CLINICAL REPORT

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Possible Association Between Complex Congenital Heart Defects and 11p15 Hypomethylation in Three Patients With Severe Silver–Russell Syndrome

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Silver–Russell syndrome (SRS) is characterized by pre- and post-natal growth restriction that spares head growth, feeding difficulties, and variable dysmorphic facial features without major malformations. Hypomethylation of the paternal 11p15 imprinting control region 1 (ICR1) and maternal uniparental disomy of chromosome 7 are found in 50–60% and in 5–10% of SRS patients, respectively. We report on the pre- and post-natal features of three unrelated SRS patients with unusual congenital heart defects (CHDs). Two patients born prematurely had total anomalous pulmonary venous return and died shortly after birth, and a third patient, now 4 years old, had cor triatriatum sinistrum, which was surgically corrected. In all three patients, the underlying molecular defect was 11p15 ICR1 hypomethylation. Based on a large cohort with molecularly proven SRS, the prevalence of CHD in SRS is estimated at 5.5%. We suggest that the occurrence of CHD in SRS with 11p15 ICR1 hypomethylation is not coincidental, but specific to this genotype.

Key words: congenital heart defect; Silver–Russell syndrome; 11p15 ICR1 hypomethylation; total anomalous pulmonary venous return; cor triatriatum

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INTRODUCTION

Silver–Russell syndrome (SRS) is characterized by severe intrauterine growth restriction (IUGR), postnatal growth delays, normal head growth resulting in relative macrocephaly, a prominent forehead in young patients, variable dysmorphic facial features, frequent asymmetry and feeding difficulties [Netchine et al., 2007]. SRS has been reported in over 800 patients using different clinical scoring systems, including one developed by our group [Netchine et al., 2007]. However, the range of the SRS phenotypic spectrum is unclear, reflecting, in part, its heterogeneous genetic etiology

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[Eggermann et al., 2010]. Two major molecular mechanisms have been implicated in SRS: maternal uniparental disomy of chromosome 7 (UPD(7)mat) in 5–10% of patients, and hypomethylation of the 11p15 imprinting control region 1 (ICR1) in 50–60% of patients [Netchine et al., 2007; Eggermann et al., 2010]. Genotype–phenotype studies suggest a milder SRS phenotype in UPD(7)mat but with more frequent developmental delays, dominant speech difficulties and myoclonus-dystonia [Guettard et al., 2008; Wakeling et al., 2010]. ICR1 hypomethylation is associated with more typical SRS features (characteristic craniofacial features, asymmetry and severe IUGR) and more congenital defects (cleft palate, limb defects, genital anomalies, and CHDs) [Wakeling et al., 2010], although the latter difference is not statistically significant.

The association of CHD with SRS is believed to be rare and is considered by some authors to be coincidental [Patton, 1988; Khalil et al., 2008]. Moreover, the presence of uncommon forms of CHD is discussed as a possible exclusion factor for SRS, and indeed, may have been the reason for not considering SRS in a child with a major CHD [Horike et al., 2009]. To increase awareness among clinicians about the possible under-diagnosis of SRS in the presence of major CHDs, we report here on three SRS patients with rare complex CHDs. We also provide supplemental data about the frequency of CHDs in a large cohort of SRS patients (n = 145) identified using molecular markers at Armand Trousseau Children's Hospital (5-year extension, still ongoing, of our previously published study of epigenotype–phenotype correlations in SRS [Netchine et al., 2007]).

