A family study of complex chromosome rearrangement involving chromosomes 1, 8, and 11 and its reproductive consequences

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Abstract Complex chromosome translocations are structural chromosomal rearrangements involving three or more chromosomes and more than two breakpoints. A complex chromosome rearrangement was detected in a phenotypically normal female patient that was referred to the hospital for genetic counseling due to reproductive failure. A cytogenetic evaluation was performed, according to standard method of chromosomal analysis, using G-banding technique. The patient's karyotype showed a balanced complex chromosome rearrangement (BCCR) involving chromosomes 1, 8, and 11 with three breakpoints 1p31, 8q13, and 11q23. The karyotype designed according to ISCN (2013), is 46,XX,t(1;8;11)(p31;q13;q23) (8qter→8q13::1p31→1qter;8pter→8q13::11q23→11qter;11pter→11q23::1p31→1pter). Additionally, the proband's mother and brother were tested, resulting in the same exact translocation. In this study, we describe all possible meiotic segregations regarding this translocation, as well as the clinical phenotypes which could arise, if unbalanced products of conception survive. This is a rare case of familial complex chromosome rearrangement, giving a view for its reproductive consequences.

Keywords Complex translocations · Reproduction · CCRs · Chromothripsis

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Introduction

Complex chromosomal rearrangements (CCRs) are constitutive structural aberrations involving three or more chromosomal breaks accompanied by exchange of genetic material [1]. The balanced CCRs (BCCR) range from simple three-way exchanges between three chromosomes to highly complex translocation involving four or five chromosomes with multiple breaks, insertions, or inversions [2, 3]. Translocations involving three or more chromosomes frequently lead to a severe reproductive impairment, secondary to meiotic irregularities in males and to chromosomal imbalances in gametes in female [3]. Also, more than one aberration, such as translocation and an inversion, can coexist in the same chromosome. CCRs can be classified into three groups, based on the type of rearrangement and the number of breakpoints [4]. These are the following:

1. Three-way exchange with three breaks from three chromosomes: most three-way CCRs are familial and are usually transmitted through the mother. They are the most common type of CCRs.
2. Double two-way exchange with a coincidence of two separate simple reciprocal translocations: the double two-way CCR is not a true CCR and might be described as a double or a multiple rearrangement.
3. Exceptional CCRs with more complicated rearrangements: most exceptional CCRs are de novo rearrangements and they are more commonly associated with abnormal phenotype.

Most phenotypically normal female CCR carriers are usually investigated due to recurrent abortions or after the birth of an abnormal child. In contrast, phenotypically normal male CCR carriers are more frequently diagnosed following an investigation for infertility [5–8]. Genetic counseling for CCRs

Column 1—patient's gamete chromosomes	Column 2—patient's gamete chromosomes	Column 1 + normal gamete (1, 8, 11)	Column 2 + normal gamete (1, 8, 11)
Segregation 3:3		Normal	Normal
1, 8, 11	der(1), der(8), der(11)	Monosomy 11, partial trisomy 1p31-qter and 8q13qter	Trisomy 11, partial monosomy 1 and 8
1, der(1), 8	der(8), 11, der(11)	<i>Partial monosomy 11q23-qter, partial trisomy 1p31-pter</i>	<i>Partial trisomy 11pter-q23, partial monosomy 8pter-q13</i>
1, 8, der(11)	der(1), 11, der(11)	<i>Partial monosomy 8q13-qter, partial trisomy 11q23-qter</i>	<i>Partial trisomy 8q13-qter, partial monosomy 11q23-qter</i>
1, der(8), 11	der(1), 8, der(11)	Monosomy 8, partial trisomy 1p31-pter and 11pter-q23	Trisomy 8, partial monosomy 1 and 11
1, 11, der(11)	der(1), 8, der(8)	Trisomy 1, partial monosomy 8 and 11	Monosomy 1, partial trisomy 8 and 11
1, der(1), der(11)	8, der(8), 11	<i>Partial trisomy 1p31-qter, partial monosomy 8pter-q13</i>	<i>Partial monosomy 1p31-qter, partial trisomy 8pter-q13</i>
1, der(1), 11	8, der(8), der(11)	Partial trisomy 1, partial monosomy 11	Partial monosomy 1, partial trisomy 11
1, der(1), der(8)	8, 11, der(11)	Partial monosomy 1, partial trisomy 8	Partial trisomy 1, partial monosomy 8
der(1), 8, 11	1, der(8), der(11)	Partial monosomy 1, partial trisomy 8	Partial trisomy 1, partial monosomy 8
der(1), der(8), 11	1, 8, der(11)	Partial monosomy 1, partial trisomy 11	Partial trisomy 1, partial monosomy 11
Segregation 4:2		Trisomy 8, partial trisomy 1 and partial monosomy 11	Monosomy 8, partial monosomy 1 and partial trisomy 11
1, der(1), 8, der(8)	11, der(11)	<i>Partial trisomy 8pter-q13 and 11q23-qter</i>	<i>Partial monosomy 8q13-qter and 11pter-q23</i>
1, 8, der(8), 11	der(1), der(11)	Trisomy 11, partial trisomy 1 and partial monosomy 8	Monosomy 11, partial monosomy 1 and partial trisomy 8
1, der(8), 11, der(11)	der(1), 8	Trisomy 8, partial monosomy 1 and partial trisomy 11	Monosomy 8, partial trisomy 1 and partial monosomy 11
der(1), 8, der(8), 11	1, der(11)	Trisomy 11	Monosomy 11
der(1), der(8), 11, der(11)	1, 8	Trisomy 1, partial monosomy 8 and partial trisomy 11	Monosomy 1, partial trisomy 8 and partial monosomy 11
1, der(1), 11, der(11)	8, der(8)	Trisomy 11, partial monosomy 1 and partial trisomy 8	Monosomy 11, partial trisomy 1 and partial monosomy 8
8, der(8), 11, der(11)	1, der(1)	<i>Partial trisomy 1p31-pter and 11pter-q23</i>	<i>Partial monosomy 1p31-qter and 11q23-qter</i>
1, 8, 11, der(11)	der(1), der(8)	Trisomy 1, partial monosomy 11 and partial trisomy 8	Monosomy 1, partial trisomy 11 and partial monosomy 8
1, der(1), 8, der(11)	der(8), 11	Trisomy 1	Monosomy 1
1, der(1), der(8), der(11)	8, 11	Partial trisomy 1 and 8	Partial monosomy 1 and 8
1, der(1), 8, 11	1, 11	Trisomy 8	Monosomy 8
der(1), 8, der(8), der(11)	1, 11	Partial trisomy 1 and 11	Partial monosomy 1 and 11
1, der(1), der(8), 11	8, der(11)	Partial trisomy 1 and 8	Partial monosomy 1 and 8
1, 8, der(8), der(11)	der(1), 11	Partial trisomy 8 and 11	Partial monosomy 8 and 11
der(1), 8, 11, der(11)	1, der(8)	Trisomies 8 and 11	Monosomies 8 and 11
Segregation 5:1		Trisomies 1 and 11	Monosomies 1 and 11
der(1), 8, der(8), 11, der(11)	1	Trisomies 1 and 8	Monosomies 1 and 8
1, der(1), der(8), 11, der(11)	8	Trisomy 11, partial trisomies 1 and 8	Monosomy 11, partial monosomies 1 and 8
1, der(1), 8, der(8), der(11)	11	Trisomy 1, partial trisomies 8 and 11	Monosomy 1, partial monosomies 8 and 11
1, 8, der(8), 11, der(11)	der(1)	Trisomy 8, partial trisomies 1 and 11	Monosomy 8, partial monosomies 1 and 11
1, der(1), 8, 11, der(11)	der(8)	Trisomies 1, 8 and 11	Monosomies 1, 8 and 11
der(1), 8, 11, der(11)	der(11)		
Segregation 6:0			
1, der(1), 8, der(8), 11, der(11)	—		

