

## Diagnosis and management of Silver–Russell syndrome: first international consensus statement

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# Diagnosis and management of Silver–Russell syndrome: first international consensus statement

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## **ABSTRACT**

This Consensus Statement summarises recommendations for clinical diagnosis, investigation and management of patients with Silver–Russell syndrome (SRS), an imprinting disorder that causes prenatal and postnatal growth retardation. Considerable overlap exists between the care of individuals born small for gestational age and those with SRS. However, many specific management issues exist and evidence from controlled trials remains limited. SRS is primarily a clinical diagnosis; however, molecular testing enables confirmation of the clinical diagnosis and defines the subtype. A ‘normal’ result from a molecular test does not exclude the diagnosis of SRS. The management of children with SRS requires an experienced, multidisciplinary approach. Specific issues include growth failure, severe feeding difficulties, gastrointestinal problems, hypoglycaemia, body asymmetry, scoliosis, motor and speech delay and psychosocial challenges. An early emphasis on adequate nutritional status is important, with awareness that rapid postnatal weight gain might lead to subsequent increased risk of metabolic disorders. The benefits of treating patients with SRS with growth hormone include improved body composition, motor development and appetite, reduced risk of hypoglycaemia and increased height. Clinicians should be aware of possible premature adrenarche, fairly early and rapid central puberty and insulin resistance. Treatment with gonadotropin-releasing hormone analogues can delay progression of central puberty and preserve adult height potential. Long-term follow up is essential to determine the natural history and optimal management in adulthood.

Silver–Russell syndrome (SRS, OMIM #180860, also known as Russell–Silver syndrome, RSS) is a rare, but well-recognised, condition associated with prenatal and postnatal growth retardation. The syndrome was first described by Silver et al.<sup>1</sup> and Russell<sup>2</sup>, who independently described a subset of children with low birth weight, postnatal short stature, characteristic facial features and body asymmetry. Almost all patients with SRS are born small for gestational age (SGA; Box 1). The aetiology of intrauterine growth retardation (IUGR) and SGA is extremely heterogeneous. Children with SRS can be distinguished from those with idiopathic IUGR or SGA and postnatal growth failure by the presence of other characteristic features, including relativemacrocephaly (defined as a head circumference at birth  $\geq 1.5$  SDS above birth weight and/or length SDS), prominent forehead, asymmetry and feeding difficulties<sup>3-6</sup>.

The incidence of SRS generally ranges from 1:30,000 to 1:100,000 <sup>7</sup>. In 2015, a study in Estonia <sup>8</sup> estimated an incidence of 1:70,000; however, only molecularly confirmed cases were included, which could have resulted in underdiagnosis. Overall, SRS is probably more common than some previous estimates have suggested, but the exact incidence remains unknown.

An underlying molecular cause can currently be identified in around 60% of patients clinically diagnosed with SRS<sup>4</sup>. The most common underlying mechanisms are loss of methylation on chromosome 11p15 (11p15 LOM; seen in 30–60% of patients) and maternal uniparental disomy for chromosome 7 (upd(7)mat; seen in ~5–10% of patients) <sup>4,9,10</sup>. However, the molecular aetiology remains unknown in a substantial proportion of patients.

Although considerable overlap exists in the clinical care of individuals born SGA and those with SRS, many management issues are specific to SRS. These include notable feeding difficulties, severe postnatal growth failure with no catch-up, recurrent hypoglycaemia, premature adrenarche, fairly early and rapid central puberty, insulin resistance and body asymmetry. Identification of the molecular cause in many patients has also raised questions about the management in individual molecular subtypes of SRS. As evidence from controlled trials is limited, a consensus meeting was organised to develop guidelines for diagnosis and management of patients with SRS.

This Consensus Statement was produced on behalf of the COST action BM 1208 (European Network for Human Congenital Imprinting Disorders, <http://www.imprinting-disorders.eu>), European Society of Pediatric Endocrinology (ESPE), Pediatric Endocrine Society (PES), Asian Pacific Pediatric Endocrine Society (APPES) and Sociedad Latino-Americana de Endocrinología Pediátrica (SLEP).

