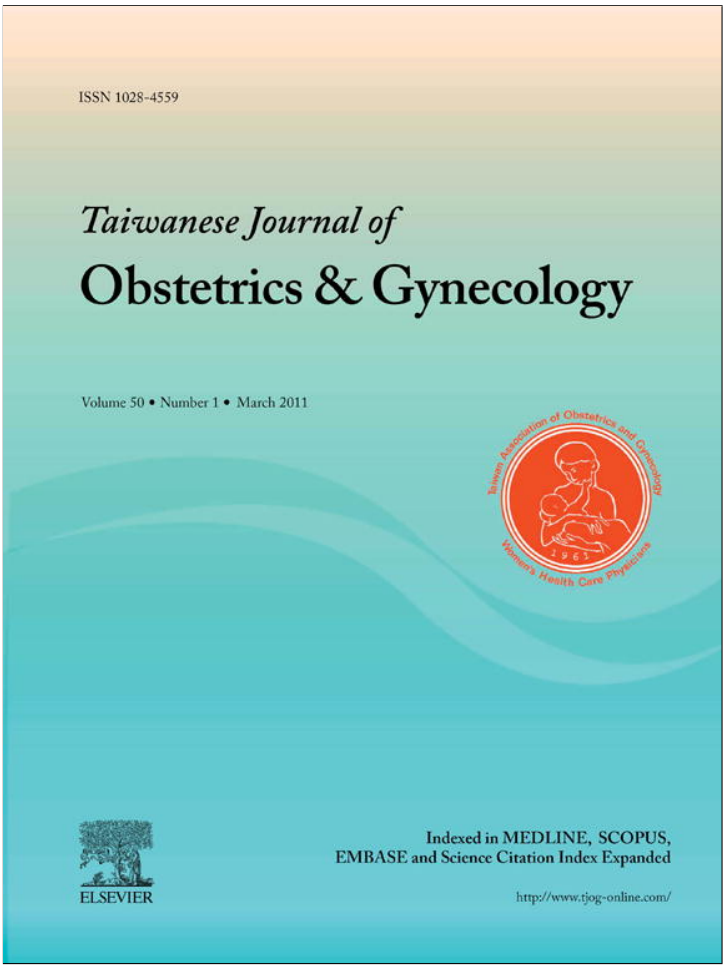

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Short Communication

Inv dup del(9p): Prenatal diagnosis and molecular cytogenetic characterization by fluorescence *in situ* hybridization and array comparative genomic hybridization

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Abstract

Objective: To present molecular cytogenetic characterization of prenatally detected inverted duplication and deletion of 9p, or inv dup del(9p).
Materials, Methods, and Results: A 35-year-old primigravid woman underwent amniocentesis at 16 weeks of gestation because of advanced maternal age. Amniocentesis revealed a derivative chromosome 9, or der(9) with additional material at the end of the short arm of one chromosome 9. Parental karyotypes were normal. Level II ultrasound showed ventriculomegaly and normal male external genitalia. Repeated amniocentesis was performed at 20 weeks of gestation. Array comparative genomic hybridization revealed a 0.70-Mb deletion at 9p24.3 and an 18.36-Mb duplication from 9p24.3 to 9p22.1. The distal 9p deletion encompassed the genes of *DOCK8*, *ANKRD15*, *FOXD4*, *DMRT1*, and *DMRT3*. Fluorescence *in situ* hybridization analysis using bacterial artificial chromosome clone probes specific for 9p confirmed that the der(9) was derived from the inv dup del (9p). The karyotype of the fetus was 46,XY,inv dup del(9)(:p22.1→p24.3::p24.3→qter)dn or 46,XY,der(9) del(9)(p24.3) inv dup(9)(p22.1p24.3) dn. Polymorphic DNA marker analysis determined a maternal origin of the inv dup del(9p). A 512-g male fetus was subsequently terminated at 22 weeks of gestation with facial dysmorphism. The fetus had normal male external genitalia without sex reversal.
Conclusion: Fluorescence *in situ* hybridization and array comparative genomic hybridization are useful to determine the nature of a prenatally detected aberrant chromosome derived from the inv dup del. Male fetuses with inv dup del(9p) and haploinsufficiency of *DMRT1* and *DMRT3* may present normal male external genitalia without sex reversal.

