assumed for the 11p15.5 imprinted regions including the *IGF2–H19* domain on the basis of SRS or Beckwith–Wiedemann syndrome (BWS) phenotype in patients with multilocus hypomethylation[16] and BWS-like phenotype in patients with a upid (AC)pat cell lineage,[17] a mirror image of a upid(AC)mat cell lineage), (4) expression levels of imprinted genes in upid(AC)mat cells (although *SNRPN* expression of this patient was consistent with upid(AC)mat cells being predominant in leukocytes, complicated expression patterns have been identified for several imprinted genes in androgenetic and parthenogenetic fetal mice, probably because of perturbed *cis*- and *trans*-acting regulatory mechanisms)[18] and (5) unmasking of possible maternally inherited recessive mutation(s) in upid(AC)mat cells.[19] Collectively, it appears that the extent of overall (epi)genetic aberrations exceeded the threshold level for the development of SRS phenotype and horseshoe kidney characteristic of TS[4] but remained below the threshold level for the occurrence of other imprinting disorders or recessive Mendelian disorders.

In summary, we identified a upid(AC)mat 46,XX cell lineage in a woman with an SRS-like phenotype and a 45,X cell lineage accompanied by autosomal haploid sets of biparental origin. This report will facilitate further identification of patients with a upid(AC)mat cell lineage and better clarification of the clinical phenotypes in such patients.

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Parthenogenetic chimaerism/mosaicism with a Silver-Russell syndrome-like phenotype

K Yamazawa, K Nakabayashi, M Kagami, et al.

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Notes

RESEARCH LETTER

AMERICAN JOURNAL OF medical genetics PART A

Prenatal Findings of Paternal Uniparental Disomy 14: Delineation of Further Patient

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TO THE EDITOR:

Human chromosome 14q32.2 carries a cluster of imprinted genes including paternally expressed genes such as *DLK1* and *RTL1* and maternally expressed genes such as *MEG3* (alias *GTL2*) and *RTL1as* (*RTL1* antisense), together with the germline-derived intergenic differentially methylated region (IG-DMR) and the postfertilization-derived *MEG3*-DMR [da Rocha et al., 2008; Kagami et al., 2008a]. Consistent with this, paternal uniparental disomy 14 (upd(14)pat) results in a unique phenotype characterized by facial abnormality, small bell-shaped thorax with coat-hanger appearance of the ribs, abdominal wall defects, placentomegaly, and polyhydramnios [Kagami et al., 2008a,b], and maternal uniparental disomy 14 (upd(14)mat) leads to less-characteristic but clinically discernible features including growth failure [Kotzot, 2004; Kagami et al., 2008a].

For upd(14)pat, this condition has primarily been identified by the pathognomonic chest roentgenographic findings that are obtained immediately after birth because of severe respiratory dysfunction [Kagami et al., 2008a]. However, upd(14)pat has also been suspected prenatally by fetal radiological findings suggestive of small thorax and other characteristic findings [Curtis et al., 2006; Yamanaka et al., 2010]. Here, we report on prenatal findings in a hitherto unreported upd(14)pat patient. The results will serve to the prenatal identification of similarly affected patients and appropriate neonatal care including respiratory management.

A 41-year-old gravida 1, para 0 Japanese woman was referred to Nagoya City University Hospital because of polyhydramnios at 24 weeks of gestation. The polyhydramnios was severe and required repeated amnioreduction (1,600 ml at 26 weeks, 1,800 ml at 29 weeks, 2,000 ml at 32 weeks, and 2,100 ml at 35 weeks). The fetal urine volume was normal (5–12 ml per hr). At 28 weeks of gestation, 3D ultrasound studies were performed, delineating dysmorphic face, anteverted nares, micrognathia and small thorax characteristic of upd(14)pat (Fig. 1), although the differential diagnosis included Beckwith–Wiedemann syndrome and several types of skeletal dysplasia. Thereafter, ultrasound studies were weekly carried out, indicating almost normal fetal growth and normal umbilical artery Doppler.

