RESEARCH REVIEW

AMERICAN JOURNAL OF medical genetics PART A

OEIS Complex Associated With Chromosome 1p36 Deletion: A Case Report and Review

Ayman W. El-Hattab,[1] Josh C. Skorupski,[2] Michael H. Hsieh,[3] Amy M Breman,[1,4] Ankita Patel,[1,4] Sau Wai Cheung,[1,4] and William J. Craigen[1,5]*

[1]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas

[2]Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, Michigan

[3]Department of Urology, Standford University School of Medicine, Standford, California

[4]Medical Genetics Laboratories, Baylor College of Medicine, Houston, Texas

[5]Department of Pediatrics, Baylor College of Medicine, Houston, Texas

Received 14 August 2009; Accepted 15 November 2009

OEIS complex (Omphalocele, Exstrophy of the cloaca, Imperforate anus, and Spine abnormalities) is a rare defect with estimated incidence of 1 in 200,000 live births. Most cases are sporadic, with no obvious cause. However, it has been rarely reported in patients with family members having similar malformations or with chromosomal anomalies. In addition, OEIS complex has been observed in association with environmental exposures, twinning, and in vitro fertilization. Monosomy 1p36 is the most common terminal deletion syndrome, with a prevalence of 1 in 5,000 newborns. It is characterized by specific facial features, developmental delay, and heart, skeletal, genitourinary, and neurological defects. We describe an infant with OEIS complex and 1p36 deletion who had features of both disorders, including omphalocele, cloacal exstrophy, imperforate anus, sacral multiple segmentation, renal malposition and malrotation, genital anomalies, diastasis of the symphysis pubis, microbrachycephaly, large anterior fontanel, cardiac septal defects, rib fusion, a limb deformity, developmental delay, and typical facial features. Chromosomal microarray analysis detected a 2.4 Mb terminal deletion of chromosome 1p. This is the first reported case with OEIS complex in association with a chromosome 1p36 deletion.

Key words: OEIS complex; cloaca exstrophy; chromosome 1p36 deletion

How to Cite this Article:
El-Hattab AW, Skorupski JC, Hsieh MH, Breman AM, Patel A, Cheung SW, Craigen WJ. 2009. OEIS complex associated with chromosome 1p36 deletion: A case report and review.
Am J Med Genet Part A 152A:504–511.

INTRODUCTION

OEIS complex (Omphalocele, Exstrophy of the cloaca, Imperforate anus, and Spine abnormalities) is a rare congenital defect that was initially described by Carey et al. [1978]. He and his coworkers reported a series of cases with an abnormality of body wall development and proposed the term OEIS complex. Subsequently, it was statistically demonstrated that OEIS complex is a clinically recognized nonrandom association that, in addition to the four classic malformations (omphalocele, exstrophy of the cloaca, imperforate anus, and spine abnormalities), is variably associated with spina bifida, genital abnormalities, renal malformation, symphysis pubis diastasis, and limb abnormalities [Kallen et al., 2000]. It has been suggested that OEIS complex and exstrophy of the cloaca should be used synonymously [Carey, 2001; Bohring, 2002].

The frequency of OEIS complex has been estimated to be 1:200–400,000 live births [Hayden et al., 1973; Carey et al., 1978; Hurwitz et al., 1987; Kallen et al., 2000; Martinez-Frias et al., 2001]. More recently, Keppler-Noreuil et al. [2007] reported a prevalence of 1:100,000 live births. Martinez-Frias et al. [2001] reported a male to female ratio of 1:2.

Most cases are sporadic with no obvious etiology. The few reported patients with family members having similar malformations or with chromosomal anomalies suggest a genetic contribution. Other reports have linked cloacal exstrophy to certain exposures, twinning, and in vitro fertilization.

Monosomy 1p36 is the most common terminal deletion syndrome, and is characterized by microbrachycephaly, brachy/

*Correspondence to:
William J. Craigen, M.D., Ph.D., Department of Molecular and Human Genetics, Baylor College of Medicine, One Baylor Plaza, MS BCM225, Houston, TX 77030. E-mail: wcraigen@bcm.edu
Published online 22 January 2010 in Wiley InterScience (www.interscience.wiley.com)
DOI 10.1002/ajmg.a.33226

camptodactyly, heart defects, eye/visual abnormalities, sensorineural deafness, renal abnormalities, seizures, developmental delay, hypotonia, behavior disorder, and a specific set of facial features, including straight eyebrows, deep-set eyes, midface hypoplasia, a broad nasal root/bridge, long philtrum, pointed chin, epicanthal folds, large anterior fontanel, and posteriorly rotated, low-set ears [Battaglia et al., 2008].

We describe a child with OEIS complex and a chromosome 1p36 deletion with features of both disorders. We also provide a literature review of the cause, pathogenesis, and clinical features of OEIS complex.

