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SHORT REPORT

Molecular and clinical analyses of two patients with UPD(16)mat detected by screening 94 patients with Silver-Russell syndrome phenotype of unknown aetiology

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/jmedgenet-2018-105463>).

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Received 30 April 2018

Revised 23 August 2018

Accepted 24 August 2018

Published Online First 21

September 2018

ABSTRACT

Background Recently, a patient with maternal uniparental disomy of chromosome 16 (UPD(16)mat) presenting with Silver-Russell syndrome (SRS) phenotype was reported. SRS is characterised by growth failure and dysmorphic features.

Objective To clarify the prevalence of UPD(16)mat in aetiology-unknown patients with SRS phenotype and phenotypic differences between UPD(16)mat and SRS.

Methods We studied 94 patients with SRS phenotype of unknown aetiology. Sixty-three satisfied the Netchine-Harbison clinical scoring system (NH-CSS) criteria, and 25 out of 63 patients showed both protruding forehead and relative macrocephaly (clinical SRS). The remaining 31 patients met only three NH-CSS criteria, but were clinically suspected as having SRS. To detect UPD(16)mat, we performed methylation analysis for the *ZNF597*:TSS-differentially methylated region (DMR) on chromosome 16 and subsequently performed microsatellite, SNP array and exome analyses in the patients with hypomethylated *ZNF597*:TSS-DMR.

Results We identified two patients (2.1%) with a mixture of maternal isodisomy and heterodisomy of chromosome 16 in 94 aetiology-unknown patients with SRS phenotype. Both patients exhibited preterm birth and prenatal and postnatal growth failure. The male patient had ventricular septal defect and hypospadias. Whole-exome sequencing detected no gene mutations related to their phenotypes.

Conclusion We suggest considering genetic testing for UPD(16)mat in SRS phenotypic patients without known aetiology.

two identical chromosomes from only the mother.¹ Consistent with this, isodisomy can unmask autosomal recessive mutations.¹ In many UPD cases, a mixture of both heterodisomy and isodisomy exists.¹

Maternal UPD of chromosome 16 (UPD(16)mat) results in abnormal expression of the imprinted genes on chromosome 16. Seven (candidate) imprinted genes, *SOX8*, *ZNF597*, *NAA60*, *SALL1*, *C16orf57*, *ACD* and *FOXF1*, have been identified on chromosome 16,² but their functions remain to be clarified. To our knowledge, 49 live-born UPD(16)mat patients without chromosomal abnormalities other than those in chromosome 16 have been reported.^{3–5} UPD(16)mat can be caused by trisomy rescue for trisomy 16.¹ In 63.3% of 49 previously reported cases, UPD(16)mat was diagnosed following detection of trisomy 16 cells in prenatal diagnosis or placental examination. In 26.5% of them, UPD(16)mat was accidentally detected by genetic testing for autosomal recessive diseases.^{3–5} UPD(16)mat patients present with non-specific clinical features, including preterm birth, growth retardation, congenital heart diseases (CHDs), hypospadias and maternal hypertensive disorders of pregnancy.^{3–5} UPD(16)mat phenotype can be caused by abnormal expression of the imprinted genes on chromosome 16, unmasked autosomal recessive mutations due to isodisomy, placental insufficiency due to trisomy 16 cells and (hidden) mosaic trisomy 16⁶; however, these aetiologies have not been fully investigated.

