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Short Communication

Chromosome 1p32-p31 deletion syndrome: Prenatal diagnosis by array comparative genomic hybridization using uncultured amniocytes and association with *NFIA* haploinsufficiency, ventriculomegaly, corpus callosum hypogenesis, abnormal external genitalia, and intrauterine growth restriction

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Abstract

Objective: To present prenatal diagnosis of chromosome 1p32-p31 deletion syndrome with *NFIA* haploinsufficiency, ventriculomegaly, corpus callosum hypogenesis, abnormal external genitalia, and intrauterine growth restriction and to review the literature.

Materials, Methods, and Results: A 26-year-old, primigravid woman was referred for amniocentesis at 30 weeks of gestation because of hydrocephalus and short limbs. Prenatal ultrasound showed macrocephaly, prominent forehead, ventriculomegaly, corpus callosum hypogenesis, micrognathia, and ambiguous external genitalia. Amniocentesis was performed, and array comparative genomic hybridization using uncultured amniocytes revealed a 22.2-Mb deletion of 1p32.3-p31.1 [arr cgh 1p32.3p31.1 (55,500,291 bp–77,711,982 bp)×1] encompassing the genes of *NFIA*, *GPR177*, and 89 additional genes. Cytogenetic analysis revealed a karyotype of 46,XX,del(1)(p31.1p32.3)dn. At 33 weeks of gestation, a dead fetus was delivered with a body weight of 1536 g (<5th centile); relative macrocephaly; a broad face; prominent forehead; hypertelorism; anteverted nostrils; micrognathia; low-set ears; and abnormal female external genitalia with labial fusion, labial hypertrophy, absence of vaginal opening, and clitoral hypertrophy. Polymorphic DNA marker analysis determined a paternal origin of the deletion.

Conclusion: Prenatal diagnosis of ventriculomegaly with an abnormal corpus callosum should alert subtle chromosome aberrations and prompt molecular cytogenetic investigation if necessary. Fetuses with chromosome 1p32-p31 deletion syndrome and haploinsufficiency of the *NFIA* gene may present ventriculomegaly, corpus callosum hypogenesis, abnormal external genitalia, and intrauterine growth restriction in the third trimester.

Keywords: Abnormal external genitalia; Chromosome 1p32-p31 deletion syndrome; Corpus callosum hypogenesis; Ventriculomegaly

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Introduction

Chromosome 1p32-p31 deletion syndrome [Online Mendelian Inheritance in Man (OMIM) 613735], a contiguous gene deletion syndrome, is associated with haploinsufficiency of the *NFIA* gene. The gene *NFIA* (OMIM 600727) locates at 1p31.3-p31.2 and encodes nuclear factor IA (NFIA) protein. Chromosome 1p32-p31 deletion syndrome is characterized by macrocephaly; hydrocephalus/ventriculomegaly; hypoplastic/absent corpus callosum; developmental delay; urinary tract defects such as vesicoureteral reflux and urinary incontinence; facial dysmorphism of a broad face with prominent forehead, low-set ears, a small mouth and chin, anteverted nostrils, a high palate and sparse eyebrows, and variable features of pigmentary retinopathy; inguinal hernia; cryptorchidism; polydactyly; hip dysplasia; and cutis marmorata [1,2]. To date, only seven cases with chromosome 1p32-p31 deletion syndrome have been reported [1–5], and all were diagnosed in infancy or childhood. Herein, we present an additional case, which, to our knowledge, is the first prenatally diagnosed case

