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BRIEF COMMUNICATION

A severely short-statured girl with 47,XX, + 14/46,XX,upd(14)mat, mosaicism

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Abstract

The predominant symptoms of trisomy 14 mosaicism are prenatal and postnatal growth failure, ear abnormalities, congenital heart disease, developmental delay, and genitourinary abnormalities. Maternal uniparental disomy of chromosome 14 (upd(14)mat) presents discernible clinical features such as prenatal and postnatal growth failure, hypotonia, precocious puberty, and obesity. Given the small number of previously reported patients with a combination of trisomy 14 mosaicism and upd(14)mat, the detailed clinical features of these patients remain to be elucidated. Here we report a severely short-statured girl with feeding difficulties and failure to thrive, ear abnormalities, deafness, small hands, and developmental delay. Karyotyping, FISH analysis, methylation analysis, and microsatellite marker analysis using her leukocytes and buccal cells showed that she had a combination of trisomy 14 mosaicism and upd(14)mat. Furthermore, a comparison of the clinical features of this patient with those of previously reported patients with genetic anomalies including the combination of trisomy 14 mosaicism and upd(14)mat or upd(14)mat suggested that the severe short stature observed in patients with a combination of trisomy 14 mosaicism and upd(14)mat stemmed from the synergic effect of these two events. In severely short-statured patients with trisomy 14 mosaicism, we should be aware of the possible coexistence of upd(14)mat.

Human chromosome 14q32.2 has a cluster of imprinted genes including paternally expressed genes such as *DLK1* and *RTL1* and maternally expressed genes such as *MEG3*, *RTL1* antisense and *MEG8* [1]. The expression of these genes is controlled by the *DLK1-MEG3* intergenic differentially methylated region (IG-DMR) and *MEG3*-DMR [2]. The IG-DMR and *MEG3*-DMR are methylated after paternal transmission and unmethylated after maternal transmission [3].

Trisomy 14 mosaicism has been reported in approximately 30 patients (Additional file 1). The predominant symptoms of trisomy 14 mosaicism are prenatal and postnatal growth failure, ear abnormalities, congenital heart disease, developmental delay, and genitourinary abnormalities [4–6]. Maternal uniparental disomy of chromosome 14 (upd(14)mat) is a condition in which two copies of chromosome 14 are inherited from the mother [7, 8]. Upd(14)mat is one of the genetic causes of Temple syndrome (OMIM 616222) and presents discernible clinical features such as pre- and postnatal growth failure, hypotonia, feeding difficulties, precocious puberty, and obesity [9]. Concomitant trisomy 14 mosaicism and upd(14)mat has been reported in only four patients [10–13], and its detailed clinical features remain unclear. Here, we report a severely short-statured 3-year-old girl with a concomitant trisomy 14 mosaicism and upd(14)mat.

A 3-year-old Japanese girl was referred to Kurume University hospital due to severe growth failure, failure to thrive, hypotonia, and developmental delay. She was born at 37 weeks of gestation to healthy parents without a family history of genetic diseases. Her birth weight was 2162 g (–1.5SD) and her birth length was 42.7 cm (–2.0SD). She had been admitted to the neonatal intensive care unit for 44 days because of feeding difficulties and failure to thrive. She presented with mild deafness, coloboma, and a small ventricular septal defect but no genitourinary abnormalities. At 3 years of age, her height was 78.8 cm (–5.1SD) and her weight was 8.8 kg (–3.3SD). She showed a hypotonic face,

