RESEARCH LETTER

AMERICAN JOURNAL OF medical genetics PART A

A Patient with Temple Syndrome Satisfying the Clinical Diagnostic Criteria of Silver–Russell Syndrome

Masahide Goto,[1,2] Masayo Kagami,[3]* Gen Nishimura,[4] and Takanori Yamagata[2]

[1]Department of Pediatrics, Kitaibaraki Municipal General Hospital, Kitaibaraki, Japan

[2]Department of Pediatrics, Jichi Medical University, Shimotsuke, Japan

[3]Department of Molecular Endocrinology, National Research Institute for Child Health and Development, Tokyo, Japan

[4]Department of Pediatric Imaging, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan

Manuscript Received: 21 February 2016; Manuscript Accepted: 16 June 2016

TO THE EDITOR:

Parental-origin-specific monoallelic expression of imprinted genes is regulated by CpG methylation in differentially methylated regions (DMRs) [Azzi et al., 2014]. The human chromosome 14q32.2 imprinted region harbors a cluster of imprinted genes, including paternally expressed genes (*DLK1* and *RTL1*) and maternally expressed genes (*MEG3*, *RTL1as*, *MEG8*, *snoRNA*, and *microRNAs)*. The region includes two DMRs, the germ-line derived primary *DLK1-MEG3* intergenic-DMR (IG-DMR) and the post fertilization-derived secondary *MEG3*-DMR, which are methylated after paternal transmission and unmethylated after maternal transmission [Kagami et al., 2008]. Maternal uniparental disomy of chromosome 14, paternal deletions affecting the 14q32.2 imprinted region, and hypomethylation of the IG-DMR and/or *MEG3*-DMR are responsible for a disease entity termed Temple syndrome (TS14) (OMIM #616222) [Ioannides et al., 2014].

The clinical constellation of TS14 comprise pre- and post-natal growth failure, small hands and feet, muscular hypotonia, motor delay, feeding difficulties, central obesity, premature puberty, and abnormal facial features, including a broad forehead and short nose with a wide nasal tip [Ioannides et al., 2014]. Because clinical signs of TS14 are not so discriminative, particularly in infancy, the affected individuals may be clinically diagnosed with other malformation syndromes, such as Silver–Russell syndrome (SRS) and Prader–Willi syndrome [Berends et al., 1999; Poole et al., 2013; Ioannides et al., 2014; Azzi et al., 2015; Kagami et al., 2015]. In fact, one of the authors (MK) previously reported two TS14 patients with SRS-compatible phenotype [Kagami et al., 2015]. Here, we report another example of a Japanese patient with TS14 with SRS-like manifestation.

This patient was born to healthy parents. His two older sisters were healthy. The mother noticed decreased fetal movement during pregnancy. He was normally delivered at 39 weeks of gestation. Birth length was 44.9 cm (−2.3 SD), weight was 2150 g (−3.2 SD), occipitofrontal circumference (OFC) was 30.5 cm (−2.1 SD), and chest circumference was 28 cm (−2.9 SD). He presented with lethargy and weak cry as a neonate.

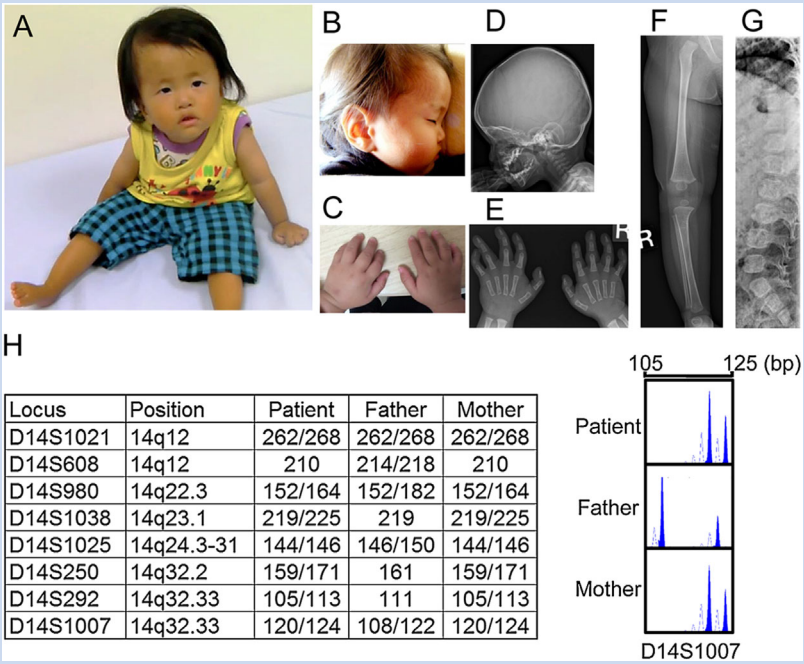
How to Cite this Article:
Goto M, Kagami M, Nishimura G, Yamagata T. 2016. A patient with temple syndrome satisfying the clinical diagnostic criteria of Silver–Russell syndrome.
Am J Med Genet Part A 170A:2483–2485.