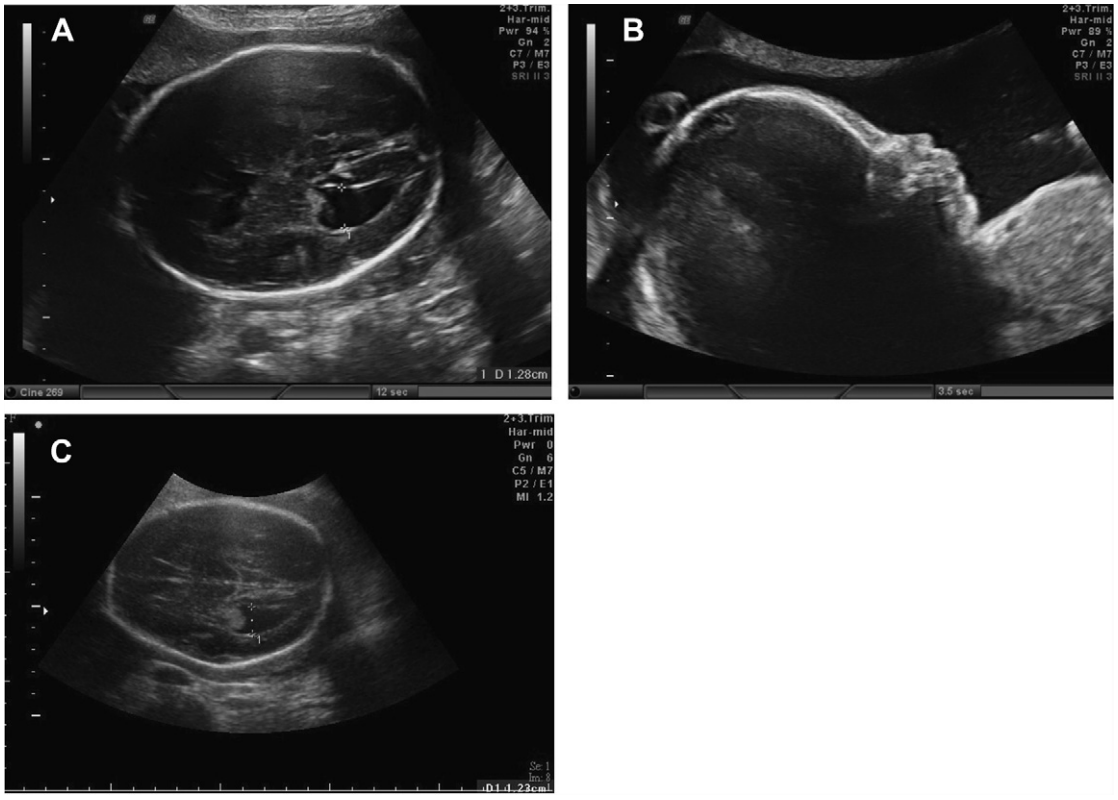

Fig. 1. (A) Ventriculomegaly; (B) macrocephaly with prominent forehead and micrognathia; and (C) corpus callosum hypogenesis with absence of cavum septum pellucidum on prenatal ultrasound at 30 weeks of gestation.

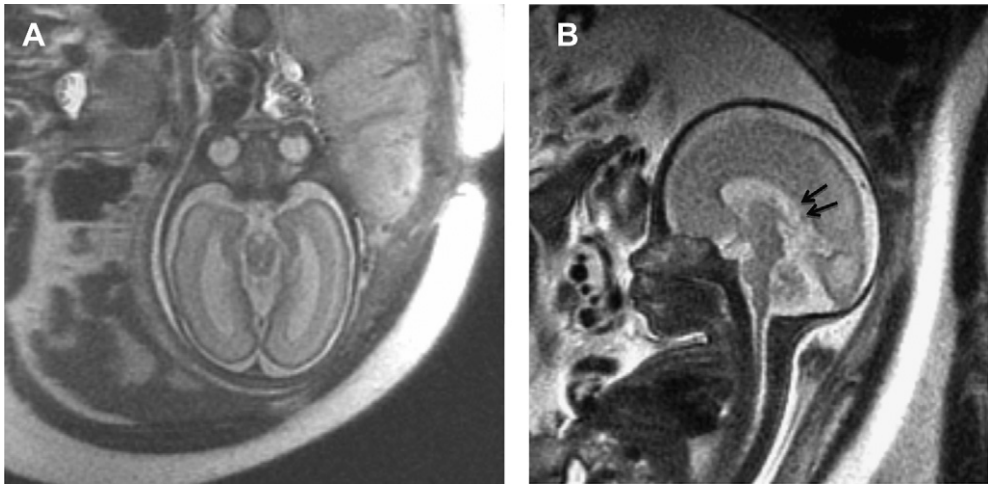

Fig. 2. (A) Ventriculomegaly and (B) hypoplasia of the splenium of corpus callosum (arrow) on ultrafast magnetic resonance imaging at 30 weeks of gestation.