Silver-Russell syndrome (SRS), characterised by prenatal and postnatal growth failure and dysmorphic features, is diagnosed based on a combination of clinical findings. Recently, an international consensus statement which summarised the recommendations for clinical and molecular diagnosis and management of SRS was published.⁷ This statement recommended adopting the Netchine-Harbison clinical scoring system (NH-CSS) for SRS. Six criteria are included in NH-CSS: (1) small for gestational age (SGA), (2) postnatal growth failure, (3) relative macrocephaly at birth, (4) protruding forehead, (5) body asymmetry and (6) feeding difficulties and/or low body mass index (BMI). Patients meeting four or more of these six criteria receive a diagnosis of SRS. This statement also recommended that patients

INTRODUCTION

Maternal uniparental disomy (UPD) is defined as the presence of two homologous chromosomes inherited from only the mother.¹ Because imprinted genes are expressed in a parental origin-specific manner, maternal UPD causes overexpression of maternally expressed genes and no expression of paternally expressed genes on an affected chromosome.¹ UPD includes uniparental heterodisomy and isodisomy. Patients with maternal heterodisomy inherit both maternal homologous chromosomes, whereas those with maternal isodisomy inherit



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To cite: Inoue T, Yagasaki H, Nishioka J, et al. *J Med Genet* 2019;**56**:413–418.

meeting NH-CSS criteria including both protruding forehead and relative macrocephaly, but normal in all molecular testing, should receive a diagnosis of clinical SRS. Furthermore, this statement suggested that patients with four or more NH-CSS criteria and patients meeting three NH-CSS criteria, but with continued clinical suspicion of SRS, should be eligible for molecular testing.⁷ Loss of methylation on chromosome 11p15 (11p15 LOM) and maternal UPD of chromosome 7 (UPD(7)mat) are major genetic causes of SRS. In some of the remaining patients, other imprinting disorders (Temple syndrome and maternal UPD of chromosome 20) and pathogenic CNVs (PCNVs) were identified.⁷ Recently, three small screening studies of UPD(16)mat in patients with SRS phenotype were reported, and one UPD(16)mat patient satisfying NH-CSS was detected.^{3 8 9} However, the prevalence of UPD(16)mat in aetiology-unknown patients with SRS and phenotypic differences between UPD(16)mat and SRS have been insufficiently documented.

Here, we report the results of comprehensive molecular analyses and the detailed clinical features in two patients with UPD(16)mat detected by screening 94 patients with SRS phenotype of unknown aetiology. Our study provides pivotal information about the frequency of UPD(16)mat among aetiology-unknown patients with SRS phenotype, clinical features of UPD(16)mat and developmental pathogenesis of the UPD(16)mat phenotype.

METHODS

Ethical approval

This study was approved by the Institutional Review Board Committee at the National Center for Child Health and Development and performed after obtaining written informed consent from all individuals.

Patients

We describe the inclusion criteria in online supplementary figure 1 and supplementary methods. Ninety-four aetiology-unknown patients with SRS phenotype were included in our study. These patients had no PCNVs and normal methylation levels for nine differentially methylated regions (DMRs) related to known imprinting disorders, namely, the *H19/IGF2:IG-DMR*, *PEG10:TSS-DMR*, *MEST:alt-TSS-DMR*, *PLAGL1:alt-TSS-DMR*, *KCNQ1OT1:TSS-DMR*, *MEG3/DLK1:IG-DMR*, *MEG3:TSS-DMR*, *SNURF:TSS-DMR* and *GNAS A/B:TSS-DMR*.

We collected clinical information from attending physicians by questionnaires. Attending physicians were mainly general paediatricians unfamiliar with SRS and some paediatric endocrinologists and paediatric geneticists who were more familiar with SRS. Of the 94 patients, 63 patients satisfied NH-CSS, and 25 out of 63 patients showed both protruding forehead and relative macrocephaly, which corresponded to clinical SRS.⁷ The remaining 31 patients met only three NH-CSS criteria, but were clinically suspected as having SRS.

