Chromosome 1p36 Deletion Syndrome: Prenatal Diagnosis, Molecular Cytogenetic Characterization and Fetal Ultrasound Findings

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SUMMARY

Objective: To present prenatal diagnosis and molecular cytogenetic characterization of *de novo* partial monosomy 1p (1p36.23→pter) and partial trisomy 20p (20p12.1→pter) associated with ventriculomegaly, ventricular septal defect and midface hypoplasia.

Materials, Methods and Results: A 31-year-old, primigravid woman was referred for amniocentesis at 20 gestational weeks because of ventriculomegaly, ventricular septal defect, and midface hypoplasia. Amniocentesis revealed an aberrant derivative chromosome 1, or der(1). Parental karyotypes were normal. Spectral karyotyping analysis revealed that the der(1) contained a segment of chromosome 20 in the distal end of the short arm of chromosome 1. Array comparative genomic hybridization demonstrated an 8.4-Mb distal 1p deletion and a 14-Mb distal 20p duplication. The karyotype was 46,XX,der(1)t(1;20)(p36.23;p12.1)dn. Polymorphic DNA marker analysis determined the paternal origin of the aberrant chromosome. The pregnancy was subsequently terminated. A 462-g malformed female fetus was delivered at 22 gestational weeks with a prominent forehead, midface hypoplasia, a flat nasal bridge, low-set ears, a long philtrum, a pointed chin and micrognathia.

Conclusion: Spectral karyotyping, fluorescence *in situ* hybridization and array comparative genomic hybridization are useful for the prenatal investigation of the nature of a *de novo* aberrant derivative chromosome. Partial monosomy 1p (1p36.23→pter) and partial trisomy 20p (20p12.1→pter) are associated with ventriculomegaly, ventricular septal defect and midface hypoplasia on prenatal ultrasound. Prenatal diagnosis of ventriculomegaly, congenital heart defects and midface hypoplasia should alert clinicians to chromosome 1p36 deletion syndrome and prompt molecular cytogenetic analysis if necessary. [*Taiwan J Obstet Gynecol* 2010;49(4):473–480]

Key Words: chromosome 1, chromosome 1p36 deletion syndrome, chromosome 20, monosomy 1p36, prenatal diagnosis, ultrasound

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Introduction

Prenatal diagnosis of a *de novo* unbalanced reciprocal translocation involving chromosomal segments with a subtle difference in banding results in difficulties in

interpretation and genetic counseling, and requires molecular cytogenetic technologies such as spectral karyotyping (SKY), fluorescence *in situ* hybridization (FISH), and array-based comparative genomic hybridization (aCGH) to identify the nature of the aberrant chromosome. We previously reported the utility of SKY and FISH in the identification of a *de novo* aberrant chromosome derived from an unbalanced reciprocal translocation [1]. We additionally report here the prenatal diagnosis and molecular cytogenetic characterization of *de novo* partial monosomy 1p (1p36.23→pter) and partial trisomy 20p (20p12.1→pter) associated with ventriculomegaly, a ventricular septal defect (VSD) and midface hypoplasia.

Materials, Methods and Results

A 31-year-old, primigravid woman was referred to the genetic counseling center for amniocentesis at 20 gestational weeks because of abnormal ultrasound findings of ventriculomegaly, VSD and midface hypoplasia (Figure 1). Amniocentesis revealed an aberrant derivative chromosome 1, or der(1) (Figure 2). Chromosome

