Prenatal diagnosis and molecular cytogenetic characterization of a de novo pure distal 9p deletion and literature review

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ABSTRACT

We present rapid aneuploidy diagnosis of distal 9p deletion by array comparative genomic hybridization using uncultured amniocytes in a pregnancy associated with an abnormal maternal serum screening result and intra-uterine growth restriction (IUGR) in the fetus. We review the literature of prenatal diagnosis of distal 9p deletion, and add abnormal maternal serum biochemistry and fetal IUGR in the distinctive prenatal findings in pregnancy with fetal distal 9p deletion. We discuss the consequence of haploinsufficiency of DOCK8, KANK1, VLDLR and DMRT1 in this case.

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1. Introduction

Chromosome distal 9p deletion syndrome (OMIM 158170) is a clinically well-defined syndrome characterized by major clinical features such as mental retardation, hypotonia, seizures; craniofacial dysmorphisms of trigonocephaly, synophrys, midface hypoplasia, short nose, depressed nasal bridge, anteverted nares, hypertelorism, up-slanting palpebral fissures, long philtrum, microstomia, high and narrow palate, and small posteriorly rotated ears; abnormal genitalia of hypoplastic labia majora, prominent labia minora and clitoris, cryptorchidism and 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 such as 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 [1–13].

Prenatal diagnosis of chromosome aberration associated with distal 9p deletion is very rare. The reported cases have been associated with unbalanced translocations [14,15], inverted duplication and deletion of distal 9p [4], mosaic ring chromosome 9 [16,17] and pure distal 9p deletion [18]. To our knowledge, only two cases of prenatally detected pure 9p deletion have been described [18]. Here, we report prenatal diagnosis and array comparative genomic hybridization (aCGH) characterization of a de novo pure distal 9p deletion associated with abnormal maternal serum screening.

2. Materials and methods

2.1. Array-CGH

Whole-genome aCGH on uncultured amniocytes derived from 10 mL amniotic fluid and on parental bloods was performed using NimbleGen ISCA Plus Cytogenetic Array (Roche NimbleGen, Madison, WI, USA). The NimbleGen ISCA Plus Cytogenetic Array has 630,000 probes and a median resolution of 15–20 kb across the entire genome according to the manufacturer's instruction.

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2.2. Conventional cytogenetic analysis

20 mL amniotic fluid was collected, and the sample was subjected to in situ amniocyte culture according to the standard cytogenetic protocol. Parental bloods and cord blood were collected for cytogenetic analysis according to the standard protocol. Routine cytogenetic analysis by G-banding techniques at the 550 bands of resolution was performed.

2.3. Clinical description

A 32-year-old, gravida 2, para 0, woman underwent first-trimester screening for Down syndrome using maternal serum biochemistry and nuchal translucency (NT) thickness at 12 weeks of gestation. Her husband was 31 years old, and there was no family history of congenital malformations. The levels of free β-human chorionic gonadotrophin (β-hCG) and pregnancy-associated plasma protein A (PAPP-A) were 1.086 multiples of the median (MoM) and 0.519 MoM, respectively. The NT thickness was measured 2.7 mm. The woman was screened positive for a Down syndrome risk of 1/147. She consulted the hospital and requested for amniocentesis at 25 weeks of gestation. Prenatal ultrasound at 25 weeks of gestation showed a female fetus with severe intrauterine growth restriction (IUGR). The biparietal diameter measured 5.01 cm, and the femur length measured 3.57 cm, equivalent to 21 weeks of gestation. aCGH using uncultured amniocytes showed a 6-Mb deletion at 9p24.3-p24.1 (Fig. 1). Amniocentesis revealed a female fetus with del(9)(p24.1p24.3) (Fig. 2). The parental karyotypes were normal. Prenatal ultrasound at 26 weeks of gestation revealed a fetus with fetal biometry equivalent to 24 weeks. A 586-g female fetus was subsequently delivered with a midface hypoplasia, short nose, depressed nasal bridge, hypertelorism, up-slanting palpebral fissures, long philtrum, microstomia and small posteriorly rotated ears. The female external genitalia were normal. Postnatal cytogenetic analysis of cord blood confirmed the prenatal diagnosis.

