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Case Report

Prenatal diagnosis and molecular cytogenetic characterization of a *de novo* unbalanced reciprocal translocation of der(9) t(9;14)(p24.2;q32.11) associated with 9p terminal deletion and 14q distal duplication

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ABSTRACT

Objective: We present molecular cytogenetic characterization of a prenatally detected derivative chromosome 9 [der(9)] of unknown origin.

Case Report: A 35-year-old woman underwent amniocentesis at 18 weeks of gestation because of advanced maternal age, which revealed a der(9) chromosome of unknown origin. The parental karyotypes were normal. Array comparative genomic hybridization (aCGH) analysis revealed a 2.593 Mb deletion of 9p24.3-p24.2 encompassing *DOCK8*, *KANK1*, *DMRT1*, and *VLDLR* and a 16.65 Mb duplication of 14q32.11-q32.33 encompassing *DLK1*, *RTL1*, *MEG3*, *RTL1as*, and *MEG8*. Quantitative fluorescent polymerase chain reaction (QF-PCR) analysis using D9S937 (9p24.2) and D14S605 (14q32.2) showed a paternal origin of 9p24.2 deletion and a paternal origin of 14q32.2 duplication consistent with a paternal origin of the *de novo* aberrant chromosome of der(9)t(9p;14q). The fetal karyotype was 46,XX,der(9)t(9;14)(p24.2;q32.11). Metaphase fluorescence *in situ* hybridization (FISH) analysis using RP11-57K23 (14q32.33), RP11-31F19 (9p24.3), RP11-30O14 (9p21.1), and RP11-1105I14 (14q11.2) confirmed an unbalanced reciprocal translocation of der(9)t(9p;14q). We discuss 9p deletion syndrome and 14q duplication syndrome in this case.

Conclusion: Molecular cytogenetic techniques such as aCGH, FISH, and QF-PCR are useful in the determination of the origin and nature of a prenatally detected *de novo* derivative chromosome of unknown origin.

Introduction

Prenatal diagnosis of *de novo* chromosome aberration of unknown origin may require molecular cytogenetic characterization such as array comparative genomic hybridization (aCGH), fluorescence *in situ* hybridization (FISH), and quantitative fluorescent polymerase chain reaction (QF-PCR) to delineate the nature and the parental origin of the aberration [1].

Here, we present our experience of molecular cytogenetic characterization of a prenatally detected derivative chromosome 9 [der(9)] of unknown origin by the use of aCGH, FISH, and QF-PCR, and the result was a *de novo* unbalanced reciprocal translocation

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of der(9)t(9;14) (p24.2;q32.11) of paternal origin. Our presentation demonstrates the usefulness of molecular cytogenetic techniques such as aCGH, FISH, and QF-PCR in the determination of the origin and nature of a prenatally detected *de novo* derivative chromosome of unknown origin.

