Comparison of the clinical scoring systems in Silver–Russell syndrome and development of modified diagnostic criteria to guide molecular genetic testing

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ABSTRACT
Background About half of all children with a clinical diagnosis of Silver–Russell syndrome (SRS) have a detectable molecular genetic abnormality (maternal uniparental disomy of chromosome upd(7)mat or hypomethylation of H19 differentially methylated region (DMR)). The selection of children for molecular genetic testing can be difficult for non-specialists because of the broad phenotypic spectrum of SRS and the tendency of the facial features to mitigate during late childhood. Several clinical scoring systems for SRS have been developed by specialist researchers, but the utility of these for guiding molecular genetic testing in routine clinical practice has not been established.

Objectives To evaluate the utility of four published clinical scoring systems for genetic testing in a cohort of patients referred to a clinical service laboratory.

Patients Individuals with suspected SRS referred for molecular genetic testing of H19 DMR methylation status or upd(7)mat.

Results 36 of 139 (25.9%) patients referred for testing had a genetic abnormality identified. Comparison of four published clinical scoring systems demonstrated that all included subjective criteria that could be difficult for the general clinician to assess. We developed a novel, simplified, scoring system utilising four objective, easily measured parameters that performed similarly to the most sensitive and specific published scoring system.

Discussion Effective utilisation of genetic testing by clinicians without specialist clinical genetics training will be facilitated by the development of targeted testing protocols that are based on robust objective clinical features and are designed for use in a busy clinical practice rather than a research setting.

INTRODUCTION
Silver–Russell syndrome (SRS; OMIM 180860) is a clinically and genetically heterogeneous condition characterised by low birthweight, variable poor postnatal growth, and a number of dysmorphic features including a distinctive triangular facies, relative macrocephaly, and limb/facial asymmetry. The incidence of the syndrome is estimated between 1 in 3000 to 1 in 1 000 000 depending on the stringency of criteria used.1 Approximately 10% of children with SRS are known to have maternal uniparental disomy of chromosome 7(upd(7)mat).2 A further 40–50% will have hypomethylation of H19 differentially methylated region (DMR) at the 11p15 locus.3 4 However, up to 50% of children with clinical features of SRS will have no identified genetic abnormality.

The absence of agreed consensus diagnostic criteria and the wide phenotypic variability of secondary clinical features means that SRS is often considered as a potential diagnosis but only a fraction of potential cases are confirmed by molecular analysis. Although patients with H19 DMR hypomethylation are more likely to have a ‘classical SRS phenotype’ than those without a detectable abnormality, it is widely recognised that the selection of potential SRS cases for genetic testing can be challenging.3 Furthermore, it is well recognised that the facial dysmorphism tends to become less obvious during late childhood. Hence several research groups have suggested clinical feature scoring systems that can be used for the clinical diagnosis of SRS and/or selection of potential cases for genetic testing.1 4–6 However, there are no universally agreed clinical scoring systems and those that have been developed have usually been based on the results of testing in a research laboratory, in patient cohorts that were ascertained for research studies, and assessed by clinicians with a special interest in SRS. For genetic testing to become an integral part of mainstream clinical medicine it is important that reliable guidelines for selecting those patients who will benefit from molecular testing are provided to non-specialist clinicians. We therefore decided to compare four SRS clinical feature scoring systems in a large cohort of potential SRS patients who were ascertained through referral for genetic testing for SRS in a clinical diagnostic laboratory. Following on from this analysis we developed a simplified four point clinical assessment scoring system, suitable for a broad range of specialist and non-specialist clinicians that we suggest will provide robust criteria for selecting potential SRS patients for molecular testing.

METHODS
Patients We studied individuals with a clinically suspected diagnosis of SRS who were referred to the West Midlands Regional Genetics laboratory for NHS diagnostic testing for SRS between January 2002 and December 2012. All SRS referrals were logged
into a database and the referring clinicians (clinical geneticists, general paediatricians, and paediatric endocrinologists from across the UK) were asked to complete a standardised clinical features form (see online supplementary data).

