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Fatal Outcome in a Newborn Calf Associated with Partial Trisomy 25q and Partial Monosomy 11q, 60,XX,der(11)t(11;25)(q11;q14 ~ 21)

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Abstract

A newborn calf of the Agerolese cattle breed underwent clinical cytogenetic investigation because of hyperflexion of the forelimbs, red eyes and the inability to stand. Anamnesis revealed that the mother, phenotypically normal, carried a chromosomal aberration. The newborn died after 2 weeks, and no remarkable alterations were found by the veterinarian on postmortem examination. The mother was a carrier of a reciprocal balanced translocation rcp(11; 25)(q11,q14 ∼ 21) detected after a cytogenetic investigation in 2011; however, the analysis of the newborn revealed a different chromosomal aberration with partial trisomy of chromosome 25 and partial monosomy of chromosome 11. In fact, the results showed both chromosomes 25, one chromosome 11 and only one long derivative chromosome (der11). FISH analysis, performed using BAC clones, confirmed the chromosomes and their regions involved. Finally, both the localization of the breakpoints on band q11 (centromere) of chromosome 11 and band q14–21 of chromosome 25, and the complete loss of the der25 identified the aberration as an unbalanced translocation 60,XX,der(11)t(11; 25)(q11;q14 ∼ 21). A comparison with human chromosomes was also performed to search for similarities and possible genes involved in order to study their effects, thus extending the knowledge of these aberrations by case reports.

Key Words

Agerolese cattle breed, Chromosomal aberrations, Fatal disease, FISH analysis

INTRODUCTION

Case reports represent a relevant, timely, and important study design in advancing medical scientific knowledge, especially for animals where the majority of chromosomal aberrations are not detected. Individuals with balanced reciprocal translocations are usually associated with a normal phenotype, fertility problems [Molteni et al., 2007; Ducos et al., 2008] and formation of unbalanced gametes that give rise to unbalanced aberrations characterized by an abnormal phenotype, abortion or death after birth [Villagómez and Pinton, 2008]. For this reason, the cytogenetic screening results appear to be the best option to select animals free from chromosomal aberrations.

Robertsonian translocations and reciprocal translocations are responsible for significant economic losses [Dyrendahl and Gustavsson, 1979; Schmutz et al., 1991, 1997; Lonergan et al., 1994; Mäkinen et al., 1997; Ducos et al., 2008; Rodríguez et al., 2010]; thus, their identification in animals intended for reproduction represents an important step in modern genetic selection programs.

In cattle, the most commonly detected chromosome abnormalities are the Robertsonian or centric-fusion translocations [for reviews, see Ducos et al., 2008; Iannuzzi et al., 2009]. In fact, according to De Lorenzi et al. [2012], only 16% of reciprocal translocations can be detected using simple Giemsa techniques, and consequently, they could be present in <0.14% of cattle subjects, a frequency 5× higher than that shown by de novo Robertsonian translocations, making the frequency of reciprocal translocations very undervalued.

At present, only few cases of reciprocal translocations have been reported in cattle (table 1), probably because of the difficulty in detecting this type of abnormality when chromosomes are conventionally stained, as suggested by De Lorenzi et al. [2012]. Indeed, routine Giemsa standard staining allows the identification of reciprocal translocations only in the presence of chromosomes that are longer or shorter than the largest and smallest chromosome.

In this clinical case, we have set an example of how a balanced translocation gives rise to an unbalanced karyotype incompatible with life.

The aims of this study were: (a) to report a fatal chromosomal aberration detected in a female newborn of the Agerolese cattle breed; (b) to highlight how a balanced chromosomal aberration can generate in the progeny by a wrong meiotic disjunction an unbalanced chromosomal constitution incompatible with adult life; (c) to analyse cytogenetic findings between the cow/calf aberration; (d) to underline the abnormal gametogenesis that has generated the unbalanced zygote, and (e) to perform a comparison with human chromosomes to identify genes likely involved in the reported aberration and its association to potential diseases.

Materials and Methods

Animal

A newborn calf of the Agerolese cattle breed from the ConSDABI (Sub-National Focal Point of FAO – Mediterranean Biodiversity) center underwent cytogenetic investigation because of hyperflexion of the forelimbs, red eyes and the inability to stand (fig. 1 A). Anamnesis revealed that the mother, phenotypically normal, was a carrier of a t(11; 25)(q11,q14 ~ 21) [Perucatti et al., 2011].

