Imprinting defects and copy number variations in short children born small for gestational age

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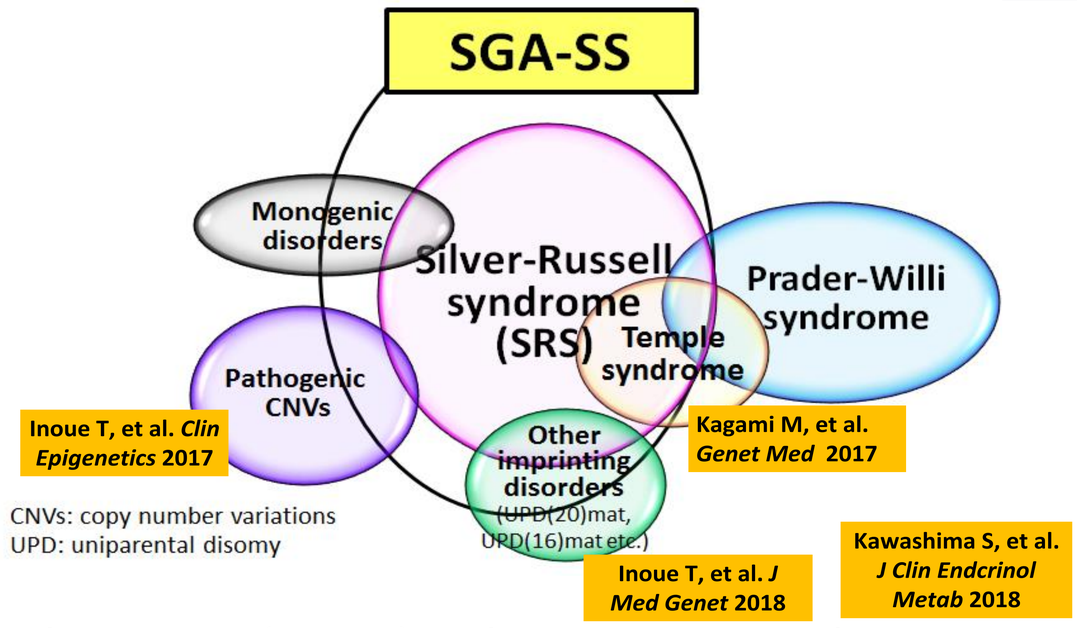
Introduction



- SGA-short stature (SGA-SS) is a heterogeneous condition.
- Some imprinting disorders, monogenic disorders, and pathogenic copy number variations lead to SGA-SS.
- Silver-Russell syndrome (SRS) is a typical imprinting disorder having SGA-SS.

Aim

To clarify the contribution of imprinting defects and pathogenic copy number variations to SGA-SS.

Subject

Subjects:
346 patients clinically diagnosed with SRS or SGA-SS by presenting doctors

Inclusion criteria
SGA : Birth weight and height < 10 percentile
Short stature:
- Age ≥ 2years
- Height < -2.0 SDS before initiation of GH treatment