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At 37 weeks of gestation, a 2,778 g male infant was delivered by cesarean because of fetal distress. The placenta was 1,384 g (gestational age-matched reference, 510 ± 98 g) [Kagami et al., 2008b]. The patient had severe asphyxia, and immediately received appropriate management including mechanical ventilation for 6 days and nasal directional positive airway pressure at the neonatal intensive care unit. At birth, physical examination revealed hairy forehead, blepharophimosis, depressed nasal bridge, anteverted nares, small ears, protruding philtrum, puckered lips, micrognathia, short webbed neck, joint contractures, and diastasis recti, and roentgenograms showed typical bell-shaped thorax with coat-hanger appearance of the ribs (Fig. 2). Coax valga or kyphoscoliosis was uncertain. Discharge from hospital was 35 days after birth. On the last examination at 8 months of age, the patient

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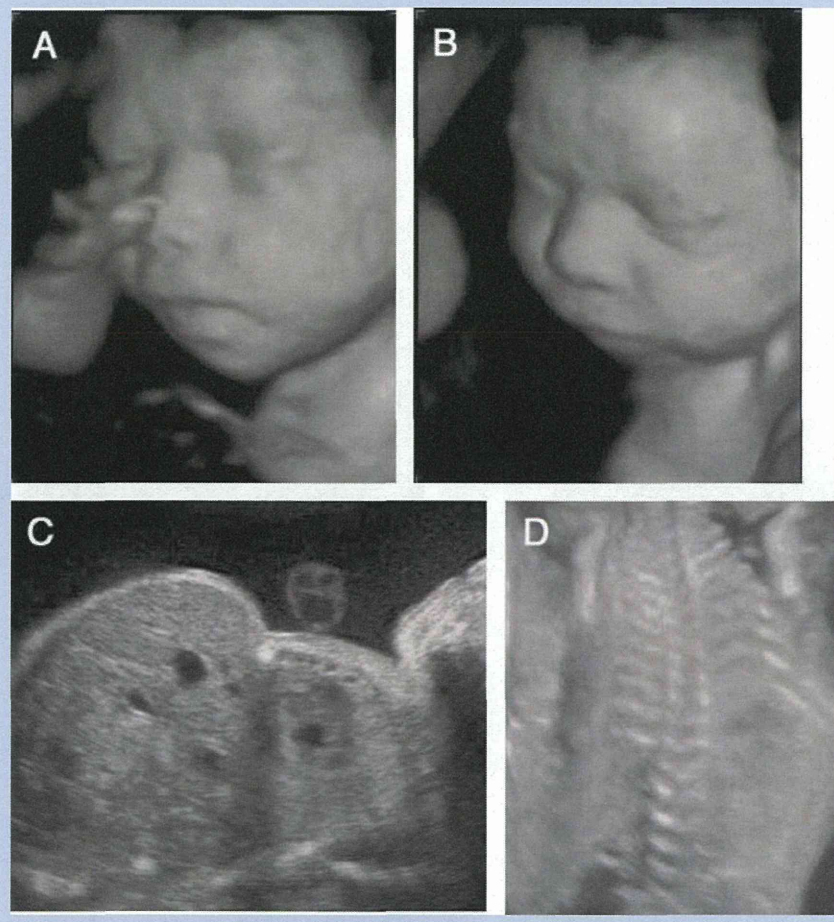

FIG. 1. Prenatal 3D findings at 28 weeks of gestation. A,B: Face appearance with blepharophimosis, depressed nasal bridge, anteverted nares, and micrognathia. C: Small thorax and polyhydramnios. D: Coat-hanger like appearance of the ribs.

required regular oropharyngeal suction and nasogastric tube feeding due to a poor swallowing reflex, and showed developmental delay. At the time of the last evaluation there was no seizure disorder.