Because of feeding difficulty and poor weight gain, he was tube-fed during infancy. Developmental milestones were mildly delayed: head control at 8 months, rolling over at 11 months, sitting without support at 13 months, and jargon at 15 months. At 19 months of age, height was 71.0 cm (−3.7 SD), weight was 6.1 kg (−4.1 SD), OFC was 44.5 cm (−2.1 SD), and arm span was 66 cm. He was remarkably hypotonic. At 23 months of age, catch-up growth was not observed, and he was not able to stand without support. The

Conflict of interest: The authors declare no conflicts of interest.
Grant sponsor: Japan Society for the Promotion of Science; Grant number: 15K15096; Grant sponsor: National Center for Child Health and Development; Grant number: 25-10; Grant sponsor: Takeda Science Foundation; Grant sponsor: Daiichi Sankyo Foundation; Grant sponsor: Japan Agency for Medical Research and Development; Grant numbers: 16ek0109030h0003, 16ek0109141h0002.

*Correspondence to:
Masayo Kagami, Department of Molecular Endocrinology, National Research Institute for Child Health and Development, Tokyo 157-8535, Japan.
E-mail: kagami-ms@ncchd.go.jp

Article first published online in Wiley Online Library (wileyonlinelibrary.com): 30 June 2016
DOI 10.1002/ajmg.a.37827



Locus	Position	Patient	Father	Mother
D14S1021	14q12	262/268	262/268	262/268
D14S608	14q12	210	214/218	210
D14S980	14q22.3	152/164	152/182	152/164
D14S1038	14q23.1	219/225	219	219/225
D14S1025	14q24.3-31	144/146	146/150	144/146
D14S250	14q32.2	159/171	161	159/171
D14S292	14q32.33	105/113	111	105/113
D14S1007	14q32.33	120/124	108/122	120/124

FIG. 1. Physical features at the age of 18 months. (A) Physical features comprised a facial appearance with a broad prominent forehead, flat nose root, downturn of the corners of the mouth, micrognathia, high-arched palate, and low posterior hairline. There were no abnormalities of the eyes or ears. Asymmetrical body parts were absent. (B) A mildly prominent forehead was exhibited, as mentioned by Azzi et al. [2015]. (C) Clinodactyly of the fifth fingers and mild micromelia were present. (D) Craniofacial disproportion. (E) Clinodactyly of the fifth fingers. (F) Slender long bones of the right arm. (G) Tall vertebral bodies. (H) Microsatellite analysis. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmga].

developmental quotient was 73 (Kinder Infant Development Scale, issued by the Center of Developmental Education and Research, Tokyo, Japan, 1989). Facial and body features of the patient are shown in Figure 1A–C and Table S1. Radiological examination demonstrated craniofacial disproportion, slender bones, and dolichospondyly (tall vertebral bodies) (Fig. 1D–G). The clinical features satisfied four of six Netchine–Harbison (N–H) SRS clinical scoring system features; (i) prenatal growth retardation; (ii) postnatal growth retardation; (iii) relative macrocephaly at birth; (iv) protruding forehead; (v) body asymmetry; (vi) feeding difficulties and/or low body mass index (BMI) [Azzi et al., 2015].

With written informed consent from the parents and under approval by an ethical committee (Institutional Review Board Committees of National Center for Child Health and Development), we performed methylation analyses for two DMRs responsible for SRS (the *H19*-DMR at the 11p15 imprinted region and *PEG1*-DMR on chromosome 7), as previously reported [Kagami et al., 2015]. The methylation levels of these DMRs were normal (Table S2). Further, because previous reports and our experiences of phenotypic overlap between SRS and TS14, we performed methylation analyses for the IG-DMR and *MEG3*-DMR at the 14q32.2 imprinted region [Kagami et al., 2015], which revealed hypomethylation of these DMRs (Table S2). Microsatellite analysis for chromosome 14 identified maternal uniparental heterodisomy of chromosome 14 (Fig. 1H). Array comparative genomic hybridization did not reveal any obvious copy number change.

The clinical manifestations in a small subset of TS14 apparently overlap with those of SRS. We summarized the clinical manifestations of TS14 patients with SRS-like phenotype, including the present patient [Poole et al., 2013; Azzi et al., 2015; Kagami et al., 2015], those in a large cohort of TS14 [Ioannides et al., 2014], and those in a large cohort of SRS [Fuke et al., 2013] (Table S1). No patient with the phenotype satisfied all of the six key findings in the N–H SRS clinical scoring system. The manifestations of body asymmetry and feeding difficulty in the six key findings are lower in patients with TS14 having the SRS phenotype than in patients with SRS and higher in patients with TS14. Obesity was not a feature in patients with SRS-like TS14, similar to that in SRS [Sienko et al., 2014]. Because it was reported that increased BMI in TS14 tends to be apparent after 7 years of age [Ioannides et al., 2014], differences of weight gain rate between TS14 and SRS after later childhood may enable an easier clinical diagnosis of TS14. Muscular hypotonia is observed more in TS14 than in SRS (Table S1). In fact, our patient was not able to stand without support because of his hypotonia at 23 months of age. For children with SRS phenotype together with moderate to severe muscular hypotonia, genetic testing of TS14 should be considered. Radiological examination may be beneficial for the diagnosis of SRS-like TS14. Slender bones and dolichospondyly in the present patient were distinctive. Currently, however, very little is known about the skeletal changes in TS14. In literature search, we found only one case report on a