PATIENT REPORTS

Patient 1

This Caucasian female infant was the second child of a healthy 24-year-old woman and her healthy nonconsanguineous 25-year-old husband. Pregnancy was assisted by gonadotrophin treatment. IUGR with limb asymmetry was detected during the second fetal ultrasound at 23 weeks of gestation (WG): humerus and femur length, abdominal diameter and fetal weight were below the 3rd centile, crown-rump length was at the 25th centile, and biparietal diameter and head circumference were between the 10th and 50th centiles. The etiological evaluation (uterine and umbilical artery Doppler, fetal karyotyping, FISH with a Wolf–Hirschhorn [4p−] syndrome probe and fetal-maternal infectious screening) was normal. IUGR was complicated by oligohydramnios at 31 WG. A delivery by cesarean (CS) was performed at 32 WG because of significantly altered fetal growth. The female newborn was small for gestational age (SGA) with relative macrocephaly: weight 876 g (−3.8 SD), length 34 cm (−4.9 SD), head circumference 28 cm (−1.1 SD). She had severe respiratory distress that required her transfer to the neonatal intensive care unit. Echocardiography detected systemic pulmonary hypertension with total anomalous pulmonary venous return (TAPVR). She had dysmorphic facial features suggestive of SRS (Fig. 1). She died on the second day after birth and an autopsy was declined. The placenta was hypotrophic (weight 210 g; −1.5 SD) with signs of subacute chorioamnionitis and discrete ischemic villi. Investigations excluded Smith–Lemli–Opitz syndrome (normal plasma levels of 7-dehydrocholesterol) and genomic rearrangement (Agilent 44 K array-CGH). SRS was confirmed by the detection of hypomethylation of the 11p15.5 ICR1 in leukocytes by allele-specific methylated multiplex real-time quantitative PCR (ASMM RTQ-PCR), as previously described [Azzi et al., 2011]. The methylation status of seven other imprinted loci (11p15 ICR2, *SNRPN* at 15q11, *DLK1-GTL2 IG-DMR* at 14q32, *ZAC1* at 6q24, *PEG1/MEST* at 7q32 and *GNAS XL*, and *NESP DMRs* at 20q13) as determined by ASMM RTQ-PCR was normal.

Patient 2

This Caucasian male infant was the first child born of a healthy 18-year-old woman and her healthy nonconsanguineous 20-year-old husband. The father's family history was marked by recurrent neural tube defects. This spontaneous pregnancy was complicated by asymmetric IUGR detected at 22 gestational weeks: fetal weight was below the 3rd centile, and head circumference was between the 10th and 50th centile. An etiological evaluation as described for patient 1 was normal. Severe oligohydramnios at 28 gestational weeks and stagnation of fetal growth led to a preterm cesarean delivery at 30 gestational weeks. The dysmorphic male newborn was SGA: weight 600 g (−4.4 SD), length 29.5 cm (−6.6 SD), head

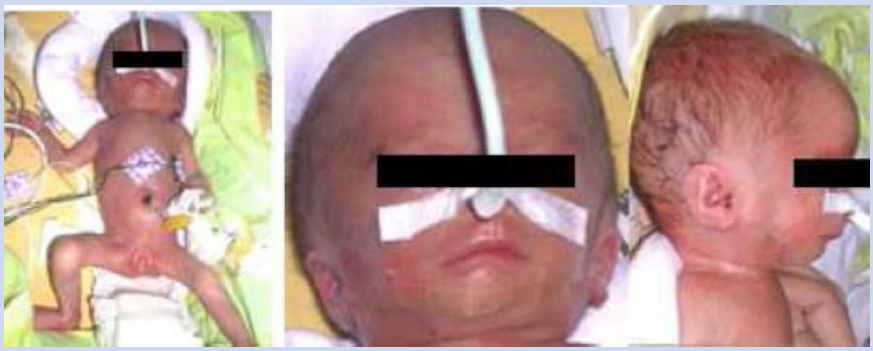

FIG. 1. Patient 1. Note triangular face, prominent forehead, microretrognathia, low-set ears, hypertelorism, widely spaced nipples, and adducted thumb. The latter three cannot be seen in the photos presented here. There was neither body asymmetry nor clinodactyly. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmga]