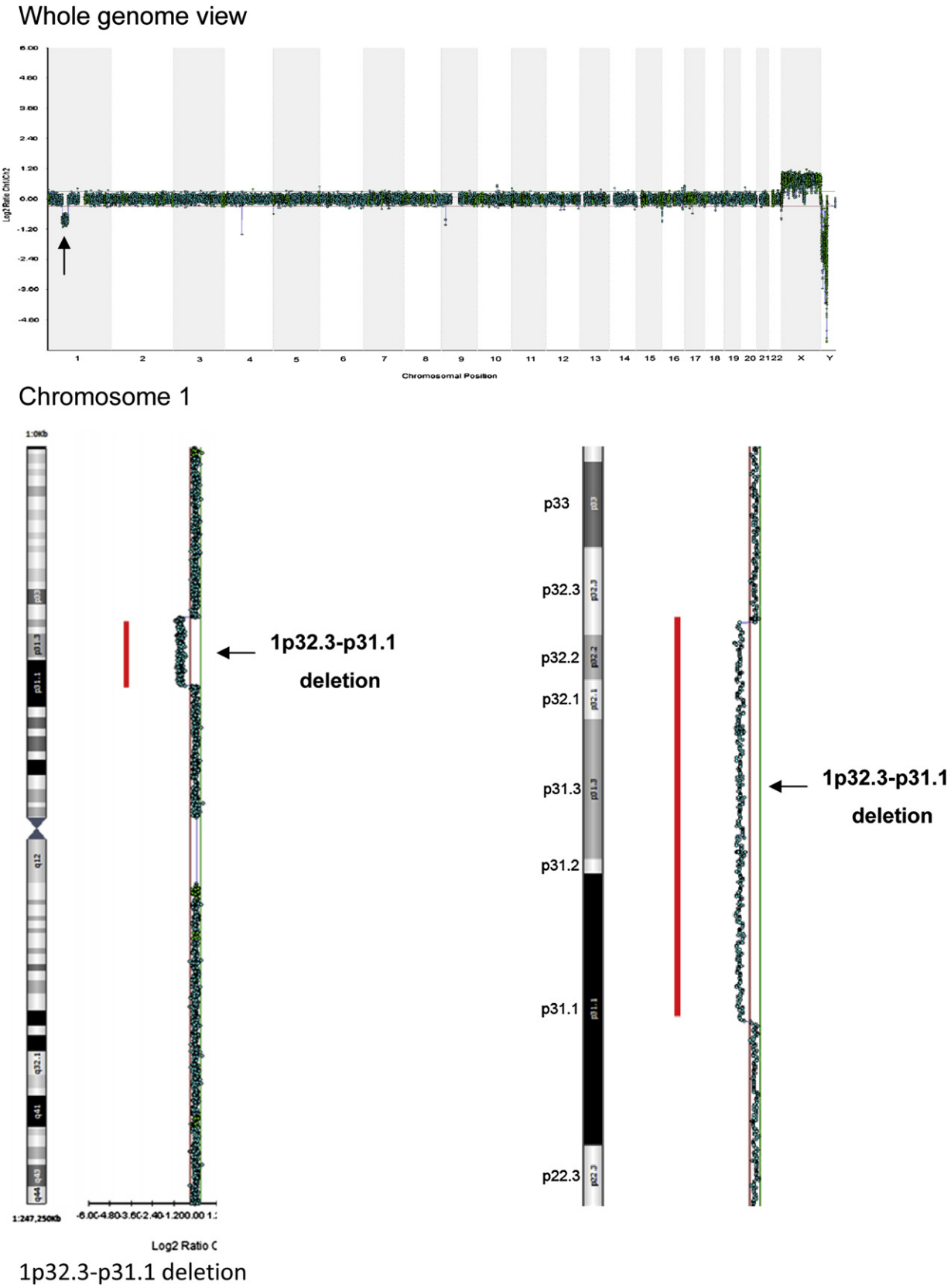

Fig. 3. Oligonucleotide-based array comparative genomic hybridization shows a 22.2-Mb deletion from 1p32.3 to 1p31.1 [arr cgh 1p32.3p31.1 (55,500,291–77,711,982)×1] (arrow). arr cgh = array comparative genomic hybridization.

with chromosome 1p32-p31 deletion syndrome. We also review the literature.

Materials, methods, and results

A 26-year-old, primigravid woman was referred for amniocentesis at 30 weeks of gestation because of hydrocephalus and short limbs. Her husband was 29-year-old, and there was no family history of congenital malformations. Prenatal ultrasound at 30 weeks of gestation revealed a biparietal diameter of 7.91 cm (31.89 weeks), an abdominal circumference of 23.49 cm (27.81 weeks), a femur length of 4.88 cm (26.4 weeks), prominent forehead, micrognathia, ambiguous external genitalia, ventriculomegaly, and corpus callosum hypogenesis (Fig. 1). Other internal organs were unremarkable. Ultrafast magnetic resonance imaging showed ventriculomegaly and hypoplasia of the splenium of corpus callosum (Fig. 2). Amniocentesis was performed at 30 weeks of gestation, and 56 mL of amniotic fluid was aspired, of which 20 mL was for array comparative genomic hybridization (aCGH) using uncultured amniocytes, 20 mL for culture and conventional cytogenetic analysis, and 12 mL for mutational analysis of the *FGFR3* gene. Oligonucleotide-based aCGH of CytoChip Oligo Array (BlueGnome, Cambridge, UK) was applied in the uncultured amniocytes. The aCGH analysis revealed a female with a 22.2-Mb deletion of 1p32.3-p31.1 encompassing the genes of *NFIA* (61,103,519–61,694,617 bp), *GPR177*, and 89 additional genes. The result was arr cgh 1p32.3p31.1 (55,500,291–77,711,982 bp)×1, according to CytoChip Oligo Array [UCSC genome browser on human, March 2006 (NCBI 36/hg 18) assembly] (Fig. 3). Subsequent conventional cytogenetic analysis revealed a karyotype of 46,XX,del(1)(p31.1p32.3)dn (Fig. 4). The parental karyotypes were normal. Fluorescence *in situ* hybridization analysis using bacterial artificial chromosome clone probes RP11-31P4 (61,339,876–61,527,391 bp) (spectrum red) at 1p31.3 encompassing the *NFIA* gene and RP11-438F14 (spectrum green) at 1q44 as internal control showed absence of the red signal in the del(1) (p31.1p32.3) chromosome (Fig. 5). The fluorescence *in situ* hybridization result was consistent with haploinsufficiency of the *NFIA* gene. Mutational analysis of the *FGFR3* gene revealed no mutation and thus excluded achondroplasia. At 33 weeks of gestation, a dead fetus was delivered with a body weight of 1536 g (<5th centile); a body length of 41 cm (<5th centile); relative macrocephaly; a broad face; prominent forehead; hypertelorism; anteverted nostrils; micrognathia; low-set ears; and ambiguous external genitalia with labial fusion, labial hypertrophy, absence of vaginal opening, and clitoral