Table 2 Possible clinical phenotypes, corresponding to the partial chromosome aberrations

Chromosomal aberration	Clinical findings
Partial monosomy 11q23-qter	Jacobsen syndrome—prenatal and postnatal growth retardation, psychomotor retardation; craniofacial malformations, abnormalities of the eyes, hands, feet, bleeding due to platelet abnormalities, and/or congenital heart and immunological defects, renal duplication and hydronephrosis [10] Hyperthelormism, a depressed nasal bridge, orofacial clefts, and holoprosencephaly-premaxillary agenesis, orofacial clefts, pyelectasis, and a unilateral duplex renal system [11]
Partial trisomy 11q23-qter	Dysmorphic facial features, microcephaly, micrognathia, dysplastic ears, pre/postnatal growth retardation, speech delay, mental retardation, hypotonia, neural tube defects, as well as cardiac, vertebral, limb, urinary tract, and genital anomalies [12]. Macroglossia, umbilical and inguinal hernias, hypotonia, soft and wrinkled skin, dysmorphic face, high-arched palate, hepatosplenomegaly, intestinal malrotation, Meckel's diverticulum, and mental retardation [13]
Partial monosomy 8q13-qter	Eye, ear, and kidney abnormalities, mental retardation; cerebellar vermis hypoplasia, intellectual, speech and language impairment, unilateral facial nerve weakness, marked constipation, and bilateral hand and foot anomalies [14]
Partial monosomy 8pter-q13	Congenital heart defects; malformation in the septum; atrioventricular septal defect, causing pulmonary hypertension [14], slow growth, high forehead, broad chest, wide-set nipples, pulmonary stenosis with atrial and/or ventricular septal defect, hypoplasia of the genitalia, dermatoglyphic stigmata [15] (http://rarediseases.org/rare-diseases/chromosome-8-monosomy-8p)
Partial trisomy 8pter-q13	Craniofacial defects, brevicollis with redundant skin folds, mental retardation, absence of the corpus callosum, multiple minor skeletal abnormalities, and autism, mild dysmorphic features, and moderate learning disability [16, 17], hypertelorism, large, dysplastic, anteverted ears, a pronounced mandible [18].
Partial trisomy 8q13-qter	Unusual and characteristic multi-organ clinical features, which include hearing loss, congenital heart defects, intellectual disability, hypotonia in infancy, and Duane anomaly (form of complex strabismus—limited ocular abduction and variably limited adduction accompanied by retraction of the globe, which narrows the palpebral fissure) [19, 20]
Partial trisomy 1p31-pter	Facial dysmorphism, small stature and syndactyly of 4th and 5th toes; mental and statomotoric impairment [21], microcephaly, craniosynostosis, depressed nasal bridge, malformed pinnae, hyperthelormism, cleft palate, brachydactyly and cryptorchidism [22]
Partial monosomy 1p31-pter	Large anterior fontanelle (100%), motor delay/hypotonia (92%), mental retardation (92%), growth delay (85%), pointed chin (80%), eye/vision problems (75%), seizures (72%), flat nasal bridge (65%), clinodactyly and/or short fifth finger(s) (64%), low-set ear(s) (59%), ear asymmetry (57%), hearing deficits (56%), abusive behavior (56%), thickened ear helices (53%), and deep-set eyes (50%) [23]

carriers requires a detailed pedigree analysis and genetic testing, considering the small number of reported cases with such rearrangement [9] (Tables 1 and 2).