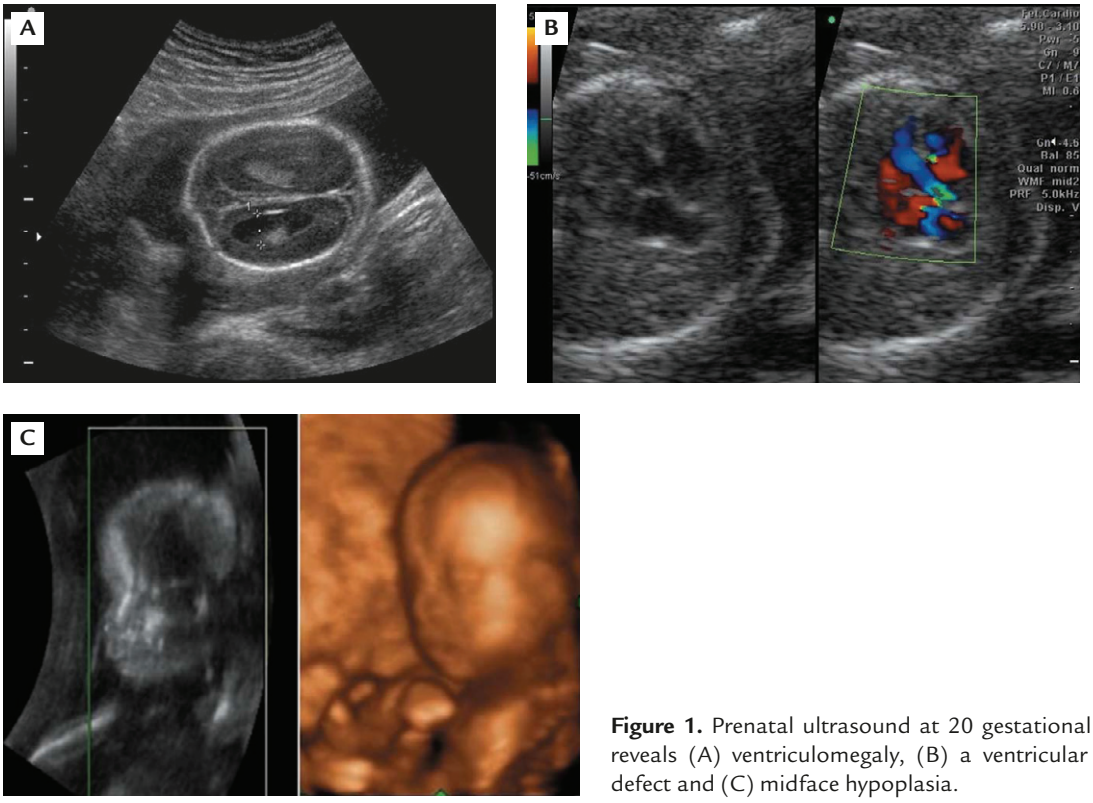

Figure 1. Prenatal ultrasound at 20 gestational weeks reveals (A) ventriculomegaly, (B) a ventricular septal defect and (C) midface hypoplasia.

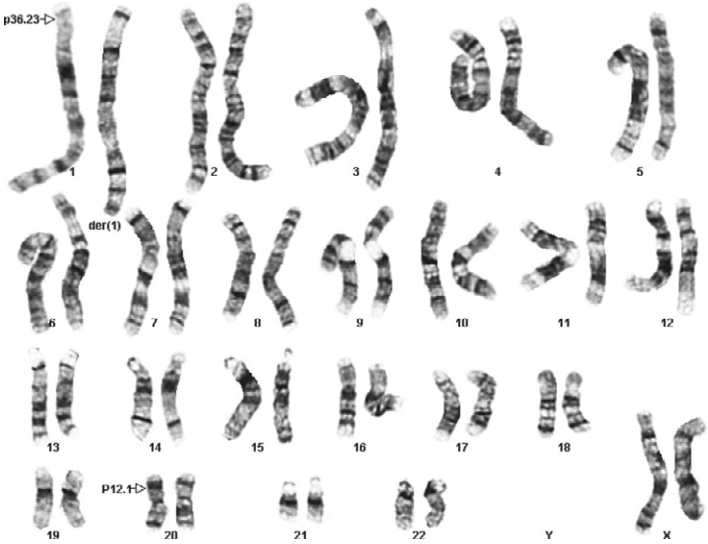

Figure 2. G-banded karyotype shows a derivative chromosome 1, or der(1). The proband's karyotype is 46,XX,der(1)t(1;20)(p36.23;p12.1)dn. The arrows indicate the breakpoints.

preparations of blood lymphocytes from the parents revealed normal karyotypes. The derivative chromosome was characterized by SKY using 24-color SKY probes (Applied Spectral Imaging, Carlsbad, CA, USA). SKY analysis revealed that the der(1) contained a segment of chromosome 20 in the distal end of the short arm of chromosome 1 (Figure 3). Repeat amniocentesis was performed at 22 gestational weeks, and 20 mL of aspired amniotic fluid was applied for aCGH using uncultured amniocytes. Bacterial artificial chromosome (BAC)-based aCGH using CMDX BAC-based aCGH CA2500 chips (CMDX, Irvine, CA, USA) demonstrated partial monosomy 1p and partial trisomy 20p [arr 1p36.33p36.23 (RP11-668E2→RP11-81J7)×1, 20p 13p12.1 (RP11-530N10→RP11-238I2)×3] (Figure 4). Oligonucleotide-based aCGH using HumanCytoSNP-12vl BeadChips (Illumina, San Diego, CA, USA) further demonstrated an 8.4-Mb distal 1p deletion and a 14-Mb

