Various imprinting disorders underlying Silver-Russell Syndrome-compatible phenotype

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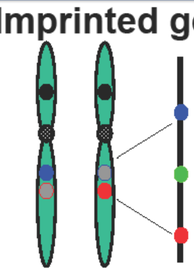
Disclosure of Conflict of Interest
Masayo Kagami: National Research Institute for Child Health and Development, Tokyo, Japan
I have no COI with regard to our presentation.

Background

Imprinted genes

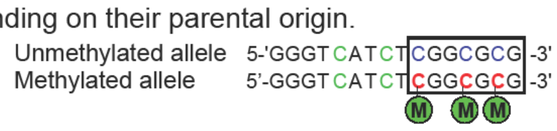


Paternal Expressed Genes (PEGs)

Differentially methylated region (DMR)

- Different methylation statuses depending on their parental origin.
- Function as imprinting center

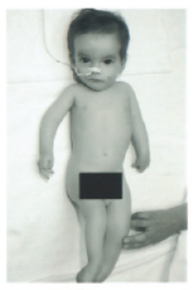
Maternal Expressed Genes (MEGs)



Silver-Russell syndrome (SRS)

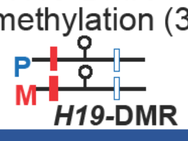
SRS diagnosis criteria (Netchine et al. 2007)

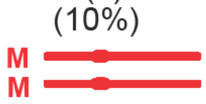
Birth length and/or Birth weight ≤ –2 SDS
1)Relative macrocephaly at birth (BL or BW-BOFC SD≤–1.5)
2)Present height ≤ –2 SDS (at 2 years)
3)Prominent forehead
4)Body asymmetry
5)Feeding difficulties



Genetic causes

H19-DMR Hypomethylation (30%)	UPD(7)mat (10%)	Unknown (60%)





Imprinting disorders

	Chr	DMR	Clinical findings
Silver-Russell syndrome (SRS)	11p15 Ch 7	*H19*	Growth failure, Relative macrocephaly, Body asymmetry, Hypotonia, Small hands
Beckwith-Wiedemann syndrome (BWS)	11p15	*H19*, Kv	Over growth, Macrosomia, Hemihypertrophy, Hypoglycemia, Placentomegaly
Kagami-Ogata syndrome (KOS)	14q32.2	IG, *MEG3*	Bell-shaped small thorax, Abdominal wall defects, Placentomegaly, Developmental delay
Temple syndrome (TS14)	14q32.2	IG, *MEG3*	Growth failure, Early onset puberty, Hypotonia, Small hands
Prader-Willi syndrome (PWS)	15q11-13	*SNRPN*	Growth failure, Obesity, Hypotonia, Small hands, Developmental delay
Angelman syndrome (AS)	15q11-13	*SNRPN*	Developmental delay, Epilepsy
Transient neonatal diabetes (TNDM)	6q24	*ZAC1*	Hyperglycemia, Growth failure
Pseudohypoparathyroidism (PHP)	20q13.3	*GNAS* A/B	PTH resistance, AHO (Growth failure, Shortened fourth metacarpals, Rounded faces, Mental retardation)

Clinical findings overlap in different imprinting disorders.

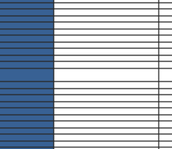
Objectives

To clarify the relevance of imprinting disorders other than SRS to SRS-like phenotypes.

Methods

Patients with SRS-like phenotypes

Methylation analysis for 9 DMRs using pyrosequencing



- *H19*-DMR (ch11)
- *PEG1, PEG10*-DMR (ch7)
- *PLAGL1*-DMR (ch6)
- KvDMR (ch11)
- IG-DMR (ch14)
- *MEG3*-DMR (ch14)
- *SNRPN*-DMR (ch15)
- *A/B*-DMR (ch20)

Hypomethylation of the *H19*-DMR → *H19*-DMR Hypomethylation

Hypermethylation of the *PEG1, PEG10*-DMR (Chr7) → Microsatellite analysis for chromosome 7 → UPD(7)mat

Aberrant methylation status of the DMRs other than SRS responsible DMR (+) → •MLPA •aCGH analysis •FISH → Imprinting disorders other than SRS

Normal methylation status in 9 DMRs → Unknown

Results

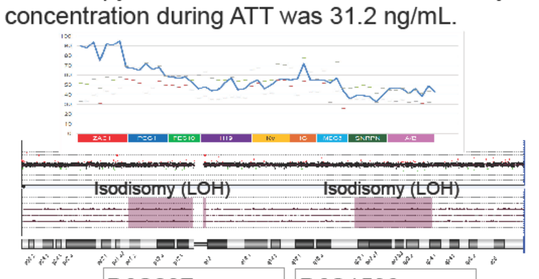
Imprinted region	11p15	7q32	7q21	11p15	14q32	14q32	6q24	15q11-13	20q13.3
DMR	*H19*	*PEG1*	*PEG10*	Kv	IG	*MEG3*	*PLAGL1*	*SNRPN*	*A/B*
Hypomethylation of the *H19*-DMR: 46 (29.8 %)									
UPD(7)mat: 13 (8.4 %)									
IDs other than SRS: 6 (3.9%)									
Unknown: 89 (57.8%)									