Case Report

A 35-year-old, gravid 2, para 1, woman underwent amniocentesis at 18 weeks of gestation because of advanced maternal age. Her husband was 40 years of age. The couple had a healthy 4-year-old boy, and there was no family history of congenital malformations. Amniocentesis revealed a der(9) with a deletion of terminal 9p and an addendum of an unknown segment at the breakpoint of 9p. The parental karyotypes were normal. aCGH analysis on cultured amniocytes by CytoScan 750K Array (Affymetrix, Santa Clara, CA, USA) showed the result of arr 9p24.3p24.2 (208,454–2,801,321) × 1.0, 14q32.11q32.33 (90,637,774–107,284,437) × 3.0, indicating a 2.593 Mb deletion of 9p24.3-p24.2 encompassing 16 genes including 8 Online Mendelian Inheritance in Man (OMIM) genes of *DOCK8*, *KANK1*, *DMRT1*, *DMRT3*, *DMRT2*, *SMARCA2*, *VLDLR*, and *KCNV2*, and a 16.65 Mb duplication of 14q32.11-q32.33 encompassing 519 genes including 142 OMIM genes that contain the paternally expressed genes (PEGs) of *DLK1* and *RTL1*, and the maternally expressed genes (MEGs) of *MEG3*, *RTL1as*, and *MEG8* (Figure 1). Metaphase FISH analysis on cultured amniocytes using the bacterial artificial chromosome probes of RP11-57K23 (14q32.33, 106,882,918–106,976,919, dye: FITC, spectrum green) [hg 19], RP11-31F19 (9p24.3, 547,217–692,143, dye: Texas Red, spectrum red) [hg 19], RP11-30O14 (9p21.1, 28,765,550–28,966,389, dye: Cy5, spectrum yellow) [hg 19], and RP11-1105I14 (14q11.2, 19,662,704–19,861,854, dye: DEAC, spectrum blue) [hg 19] showed the presence of one blue signal and one green signal in the normal chromosome 14, one yellow signal and one red signal in the normal chromosome 9, and one yellow signal and one green signal in the der(9) chromosome, indicating an unbalanced reciprocal translocation of der(9)t(9p;14q) (Figure 2). The fetal karyotype was 46,XX,der(9)t(9;14)(p24.2;q32.11) (Figure 3). Prenatal ultrasound findings were unremarkable. The pregnancy was subsequently terminated at 22 weeks of gestation, and a 408 g fetus was delivered with mild facial dysmorphism of micrognathia and low-set ears. The female external genitalia were normal. QF-PCR analysis on the DNAs extracted from the placental tissue and the parental bloods using informative markers of D9S937 (9p24.2), D9S2149 (9p21.1), D14S140 (14q31.3), and D14S605 (14q32.2) showed only one maternal allele at D9S937 (9p24.2) and a paternal allele:maternal allele ratio of 2:1 at D14S605 (14q32.2) in the fetus, indicating a paternal origin of the der(9) chromosome (Figure 4).

Discussion

The present case had a 2.593 Mb deletion of 9p24.2→pter encompassing the critical genes of *DOCK8*, *KANK1*, *DMRT1*, and *VLDLR* that may be responsible for the chromosome distal 9p deletion syndrome (OMIM 158170). Chromosome distal 9p deletion syndrome is characterized by major clinical features of mental retardation, hypotonia, seizures, trigonocephaly, synophrys, midface hypoplasia, short nose, depressed nasal bridge, anteverted nares, hypertelorism, up-slanting palpebral fissures, long philtrum, microstomia, high and narrow palate, small posteriorly rotated ears, hypoplastic labia majora, prominent labia minora and clitoris, cryptorchidism, hypospadias, wide-set nipples, hernias, scoliosis, diastasis recti, short and broad distal phalanges of fingers, square-shaped nails, and foot position anomalies; and relatively rare malformations of congenital heart defects, microphthalmia, choanal atresia, stenostic external ear canals, cleft palate, diaphragmatic hernia, hydronephrosis, hypoplasia of the corpus callosum, enlarged cisterna magna, and postaxial hexadactyly of the fingers [2].

A 9p24.3 deletion is associated with 46,XY sex reversal (SRXY4; OMIM 154230) because the *DMRT* cluster of *DMRT1*, *DMRT2*, and *DMRT3* is located at 9p24.3, and *DMRT1* is the strongest candidate gene for the sex reversal [3–6]. *DMRT1* (OMIM 602424) encodes a male-specific transcriptional regulator of doublesex- and MAB3-related transcription factor 1 (DMRT1) that is involved in sex determination and differentiation [7,8]. DMRT1 suppresses female differentiation in testes, and involves inhibition of meiosis in testes [3–5]. Haploinsufficiency of *DMRT1* will cause 46,XY gonadal dysgenesis and 46,XY ovotesticular disorder of sexual development [6]. Heterozygous disruption of *DOCK8* (OMIM 611432) either by a deletion or by a translocation breakpoint is associated with autosomal dominant mental retardation 2 (MRD2; OMIM 614113) [9]. Deletion of *KANK1* (OMIM 607704) causes familial cerebral palsy (cerebral palsy spastic quadriplegic 2; OMIM 612900) which is associated with parent-of-origin-dependent inheritance, and the affected individuals inherit the deletion of *KANK1* from paternal origin [10]. *VLDLR* encodes very low-density lipoprotein receptor (VLDLR) and is involved in Reelin signaling pathway and neuronal migration. Mutations of *VLDLR* (OMIM 192977) cause abnormal gyration, psychiatric disorders, and autosomal recessive cerebellar ataxia, mental retardation and dysequilibrium syndrome 1 (CAMRQ1; OMIM 224050) [11–14].