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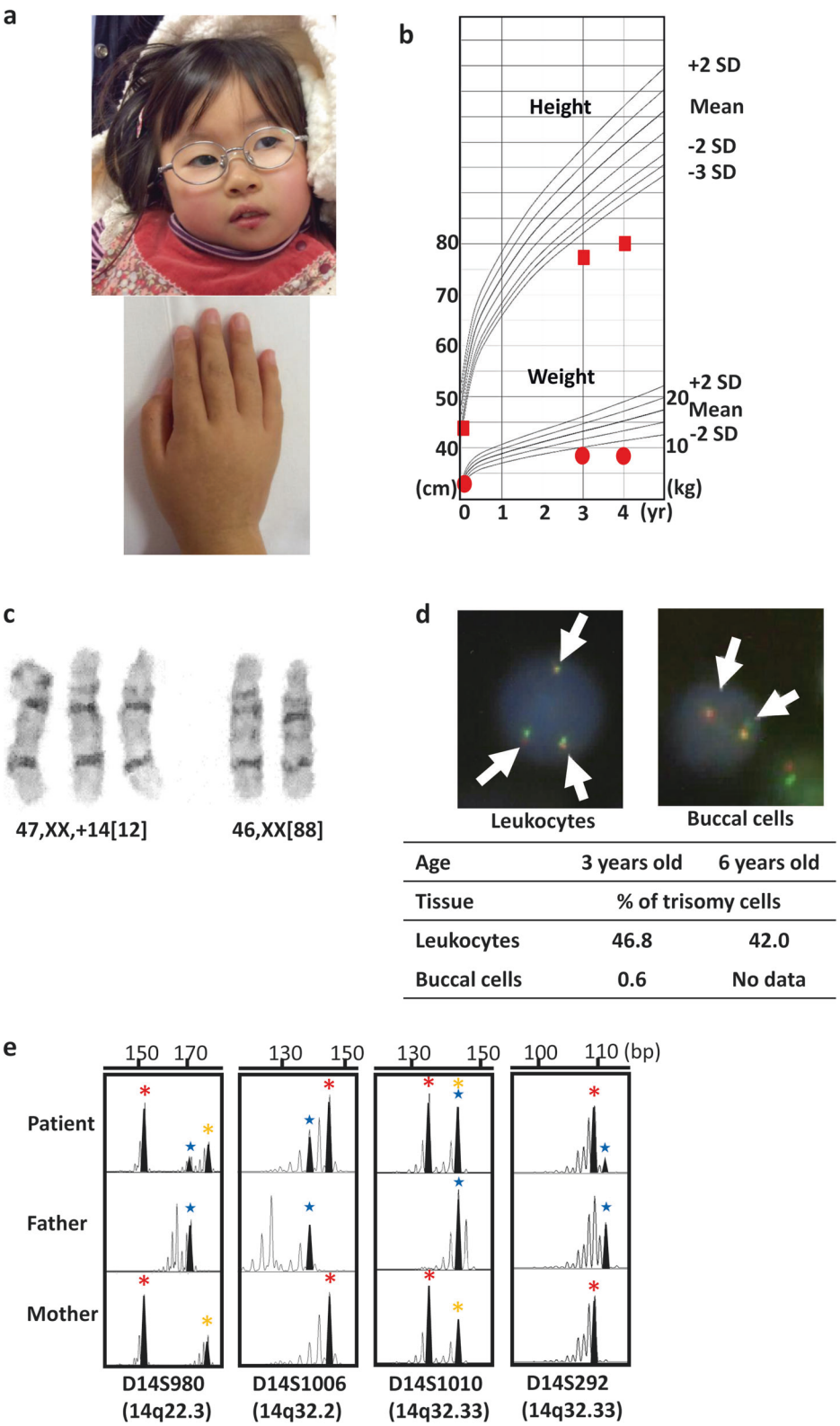

Age	3 years old	6 years old
Tissue	% of trisomy cells	
Leukocytes	46.8	42.0
Buccal cells	0.6	No data

Fig. 1 Clinical, cytogenetic, and molecular findings of our patient. **a** Photographs. Mild dysmorphic features with hypotonic face and small hands at 3 years of age. **b** Growth charts. **c** G-banding karyotype of the patient's leukocytes showing trisomy 14 mosaic. **d** The results of FISH analysis in patient's leukocytes and buccal cells. IgH probes for 14q32 indicated by arrows showing trisomy 14 in leukocytes. **e** Microsatellite analysis. Maternally and paternally-derived peaks are denoted by red and yellow asterisks and blue stars, respectively

ear abnormalities, deafness, small hands, and closed ventricular septal defect (Fig. 1a, b, Table 1). She was nonverbal and unable to walk at the time. Her plasma hormone levels including thyroid hormone, lutenizing hormone, Follicle-stimulating hormone, and E_2 were within the normal range and the GH responses to a provocation test were normal. Her brain magnetic resonance imaging scans showed no abnormalities. To detect the genetic cause of the

Table 1 Clinical features of the current and previously reported patients with a combination of trisomy 14 mosaicism and upd(14)mat or upd(14)mat