2.4. Next-generation sequencing

We used next-generation sequencing in order to further confirm our results from karyotyping and aCGH shown in Figs. 1 and 2, we called single nucleotide polymorphism (SNP) variants as well as indels (insertions and deletions), and mapped to human genome reference sequence (GRCh37/hg19) in chromosome 9.

3. Results

aCGH showed a 6-Mb deletion at 9p24.3-p24.1, or arr 9p24.3p24.1 (198,350-6,256,729) × 1 (NCBI build 37) (Fig. 1). The deleted region encompasses the genes of DOCK8, KANK1, DMRT1, DMRT3, DMRT2 and VLDLR. The fetal karyotype was 46,XX,del(9)(p24.1p24.3)dn (Fig. 2). The father's karyotype was 46,XY. The mother's karyotype was 46,XX. We differentiated heterozygous and homozygous variants and noted that continuous homozygous variants are scored from position 178,806 to 6,535,975, indicate that it lacks differences at these SNPs in the region and shows loss of heterozygosity (LOH) (Fig. 3).

4. Discussion

The present case was associated with IUGR, abnormal maternal serum biochemistry and the 9p deletion syndrome. An abnormal maternal serum biochemistry result in the first or second trimester may result in early prenatal detection of rare fetal chromosomal abnormalities [19–22]. The present pregnant woman was 32 years of age. She underwent amniocentesis because of a positive Down syndrome screen risk of 1/147 calculated by first-trimester maternal serum levels of free β-hCG and PAPP-A and NT thickness. The association of fetuses with the chromosome 9p deletion syndrome with abnormal first-trimester screening for Down syndrome in this presentation indicates that fetal distal 9p deletion may be associated with abnormal first-trimester Down syndrome screening.
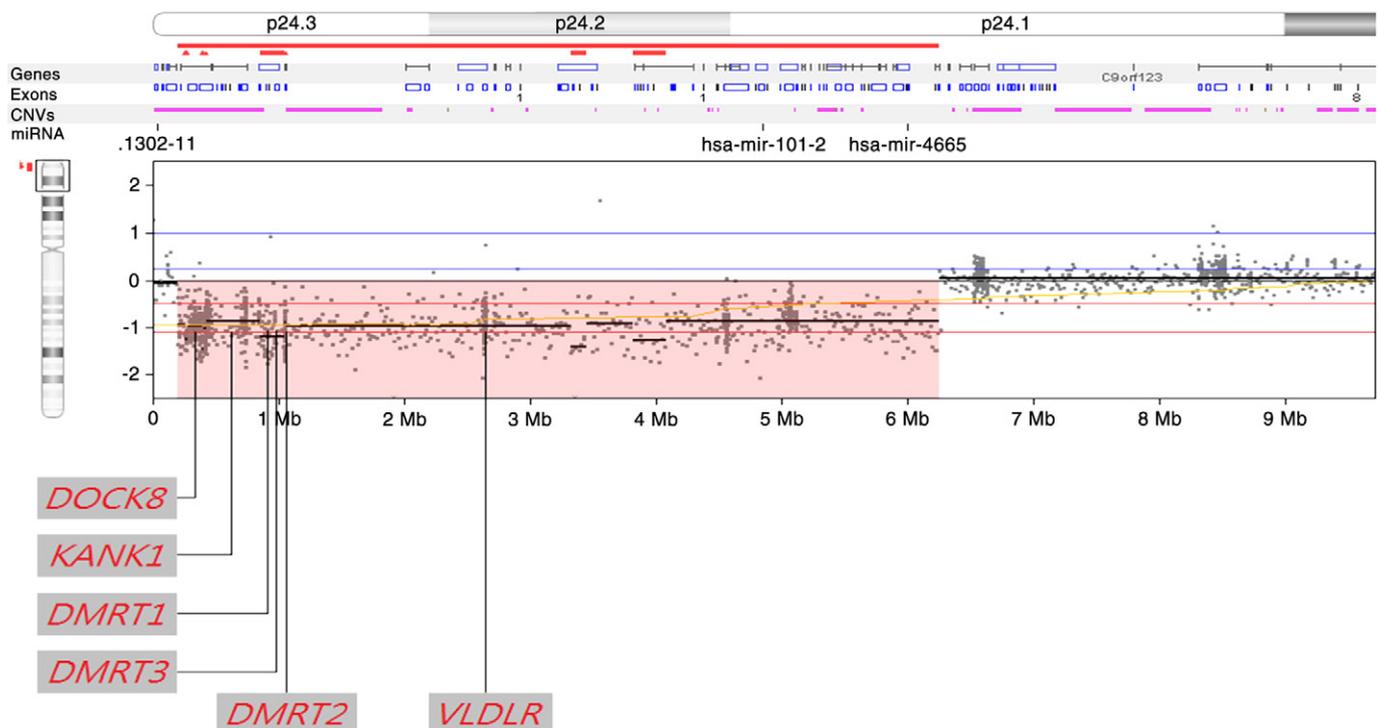
Chromosome 9: 198,350-6,256,729