Keywords: 9p; Array comparative genomic hybridization; Deletion; FISH; Inverted duplication; inv dup del(9p)

Introduction

An inverted duplication with a terminal deletion (inv dup del) is a rare complex chromosomal rearrangement that involves an inverted duplication of a part of a chromosome in association with a deletion distal to the site of duplication. The

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inv dup del has been reported in several chromosomes, such as 1p [1,2], 1q [3,4], 2p [5,6], 2q [7–10], 3p [11,12], 4p [13–15], 4q [16], 5p [17,18], 6p [19], 7q [20,21], 8p [22–29], 9p [30–35], 10p and 10q [20], 11p [36], 14q [37,38], 15q [39], 20p [40], 21q [41], and Xp [42,43].

Proposed mechanisms of the inv dup del include the U-type exchange model in which an intrachromosomal recombination and an end-to-end fusion occur in two homologous chromosomes resulting in a dicentric chromosome; and following division, the dicentric chromosome can break and result in a recombinant chromosome with an inverted duplication and a loss of chromosomal material distal to the site of recombination [44]; the nonallelic homologous recombination model mediated by an unequal crossover between inverted low-copy repeats [24]; and the premeiotic nonhomologous end joining model in which a terminal deleted chromosome is generated in the germline and passes through at least one breakage-fusion-bridge cycle leading to a sister chromatid fusion by an nonhomologous end joining and the production of gametes with terminal deletions and interrupted inverted duplications [1].

Prenatal diagnosis of the inv dup del(9p) has not been previously described. Here, we report prenatal diagnosis, molecular cytogenetic analysis, and perinatal findings of a male fetus with inv dup del(9p).

Materials, methods, and results

A 35-year-old primigravid woman underwent amniocentesis at 16 weeks of gestation because of advanced maternal age. Cytogenetic analysis then revealed a derivative chromosome 9, or der(9), with additional material at the end of the short arm of one chromosome 9. The parental karyotypes were normal. The woman requested repeated amniocentesis at 20 weeks of gestation, which revealed an inv dup del(9p) (Fig. 1). Using uncultured amniocytes, bacterial artificial chromosome (BAC)-based array comparative genomic hybridization (aCGH) (CMDX BAC-based aCGH CA3000 chips) (CMDX, Irvine, CA, USA) demonstrated a 9p deletion encompassing about 0.37 Mb from clone RP11-1112G24 to RP11-130C19 and a 9p duplication encompassing about 17.87 Mb from clone RP11-690N7 to RP11-322J7. The result of BAC-aCGH was arr cgh 9p24.3p24.3 (RP11-1112G24→RP11-130C19)×1, 9p24.3p22.1 (RP11-690N7→RP11-322J7)×3 (Fig. 2).

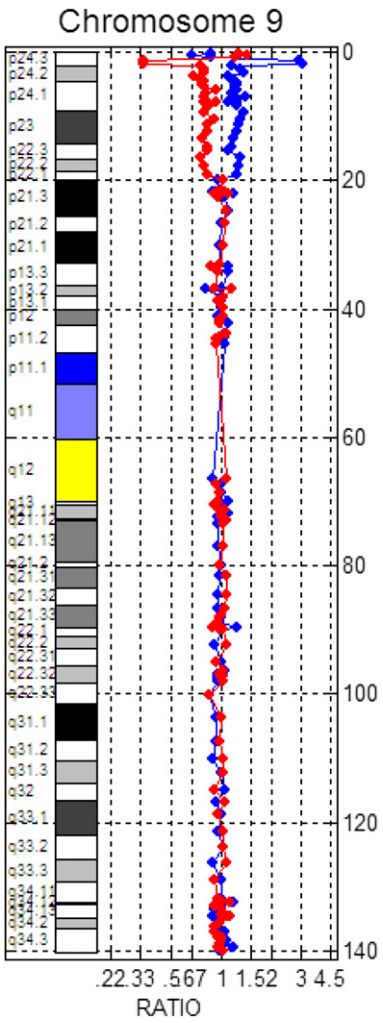

Fig. 2. BAC based-aCGH shows a deletion of terminal 9p [arr cgh 9p24.3p24.3 (RP11-1112G24→RP11-130C19)×1] and a duplication of distal 9p [arr 9p24.3p22.1 (RP11-690N7→RP11-322J7)×3]. aCGH = array comparative genomic hybridization; BAC = bacterial artificial chromosome.