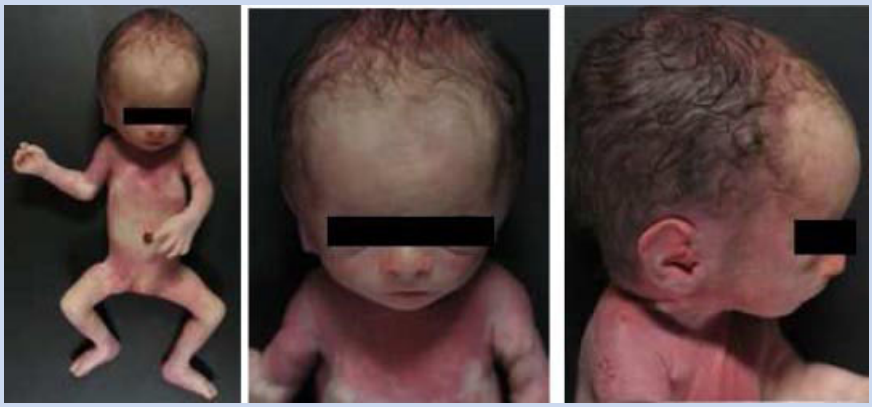

FIG. 2. Patient 2. Note prominent forehead, large anterior fontanel, low-set ears, downturned corners of the mouth, microretrognathia and bilateral 5th finger clinodactyly and small toes. In addition, there were two transverse palmar creases and a prominent fissure between the first and the second toes (cannot be seen in the photos). [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmga]

circumference 27 cm (−0.4 SD; Fig. 2). Echocardiography showed an atrioventricular septal defect, interrupted aortic arch, type A and TAPVR. He died a few hours later. The autopsy showed hypospadias, agenesis of the right kidney, right arhinencephaly, and a large cyst of the septum pellucidum (6 mm × 5 mm). The placenta was severely hypotrophic (132 g: −2.2 SD) with hypertrophic villous trunks. Post-mortem etiological investigations, array-CGH (Agilent 44 K) and plasma levels of 7-dehydrocholesterol were normal. SRS was confirmed by the detection of 11p15 ICR1 hypomethylation in leukocytes by the same method used in Patient 1. The methylation status of the other seven imprinted loci studied was normal.

Patient 3

The patient is a 4-year-old girl born to a healthy 43-year-old Caucasian woman and her 45-year-old nonconsanguineous husband, with no family history of genetic diseases. IUGR was detected during the 2nd trimester ultrasound, and placental insufficiency was suspected. She was enrolled in a fetal MRI study. Fetal echocardiography showed an abnormal left atrium. Owing to the stagnation of fetal growth, the child was delivered at 32 WG by CS. Birth weight was 1,110 g (−2.7 SD). Length and head circumference were not recorded. She was hospitalized for 11 weeks for poor feeding but with no history of hypoglycemia. She had cor triatriatum sinistrum (division of the left atrium into two compartments by a fibromuscular membrane). The atrial septal defect was surgically corrected at 14 months. She was referred for genetic diagnosis at 16 months, with a length of 84 cm (−1.5 SD), weight of 9 kg (−4 SD) and head circumference of 48 cm (median). She had dysmorphic features (Fig. 3), a high-pitched voice and delayed active postural skills. At the age of 2 years, the patient had a gastrostomy because of prolonged feeding difficulties and gastroesophageal reflux. At 2.5 years, her psychomotor development was judged appropriate. A standard karyotype and array-CGH were normal. She had no UPD(7)mat. An analysis of DNA methylation showed hypomethylation of the 11p15 ICR1 in leukocytes by

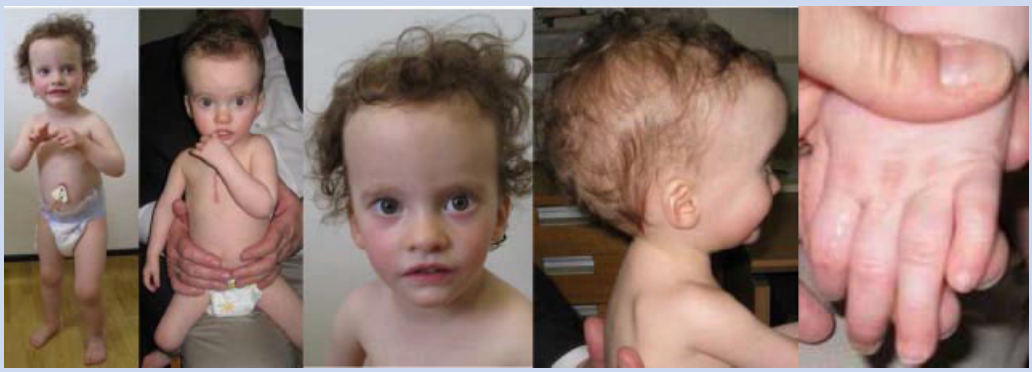

FIG. 3. Patient 3. Note frontal bossing, giving the face a triangular shape, scaphocephaly, minimal epicanthic folds, 5th finger clinodactyly and body asymmetry with the right side smaller than the left. Dysmorphic features not shown in the photos include a small pigmented nevus on the right arm, capillary hemangiomata overlying the forehead and at the nape of the neck, and a straight spine with a sacral dimple on the left. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmga]