CLINICAL REPORT

A female infant was born vaginally at 36 weeks gestational age to a nonconsanguineous couple. During pregnancy the maternal serum screen showed border line elevated alpha-feto protein, with a subsequent normal screen. Prenatal ultrasound detected enlarged labia at 18 weeks and again at 32 weeks gestation, but was otherwise unremarkable. The birth weight was 2,610 g, with length and head circumference about 1 standard deviation (SD) below the mean. Multiple anomalies were present at birth, including omphalocele, cloacal exstrophy, imperforate anus, and ambiguous genitalia, with prominent rugated labioscrotal folds and no apparent genital tubercle (Fig. 1a). Abdominal sonography showed renal malposition and malrotation, with both kidneys positioned more inferior and the lower pools facing medially. Abdomen magnetic resonance imaging (MRI) showed two hemi-uteri and two hemi-vagina widely separated and terminating blindly within the pelvis. An echocardiogram revealed a ventricular septum defect (VSD), atrial septum defect (ASD), patent ductus arteriosus (PDA), and right aortic arch. A head sonogram showed germinal matrix cysts that were thought to represent an in utero germinal matrix hemorrhage. Skeletal deformities were present, including superior deviation of the left great toe with a large cleft between the great toe and remaining toes, a syndactyly between second and third left toes, fusion of right 9th and 10th rib, multiple sacral segmentation defects, and diastasis of the symphysis pubis (Figs. 1b and 2). Unusual craniofacial features were noted, including microbrachycephaly, a large anterior fontanel, low set ears, deep set eyes, epicanthal folds, a flat nasal bridge, midface hypoplasia, and a high arched palate. A hearing screen and ophthalmologic exam were normal. The family history was unremarkable, with one healthy female sibling and no other similarly affected individuals. A chromosome study revealed a normal female karyotype (46, XX). Chromosomal microarray analysis using a 44K Agilent array showed an apparent terminal deletion of chromosome 1p36 and confirmed by FISH analysis (Fig. 3a–c). A genome-wide single nucleotide polymorphism array (AFFY SNP array 6.0) further refined the proximal breakpoint to 2,408,795 and showed no evidence of uniparental disomy (data not shown).

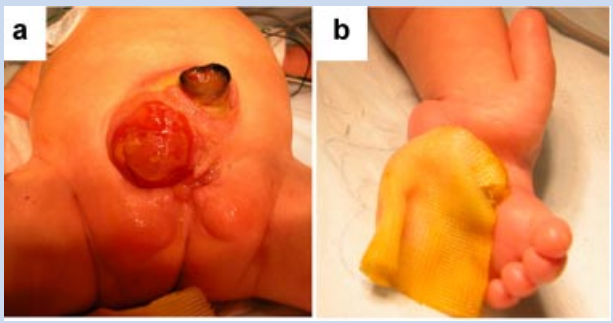

FIG. 1. a: Cloacal exstrophy and prominent labioscrotal folds. b: Left foot deformities with the first digit deviated superiorly and a large cleft between the great toe and remaining toes. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

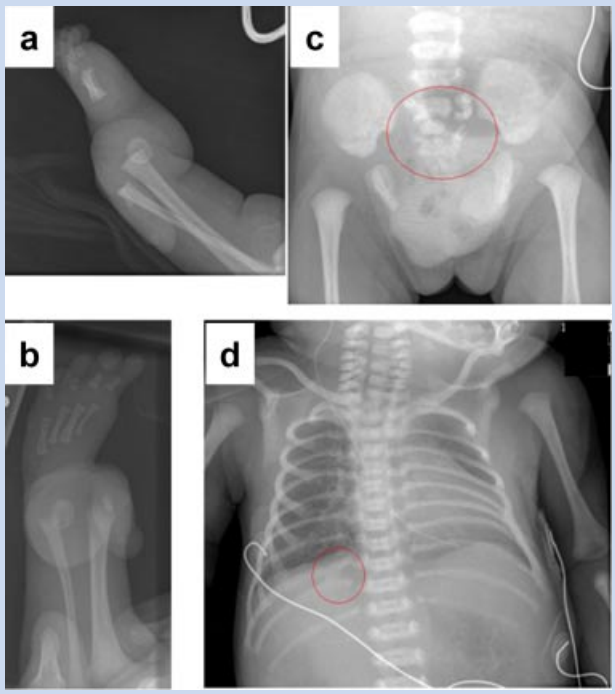

FIG. 2. a,b: Foot XR showing the first digit deviated superiorly with large cleft between the great toe and remaining toes. c: Pelvic XR showing multiple segmentation anomalies involving the sacrum (circled) and diastasis of the symphysis pubis. d: Chest XR showing the fusion of the right 9th and 10th rib (circled). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

At the age of 4 days she had corrective surgery, with the ileum and colon mobilized from the bladder plate and a primary closure of exstrophic bladder performed. A colostomy was created, bilateral pelvic osteotomy performed, and amputation of the ectopic left great toe carried out. At the age of 2 months she developed renin -mediated hypertension that was attributed to the renal malposition. She subsequently had a urinary tract infection, a prolapsed bladder that was repaired, oromotor incoordination that required nasogastric tube feeding, and she developed an enterocutaneous fistula that was the source of multiple infections.