Fig. 1. Array comparative genomic hybridization shows a 6-Mb deletion at chromosome 9p24.3-p24.1 [arr 9p24.3p24.1 (198,350-6,256,729 × 1) (NCBI build 37) encompassing the genes of DOCK8, KANK1, DMRT1, DMRT3, DMRT2 and VLDLR.
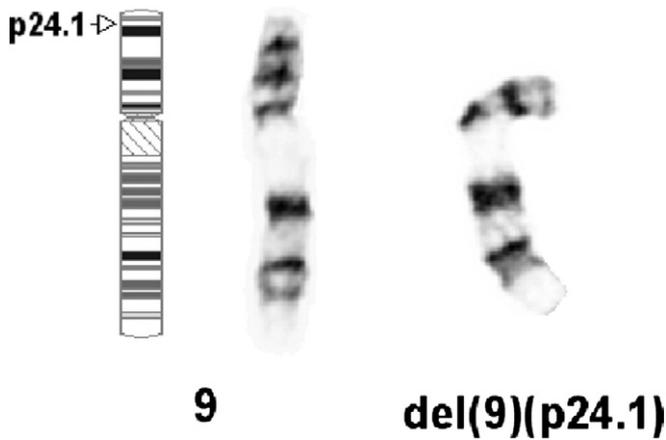
Fig. 2. A karyotype of 46,XX, del(9)(q24.1p24.3). The arrow indicates the breakpoint.

Table 1 presents the perinatal findings and prenatal diagnoses of reported cases with the chromosome distal 9p deletion syndrome. Abnormal maternal serum biochemistry, increased NT thickness, ambiguous external genitalia, male-to-female sex reversal, IUGR and fetal structural abnormalities can be distinctive prenatal findings in pregnancy with fetal distal 9p deletion. Chen et al. [4] reported prenatal ultrasound diagnosis of ventriculomegaly in a male fetus with inv dup del(9)(:p22.1 → p24.3::p24.3 → qter). Chen et al. [2] reported IUGR in the third trimester in a fetus with partial monosomy 9p (9pter → p22) and partial trisomy 7p (7pter → p15.1). Brisset et al. [15] reported increased NT thickness of 4.4 mm, IUGR, a single umbilical artery, partial agenesis of the cerebellar vermis, bilateral choroid plexus cysts and facial dysmorphisms on ultrasound in a female fetus with partial monosomy 9p (9pter → p24.3) and partial trisomy 17q (17q24.3 → qter). Chen et al. [17] reported abnormal second-trimester maternal serum screening with a positive risk of 1/57 for Down syndrome and ambiguous external genitalia on prenatal ultrasound in a male fetus with mosaic r(9)(p24q34.3).

