the dicentric nature and the chromosome 1 origin of the rearranged chromosome, we performed fluorescence-in-situ hybridisation (FISH) with an alpha-satellite probe specific for the centromeric region of chromosome 1 (probe CEP1) and a 1q12 satellite probe (probe

Table 2: Comparison of clinical features of the fetus presented here and findings in 1q duplication carriers reported in the literature. (M=Male; F=female; + present; - absent; (+) mild)

Duplication 1q	*Cases from the literature*		*Present case*	
Clinical features	*Partial and complete duplications* (n=79)*	*Complete duplications 1q (mosaic and non- mosaic)* (n=8)*	*Ultrasound*	*Pathology*
Sex; Male/Female	18: 9	7: 1	M	M
General symptoms				
Growth retardation	14/26		-	-
Brain abnormalities	17/24	2/8		
Hypoplastic cerebellum	1/8	2/8	-	-
Ventriculomegaly/ enlarged	18/79	3/8	+ (mild)	+
Neurorocranium				
Skull abnormalities	6/20		+	+
Wide sutures and fontanelles	7/20		+	+
Craniofacial dysmorphisms	16/20		+	+
Prominent wide forehead	2/3		+	+
abnormalities of the eyes	8/19		+	+
Antimongoloid slanted palpebral fissures	8/18		+	+
Short palpebral fissures	7/20		+	+
Hypertelorism	10/79		+	+
Hypoplastic midface	5/17		+	+
Broad nasal bridge	6/20		+	+
Long philtrum	5/20		-	-
Small mouth or jaw	6/23		-	-
Microgenia/retrognathia	15/24	3/8	+	+
Low set/ dysmorphic ears	17/23	6/8	+	+
Shortened neck	8/20		-	-
Nuchal thickening/edema	2/2		+	+
Thorax and abdomen				
Respiratory anomalies	6/79		-	(+)
Genital abnormalities	14/79	2/8	-	(+)
Extremities				
Hand/foot abnormalities	22/25	5/8	+	+
Skeletal abnormalities	7/79		+	+
Malformations				
Microphthalmia/anopthalmia	13/79	3/8	+	+
Omphalocele	8/79	2/8	(+)	-
Abnormal palate	13/20		+	+
Cleft lip and palate	11/79	1/8	+	+
Stenosis/atresia of aur. canal	1/79		-	+
Congenital heart defect	34/79	4/8	-	-
Urogenital malformation	11/9	4/8	-	+

mild)

* It is to be assumed that the different characteristic symptoms of trisomy 1q are localised in different regions of 1q. Therefore, summarising all cases of partial trisomy 1q does not provide a sufficiently realistic distribution of the frequency of the symptoms. However, 8 cases of trisomy 1q are too small a number for a plausible distribution . For this reason we have listed both groups.

1q12) in the various tissues according to the manufacturers´ protocol (Boehringer, Mannheim, D; Oncor, Gaithersburg, MD/USA). Signals for both CEP1 and 1q12 probes were detected on the der(14) in metaphases and the signals were also identified in a significant number of interphase nuclei (Fig. 2).

In order to determine the formation mechanism of the rearranged chromosome, genomic DNA of the foetus was isolated from paraffin embedded tissues (lung, kidney, skin, umbilical cord and placenta). Parental DNA was extracted from peripheral lymphocytes. Microsatellite markers on chromosomes 1q and 14q were analysed by PCR and subsequent denaturing capillary electrophoresis according

Table 3: Investigated tissues and their specific degree of mosaicism. Microsatellite analyses confirmed the finding of trisomy 1q in four different tissues.

Tissue	*GA*	*Time of cultivation*	*Rate of aberrant cells*	*Microsatellite typing*
Chorionic villi	11+3	7 days	4% (134)	Three alleles
Amniocytes	14+3	10 days	67% (45)	n.a.
Skin	15+2	14 days	37% (30)	Three alleles
Lung	15+2	14 days	93% (30)	Three alleles
Umbilical cord	15+2	14 days	17% (30)	Three alleles
Kidney	15+2	14 days	70% (30)	n.a.
Achilles tendon	15+2	14 days	16% (32)	n.a.

(n.a. not analysed; the number of cells are given in parentheses)

to standard methods. Alleles were visualised by fluorescence. The markers and the typing results are listed in Table 4. Microsatellite marker D1S225 in 1q42.2 revealed the paternal origin of the duplicated segment, and the presence of three alleles in the marker D1S225 indicated a meiotic origin of the aberration. In addition, we typed three markers in 14q in order to exclude uniparental disomy of chromosome 14. Based on the results of these investigations, we were able to delineate the complex formation mechanism of the foetal karyotype and the development of the pathologic cell line.