Cell Cultures

Peripheral blood samples were cultured in RPMI medium enriched with fetal calf serum (10%), antibiotic-antimycotic mixture (1%), L-glutamine (1%) and concanavalin A (15 μg/ml). Two types of cell cultures were conducted: either without adding any base analog (normal cultures) or with BrdU to obtain an R-banding (by late incorporation of BrdU) pattern as follows. BrdU (15 μg/ml) and Hoechst 33258 (30 μg/ml) were added 6 h before the end of the cell culture, whereas the colcemid treatment (0.1 μg/ml) was performed for the last hour. Chromosome preparations were obtained by hypotonic treatment and 3 successive fixations in methanol/ acetic acid (3: 1).

Banding Techniques

Slides obtained from normal and BrdU-treated cells were used to perform CBA- and RBA-banding, respectively. Chromosomes were also treated with sequential RBA- and Ag-NOR techniques. Details concerning these techniques can be found in Iannuzzi and Di Berardino [2008].

Probes Used

BACs belonging to the INRA bovine BAC library [Eggen et al., 2001] were used as probes: in particular, the BAC 533C11 located on BTA11q12 (our result), the BAC 142G06 on BTA25q14 (our result) and the BAC 533H08 containing the ISCNDB reference marker of BTA25 *(ELN)* located on BTA25q22 [Hayes et al., 2000; ISCNDB 2000, 2001]. DNA isolation was performed using CHORI- (Children's Hospital Oakland Research Institute) recommended protocol, whereas the labeling was accomplished with biotin and digoxigenin using the nick-translation kit (Roche Applied Science Inc.).

FISH Mapping

FISH analysis was performed with the same 3 BAC clones used to detect the translocation in the mother, according to the previously reported protocol [Iannuzzi and Di Berardino, 2008]. Rbanded slides were treated for FISH with BAC clones overnight in the presence of bovine COT-l DNA and sonicated salmon sperm allocated in a moist chamber. After detection steps with FITCavidin and TRIC-anti-digoxigenin antibody, chromosomes were counterstained with Vectashield DAPI H-1500 in Vectashield H-1000 (Vector Lab) antifade solution. R-banding metaphases, fluorescent FITC and TRIC signals were separately captured by a CCD-camera (Photometrics, cool SNAP, Nikon) and processed by superimposing FITC and TRIC signals on RB-banding preparations. Thirty metaphase plates for each probe were analyzed, and chromosome identification was performed according to ISCNDB 2000 [2001].

Results

The calf was delivered vaginally and showed a hyperflexion of the forelimbs, red eyes and the inability to stand; the mother, born in 2008, seconded after about 2 h of birth. Its parents were an Agerolese cattle breed (mother) carrying the reciprocal translocation 11; 25 (inbreeding coefficient *F* = 0.0234) and an Agerolese bull breed (inbreeding coefficient *F* = 0). They had the relationship coefficient of 0.23438. Furthermore, the mother, underwent 6 cycles of artificial insemination (from 2011 to 2013) resulting in pregnancy only in this case. Physical characteristics of the newborn were: weight 25.5 kg, a withers height of 79 cm, a body length of 80 cm (from the ischial tuberosity to the front side of the muzzle), forelimbs 47 cm and hind limbs 54 cm. The calf died after 2 weeks, and no remarkable alterations were found by the veterinarian on a postmortem examination (fig. 1 B–F).

Cytogenetic analysis revealed a normal diploid number (2n = 60) in the calf, but after C- and R-banding, it showed the presence of a chromosomal aberration. Indeed, a large autosome, showing 2 distinct and prominent constitutive heterochromatin blocks (C-bands), was detected (fig. 2 A). Furthermore, sequential RBA/Ag-NOR techniques confirmed the presence in the autosome of the NOR-bearing bovine chromosomes (fig. 2 B) [ISCNDB 2000, 2001; Iannuzzi et al., 2009]. RBA-banding (fig. 3 A) and the analysis of the corresponding karyotype (fig. 3 B) demonstrated that the large autosome was the result of a translocation between chromosomes 11 and 25, as in the mother; it was classified as a derivative chromosome (der11). This data was further confirmed by FISH analysis using the same 3 BAC probes employed to detect the translocation in the mother: the BAC 142G06 mapped to the proximal (subcentromeric) region of both BTA25 chromosomes and der11 (fig. 4 A), the BAC 513H08 *(ELN)* mapped to the distal region of BTA25 chromosomes (fig. 4 B), and the BAC 533C11 mapped to the proximal region of BTA11 chromosome and der11 (fig. 4 C). Figure 3 C shows an ideogrammatic representation of the possible origin of this chromosomal aberration with FISH-mapping localizations. The newborn presented a partial trisomy of chromosome 25q and partial monosomy of chromosome 11q. Finally, the aberration was classified as 60,XX,der(11)t(11; 25)(q11;q14 ~ 21) according to ISCN 2013 [Simons et al., 2013].