Stumm et al. [16] reported second-trimester sonographic diagnosis of male-to-female sex reversal in a male fetus with ring chromosome 9. Witters et al. [14] reported prenatal ultrasound diagnosis of sex reversal and multiple anomalies in a male fetus with partial monosomy 9p (9pter → p24) and partial trisomy 3p (3pter → p14.2). Vialard et al. [18] reported prenatal diagnosis of ambiguous external genitalia in a male fetus with del(9)(p22) in the second trimester, and hypoplastic left heart and a single umbilical artery in a female fetus with del(9)(p22). Distal 9p deletion has been associated with 46, XY gonadal dysgenesis and sex reversal [23–27]. Therefore, prenatal diagnosing sex reversal or ambiguous external genitalia should alert fetal 9p deletion.

The present case had haploinsufficiency of the genes of *DOCK8*, *KANK1*, *DMRT1*, *DMRT3*, *DMRT2* and *VLDLR*. Genetic aberrations in *DOCK8*, *KANK1* and *VLDLR* may result in neurological and/or psychiatric disorders. *DOCK8* (OMIM 611432) encodes dedicator of cytokinesis 8, which is a member of the DOCK180-related protein family [28]. Heterozygous disruption of *DOCK8* either by a deletion or by a translocation breakpoint has been associated with autosomal dominant mental retardation 2 (MRD2; OMIM 614113) [29]. *KANK1* (OMIM 607704) encodes kidney ankyrin repeat-containing protein and is a maternally imprinted gene that is expressed only from the paternal allele [30]. Deletion of *KANK1* will cause parent-of-origin-dependent inheritance of familial cerebral palsy (cerebral palsy spastic quadriplegic 2; OMIM 612900) with affected individuals inheriting the deletion from paternal origin [30]. *VLDLR* (OMIM 192977) encodes very low-density lipoprotein receptor (VLDLR) and is involved in Reelin signaling pathway and neuronal migration. Mutations of *VLDLR* can cause autosomal recessive cerebellar ataxia, mental retardation and dysequilibrium syndrome 1 (CAMRQ1; OMIM 224050) [31–34]. Mutations in *Reelin* and *VLDLR* will result in similar abnormal gyration and psychiatric disorders because VLDLR is a part of the Reelin signaling pathway which regulates cortical neuronal migration, promotes maturation of dendrites and dendritic spines, and modulates synaptic function [31,35–37]. 9p24.3 deletions have been associated with 46,XY sex reversal (SRXY4; OMIM 154230). The DMRT cluster is located at 9p24.3, and among *DMRT1*, *DMRT2* and *DMRT3*, only *DMRT1* has been shown to be the strongest candidate gene for
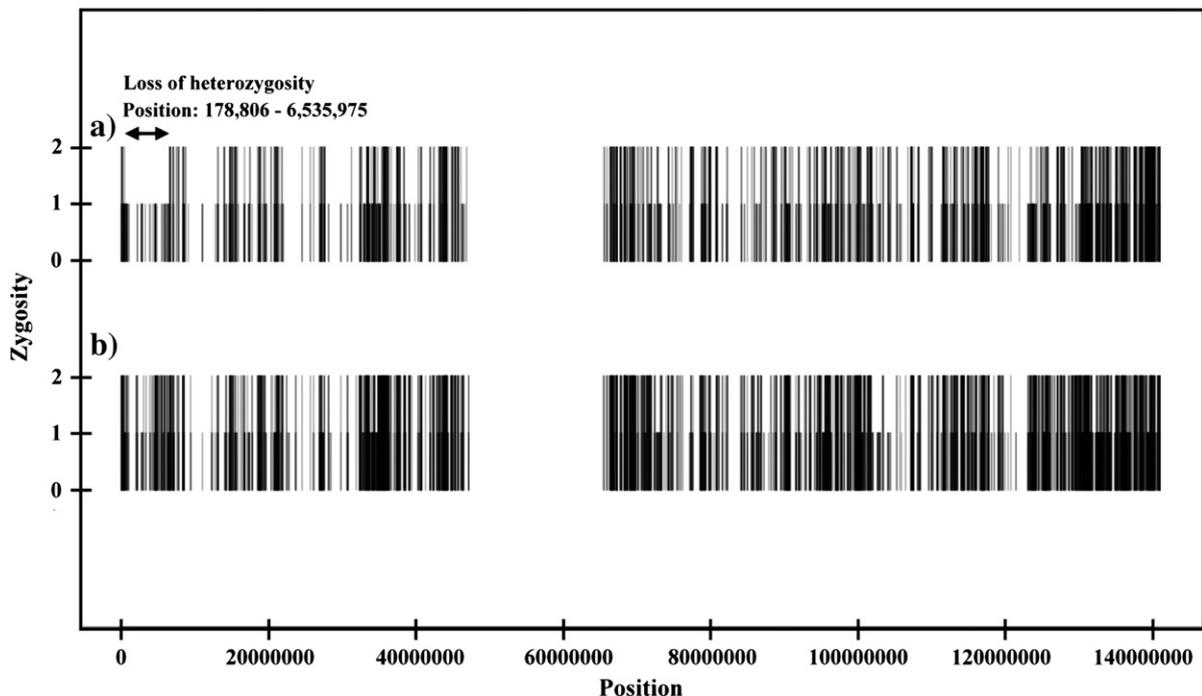