## **[H1]**

### **Methods**

41 task force members from 16 countries, chosen for their publication record and expertise in SRS, collaborated to develop this consensus statement. They included paediatric endocrinologists, clinical geneticists, molecular geneticists, a gastroenterologist and five non-voting representatives from a parent support group. Participants included representatives nominated by the council and clinical practice committees from four international paediatric

endocrine societies. All participants signed a conflict of interest declaration, and the consensus was supported by academic funding, without pharmaceutical support. A Delphi-like consensus methodology was adopted<sup>11</sup>. A comprehensive literature search was conducted using PubMed and the search terms “Silver Russell syndrome” and “Russell Silver syndrome”. Additional relevant articles on SGA, differential diagnoses and growth hormone (GH) were also identified by PubMed searches when supplementary information was necessary. A comprehensive review of >600 articles formed the basis of discussion by three working groups. These groups focused on clinical diagnosis (working group 1: E.W., J.S., K.H.C., M.E., R.D.; P.G.M., T.O., E.S., M.T., I.K.T.), molecular testing (working group 2: F.B., J.B., K.G., M.K., D.M., G.M., S.R., Z.T., T.E., D.J.G.M) or clinical management (working group 3: K.L.-S., S.M.O’C., J.H.D.,A;C.; D.B., E.G., A.G., A.H.-K., A.A.J., A.L., M.M., K.M., I.O.P., G.B., M.D.H., I.N.), with 10, 10 and 16 members, respectively. Preparations for the consensus took place over 10 months, including two preparatory meetings and regular teleconference discussions between the working group members. At the final consensus meeting, propositions and recommendations were considered by participants and discussed in plenary sessions, enabling reformulation of the recommendations if necessary. Where published data were unavailable or insufficient, experts’ clinical experiences and opinions were considered. Finally, all experts voted on the recommendations of each working group using the following system.

<b>A</b>	Evidence or general agreement allow full agreement with the recommendation
<b>B</b>	Evidence or general agreement are in favour of the recommendation
<b>C</b>	Evidence or general agreement are weak for the recommendation
<b>D</b>	There is not enough evidence or general agreement to agree with the recommendation

Depending on the proportion of votes received, the strength of the recommendation was recorded as follows.

<b>+</b>	26–49% of the votes
<b>++</b>	50–69% of the votes

+++

≥70% of the votes

## **[H1] Clinical diagnosis**

SRS is currently a clinical diagnosis based on a combination of characteristic features. Molecular testing can confirm the diagnosis in around 60% of patients<sup>4</sup>. Molecular testing enables stratification of patients with SRS into subgroups, which can lead to more tailored management. However, molecular investigations are negative in a notable proportion of patients with characteristic clinical features of SRS. For these patients, an established clinical diagnosis enables access to appropriate support groups, treatment (including GH) and further research into the underlying incidence, natural history and aetiology of the SRS phenotype.

However, the diagnosis of SRS can be difficult, as the condition varies widely in severity among affected individuals and many of its features are nonspecific<sup>4-6</sup>. Until now, no consensus has been reached on the clinical definition of SRS. Historically, this lack of consensus has probably led to underdiagnosis and overdiagnosis, particularly by clinicians unfamiliar with SRS.

Several clinical scoring systems for SRS have been proposed, which reflects the challenge in reaching a confident diagnosis<sup>4,5,12-15</sup>. All the systems use similar criteria, but vary in the number and definition of diagnostic features required for diagnosis. The relative sensitivity and specificity of these scoring systems have been compared in patients with confirmed molecular diagnoses<sup>14,15</sup>.

## **[H2] Netchine–Harbison clinical scoring system**

The Netchine–Harbison clinical scoring system (NH-CSS; Table 1), which was proposed by Azzi and colleagues in 2015<sup>15</sup> is the only scoring system for the diagnosis of SRS that was developed using prospective data. Four of the six criteria are objective; protruding forehead and feeding difficulties remain subjective, but clear clinical definitions are given. Using the same cohort, the NH-CSS proved more sensitive (98%) than previous systems<sup>4,14</sup>. The NH-CSS also had the highest negative predictive value (89%), which gives a high degree of confidence that patients who have less than four of the six clinical criteria for diagnosis are truly unaffected by SRS. The system is easy to use in a busy clinical setting. The NH-CSS is

also flexible enough to use even if data are incomplete, which is important as the diagnosis is often made in infancy, before information about postnatal growth and BMI is available.