Feature	Our case	Trisomy 14 mosaicism + upd(14)mat[a] (Group 1)	Upd(14)mat[a] (Group 2)	*p*-value[b] G1 vs. G2
Craniofacial appearance				
Microcephaly	−	0/5	NA	−
Macrocephaly	−	0/5	4/9	0.22
Prominent forehead	−	0/5	13/22	$\mathbf{4.07 \times 10^{-2}}$
Hypertelorism	−	1/5	NA	−
Coloboma	+	1/5	NA	−
Short neck	−	1/5	NA	−
Ear anomalies	+	1/5	3/20	1.00
Broad nose	−	2/5	NA	−
High arched palate	−	2/5	12/20	0.62
Micrognathia	−	0/5	NA	−
Cleft palate or lip	−	0/5	NA	−
Irregular teeth	−	1/5	6/17	1.00
Growth and maturation				
Pre-natal growth failure	+	5/5	21/23	1.00
Post-natal growth failure	+	5/5	21/23	1.00
Present height cm [SDS]	−5.1	−5.1 [−6.0 ~ −4.7]	−2.3 [−3.5 ~ −1.6]	$\mathbf{3.29 \times 10^{-2}}$
Present weight kg [SDS]	−3.3	−1.5 [−2.1 ~ 0.0]	−1.5 [−2.6~ + 4.3]	0.67
Present OFC cm [SDS]	NA	NA	−2.2 [−4.9 ~ −0.7]	−
Central obesity	−	4/5	1/10	$\mathbf{1.70 \times 10^{-2}}$
Body asymmetry	−	1/5	4/22	1.00
Precocious puberty	−	2/5	8/10	0.25
Developmental status				
Global developmental delay	+	5/5	5/17	$\mathbf{9.57 \times 10^{-3}}$
Other findings				
Maternal age at child birth [year]	40	NA	30 [28 ~ 36]	−
Small hands and/or feet	+	2/5	20/23	$\mathbf{5.04 \times 10^{-2}}$
Hypotonia (with poor suck)	+	4/5	16/23	1.00
Congenital heart anomaly	+	1/5	NA	−
Scoliosis	−	2/5	6/23	0.61
Feeding difficulties and/or low BMI	+	4/5	15/22	1.00
Genitourinary anomaly	−	1/5	NA	−
Abnormal pigmentation	−	2/5	NA	−
Diabetes mellitus	−	1/5	1/19	0.38
References[b]		10–13	16	

The denominators indicate the number of patients evaluated for the presence or absence of each feature, and the numerators represent the number of patients assessed to be positive for that feature

BMI body mass index, *NA* not available, *OFC* occipitofrontal circumference, *SDS* standard deviation score

[a]Previously reported patients with a combination of trisomy 14 mosaicism and upd(14)mat and patients with upd(14)mat underwent molecular analysis to confirm parental origin. Only one patient with upd(14)mat showed mosaicism for 46,XX/46,XX,upd(14)mat

[b]The statistical significance of the differences between two groups was analyzed using the Fisher's exact test for categorical variables, and the Mann–Whitney U test for continuous variables. A-two tailed *p*-value with an alpha level for significance was determined as ≤ 0.05. All statistical analyses were performed using the EZR system (version 1.32, http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedOSX.html), a graphical user interface for R. Significant *p*-value (≤ 0.05) are boldfaced

clinical findings, we first performed karyotyping and detected mosaic 47,XX, + 14[12]/46,XX[88] (Fig. 1c). Subsequently, we performed fluorescence in situ hybridization (FISH) analysis of the leukocytes and the buccal cells using probes for 14q32 at 3 years of age. Trisomy cells were identified in 46.8% of the leukocytes but not in the buccal cells (Fig. 1d). To detect the parental origin of the extra copy of trisomy 14, we performed methylation analysis for the IG-DMR and *MEG3*-DMR using pyrosequencing as previously reported [14], and identified the mild hypomethylation of these DMRs (Supplementary Table S1). These results indicated that the extra copy of chromosome 14 was inherited from the mother. Next, we performed microsatellite analysis for chromosome 14 using leukocyte DNA samples from the patient and her parents (Supplementary Table S2) and compared the peak area under the curve (AUC) of the maternally-inherited allele to that of the paternally-inherited allele (see Supplementary Methods). In the AUC ratio of *D14S292*, the patient's maternally derived peak was significantly higher than the paternally derived peak. Furthermore, the microsatellite data for *D14S980* showed three peaks (Fig. 1e). These results indicated that she had a trisomy 14 cell lineage with an extra copy deriving from her mother and a upd(14)mat cell lineage.

Microsatellite analysis for chromosome 14 showed proximal maternal isodisomy and distal maternal heterodisomy (Supplementary Table S2). Figure 2 shows the hypothetical mechanisms by which the trisomy 14 cells and upd(14)mat cells were generated in our patient. The results of microsatellite analysis suggested that crossing over between *D14S608* and *D14S980* occurred during meiosis I (Supplementary Table S2 and Fig. 2). After fertilization between a diploid oocyte caused by maternal nondisjunction during meiosis II and a normal sperm, the loss of the paternal homologue in a trisomy 14 cell, a condition known as trisomy rescue, leads to a upd(14)mat cell (Fig. 2a). Similarly, the elimination of one maternal chromosome could result in trisomy 14 mosaicism (Fig. 2b). However, the results of the AUC ratio of *D14S292* were not consistent with the hypothesis shown in Fig. 2b.