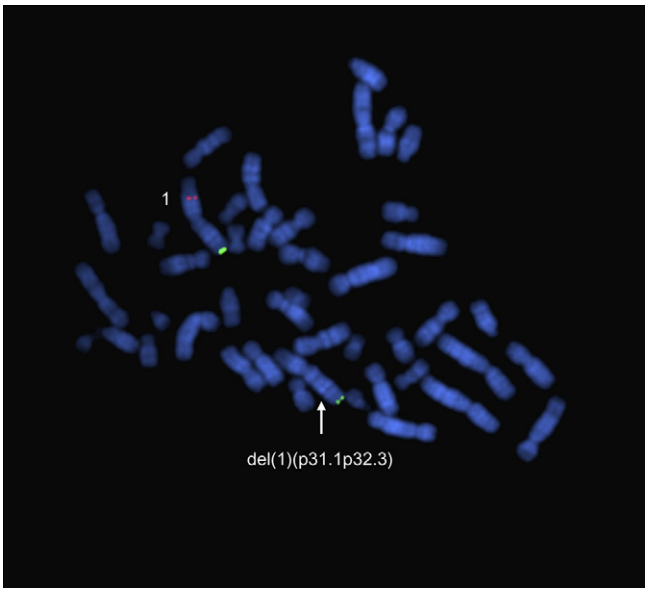

Fig. 5. Fluorescence *in situ* hybridization using bacterial artificial chromosome clone probes RP11-31P4 (61,339,876–61,527,391 bp) (spectrum red) at 1p31.3 encompassing the *NFIA* gene and RP11-438F14 (spectrum green) at 1q44 as internal control shows absence of the red signal in the del(1)(p31.1p32.3) chromosome. del = deletion.

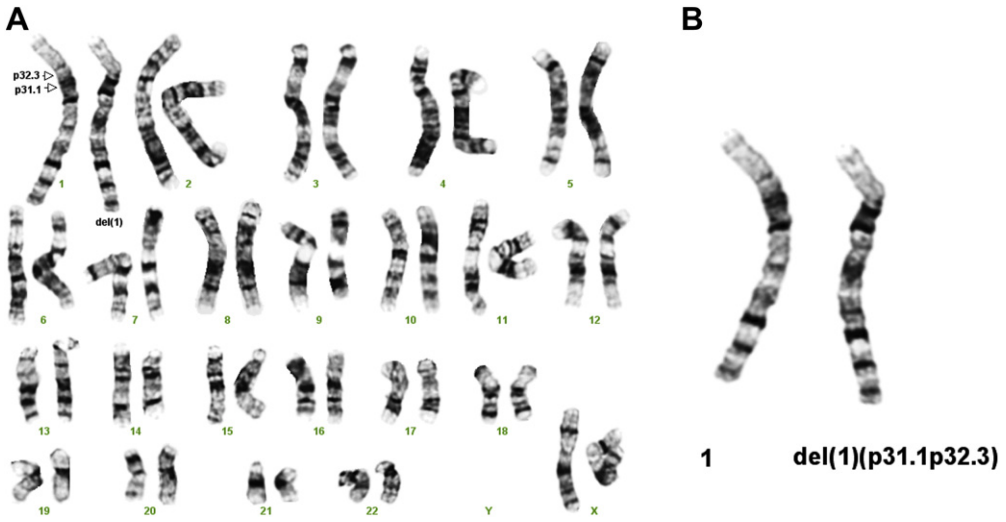

Fig. 4. (A) A karyotype of 46,XX,del(1)(p31.1p32.3). The arrows indicate the breakpoints. (B) Partial G-banded karyotype of the fetus shows one normal chromosome 1 and one aberrant chromosome 1 of del(1)(p31.1p32.3). del = deletion.