To confirm the findings, cytogenetic and molecular studies were performed for the cord blood of the patient by the previously described methods [Kagami et al., 2008a]. This study was approved by the Institutional Review Board Committees at National Center for Child Health and Development and Nagoya City University, and performed after obtaining written informed consent. The karyotype was normal, and metaphase fluorescence in situ hybridization (FISH) analysis with a 202 kb BAC probe containing *DLK1* (RP11-566J3) and a 165 kb BAC probe containing *MG3* and *RTL1/RTL1as* (RP11-123M6) (http://bacpac.-chori.org/) delineated two signals with a similar intensity, respectively. Methylation analysis for bisulfite-treated genomic DNA indicated the presence of paternally derived hypermethylated IG-DMR (CG4 and CG6) and *MEG3*-DMR (CG7) and the absence of maternally derived hypomethylated DMRs. Furthermore, microsatellite analysis was performed using leukocyte genomic DNA of patient and parents, revealing uniparental paternal isodisomy for chromosome 14 (Table I, Fig. 3).

In this patient with molecularly confirmed upd(14)pat, ultrasound studies unequivocally showed typical upd(14)pat phenotypes such as thoracic abnormality and facial dysmorphic features. While this is the first report documenting the facial appearance of the affected fetus, small thorax has been suspected prenatally in five patients with upd(14)pat or epimutations of the IG-DMR and the *MEG3*-DMR, with coat-hanger appearance of the ribs being delineated in one patient [Curtis et al., 2006; Yamanaka et al., 2010]. In this regard, it is notable that polyhydramnios has invariably been identified in upd(14)pat by the second trimester [Kagami et al., 2008a]. It is recommended, therefore, to perform radiological studies for pregnant women with polyhydramnios, to suspect upd(14)pat-compatible clinical features of the fetus. This will permit appropriate counseling and delivery planning at a tertiary

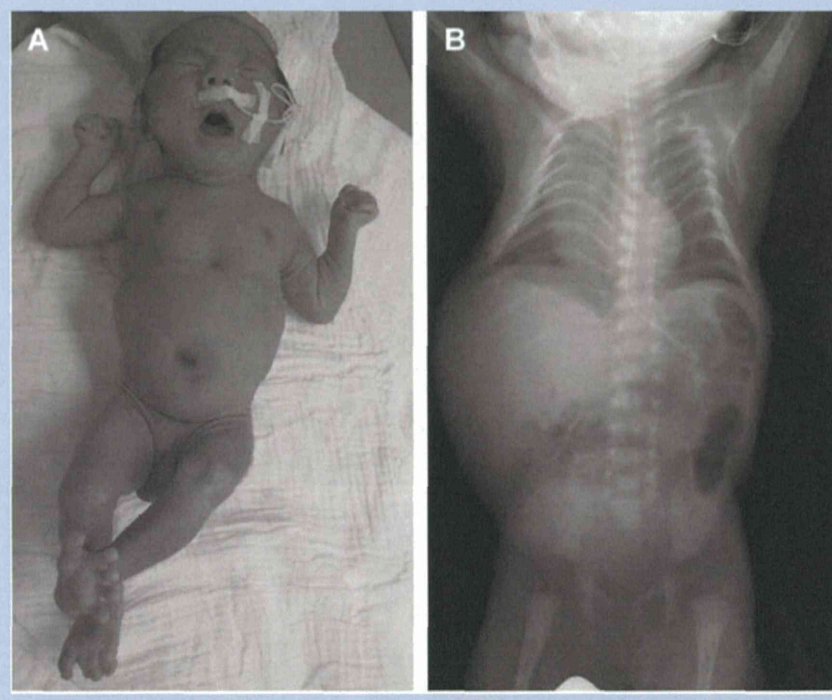

FIG. 2. Postnatal findings at 1 month of age. A: Front view. B: Chest roentgenogram showing bell-shaped thorax with coat-hanger appearance of the ribs.

center with neonatal intensive care as well as pertinent molecular studies using cord blood.

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TABLE I. The Results of Microsatellite Analysis

Locus	Location	Mother	Patient	Father	Assessment
D14S80	14q12	98	98	98	N.I.
D14S608	14q12	200	194	194/210	Isodisomy
D14S588	14q23–24.1	114/126	114	114/122	N.I.
D14S617	14q32.12	139/169	143	143/165	Isodisomy
D14S250	14q32.2	159	159	159/167	N.I.
D14S1006	14q32.2	127/139	127	127/139	N.I.
D14S985	14q32.2	135/137	131	131/133	Isodisomy
D14S1010	14q32.33	134/142	142	142/144	N.I.
D14S1007	14q32.33	119	119	119	N.I.