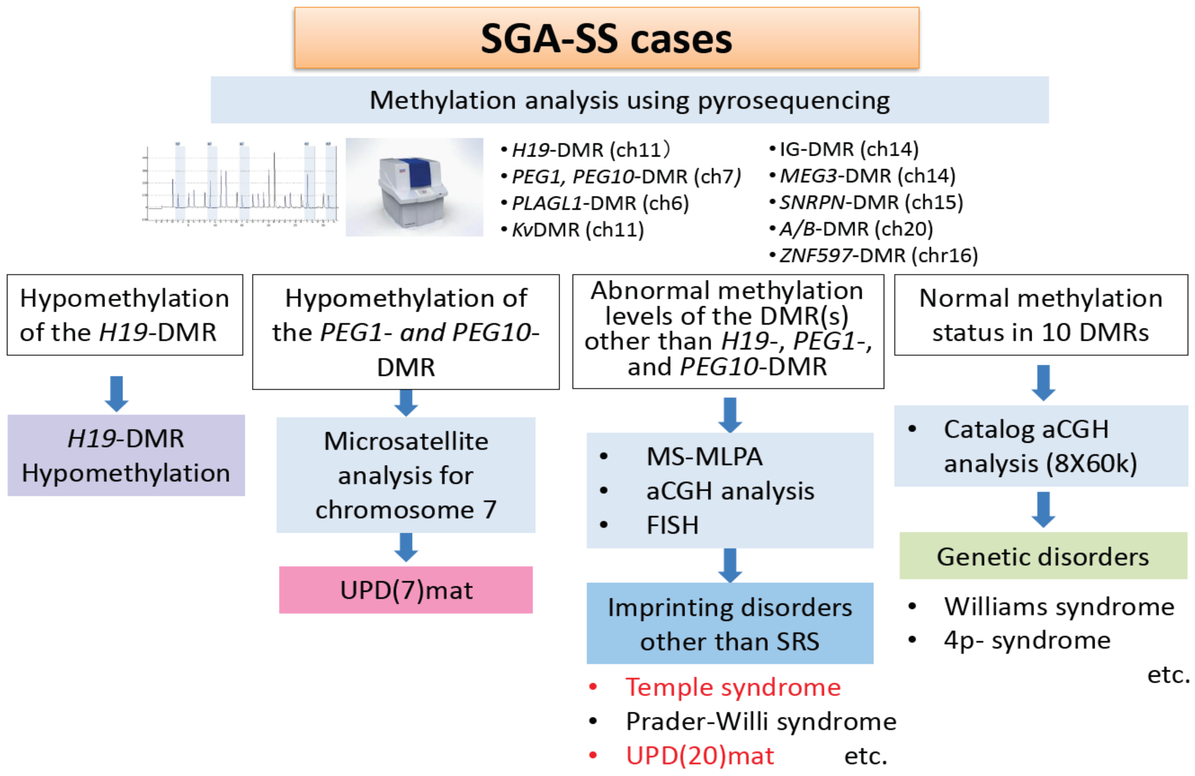
The cases clinically or genetically diagnosed as known syndromes were not included (ex. Prader-Willi syndrome, Turner syndrome).

Netchine-Harbison clinical scoring system (NH-CSS)
1. SGA (birth weight and/or 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 and/or low BMI (≤-2 SD)

SRS : ≥4 of 6 items

- NH-CSS≥4 : SRS compatible group (n=163)
- NH-CSS=3+α (triangular face and/or fifth finger clinodactyly): SRS-like group (n=52)
- NH-CSS≤3 : non-SRS group (n=131)

Methods



Results

Genetic causes	SRS-compatible	SRS-like	non-SRS
	n=163	n=52	n=131
Genetic causes of SRS	**47 (29%)**	**11 (21%)**	**5 (4%)**
•Hypomethylation of the *H19*-DMR	40	8	3
•UPD(7)mat	7	3	2
Imprinting disorders other than SRS	**20 (12%)**	**4 (8%)**	**7 (5%)**
•Temple syndrome	8	1	2
•Prader-Willi syndrome	2	0	1
•UPD(20)mat	3	1	1
•UPD(16)mat	2	0	0
•UPD(6)mat	1	1	1
•Parthenogenesis	1	0	0
•UPD(11)mat mosaic	1	0	0
•Trisomy 14/UPD(14)mat mosaic	0	0	1
•11p15 maternal duplication	2	1	0
•20q13 maternal duplication	0	0	1
Pathogenic CNVs	**5 (3%)**	**7 (14%)**	**7 (5%)**
Unknown	91 (56%)	30 (58%)	112 (85%)

Details of pathogenic CNVs	SRS-Compatible	SRS-like	non-SRS
4p deletion (Wolf-Hirschhorn syndrome)	1	1	
1q24q25 deletion	1		
Mosaic trisomy 18	1		
17p12 duplication	1		
Xq26.2 duplication	1		
12q14 deletion (including *HMGA2*)		2	
7q11.23 deletion (Williams syndrome)		2	
19q13.11-12 deletion		1	
2p21.1 duplication		1	
1q21.2 deletion			1
22q11.2 deletion (22q11.2 deletion syndrome)			1
1p32.2duplication/3p12.1duplication/Xp22.33 duplication			1
8p23.2 duplication/19p13.12 deletion			1
5q35.2 duplication (including *NSD1*)			2
Xp deletion (Turner syndrome)			1

Discussion

- In this study, we clarified the involvement of the imprinting disorders and pathogenic copy number variations for SRS and SGA-SS.
- Imprinting disorders other than SRS with hypomethylation of the *H19*-DMR and UPD(7)mat were detected over 10% of SRS-compatible group.
- For the patients with negative SRS genetic test results, genetic testing of TS14 should be considered.
- Our results highlight the clinical importance of imprinting defects and pathogenic CNVs as genetic causes of SGA-SS.

Conclusion

A part of SRS and SGA-SS is caused by imprinting defects other than *H19*-hypo and UPD(7)mat and pathogenic CNVs.

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Growth and syndromes (to include Turner syndrome)
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