Approximately 255 cases of CCRs involving 3 or more chromosomes have been published to date, none of which include all of the 3 chromosomes presented in this case. In Table 3, we present a list of published cases of complex chromosome rearrangement including chromosomes 1, 8, and 11. In an analysis of CCRs cases and review of familial cases, Batista et al. [43] stated that the risk of spontaneous abortion in a pregnancy from a CCR carrier can be as high as 50 to 100%. The CCR carrier phenotype varies from normal to abnormal, with congenital abnormalities and/or intellectual disability. The meiotic segregation of CCRs can theoretically lead to numerous unbalanced chromosomal configurations, therefore the carriers of BCCR are considered to have a high risk for spontaneous abortion or chromosomally abnormal offspring [43]. According to the literature, about 70% of CCRs are detected in phenotypically normal subjects, 20–25% in patients with congenital abnormalities and/or mental retardation, and 5–10% are detected during prenatal diagnosis. When a CCR is detected in a phenotypically normal subject, the rearrangement is generally assumed to be balanced,

meaning that there is equal exchange of genetic material between the chromosomes involved. Such familial transmission mainly occurs through female carriers [43]. In contrast, unbalanced CCRs change the dosage of genetic material and result in loss of one copy or addition of an extra copy, deletion or duplication, respectively, which leads to a more dramatic phenotypic outcome [43]. The probability of an abnormal phenotype increases with the number of breakpoints associated with the de novo BCCR [48]. According to Gorski et al. [49], 18% of all live births with CCR result in phenotypically abnormal offspring. Therefore, BCCR are usually identified in women who are investigated for repeated spontaneous abortion or birth of a malformed child [7–9, 43, 48–51]. According to the literature, about 70–75% of CCR are de novo in origin. The de novo CCRs are found in equal proportion among phenotypically normal subjects (49%) and individuals with phenotypic abnormalities (51%) due to submicroscopic imbalances or other genetic defects [52, 53]. The de novo CCRs appear to be mostly of paternal origin. This hypothesis agrees with the epidemiological finding that most of the prenatally diagnosed BCCRs are maternal in origin (70% maternal versus 30% paternal) and that 80% of de novo structural abnormalities found in newborns are of paternal origin [2]. These

Table 3 A list of published cases of complex chromosome rearrangement including chromosomes 1, 8, and 11

CCR cases, including chromosome 1	<p>Borg K, Nowakowska B. (2007) t(<i>I</i>;5;7) (p32.1;q14.3;p21.3) [24]</p> <p>Li L, Heng X, et al. (2013) t(<i>I</i>;3;13) [25]</p> <p>van Bisbergen E et al. (2012) t(<i>I</i>;3;5) [26]</p> <p>Kirkpatrick G, Ma S. (2012) t(<i>I</i>;2;10) [27]</p> <p>Godo A, Blanco J, et al. (2013) t(<i>I</i>;8;2) (q42;p21;p15) [28]</p> <p>Loup V, Bernicot J, et al. (2010) t(<i>I</i>;19;13) (p31;q13.2;q31) [29]</p> <p>Salahshourifar I, Shahrokhshahi N et al. (2009) t(<i>I</i>;22;4) (p22.3;q11.1;q31.1) [30]</p> <p>Bartels I, Starke H et al. (2007) t(<i>I</i>;3;9;14) [31]</p> <p>Smigiel R, Laczmanska I et al. (2007) t(<i>I</i>;4;10;12;20) [32]</p> <p>Cui YX, Wang YM et al. (2004) t(<i>I</i>;5;12) (q25;q24;p11) [33]</p> <p>Melo DG, Huber J et al. (2004) t(<i>I</i>;2;3;4;12) [34]</p> <p>Curotti G et al. (1999) t(<i>I</i>;7;10;21) [35]</p> <p>Sawicka A, Lesniewicz R et al. (1998) t(<i>I</i>;4;10) (q21.3; q27; q26.1) [36]</p> <p>Johannesson T, et al. (1998) t(<i>I</i>;4;16) [37]</p> <p>Gibson LH, McGrath J, Yang-Feng TL (1997) t(<i>I</i>;5;2) (q42.3;q23.2;q35) [38]</p> <p>Barros A, et al. (1987) t(<i>I</i>;19;6;14) (1p11; 19p11; 6q25; 14q21) [39]</p> <p>Seabright M et al. (1978) t(X;<i>I</i>;7;13) [40]</p>
CCR cases, including chromosome 8	<p>Guilherme RS, et al. (2013) t(3; 6; 8; 14) [41]</p> <p>Karmous-Benaïly H et al. (2006) t(8;3;11;16) [10]</p> <p>Berend SA, et al. (2002) t(3;8;16) [42]</p> <p>Batista DA et al. (1994) t(7;8;13) [43]</p> <p>Masuno M, et al. (1993),t(8;12) (9;12) (q23; q12; q32;p23) [44]</p> <p>Ten SK, Chin YM et al. (1987) t (6;8;9) (q27;p23;q32;q13) [45]</p>
CCR cases, including chromosome 11	<p>Goumy S et al. (2006) t(8;6;<i>II</i>) (q21;q14;q23;q12) [46]</p> <p>Kleczkowska A et al. (1988) t(<i>II</i>;13;21) [47]</p> <p>Al-Awadi SA, et al. (1985) t(<i>II</i>;13;14;18) [10]</p>

observations are also in good concordance with the biological finding of a higher rate of structural chromosome aberrations in human male gametes [2]. This has led to the assumption that CCRs could arise preferentially during spermatogenesis and are mainly transmitted in families through oogenesis [2]. Most of the male carriers of balanced de novo CCRs are diagnosed because of infertility troubles [54], although a few cases of fertile carriers have been reported [55].

Different published findings suggest that the risk of phenotype alterations increases with the number of chromosomes involved, as well as with the number of break points [56].

Case presentation

The proband is a 31-year-old female, who has been referred to the in vitro fertilization unit due to fertility issues. She has been a patient of a reproductive clinic since 2014, and she underwent three consecutive cycles of fertility treatment—intracytoplasmic sperm injection (ICSI) due to a male

infertility factor. Her husband, a 33-year-old male, underwent a semen analysis, resulting in asthenozoospermia.