Similarly to other clinical scoring systems, the NH-CSS has a low specificity (36%)<sup>15</sup>, which could result in false positive results when the diagnosis is just based on clinical findings. Relative macrocephaly at birth (defined as a head circumference at birth  $\geq 1.5$  SDS above birth weight and/or length SDS). and protruding forehead are the two features in the NH-CSS that best distinguish SRS from non-SRS SGA (see supplemental table 1)<sup>4,15-18</sup>. To maintain confidence in the clinical diagnosis if all molecular testing is normal, we recommend that only patients scoring at least four of six criteria, including both prominent forehead and relative macrocephaly, should be diagnosed as 'clinical SRS' (previously known as 'idiopathic SRS'); see the flow diagram for investigation and diagnosis of SRS (FIG 1).

## **[H2] Diagnosis in late childhood or adulthood**

All scoring systems for SRS have been developed and validated in paediatric cohorts. However, an increasing number of adults with a historical diagnosis of SRS are being seen by clinicians, particularly regarding their concerns about passing the condition on to their offspring (**personal experience of working group 1 and 3**). In these patients, a clinical diagnosis is frequently challenged by lack of early growth data. An attempt should be made to obtain photographs of the individual aged 1–3 years, especially the face in profile, as well as measurements at birth and in the first 2 years. No current evidence exists to support an alternative approach to diagnosis in adults.

## **[H2] Additional clinical features**

In addition to the clinical features in the NH-CSS, several others are recognised in association with SRS, as shown in Table 2 and Supplementary Table 1 online. These characteristics are not specific to SRS, and might be present in children born SGA who do not have SRS, but at a lower frequency than in patients with SRS. However, a few features occur at a much higher rate in children with SRS than in those with SGA<sup>4,15,16</sup>. These features include low muscle mass, crowded or irregular teeth, micrognathia, down-turned mouth, clinodactyly and excessive sweating.

## **Recommendations**



- 1.1 SRS should remain primarily a clinical diagnosis. Molecular testing is useful for the confirmation and stratification of diagnosis in SRS. Lack of a positive molecular result does not exclude the diagnosis of SRS. (A+++)
- 1.2 The flow chart (Figure 1) based on the NH-CSS, should be adopted for the investigation and diagnosis of SRS. (A++)
- 1.3 In children <2 years, adolescents and adults, a reduced threshold for molecular testing might be required due to missing data. (A++)

## **[H1] Molecular diagnosis**

### **[H2] Investigation and diagnosis**

A positive molecular test result provides useful confirmation of the clinical diagnosis (FIG 1). This result also enables stratification into a specific molecular subgroup that, in turn, can help guide appropriate management. However, many patients are referred for molecular testing with few, or atypical, features of SRS, which leads to low diagnostic yields and incurs unnecessary expense<sup>19</sup>. We therefore recommend the use of the flow chart in Figure 1 to aid in the investigation and diagnosis of SRS.

Some patients, particularly those with upd(7)mat, have fewer typical clinical features of SRS than patients with 11p15 LOM<sup>4,5,13,16,20,21</sup>. In the cohort reported by Azzi and co-workers<sup>15</sup>, one of the nine patients scoring three of six criteria (and therefore predicted 'unlikely to have SRS') had upd(7)mat. The threshold recommended in FIG 1 for molecular testing ( $\geq 3$  of six criteria) is, therefore, lower than that needed for a clinical diagnosis of SRS ( $\geq 4$  of six criteria).

Conversely, in the same cohort, no positive molecular diagnoses were made in patients scoring less than three of six criteria<sup>15</sup>. Other studies have also excluded 11p15 LOM and upd(7)mat in patients born SGA with postnatal growth retardation but without additional features of SRS<sup>4,10,22</sup>. We, therefore, do not recommend testing for SRS in patients scoring less than three of six criteria. Of note, a small number of patients with body asymmetry have been reported to have 11p15 LOM without associated growth retardation, probably due to tissue mosaicism<sup>20,21,23</sup>. These patients would score less than three of six criteria, insufficient to justify a clinical diagnosis of SRS in these patients.