N.I., not informative.
The Arabic numbers indicate the PCR product sizes in bp.
The imprinted region resides at 14q32.2.
D14S985 is located in the intron of *MEG3*.

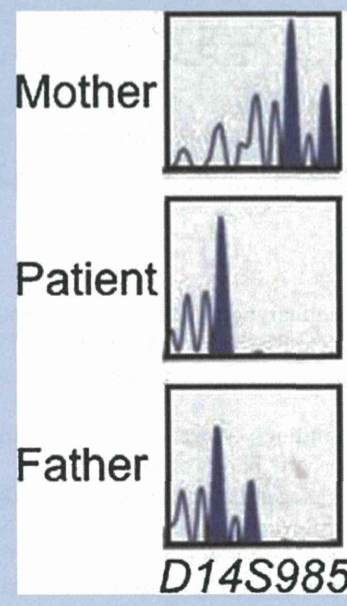

FIG. 3. Microsatellite analysis for *D14S985* residing in the intron of *MEG3*. One of the two peaks in the father is transmitted to the patient, and both of the two peaks in the mother are not inherited by the patient. The PCR fragment size: 135 and 137 bp in the mother, 131 bp in the patient, and 131 and 133 bp in the father. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

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Letter to the Editor

Placentomegaly in Paternal Uniparental Disomy for Human Chromosome 14

Sir,

Paternal uniparental disomy for chromosome 14 (upd (14)pat) causes a unique phenotype characterized by polyhydramnios, dysmorphic features, small bell-shaped thorax, and abdominal wall defect [1]. Since chromosome 14q32.2 region harbors several paternally expressed genes (*PEGs*) such as *DLK1* and *RTL1* and maternally expressed genes (*MEGs*) such as *GTL2* (alias, *MEG3*), *RTL1as* (*RTL1 antisense*), and *MEG8*, upd(14)pat phenotype is ascribed to the increased dosage of active *PEGs* and the absence of functional *MEGs* [2]. In this regard, we have suggested that increased *RTL1* dosage plays a major role in the development of upd(14)pat phenotype, on the basis of epigenotype–phenotype correlations in eight patients with upd(14)pat-like phenotypes with various microdeletions or epimutations affecting the imprinted region [2].

Virtually, all the imprinted genes studied to date are expressed in the placenta [3]. This is consistent with the notion that imprinted genes are identified from placental mammals and play a pivotal role in placental growth and development. Indeed, placental hypoplasia has been identified in SRS patients with upd(7)mat [4] or epimutations of the *H19*-differentially methylated region (DMR) [5], and placentomegaly has been described in Beckwith–Wiedemann syndrome (BWS) patients with upd(11p15.5)pat [6]. These findings, together with the results of knockout mouse experiments for imprinted genes [3], imply that placental growth is promoted by *PEGs* and suppressed by *MEGs*. However, the placental weight data remain poor in upd(14)pat, although the presence of placentomegaly has been mentioned briefly [2].

Thus, we examined placental weights in 10 patients with upd (14)pat (Table 1). This study was approved by the Institutional Review Board Committee at National Center for Child Health and Development, and performed after obtaining written informed consent. Cases 1–3 have previously been reported with no description on the placental weights [1], and cases 4–10 are hitherto unreported patients. Cases 1–10 were ascertained because of the pathognomonic bell-shaped thorax, and were found to have typical upd(14)pat phenotypes; although polyhydramnios was apparently absent in case 5, this would be due to very premature (24 weeks of gestation) delivery by an emergent Caesarean section for severe fetal distress (detailed clinical features of each case are available on request). Karyotype was normal in the nine cases examined. Microsatellite analysis was performed for 14 loci dispersed on chromosome 14 using leukocyte genomic DNA samples obtained from cases 1–10 and all of the parents, indicating segmental paternal isodisomy in case 1, full paternal isodisomy in cases 2–8, mixture of paternal heterodisomy for the proximal to middle part of 14q and isodisomy for the distal part of 14q in case 9, and full paternal heterodisomy in case 10 (the genotyping data are available on request). Thus, the 14q32.2 imprinted region was present in an isodisomic status in cases 1–9 and in a heterodisomic status in case 10. Furthermore, methylation analyses for the IG-DMR and *GTL2*-DMR [2] confirmed upd(14)pat in cases 1–10.