The ICSI procedure involves the injection of a single spermatozoa directly into a mature oocyte. The procedure begins with controlled ovarian hyper-stimulation that aims to supply enough oocytes with normal maturation and to ensure that the consequent assisted reproductive procedures will work effectively, which considerably increases the pregnancy rate [57]. The next step is aspiration of the follicles. This is indicated when the dominant ones reach a diameter over 18 mm, the thickness of the endometrium is over 8 mm, and the level of estradiol in the blood corresponds to the number of follicles. Fertilization occurs next when a motile sperm is selected for insemination, followed by oocyte maturity assessment when the cumulus cells are removed by an enzyme (hyaluronidase) [57]. Metaphase II oocytes (MII) only can be injected with ICSI. Only normally fertilized zygotes with clearly visible two pronuclei (2PN) at 16–20 h post insemination are cultured for potential future use. Depending on oocyte count, female age, cleavage rate, and type of infertility, the preimplantation embryos could be replaced by embryo transfer (ET). Two to

5 days later, the elected embryos for ET are gently loaded into a transfer catheter with a small amount of media and are slowly released under ultrasound guidance into the uterus. The spare good-quality embryos are frozen for potential use. A pregnancy blood test will be performed approximately 10 days after the embryo transfer [58].

The patient underwent three consecutive ICSI procedures and two frozen embryo transfers (FET). The first one took place in 2014, but no pregnancy was observed (Fig. 1a). A (FET) was performed few months later (Fig. 1b). It resulted only in a positive blood test for the human chorionic gonadotrophin hormone (hCG) on day 10th post FET. Subsequently, a pregnancy did not develop, since a gestational sac was not detected on ultrasound scanning at 7 week of gestation. In addition, the patient underwent a second ICSI procedure in 2015, reporting no pregnancy (Fig. 1c) and a third ICSI cycle in 2016, where the same result was obtained (Fig. 1d). Additionally, another FET was performed, resulting with an unsuccessful pregnancy (Fig. 1e selected embryos for FET).

The patient had no other relevant medical issues. However, there have been reports of reproductive failures within the family, as seen in Fig. 2. The patient's mother has had five

failed pregnancies and the patient's brother had also experienced three unsuccessful reproductive outcomes.

Results

Cytogenetic analysis was carried out on our patient's 20 metaphase cells from peripheral blood cultures, using standard procedures and GTG banding. According to ISCN 2013 [59], 460-band level analysis undertaken on metaphase chromosomes from the proband, showed the following unbalanced karyotype: 46,XX,t(1;8;11)(p31;q13;q23) (8qter→8q13::1p31→1qter;8pter→8q13::11q23→11qter;11pter→11q23::1p31→1pter) (Fig. 3). The patients' husband karyotype was normal. Additionally, the proband's mother and brother were analyzed, using the same technique, resulting in the same pattern (Fig. 4a, b).

Discussion

The simplest explanation for the underlying mechanism of CCRs could be that CCRs originate from three coincidental

Fig. 1 a–e Embryos that have been selected and transferred in three consecutive cycles of ICSI procedures

Fig. 2 Patient's Pedigree, showing the carriers of the complex chromosome translocation in the family (*dark symbols*) and miscarriages (*small dark circles*); offsprings with unknown gender

classical translocations. Several studies have been exploring the hypothesis that such an aberration is produced by multiple chromosome breakages and formation of derivative chromosomes within a single cell division [60, 61]. Cases of CCRs that involve the same set of chromosomes, specifically chromosomes 1, 8, and 11 have not been reported to this date (Table 1). The difficulty of analysis of the meiotic behavior and consequences of CCRs is mainly due to limited data concerning the meiotic segregation of CCRs. Useful information regarding a pregnancy outcome have been given in 1988, when Gorski et al. [49] collected data on 67 pregnancies in 25 families where CCRs were identified. They found an overall

incidence of 48.3% being spontaneous abortions, then 57.3% being abnormal pregnancy outcomes, including 18.4% with malformation in live born children. Also, Batista et al. reviewed 63 karyotyped individuals from CCR carriers' families [43]. Among them, 27% subjects had normal karyotypes, 31.7% were balanced carriers, and 41.3% displayed an unbalanced karyotype. In accordance with Gorski's data, the authors reported a 50% risk of miscarriage. Maddan et al. [5] reviewed 60 familial and de novo cases of balanced CCRs, and also estimated that carriers have 50% risk of spontaneous abortions and a 20% risk of having an offspring with unbalanced karyotype. Among these 60 cases, 27 with postnatal detection

Fig. 3 Patient's karyotype—46,XX,t(1;8;11)(p31;q13;q23) (8qter→8q13::1p31→1qter;8pter→8q13::11q23→11qter;11pter→11q23::1p31→1pter)

Fig. 4 Patient's brother karyotype (a) and patient's mother karyotype (b), both presenting the same chromosome rearrangement

showed 48% normal individuals and 52% phenotypically abnormal subject. A successful pregnancy is rare, because of the risk for an abnormal conception due to malsegregation of derivative chromosomes or generation of recombinant chromosomes.

Several reported familial CCRs described mostly unbalanced karyotypes [32, 62, 63]. According to the structure of the CCRs, the meiotic segregation can be explained using the classification introduced by Kausch et al. [63]. The three-way exchange type of CCRs would form a hexavalent configuration, during meiosis I. This configuration allows the efficient synapsis of the six chromosomes involved in the complex rearrangement. For such three-way CCRs, the modes of

meiotic segregation are theoretically 3:3, 4:2, 5:1, and 6:0, producing a large variety of imbalances [4]. If the disjunction is symmetric (i.e., 3:3 mode), 2 (normal and balanced) chromosomal combinations can occur and 18 unbalanced combinations. If the disjunction is asymmetric (modes 4:2, 5:1, or 6:0), 44 extremely unbalanced different gametes can be produced (30 types for 4:2, 12 for 5:1, and 2 for 6:0, respectively) [4]. The chromosome segregation in this particular translocation is presented in Table 1.