TABLE I. Literature Cases of SRS With ICR1 Hypomethylation Which Reported CHDs

References	Number of SRS/SRS-like patients with ICR1 hypomethylation	CHD
Bliek et al. [2006]	9	2 VSD, 1 ASD
Khalil et al. [2008]	1	1 perimembranous VSD
Bruce et al. [2009]	26	1 unspecified
Wakeling et al. [2010]	44	2 VSD, 1 ASD, 1 PDA
Turner et al. [2010]	23	1 VSD, 1 valve defect
5-year extension, still ongoing, of our previously published study of epigenotype-phenotype correlations in SRS [Netchine et al., 2007]	145[a]	1 VSD 2[b] TAPVR 1 TAPVR with ASD and interrupted aortic arch 1 muscular VSD 1 VSD and stenosis of the pulmonary artery 1 VSD 1 aortic stenosis with dysplastic valve

ASD, atrial septal defect; PDA, patent ductus arteriosus; VSD, ventricular septal defect; TAPVR, total anomalous pulmonary venous return.
[a]1 patient with dilatation of the aortic root, mitral valve prolapse.
[b]Patients 1 and 2 described in this article.

methylation-specific-multiplex-ligation-dependent probe amplification assay (MS-MLPA), as previously described [Wakeling et al., 2010]. The methylation status of other imprinted loci was not assessed. Growth hormone therapy was started at the age of 3 years with good response.

DISCUSSION

The prevalence of CHD at birth in the general population is approximately 1% [Van der Bom et al., 2011]. We report here on the first association between rare major CHDs (TAPVR and cor triatriatum) and SRS due to ICR1 hypomethylation. In our three patients, all established CHD risk factors were absent [Van der Bom et al., 2011]. Given the rarity of TAPVR (~1% of CHDs) and cor triatriatum (~0.1% of CHDs), the likelihood of a coincidental association with SRS is negligible.

Mild and severe forms of SRS, as opposed to typical forms, are under-diagnosed [Eggermann et al., 2009]. Notably, despite the lack of exclusion criteria for SRS, the presence of atypical findings such as major malformations could lead to diagnostic confusion [Donnai et al., 1989; Eggermann et al., 2009; Horike et al., 2009]. The association of CHD and SRS has rarely been reported. In the pre-epigenetic era, Cole and Levin [1973] first described a CHD (pulmonary valve stenosis) in SRS in 1973. In their 1977 review, Marks and Bergeson [1977] reported that 4.7% of SRS patients (7/148) had suspected CHD on physical examination. Furthermore, CHD was described in several isolated SRS patients but without genetic confirmation [e.g., Donnai et al., 1989]. A 1988 review considered the association of CHD with SRS to be coincidental [Patton, 1988]. However, this suggestion has been contradicted by at least two more recent studies in which CHDs were reported in 14% (9/65) and 12% (3/25) of SRS patients, respectively [Anderson et al., 2002; Abraham et al., 2004]. Nevertheless, no strict conclusion can be drawn, as most of these studies lack detailed clinical and genetic analyses.

In the post-epigenetic era, Wakeling et al. [2010] have reported CHDs in 9% (4/44) of SRS due to hypomethylation of the ICR1 while no CHD was found in 20 other patients with UPD(7)mat. Additionally, among subgroups with ICR1 hypomethylation in two other publications, CHDs were reported in 9% (2/23) [Turner et al., 2010)] and 33% (3/9) of patients [Bliek et al., 2006]. Bruce et al. [2009] discussed a correlation between CHD and ICR1 hypomethylation but did not describe the patient(s) in detail. Finally, CHD was described in an isolated SRS child with a ventricular septal defect [Khalil et al., 2008] (Table I). To our knowledge, no CHDs have been described in patients with UPD(7)mat [see for review, Eggermann et al., 2010; Kotzot, 2008; Wakeling et al., 2010]. Three CHD defects were reported in SRS patients with trisomy 7 mosaicism or with ring chromosome 7 [Miyoshi et al., 1999; Flori et al., 2005; Font-Montgomery et al., 2005].