**Molecular genetic analysis**

Methylation analysis for H19 DMR hypomethylation

Patients were assessed for H19 DMR hypomethylation using either SALSA MS-MLPA kit ME-030 (MRC Holland, Amstterdam, Netherlands) or pyrosequencing (Qiagen, Crawley, UK) using standard protocols. In addition, testing for upd(11) was performed using microsatellite marker analysis (D11S2071, D11S4046, D11STH, D11S1318, and D11SHBB). All DNA samples were tested twice to confirm methylation levels.

 upd(7)mat analysis

Patients were assessed for upd(7)mat using standard protocol for microsatellite analysis (six markers, three each on 7q and 7p). A positive diagnosis required evidence of unique maternal inheritance at ≥2 markers.

**Clinical scoring**

Four clinical scoring systems have been published for SRS and are summarised in table 1. Criteria underlined in the table are subjective or difficult to assess within a single examination. Of note, only the Netchine criteria have a mandatory clinical feature which is required for diagnosis (low birth weight/length SD scores (SDS)<−2 for gestational age). Patients without any clinical information on the database were excluded from further analysis.

**Statistical analysis**

Data were analysed using SPSS Statistical package (PASW Statistics 18; RD, PN). Logistic regression was used to determine the predictive power of different models and receiver operator curves (ROC) drawn to determine the accuracy of these different models (figure 1).

For all the patients referred for diagnostic testing of upd(7) mat and hypomethylation of H19 DMR in the database, with sufficient clinical information, those with and without an identified genetic abnormality were assessed using the four different scoring systems. Where criteria were missing, these patients were excluded from the analysis of sensitivity and specificity of the scoring system. Of note, very few patients had enough data available for full comparison of the Bartholdi scoring system, therefore sensitivity and specificity were calculated from the original article. For analyses, the presence of the required specified clinical features was considered a positive test result, and the result of the molecular genetics testing (upd(7)mat or H19 DMR hypomethylation) was considered to indicate the presence or absence of SRS. The caveat to this is that up to 50% of clinical cases will have a negative genetic test result.

**RESULTS**

**General demographic data**

Sufficient clinical information to evaluate the four clinical scoring systems was available for 139 (79 male, 60 female)/257 referrals.

The median age of patients referred for analysis was 3.25 (range 0.25–21 years).

Information on the method of conception was available for 106 referrals; 7/106 (6.6%) patients had been conceived by assisted reproductive technologies (ART) (1/7 ART conceived patients had H19 DMR hypomethylation and 6/7 had no genetic abnormality identified). It is now generally accepted that there is an increased frequency of children conceived by ART (intracytoplasmic sperm injection or in vitro fertilisation) in cohorts of children with Beckwith–Wiedemann syndrome (BWS). However, the link between ART and SRS is less well established, possibly because, as with our cohort, the numbers are too small. Although the frequency of children conceived by ART referred for SRS testing was higher than the UK average (5.0% vs 1.8%), this might have been ascertainment bias.

**Identification of a genetic abnormality and clinical data**

Thirty-six of 139 patients (25.9%) had an identified genetic abnormality: 11/36 (30.6%) upd(7)mat; 25/36 (69.4%) H19 DMR hypomethylation. There were no differences between mean age at testing between those with H19 DMR hypomethylation, upd(7)mat and no genetic abnormality. Of those with H19 DMR hypomethylation, the mean methylation index was 20.3% (range 36.3–8.5%; SD 4.9%).

There were two variables where there was a significant difference between the groups. Patients with H19 DMR hypomethylation had significantly lower birthweights than those with no abnormality (H19 DMR hypomethylation median birthweight SDS=−2.85 vs no abnormality median birthweight=−1.77 (p<0.05)). In addition, these patients were also significantly more likely to have asymmetry compared to either those with upd(7)mat or no genetic abnormality identified (H19=81%; upd(7)mat=10% and no abnormality=20%; p<0.001) (see online supplementary table S1).

As can be seen in table 2, the scoring system devised by Lai et al gives the best sensitivity and specificity when used on our UK based cohort. The scoring system from Bartholdi et al gives the highest sensitivity (ie, true positive when compared to genetic testing) but includes many data that are either not recorded as standard in child health records (birth length, birth occipitofrontal circumference (OFC)) or are difficult to assess at single assessments in early life when the diagnosis is most likely to be raised (genital abnormalities, developmental delay). All four systems use at least one subjective variable (prominent forehead or typical facies) which can be difficult for the clinician to judge given the rarity of the condition. Therefore, we investigated how a novel simpler scoring system based on only a few objective criteria would compare to the more complicated scoring systems developed in a research setting. The ‘Birmingham SRS screening score’ required three out of the following four criteria to be present for referral for molecular diagnosis:

1. Low birthweight (birthweight SDS<−2)
2. Poor postnatal growth (height SDS<−2 after 2 years of age)
3. Relative macrocephaly (head circumference SDS>1.5 than height SDS)
4. Limb/body asymmetry.