There are four possible pregnancy outcomes for the CCR carrier: a live born infant with unbalanced chromosomes, an offspring carrying the CCR, a live born child with normal chromosomes or abortion, according to Gorski et al. [49].

Since the large chromosome aberrations usually lead to miscarriages, here we describe only the clinical findings associated with milder imbalances which could survive till birth and cause malformative syndromes (Table 2). Considering that the majority of familial CCRs are transmitted through female carriers, the production of a phenotypically normal child indicates that human oogenesis can handle the complexity of CCRs [23]. In this particular case, the transmission is proved to be maternal (Fig. 2). The lack of transmission through males is mainly due to the impairment of spermatogenesis, commonly associated with CCRs and resulting in sterility or subfertility [64]. However, male transmission of CCRs has been reported in a few rare cases [23, 64, 65]. In such cases, ICSI procedure is suggested as a resolution for the impaired spermatogenesis in male CCRs carriers. A successful result was obtained in the case of a three-way CCR initially diagnosed as a simple balanced reciprocal translocation [66]. Despite the altered patient's karyotype, the couple rejected a preimplantation genetic screening (PGS) to be performed due to a lack of financial resources and a poor possibility of acquiring an euploid blastocyst, which would have been suitable for biopsy. They have decided to proceed with the assisted reproductive techniques without PGS, therefore undergoing a fourth cycle of ICSI procedure.

Balanced CCRs must be extensively investigated to ensure that the fetal CCRs is indeed balanced and to rule out any rearrangements which could potentially cause genetic malformations. A PGS has been suggested as a strategy for couples with CCRs in terms of resolving the problem with repeated pregnancy loss, birth of an infant with unbalanced karyotype, and malformations in live born children [67]. The goal is to select a genetically balanced embryo which if acquired would be appropriate for transfer and, therefore, to increase the chances of a successful pregnancy and a healthy child. The literature has reported successful pregnancies using a PGS in patients with CCRs [68]. A healthy live birth has been reported after four cycles of PGS in three patients, also with recurrent miscarriages [68]. Additionally, the use of microarray technologies should be taken under consideration in genetic counseling for further prenatal cases of BCCRs and the potential detection of most possible imbalances. Furthermore, the advances in genomic technologies, in particular whole genome sequencing, have been proven useful in defining the pathogenic mechanisms of the complex chromosomal rearrangements [69]. Studies of breakpoints in translocations revealed the most common underlining structural variations, leading to an inter-chromosomal exchange. Genomic repeats of different types, such as long interspersed nuclear elements (LINE), human endogenous retrovirus (HERV) repeats, shorter paralogous repeats, or Alu repeats and segmental duplications can cause, to a high extent, various genomic

rearrangements based on sequence identity [70]. In these cases, a non-allelic homologous recombination (NAHR) is the main mutational mechanism. The absence of sequence homology points to rearrangements by non-homologous end-joining (NHEJ). Inserted or inverted sequences at breakpoints are suggested to be the cause for a microhomology-mediated break-induced replication (MMBIR) in the pathogenesis of translocations [70]. NAHR between homologous sequences on different chromosomes, like palindromic AT-rich repeats at chromosomes 3, 8, 11, 17, and 22, is the reason for recurrent chromosomal translocations [70]. However, most of the constitutional chromosome translocations are non-recurrent, as is the translocation represented in this case. In addition, the involvement of more than two chromosomes in a translocation has a much more complex mechanism. Some cases of CCRs are explained by chromothripsis, which is determined as the presence of multiple breakpoints per genome [71]. The chromosome shattering occurs at once, in the germline, as it was suggested to be event of male germline mostly. Intensive studies of breakpoints in complex translocations involving three or more different chromosomes revealed they are likely formed via chromothripsis [71]. This is especially the mechanism underlying de novo complex rearrangements, where shattered chromosomal fragments are joined in the formation of translocation. Regarding this case, the visible breakpoints are three, as described in the patient's karyotype 46,XX,t(1;8;11)(p31;q13;q23), but only NGS analysis could resolve the real number of fusion points between regions of these chromosomes. Kloosterman et al. [72] reported triple chromosomes translocation t (1, 4, and 10) with 12 fusion points between regions on these chromosomes and proved a chromothriptic genomic rearrangement. The most severe form of a genomic reorganization is called "chromoanagenesis," which has recently become a point of interest.

Genetic counseling for families with CCR is difficult mainly because of the risk of imbalances in the karyotype which depends on the variations in the number of chromosomes involved and the number of breakpoints. Each carrier has a different reproductive risk; therefore, a precise prevalence cannot be established.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