Despite recurrent hospitalizations her development progressed such that by the age of 10 months she was able to sit without

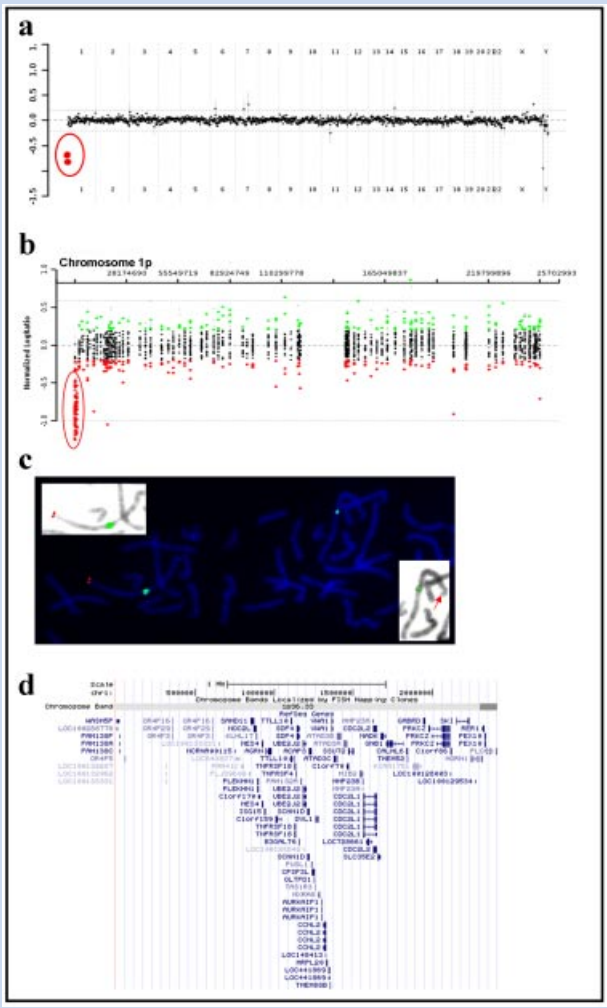

FIG. 3. a: Array CGH plot obtained with V6.3 OLIGO (Agilent 44K) showing a loss of chromosome 1 material in the patient at band 1p36.33-p36.32 (red circle). b: An overview of oligonucleotides covering the entire chromosome 1 indicating the loss at band 1p36.3 (in red circle). c: The deletion is confirmed by FISH analysis using RP11-465B22 as target probe in red while control probe for centromere is in green. d: The RefSeq genes in the terminal 2.4 Mb of chromosome 1p (http://genome.ucsc.edu). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

support, hold a bottle, transfer objects, and babble, placing her development at the level of 6–7 months. Her weight was between 10th and 25th centile, length at the 3rd centile, and head circumference 2.5 SD below the mean. At 12 months of age the patient developed bowel obstruction which progressed to septic shock and multi-organ failure and she died.

DISCUSSION

Clinical Presentation of OEIS Complex

Table I summarizes the clinical manifestations of OEIS documented in four case series [Meglin et al., 1990; Keppler-Noreuil, 2001; Martinez-Frias et al., 2001; Keppler-Noreuil et al., 2007]. Cloacal exstrophy is associated with the other three classical malformations (omphalocele, imperforate anus, and spine abnormalities) in 35–65% of the cases [Keppler-Noreuil, 2001; Martinez-Frias et al., 2001]. It is variably associated with genital abnormalities, symphysis pubis diastasis, limb abnormalities, and spina bifida, which has been described as lumbar in 72% of the cases, sacral in 14%, and thoracic in 14% [Howell et al., 1983]. Low birth weight and prematurity have been observed more frequently [Martinez-Frias et al., 2001]. However, Keppler-Noreuil [2001] reported a mean gestational age of 37.5 weeks with appropriate birth weights, lengths, and head circumferences in their series of patients with OEIS complex. Prenatal diagnosis of OEIS complex depends on sonographic criteria that include an infra-umbilical abdominal wall defect with a protruding mass, absent bladder, and spinal defects. Other findings include a more inferior umbilical cord insertion site, omphalocele, absent or abnormal pubic rami, and iliac wings that have an increased pelvic angle. Typically there is a slightly elevated serum and amniotic fluid alpha-feto protein level [Tiblad et al., 2008].

The patient described in this report had the classic malformations (omphalocele, cloacal exstrophy, imperforate anus, sacral multiple segmentation), in addition to renal malposition and malrotation, genital anomalies, diastasis of the symphysis pubis, and limb deformities.