Discussion

This clinical case has underlined several important issues: (a) a case report of a fatal disease, (b) the necessity of cytogenetic screening analysis in farm animals in order to eliminate carriers of chromosomal aberrations, and (c) incorrect gametogenesis in an animal carrying a reciprocal translocation.

As described previously, the mother was a carrier of a balanced reciprocal translocation between chromosomes 11 and 25 [Perucatti et al., 2011]. The results of the newborn show a significant difference when compared to themother's aberration. First, with conventional staining techniques, it was not possible to detect any chromosomal alteration because both number and type of chromosomes were normal, whereas in the karyotype of the mother, a very small derivative chromosome was detected (smaller than any other chromosome). The CBA technique, however, showed an unusually large autosome (der11) (fig. 2 A) with 2 distinct and prominent constitutive heterochromatin blocks because one break had occurred in the centromeric region of BTA11 (fig. 3 C). This result is similar to that of the mother: der11 was present, but der25 was not detected, assuming the loss of some chromosome parts. The RBA technique validated the hypothesis considered after the CBA result. In fact, the karyotype highlighted the presence of just one derivative, one chromosome 11 and 2 chromosomes 25, showing a different result in comparison to the mother that had shown the presence of der25, der11, one chromosome 11 and one chromosome 25. Furthermore, the sequential RBA/Ag-NOR techniques validated the presence of the der11, showing the NORs in the telomeric part of this der (same result in the mother) (fig. 2 B). The FISH technique was a complementary approach to characterize the rearrangements. In this analysis, we used the same BAC probes employed to detect the reciprocal translocation in the mother. Three specific BAC were used (142G06, 513H08 and 533C11) again giving different results in respect to the mother. The BAC 142G06 mapped to the proximal (subcentromeric) region of both BTA25 chromosomes and der11 in the calf (fig. 4 A), while in the mother it mapped to the der11 and the chromosome BTA25. The BAC 513H08 *(ELN)* mapped to the distal region of BTA25 chromosomes (fig. 4 B) in the calf, while in the mother it mapped to der25 and the only BTA 25. The BAC 533C11 mapped to the proximal region of the BTA11 chromosome and der11 (fig. 4 C) in the calf, while in the mother it mapped to BTA11 and to der25, der11. Furthermore, an ideogrammatic representation of the possible origin of this chromosomal aberration using the FISH-mapping localizations validating the same breakpoints observed in the mother is shown in figure 3 C. At this point, we have assumed that the translocation identified in the newborn female is the result of the fertilization of an unbalanced oocyte. In fact, due to the chromosomal aberration (reciprocal translocation) found in the mother, 6 different types of zygotes could be produced: only 1 of them normal and the other 5 abnormal (of which only one was a balanced translocation). Considering that several kinds of segregation patterns of chromosomes can be generated from the mother's oocytes (alternate, adjacent, normal and 3: 1) [Basrur et al., 2001a, b], not all these oocytes can generate an embryo because most of them, especially normal and 3: 1, result in unbalanced outcomes [Honda et al., 1999; Machatkova et al., 2005; Bonnet-Garnier et al., 2008]. In this way, one of the abnormal oocytes, carrying chromosome BTA25 and der11, was fertilized by a normal sperm generating the new unbalanced aberration (fig. 5). Both chromosomes involved and their breakpoints have been preserved in the female calf. The mother carried a balanced translocation, whereas in the newborn, both chromosomes 25 and only one derivative were detected. This unbalanced translocation, due to the absence of the small der25, i.e. loss of genetic material and the presence of a partial trisomy of BTA25 and partial monosomy of BTA11, has probably determined the early death of the calf. Furthermore, this result may explain the reduced fertility of the mother. In fact, considering that the mother had 6 cycles of artificial insemination (from 2011 to 2013) resulting in pregnancy only in this case, the zygotes produced after artificial insemination were probably all unbalanced with subsequent early embryonic death and delayed the return to estrus in the cow. Finally, we performed a comparison with human diseases that involve the portion of the correspondent chromosome both in the case of monosomy 11q and trisomy 25q (table 2). We did not identify similarities with human diseases as shown in table 2 ; however, these chromosomal regions contain many other genes so far not investigated or reported to be associated with known disease. Therefore, further molecular investigations at gene level would be of interest in the future, in order to find the cause for the aberration reported in this study.