To date, at least 10 cases with fetal distal 9p deletion detected by prenatal invasive diagnostic procedures have been reported because of various indications such as abnormal maternal serum biochemistry, increased nuchal translucency, ambiguous external genitalia, male-to-female sex reversal, intrauterine growth restriction, advanced maternal age, familial chromosomal translocation and fetal structural abnormalities [2,15–22]. Stumm et al [15] reported prenatal diagnosis of mosaic r(9)(p24q34) in a male fetus because of the fetal ultrasound finding of male-to-female sex reversal. Vialard et al [16] reported prenatal diagnosis of del(9)(p22) in a male fetus with ambiguous external genitalia and in a female fetus associated with hypoplastic left heart and a single umbilical artery on fetal ultrasound. Witters et al [17] reported prenatal diagnosis of der(9)t(3;9)(p14.2;p24) in a male fetus associated with sex reversal and multiple anomalies on fetal ultrasound. Brisset et al [18] reported prenatal diagnosis of der(9)t(9;17)(p24.3;q24.3) in a female fetus associated with increased nuchal translucency, a single umbilical artery and partial agenesis of the cerebellar vermis on fetal ultrasound. Chen et al [19] reported prenatal diagnosis of mosaic r(9)(p24q34.3) in a male fetus with abnormal maternal serum screening and ambiguous external genitalia on fetal ultrasound. Chen et al [20] reported prenatal diagnosis of inv dup del(9) (:p22.1→p24.3::p24.3→qter) in a male fetus with ventriculomegaly on fetal ultrasound. Chen et al [2] reported prenatal diagnosis of 46,XX,del(9)(p24.1p24.3) because of abnormal maternal serum screening. Hou et al [21] reported prenatal diagnosis of del(9)(p13) in a female fetus associated with symbrachydactyly and omphalocele on fetal ultrasound. Penacho et al [22] reported prenatal diagnosis of r(9)(p24q34) in a female fetus associated with intrauterine growth restriction and slight craniofacial dysmorphism. The peculiar aspect of the present case is the diagnostic indication of advanced maternal age for amniocentesis with a result of a *de novo* unbalanced reciprocal translocation of der(9)t(9;14)(p24.2;q32.11) of paternal origin. This information is very important in the genetic counseling for the pathogenesis of a *de novo* chromosome aberration.

The 14q duplication syndrome involving dup 14q (14q22→q32) is characterized by high forehead, wide sutures and fontanels,