DISCUSSION

Trisomy of the whole arm of chromosome 1 is an extremely rare finding: to date, only eight cases have been reported in the literature (for review: Scheuerle et al. 2005). The foetus with complete trisomy 1q presented here exhibited a number of clinical symptoms which are comparable to those described in publications about live-born children with 1q dup. However, he also displayed unspecific peculiarities also detectable in other chromosomal syndromes such as intrauterine developmental abnormalities (as evidenced by ultrasound and pathoanatomic findings) and nuchal thickening. In the present case we were able to monitor the development of the aberrant phenotype of trisomy 1q in early pregnancy through the use of advanced ultrasound techniques (3D/4D).

Of the more than 30 different clinical features

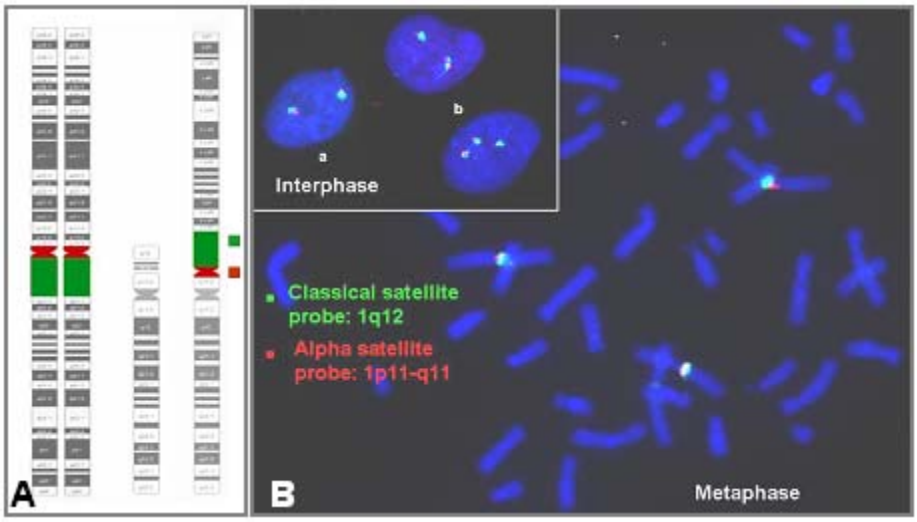

Fig. 2. Molecular cytogenetic findings in the foetus with 1q trisomy.
A. Ideogram of two normal chromosomes 1, one normal chromosome 14 and the translocation chromosome der(14),t(1;14)(p11;p11.2). B. Metaphase from amniocyte culture with duplication 1q by de novo unbalanced translocation 1/14. Two colour interphase-FISH: a) Nucleus containing 2 signals for chromosome 1. b) Nuclei containing 3 signals, representing two chromosomes 1 and the translocation chromosome. (DAPI

Table 4: Microsatellite typing in the fetus and his parents revealing the paternal origin of the rearrangement.

Marker	*chromosomal band*	*Father*	*Mother*	*Fetus*	*Informativity*
D1S2833	1q42.2	1-3	1-2	1-2-3	trisomic
D1S103		1-2	1-3	1-1-3	trisomic
D1S1656		1-1	1-1	1-1	-
D1S225		1-2	3-4	2-2-3	trisomic, paternal origin
D14S283	14q11.2	2-2	1-3	2-3	biparental
D14S64	14q11.2	1-2	2-2	2-2	-
D14S80	14q12	1-2	2-3	1-2	-

of trisomy 1q carriers reported so far, 15 were present in more than 50% of patients (Table 2). 9 of these 15 symptoms were present in our patient as well. However, it must be taken into account that some symptoms such as growth retardation and brain abnormalities develop only in later stages of pregnancy.

The presence of three different alleles in the foetal DNA in the case of marker D1S2833 indicates a nondisjunctional error in meiosis. Typing of marker D1S225 (Table 4) confirmed the paternal origin of the supernumerary material. Based on these data we propose the following two possible formation mechanisms.

(a) The initial event resulting in the translocation 1;14 may have occurred in paternal meiosis and resulted in a sperm carrying the derivative chromosome. Functionally, this gamete should have been disomic for chromosomes 1q and 14. After fertilisation, the der(14) or the free paternal chromosome 14 would have been lost in postzygotic mitoses, leading to mosaicism of normal disomic cells on the one hand and trisomic cells carrying the der(14) on the other hand.

(b) The second possible mechanism starts with a trisomic zygote carrying a supernumerary paternal chromosome 1. In one of the following mitoses, one of the paternal chromosomes 1 would have been lost and a cell line with normal karyotype would have developed. In addition, in another cell-lineage the translocation 1/14 accompanied by the loss of the acentric short arm of chromosome 1 would have occurred in one early trisomic postzygotic cell. This cell line would have developed further while the original cells with trisomy 1, not being viable, would have disappeared.

In conclusion, the characterisation of our case illustrates quite clearly that relevant new insight into prenatal phenotypes of rare chromosome disorders can only be achieved by combining different cytogenetic, molecular-cytogenetic and molecular findings with the results of ultrasonographic scanning and foetal pathological examination.

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