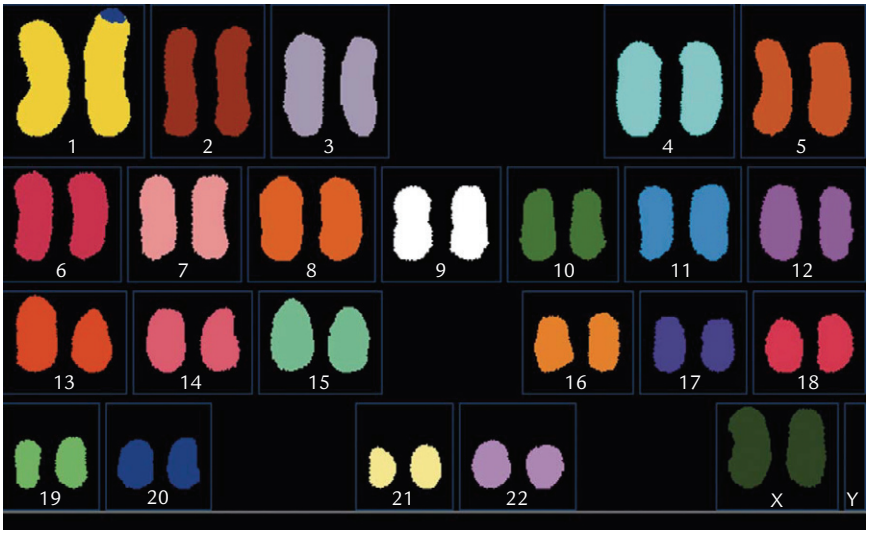

Figure 3. Spectral karyotyping using 24-color SKY probes shows a der(1) derived from a translocation between chromosomes 1 and 20.

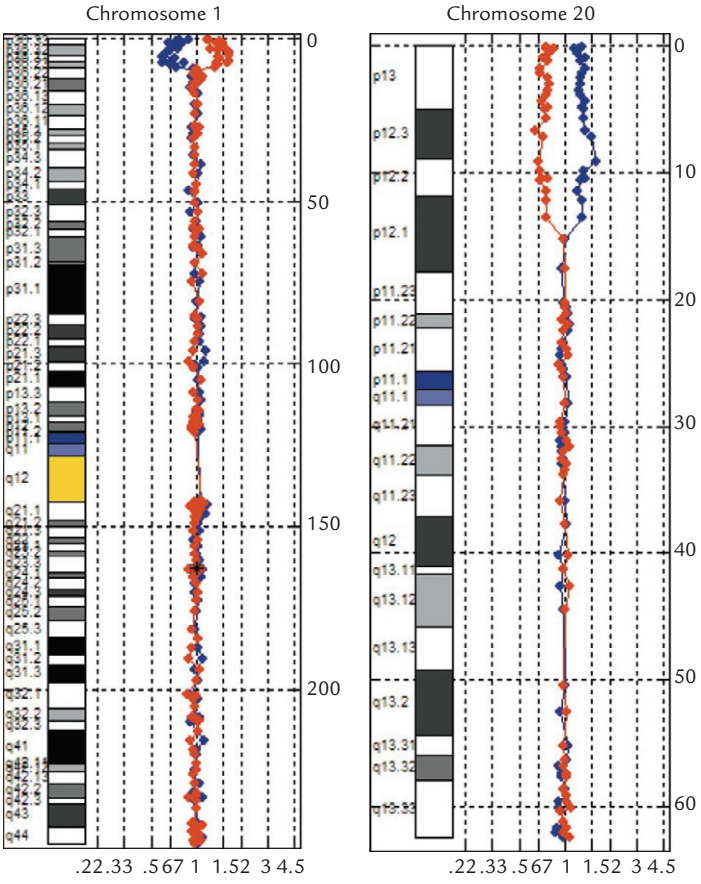

Figure 4. Bacterial artificial chromosome-based array comparative genomic hybridization shows a distal 1p deletion [arr 1p36.33p36.23 (RP11-668E2→RP11-81J7)×1] and a distal 20p duplication [arr 20p13p12.1 (RP11-530N10→RP11-238I2)×3].

