Molecular and clinical analyses of two UPD(16)mat patients detected by screening of 94 Silver-Russell syndrome patients without known etiology

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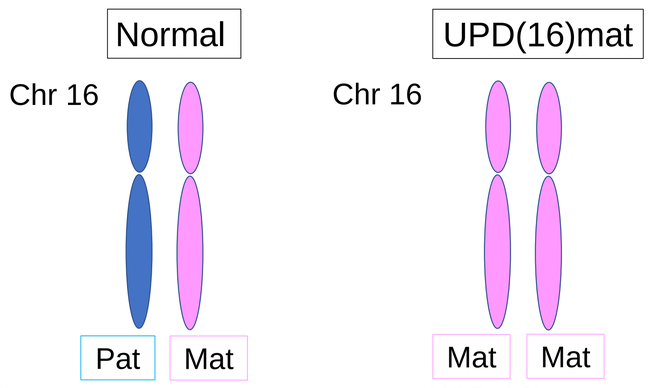
Introduction

[Maternal uniparental disomy of chromosome 16 (UPD(16)mat)]



- Forty-nine live-born patients with UPD(16)mat have been reported.
- Common clinical features
  : preterm birth, growth retardation, congenital heart diseases, hypospadias[1–3)]

[Silver-Russell syndrome (SRS)]

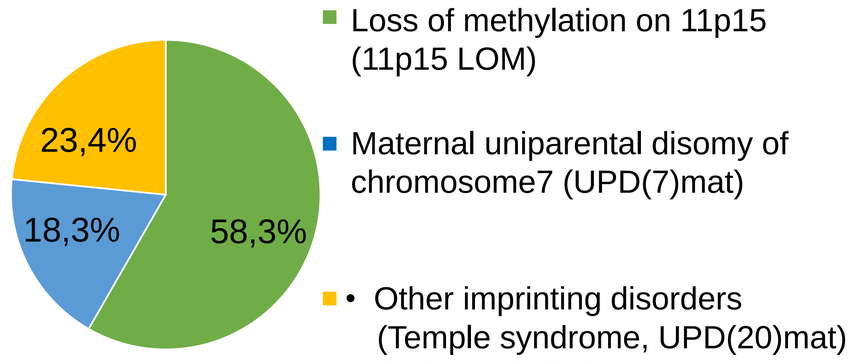
Netchine-Harbison clinical scoring system (NH-CSS)

Clinical criteria
① SGA (birth weight / birth length ≤-2 SD)
② Postnatal growth failure (height ≤-2 SD)
③ Relative macrocephaly at birth
④ Protruding forehead
⑤ Body asymmetry
⑥ Feeding difficulties / low BMI (≤-2 SD)

SRS： ≥4 of 6 criteria
- NH-CSS ≧4 of 6
- 3 of 6, but with continued clinical suspicion

➡ Eligible for molecular testing[4)]

[Etiology of SRS[5)]]



Objectives

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

Methods

【Patients】

Patients referred to us for genetic testing for SRS (n=330)

- 11p15 LOM (n=90)
- UPD(7)mat (n=24)

- NH-CSS ≥4 of 6
- 3 of 6, but with continued clinical suspicion of SRS

- Insufficient clinical information (n=51)
- NO (n=43)

YES (n=122)

Methylation analysis for 6 DMRs related to other imprinting disorders using pyrosequencing

- Normal methylation levels (n=101)
- Abnormal methylation levels
  - 11p15 duplication (n=3)
  - Other imprinting disorders (n=18)

Pathogenic CNVs (n=7)

- NH-CSS ≥4 of 6 (n=63)
- 3 of 6, but with continued clinical suspicion of SRS (n=31)