Fig. 3. Diagram depicting the zygosity of chromosome 9 in (a) this case and (b) wild type. Zygosity: 0 = none, 1 = homozygous and 2 = heterozygous.

Table 1
Prenatal diagnosis and perinatal findings in the reported cases with the chromosome distal 9p deletion syndrome.

Authors	Maternal age	Prenatal diagnosis and karyotype	Indication	Molecular study	Perinatal findings and outcome
Stumm et al. [16]	35 yr	*Amniocentesis:* 46,XY,r(9)(p24q34)[69]/45,XY,-9[11] *Cordocentesis:* 46,XY,r(9)(p24q34)	AMA	FISH	TOP. Postnatal findings: presence of uterus, fallopian tubes and vagina, ovarian stroma and/or dysgenetic gonads in internal genitalia
Vialard et al. [18] Fetus 1	NA	*Amniocentesis:* 46,XY,del(9)(p22)	Ultrasound abnormalities	FISH, microsatellites	Ultrasound at 24 wk: ambiguous genitalia with clitoral hypertrophy, normal growth. TOP. Postnatal findings: mild craniofacial dysmorphism, ambiguous genitalia
Fetus 2	47 yr	*Amniocentesis:* 46,XX,del(9)(p22)	AMA; ultrasound abnormalities	NA	Ultrasound at 24 wk: hypoplastic left heart, single umbilical artery, normal growth. TOP. Postnatal findings: normal female external genitalia, facial dysmorphisms of hypertelorism, bulging ocular globes, flat nose, low-set ears with abnormal auticles, large mouth, bilateral choanal atresia, a short neck, two cava vessels, a large pulmonary artery, hypoplasia of the arterial arch, mitral and aortic atresia, three-lobe left lung, single umbilical artery
Witters et al. [14]	NA	*CVS:* 46,XY,der(9)t(3;9)(p14.2;p24)	Ultrasound abnormalities	FISH	Ultrasound at 12 wk: micrognathia, an enlarged posterior fossa, bilateral pes equinovarus, single umbilical artery, a thickened umbilical cord, NT = 2.5 mm. TOP. Postnatal findings: mandibular hypoplasia, microstomia, cleft palate, low-set ears, single umbilical artery, anal atresia, ambiguous external genitalia with an enlarged clitoris, fused labia majora and a polypoid phallus-like structure, abnormal internal genital organs
Brisset et al. [15]	29 yr	*Amniocentesis:* 46,XX,der(9)t(9;17)(p24.3;q24.3)	Increased NT	aCGH	Ultrasound at 12 wk: NT = 4.4 mm. Ultrasound at 22 wk: NT = 9.5 mm, single umbilical artery, partial agenesis of the cerebellar vermis, bilateral cystic choroid plexus, facial dysmorphisms, IUGR. TOP. Postnatal findings: high forehead, hypertelorism, short nose with a broad nasal bridge, long philtrum, down-turned corners, thin upper lip, low-set asymmetric ears, broad neck, widely spaced nipples, short long bones, short ribs, single umbilical artery