Pathogenesis of OEIS Complex

The cloaca is the primitive structure from which the rectum and urogenital sinus develop. At the caudal end of the cloaca, ectoderm lies directly over endoderm, forming the cloacal membrane, which by the 4th week of development constitutes the ventral wall of the urogenital sinus. During the 6th week of development mesoderm grows toward the midline, forming the infra-umbilical abdominal wall. Simultaneously, the urorectal septum extends caudally toward the cloacal membrane, and lateral tissue folds extend from the lateral aspects of the hindgut and meet in the midline. By the 7th week of gestation, the cloaca is divided into an anterior chamber (the primitive urogenital sinus) and a posterior chamber (the rectum). Normally the cloacal membrane ruptures at the end of the 8th week of gestation [Maizels, 1998; Martinez-Frias et al., 2001]. OEIS complex occurs if there is an early insult affecting the mesenchyme that contributes to the infra-umbilical mesoderm, the urorectal septum, and the lumbosacral somites. Infra-umbilical mesoderm gives rise to the lower abdominal wall, genital tubercles, and rami of the pubis. Therefore, abnormal mesodermal migration leads to premature rupture of the cloacal membrane, causing exstrophy of the cloaca and omphalocele, failure of fusion of the genital tubercles leading to genital anomalies, and separation of the rami of the pubis. The urorectal septum abnormalities lead to failure of cloacal septation, a persistent cloaca, and a rudimentary hindgut with an imperforate anus. The lumbosacral somite abnormalities lead to incomplete development of the lumbosacral vertebrae [Keppler-Noreuil, 2001; Martinez-Frias et al., 2001; Siebert et al., 2005]. The abnormal mesodermal migration can be due to an abnormality in the cloacal membrane, which may develop more extensively and serve as a wedge that prohibits the invasion of

TABLE I. Clinical Manifestations of OEIS Complex

	Keppler-Noreuil et al. [2007] (%)	Martinez-Frias et al. [2001] (%)	Keppler-Noreuil [2001] (%)	Meglin et al. [1990] (%)
Gastrointestinal				
Omphalocele	100	65	36	23
Imperforate anus	58	100	64	83
Duplicated colon/intestine	8		21	8
Intestinal malrotation	33		21	46
Anal atresia			15	
Anteriorly placed anus			31	
Fistulas (bladder or vagina)	8		100	
Intestinal atresia	17		7	8
Urinary				
Cloacal exstrophy	93	100	100	100
Renal agenesis/hypoplastic kidney	17		28	7
Pelvic kidney			7	7
Duplicated collecting system			7	15
Hydroureter/hydronephrosis	17		14	23
Genital				
Ambiguous genitalia	18		50	54
Genital abnormalities			100	100
Genital anomalies in male			36	62
Small penis and Epispadias			80	
Abnormal or absent scrotum			60	
Cryptorchidism			60	71
Genital abnormalities in female			64	38
Hypoplastic labia			44	
Widely separated labioscrotal folds	8		56	
Bifid uterus	8		22	80
Clitoris and labia minora splayed to one side			50	
Bifid clitoris			11	
Vaginal remnants (with duplication)			11	40
Absent uterus			33	
Vesico-vaginal or recto-vaginal fistula	17		89	
Hypoplastic fallopian tube				20
Skeletal				
Spine abnormalities	100		78	92
Hemivertebrae			45	50
Sacral anomalies: hypogenesis or segmentation			82	92
Limb abnormalities			28	54
Arthrogryposis			7	
Syndactyly			7	
Thumb hypoplasia			7	
Club feet	38		7	46
Dysplastic/hypoplastic lower extremity			7	8
Symphysis pubis diastasis			100	100
Congenital hip dislocation			14	67
Neurologic				
Tethered cord			67	58
Spina bifida		55	27	92
Chiari malformation	8		7	8
Hydrocephalus	17			
Developmental delay			14	0

mesoderm. Alternatively, the primary abnormality may be a defect of blastogenesis, where a localized defect in the caudal mesoderm leads to abnormal mesodermal migration [Keppler-Noreuil, 2001; Martinez-Frias et al., 2001; Siebert et al., 2005]. It has been suggested that the breakdown of the cloacal membrane causes exstrophy and prolapse of the cloaca, which pulls the notochord away from the neural tube, interrupting the signal for differentiation and leading to spina bifida [Cohen, 1991; Keppler-Noreuil, 2001].

Etiology of OEIS Complex

Most cases of OEIS complex are sporadic with no obvious etiology. However, OEIS complex has been reported in siblings from separate pregnancies [Smith et al., 1992] and in patients with a family history of similar malformations, including bladder exstrophy, epispadias, and imperforate anus [Keppler-Noreuil, 2001]. Moreover, cloacal exstrophy has been reported in patients with chromosomal anomalies, including a 9q34.1-qter deletion [Thauvin-Robinet et al., 2004], a 3q12.2-3q13.2 deletion [Kosaki et al., 2005], and trisomy 18 [Carey et al., 1978]. It has been suggested that single gene defects may also lead to OEIS complex, although definitive evidence is lacking. For example, Nye et al. [2000] reported a case of myelocystocele-cloacal exstrophy associated with a mitochondrial 12SrRNA mutation previously reported to cause aminoglycoside-induced deafness. It has been suggested that homeobox genes such as *HLXB9* and retinoic acid or its receptor may play a role in OEIS complex [Keppler-Noreuil, 2001].