Conclusion

Unbalanced chromosomal changes underlie fetal malformations and disturbed viability. In our case, the translocation was hereditary and meiotic segregation of the mother's reciprocal translocation was thought to be the cause for the disturbed viability and mortality in the earliest period of the life of the calf.

Case reports provide an important starting point for further research by comparing and reporting novel clinical phenomena. These comparisons, together with the interactions between farmers, veterinarians and researchers allowed a better genetic selection of farm animals using cytogenetic screening analysis. This study suggests that clinical case reports maintain a unique and important role in the field of animal science.

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Table 1. Balanced translocations in *Bos taurus*

Reference	Balanced translocation
Mayr et al., 1979	t(10;11)(41;14)
De Schepper et al., 1982	t(2q−;20q+),t(8q−;27q+)
Mayr et al., 1983	t(8;15)(21;24)
Kovács et al., 1992	t(1;8;9)(q43;q13;q26)
Basrur et al., 1992	t(X; 23)(p+;q)
Christensen et al., 1992	rcp(1;8)
Villagómez et al., 1993	rcp(20;24)(q17;q25)
Ansari et al., 1993	rcp(8;13)(q11;q24)
Mayr et al., 1998	rcp(X;1)(42;13)
Ducos et al., 2000	rcp(12;17)(q22;q14)
Iannuzzi et al., 2001a	rcp(Y;9)(q12.3;q21.1)
Iannuzzi et al., 2001b	rcp 1(q21→qter) and 5(q11→q33)
De Lorenzi et al., 2007	rcp(9;11)(q27;q11)
Molteni et al., 2007	rcp(11;21)(q28;q12)
Switonski et al., 2008	rcp(2;4)(q45;q34)
Ducos et al., 2008	t(7p+;7q−)
	t(1q−;15q+)
De Lorenzi et al., 2010	t(4;7)(q14;q28)
Switonski et al., 2011	t(Y;21)(p11;q11)
Perucatti et al., 2011	rcp(11;25)(q11;q14−21)
De Lorenzi et al., 2014	t(5;6)(q13;q34)

Table 2. Comparison between BTA *(Bos taurus)* and the corresponding HSA *(Homo sapiens)* portion of chromosomes containing genes involved in documented diseases

Chromosome		Genes involved	Related diseases
BTA	HSA		
25q12	16p13.3	*HBA1*	alpha-thalassemia hemoglobin H disease, Heinz body anemias hydrops fetalis
	16p13.3	*ABCA3*	surfactant metabolism dysfunction, pulmonary, 3 surfactant metabolism dysfunction, pulmonary, 1
25q13	16q13	*CLCN7*	osteopetrosis autosomal dominant type 2
		OSTM1	osteopetrosis autosomal recessive 4 osteopetrosis autosomal recessive 1
	16q13.3	*CREBBP*	RSTS
	16p13.3	*GNPTG*	ML III gamma
11q11q14	2p13.2	*ALMS1*	
		ALMS1-IT1	Alström syndrome
	2p13.2	*DCTN1*	ALS, Perry syndrome
		DCTN1-AS1	dHMN or HMN dHMN7B
	2p13.2	*DGUOK*	
		DGUOK-AS1	mitochondrial DNA-depletion syndrome 3, hepatocerebral
	2p13.3	*DYSF*	LGMD Miyoshi myopathy LGMD myopathy, distal, with anterior tibial onset
	2p13.2	*MCEE*	methylmalonyl-CoA epimerase deficiency
	2p14	*SPR*	SPR 6-pyruvoyl-tetrahydropterin synthase deficiency

ALS = Amyotrophic lateral sclerosis; dHMN or HMN = distal hereditary motor neuronopathy; LGMD = limb-girdle muscular dystrophy; ML III gamma = mucolipidosis III gamma; RSTS = Rubinstein-Taybi syndrome; SPR = sepiaterin reductase deficiency. For further information, see http://www.ncbi.nlm.nih.gov/.