Molecular analysis

We describe the detailed methods for molecular studies in online supplementary methods. In brief, to detect UPD(16)mat, we first performed methylation analysis with pyrosequencing for the paternally methylated *ZNF597:TSS-DMR* using bisulfite-treated genomic DNA (gDNA) from the leucocytes, as previously reported.^{10 11} We examined the methylation levels of the maternally methylated *ZNF597:3'* DMR in the patients with low methylation levels of the *ZNF597:TSS-DMR*. We performed microsatellite analysis for chromosome 16 in patients

with abnormal methylation levels of these DMRs using gDNA from the leucocytes of these patients and their parents. To detect hidden mosaic trisomy 16, we examined patients' gDNA from buccal cells. Sequences of the primer sets are shown in online supplementary table 1. We carried out array comparative genomic hybridisation (aCGH) and SNP array analysis. Finally, we performed whole-exome sequencing of these patients and their parents to detect gene mutations associated with their phenotypes. We screened 356 genes related to growth failure,¹² 25 known causative/candidate/susceptible genes for non-syndromic hypospadias¹³ (online supplementary table 2) and the genes causing known genetic syndromes based on the Online Mendelian Inheritance in Man.¹⁴

Statistical analysis

The frequencies of clinical feature differences between patients with UPD(16)mat, 11p15 LOM and UPD(7)mat were analysed by Fisher's exact test using the R environment (<http://cran.r-project.org/bin/windows/base/old/2.15.1/>). A value of $p < 0.05$ was considered significant.

RESULTS

Molecular analysis

We identified two patients (2.1%) with low methylation levels of the *ZNF597:TSS-DMR* and high methylation levels of the *ZNF597:3'* DMR out of 94 aetiology-unknown patients with SRS phenotype (figure 1A). Microsatellite analysis with gDNA from leucocytes and buccal cells revealed a mixture of maternal isodisomy and heterodisomy of chromosome 16 and no paternally inherited peak (figure 1B). aCGH+SNP array analysis showed no PCNVs on chromosome 16 and loss of heterozygosity of the telomeric region of chromosome 16p in both patients (figure 1C). Although the result of microsatellite analysis in patient 2 was 'not informative' in all examined loci on chromosome 16q, SNP genotyping of patient 2 and her parents showed maternal uniparental heterodisomy in chromosome 16q (data not shown). Whole-exome sequencing of patients 1 and 2 and the mother of patient 1 did not detect gene mutations related to their phenotypes. The mother of patient 1 presented normal methylation levels in the nine DMRs and the *ZNF597:TSS-DMR* (data not shown).

Case reports

Clinical features of the two patients with UPD(16)mat are summarised in online supplementary table 3. Patient 1 was naturally conceived by healthy parents and born at 27 weeks of gestation by caesarean section due to fetal growth restriction. His mother did not show hypertensive disorders of pregnancy. She was 138.0 cm tall (−3.83 SD score (SDS)) and had no other dysmorphic features. At birth, his father and mother were 40 and 44 years of age, respectively. Macroscopic and microscopic placental examination only demonstrated mild chorioamnionitis. His karyotype was 46,XY. Birth length, birth weight and birth occipitofrontal circumference (OFC) were 31.0 cm (−1.96 SDS), 698 g (−2.38 SDS) and 23.0 cm (−1.02 SDS), respectively. He had ventricular septal defect, hypospadias and cryptorchidism. He required tube feeding due to poor body weight gain. Protruding forehead was detected at toddler age by his presenting physician. At 5 years of age, his height and weight were 89.9 cm (−4.24 SDS) and 11.0 kg (−5.03 SDS), respectively (figure 2A). He satisfied four NH-CSS criteria including SGA, postnatal growth failure, protruding forehead and feeding difficulties (figure 2B). The results of his biological and hormonal examinations were within normal range (data not shown). He started growth hormone (GH) treatment for SGA-short stature (SS) at