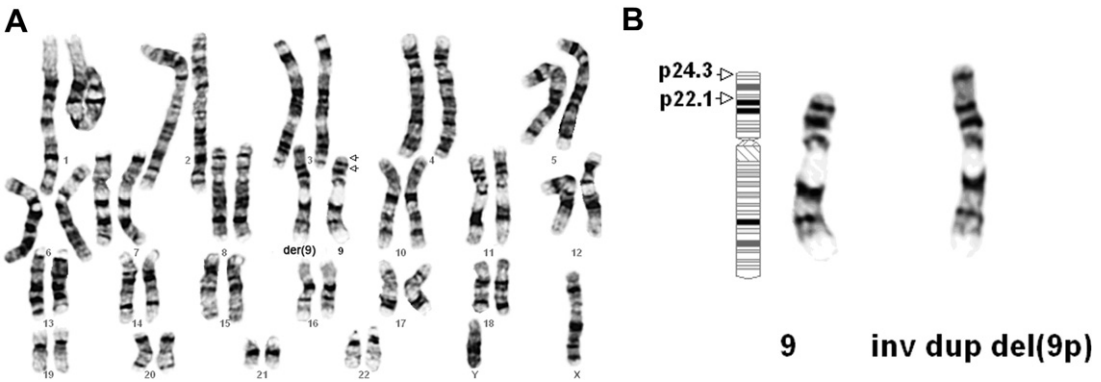

Fig. 1. (A) A karyotype 46,XY,inv dup del(9)(:p22.1→p24.3::p24.3→qter) or 46,XY,der(9)del(9)(p24.3) inv dup(9)(p22.1p24.3) in the fetus; (B) Partial G-banded karyotype of the fetus showing one normal chromosome 9 and one derivative chromosome 9, or der(9), with inv dup del(9p). The arrows indicate the breakpoints. inv dup del = inverted duplication with a terminal deletion.

For fluorescence *in situ* hybridization determination of the inv dup del in the der(9), the BAC clone probe mapping the genomic region of the distal chromosome 9p, and the telomeric region of 9p were used. The BAC clone probes RP11-32F11 (3,104,722–3,267,008) (spectrum green) at 9p24.2 and RP11-340N12 (17,136,369–17,298,494) (spectrum red) at 9p22.2 were used to determine the inverted duplication. The BAC clone probe RP11-31F19 (537,217–682,143) (spectrum green) at 9p24.3 and the Telomere 9q probe (TelVysion 9q; Vysis, Downers, Grove, IL, USA) (spectrum red) (control) were used to determine the terminal 9p deletion. Fluorescence *in situ* hybridization analysis showed an inverted duplication of distal 9p with an inverted duplication orientation of red-green-green-red (Fig. 3) and a terminal deletion with absence of a green signal on der(9) (Fig. 4). The karyotype of the fetus was 46,XY,inv dup del(9)(:p22.1→p24.3::p24.3→qter)dn or 46,XY,der(9) del(9)(p24.3) inv dup(9)(p22.1p24.3)dn.

Level II ultrasound showed ventriculomegaly and normal male external genitalia at 21 weeks of gestation. The parents opted to terminate the pregnancy at 22 weeks of gestation. A 518-g male fetus was delivered with dysmorphism of hypertelorism, a prominent nose, and low-set ears (Fig. 5). The male external genitalia were normal (Fig. 6). Cytogenetic analysis of the cord blood confirmed the prenatal diagnosis. Using fetal blood, oligonucleotide-based (oligo) aCGH (SurePrint G3 Human CGH Microarray kit 60K; Agilent Technologies, Santa Clara, CA, USA) demonstrated a 0.70-Mb deletion at 9p24.3 (271,057–974,003) (NCBI build 36 March 2006) and an 18.36-Mb duplication from 9p24.3 to 9p22.1 (1,036,210–19,396,808) (Fig. 7). The result of oligo-aCGH was arr cgh 9p24.3p24.3 (271,057–974,003)×1, 9p24.3p22.1 (1,036,210–19,396,808)×3. Microsatellite analysis using the fetal and parental DNA demonstrated that the deletion and duplication of 9p were maternal in origin. In the duplicated segment of 9p, all the informative microsatellites were homozygous indicating an intrachromosomal event.