The placental weights in cases 1–10 are shown in Table 1. They were obtained from the hospital records, and were assessed by the Japanese placental weight data collected during the years 1981–1984 [7] and by those collected from January 2006 to April 2008 (our unpublished observation). The placental weights were above the mean in all cases and above the +2 SD of the mean in most cases, while there was a considerable degree of variation. In particular, they were ~2 times increased in cases 1, 4, and 8 with paternal isodisomy and in case 10 with paternal heterodisomy. Unfortunately, since placental tissues were not preserved, histological examination could not be performed, except for the placenta of case 3 which was characterized by proliferation of dilated and congested chorionic villi [the histological findings have been reported in Ref. [2]].

The present study showed the presence of placentomegaly in upd(14)pat. In this context, the human 14q32.2 imprinted region is highly conserved on the distal part of the mouse chromosome 12, and paternal uniparental disomy for chromosome 12 (PatDi(12)) results in placentomegaly, whereas MatDi(12) leads to placental hypoplasia [8]. In addition, mice with 2.5–3.0 times of *Rtl1* expression caused by maternally derived *Rtl1as* deletion have placentomegaly, whereas mice with null *Rtl1* expression caused by paternally derived *Rtl1* deletion have placental hypoplasia [9]. Collectively, these findings suggest that *RTL1/Rtl1* expression dosage plays a critical role in the placental growth. Consistent with this, mouse Rtl1 protein is identified exclusively in the labyrinth zone of the placenta [9].

Several points should be made in reference to the placentomegaly in upd(14)pat. First, the degree of placentomegaly was considerably variable in cases 1–10. This may imply

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Table 1
Summary of patients with paternal uniparental disomy for chromosome 14

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Sex	Female	Male	Female	Female	Male	Male	Female	Female	Male	Male
Polyhydramnios	+	+	+	+	−	+	+	+	+	+
Dysmorphic features	+	+	+	+	+	+	+	+	+	+
Bell-shaped thorax	+	+	+	+	+	+	+	+	+	+
Abdominal wall defects	+	+	+	+	+	+	+	+	+	+
Karyotype	46,XX	N.E.	46,XX	46,XX	46,XY	46,XY	46,XX	46,XX	46,XY	46,XY
Pathogenesis	Seg-iso	Full-iso	Full-iso	Full-iso	Full-iso	Full-iso	Full-iso	Full-iso	Hetero/Iso	Full-hetro
Imprinted region	Isodisomy	Isodisomy	Isodisomy	Isodisomy	Isodisomy	Isodisomy	Isodisomy	Isodisomy	Isodisomy	Heterodisomy
Gestational age (wks)	36	34	32	34	24	36	37	36	34	37
Placental weight (g)	1108	556	635	1108	278	570	750	970	640	1030
Placental weight (%)[a]	227	114	161	227	114	117	142	198	131	195
Placental weight (SDS)[b]	+6.1	+1.6	+3.4	+8.0	N.A.	+0.9	+2.4	+4.9	+2.6	+5.3

N.E.: not examined; SDS: standard deviation score; and N.A.: not available.
[a] Evaluated by the Japanese placental weight data obtained between the years 1981–1984 [7]; the mean placental weight is 244 g for 21–24 weeks of gestation ($n = 40$), 300 g for 25–28 weeks ($n = 181$), 394 g for 29–32 weeks ($n = 333$), 489 g for 33–36 weeks ($n = 483$), and 527 g for 37–40 weeks ($n = 2282$).
[b] Assessed by the Japanese placental weight data collected between January 2006 and April 2008; the placental weight (mean ± SD) is not available for 24 weeks of gestation, 375 ± 75 g for 32 weeks ($n = 7$), 423 ± 85 g for 34 weeks ($n = 15$), 478 ± 101 g for 36 weeks ($n = 28$), and 510 ± 98 g for 37 weeks ($n = 36$).