### **[H2] Chromosome 11p15**

Both SRS and the overgrowth condition Beckwith–Wiedemann syndrome are associated with molecular abnormalities of chromosome 11p15.5, which contains two imprinted domains (Figure 2). Imprinting of the telomeric domain, which is strongly implicated in SRS <sup>24,25</sup>, is controlled by the paternally-methylated imprinting control region H19/IGF2 IG-DMR (H19/IGF2 intergenic differentially-methylated region), previously known as IC1, ICR1 and H19 DMR). The centromeric domain contains the maternally-expressed growth repressor *CDKN1C*; the imprinting of this gene is controlled by the maternally-methylated imprinting control region KCNQ1OT1 TSS-DMR (previously known as IC2, ICR2, LIT1 or KvDMR1). FIG 3 summarises the more common molecular changes of chromosome 11p15 associated with SRS. Hypomethylation of the H19/IGF2 IG-DMR results in reduced paternal *IGF2* expression and increased maternal *H19* expression, which leads to growth restriction <sup>9</sup>. Numerous copy number variants (CNVs) involving the 11p15.5 region have been reported; the phenotype dependent on CNV size, location and parental origin <sup>24,26</sup> (supplementary table 2 online).

Molecular testing must robustly and accurately measure DNA methylation of CpG dinucleotides at H19/IGF2 IG-DMR <sup>27</sup>. Assays involve either bisulphite analysis <sup>28-30</sup> or enzymatic methods, such as methylation-specific multiplex ligation-mediated PCR amplification (MS-MLPA) or Southern blotting <sup>9,31</sup>. The most common test in diagnostic use is MS-MLPA, which is economical on DNA, cost-effective and enables parallel analysis of copy number and DNA methylation <sup>31,32</sup>. Hypomethylation of H19/IGF2 IG-DMR is frequently incomplete and low levels of hypomethylation might elude detection. Methylation patterns might vary between different tissues and cells (leucocytes, samples from a buccal swab and skin fibroblasts) <sup>21,33,34</sup> and could explain cases of a negative molecular diagnosis using a blood sample.

Although copy number change can be detected by MS-MLPA, additional array analysis might be effective in characterising the size and gene content of any CNV identified.

## [H2] Chromosome 7

Of individuals with SRS, ≤10% have upd(7)mat <sup>35,36</sup>. The SRS phenotype of upd(7)mat is thought to result from altered expression of an imprinted growth-regulatory gene (or genes) <sup>37</sup>. In addition, the duplication of pre-existing pathogenic variations by isodisomy can lead to the clinical expression of recessive disorders (such as cystic fibrosis) in upd(7)mat <sup>38-40</sup>

Candidate SRS regions have been suggested through identification of patients with segmental upd(7)mat or CNVs (supplementary table 3) and the primary candidate SRS genes on chromosome 7 are currently *GRB10* (7p12.1) and *MEST* (7q32)<sup>41-48</sup>.

Microsatellite analysis was the first diagnostic test for upd(7)mat<sup>35,36</sup>; however, this analysis cannot detect imprinting defects (epimutations) and requires DNA from at least one parent. DNA methylation analysis, including at least the imprinting control regions GRB10 alt-TSS DMR and MEST alt-TSS DMR, can identify upd(7)mat, epimutations, CNVs and segmental or whole-chromosome variations. DNA methylation analysis, for example by MS-MLPA, is economical on DNA, cost-effective and compatible with parallel analysis of 11p15<sup>30,49,50</sup>.

## **[H2] Additional testing**

If testing of both 11p15 and chromosome 7 is negative, additional molecular testing can be considered.

*[H3] CNVs.* Over 30 different pathogenic CNVs have been described in patients with suspected SRS<sup>15,51-53</sup>; a Leiden Open Variation Database (LOVD) entry for structural variations is currently in submission). Patients with these CNVs usually have more severe developmental delay and/or intellectual disability than is typically seen in SRS<sup>52,53</sup>. Some patients fulfil the NH-CSS for diagnosis; others either do not meet NH-CSS criteria, or insufficient data are given to use the criteria for their assessment. Although features of SRS can be present in individuals with a pathogenic CNV, clinical diagnosis of SRS is not helpful in these cases and management needs to be tailored specifically to the phenotypic consequences of the individual CNV.

While either array comparative genomic hybridization or single nucleotide polymorphism array can be used to detect CNVs, single nucleotide polymorphism array can also detect regions of segmental isodisomy<sup>54</sup>.