- Madan K. Balanced complex chromosome rearrangements: reproductive aspects. A review. *Am J Med Genet Part A*. 2012;158A:947–63.
- Pellestor F, Anahory T, Lefort G, Puechberty J, Liehr T, Hedon B, et al. Complex chromosomal rearrangements: origin and meiotic behavior. *Hum Reprod Update*. 2011;17(4):476–94.
- Lespinasse J, North MO, Paravy C, Brunel MJ, Malzac P, Blouin JL. A balanced complex chromosomal rearrangement (BCCR) in a family with reproductive failure. *Hum Reprod*. 2003;18(10):2058–66.
- Gardner RJM, Sutherland GR, Lisa G. Shaffer, chromosome abnormalities and genetic counselling. UK: Oxford University Press; 2012.
- Madan K, Nieuwint AWM, van Bever Y. Recombination in a balanced complex translocation of a mother leading to a balanced reciprocal translocation in the child. Review of 60 cases of balanced complex translocations. *Hum Genet*. 1997;99(6):806–15.
- De Gregory M, Ciccone R, Magini P, Pramparo T, Gimelli S, Messa J, et al. Cryptic deletions are a common finding in “balanced” reciprocal and complex chromosome rearrangements: a study of 59 patients. *J Med Genet*. 2008;44(12):750–62.
- Timar L, Be res J, Kosztolanyi G, Ne meth I. De novo complex chromosomal rearrangement in a woman with recurrent spontaneous abortion and one healthy daughter. *Hum Genet*. 1991;86:421.
- Kotzot D, Holland H, Koehler M, Froster UG. A complex chromosome rearrangement involving chromosome 8, 11, and 12 analyzed by conventional cytogenetic investigations, fluorescence in situ hybridization, and spectral karyotyping. *Ann Genet*. 2001;44:135–8.
- Lazarczyk E, Drozniewska M, Pasinska M, Stasiewicz-Jarocka B, Midro AT, Haus O. Complex balanced chromosomal translocation t(2;5;13)(p21;p15;q22) in a woman with four reproductive failures. *Mol Cytogenet*. 2014;7:83.
- Karmous-Benailly H, Giuliano F, Massol C, Bloch C, De Ricaud D, Lambert J-C, et al. Unbalanced inherited complex chromosome rearrangement involving chromosome 8, 10, 11 and 16 in a patient with congenital malformations, and delayed development. *Eur J Med Genet*. 2006;49(5):431–8.
- Chen C, Wang T, Lin C-C, Tsai F, Hsieh L, Wang W. Prenatal diagnosis of partial trisomy 3p (3p21→pter) and Partial Monosomy 11q (11q23→qter) associated with abnormal sonographic findings of holoprosencephaly, orofacial clefts, pyelectasis and a unilateral duplex renal system. *J Formos Med Assoc*. 2008;107(10):822–6.
- Zou P-S, Li H-F, Chen L-S, Ma M, Chen X-H, Xue D et al. A rare case of trisomy 11q23.3-11q25 and trisomy 22q11.1-22q11.21. *Genet. Mol. Res*. 2016;15(2). doi:10.4238/gmr.15028140.
- Okano Y, Osasa Y, Yamamoto H, Hase Y, Tsuruhara T, Fujita H. An infant with Beckwith-Wiedemann syndrome and chromosomal duplication 11p13→pter.: correlation of symptoms between 11p trisomy and Beckwith-Wiedemann syndrome. *Jpn J Hum Genet*. 1986;31:365–72.
- Amouroux C, Vincent M, Blanchet P, Puechberty J, Schneider A, Chaze AM, et al. Duplication 8q12: confirmation of a novel recognizable phenotype with duane retraction syndrome and developmental delay. *Eur J Hum Genet*. 2012;20:580–3. published online 18 January 2012.
- Rodewald A, Stengel-Rutkowski S, Schulz P, Cleve H. New chromosomal malformation syndromes. I. Partial monosomy 8p. An attempt to establish a new chromosome deletion syndrome. *Eur J Pediatr*. 1977;125(1):45–57.
- Guanti G, Mollica G, Polimeno L, Maritato F. rDNA and acrocentric chromosomes in man. I. rDNA levels in a subject carrier of a 8p/13p balanced translocation and in his unbalanced son. *Hum Genet*. 1976;33(2):103–7.
- Mahjoubi F, Totian S, Kareeme S, Shafegate Y. Trisomy 8p (p11.2-pter) due to maternal translocation t(8;13)(p11;p12) in a child with dysmorphic features. *Indian J. Hum. Genet*. 2005; 11 2.
- Plomp AS, Engelen JJ, Albrechts JC, de Die-Smulders CE, Hamers AJ. Two cases of partial trisomy 8p and partial monosomy 21q in a family with a reciprocal translocation (8;21)(p21.1;q22.3). *Med Genet*. 1998;35(7):604–8.
- Baroncini A, Bertuzzo S, Quarantini R, Ricciardelli P, Giorda R, Bonaglia MC. 8q12 microduplication including CHD7: clinical report on a new patient with Duane retraction syndrome type 3. *Mol Cytogenet*. 2013. 6(1):49. doi: 10.1186/1755-8166-6-49.
- Schurmann M, Wethling H, Niemeyer ML, Schwinger E. Familial chromosome translocation (1;5;15) as a cause of partial trisomy 1p. *Klin Padiatr*. 1987;199(1):27–31.
- Gorlin RJ, Cohen Jr. MM, Hennekam RCM. Syndromes of the head and neck. Oxford Monogr Med Gent 2001; 42
- Shapira SK, McCaskill C, Northrup H, Spikes AS. Chromosome 1p36 deletions: the clinical phenotype and molecular characterization of a common newly delineated syndrome. *Am J Hum Genet*. 1997;61(3):642–50.
- Salahshourifar I, Shahrokhshahi N, Tavakolizadeh T, Beheshti Z, Gourabi H. Complex chromosomal rearrangement involving chromosomes 1, 4 and 22 in an infertile male: case report and literature review. *J Appl Genet*. 2009;50:69–72.
- Borg K, Nowakowska B, Obersztyn E, Cheung SW, Brycz-Witkowska J, Korniszewski L, et al. Complex balanced translocation t(1;5;7)(p32.1;q14.3;p21.3) and two microdeletions del(1)(p31.1p31.1) and del(7)(p14.1p14.1) in a patient with features of Greig cephalopolysyndactyly and mental retardation. *Am J Med Genet Part A*. 2007;143A:2738–43.
- Li L, Heng X, Yun W, Zheng S, Zhang J, Fan W. Familial complex chromosome rearrangement (CCR) involving 5 breakpoints on chromosomes 1, 3 and 13 in a severe oligozoospermic patient. *J Assist Reprod Genet*. 2013;30(3):423–9. doi:10.1007/s10815-013-9934-z.
- van Binsbergen E, Hochstenbach R, Giltay J, Swinkels M. Unstable transmission of a familial complex chromosome rearrangement. *Am J Med Genet A*. 2012;158A(11):2888–93. doi:10.1002/ajmg.a.35580.
- Kirkpatrick G, Ma S. Meiotic segregation and interchromosomal effects in a rare (1:2:10) complex chromosomal rearrangement. *J Assist Reprod Genet*. 2012;29(1):77–81. doi:10.1007/s10815-011-9655-0.
- Godo A, Blanco J, Vidal F, Parriego M, Boada M, Anton E. Sequential FISH allows the determination of the segregation outcome and the presence of numerical anomalies in spermatozoa from a t(1;8;2)(q42;p21;p15) carrier. *J Assist Reprod Genet*. 2013;30(9):1115–23. doi:10.1007/s10815-013-0063-5.
- Loup V, Bernicot I, Janssens P, Hedon B, Hamamah S, Pellestor F, et al. Combined FISH and PRINS sperm analysis of complex chromosome rearrangement t(1;19;13): an approach facilitating PGD. *Mol Hum Reprod*. 2010;16(2):111–6. doi:10.1093/molehr/gap105.
- Salahshourifar I, Shahrokhshahi N, Tavakolizadeh T, Beheshti Z, Gourabi HJ. Complex chromosomal rearrangement involving chromosomes 1, 4 and 22 in an infertile male: case report and literature review. *Appl Genet*. 2009;50(1):69–72. doi:10.1007/BF03195655.
- Bartels I, Starke H, Argyriou L, Sauter SM, Zoll B, Liehr T. An exceptional complex chromosomal rearrangement (CCR) with eight breakpoints involving four chromosomes (1;3;9;14) in an azoospermic male with normal phenotype. *Eur J Med Genet*. 2007;50(2):133–8.
- Smigiel R, Laczanska I, Sasiadek M. Maternal complex chromosome rearrangements involving five chromosomes 1,4,10, 12 and