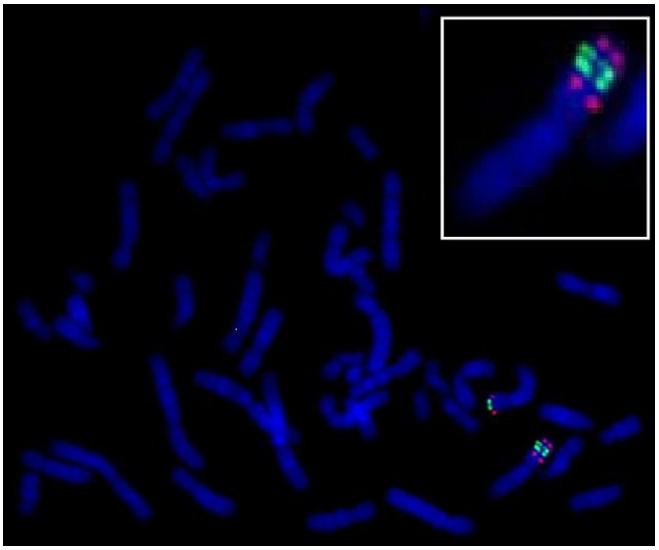

Fig. 3. FISH using BAC RP11-340N12 (red) at 9p22.2 and RP11-32F11 (green) at 9p24.2. The der(9) shows four signals in the order of red-green-green-red indicating an inverted duplication of 9p. BAC = bacterial artificial chromosome; FISH = fluorescence *in situ* hybridization.

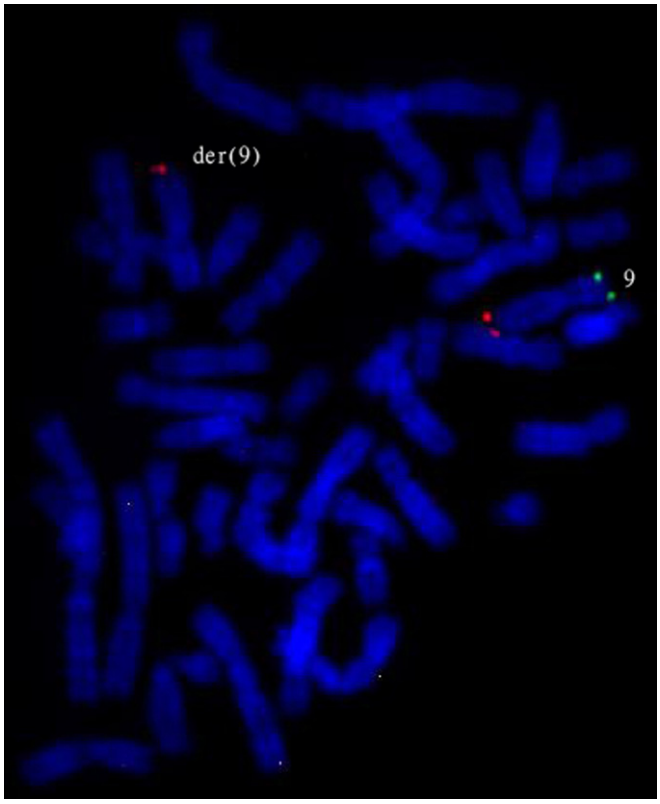

Fig. 4. FISH using BAC RP11-31F19 (green) at 9p24.3 and the Telomere 9q probe (TelVysion 9q) (red) shows absence of a green signal on der(9) indicating a terminal deletion of 9p. BAC = bacterial artificial chromosome; FISH = fluorescence *in situ* hybridization.

Discussion

We have reported an inverted duplication of the distal portion of the short arm of chromosome 9 (9p22.1→p24.3) and a deletion of the distal portion (9p24.3→pter) in a male fetus who manifested ventriculomegaly on prenatal ultrasound and facial dysmorphism at birth. The inv dup del(9p) was maternal in origin and intrachromosomal. The homozygosity throughout the duplicated segment implicates a possible U-type exchange mechanism, although other mechanisms cannot be completely excluded. To date, at least six cases with 9p duplication/deletion have previously been reported, and all were females. Teebi et al [30] first reported a 20-month-old female with an inverted duplication of proximal 9p and a deletion of distal 9p, or inv dup del(9)(:p13→p22::p22→qter), prenatal intrauterine growth restriction, psychomotor developmental delay, a small umbilical hernia, and craniofacial dysmorphisms, including a narrow forehead with metopic ridging, a small anterior fontanelle, a small nose, midface hypoplasia, mild upward slant of palpebral fissures, mild epicanthic folds, thin and long eyebrows with mild synophrys, thin lips, and a short neck. The girl had an inverted duplication of proximal 9p (9p13→p22) and a deletion of distal 9p (p22→pter). In this case, during pregnancy, intrauterine

