

Supplementary Table 1. Overview of the three SRS Scoring Systems tested

<b><u>Netchine-Harbison CSS</u></b>	<b><u>Netchine <i>et al.</i> (2007) (7)</u></b>	<b><u>Birmingham (9)</u></b>
<b>6-factor system (4 or more positive = "likely-SRS")</b>	<b>SGA mandatory + 5-factor system (3 of 5 positive = "likely-SRS")</b>	<b>4-factor system (3 or more positive = "likely-SRS")</b>
1) SGA birth weight and/or length $\leq$ -2SDS	<b>MANDATORY:</b> SGA birth weight and/or length $\leq$ -2SDS	1) SGA birth weight $\leq$ -2SDS
2) Postnatal growth $\leq$ -2SDS at 24 months <sup>a</sup> or $\leq$ -2SDS from MPTH at 24 months <sup>a</sup>	1) Postnatal growth $\leq$ -2SDS at 24 months <sup>a</sup>	2) Postnatal growth $\leq$ -2SDS any time after 2 years
3) Relative macrocephaly at birth <sup>b</sup>	2) Relative macrocephaly at birth <sup>b</sup>	3) Relative macrocephaly <sup>b'</sup>
4) Body asymmetry <sup>c</sup>	3) Body asymmetry	4) Body asymmetry
5) Feeding difficulties <sup>d</sup> and/or low BMI (BMI $\leq$ -2SDS at 24 months) <sup>a</sup>	4) Feeding difficulties <sup>c</sup> and/or low BMI (BMI $\leq$ -2SDS at 24 months) <sup>a</sup>	
6) Protruding forehead as a toddler	5) Protruding forehead as a toddler	

<sup>a</sup> at 24 mo  $\pm$  1mo

<sup>b</sup> defined as head circumference SDS  $\geq$ 1.5 SDS higher than birth weight or length

<sup>b'</sup> defined as head circumference SDS  $\geq$ 1.5 SDS higher than weight or length at the time of measurement

<sup>c</sup> defined as LLD of  $\geq$ 0.5cm OR arm asymmetry OR LLD  $<$ 0.5cm with at least two other asymmetric body parts (one not relating to the face)

<sup>d</sup> defined as use of a feeding tube or cyproheptadine (appetite stimulation) for a child with a very low spontaneous food intake

Supplementary Table 2. Pair-wise comparison for the overall NH-CSS SRS Scoring System. These post-hoc tests were run using the Z-test for the equality between two proportions

		SRS 11p15 ICR1 hypomethylation	SRS mUPD7	L-SRS-dblneg	UL-SRS	Mean # factors
	N	Z (p-value)	Z (p-value)	Z (p-value)	Z (p-value)	
SRS 11p15 ICR1 hypomethylation	29	n/a	0.000	0.000	0.000	5.86 (min 5; max 6)
mUPD7	11	0.000	n/a	NS .361	0.000	4.73 (min 4; max 6)
L-SRS-dblneg	12	0.000	NS .361	n/a	0.000	4.42 (min 4; max 5)
UL-SRS	8	0.000	0.000	0.000	n/a	2.88 (min 2; max 3)

<sup>a</sup> For each significant  $\chi^2$  result, post-hoc tests were run using the Z-test for the equality between two proportions

<sup>b</sup>The single mUPD7 subject who "failed" the scoring system is excluded from this analysis

<sup>c</sup> Only subjects with data for all 6 factors were included in this "overall" top-level analysis so as to be able to compare group mean factor numbers

Supplementary Table 3. Pair-wise comparison for the relative macrocephaly at birth<sup>ab</sup>

		SRS 11p15 ICR1 hypomethylation	SRS mUPD7	L-SRS-dblneg	UL-SRS
	N	P	P	P	P
SRS 11p15 ICR1 hypomethylation	32	n/a	ns	ns	4.79 (p<.001)
mUPD7	11	ns	n/a	ns	2.48 (p<.05)
L-SRS-dblneg	13	ns	ns	n/a	ns
UL-SRS	8	ns	ns	ns	n/a