*[H3] Chromosome 14q32 abnormalities.* Molecular abnormalities at the paternally-methylated imprinted locus on chromosome 14q32 include upd(14)mat, paternal microdeletions and hypomethylation of the DLK1/GTL2 IG-DMR (also referred to as MEG3-DMR, 14q32 DMR or IG-DMR). These result in Temple syndrome, which has clinical overlap with SRS<sup>55,56</sup>, including being born SGA, postnatal growth retardation, hypotonia, [delay in the development of motor skills](#) and early puberty<sup>55</sup>.

In cohorts of patients with SRS, a small number of patients have been found to have Temple syndrome: 1 of 127 patients<sup>57</sup>, 2 of 85 patients<sup>56</sup> and 1 of 26 patients<sup>15</sup>. However, the true incidence of 14q32 abnormalities in patients meeting the NH-CSS criteria for diagnosis remains unknown.

[H3] *upd(20)mat and upd(16)mat*. Patients with both *upd(20)mat* and *upd(16)mat* have occasionally been detected among cohorts of patients investigated for prenatal and postnatal growth failure or SRS<sup>15,57,58</sup>. However, in a study published in 2015, none of eight patients with *upd(20)mat* had relative macrocephaly or asymmetry<sup>59</sup>, two important criteria of the NH-CSS, so that these patients might have eluded formal clinical diagnosis of SRS.

[H3] *CDKN1C and IGF2 mutations*. *CDKN1C* and *IGF2* are the coding genes on chromosome 11p15 that are responsible for the growth anomalies in SRS and Beckwith–Wiedemann syndrome. Maternally-transmitted SRS was described in a four-generation family with a *CDKN1C* gain-of-function mutation<sup>60</sup>, and paternally-transmitted SRS in a family with an *IGF2* loss-of-function mutation<sup>61</sup>. However, no additional mutations have been reported to date in sporadic or familial cases of SRS<sup>60,62,63</sup>. Sequence analysis of either gene may be considered, particularly in familial cases of SRS where the inheritance pattern is consistent but coding variants in these genes are rare<sup>60,62,63</sup>.

[H3] *Multi-locus imprinting disturbance*. A significant proportion (15–38%) of individuals with 11p15 LOM have multi-locus imprinting disturbance (MLID)<sup>33,57,64–66</sup>. High-density methylation arrays have revealed methylation changes involving both (maternally and paternally) imprinted and non-imprinted loci<sup>67,68</sup>. However, despite welcome advances in genome-wide methylation screening<sup>67,69,70</sup>, standardisation is required to ensure accurate description of MLID and comparison between cohorts.

The effect of MLID on clinical phenotype remains unclear. No difference in growth parameters was found at birth or at 2 years of age between patients with 11p15 LOM with and without MLID<sup>64</sup>. Although developmental delay and congenital anomalies were reported in patients with MLID, this finding might have been affected by ascertainment bias<sup>57</sup>.

In principle, MLID might be caused by *trans*-acting genetic mutations that affect the acquisition or maintenance of imprints, but in practice, very few have been identified<sup>71,72</sup>. Although yet to be identified, such mutations may also be present in individuals with MLID presenting as SRS.

Overall, the effect of MLID on clinical phenotype and its relevance for genetic counselling remain uncertain. Further information is needed before recommending testing for MLID outside the research setting.

## Recommendations

- 2.1 Molecular genetic testing should be performed by a health professional experienced in the field of imprinting disorders. Consistent and logical nomenclature should be adopted in publications and in test reporting. (A+++)
- 2.2 First-line molecular testing should include DNA methylation analysis of the H19/IGF2 IG-DMR and KCNQ1OT1 TSS DMR. (A+++)
- 2.3 First-line molecular testing should include analysis of DNA methylation at the GRB10 alt-TSS DMR and the MEST alt-TSS DMR. (A+++)
- 2.4 In case of a positive test result at either 11p15 or chromosome 7, discrimination between epimutation, CNV and upd should be considered to estimate recurrence risk. (A+++)
- 2.5 After exclusion of changes in 11p15 and chromosome 7, a clinical decision should be sought about the direction of further testing. Depending on the clinical features and family history of the patient, further testing might include CNV analysis and DNA methylation analysis at chromosome 14q32. Testing might also be considered for very rare molecular anomalies, including upd(20)mat, upd(16)mat and mutations in *CDKN1C* and *IGF2*, as well as analysis of further tissues to detect somatic mosaicism. (A++)
- 2.6 When an underlying pathogenic CNV is identified, the diagnosis should focus on this feature, even if features of SRS are present. (A+)