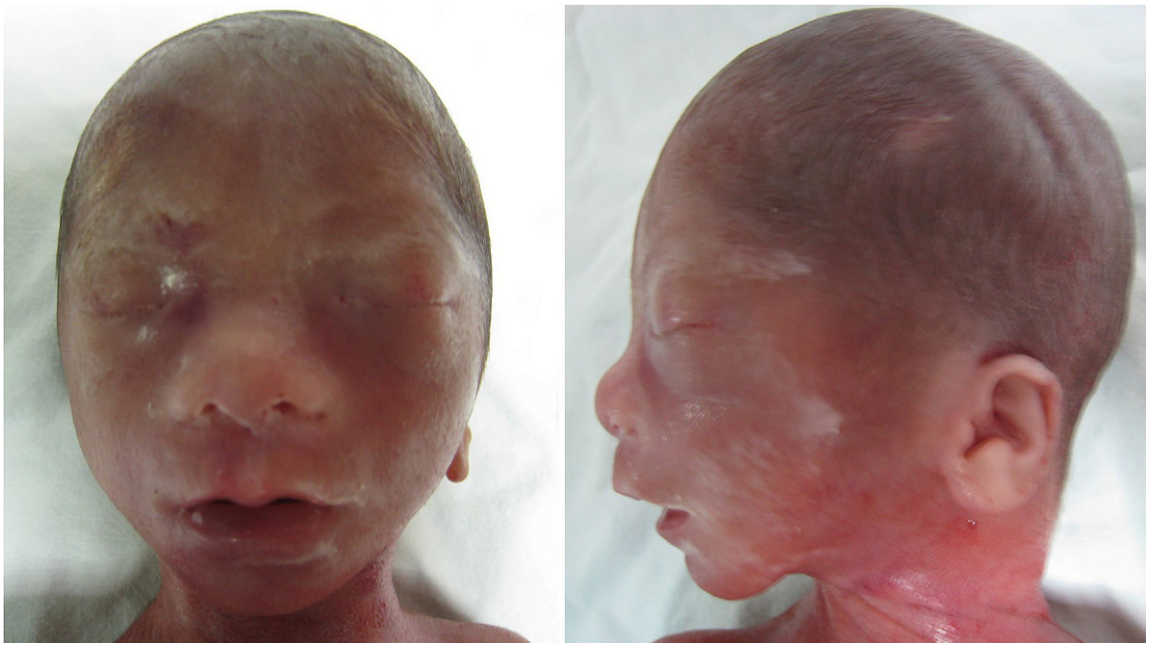

Fig. 5. The craniofacial appearance of the fetus at birth.

growth restriction was noted but a chromosome analysis of amniocytes was reportedly normal. Krepischi-Santos and Vianna-Morgante [31] reported a 16-year-2-month-old female with terminal deletion and an inverted duplication involving at least 9p23-p25.1. The duplication was paternal in origin. The girl manifested microcephaly, frontal bossing, a low-set frontal hairline, facial hirsutism, hypertelorism, deep-set and downslanting eyes, epicanthus, a broad-based nose with a bulbous tip, a short and well-defined philtrum, downturned corners of the mouth, retrognathia, low-set large and protruding ears, hypoplastic nails, and bilateral single transverse creases. Her menstrual cycles were normal. Chabchoub et al [32] reported a 10-year-old female with mosaicism for inv dup del(9p) and a karyotype of 46,XX,del(9)(p22.1)/46,XX,der(9)t(5;9)(p13.3;p22.1), del(9)(p22.1),dup(9) (p13.3→p22.1::p22.1→qter). The girl manifested psychomotor developmental delay, mild synophrys, hypoplastic alae nasi, long and smooth philtrum, a thin upper lip, small and dysmorphic ears, camptodactyly of the fifth fingers, upslanting palpebral fissures, prominent metopic suture, depressed and broad nasal root, plagiocephaly, a hypoplastic ectopic right kidney, and vesiculoureteral reflux. The inv dup del(9p) was paternal in origin. Swinkels et al [33] in 2008 reported a 2-year-old female (Case 7) with a deletion of 9p (p22.3→pter) and an inv dup(9)(p22.1p22.3). The girl manifested developmental speech and motor delay, hypotonia, short stature, trigonocephaly, upward slant short palpebral fissures, epicanthal folds, low-set posteriorly angulated ears, a short flat nose with anteverted nostrils, a flat philtrum, a thin upper lip, a high/narrow palate, broad internipple distance, tapering fingers, hyperconvex nails, and cardiac defects. Hulick et al [34] reported a 4-month-old female with a deletion of 9p (p24.2→pter) and an inv dup(9)(p21.3p24.2). The girl manifested hypotonia, growth and developmental delay, cleft palate, absent uvula, clinodactyly, large palpebral fissures, hypertelorism, a bulbous nose, abnormal ears, and dystrophic nails. Mosca et al [35] reported a 12-year-old female with 22q11.2 microdeletion and inv dup del(9p) consisting of a deletion region spanning 0.4–0.6 Mb and a duplication region spanning 1.6–11.8 Mb. The girl manifested mental retardation and asymmetric polymicrogyria predominantly affecting the right occipital lobe.