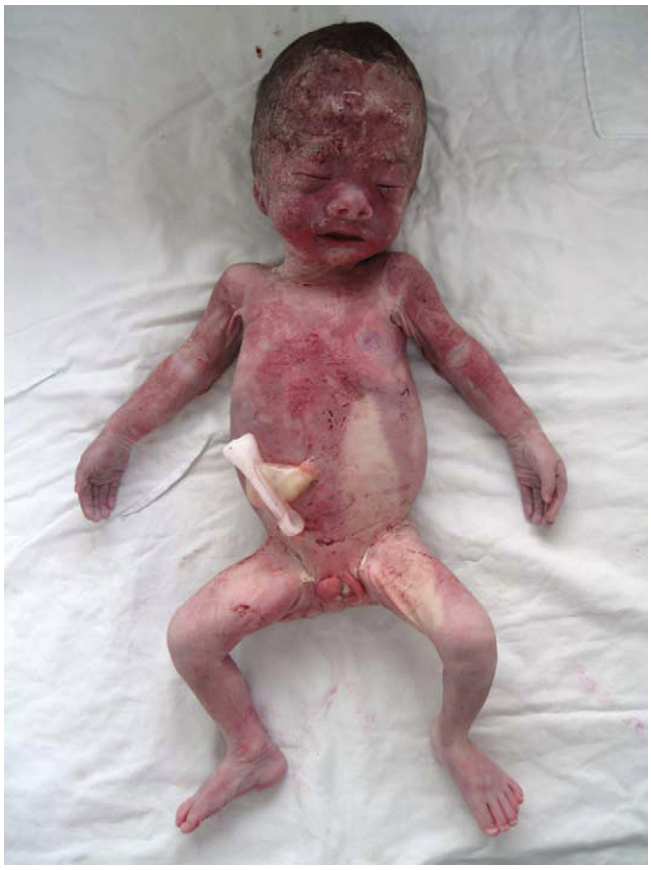

Fig. 6. Whole body view of the fetus at birth.

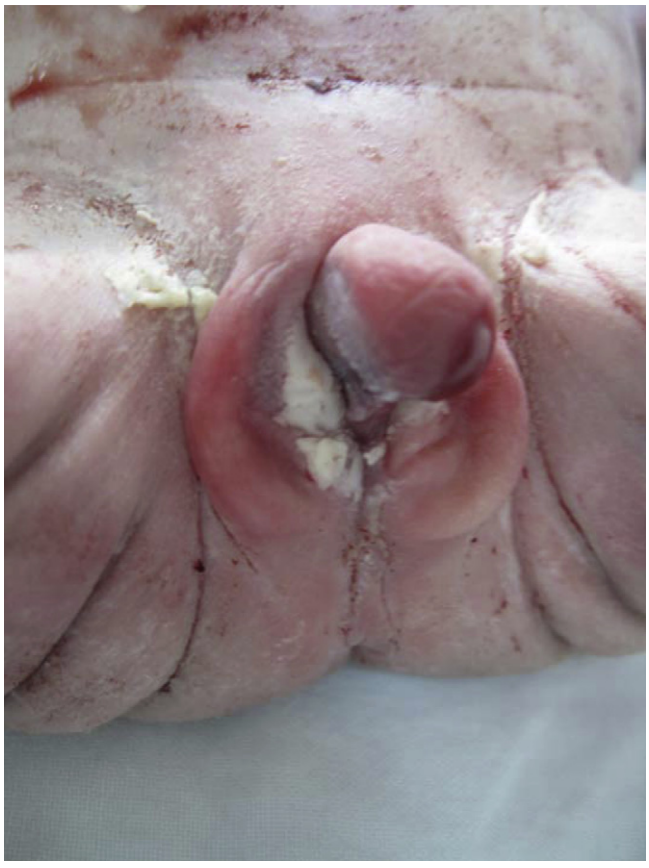

Fig. 8. Abnormal female external genitalia with labial fusion, labial hypertrophy, clitoral hypertrophy, and absence of vaginal opening.

hypertrophy (Figs. 6–8). Polymorphic DNA marker analysis determined a paternal origin of the deletion (Fig. 9) (Table 1).

Discussion

The *de novo* deletion of 22.2 Mb encompassing 1p32.3-p31.1 in the present case mainly affects the proximal region of 1p32.3, the entire regions of 1p32.2, 1p32.1, 1p31.3, and 1p31.2, and the distal region of 1p31.1. A critical region for hypoplastic/absent corpus callosum and ventriculomegaly has been proposed at 1p31.3-p31.2 in a series of five patients of chromosome 1p32-p31 deletion syndrome with haploinsufficiency of the *NFIA* gene [1]. Table 2 shows the clinical findings of eight individuals, including the present case with chromosome 1p32-p31 deletion syndrome.

Sivasankaran et al [3] first reported the association of interstitial deletion of chromosome 1p with absent corpus callosum.