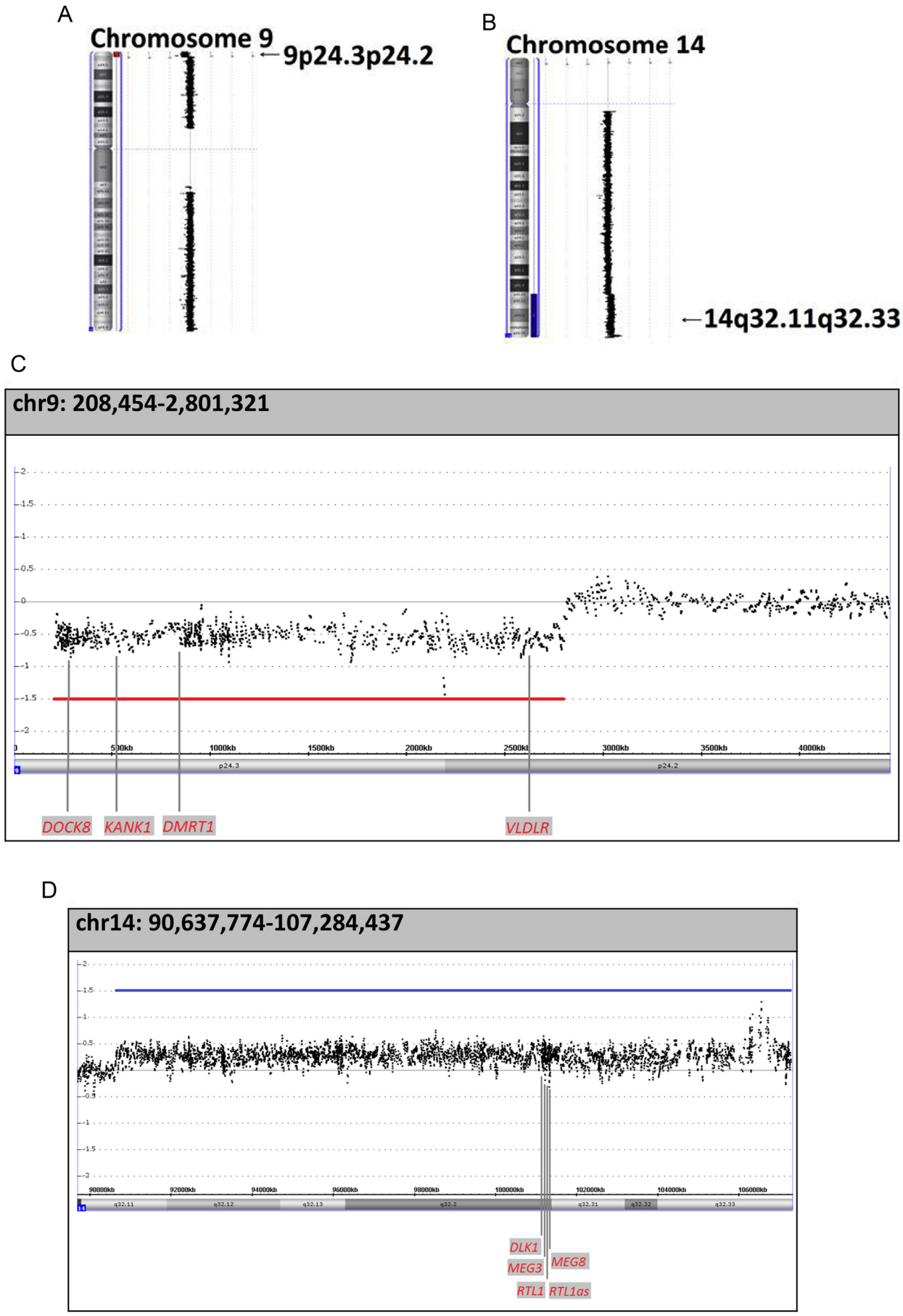

Figure 1. aCGH on cultured amniocytes shows a 2.593 Mb deletion of 9p24.3-p24.2 encompassing *DOCK8*, *KANK1*, *DMRT1*, and *VLDLR*, and a 16.65 Mb duplication of 14q32.11-q32.33 encompassing *DLK1*, *RTL1*, *MEG3*, *RTL1as*, and *MEG8*. (A, C) chromosome 9 zoom-in view; (B, D) chromosome 14 zoom-in view. aCGH = array comparative genomic hybridization.

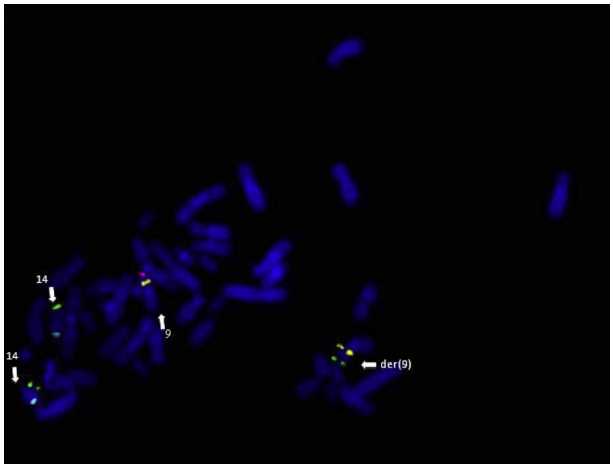

Figure 2. Metaphase FISH analysis on cultured amniocytes using the bacterial artificial chromosome probes of RP11-57K23 (14q32.33, 106,882,918–106,976,919, dye: FITC, spectrum green) [hg 19], RP11-31F19 (9p24.3, 547,217–692,143, dye: Texas Red, spectrum red) [hg 19], RP11-30O14 (9p21.1, 28,765,550–28,966,389, dye: Cy5, spectrum yellow) [hg 19], and RP11-1105I14 (14q11.2, 19,662,704–19,861,854, dye: DEAC, spectrum blue) [hg 19] shows the presence of one blue signal and one green signal in the normal chromosome 14, one yellow signal and one red signal in the normal chromosome 9, and one yellow signal and one green signal in the der(9) chromosome, indicating an unbalanced reciprocal translocation of der(9)t(9p;14q). FISH = fluorescence *in situ* hybridization.