Chen et al. [17]	41 yr	*Amniocentesis* (1st): 45,XY,-9[9]/46,XY,r(9) (p24q34.3)[34]/46,XY,idic r(9) (p24q34.3;p24q34.3)[3] *Amniocentesis* (2nd): 45,XY,-9[2]/46,XY,r(9) (p24q34.3)[9] *Cord blood* (postnatal): 45,XY,-9[14]/46,XY,r(9) (p24q34.3)[96]/46,XY,idic r(9) (p24q34.3;p24q34.3)[2]	AMA; abnormal maternal serum screening	FISH	Maternal serum screening at 15 wk: Down syndrome risk = 1/57, MSAFP = 0.63 MoM, MS free βhCG = 1.15 MoM. Ultrasound at 21 wk: ambiguous external genitalia. TOP. Postnatal findings: hypertelorism, down-slanting palpebral fissures, low-set ears, narrow hands and feet, micropenis
Chen et al. [4]	35 yr	*Amniocentesis:* 46,XY,inv dup del(9) (:p22.1 → p24.3::p24.3 → qter)	AMA	FISH, aCGH, microsatellites	Ultrasound at 21 wk: ventriculomegaly, normal male external genitalia. TOP. Postnatal findings: facial dysmorphisms, hypertelorism, prominent nose, low-set ears, normal male external genitalia
Present case	32 yr	*Amniocentesis:* 46,XX,del(9)(p24.1p24.3)	Abnormal maternal serum screening	aCGH	Maternal serum Down syndrome screening positive risk = 1/147, NT = 2.7 mm, MS free βhCG = 1.086 MoM, PAPP-A = 0.519MoM. Ultrasound at 25 wk: IUGR. TOP. Postnatal findings: midface hypoplasia, short nose, depressed nasal bridge, hypertelorism, up-slanting palpebral fissures, long philtrum, microstomia, small low-set ears

NA: not available, AMA: advanced maternal age, FISH: fluorescence in situ hybridization, TOP: termination of pregnancy, yr: years, wk: weeks, CVS: chorionic villus sampling, NT: nuchal translucency, aCGH: array comparative genomic hybridization, IUGR: intrauterine growth restriction, MSAFP: maternal serum α-fetoprotein, MS free βhCG: maternal serum free β-human chorionic gonadotrophin; PAPP-A: pregnancy-associated plasma protein A, MoM: multiples of the median.

sex reversal [38–41]. *DMRT1* (OMIM 602424) encodes doublesex-and MAB3-related transcription factor 1, which is a male-specific transcriptional regulator involved in sex determination and differentiation [42,43]. *DMRT1* suppresses female differentiation in testes, and involves inhibition of meiosis in testes [38–40]. Haploinsufficiency of *DMRT1* has been shown to be sufficient for both 46,XY gonadal dysgenesis and 46, XY ovotesticular disorder of sexual development [41].

In summary, we present prenatal diagnosis and molecular cytogenetic characterization of *de novo* pure distal 9p deletion associated with abnormal maternal serum screening and IUGR by aCGH using uncultured amniocytes. We review the literature of prenatal diagnosis of distal 9p deletion. We discuss the consequence of haploinsufficiency of *DOCK8*, *KANK1*, *VLDLR* and *DMRT1* in this case.

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