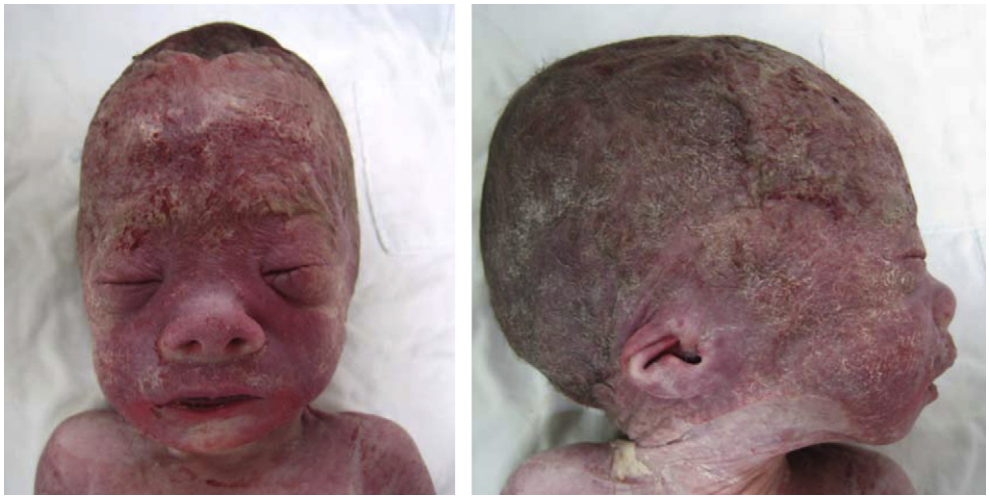

Fig. 7. Craniofacial appearance of the fetus at birth.

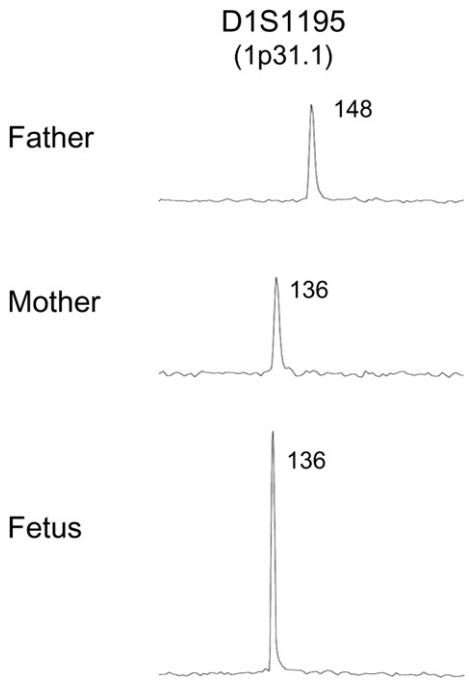

Fig. 9. Representative electrophoretograms of quantitative fluorescent polymerase chain reaction assays. The marker D1S1195 shows only one maternal allele (136 bp) in the fetus indicating a paternal origin of the deletion.

The baby girl had a karyotype of 46,XX,del(1)(p22p32)dn, absent corpus callosum, ocular hypertelorism, low-set ears, upturned nostrils, mesomelic shortening of the limbs, hypoplastic labia minora, and absent clitoris, and the clinical features were similar to chromosome 1p32-p31 deletion syndrome. Campbell et al [4] and Lu et al [1] reported two half-siblings with a maternally inherited unbalanced interstitial deletion of del(1)(p31.2p32.3) encompassing a region of 12 Mb and containing the entire *NFIA* gene and 47 additional genes. Both patients exhibited ventriculomegaly or hydrocephalus, a thin or agenesis of the corpus callosum (ACC), syringomelia, a tethered spinal cord, and/or left vesicoureteral reflux. Shanske et al [5] and Lu et al [1] reported a boy with a 12-Mb deletion of 2q14.3→q21 involving 39 genes and a reciprocal translocation of t(1;2)(p31.3;q22.1) involving a 3.9-kb breakpoint between Exons 7 and 8 of the *NFIA* gene. The patient exhibited hypoplastic corpus callosum, nonprogressive ventriculomegaly, and a gray matter heterotopia. Lu et al [1] investigated two new cases with chromosome 1p32-p31 deletion syndrome in addition to three cases previously reported by Campbell et al [4] and Shanske et al [5]. The first new case was a 6-year-old girl with congenital hydrocephalus, a thin corpus callosum, Type I Chiari malformation, a tethered spinal cord, a low vertebral deformity, congenital bilateral dysplastic kidneys, bilateral ureterovesical reflux, hydronephrosis, and a karyotype of 46,XX,t(1;20)(p31.3;q13.31)dn. In that case, the breakpoint at 1p31.3 had disrupted Intron 2 of the *NFIA* gene. The second new case presented ACC and ventriculomegaly on second trimester ultrasound and manifested additional abnormalities of a tethered spinal cord, Type I Chiari malformation, and dysplasia of the anterior left temporal fossa in childhood. The patient had a karyotype of 46,XY,t(1;3)(p31.1;q25.1) del(1)(p31.3p32.1)dn with a 2.2-Mb chromosome deletion of 1p32.1-p31.3, including the complete deletion of the *NFIA* gene and eight additional genes. Koehler et al [2] recently reported an infant girl who had a karyotype of 46,XX,del(1)(p31.3p32.2)dn with a 4.9-Mb deletion of 1p32.2-p31.3. The deleted region included the *NFIA* gene and 16 additional genes. The patient manifested characteristic facial dysmorphism, a high palate, cutis marmorata, macrocephaly, hypotonia, and developmental delay. Radiological examinations showed hypoplastic corpus callosum, ventriculomegaly, a large retrocerebellar cyst, and hypoplastic cerebellar vermis.