sparse hair and eyebrows, board nasal bridge, hypertelorism, thin upper lip, abnormal ears, broad mouth, micrognathia, developmental delay, mild mental retardation, spasticity, hyperreflexia, premature puberty, and primordial short stature [23–27]. The 14q duplication syndrome involving dup 14q (14q31→qter) is characterized by an asymmetric face, frontal bossing, low-set and dysplastic ears, hypertelorism, sparse eyebrows and lashes, prominent nasal bridge, small mandible, growth retardation, and moderate mental retardation [28–36].

The present case had a 16.65 Mb duplication of 14q32.11→qter of paternal origin encompassing PEGs of *DLK1* and *RTL1*, MEGs of *MEG3*, *RTL1as* and *MEG8*, and the differentially methylated regions (DMRs) of intergenic DMR (IG-DMR) and *MEG3*-DMR [37–40]. IG-DMR and *MEG3*-DMR, which are located between *DLK1* and *MEG3*, are respectively methylated on the paternal chromosome 14 and unmethylated on the maternal chromosome 14, and after paternal transmission, both DMRs are hypermathylated and after maternal transmission, both DMRs are hypomathylated [38,40–43]. Paternal uniparental disomy 14 [upd(14)pat] or Kagami–Ogata syndrome (OMIM 608149) is an imprinting disorder involving 14q32 imprinted genes and is characterized by skeletal abnormalities, joint contractures, dysmorphic facial features, developmental delay, mental retardation, a narrow and bell-shaped thorax with caudal bowing of the anterior ribs, cranial bowing of the posterior ribs, flaring of the iliac wings, abdominal wall defects, placentomegaly and polyhydramnios [44,45]. Maternal uniparental disomy 14 [upd(14)mat] or Temple syndrome (OMIM 616222) is an imprinting disorder involving 14q32 imprinted genes and is characterized by low birth weight, hypotonia, motor delay, feeding problems early in life, early puberty, a broad forehead, short nose, a wide nasal tip, small hands and feet [46,47]. Kagami–Ogata syndrome is caused by full or segmental upd(14)pat of normal chromosome, abnormal chromosome of Robertsonian 13q;14q translocation or i(14q), epimutations and microdeletions of 14q of maternal origin. The present case is not associated with