Fig. 1. A new born calf of the Agerolese breed carrying the chromosomal aberration. **A, B** Alive and dead animal showing hyperflexion of the forelimbs. **C** Abdominal cavity and its contents. **D** Post-mortem examination showing liver and gall bladder. **E** Ruminant stomachs and abomasum, lungs and heart, liver and gall bladder, spleen and kidneys (from left to right). **F** Brain.

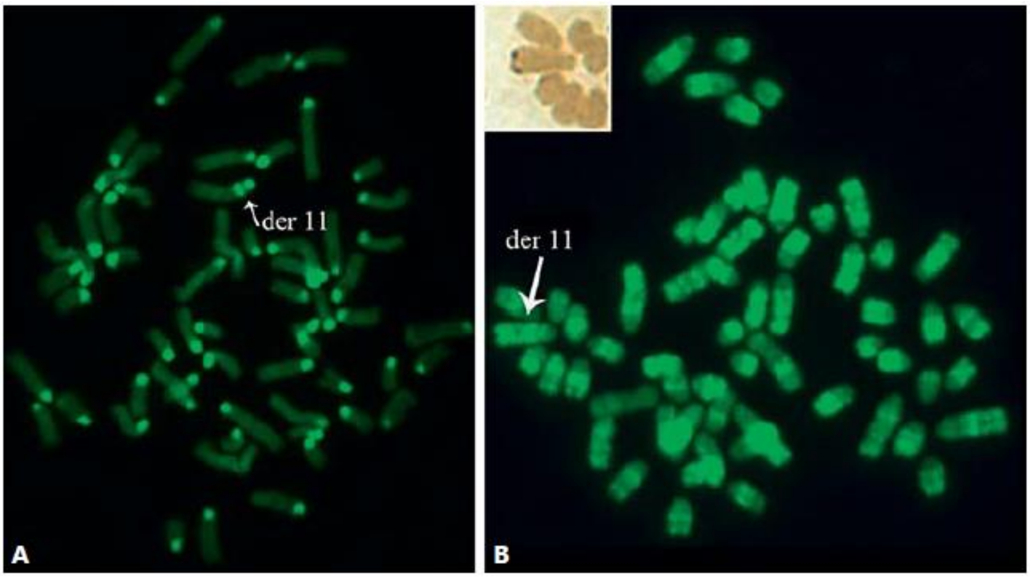

Fig. 2. Metaphase plates of the calf carrying the t(11;25). **A** CBA-banded metaphase showing the der11 charaterozed by a prominent constitutive heterochromatin block (C-bands). **B** sequential RBA/ag-NOR techniques confirmed the presence of the NOR on the der 11 (**Inset**).