Cloacal exstrophy is observed in chicks following exposure to the fungal toxin ochratoxin A [Wei and Sulik, 1996], the antiparasitic drug suramin, and Trypan blue [Manner and Kluth, 2003]. In humans, cloacal exstrophy has been reported in association with maternal exposure to diphenylhydantoin [Carey et al., 1978], diazepam [Lizcano-Gil et al., 1995], valproic acid, methamphetamine, and cigarette smoking [Keppler-Noreuil et al., 2007], and maternal obesity, diabetes mellitus, and multiple uterine fibroids [Keppler-Noreuil et al., 2007]. All these associations have been limited to one or two cases. Therefore, there are insufficient data to link OEIS complex to specific teratogens.

It has been observed that 10–30% of cloacal exstrophy cases occur in twin pregnancies [Schinzel et al., 1979; Martinez-Frias et al., 2001]. To explain the notion that cloacal exstrophy occurs more frequent with twinning, it was suggested that early malformations such as OEIS complex and monozygotic twinning are manifestations of the same disturbance of early blastogenesis [Lee et al., 1999]. Another hypothesis states that the mesodermal defect that leads to cloacal exstrophy is initiated by conjoined twinning. Conjoined twins occur when there are two organizing centers (primitive streaks) on the surface of a single embryonic disc. Asymmetric orientation of embryonic tissues approximates caudal organizing centers, resulting in failure to populate each region with sufficient mesoderm, leading to compromise the caudal eminence mesoderm from which the infra-umbilical portion of the lower abdominal is derived. Subsequently, spontaneous separation or separation with disappearance of conjoined twins with lower abdominal defects could occur [Siebert et al., 2005]. We reviewed the literature and found 26 cases of OEIS complex in twin pregnancies (Table II) with a 50% concordance rate in monozygotic twins (Table III). Three conjoined twins with cloacal exstrophy have been reported [Ornoy et al., 1980; Kapur et al., 1994; Goldfischer et al., 1997].

Cloacal exstrophy has also been reported in infants who were conceived by in vitro fertilization (IVF), and it was suggested that ex vivo manipulation of the embryo or the altered biochemical

TABLE II. The Reported 26 Cases of OEIS Complex in Twins

	Refs.	Zygozity	Concordance
1	Koffler et al. [1978]	Monozygotic	Discordant
2	Schinzel et al. [1979]	Monozygotic	Discordant
3	Ornoy et al. [1980]	Monozygotic	Discordant
4	Nance [1981]	Monozygotic	Discordant
5	Redman et al. [1981]	Monozygotic	Concordant
6	Lowry and Baird [1982]	Not reported	Concordant
7		Monozygotic	Concordant
8	Hesser et al. [1984]	Not reported	Discordant
9	Langer et al. [1992]	Monozygotic	Discordant
10	Chitrit et al. [1993]	Monozygotic	Concordant
11	Kapur et al. [1994]	Monozygotic	Concordant
12	Meizner et al. [1995]	Monozygotic	Discordant
13		Monozygotic	Discordant
14	Bruch et al. [1996]	Dizygotic	Discordant
15	Pinette et al. [1996]	Not reported	Discordant
16	Goldfischer et al. [1997]	Monozygotic	Concordant
17	Kramer et al. [1997]	Monozygotic	Concordant
18	Lee et al. [1999]	Monozygotic	Concordant
19	Siebert et al. [2005]	Monozygotic	Concordant
20	Noack et al. [2005]	Dizygotic	Concordant
21	Ben-Neriah et al. [2007]	Dizygotic	Discordant
22		Monozygotic	Concordant
23	Keppler-Noreuil et al. [2007]	Monozygotic	Discordant
24		Not reported	Discordant
25		Not reported	Discordant
26	Tiblad et al. [2008]	Monozygotic	Discordant

TABLE III. The Monozygozity and Concordance in Twins With OEIS Complex

Twins	Monozygotic	Dizygotic	Not reported	Total
Concordance				
Concordant	9	1	1	11
Discordant	9	2	4	15
Total	18	3	5	26

milieu of IVF pregnancies affects embryogenesis and leads to such anomalies [Shanske et al., 2003; Wood et al., 2003]. Finally, uteroplacental vascular insufficiency has been suggested to play role in pathogenesis of cloacal exstrophy [Shanske et al., 2003; Keppler-Noreuil et al., 2007].