Table 1
Molecular results using polymorphic DNA markers specific for chromosome 1p[a]

Markers	Father	Mother	Fetus	Location
D1S3175	137, 137	137, 141	137, 141	1p34.1 (44,128,994–44,129,123)
D1S1195	148, 148	136, 136	136	1p31.1 (71,531,646–71,531,782)
D1S3471	161, 161	157, 165	157, 161	1p22.3 (84,079,923–84,080,083)

[a] Alleles (base pair sizes) are listed below each individual.

The present case had haploinsufficiency of the *NFIA* gene. There are four independent *NFI* genes in mammals: *NFIA* (OMIM 600727), *NFIB* (OMIM 600728), *NFIC* (OMIM 600729), and *NFIX* (OMIM 164005) [6]. NFI proteins act as cellular transcription/replication factors and play a key role in central nervous system development, including axonal outgrowth, and guidance as well as glial and neuronal cell differentiation [7]. NFIA has been shown to be highly expressed in heart, liver, brain, lung, ovary, skeletal muscle, kidney, testis, pancreas, spleen, and fetal liver and brain [8]. das Neves et al [9] found that disruption of the *NFIA* gene in mice caused perinatal lethality. They also found that the rare surviving homozygous $NFIA^{-/-}$ mice had absent corpus callosum, hydrocephalus, neurological defects, male sterility, and low female fertility. Shu et al [10] found altered formation of forebrain midline glial structure and commissural projections in *NFIA* knockout mice. Deneen et al [11] found that NFIA regulated gliogenesis and oligodendrocyte differentiation in developing spinal cord. Plachez et al [12] found that in addition to regulating the formation of axon guidance substrates, NFIA has a cell-autonomous role in cortical development. Lu et al [1] additionally found that *NFIA* haploinsufficiency can cause central nervous system malformation and urinary tract defects.

The present case also had haploinsufficiency of the *GPR177* gene. *GPR177*, the mouse orthologue or *Drosaphila Wntless/Evi/Srt*, is required for embryonic axis formation [13]. GPR177 is a transmembrane protein pivotal to mediating the secretion of Wnt signal proteins, which are essential for regulating neuronal development [14]. Recently, Fu et al [15] found that loss of *GPR177* in the Wnt1-expressing cells causes abnormalities of mid/hindbrain and craniofacial defects.

Chromosome 1p32-p31 deletion with haploinsufficiency of the *NFIA* gene in the present case was rapidly diagnosed by aCGH using uncultured amniocytes obtained by late

Table 2
Clinical findings of the reported cases with chromosome 1p32-p31 deletion syndrome