TS14 patient with shortened long bones [Eggermann et al., 2001]. Further case accumulation of skeletal changes in TS14 and SRS-like TS14 is required to elucidate this issue.

In conclusion, a small subset of children with TS14 clinically resembles SRS. Methylation analyses for the IG-DMR and *MEG3*-DMR at the 14q32.2 imprinted region should be considered in children who have SRS-compatible phenotype, but not hypomethylation of the *H19*-DMR at the 11p15 imprinted region or hypermethylation of the *PEG1*-DMR on chromosome 7.

ACKNOWLEDGMENTS

This work was supported by Grants-in-Aid for Challenging Exploratory Research (15K15096) from the Japan Society for the Promotion of Science, grants from the National Center for Child Health and Development (25–10), grant from Takeda Science Foundation, grant from Daiichi Sankyo Foundation, and grant from the Japan Agency for Medical Research and Development (H26-038, H27-141).

REFERENCES

Azzi S, Brioude F, Le Bouc Y, Netchine I. 2014. Human imprinting anomalies in fetal and childhood growth disorders: Clinical implications and molecular mechanisms. Curr Pharm Des 20:1751–1763.

Azzi S, Salem J, Thibaud N, Chantot-Bastaraud S, Lieber E, Netchine I, Harbison MD. 2015. A prospective study validating a clinical scoring system and demonstrating phenotypical-genotypical correlations in Silver–Russell syndrome. J Med Genet 52:446–453.

Berends MJ, Hordijk R, Scheffer H, Oosterwijk JC, Halley DJ, Sorgedrager N. 1999. Two cases of maternal uniparental disomy 14 with a phenotype overlapping with the Prader–Willi phenotype. Am J Med Genet 84:76–79.

Eggermann T, Mergenthaler S, Eggermann K, Albers A, Linnemann K, Fusch C, Ranke MB, Wollmann HA. 2001. Identification of interstitial maternal uniparental disomy (UPD) (14) and complete maternal UPD(20) in a cohort of growth retarded patients. J Med Genet 38:86–89.

Fuke T, Mizuno S, Nagai T, Hasegawa T, Horikawa R, Miyoshi Y, Muroya K, Kondoh T, Numakura C, Sato S, Nakabayashi K, Tayama C, Hata K, Sano S, Matsubara K, Kagami M, Yamazawa K, Ogata T. 2013. Molecular and clinical studies in 138 Japanese patients with Silver–Russell syndrome. PLoS ONE 8:e60105.

Ioannides Y, Lokulo-Sodipe K, Mackay DJ, Davies JH, Temple IK. 2014. Temple syndrome: Improving the recognition of an underdiagnosed chromosome 14 imprinting disorder: An analysis of 51 published cases. J Med Genet 51:495–501.

Kagami M, Sekita Y, Nishimura G, Irie M, Kato F, Okada M, Yamamori S, Kishimoto H, Nakayama M, Tanaka Y, Matsuoka K, Takahashi T, Noguchi M, Tanaka Y, Masumoto K, Utsunomiya T, Kouzan H, Komatsu Y, Ohashi H, Kurosawa K, Kosaki K, Ferguson-Smith AC, Ogata T. 2008. Deletions and epimutations affecting the human 14q32.2 imprinted region in individuals with paternal and maternal upd(14)-like phenotypes. Nat Genet 40:237–242.

Kagami M, Mizuno S, Matsubara K, Nakabayashi K, Sano S, Fuke T, Fukami M, Ogata T. 2015. Epimutations of the IG-DMR and the MEG3-DMR at the 14q32.2 imprinted region in two patients with Silver–Russell Syndrome-compatible phenotype. Eur J Hum Genet 23:1062–1067.

Poole RL, Docherty LE, Al Sayegh A, Caliebe A, Turner C, Baple E, Wakeling E, Harrison L, Lehmann A, Temple IK, Mackay D.; International Clinical Imprinting Consortium 2013. Targeted methylation testing of a patient cohort broadens the epigenetic and clinical description of imprinting disorders. Am J Med Genet Part A 161: 2174–2182.

Sienko M, Petriczko E, Zajaczek S, Zygmunt-Gorska A, Starzyk J, Korpysz A, Petriczko J, Walczak A, Walczak M. 2014. A ten-year observation of somatic development of a first group of Polish children with Silver–Russell syndrome. Neuro Endocrinol Lett 35:306–313.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.