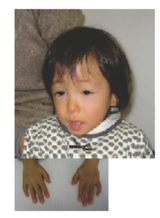
Hypomethylated DMR (sever)
Hypomethylated DMR (mild)
Hypermethylated DMR (sever)
Hypermethylated DMR (mild)

Hypermethylation of the *PLAGL1*-DMR: UPD(6)mat

	Pat. 1
Clinical diagnosis	SRS
SRS diagnosis criteria	4/5
Last examination (y)	4 6/12
Karyotype	46,XX
Gestational age (wks)	28
Prenatal growth failure	+
Birth length cm (SD)	27.5 (–3.5)
Birth weight kg (SD)	0.47 (–4.3)
Postnatal growth failure	+
PH cm (SDS)	95.2(–1.9)
PW kg (SDS)	10.3 (–2.7)
Developmental delay	+
Speech delay	–
Muscular hypotonia	–
Scoliosis	–
Small hands	+

- For hypothyroidism, levothyroxine was administrated from neonate to 3 10/12 years of age.
- GH therapy for SGA short stature started at 3 years of age. Peak GH concentration during ATT was 31.2 ng/mL.

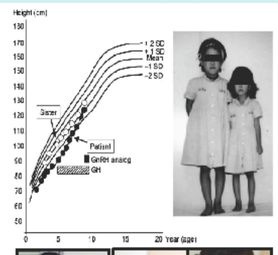




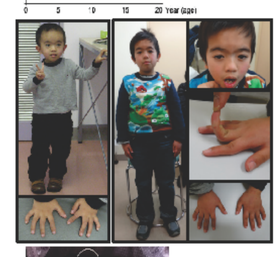
Patient 1

Hypomethylation of the IG-DMR and/or *MEG3*-DMR: TS14 (Epimutation)

	Pat. 2	Pat. 3	Pat. 4
Clinical diagnosis	SRS	SRS	SRS
SRS diagnosis criteria	4/5	4/5	5/5
Last examination (y)	9 2/12	9 6/12	1 7/12
Karyotype	46,XX	46,XY	46,XX
Gestational age (wks)	37	41	34
Prenatal growth failure	+	+	+
Birth length cm (SD)	36.5 (–6.0)	46.5 (–2.1)	36.8 (–2.9)
Birth weight kg (SD)	1.2 (–4.6)	2.2 (–2.7)	1.2 (–3.8)
Postnatal growth failure	+	+	+
PH cm (SDS)	125.5 (–1.0)	120.4 (–2.3)	66 (–5.1)
PW kg (SDS)	22.3 (–1.2)	26.5 (–0.7)	4.79 (–4.9)
Developmental delay	–	–	+
Speech delay	–	+	+
Muscular hypotonia	–	+	+
Scoliosis	–	–	–
Small hands	+	+	+
Early onset of puberty	+	–	…
LH-RH analog	+ (since 7y)	–	…
Menarche (years:months)	+ (8 8/12)	…	…



Patient 2



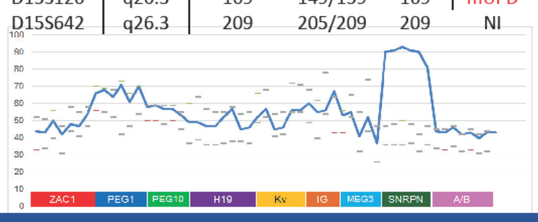
Patient 3

Patient 4

Hypermethylation of the *SNRPN*-DMR: PWS (UPD(15)mat)

	Pat. 5
Clinical diagnosis	SRS
SRS diagnosis criteria	4/5
Last examination (y)	4 9/12
Karyotype	46,XY
Gestational age (wks)	34
Prenatal growth failure	+
Birth length cm (SD)	39 (–1.9)
Birth weight kg (SD)	1.4 (–2.3)
Postnatal growth failure	+
PH cm (SDS)	96.2 (–2.1)
PW kg (SDS)	16.8 (–0.1)
Developmental delay	+
Speech delay	+
Muscular hypotonia	+
Scoliosis	+
Small hands	+
Almond-shaped eyes	+
Hypospadias	+
Hypospadias	+

	location	Pt. 5	Father	Mother	
D15S541	q11.2	148	148	140/148	NI
D15S1035	q11.2	243	247	175/243	mUPD(i)
D15S11	q12	243	243/249	243/249	NI
D15S128	q12	212	190/198	204/212	mUPD(i)
D15S1048	q13.3	200	200/214	200	NI
D15S1007	q14	169	169/175	169/171	NI
D15S117	q14	143	137/145	131/143	mUPD(i)
D15S131	q23	250	238/256	250/254	mUPD(i)
D15S205	q25.3	151	157/161	151	mUPD
D15S127	q26.1	125/135	127/147	125/135	mUPD(h)
D15S120	q26.3	169	149/159	169	mUPD
D15S642	q26.3	209	205/209	209	NI



Summary

- We identified three TS14 patients with epimutation, two PWS patients with UPD(15)mat and one patient with UPD(6)mat in 95 patients with SRS-like phenotypes.
- These results suggest that the imprinting disorders other than SRS also demonstrate SRS-compatible phenotype.

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