【Molecular analysis】

Methylation analysis using pyrosequencing for *ZNF597*-DMR on chromosome 16

- Low methylation levels
- Normal methylation levels

Microsatellite analysis, aCGH+SNP array

Diagnosis as UPD(16)mat

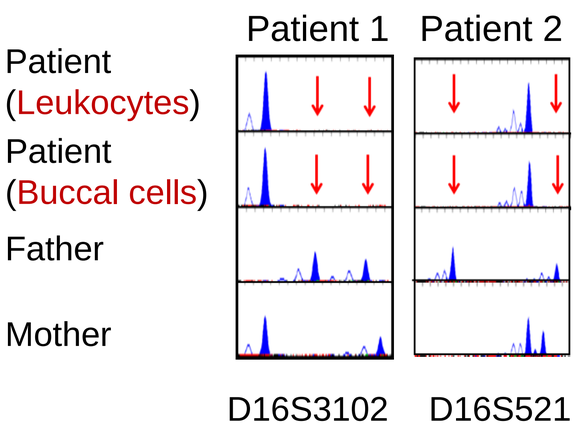
Whole-exome sequencing

Results

【Molecular analysis】

We identified two patients (2.1%) with UPD(16)mat in 94 patients.

[Microsatellite analysis]



No peak of paternal origin

⬇

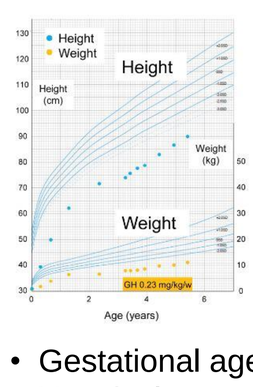
No trisomy 16 cells in the leukocytes and buccal cells

[Whole-exome sequencing]

- Patients 1 and 2 did not have gene mutations related to their phenotypes.

Patient 1 (5y Male)

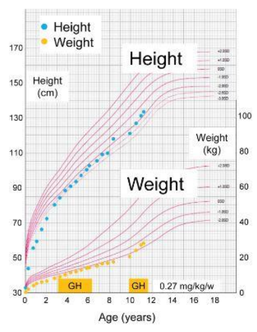
• SGA	+
Birth length in cm (SDS)	31.0 (–1.96)
Birth weight in g (SDS)	698 (–2.38)
• Postnatal growth failure	+
Present height in cm (SDS)	89.9 (–4.24)
• Relative macrocephaly at birth	–
• Protruding forehead	+
• Body asymmetry	–
• Feeding difficulties / low BMI	+
NH-CSS	**4/6**



- Gestational age: 27 weeks
- Ventricular septal defect
- Hypospadias, cryptorchidism

Patient 2 (11y Female)

• SGA	+
Birth length in cm (SDS)	33.0 (–2.38)
Birth weight in g (SDS)	806 (–2.60)
• Postnatal growth failure	+
Present height in cm (SDS)	133.3 (–1.72)
• Relative macrocephaly at birth	+
• Protruding forehead	+
• Body asymmetry	–
• Feeding difficulties / low BMI	+
NH-CSS	**5/6**



- Gestational age: 29 weeks

Discussion

[Phenotypical comparison between patients with UPD(16)mat in the literature and in this report and previously reported patients with SRS[1–3, 5–7)]]

	UPD(16)mat	SRS		*P* value	
		11p15 LOM	UPD(7)mat	UPD(16)mat vs. 11p15 LOM	UPD(16)mat vs. UPD(7)mat
Gestational age in weeks	**35.0 (27.3~40.0)**	**38.0 (34.4~40.0)**	**38.0 (34.6~40.0)**		
SGA	**26/40**	**43/43**	**9/9**	**0.000**	**0.045**
Congenital heart disease	**11/33**	**8/145**	**0/17**	**0.000**	**0.009**
Hypospadias, cryptorchidism	**7/18**	**12/22**	**2/7**	**0.360**	**1.000**

Genetic testing for UPD(16)mat should be considered for patients with preterm birth and congenital heart diseases, even if they are not SGA.

Conclusions

- **Two patients (2.1%) of 94 etiology-unknown patients with SRS-phenotype had UPD(16)mat.**
- **We suggest considering genetic testing for UPD(16)mat in SRS-phenotypic patients without known etiology.**

References

1) Scheuvens R, et al. *Clin Genet* 2017. 2) Helm BM, et al. *Hum Genomics* 2017. 3) Bravo García-Morato M, et al. *J Allergy Clin Immunol Pract* 2017. 4) Wakeling EL,et al. *Nat Rev Endocrinol* 2017. 5) Azzi S,et al. *J Med Genet* 2015. 6) Fuke T, et al. *PLoS One* 2013. 7) Ghanim M, et al. *Am J Med Genet A* 2013.

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Growth and syndromes (to include Turner syndrome)

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