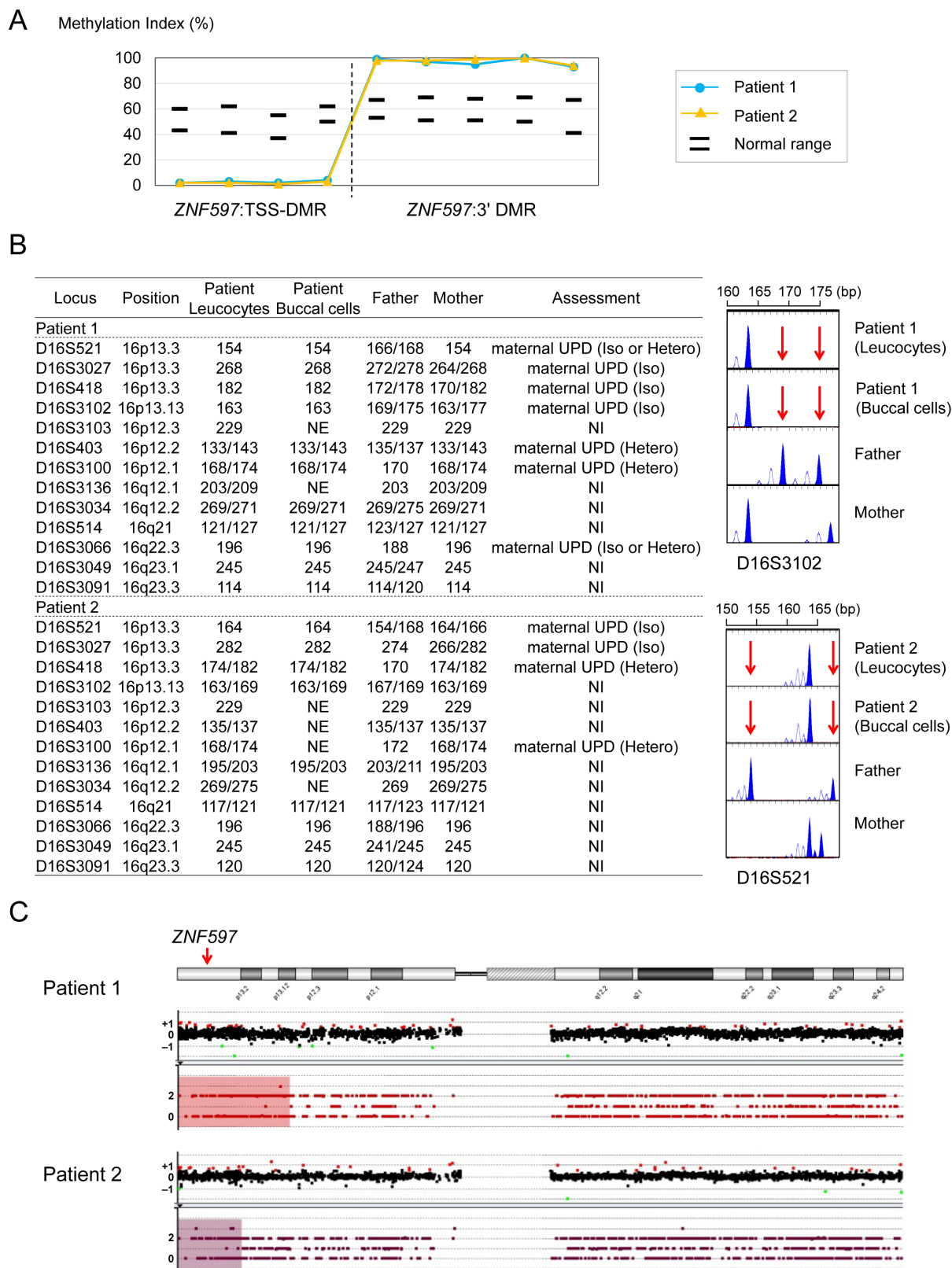


Figure 1 Results of molecular analysis. (A) Methylation analysis with pyrosequencing for the *ZNF597*:TSS-DMR and *ZNF597*:3' DMR using bisulfite-treated genomic DNA from the leucocytes. (B) Microsatellite analysis. UPD, uniparental disomy; Iso, isodisomy; Hetero, heterodisomy; NE, not examined; NI, not informative. The numbers indicate the PCR product sizes in bp. Red arrows indicate there was no peak of paternal origin in both patients 1 and 2. (C) aCGH+SNP array analysis for chromosome 16. The black, red and green dots denote signals indicative of the normal, increased ($>+0.5$) and decreased (<-1.0) copy numbers, respectively. Coloured rectangles show loss of heterozygosity regions. aCGH, array comparative genomic hybridisation.