<sup>a</sup> For each significant  $\chi^2$  result, post-hoc tests were run using the Z-test for the equality between two proportions

<sup>b</sup>The single mUPD7 subject who "failed" the scoring system is excluded from this analysis

Supplementary Table 4. Pair-wise comparison for the protruding forehead<sup>ab</sup>

		SRS 11p15 ICR1 hypomethylation	SRS mUPD7	L-SRS-dblneg	UL-SRS
	N	P	P	P	P
SRS 11p15 ICR1 hypomethylation	33	n/a	ns	ns	3.64 (p<.001)
mUPD7	11	ns	n/a	ns	2.64 (p<.01)
L-SRS-dblneg	14	ns	ns	n/a	ns
UL-SRS	8	ns	ns	ns	n/a

<sup>a</sup> For each significant  $\chi^2$  result, post-hoc tests were run using the Z-test for the equality between two proportions

<sup>b</sup>The single mUPD7 subject who "failed" the scoring system is excluded from this analysis

Supplementary Table 5. Pair-wise comparison for the body asymmetry<sup>ab</sup>

		<b>SRS 11p15 ICR1 hypomethylation</b>	<b>SRS mUPD7</b>	<b>L-SRS-dblneg</b>	<b>Non SRS</b>
	<b>N</b>	<b>P</b>	<b>P</b>	<b>P</b>	<b>P</b>
<b>SRS 11p15 ICR1 hypomethylation</b>	35	n/a	4.70 (p<.001)	3.18 (p<.01)	5.13 (p<.001)
<b>mUPD7</b>	11	ns	n/a	ns	ns
<b>L-SRS-dblneg</b>	14	ns	ns	n/a	2.05 (p<.05)
<b>UL-SRS</b>	8	ns	ns	ns	n/a

<sup>a</sup> For each significant  $\chi^2$  result, post-hoc tests were run using the Z-test for the equality between two proportions

<sup>b</sup>The single mUPD7 subject who "failed" the scoring system is excluded from this analysis

Supplementary Table 6. Pair-wise comparison for the feeding difficulties and/or BMI  $\leq$ -2SDS<sup>ab</sup>

		<b>SRS 11p15 ICR1 hypomethylation</b>	<b>SRS mUPD7</b>	<b>L-SRS-dblneg</b>	<b>Non SRS</b>
	<b>N</b>	<b>P</b>	<b>P</b>	<b>P</b>	<b>P</b>
<b>SRS 11p15 ICR1 hypomethylation</b>	35	n/a	ns	ns	3.04 (p<.01)
<b>mUPD7</b>	11	ns	n/a	ns	3.05 (p<.01)
<b>SRS dbl neg</b>	13	ns	ns	n/a	3.43 (p<.001)
<b>Non SRS</b>	8	ns	ns	ns	n/a

<sup>a</sup> For each significant  $\chi^2$  result, post-hoc tests were run using the Z-test for the equality between two proportions

<sup>b</sup>The single mUPD7 subject who "failed" the scoring system is excluded from this analysis

Supplementary Table 7. Clinical characteristics of the four L-SRS-dblneg and three UL-SRS-dblneg (grey columns) subjects displaying the newly identified molecular abnormalities and one UL-SRS-dblneg mUPD7 (dark grey column).