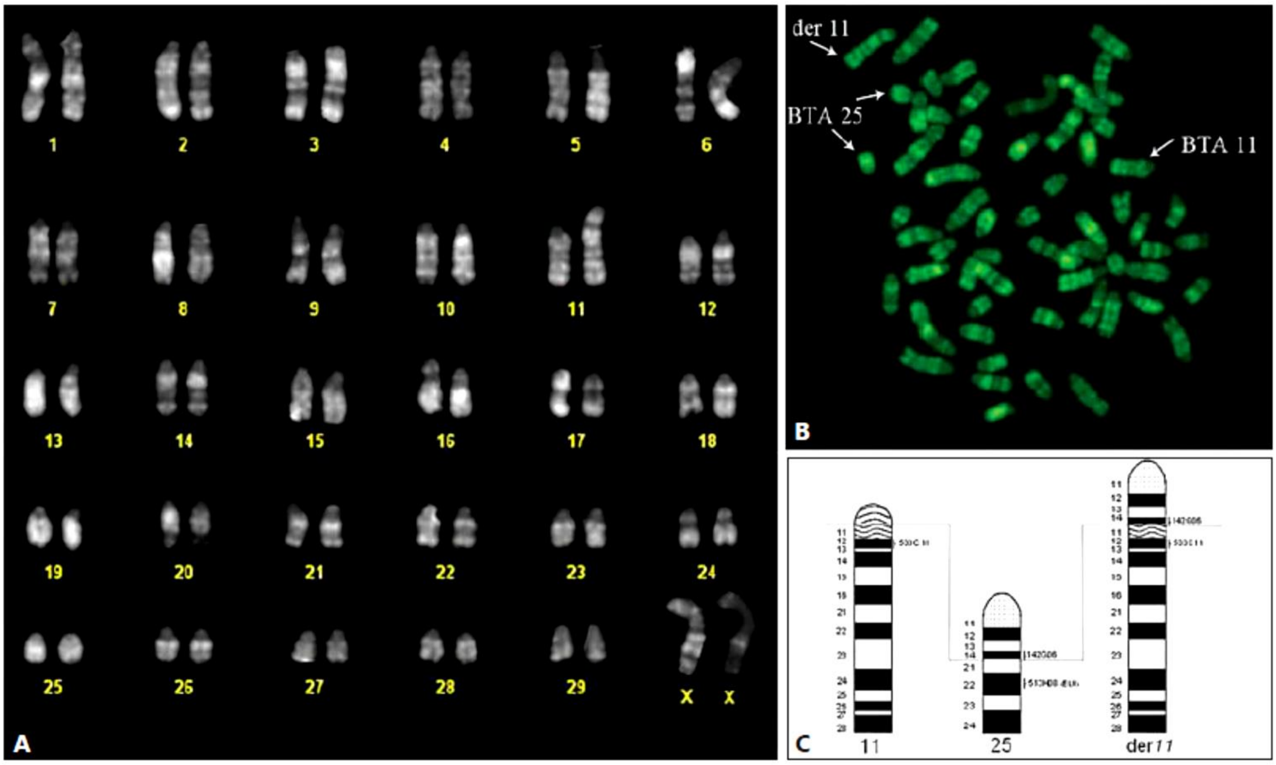

Fig. 3. RBA-stained karyotype (**A**) and metaphase plate (**B**) showing der11. BTA11 and the 2 BTA25 (arrows). **C** Ideogrammatic representation of the BTA chromosomes involved in the translocation t(11;25)(q11;q14~21) with the breakpoints (dotted line) and the localization of BACs.