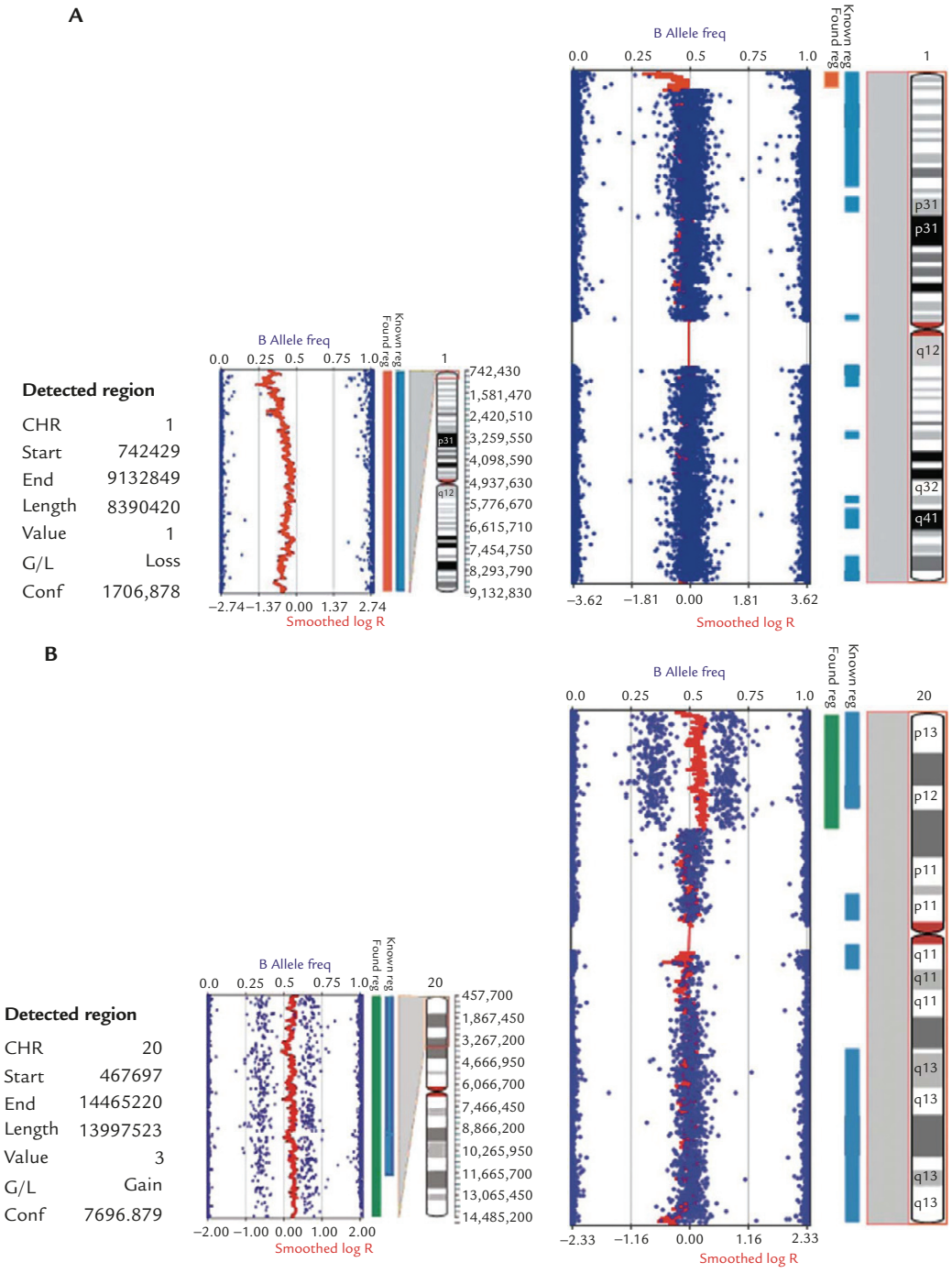

Figure 5. Oligonucleotide-based array comparative genomic hybridization shows (A) an 8.4-Mb distal 1p deletion [arr 1p36.33p36.23 (742,429-9,132,849)×1] and (B) a 14-Mb distal 20p duplication [arr 20p13p12.1 (467,697-14,465,220)×3].