Prognosis of Patients With OEIS Complex

Patients with OEIS complex require the care of a multidisciplinary team of neonatologists, pediatric surgeons, pediatric urologists, pediatric neurosurgeons and pediatric orthopedic surgeons. Most of the patients will need multiple surgeries, with many potential complications, including renal impairment, sexual dysfunction and impaired reproduction, impaired ambulation in the presence of damage to the spinal cord or malformations of the pelvis and extremities, and psychosocial consequences of the diagnosis. In the absence of open neural tube defects, the brain is structurally and functionally normal, and normal cognitive development can be expected [Tiblad et al., 2008].

Chromosome 1p36 Deletion Syndrome

Monosomy 1p36 is the most common terminal deletion syndrome with prevalence of 1 in 5,000 newborns. It accounts for 0.5–1.2% of idiopathic mental retardation [Heilstedt et al., 2003; Battaglia et al., 2008]. The patient described in this report had a 2.4 Mb terminal deletion of chromosome 1p36 and clinical features of 1p36 deletion syndrome, including microbrachycephaly, large anterior fontanel, cardiac anomalies (VSD, ASD, PDA), developmental delay, skeletal anomalies (fusion of right 9th and 10th rib and fifth finger clinodactyly), and characteristic facial features, including deep set eyes, epicanthus, flat nasal bridge, mid-face hypoplasia, low set ears, and high arches palate.

This is the first reported case of OEIS in association with chromosome 1p36 deletion. The deleted region harbors approximately 70 genes (http://genome.ucsc.edu/) (Fig. 1d), and we speculate that three may have possible contributing roles to OEIS complex. The *NOC2L* gene encodes an inhibitor of histone acetyltransferase and, therefore, can play a role in transcriptional regulation [Hublitz et al., 2005]. *DVL1*, the human homolog of the Drosophila dishevelled gene (*dsh*), encodes a cytoplasmic phosphoprotein that functions as a mediator of the WNT signaling pathway [Rosso et al., 2005; Bilic et al., 2007; Dollar et al., 2007]. Both may affect early embryonic development. *MMP23B* gene encodes a member of the matrix metalloproteinase family proteins that are involved in the breakdown of extracellular matrix in several processes such as embryonic development and tissue remodeling [Gururajan et al., 1988]. A defect in such a gene may play a role in the cloacal membrane abnormality. Since OEIS complex has not previously been observed with 1p36 deletion, haplo-insufficiency for a gene in this region would not account for the condition, however, it is possible that OEIS complex is caused by a recessive mutation of a gene located in the 1p36 region and the deletion uncovered a mutation located on the intact homologue. Large deletions uncover autosomal recessive disorders have been described in pseudoxanthoma elasticum [Miksch et al., 2005], cystinuria [Bisceglia et al., 2009], and cystic fibrosis [Hantash et al., 2009]. However, no obvious candidate gene has been annotated within the deletion interval, hence it also remains possible that this case reflects a chance occurrence of two independent conditions.

ACKNOWLEDGMENTS

We would like to thank the parents, who were very cooperative and helpful in providing information about their child.

REFERENCES

Battaglia A, Eugene Hoyme H, Dallapiccola B, Zackai E, Hudgins L, McDonald-McGinn D, Bahi-Buisson N, Romano C, Williams C, Brailey L, Zuberi S, Carey J. 2008. Further delineation of deletion 1p36 syndrome in 60 patients: A recognizable phenotype and common cause of developmental delay and mental retardation. Pediatrics 121: 404–410.

Ben-Neriah Z, Withers S, Thomas M, Toi A, Chong K, Pai A, Velscher L, Vero S, Keating S, Taylor G, Chitayat D. 2007. OEIS complex: Prenatal ultrasound and autopsy findings. Ultrasound Obstet Gynecol 29: 170–177.

Bilic J, Huang YL, Davidson G, Zimmermann T, Cruciat CM, Bienz M, Niehrs C. 2007. Wnt induces LRP6 signalosomes and promotes dishevelled-dependent LRP6 phosphorylation. Science 316:1619–1622.

Bisceglia L, Fischetti L, Bonis PD, Palumbo O, Augello B, Stanziale P, Carella M, Zelante L. 2009. Large rearrangements detected by MLPA, point mutations, and survey of the frequency of mutations within the SLC3A1 and SLC7A9 genes in a cohort of 172 cystinuric Italian patients. Mol Genet Metab (in press).

Bohring A. 2002. OEIS complex, VATER, and the ongoing difficulties in terminology and delineation (Letter). Am J Med Genet 107:72–76.

Bruch SW, Adzick NS, Goldstein RB, Harrison MR. 1996. Challenging the embryogenesis of cloacal exstrophy. J Pediatr Surg 31:768–770.

Carey JC. 2001. Exstrophy of the cloaca and the OEIS complex: One and the same (Letter). Am J Med Genet 99:270.