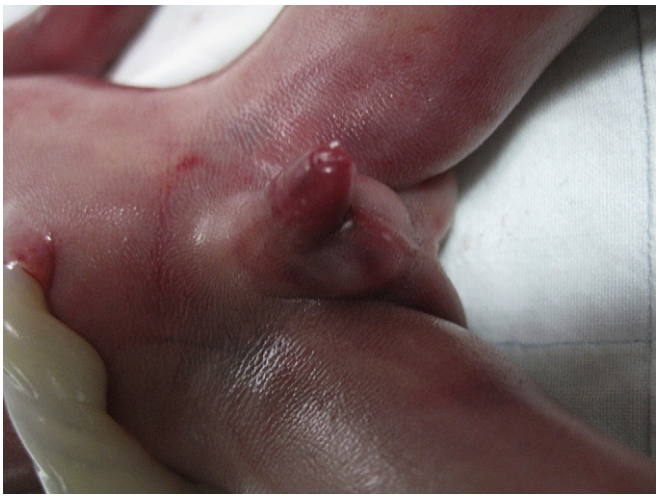

Fig. 6. The male external genitalia of the fetus at birth.

The present case was associated with partial trisomy 9p and ventriculomegaly. Gene dosage effect on chromosome 9p is responsible for normal development of the central nervous system. Partial trisomy 9p has been reported to be associated with abnormal neural migration, subcortical band heterotopia,