distal 20p duplication [arr 1p36.33p36.23 (742,429-9,132,849)×1, 20p13p12.1 (467,697-14,465,220)×3] (Figure 5). The karyotype was 46,XX,der(1)t(1;20)(p36.23;p12.1)dn (Figure 2). Polymorphic DNA marker analysis determined the paternal origin of the aberrant chromosome. The parents opted to terminate the pregnancy. A 462-g malformed female fetus was delivered with a prominent forehead, midface hypoplasia, a flat nasal bridge, low-set ears, a long philtrum, a pointed chin and micrognathia (Figure 6).

Discussion

Chromosome 1p36 deletion syndrome (OMIM 607872), or monosomy 1p36 syndrome, is the most common subtelomeric terminal deletion syndrome, and it is associated with multiple congenital anomalies and mental retardation [2]. Chromosome 1p36 deletion syndrome has an estimated frequency of 1 in 5,000 live births [3] and is characterized by a typical craniofacial dysmorphism of straight eyebrows, deep-set eyes, midface

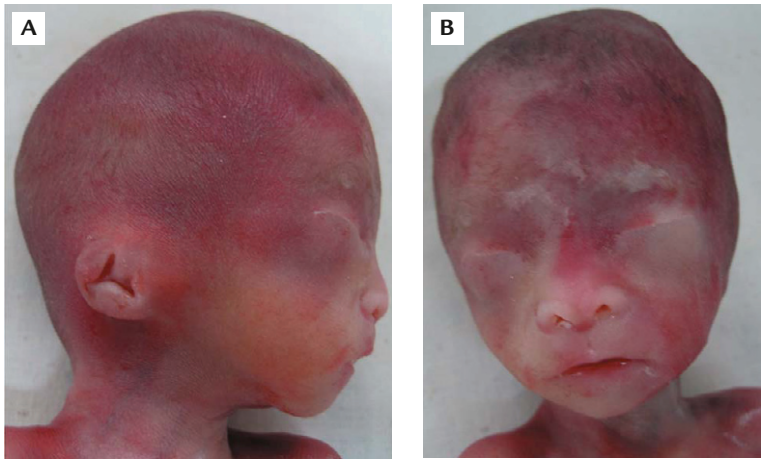

Figure 6. Anterior and lateral views of the craniofacial appearance of the proband.

hypoplasia, a broad nasal bridge, a long philtrum, a pointed chin, large anterior fontanel, microbrachycephaly, epicanthal folds, low-set ears, brachydactyly, camptodactyly, short feet, developmental delay, mental retardation, hypotonia, seizures, structural brain abnormalities, congenital heart defects, eye problems, hearing loss and skeletal, renal and genital abnormalities [4,5].

The present case prenatally manifested ventriculomegaly, VSD, and midface hypoplasia during second-trimester ultrasound. In a study of 60 patients with chromosome 1p36 deletion syndrome, Battaglia et al [5] found midface hypoplasia in 100% (60/60), brain abnormalities in 88% (43/49) and congenital heart defects in 71% (34/48) of patients. In their study, the reported congenital heart defects included atrial septal defect (28%), VSD (23%), patent ductus arteriosus (12%), valvular anomalies (20.5%), tetralogy of Fallot (7.7%), coarctation of the aorta (5.1%), infundibular stenosis of the right ventricle (2%) and Ebstein's anomaly (2%), and brain magnetic resonance imaging abnormalities included enlargement of the lateral ventricles (37%), cortical atrophy (20%), enlargement of the subarachnoid spaces (22%), diffuse brain atrophy (10%), and enlargement of the frontotemporal opercula (4%).