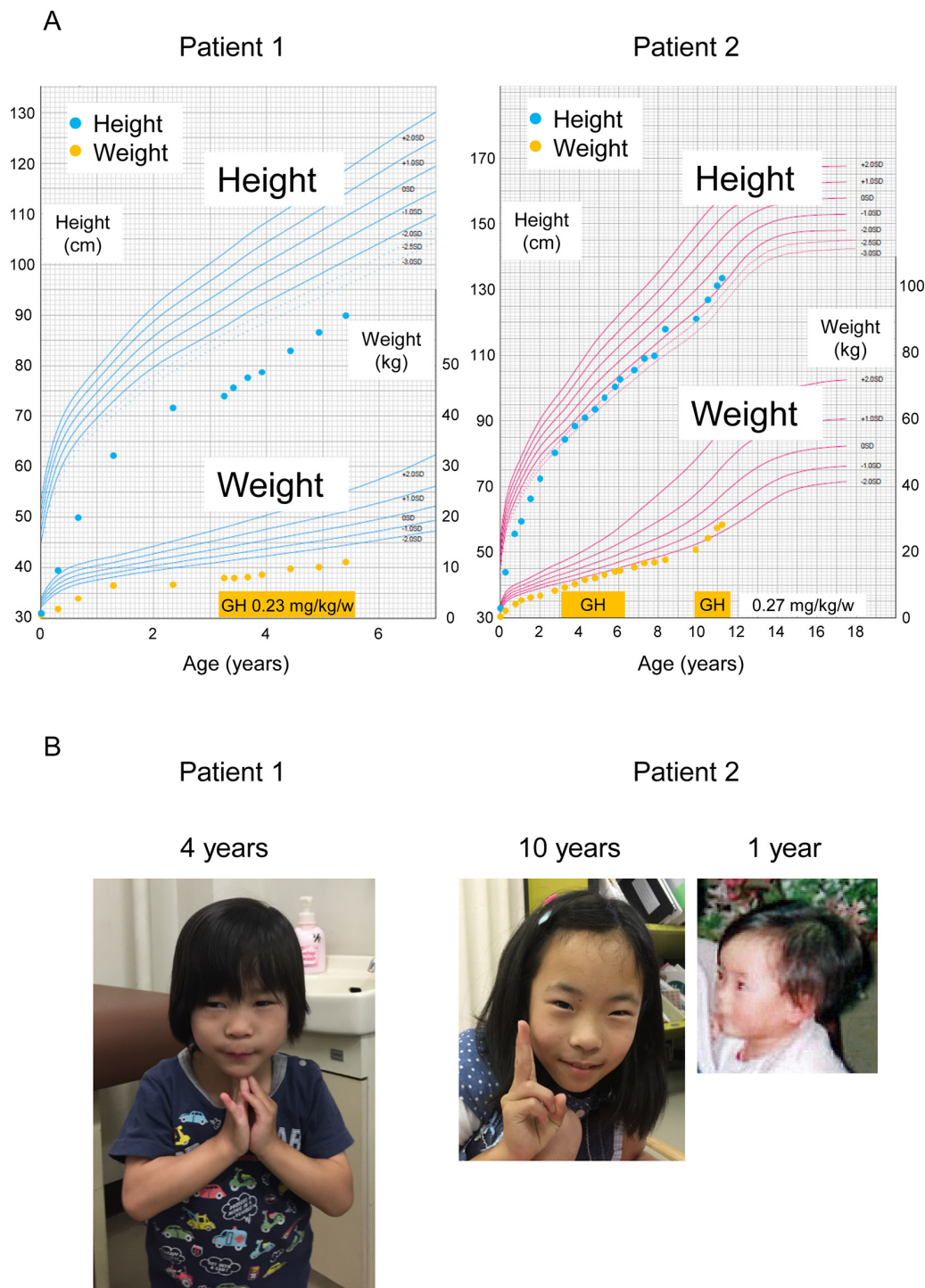


Figure 2 Clinical findings of the patients with UPD(16)mat. (A) Growth charts. Growth hormone (GH) treatment for small for gestational age-short stature without GH deficiency is covered by national health insurance and local governmental public assistance in Japan. GH treatment of patient 2 was discontinued at 6 years of age based on the local governmental policy. After change of the local governmental policy, she restarted GH treatment at 9 years of age. (B) Photographs of the patients. Unfortunately, patient 1 did not have a photograph taken from the side at toddler age.

3 years of age. His motor development was mildly delayed, and developmental quotient at 3 years of age was 51.

Patient 2 was born at 29 weeks of gestation by caesarean section due to threatened premature labour to healthy parents. Her mother did not show hypertensive disorders of pregnancy. At birth, her father and mother were 30 and 36 years of age, respectively. Placental findings were apparently normal and the weight was 295 g (-0.25 SDS).¹⁵ Her karyotype was 46,XX. Birth length, birth weight

and birth OFC were 33.0 cm (-2.38 SDS), 806 g (-2.60 SDS) and 25.2 cm (-0.84 SDS), respectively. At 11 years of age, her height and weight were 133.3 cm (-1.72 SDS) and 28.4 kg (-1.48 SDS) (figure 2A). She satisfied five NH-CSS criteria including protruding forehead and relative macrocephaly (figure 2B) and received a diagnosis of clinical SRS. The results of her biological and hormonal examinations were within normal range (data not shown). She started GH treatment for SGA-SS at 3 years of age. She had normal