	Likely-SRS				Unlikely-SRS			
	mUPD16	mUPD20	1q21 del	IG-DMR <i>DLK1/GTL2</i> hypomethylation	1q24-31 del	11p13p12 del	22q11.21 dupl	mUPD7
<b>Mean number of scoring system factors recorded as positive</b>	<b>4</b>	<b>5</b>	<b>4</b>	<b>5</b>	<b>3</b>	<b>3</b>	<b>3</b>	<b>3</b>
Small-for-gestational age (wt, lth or both)	Yes	Yes	No	Yes	Yes	Yes	Yes	No
Postnatal growth failure	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Relative macrocephaly at birth	No	No	No	Yes	No	Yes	Yes	No
Protruding forehead	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Body asymmetry	No	Yes	Yes	Yes	No	No	No	No
Feeding failure	Yes	Yes	Yes	No	Yes	No	No	Yes
Target height (SDS)	-0.17	-0.27	0.19	-0.39	0.76	0.73	-0.18	1.59
Gestational age	34.4	36.7	40.0	38.7	36.1	38.29	38.57	38.00
Birth weight (SDS)	-3.01	-2.40	-1.36	-2.64	-2.63	-2.62	-2.50	-1.78
Birth length (SDS)	-3.49	-2.48	-0.63	-2.89	-3.44	-3.03	-2.33	-1.51
Head circumference at birth (SDS)	-2.10	-1.50	-1.40	-1.00	-3.00	-1.10	-0.30	-1.10
Head sparing wt at birth (SDS)	0.91	0.90	-0.04	1.64	-0.37	1.52	2.20	0.68
Head Sparing lth at birth (SDS)	1.39	0.98	-0.77	1.89	0.44	1.93	2.03	0.41
24 mo weight (SDS)	-5.31	-5.28	-2.57	-3.63	-4.30	-1.43	-3.04	-2.81
24 mo length (SDS)	-2.32	-2.99	-2.24	-3.37	-4.68	-1.92	-1.79	-2.58
24 mo head circumference (SDS)	0.50	-0.50	-0.50	0.25	-2.00	2.00	1.25	2.50
24 mo BMI**	12.5	13.2	15.2	15.7	16.9	16.7	14.1	15.5
Downturned mouth	No	Yes	No	No	Yes	Yes	Yes	Yes
Abnormal ears - low-set &/or posteriorly rotated	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Clinodactyly of 5th finger	Yes	No	No	No	Yes	Yes	Yes	Yes
Shoulder dimples	No	Yes	No	Yes	No	No	No	Yes
Syndactyly of toes 2/3	No	No	Yes	No	Yes	No	Yes	No
Prominent heel	No	Yes	No	Yes	No	Yes	Yes	Yes
Muscle mass - too small	No	Yes	No	Yes	Yes	No	No	Yes
Genital abnormalities - males (undescended testicles &/or hypospadias)	n/a	n/a	No	n/a	N/A	Yes	N/A	N/A
Autism/PDD	No	No	No	No	No	No	Yes	Yes
Diagnosed cognitive disabilities (only school-age, 5 yrs+, if not diagnosed yet)	No	No	Yes	Yes	Yes	No	Yes	No

\*\* The BMI variable should be viewed with caution as most children with 11p15 or mUPD7 were tube-fed or were on cyproheptadine for appetite stimulation.

Supplementary Table 8. Comparison of the general measurement data for the different molecular groups and other physical characteristics that have been found to be common in groups of patients with certain molecular etiologies of SRS and could guide the clinical diagnosis of SRS by physicians.