In chromosomal abnormalities observed in chromosome 1p36 deletion syndrome, 52% of the rearrangements are terminal deletions, 29% are interstitial deletions, 12% are complex rearrangements including more than one deletion or deletions with duplications, triplications, insertions and/or inversions, and only 7% are derivative chromosomes derived from unbalanced translocations [4,6]. The present case had a karyotype of 46,XX,der(1)t(1;20)(p36.23;p12.1)dn. To our knowledge, this case is the fourth reported case of monosomy 1p36 associated with an unbalanced translocation between chromosome 1p and 20p. Howard-Peebles and Black [7] first reported the diagnosis of monosomy 1p36 and a karyotype of 46,XY,der(1)t(1;20)(p36;p13) in a fetus conceived by a carrier mother who had a previous aneuploid child with 46,XX,der(1)t(1;20)(p36;p13) and multiple anomalies. The male fetus prenatally manifested hydrocephalus and complex congenital heart defects during prenatal ultrasound at 16 gestational weeks, and postnatally manifested truncus arteriosus, VSD, agenesis of the corpus callosum and dilated ventricles. The female aneuploid child had microcephaly, microphthalmia, optic nerve colobomas, facial dysmorphism, agenesis of the corpus callosum, hydrocephalus, tetralogy of Fallot and neonatal death. Campeau et al [8] additionally reported prenatal diagnosis of monosomy 1p36 and a karyotype of 46,XX,der(1)t(1;20)(p36.1;p12.2) by amniocentesis in a fetus conceived by a 30-year-old carrier mother because of severe fetal ventriculomegaly on prenatal ultrasound at 21 gestational weeks. Parental cytogenetic analysis showed that the mother's karyotype was 46,XX,t(1;20)(p36.1;p12.2). The phenotype of partial trisomy 20p includes a low birth weight, occipital flattening, a round face, prominent cheeks, upslanting palpebral fissures, hypertelorism, epicanthal folds, a short nose, coarse hair, congenital heart defects, vertebral anomalies and clinodactyly [9]. Although some of the clinical features observed in our patient could be due to the effect of partial trisomy 20p in addition to monosomy 1p36, partial trisomy 20p has been shown to be associated with no structural brain malformations [9–10].

To date, at least 10 cases of prenatally detected chromosome 1p36 deletion syndrome have been reported [8,11–19]. Chromosome 1p36 deletion syndrome may prenatally manifest elevated maternal serum α-fetoprotein levels, congenital heart defects and cerebral malformations (Table). Our case additionally shows that midface hypoplasia can be a cardinal prenatal sonographic feature of chromosome 1p36 deletion syndrome. Heilstedt et al [16] reported increased maternal serum

Table. Clinical findings of cases with prenatally detected or undetected chromosome 1p36 deletion syndrome

Author (year)	Maternal age (yr)	Indication for prenatal genetic diagnosis	Chromosomal aberration	Inheritance	Outcome
Howard-Peebles & Black [7] (1994)	NA	Abnormal ultrasound: hydrocephalus and complex congenital heart defects at 16 wk	Prenatal diagnosis: 46,XY Postnatal diagnosis: 46,XY,der(1)t(1;20)(p36;p13)mat	Maternal	Termination: truncus arteriosus, VSD, ACC and dilated ventricles
Chen et al [11] (1997)	33	Elevated MSAFP, abnormal ultrasound: polyhydramnios, hydronephrosis, cerebellar and ventricular enlargement	46,XY,der(1)t(1;4)(p36.13;q33)mat	Maternal	Delivered with postnatal growth retardation, microcephaly, plagiocephaly and minor anomalies; seizures began at 13 weeks old
Kulharya et al [12] (1997)	NA	Abnormal ultrasound: absence of cerebellar vermis, thick nuchal folds, bilateral hydronephrosis, ascites, club feet, arthrogryposis and a single umbilical artery at 23.5 wk	46,XY,der(1)t(1;6)(p36.3;q22.2)	*De novo*	Delivery at 37 wk, facial dysmorphism, ASD, PDA, ambiguous genitalia, hypospadias, hydronephrosis, rudimentary postaxial polydactyly of the left hand, equinovarus deformity of the feet, neonatal death
Robbins-Furman et al [13] (1997)	NA	Elevated MSAFP	46,XX,del(1)(p36.3)	*De novo*	Oligohydramnios; delivery at 37 wk with dysmorphic features; neonatal seizures began at 9 weeks old
Faivre et al [14] (1999)	34	Abnormal ultrasound: ventriculomegaly, hypertelorism and Ebstein's anomaly at 24 wk	46,XY,del(1)(p36)	*De novo*	Termination at 28 wk, hydrops fetalis, ventriculomegaly, pleural effusion, Ebstein's anomaly
Cavani et al [15] (2003)					
Case III, 3	33	Abnormal ultrasound: IUGR and anomaly of the corpus callosum at 31 wk	46,XY,der(1)t(1;6)(p36.3;q25.2)mat	Maternal	Delivered at 34 wk, IUGR, macrocephaly, lobar holoprosencephaly, right optic nerve coloboma, dilated third and lateral ventricles, VSD, neonatal death
Case III, 5	NA	Previous aneuploid child The same mother as Case III, 3	46,XX,der(1)t(1;6)(p36.3;q25.2)mat	Maternal	Termination, ventriculomegaly, diffuse edema, pulmonary segmentation defects
Case III, 6	NA	Previous aneuploid child The same mother as Case III, 3	46,XY,der(1)t(1;6)(p36.3;q25.2)mat	Maternal	Termination