Carey JC, Greenbaum B, Hall BD. 1978. The OEIS complex (omphalocele, exstrophy, imperforate a.u., spinal defects). Birth Defects 14:253–263.

Chitrit Y, Zorn B, Filidori M, Robert E, Chasseray JE. 1993. Cloacal exstrophy in monozygotic twins detected through antenatal ultrasound scanning. J Clin Ultrasound 21:339–342.

Dollar GL, Weber U, Mlodzik M, Sokol SY. 2007. Regulation of lethal giant larvae by dishevelled. Nature 437:1376–1380.

Cohen AR. 1991. The mermaid malformation: Cloacal exstrophy and occult spinal dysraphism. Neurosurgery 28:834–843.

Goldfischer ER, Almond PS, Statter MB, Miller G, Arensman RM, Cromie WJ. 1997. Omphalopagus twins with covered cloacal exstrophy. J Urol 157:1004–1005.

Gururajan R, Grenet J, Lahti JM, Kidd VJ. 1988. Isolation and characterization of two novel metalloproteinase genes linked to the Cdc2L locus on human chromosome 1p36.3. Genomics 52:101–106.

Hantash FM, Rebuyon A, Peng M, Redman JB, Sun W, Strom CM. 2009. Apparent homozygosity of a novel frame shift mutation in the CFTR gene because of a large deletion. J Mol Diagn 11:253–256.

Hayden PW, Chapman WH, Stevenson JK. 1973. Exstrophy of the cloaca. Am J Dis Child 125:879–883.

Heilstedt HA, Ballif BC, Howard LA, Lewis RA, Stal S, Kashork CD, Bacino CA, Shapira SK, Shaffer LG. 2003. Physical map of 1p36, placement of breakpoints in monosomy 1p36, and clinical characterization of the syndrome. Am J Hum Genet 72:1200–1212.

Hesser JW, Murata Y, Swalwell CI. 1984. Exstrophy of cloaca with omphalocele: Two cases. Am J Obstet Gynecol 150:1004–1006.

Howell C, Caldamone A, Snyder H, Snyder H, Ziegler M, Duckett J. 1983. Optimal management of cloacal exstrophy. J Pediatr Surg 18:365–369.

Hublitz P, Kunowska N, Mayer UP, Muller JM, Heyne K, Yin N, Fritzsche C, Poli C, Miguet L, Schupp IW, van Grunsven LA, Potiers N, van Dorsselaer A, Metzger E, Roemer K, Schule R. 2005. NIR is a novel INHAT repressor that modulates the transcriptional activity of p53. Genes Dev 19:2912–2924.

Hurwitz R, Manzoni G, Ransley P, Stephens F. 1987. Cloacal exstrophy: A report of 34 cases. J Urol 138:1060–1064.

Kallen K, Castilla E, Robert E, Mastroiacovo P, Kallen B. 2000. OEIS complex—A population study. Am J Med Genet 92:62–68.

Kapur RP, Jack RM, Siebert JR. 1994. Diamniotic placentation associated with omphalopagus conjoined twins: Implications for a contemporary model of conjoined twinning. Am J Med Genet 52:188–195.

Keppler-Noreuil KM. 2001. OEIS complex (omphalocele-exstrophy-imperforate anus-spinal defects): A review of 14 cases. Am J Med Genet 99:271–279.

Keppler-Noreuil K, Gorton S, Foo F, Yankowitz J, Keegan C. 2007. Prenatal ascertainment of OEIS complex/cloacal exstrophy—15 new cases and literature review. Am J Med Genet Part A 143A:2122–2128.

Koffler H, Aase JM, Papile L-A, Coen RW. 1978. Persistent cloaca with absent penis and anal atresia in one of identical twins. J Pediatr 93:821–822.

Kosaki R, Fukuhara Y, Kosuga M, Okuyama T, Kawashima N, Honna T, Ueoka K, Kosaki K. 2005. OEIS complex with del(3)(q12.2q13.2). Am J Med Genet Part A 135A:224–226.

Kramer R, Johnson M, Qureshi F, Jacques S, Yaron Y, Evans M. 1997. Concordance for cloacal dysgenesis. Fetal Diagn Ther 12:279–282.

Langer JC, Brennan B, Lappalainen RE, Caco CC, Winthrop AL, Hollenberg RD, Paes BA. 1992. Cloacal exstrophy: Prenatal diagnosis before rupture of the cloacal membrane. J Pediatr Surg 27:1352–1355.

Lee DH, Cottrell JR, Sanders RC, Meyers CM, Wulfsberg EA, Sun CCJ. 1999. OEIS complex (omphalocele-exstrophy-imperforate anus-spinal defects) in monozygotic twins. Am J Med Genet 84:29–33.

Lizcano-Gil LA, García-Cruz D, Sánchez-Corono J. 1995. Omphalocele-exstrophy-imperforate anus-spina bifida (OEIS) complex in a male prenatally exposed to diazepam. Arch Med Res 26:95–96.