Authors	Karyotype	Molecular findings	Clinical features
Sivasankaran et al [3]	46,XX,del(1)(p22p32)dn	NA	Low birth weight (2800 g), absent corpus callosum, macrocephaly, ocular hypertelorism, low-set ears, upturned nostrils, short philtrum, high-arched palate, webbed neck, widely spaced nipples, mesomelic shortening of limbs, clinodactyly, patent ductus arteriosus, atrial septal defect, abnormal external genitalia, hypoplastic labia minora, and absent clitoris.
Campbell et al [4] patient 1, same as Lu et al [1] case DGAP 205-1s	46,XX,del(1)(p31.2p32.3)mat	12-Mb deletion of 1p32.3-p31.2 containing *NFIA* and 47 additional genes	Low-birth weight (41 weeks, 2770 g), macrocrania, small nose, mouth and chin, narrow up-slanting palpebral fissures, ventriculomegaly, absent corpus callosum, congenital dysplasia of the hip, developmental delay, urinary incontinence, Chiari I malformation, syringomelia, and tethered spinal cord.
Campbell et al [4] patient 2, same as Lu et al [1] case DGAP 205-1	46,XY,del(1)(p31.2p32.3)mat	12-Mb deletion of 1p32.3-p31.2 containing *NFIA* and 47 additional genes	Inguinal hernia, bilateral undescended testes, macrocephaly, right hemiplegia, mild left posterior plagiocephaly, telocanthus, hypertelorism, long flat feet, cutis marmorata, a thin corpus callosum, ventriculomegaly, decreased periventricular white matter, flattening of the frontal and parietal gyri, small nose, mouth and chin, narrow up-slanting palpebral fissures, tethered spinal cord, bilateral urinary reflux, and developmental delay.
Shanske et al [5] same as Lu et al [1] case DGAP 089	46,XY,t(1;2)(p31.3;q22.1)del(2)(q14.3q21)dn	12-Mb deletion of 2q14.3-q21 involving 39 genes, and 3.9-kb breakpoint at 1p31.3 locating between Exons 7 and 8 of *NFIA*	Low birth weight (term 2800 g), patent ductus arteriosus, seizures, a gray matter heterotopia, ventriculomegaly, hypoplastic corpus callosum, developmental delay, relative macrocephaly, hypotelorism, hypoplastic nasal ala, hypotonia, and cryptorchidism.
Lu et al [1] case DGAP 104	46,XX,t(1;20)(p31.3;q13.31)dn	Disruption of Intron 2 of *NFIA* at 1p31.3 and disruption of C20orf32 at 20q13.31	Congenital hydrocephalus, thin corpus callosum, Chiari I malformation, tethered spinal cord, and low vertebral deformity at birth. Congenital bilateral dysplastic kidneys, bilateral vesicoureteral reflux, ureterovesical junction diverticulum, hydronephrosis, and ureteral reimplantation surgery at age 2 years.
Lu et al [1] case DGAP 174	46,XY,t(1;3)(p31.1;q25.1)del(1)(p31.3p32.1)dn	Disruption of *NEGR1* at 1p31.1, deletion of *NFIA* and eight additional genes	Agenesis of the corpus callosum and ventriculomegaly on second trimester ultrasound. Additional findings after birth: tethered spinal cord, Chiari I malformation, and dysplasia of the anterior left temporal fossa.
Koehler et al [2]	46,XX,del(1)(p31.3p32.2)dn	4.9-Mb deletion of 1p32.2-p31.3 containing *NFIA* and 16 additional genes	Macrocpehaly, hypotonia, board face and prominent forehead, low-set ears, concave profile of the nose, anteverted nose, small chin and mouth, high palate, sparse eyebrows, cutis marmorata, hypoplastic corpus callosum, ventriculomegaly, large retrocerebellar cyst, hypoplastic cerebellar vermis, and developmental delay.
Present case	46,XX,del(1)(p31.1p32.3)dn	22.2-Mb deletion of 1p32.3-p31.1 encompassing *NFIA*, *GPR177*, and 89 additional genes	Ventriculomegaly, corpus callosum hypogenesis, macrocephaly, micrognathia, and ambiguous external genitalia on prenatal ultrasound. Low-birth weight (33 wk, 1536 g), relative macrocephaly, anteverted nostrils, micrognathia, low-set ears, labial fusion, labial hypertrophy, absence of vaginal opening, and clitoral hypertrophy at birth.

del = deletion; dn = *de novo*; mat = maternal; NA = not available; t = translocation.

amniocentesis in the third trimester. Rapid genome-wide aneuploidy diagnosis using uncultured amniocytes and aCGH in pregnancy with abnormal ultrasound findings detected in late second and third trimesters have been well described [16,17]. Application of aCGH using uncultured amniocytes obtained by amniocentesis in late gestation, as shown in this case, is less invasive and more efficient in rapid aneuploidy diagnosis of subtle chromosome aberrations as well as identification of the candidate gene responsible for the specific phenotype.

In addition to 1p32-p31 deletion, at least 17 ACC significant critical regions, including 12 Class I regions have been identified, such as 1p36 deletion, 1q41-q42 deletion, 1q43-q44 deletion, 4p16.1-p16.3 deletion, 6p25 deletion, 6q26-q27 deletion, 8p22-p21.3 duplication, 9q34.3 deletion, 11q25 duplication, 13q32.3-q33.1 deletion, 13q34 duplication, 14q12-q13.1 deletion, 14q32.3 deletion, 21q22.11-q22.3 duplication, 21q22.2-q22.3 deletion, Xp22.3 deletion, and Xq27.3-q28 duplication [18]. In addition to *NFIA* at 1p31.3-p31.2, other candidate genes associated with ACC include

AKT3 (OMIM 611223) at 1q44 [19,20], *DISP1* (OMIM 607502) at 1q41 [21], *FOXG1* (OMIM 164874) at 14q13 [22−24], and *ZIC2* (OMIM 603073) at 13q32 [18].

In conclusion, prenatal diagnosis of ventriculomegaly with an abnormal corpus callosum should alert subtle chromosome aberrations and prompt molecular cytogenetic investigation if necessary. The present case provides evidence that fetuses with chromosome 1p32-p31 deletion syndrome and haploinsufficiency of the *NFIA* gene may present ventriculomegaly, corpus callosum hypogenesis, abnormal external genitalia, and intrauterine growth restriction in the third trimester.

Acknowledgments

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