- 20 ascertained through a del(4)(p14p15) detected in a mother's first affected daughter. *Clin Dysmorphol.* 2007;16(1):63–4.
33. Cui YX, Wang YM, Yao B, Huang YF. A de novo complex chromosomal rearrangement including translocation on 1,5 and 12 in a female carrier with her healthy girl. *Yi Chuan.* 2004;26(5):612–4.
 34. Melo DG, Huber J, Giuliani LR, Mazzucatto LF, Riegel M, Pina-Neto JM. De novo complex chromosome rearrangement: a study of two patients. *Genet Couns.* 2004;15(3):303–10.
 35. Curotti G, Benkhalifa M, Raybaud C, Picard F, Bellec V, Qumsiyeh MB. De novo highly complex chromosome rearrangement (CCR) involving five breakpoints with congenital anomalies analyzed by FISH. *Genet Couns.* 1999;10(3):259–64.
 36. Sawicka A, Leńiewicz R, Zawada M, Stasiewicz-Jarocka B, Midro AT. Familial complex chromosome translocation of t(1;4;10)(q21.3;q27;q26.1) verified by FISH. *Ginek Pol.* 1998;69(4):200–6.
 37. Johannesson T, Ehlers S, Wahlström J. Complex chromosome rearrangement involving chromosomes 1, 4 and 16 revealed by fluorescence in situ hybridization. *J Clin Genet.* 1997;51(4):281–5.
 38. Gibson LH, McGrath J, Yang-Feng TL. A complex chromosome rearrangement with at least five breakpoints studied by fluorescence in situ hybridization. *Am J Med Genet.* 1997;68(4):417–20.
 39. Barros A, Tavares MC, Castedo S, Pereira MS, Tavares MP, Almeida e Costa M. A complex balanced chromosomal rearrangement in repeated abortions. *Hum Genet.* 1987;75(4):388–90.
 40. Seabright M, Gregson N, Pacifico E, Mould S, Ryde J, Pearson J, et al. Rearrangements involving four chromosomes in a child with congenital abnormalities. *Cytogenet Cell Genet.* 1978;20(1–6):150–4.
 41. Guilherme RS, Cernach MC, Sfakianakis TE, Takeno SS, Nardoza LM, Rossi C, et al. A complex chromosome rearrangement involving four chromosomes, nine breakpoints and a cryptic 0.6-Mb deletion in a boy with cerebellar hypoplasia and defects in skull ossification. *Cytogenet Genome Res.* 2013;141(4):317–23. doi:10.1159/000353302.
 42. Berend SA, Bodamer OA, Shapira SK, Shaffer LG, Bacino SA. Familial complex chromosomal rearrangement resulting in a recombinant chromosome CA. *Am J Med Genet.* 2002;109(4):311–7.
 43. Batista DAS, Pai GS, Stetten G. Molecular analysis of a complex chromosomal rearrangement and a review of familial cases. *Am J Med Genet.* 1994;53(3):255–63.
 44. Masuno M, Asano J, Yasuda K, Kondo T, Orii T. Balanced complex rearrangement involving chromosomes 8, 9, and 12 in a normal mother, derivative chromosome 9 with recombinant chromosome 12 in her daughter with minor anomalies. *Am J Med Genet.* 1993;45(1):65–7.
 45. Ten SK, Chin YM, Tan SK, Hassan K. Three cases of partial trisomy 9q in one generation due to maternal reciprocal t(6;8;9) translocation. *Clin Genet.* 1987;31(6):359–65.
 46. Kleczkowska A, Fryns JP, Jaeken J, Van den Berghe H. Complex chromosomal rearrangement involving chromosomes 11, 13 and 21. *Ann Genet.* 1988;31(2):126–8.
 47. Al-Awadi SA, Teebi AS, Sundareshan TS. Complex chromosomal rearrangement involving chromosomes 11, 13, 14 and 18 resulting in monosomy for 13q32—qter. *Ann Genet.* 1985;28(3):181–4.
 48. de Vree PJP, Simon MEH, van Dooren MF, Stoevelaar GHT, Hilkmann JTH, Rougen MA, et al. Application of molecular cytogenetic techniques to clarify apparently balanced complex chromosomal rearrangements in two patients with an abnormal phenotype: case report. *Mol Cytogenet.* 2009;2:15.
 49. Gorski JL, Kistenmacher ML, Punnett HH, Zackai EH, Emanuel BS. Reproductive risks for carriers of complex chromosome rearrangements: analysis of 25 families. *Am J Med Genet.* 1988;29:247–61.
 50. Benzacken B, Siffroi JP, Straub B, Le Bourhis C, Sauvion S, Gaudelus J, et al. Case report: advanced paternal age and de-novo complex chromosomal rearrangement in offspring. *Hum Reprod.* 1998;13(7):1801–3.
 51. Zhang F, Carvalho CMB, Lupski JR. Complex human chromosomal and genomic rearrangements. *Trends Genet A.* 2009;25:298–307.
 52. Patsalis PC. Complex chromosomal rearrangements. *Genet Couns.* 2007;18:57–69.