Reddy and Yang [17] (2003)					
Case 1	15	Abnormal ultrasound: hydrocephalus and IUGR at 30.3 wk	Prenatal diagnosis: 46,XX Postnatal diagnosis: 46,XX,der(1)t(1;9)(p36.3;p13)[88]/46,XX[12]	*De novo*	Delivered with PDA, unilateral optic nerve hypoplasia, pes calcaneovalgus, dysmorphic features; developmental delay at 6 months of age
Hsieh et al [18] (2004)	29	Abnormal ultrasound: bilateral choroid plexus cysts, VSD, rocker-bottom feet and hydrocephalus at 18 wk	46,XY,der(1)t(1;21)(p36.3;q22.1)	*De novo*	Termination at 20 wk
Lissauer et al [19] (2007)	29	Abnormal ultrasound: ventriculomegaly, a small choroid plexus cyst and nuchal edema at 21 wk	46,XY,del(1)(p36)	*De novo*	Delivery at 40 wk, dysmorphic features, hypertonia, neonatal seizures; delayed development, enlargement of the third and lateral ventricles, small periventricular cysts, delayed myelination at 5 months of age
Campeau et al [8] (2008)					
Case 1	31	Abnormal ultrasound: ventriculomegaly, a single umbilical artery and short femurs at 17 wk; IUGR, ventriculomegaly, club foot, VSD, asymmetric ventricles and tortuous aortic arch at 31 wk	Prenatal diagnosis: 46,XX Postnatal diagnosis: 46,XX,del(1)(p36.3)	*De novo*	Delivered at 34 wk, cleft palate, ASD, VSD, PDA, dysmorphic features, hypotonia; hydrocephalus and colpocephaly on MRI at 2 years old; global developmental delay at 2.5 years old
Case 2	30	Abnormal ultrasound: severe ventriculomegaly at 21 wk	46,XX,der(1)t(1;20)(p36.1;p12.2)mat	Maternal	Termination at 21^{+5} wk, facial dysmorphism, clinodactyly, flexion contraction of lower limbs, misaligned toes, hydrocephalus, cerebellar hypoplasia, focal polymicrogyria
Vialard et al [20] (2009)					
Case 39	NA	Abnormal ultrasound: congenital heart defects and cerebral malformation	Prenatal diagnosis: 46,XY Postnatal diagnosis: 46,XY,del(1)(p36.22)	NA	Ultrasound at 27 wk revealed partial corpus callosum, vermian hypoplasia, aortic coarctation, two intraventricular communications, right heart dilation, tricuspid valve dysgenesis
Present case	31	Abnormal ultrasound: ventriculomegaly, VSD and midface hypoplasia at 20 wk	46,XX,der(1)t(1;20)(p36.23;p12.1)	*De novo*	Termination at 22 wk, facial dysmorphism

NA = not available; MSAFP = maternal serum α-fetoprotein; VSD = ventricular septal defect; ACC = agenesis of corpus callosum; ASD = atrial septal defect; PDA = patent ductus arteriosus; IUGR = intrauterine growth restriction; MRI = magnetic resonance imaging.

α-fetoprotein levels in four of five prenatally diagnosed cases of monosomy 1p36 and suggested that careful attention should be paid to chromosome 1p36 in case of prenatal cytogenetic testing for increased maternal serum α-fetoprotein levels. The Table also shows that terminal deletion 1p36 can be missed at prenatal diagnosis because of a lower level of resolution [7,8,17,20]. In this regard, aCGH using cultured or uncultured amniocytes may be needed to correctly identify subtle chromosome aberrations [21,22]. We suggest that prenatal diagnosis of ventriculomegaly, congenital heart defects and midface hypoplasia should alert clinicians to the possibility of chromosome 1p36 deletion syndrome and prompt molecular cytogenetic analysis if necessary.

Acknowledgments

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