Together, these data point to a possible correlation between ICR1 hypomethylation and CHD in SRS. Indeed, in the epigenotype-phenotype SRS Armand Trousseau children's hospital study group (n = 145 SRS) cited earlier, CHDs are present in 5.5% (8/145) of SRS patients, all with 11p15 ICR1 hypomethylation, while no CHD has been identified in UPD(7)mat patients (n = 17) (Netchine and the SRS Armand Trousseau children's hospital study group). Moreover, in the present report, we have ruled out the involvement of most other imprinted loci, especially those associated with human imprinting disorders.

Our review of the literature had several limitations, including the heterogeneous nature of the reports, the possible overlap between them, and insufficient clinical details about rare findings, which left us uncertain as to whether CHDs were absent or overlooked in certain SRS patients. Thus, no statistical tests were performed. Despite these limitations, the data suggest that the occurrence of CHD in SRS, though not very frequent, is not merely coincidental but linked to ICR1 hypomethylation. Structural CHDs are found in ~10% of patients with Beckwith–Wiedemann syndrome (BWS), an overgrowth disorder implicating an ICR1 gain-of-methylation in 5–10% of patients [Weksberg et al., 2010]. However, the (epi)genotype–phenotype correlations published so far are not sufficient to allow us to determine whether there is an association between the incidence of CHD and ICR1 methylation.

Apart from common forms of CHD found in SRS, such as ventricular septal defects, atrial septal defects, patent ductus arteriosus and valve defects, the presence of rare CHDs such as TAPVR in three patients (Patients 1 and 2 described in this article and another patient who was successfully treated; 3/145, 2%) and cor triatriatum in one patient (Table I) warrants further attention as to the possible role of ICR1 hypomethylation in pulmonary vein development. Indeed, TAPVR and cor triatriatum have a common embryological basis [Dillman et al., 2009]. TAPVR develops when the primordial pulmonary vein fails to unite with the plexus of veins surrounding the lung buds, while cor triatriatum occurs when pulmonary veins enter the proximal left atrial chamber but are separated from the distal left atrial chamber by a diaphragm. Although TAPVR is most often an isolated anomaly [Gathman and Nadas, 1970], it is sometimes seen in association with a variety of other anomalies, including partial trisomy or tetrasomy of 22q (cat-eye syndrome), Holt–Oram syndrome, asplenia syndrome [Correa-Villaseñor et al., 1991] and Smith–Lemli–Opitz syndrome [Singer et al., 1989].

In SRS, ICR1 hypomethylation leads to the downregulation of *IGF2* (insulin-like growth factor 2) and the biallelic expression of *H19* gene [Gicquel et al., 2005; Netchine et al., 2007]. *IGF2* and *H19* are both expressed and imprinted in the fetal mammalian heart [Lustig et al., 1994; Li et al., 2011]. IGF2 acts as a mitogenic factor that influences cardiomyocyte proliferation and ventricular compact-zone morphogenesis in the mouse [Li et al., 2011]. The non-coding H19 RNA plays a pivotal role in embryogenesis and fetal development, but whether it is involved in the formation of the fetal heart is currently unknown [Lustig et al., 1994]. In SRS with ICR1 hypomethylation, the severity of the SRS phenotype has been tentatively linked to the index of ICR1 hypomethylation [Bruce et al., 2009], variations in the level of hypomethylation among tissues, and a combination of defects in multiple imprinted loci [Wakeling et al., 2010]. The index of ICR1 hypomethylation in leukocytes was severe (5%) only in Patient 2. Since the 11p15 epimutation most probably occurs in a mosaic pattern after fertilization, ICR1 hypomethylation could have been selectively more severe in the cardiac tissue of the three patients described here.

The presence of severe CHD in patients with unexplained IUGR should not automatically result in their exclusion from epigenetic analysis. Moreover, we hope that this report will encourage clinicians to systematically consider a cardiac ultrasound scan when SRS is diagnosed, since CHDs could represent primary rather than coincidental findings in SRS due to ICR1 hypomethylation.

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