As can be seen from online supplementary table S2, patients with H19 DMR hypomethylation had increased risk of asymmetry and lower birthweight compared to patients with upd(7) mat (as previously reported). There is a significant difference between birthweight SDS in those patients with H19 DMR hypomethylation and patients with no genetic abnormality identified (p=0.016, Tukey’s honestly significant difference test). Furthermore there is a significant difference between the incidence of asymmetry in patients with H19 DMR hypomethylation and both upd(7)mat and without any genetic abnormality identified (p=0.007 and p<0.001, respectively, Fisher’s exact test with Bonferroni correction). Additionally, the relative macrocephaly was more pronounced in those with H19 DMR hypomethylation.
hypomethylation than in those with upd(7)mat, despite the similar postnatal growth patterns at assessment, although this was not significant (median OFC SDS H19: −0.48; upd(7)mat: −0.95 and no abnormality: −0.95; p 0.2).

Sensitivity and specificity of new scoring system

The sensitivity (82%) and specificity (80%) of the proposed new scoring system are similar to the Lai et al system.9 Nine children were tested with no genetic abnormality identified (positive predictive value 67%). In addition, four children would not have been tested but would have had a molecular genetic abnormality (negative predictive value 90.2%). In comparison, all the currently published scoring systems had lower positive predictive values (ie, more children would have been tested and no genetic abnormality identified) compared to the new proposed criteria, although the negative predictive values were similar (table 2). Many children are now tested earlier than 2 years (in our cohort almost one third were referred below the age of 2 years; 33 in total). If the criteria were applied to these children, the sensitivity and specificity are slightly lower but still comparable (sensitivity 78%, specificity 75%).

DISCUSSION

SRS is a genetically heterogeneous condition where up to 50% of all clinically diagnosed cases have no identified epi(genetic) change. It has previously been shown that patients with H19 DMR hypomethylation have a more severe growth failure phenotype and increased likelihood of asymmetry than those patients with upd(7)mat and this is seen again in our data.4 Interestingly, the differences in postnatal growth between molecular subgroups were less pronounced than either the pre-natal growth failure or other series (median height SDS: H19=−2.71; upd(7)mat=−2.89 and no abnormality=−2.32; p 0.1); table 2.4

Previous large series of patients with SRS have been largely ascertained via research studies whereas our cohort reflected those individuals who had been referred for genetic analysis in a clinical diagnostic laboratory. We note that Turnier et al16 found a similar fraction of patients testing positive for either upd(7) mat or hypomethylation of H19 DMR when referred to a clinical diagnostic laboratory with a potential diagnosis of SRS. Importantly, the new criteria seem to be applicable even when patients are tested below the age of 2 years (although the sensitivity and specificity are slightly lower).

A positive genetic test enables a precise diagnosis. Unfortunately, there is insufficient data on the long term clinical outcomes (such as responsiveness to growth hormone treatment or malignancy risk) in children with a clinical diagnosis of SRS according to whether they have hypomethylation of H19 DMR or upd(7)mat or no abnormality.17 18 However, although a positive genetic result may not directly affect clinical management, it does prevent further unnecessary investigation for alternative

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**Table 1: Summary of published scoring systems for diagnosis of Silver–Russell syndrome (SRS)**