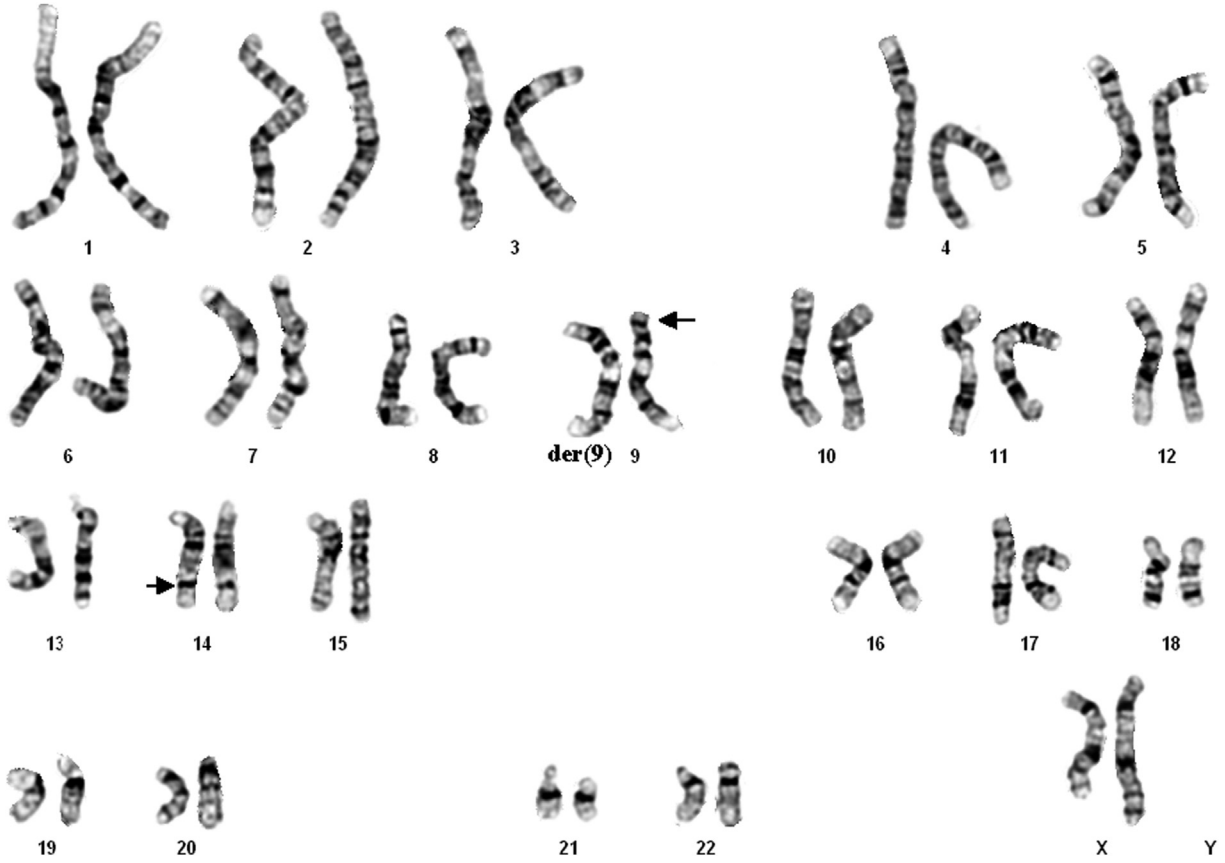

Figure 3. A karyotype of 46,XX,der(9)t(9;14)(p24.2;q32.11) in the fetus. The arrows indicate the breakpoints. der = derivative.

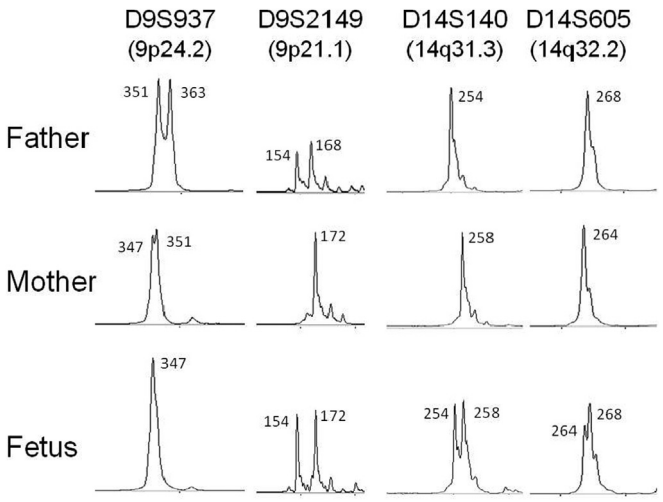

Figure 4. QF-PCR assays on the DNAs extracted from the placental tissue and the parental bloods using informative markers of D9S937 (9p24.2), D9S2149 (9p21.1), D14S140 (14q31.3), and D14S605 (14q32.2) show only one maternal allele at D9S937 (9p24.2) and a paternal allele:maternal allele ratio of 2:1 at D14S605 (14q32.2) in the fetus, indicating a paternal origin of the der(9) chromosome. QF-PCR = quantitative fluorescent polymerase chain reaction.

Kagami–Ogata syndrome. To date, no Kagami–Ogata syndrome has been reported in the case with partial trisomy 14q of paternal origin. Kagami–Ogata syndrome is associated with excessive *RTL1* expression with absent MEG expression or a ~2.5 times increased *RTL1* expression level with absence of functional *RTL1as*-encoded microRNAs [45].

In summary, we present molecular cytogenetic characterization of a prenatally detected der(9) of unknown origin which was confirmed to be der(9)t(9;14)(p24.2;q32.11). We discuss 9p deletion syndrome and 14q duplication syndrome in this case. Our presentation demonstrates the usefulness of molecular cytogenetic techniques such as aCGH, FISH, and QF-PCR in the determination of the origin and nature of a prenatally detected *de novo* derivative chromosome of unknown origin.

Conflict of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

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