Trisomy 14 cells were detected in 12.0% of the patient's leukocytes by G-band karyotyping, and in 46.8% of her leukocytes by FISH analysis at age 3 years. We performed FISH analysis again at 6 years of age, and detected trisomy cells in 42.0% of her leukocytes (Fig. 1d). The results of FISH analysis suggested that the proportion of trisomy cells remained unchanged in her leukocytes. The discrepancy between G-band karyotyping and FISH analysis resulting in our patient may be explained by the methodological differences. G-band karyotyping requires that the lymphocytes are cultured with phytohemagglutinin (PHA) to obtain a metaphase image of the chromosomes. A previous report showed that patients with certain chromosomal

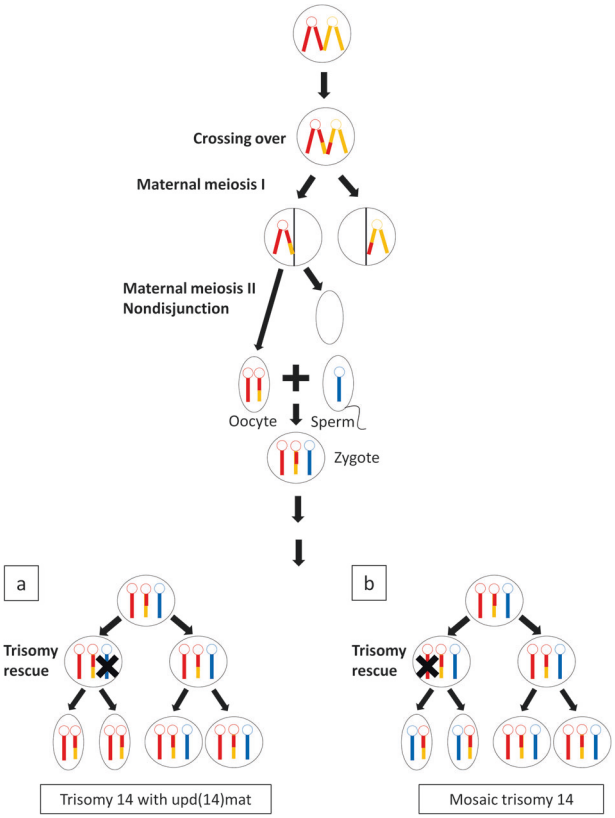

Fig. 2 Schematic representation of mechanisms in the generation of upd(14)mat from trisomy 14 zygote. The maternally-derived chromosomes are shown in red and yellow, and the paternally-derived chromosomes are shown in blue. **a** Generation of a trisomy 14 cell lineage and a upd(14)mat cell lineage resulting from the loss of the paternal homologue in the trisomy 14 cells. **b** Generation of a trisomy 14 cell lineage and a normal cell lineage resulting from the loss of the maternal homologue in the trisomy 14 cells

abnormalities like 21 trisomy were poor responders to PHA [15]. For FISH analysis, no lymphocyte culture is performed. These facts may explain why in our patient the proportion of trisomy cells examined by G-band karyotyping was smaller than that of trisomy cells examined by FISH analysis.

Table 1 compares the clinical features of this patient with two groups: previously reported patients with a combination of trisomy 14 mosaicism [10–13] and upd(14)mat or patients with upd(14)mat [16]. Global developmental delay was significantly higher in patients with trisomy 14 mosaicism and upd(14)mat than in patients with upd(14)mat, whereas, small hands and/or feet were more frequently seen in patients with upd(14)mat than in patients with trisomy 14 mosaicism and upd(14)mat. Regarding the height SDS, the patients with a combination of trisomy 14 mosaicism and upd(14)mat were significantly shorter than patients with upd(14)mat (Table 1). Severe growth failure, small hands or feet, and global developmental delay are key

clinical features of the combination of trisomy 14 mosaicism and upd(14)mat.

Of the five patients with the concomitant trisomy 14 mosaicism and upd(14)mat, our patient was the youngest. Because a high percentage of patients with upd(14)mat present with obesity and precocious puberty after early childhood [9], early genetic diagnosis of trisomy 14 mosaicism with upd(14)mat may be helpful in providing useful information for clinical follow up by drawing attention to symptoms such as obesity and precocious puberty, which become apparent with age.

In summary, we showed that trisomy 14 mosaicism with upd(14)mat led to severe short stature. For severely short-statured patients with trisomy 14 mosaicism, we should be aware of the possible coexistence of upd(14)mat [16].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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