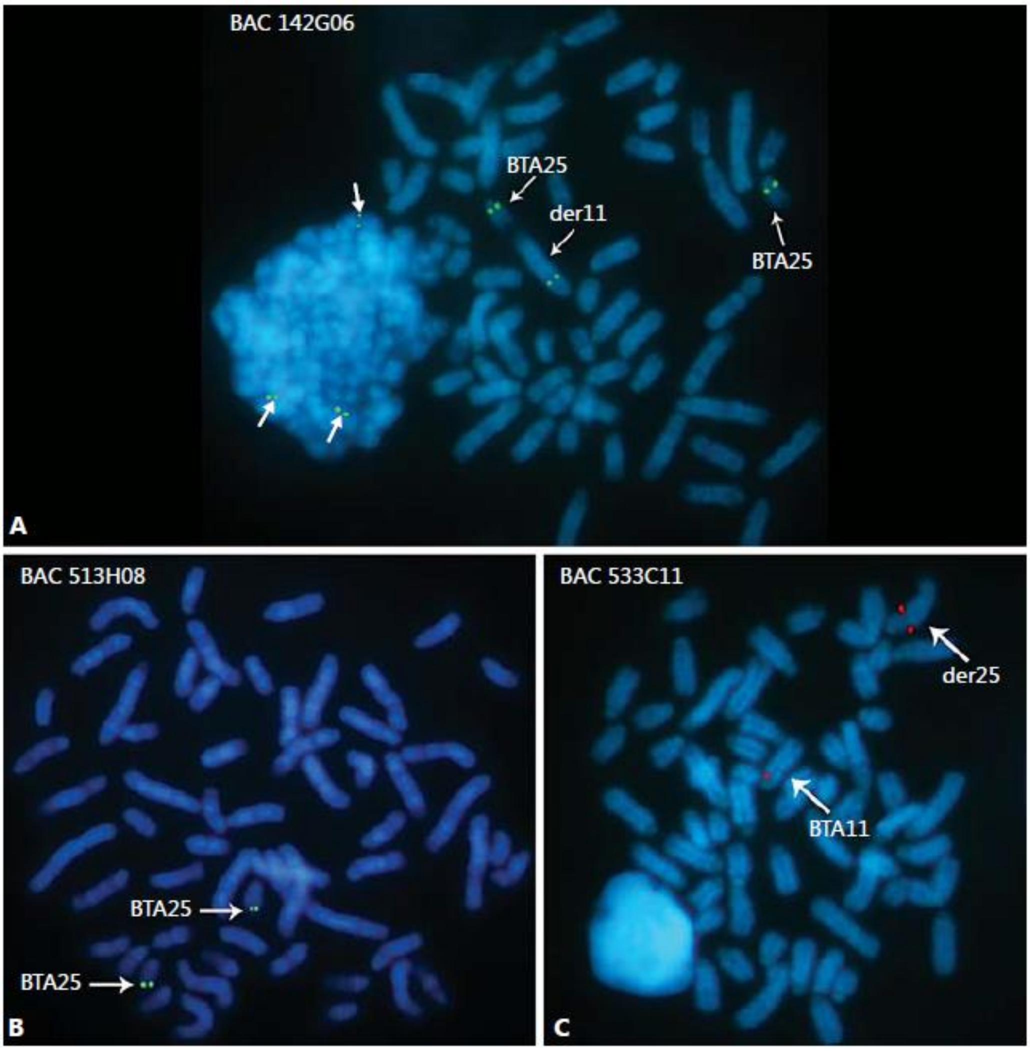

Fig. 4. FISH on R-banded metaphase spreads of the carrier using specific bovine BAC probes. **A** BAC142G06 hybridizes on both BTA25 and the der 11 (green signals). **B** BAC513H08 hybridizes on both BTA25 (green signals). **C** BAC533C11 hydridizes on BTA11 and der25 (red signals). Note the 3 hybridization signals of BAC142G06 (BTA25) on the close interphase nucleus (small arrows).

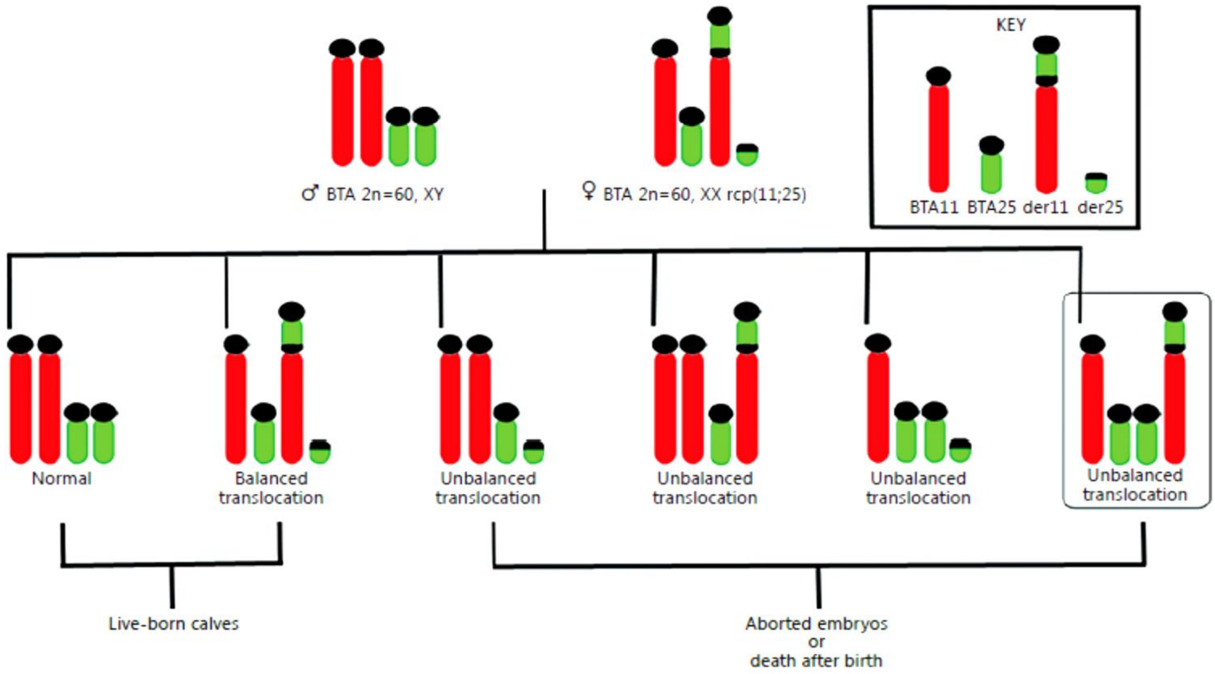

Fig. 5. Schematic representation of the fertilization between a normal bull and the cow carrying the rcp(11;25). Six different types of zygotes can be produced giving only 1 balanced, 1 normal and the other carrying the same reciprocal translocation of the mother. The chromosome constitution of the right zygote caused the fatal disease of the calf.