motor development. Her IQ at 6 years of age was 67, and she was in a regular class at school and doing well at 11 years of age.

DISCUSSION

Our study of UPD(16)mat revealed two patients (2.1%) with a mixture of maternal isodisomy and heterodisomy of chromosome 16 in 94 aetiology-unknown patients with SRS phenotype. Of 25 patients with clinical SRS, UPD(16)mat was detected in one patient (4.0%). Azzi *et al* reported one patient (9.1%) with UPD(16)mat in 11 patients satisfying NH-CSS criteria including SGA, postnatal growth failure, protruding forehead and feeding difficulties without 11p15 LOM, UPD(7)mat, PCNVs, *CDKN1C* mutation and abnormal methylation levels of some DMRs related to imprinting disorders, although their screening with SNP array for UPD(16)mat was unable to detect full uniparental heterodisomy.⁸ Two other screening studies of patients with SRS phenotype failed to detect UPD(16)mat.^{3,9} The frequency of patients with SRS phenotype among UPD(16)mat patients has not been reported. Although clinical features related to NH-CSS criteria in previously reported 49 live-born UPD(16)mat patients were insufficiently documented,^{3–5} three patients (5.9%) out of 51 UPD(16)mat patients, including our cases, met NH-CSS. Out of the three patients, only patient 2 in our study received a diagnosis of clinical SRS. Further accumulation of clinical data of UPD(16)mat patients could clarify the frequency of patients with SRS phenotype among UPD(16)mat patients.