Lowry RB, Baird PA. 1982. Familial gastroschisis and omphalocele. Am J Hum Genet 34:517–518.

Manner J, Kluth D. 2003. A chicken model to study the embryology of cloacal exstrophy. J Pediatr Surg 38:678–681.

Martinez-Frias ML, Bermejo E, Rodriguez-Pinilla E, Frias JL. 2001. Exstrophy of the cloaca and exstrophy of the bladder: Two different expressions of a primary developmental field defect. Am J Med Genet 99:261–269.

Maizels M. 1998. Normal and anomalous development of the urinary tract. In: Walsh PC, Retnik AB, Vaughan Ed, Wein AJ, editors. Campbell's urology, 7th edition. Philadelphia: W.B. Saunders Co. pp 1545–1600.

Meglin AJ, Balotin RJ, Jelinek JS, Fishman EK, Jeffs RD, Ghaed V. 1990. Cloacal exstrophy: Radiologic findings in 13 patients. Am J Roentgenol 155:1267–1272.

Miksch S, Lumsden A, Guenther UP, Foernzler D, Christen-Zäch S, Daugherty C, Ramesar RK, Lebwohl M, Hohl D, Neldner KH, Lindpaintner K, Richards RI, Struk B. 2005. Molecular genetics of pseudoxanthoma elasticum: Type and frequency of mutations in ABCC6. Hum Mutat 26:235–248.

Meizner I, Levy A, Barnhard Y. 1995. Cloacal exstrophy sequence: An exceptional ultrasound diagnosis. Obstet Gynecol 86:446–450.

Nance WE. 1981. Malformations unique to the twinning process. Prog Clin Biol Res 69:123–133.

Noack F, Sayk F, Gembruch U. 2005. Omphalocoele-exstrophyimperforate anus-spinal defects complex in dizygotic twins. Fetal Diagn Ther 20:346–348.

Nye JS, Haynes EA, Amendola M, Vaughn D, Charrow J, McLone DG, Speer MC, Nance WE, Pandya R. 2000. Myelocystocele-cloacal exstrophy in a pedigree with mitochondrial 12SrRNA mutation, aminoglycoside-induced deafness, pigmentary disturbances, and spinal anomalies. Teratology 61:165–171.

Ornoy A, Navot D, Menashi M, Laufer N, Chemke J. 1980. Asymmetry and discordance for congenital anomalies in conjoined twins: A report of six cases. Teratology 22:145–154.

Pinette MG, Pan YQ, Pinette SG, Stubblefield PG, Blackstone J. 1996. Prenatal diagnosis of fetal bladder and cloaca exstrophy by ultrasound: A report of three cases. J Reprod Med 41:132–134.

Rosso SB, Sussman D, Wynshaw-Boris A, Salinas PC. 2005. Wnt signaling through Dishevelled, Rac and JNK regulates dendritic development. Nat Neurosci 8:34–42.

Redman J, Seibert J, Page B. 1981. Cloacal exstrophy in identical twins. Urology 17:73–74.

Schinzel AAGL, Smith DW, Miller JR. 1979. Monozygotic twinning and structural defects. J Pediatr 95:921–930.

Shanske AL, Pande S, Aref K, Vega-Rich C, Brion L, Reznik S, Timor-Tritsch IE. 2003. Omphalocele-exstrophy-imperforate anus-spinal defects (OEIS) in triplet pregnancy after IVF and CVS. Birth Defects Res A 67:467–471.

Siebert JR, Rutledge JC, Kapur RP. 2005. Association of cloacal anomalies, caudal duplication, and twinning. Pediatr Dev Pathol 8:339–354.

Smith NM, Chambers HM, Furness ME, Haan EA. 1992. The OEIS complex (omphalocele-exstrophy-imperforate anus-spinal defects): Recurrence in sibs. J Med Genet 29:730–732.

Thauvin-Robinet C, Faivre L, Cusin V, Van Kien V, Callier P, Parker K, Fellous M, Borgnon J, Gounot E, Huet F, Sapin E, Mugneret F. 2004. Cloacal exstrophy in an infant with 9q34.1-qter deletion resulting from a de novo unbalanced translocation between chromosome 9q and Yq. Am J Med Genet Part A 126A:303–307.

Tiblad E, Wilson D, Carr M, Flake A, Hedrick H, Johnson M, Bebbington M, Mann S, Adzick S. 2008. OEIS sequence—A rare congenital anomaly with prenatal evaluation and postnatal outcome in six cases. Prenat Diagn 28:141–147.

Wei X, Sulik KK. 1996. Pathogenesis of caudal dysgenesis/sirenomelia induced by Ochratoxin A in chick embryos. Teratology 53:378–391.

Wood HM, Trock BJ, Gearhart JP. 2003. In vitro fertilization and the cloacal-bladder exstrophy-epispadias complex: Is there an association? J Urol 169:1512–1515.