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<tbody>
<tr>
<td>Testing context</td>
<td>Before association of H19 DMR hypomethylation with SRS</td>
<td>Before association of H19 DMR hypomethylation with SRS</td>
<td>Predominantly used in assessment of patients with H19 DMR hypomethylation</td>
<td>Used to assess patients with upd(7)mat and H19 DMR hypomethylation</td>
<td>Non-research cohort</td>
</tr>
<tr>
<td>Mandatory clinical features</td>
<td>Nil</td>
<td>Nil</td>
<td>Prenatal growth retardation (birth weight/length SDS&lt;−2)</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Total number of features assessed</td>
<td>5 (low birth weight; postnatal short stature; distinctive facies; asymmetry and clinodactyly)</td>
<td>5 (low birth weight; postnatal short stature; relative macrocephaly; distinctive facies and asymmetry)</td>
<td>6 (short stature—height SDS&lt;−2 after 2 years; relative macrocephaly; prominent forehead; asymmetry and feeding difficulties)</td>
<td>13 (extra criteria include genital abnormalities; developmental delay; other dysmorphic features and asymmetry weighted at 3—present or 0—absent)</td>
<td>4 Small for gestational age (birth weight/length SDS&lt;−2)</td>
</tr>
<tr>
<td>Minimum score for clinical diagnosis of SRS</td>
<td>3/5</td>
<td>4/5</td>
<td>3/5 plus mandatory prenatal growth failure</td>
<td>8/15</td>
<td>3</td>
</tr>
</tbody>
</table>

Criteria bold are subjective or difficult to assess within a single examination. DMR, differentially methylated region; OFC, occipitofrontal circumference.

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**Figure 1** Receiver operator curves (ROC) for systems 1–3 compared to proposed new scoring criteria. Figure shows ROC analysis for three published scoring systems compared to proposed new scoring system as per colour key. All four perform similarly at high specificity and moderate sensitivity.
Table 2  Summary of scoring outcomes using the four different diagnostic criteria

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<tbody>
<tr>
<td>Sensitivity (original article)</td>
<td>Not applicable (NA)</td>
<td>NA</td>
<td>69%</td>
<td>92%</td>
<td>NA</td>
</tr>
<tr>
<td>Specificity (original article)</td>
<td>NA</td>
<td>NA</td>
<td>100%</td>
<td>49%</td>
<td>NA</td>
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<tr>
<td>Sensitivity (Birmingham data)</td>
<td>84%</td>
<td>59%</td>
<td>70%</td>
<td>Not applicable</td>
<td>82%</td>
</tr>
<tr>
<td>Specificity (Birmingham data)</td>
<td>80%</td>
<td>97%</td>
<td>81%</td>
<td>Not applicable</td>
<td>80%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>95%</td>
<td>80%</td>
<td>91%</td>
<td>Not applicable</td>
<td>90%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>58%</td>
<td>59%</td>
<td>61%</td>
<td>Not applicable</td>
<td>67%</td>
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<tr>
<td>Most common unknown features</td>
<td>1. Cliniodactyly (n=28/139)</td>
<td>1. Relative macrocephaly (OFC) (n=59/139)</td>
<td>1. OFC (n=59/139)</td>
<td>1. Low birth length (n=114/139)</td>
<td></td>
</tr>
<tr>
<td>2. Post-natal short stature (n=32/139)</td>
<td>2. Post-natal short stature (n=32/139)</td>
<td>2. Post-natal short stature (n=32/139)</td>
<td>2. Relative macrocephaly at birth (OFC) (n=112/139)</td>
<td></td>
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</tr>
</tbody>
</table>

OFC, occipitofrontal circumference.

causes of poor growth and removes uncertainty regarding the diagnosis for parents, so allowing them to access appropriate support groups.

As this was a study based on UK patients and retrospective, not all the data points required were available for all scoring systems, particularly for the Bartholdi assessment tool. In order to evaluate the UK based experience of genetic testing for patients with SRS, we reviewed data from an 11 year period in a supra-regional genetics testing service. Currently the UK Genetic Testing Network guidelines for clinical suspicion of SRS includes prenatal growth failure (<0.4th centile) with relative macrocephaly (>25th centile) and possible limb asymmetry, (http://www.ukgtm.nhs.uk/gtm/Search+for+a+T est/Search+by +Disease+or+Gene). These criteria are much broader than current published guidelines. We propose a new four point scoring system based on objective criteria, which is simple for one-off clinical assessment for use by a broad range of clinicians, from clinical geneticists to general paediatricians, to guide which patients should be offered molecular genetic testing in the first instance, without loss of both specificity and sensitivity.