UPD(16)mat patients, including our two patients, exhibited non-specific clinical features such as preterm birth, prenatal and postnatal growth failure, CHDs, hypospadias and low BMI (online supplementary table 3). Prenatal and postnatal growth failure and low BMI are included in NH-CSS criteria.⁷ We compared the median values and frequencies of the clinical findings between patients with UPD(16)mat in the literature and in this report and previously reported patients with 11p15 LOM or UPD(7)mat (online supplementary table 3).^{8,16,17} Although statistical analysis was impossible due to lack of individual data in the previous reports, the median of gestational ages in UPD(16)mat was earlier than in 11p15 LOM and UPD(7)mat. Our statistical analysis demonstrated that the frequency of SGA was significantly lower in UPD(16)mat than in both 11p15 LOM and UPD(7)mat, and that frequency of CHDs was significantly higher in UPD(16)mat than in both 11p15 LOM and UPD(7)mat. Genetic testing for UPD(16)mat should be considered for aetiology-unknown patients with SRS phenotype together with preterm birth and CHDs, even if they are not born SGA. In addition, patient 1 had mild intellectual disability, although the association between UPD(16)mat and intellectual disability has not been clarified. Further studies of UPD(16)mat should elucidate the relationship.

The developmental pathogenesis of UPD(16)mat phenotype has been insufficiently investigated in previously reported patients. Whole-exome sequencing showed that neither of our patients had gene mutations related to their phenotypes. The mother of patient 1 with severe SS also did not have mutations in the genes associated with growth failure. These results showed that gene mutations did not lead to their phenotypes. Moreover, microsatellite analysis showed that neither the leucocytes nor the buccal cells of our patients contained trisomy 16 cells. We could not examine other tissues, including the placenta, for trisomy 16 mosaicism. However, our results suggest that abnormal expression of the imprinted genes on chromosome 16 can lead to development of the phenotype detected in our patients. Of the imprinted genes on chromosome 16, the maternally expressed *ZNF597* gene is expressed in brain, leucocytes and placenta.¹⁸ Excessive expression

of *ZNF597* in UPD(16)mat patients may cause growth failure, intellectual disability and other SRS symptoms.

Advanced maternal age carries a high risk for maternal heterodisomy caused by trisomy rescue following fertilisation between normal sperm and disomic oocyte.¹⁹ Maternal heterodisomy in our patients may be associated with the advanced ages of their mothers.

It should be pointed out that our study has the possibility of leading to underdiagnosis or overdiagnosis of SRS for patients, as many general paediatricians unfamiliar with SRS evaluated the clinical features of their patients. Furthermore, we did not have enough clinical information for scoring NH-CSS in cases with 11p15 LOM and UPD(7)mat. Thus, we could not determine the frequency of UPD(16)mat in all patients with SRS phenotype.

In summary, two patients (2.1%) of 94 aetiology-unknown patients with SRS phenotype had UPD(16)mat. We suggest considering genetic testing for UPD(16)mat in SRS phenotypic patients without 11p15 LOM, UPD(7)mat and PCNVs.

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Correction notice This article has been corrected since it was published Online First. The following supplementary files have been updated: supplementary figure 1, supplementary tables 2 and 3, and supplementary methods.

Acknowledgements We are grateful to all patients and their parents for their cooperation. We thank the physicians for providing us with detailed clinical data and materials for molecular studies.

Contributors Molecular analysis was performed by TI, AN, KM, SN and KN. Detailed clinical data and materials for molecular studies were provided by HY, JN, KY, TF and TO. The study was designed and coordinated by MK. The paper was written by TI and MK and reviewed and edited by AO and MF.

Funding This work was supported by Grants from the Japan Society for the Promotion of Science (JSPS) (15K15096), the National Center for Child Health and Development (28-6), the Japan Agency for Medical Research and Development (AMED) (16ek0109030h0003, 17ek0109141h0003, 17ek0109278h0001), Takeda Science Foundation and The Japanese Society for Pediatric Endocrinology Future Development Grant.

Competing interests None declared.

Patient consent Parental/guardian consent obtained.

Ethics approval This study was approved by the Institutional Review Board Committee at the National Center for Child Health and Development (committee's reference number: 518).

Provenance and peer review Not commissioned; externally peer reviewed.

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