a relatively weak placental growth regulation in imprinting disorders, which could be related to the differential imprinting regulation between bodies and placentas [10]. Second, placentomegaly may exaggerate the amniotic fluid production, leading to the development of polyhydramnios. In support of this, the association of placentomegaly with polyhydramnios has also been reported in BWS [11]. Third, although the degree of placentomegaly was apparently irrelevant to the type of disomy, it remains to be clarified whether placental phenotype is somewhat different between patients with isodisomy and those with heterodisomy. Indeed, since heterodisomy is usually caused by trisomy rescue [12], there may be placental confined trisomy that may influence the placental growth and development [12]. In addition, since unmasking of recessive mutations is possible in isodisomy [12], this may lead to a specific phenotype in both the body and the placenta in exceptional patients with paternally derived recessive mutations. Lastly, while placentomegaly appears to be associated with characteristic histological findings [2], further studies are required to define the histological characters in upd(14)pat.

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SHORT COMMUNICATION

Monozygotic female twins discordant for Silver–Russell syndrome and hypomethylation of the *H19*-DMR

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Abstract Silver–Russell syndrome (SRS) is characterized by growth failure and dysmorphic features, and is frequently caused by hypomethylation of the paternally derived *H19*-DMR (epimutation). We observed 5 8/12-year-old female twins discordant for SRS. One twin exhibited SRS-compatible features, such as pre- and postnatal growth failure, relative macrocephaly, triangular face, left hemihypotrophy, and bilateral fifth finger clinodactyly, whereas the other twin showed apparently normal phenotype. Microsatellite analysis for 26 loci on multiple chromosomes showed monozygosity. Methylation analysis for the *H19*-DMR indicated epimutation in roughly half of cells in the affected twin and normal patterns in the unaffected twin and the parents. X-inactivation analysis revealed random X-inactivation with a nearly identical pattern between the twins. The discordant methylation pattern of the *H19*-DMR may primarily be due to a failure to maintain the DNA methyltransferase-1-dependent methylation imprint around the pre-implantation S phase, because such failure would result in the production of two different cell clones, one with normally methylated DMR and the other with demethylated DMR, leading to the separation of cells with different characters and resultant twinning.

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Introduction

Silver–Russell syndrome (SRS; MIN 180860) is a developmental disorder characterized by pre- and postnatal growth failure, relative macrocephaly, triangular face, hemihypotrophy, and fifth-finger clinodactyly (Hitchins et al. 2001). Recent studies have shown that hypomethylation (epimutation) of the paternally derived differentially methylated region in the upstream of *H19* (*H19*-DMR) on chromosome 11p15 accounts for 30–65% of SRS patients (Gicquel et al. 2005; Bliek et al. 2006; Eggermann et al. 2006; Netchine et al. 2007). In this regard, it is known that a common enhancer is shared by the paternally expressed gene *IGF2* (insulin-like growth factor 2) and the maternally expressed gene *H19* (Leighton et al. 1995b), and that the enhancer exerts its effects on *IGF2* or *H19* depending on the methylation status of the *H19*-DMR (Leighton et al. 1995a; Thorvaldsen et al. 1998). This alternative enhancer effect is mediated by an insulator protein CTCF that binds to the unmethylated *H19*-DMR of maternal origin, but not to the methylated *H19*-DMR of paternal origin. Indeed, seven CTCF binding sites have been identified within the *H19*-DMR (Bell and Felsenfeld 2000; Hark et al. 2000). Thus, it has been postulated that the hypomethylation of the paternally derived *H19*-DMR results in maternalization of the *IGF2–H19* imprinted domain, leading to the development of SRS because of reduced *IGF2* expression (Gicquel et al. 2005). Although the exaggerated *H19* expression might also exert some clinical effect, this possibility is unlikely because the primary function of *H19* in