In the Bartholdi and Netchine cohorts, the frequency of patients with H19 DMR hypomethylation ranges from 38–69% and with upd(7)mat from 5–9%. However, no evaluation of the two UK criteria (Lai and Price) has been made following the discovery of the association of SRS with H19 DMR hypomethylation. To our knowledge there have been no previous studies comparing all four SRS scoring systems in a cohort of patients with molecular genetic testing results. As genetic testing becomes less expensive and increasingly becomes part of mainstream medical practice there is an increasing need for robust referral pathways to access molecular genetic testing in a cost effective manner, without all patients having to be seen by an expert clinician. Previously reported scoring systems for SRS have varying sensitivity and specificity, with subjective criteria that either require repeated assessment over time or previous experience of the SRS phenotype which in any case becomes more subtle in late childhood. The proposed new scoring system requires three out of four objective criteria (low birth weight, poor postnatal growth, relative macrocephaly, and asymmetry), all of which can be evaluated at a single assessment and needs no specialist training. We suggest that more sophisticated scoring systems that include subjective criteria might be more accurate in the hands of specialist clinicians with extensive experience of SRS; however, in a heterogenous group of referring clinicians (ie, outside of a research cohort), the inclusion of such variables might not improve the accuracy but might actually reduce it. Thus we note that in our referral cohort the Netchine scoring system performs less well than the simplified Birmingham criteria (table 2). For children who test negative or who do not reach the threshold for testing, but for whom a clinical diagnosis of SRS seems likely, then referral to a specialist genetics service can be undertaken for consideration of further testing (eg, if mosaicism is suspected) or alternative diagnoses (eg, microarray analysis or within a research study). An important issue for many modern health care systems is how to utilise technological advances for more accurate diagnosis while not excessively increasing healthcare expenditure. Currently commercial molecular genetic testing for SRS is between US$400–600 (£255–380, €300–450), and it is hoped that that the new scoring system proposed here will enable a wide spectrum of clinicians to utilise this in a cost effective manner in order to facilitate earlier diagnosis of SRS.

Contributors RD, ERM were involved in study design, analysis of data and writing the article. PN and GK were involved in collection of clinical data. CH, LT, FM were involved in molecular analysis. CH, LT, SP, FM and TGB were involved in the final approval of the current version of the article.

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Competing interests None.

Ethics approval Birmingham Women’s Hospital NHS Trust Research and Development Department.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES


Birmingham Audit Questionnaire Silver - Russell Syndrome

Name: 
Date of Birth: 

Clinical history:

Regarding pregnancy:

History of IVF or ICSI  yes  no  unknown
Duration of pregnancy  ..................weeks
Gestation IUGR detected  ..................weeks

Regarding perinatal period (< 1 month):

Birth weight  ...............gram
Length  ...............cm
OFC  ...............cm
Intensive care required  yes  no  unknown
Placenta small  yes  no  unknown
Feeding difficulties  yes  no  unknown
Hypoglycaemia  yes  no  unknown

Regarding postnatal period (>1month)

Feeding difficulties  yes  no  unknown
NG fed  yes  no  unknown
Gastrostomy fed  yes  no  unknown
Hypoglycaemia  yes  no  unknown
Hypogonadism  yes  no  unknown
Café au lait patches  yes  no  unknown
Seizures  yes  no  unknown
Visual defect  yes  no  unknown
Hearing loss  yes  no  unknown
Mental retardation  yes  no  unknown
GH treatment  yes  no  unknown
If yes age commenced  ..................years

Family:

Are there any more relatives with short stature or asymmetry  yes  no  unknown

if yes, who?  ................................

Laboratory findings:

Normal karyotype  yes  no  unknown
UPD Chromosome 7  yes  no  unknown
Growth hormone studies  yes  no  unknown
If yes was he/she GH deficient  yes  no
CLINICAL FEATURES:

In general:

Height ............... cm (age....... years)
Weight ............... kg (age....... years)
Head circumference ............... cm (age....... years)
Hemihypertrophy
  yes no unknown
  If yes which parts of body? ...........................................
Lack of subcutaneous fat with prominent blood vessels
  yes no unknown
Delayed bone age
  yes no unknown

Head/Neck
Facial asymmetry
  yes no unknown
Prominent forehead
  yes no unknown
Down turned mouth
  yes no unknown
Dental crowding
  yes no unknown
Micrognathia
  yes no unknown
Cleft palate
  yes no unknown
Other dysmorphism
  yes no unknown
  if yes, which? ...........................................