 53. Kumar A, Becker LA, Depinet TW, Haren JM, Kutz CL, Robin NH, et al. Molecular characterization and delineation of subtle deletions in de novo 'balanced' chromosomal rearrangements. *Hum Genet.* 1998;103:173–8.
 54. Scott Sills E, Kim JJ, Witt MA, Palermo GD. Non-obstructive azoospermia and maturation arrest with complex translocation 46, XY t(9;13;14)(p22;q21;p13) is consistent with the Luciano-Guo hypothesis of latent aberrant autosomal regions and infertility. *Cell Chromosome.* 2005;4:2–5.
 55. Karadeniz A, Mrasek K, Weise A. Further delineation of complex chromosomal rearrangements in fertile male using multicolor banding. *Mol Cytogenet.* 2008;1:17.
 56. Giardino D, Corti C, Ballarati L, Finelli P, Valtorta C, Botta G, et al. Prenatal diagnosis of a de novo complex chromosome rearrangement (CCR) mediated by six breakpoints, and a review of 20 prenatally ascertained CCRs. *Prenat Diagn.* 2006;26:565–70.
 57. Timeva T, Milachich T, Antonova I, Arabaji T, Shterev A, Omar H. Correlation between number of retrieved oocytes and pregnancy rate after in vitro fertilization/intracytoplasmic sperm injection. *Sci World J.* 2006;6:686–90.
 58. Schoolcraft WB. Importance of embryo transfer technique in maximizing assisted reproductive outcomes. *Fertil Steril.* 2016;105(4):855–60. Fertilization/IntraCytoplasmic Sperm Infec-tion.
 59. Shaffer LG, Slovak ML, Campbell LJ. An International system for human cytogenetic nomenclature. Basel: S Karger; 2013.
 60. Seller MJ, Bint S, Kavalier F, Brown RN, Mackie Ogilvie C. Multicolor banding detects a complex three chromosome, seven breakpoint unbalanced rearrangement in an ICSI-derived fetus with multiple abnormalities. *Am J Med Genet.* 2006;140:1102–7.
 61. Kuechler A, Ziegler M, Blank C, Rommel B, Bullerdiek J, Ahrens J, et al. A highly complex chromosomal rearrangement between five chromosomes in a healthy female diagnosed in preparation for intracytoplasmic sperm injection. *J Histochem Cytochem.* 2005;53(3):355–7.
 62. Meer B, Wolff G, Back E. Segregation of a complex rearrangement of chromosomes 6, 7, 8, and 12 through three generations. *Hum Genet.* 1981;58(2):221–5.
 63. Kausch K, Haaf T, Kohler J, Schmid M. Complex chromosomal rearrangement in a woman with multiple miscarriages. *Am J Med Genet.* 1988;31:415–420.27.
 64. Lee IW, Su MT, Hsu CC, Lin YH, Chen PY, Kuo PL. Constitutional complex chromosomal rearrangements in azoospermic men—case report and literature review. *Urology.* 2006;68:1343.e5–8.
 65. Grasshoff U, Singer S, Liehr T, Starke H, Fode B, Schoëning M, et al. A complex chromosomal rearrangement with a translocation 4;10;14 in a fertile male carrier: ascertainment through an offspring with partial trisomy 14q21-q22 and partial monosomy 4q27-q28. *Cytogenet Genome Res.* 2003;103:17–23.
 66. Joly-Helas G, De La Rochebrochard C, Mousset-Simeon N, Moirot H, Tiercin C, Romana SP, et al. Complex chromosomal rearrangement and intracytoplasmic sperm injection: a case report. *Hum Reprod.* 2007;22:1292–7.
 67. Escudero T, Estop A, Ficher J, Munne S. Preimplantation genetic diagnosis for complex chromosome rearrangements. *Am J Med Genet A.* 2008;146:1662–9.
 68. Lim CK, Cho JW, Kim JY, Kang IS, Shim SH, Jun JH. A healthy live birth after successful preimplantation genetic diagnosis for carriers of complex chromosome rearrangements. *Fertil Steril.* 2008;90:1680–4.

69. Weckselblatt B, Rudd MK. Human structural variation: mechanisms of chromosome rearrangements. *Trends Genet.* 2015;31(10):587–99.
70. Kato T, Kurahashi H, Emanuel BS. Chromosomal translocations and palindromic AT-rich repeats. *Curr Opin Genet Dev.* 2012;22(3):221–8.
71. Weckselblatt B, Hermetz KE, Rudd MK. Unbalanced translocations arise from diverse mutational mechanisms including chromothripsis. *Genome Res.* 2015;25(7):937–47.
72. Kloosterman WP, Guryev V, van Roosmalen M, Duran KJ, de Bruijn E, Bakker SC, et al. Chromothripsis as a mechanism driving complex de novo structural rearrangements in the germline. *Hum Mol Genet.* 2011;20(10):1916–24.