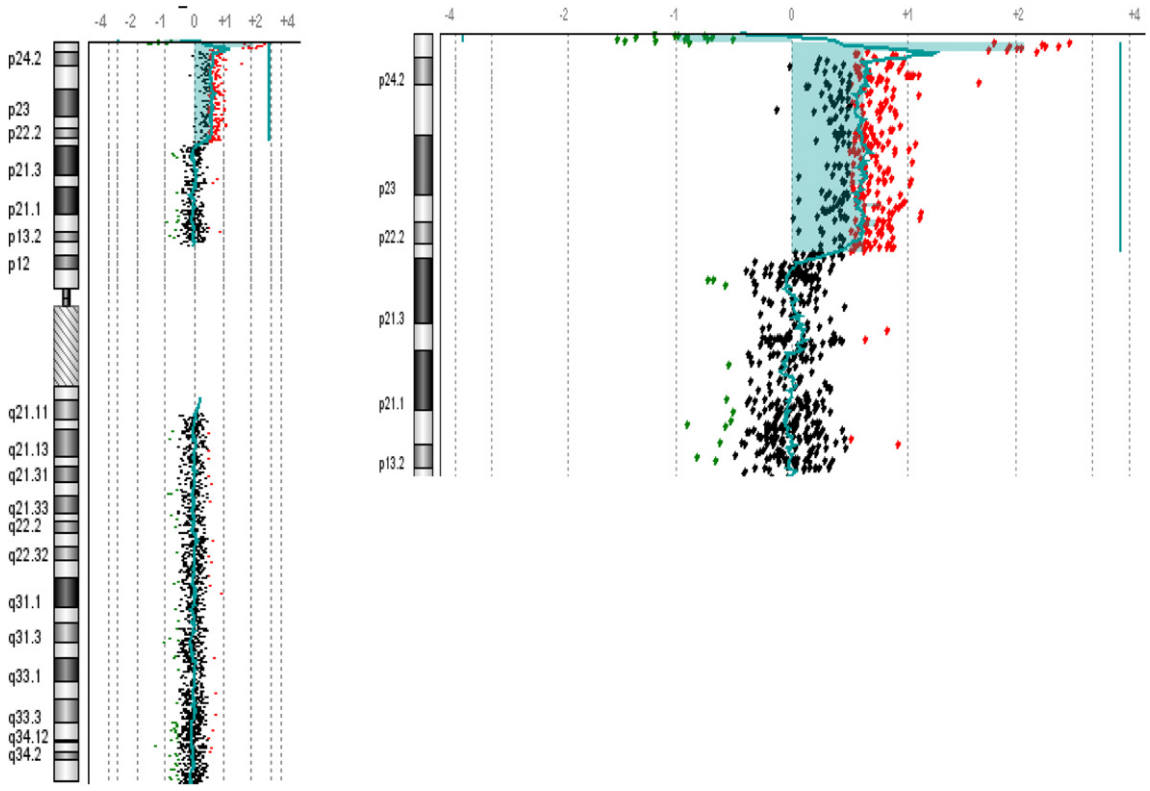

Fig. 7. Oligonucleotide-based aCGH shows a 0.70-Mb deletion at terminal 9p [arr cgh 9p24.3p24.3 (271,057–974,003)×1] and an 18.36-Mb duplication of 9p22.1→p24.3 [arr cgh 9p24.3p22.1 (1,036,210–19,396,808)×3]. aCGH = array comparative genomic hybridization.

Dandy-Walker malformation, ventriculomegaly, corpus callosum hypogenesis or agenesis, and polymicrogyria [35,45–49].

The present case was also associated with a distal 9p deletion encompassing the genes of *DOCK8*, *ANKRD15*, *FOXD4*, *DMRT1*, and *DMRT3*. Genetic aberrations in *DOCK8*, *ANKRD15*, and *FOXD4* may result in neurological and psychiatric disorders. *DOCK8* [Online Mendelian Inheritance in Man (OMIM) 611432] is a gene associated with autosomal dominant mental retardation 2 [50]. Heterozygous disruption of the *DOCK8* gene by deletion or by translocation breakpoints has been reported to cause mental retardation and developmental disability. *ANKRD15* (OMIM 607704) is a maternally imprinted gene that is expressed only from the paternal allele [51]. Deletion of the *ANKRD15* gene causes parent-of-origin-dependent inheritance of familial cerebral palsy that occurs only in individuals inheriting the deletion from the father [51]. *FOXD4* (OMIM 601092) encodes forkhead box D4 protein, which is a transcription factor. *FOXD4* is expressed in the heart, skeletal muscles, and brain [52]. Mutations in the human *FOXD4* gene can cause a complex phenotype consisting of dilated cardiomyopathy, obsessive-compulsive disorders, and suicidality [53].

Distal 9p deletion can be associated with 46,XY gonadal dysgenesis and sex reversal [54–56]. There are three *DMRT* genes, namely *DMRT1*, *DMRT2*, and *DMRT3* genes, all at 9p24.3. *DMRT1* and *DMRT2* are well-known sex-determining genes [54,56], but the role of *DMRT3* on sex determination is not clear at the present time. *DMRT1* (OMIM 602424) encodes doublesex- and MAB3-related transcription factor 1, which is a male-specific transcriptional regulator involved in sex determination and differentiation [57,58]. *DMRT2* (OMIM 604935) encodes DMRT2 protein, which is also associated with gonadal dysgenesis and XY sex reversal [54,59]. In the present case, only *DMRT1* and *DMRT3* were deleted, and *DMRT2* was intact. Our fetus showed normal male external genitalia without sex reversal. Although *DMRT1* gene is involved in sex development, incomplete penetrance with differences in the phenotype of abnormal male sex development still exists [60]. Patients with a 9p24 deletion have been reported to manifest normal male external genitalia and/or mild gonadal abnormalities [33,61–63]. Barbaro et al [60] suggested that a more complicated mechanism should be hypothesized to explain the variable penetrance. In addition to *DMRT*, other sex-determining genes, such as *SF1*, *DAX1*, *WT1*, *WNT4*, and *SOX9* are associated with male gonadal development. Investigations of the interaction among those sex-determining genes and the gene dosage threshold effect are required for further elucidation of the complicated mechanism of the variable penetrance.

Acknowledgments

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