Hands
Fifth finger clinodactyly
  yes no unknown
Camptodactyly
  yes no unknown

Thorax:
Congenital cardiac malformations
  yes no unknown
  if yes, which ...........................................

Abdomen:
Cryptorchidism
  yes no unknown
Hypospadias
  yes no unknown
Uterine or ovarian malformation
  yes no unknown

Other features ...........................................

Thank you very much for your help.

Filled in by...................................................................................
Phone.....................................................Date...........................

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Division of Medical Genetics
University of Birmingham
Birmingham Women’s Hospital
Edgbaston
BIRMINGHAM B15 2BR
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<th>Genetic Abnormality/ Clinical Feature</th>
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<td>11</td>
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<td>Median 3.25</td>
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<td>Height SDS at diagnosis</td>
<td>Median -2.56</td>
<td>Median -2.71</td>
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<td>Median -2.32</td>
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<td>OFC SDS</td>
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<td>Max +0.15</td>
<td>Max +1.74</td>
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<td>Asymmetry (%)</td>
<td>37/125; 29.6%</td>
<td>17/21; 81.0%</td>
<td>1/10; 10%</td>
<td>19/94; 20.2%</td>
<td>&lt;0.001*</td>
</tr>
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<td></td>
<td>*</td>
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<tr>
<td>ART</td>
<td>7/106; 6.6%</td>
<td>1/21; 4.8%</td>
<td>0/9; 0%</td>
<td>6/76; 7.9%</td>
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<td>Methylation Index of H19 (23/25)</td>
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<td>Median 20.6%</td>
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<td>Min 8.4%</td>
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<td>Max 36.2%</td>
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**Supplementary Table 1: Comparison of auxological and clinical features in patients with and without genetic abnormalities identified**

OFC – occipito-frontal circumference; ART – assisted reproductive technology. Statistical tests used * One way ANOVA; **Fisher’s exact test *** Kruskal-Wallis test
Supplementary Table 2: Comparison of auxological and clinical features of patients with and without genetic abnormality using the proposed new scoring system

Statistical tests used * One way ANOVA; **Fisher’s exact test ***Kruskal-Wallis test

<table>
<thead>
<tr>
<th>Genetic Abnormality/ Clinical Feature</th>
<th>H19 Hypomethylation (n=15)</th>
<th>mUPD7 (n=7)</th>
<th>No Genetic Abnormality Identified (likely SRS) (n=9)</th>
<th>No Genetic Abnormality Identified (unlikely SRS) (n=37)</th>
<th>P value for comparison of H19 Hypomethylation, mUPD7 and No Genetic Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. likely to have SRS with new criteria</td>
<td>13/15 (86.7%)</td>
<td>5/7 (71.4%)</td>
<td>9/46 (19.6%)</td>
<td>&lt;0.001 **</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (yrs)</td>
<td>Median 2.33 Mean 3.73</td>
<td>Median 2.0 Mean 2.25</td>
<td>Median 1.25 Mean 2.07</td>
<td>Median 3.17 Mean 3.86</td>
<td>0.892***</td>
</tr>
<tr>
<td>Birthweight SDS</td>
<td>Median -2.86 Mean -2.92</td>
<td>Median -2.19 Mean -2.21</td>
<td>Median -2.6 Mean -2.74</td>
<td>Median -1.69 Mean -1.67</td>
<td>0.022 *</td>
</tr>
<tr>
<td>Height SDS at diagnosis</td>
<td>Median -2.95 Mean -3.05</td>
<td>Median -3.03 Mean -2.73</td>
<td>Median -3.72 Mean -3.66</td>
<td>Median -2.17 Mean -1.97</td>
<td>0.138 *</td>
</tr>
<tr>
<td>Asymmetry (no. and %)</td>
<td>13/15; 86.7%</td>
<td>1/7; 14.3%</td>
<td>3/9; 33.3%</td>
<td>5/37; 13.5%</td>
<td>&lt;0.001 **</td>
</tr>
<tr>
<td>OFC SDS</td>
<td>Median -0.48 Mean -0.84</td>
<td>Median -0.95 Mean -1.27</td>
<td>Median -0.95 Mean -0.89</td>
<td>Median -1.49 Mean -1.76</td>
<td>0.225 *</td>
</tr>
</tbody>
</table>