	Quantitative physical characteristics and their means and numbers								P val	Statistic tests
	SRS 11p15 ICR1 hypomethylation		mUPD7 <sup>a</sup>		L-SRS-dblneg		Unlikely-SRS			
	N	Mean	N	Mean	N	Mean	N	Mean		
Sex, male/female	35	22/13	12	7/5	14	6/8	8	2/6	NS	Chi-Squared
Target height (SDS)	35	0.1426	12	0.1646	14	-0.0518	8	-0.2556	NS	ANOVA
Gestational age (wks)	35	37.2367	12	37.1905	14	38.1735	8	37.4459	NS	ANOVA
Birth weight (SDS)	35	-3.1614	12	-2.2758	14	-2.7086	8	-2.4925	0.029	ANOVA; F(3) = 3.200; p<0.05
Birth length (SDS)	35	-4.5063	12	-2.5458	14	-3.3814	8	-2.6925	0.000	ANOVA; F(3) = 9.129; p<0.001
Head circumference at birth (SDS)	32	-0.6750	12	-0.4583	13	-1.7769	8	-1.925	0.013	ANOVA; F(3) = 3.866; p<0.01
Head sparing wt at birth (SDS)	32	2.5016	12	1.8175	13	1.0069	8	0.5675	0.000	ANOVA; F(3) = 9.767; p<0.001
Head sparing lth at birth (SDS)	32	3.9478	12	2.0875	13	1.6946	8	0.6775	0.000	ANOVA; F(3) = 15.192; p<0.001
24 mo weight (SDS)	35	-4.5831	12	-4.0067	13	-3.83	8	-3.265	NS	ANOVA
24 mo length (SDS)	34	-3.0997	12	-3.0825	13	-2.5185	8	-2.3663	NS	ANOVA
24 mo head circumference (SDS)	32	0.375	11	1.0000	13	-0.5192	7	-0.3929	0.008	ANOVA; F(3) = 4.368; p<0.01
24 mo BMI <sup>b</sup>	34	13.812	12	14.492	13	14.0154	8	14.975	NS	ANOVA
Other physical characteristics typical of SRS that a physician might consider										
	SRS 11p15 ICR1 hypomethylation		mUPD7 <sup>a</sup>		L-SRS-dblneg		Unlikely-SRS		P val	Statistic tests
	Incidence		Incidence		Incidence		Incidence			
Downturned mouth	32 of 35 (91.4%)		6 of 12 (50%)		6 of 14 (42.9%)		5 of 8 (62.5%)		0.002	Chi-squared (3) = 15.335, p<0.01
Abnormal ears - low-set &/or posteriorly rotated	20 of 35 (57.1%)		8 of 12 (66.7%)		8 of 14 (57.1%)		4 of 8 (50.0%)		NS	
Clinodactyly of 5th finger	32 of 35 (91.4%)		9 of 12 (75.0%)		7 of 14 (50.0%)		4 of 8 (50.0%)		0.006	Chi-squared (3) = 12.488, p<0.05
Shoulder dimples	27 of 35 (77.1%)		8 of 12 (66.7%)		5 of 14 (35.7%)		2 of 8 (25%)		0.007	Chi-squared (3) = 12.102, p<0.01
Syndactyly of toes 2/3	33 of 35 (94.3%)		3 of 12 (25.0%)		5 of 14 (35.7%)		5 of 8 (62.5%)		0.000	Chi-squared (3) = 27.488, p<0.001
Prominent heel	9 of 35 (25.7%)		12 of 12 (100%)		6 of 14 (42.9%)		3 of 8 (37.5%)		0.000	Chi-squared (3) = 20.213, p<0.001
Muscle mass - too small	29 of 35 (82.9%)		8 of 12 (66.7%)		5 of 14 (35.7%)		2 of 8 (25%)		0.001	Chi-squared (3) = 15.537, p<0.001
Genital abnormalities - males (undescended testicles &/or hypospadias)	12 of 22 (54.5%)		2 of 7 (28.6%)		2 of 6 (33.3%)		2 of 2 (100%)		NS	
Autism/PDD <sup>c</sup>	2 of 35 (5.7%)		7 of 12 (58.3%)		2 of 14 (14.3%)		1 of 8 (12.5%)		0.001	Chi-squared (3) = 17.550, p<0.001
Diagnosed cognitive disabilities (only school-age, 5 yrs+)	4 of 23 (17.4%)		6 of 8 (75%)		5 of 11 (45.5%)		3 of 7 (42.9%)		0.027	Chi-squared (3) = 9.216, p<0.05

<sup>a</sup> In this analysis, we carried out molecular comparisons, so the mUPD7 subject not identified by the scoring system is correctly classified in the molecular "mUPD7" group

<sup>b</sup> The BMI variable should be viewed with caution as most children with 11p15 or mUPD7 were tube-fed or were on cyproheptadine for appetite stimulation.

<sup>c</sup> PDD = pervasive developmental disorders