## [H2] (Epi)genotype–phenotype correlation

The frequency of individual features in specific SRS subgroups (11p15 LOM, upd(7)mat and clinical SRS) and patients with SGA but not SRS, where data are available, are shown in Supplementary Table 1 online. Genotype–phenotype studies of patients with SRS indicate considerable overlap in clinical phenotype between (epi)genotypes, and these are generally clinically indistinguishable. However, some features are more common in particular molecular subgroups<sup>4,13,15-17,20,73</sup>.

Patients with 11p15 LOM tend to have a lower birth length and weight, more frequent body asymmetry and more frequent congenital anomalies than patients with upd(7)mat. Neurocognitive problems are more frequent in patients with upd(7)mat than those with 11p15 LOM or clinical SRS<sup>15,16,20</sup> (see later section on neurocognitive problems).

Patients with 11p15 duplication encompassing H19/IGF2 IG-DMR and KCNQ1OT1 TSS-DMR have an SRS phenotype, but usually without asymmetry and with an increased likelihood of developmental delay (reviewed in <sup>53</sup>). Of 15 patients reported to have 11p15 duplication encompassing H19/IGF2 IG-DMR and KCNQ1OT1 TSS-DMR, four were noted to have hearing loss <sup>74</sup>.

## **[H2] Differential diagnosis**

The differential diagnosis of children with short stature of prenatal onset includes many syndromic diagnoses and chromosomal rearrangements (<sup>75</sup> and see Tables 3 and 4). Particular features should prompt consideration of diagnoses other than SRS. These include relative microcephaly (head circumference SD score (SDS) below height and weight SDS), notable global developmental delay or intellectual disability (without a related explanation such as documented hypoglycaemia), absence of severe feeding difficulties, and/or the presence of additional congenital anomalies, facial dysmorphism or other features atypical for SRS. Disproportionate short stature is suggestive of skeletal dysplasia. Photosensitive skin rash or recurrent bronchopulmonary infections should prompt investigation for chromosome breakage disorders. As SRS is generally sporadic, a family history of growth failure and/or consanguinity might suggest an alternative underlying diagnosis <sup>76</sup>. The clinical features of the most important and/or likely differential diagnoses are summarised in Tables 3 and 4.

A correct diagnosis can have extremely important implications for management. Response to GH treatment, if given, varies depending on the underlying syndromic diagnosis. For instance, GH treatment is contraindicated in patients with chromosome breakage disorders, such as Bloom syndrome, due to the associated risk of malignancy <sup>77</sup>. GH treatment in patients with SHORT syndrome has been reported to precipitate insulin resistance and subsequent type 2 diabetes mellitus <sup>78</sup>. Therefore, an incorrect diagnosis of SRS leading to the recommendation of GH treatment could have adverse consequences in these patients.

Three patients have been reported with clinical features of SRS but a molecular diagnosis of osteogenesis imperfecta, with a *COL1A1* mutation <sup>79,80</sup> **one with no history of fractures. Both SRS and OI can cause prenatal onset of growth failure, relative macrocephaly, large fontanelle, blue sclerae and body asymmetry. Both diagnoses should therefore be considered in patients with features overlapping both conditions.**

## **Recommendations**

- 3.1 An alternative syndromic diagnosis, and specific investigation for this diagnosis, should be particularly considered in patients with any of the following: additional features atypical for SRS, family history of growth failure and/or consanguinity. (A+++)
- 3.2 Patients with features of SRS overlapping with osteogenesis imperfecta should have a skeletal survey to look for additional evidence for osteogenesis imperfecta, with consideration of *COL1A1/2* gene testing. (A++)

## **[H1] Management**

SRS leads to a wide spectrum of abnormal physical characteristics and functional abnormalities. Multi-disciplinary follow-up and early, specific, intervention are necessary for optimum management of this group of patients.

### **Recommendation**

- 4.1 Patients with SRS should receive multi-disciplinary care in a centre of expertise in SRS in co-ordination with their local centre. The multi-disciplinary team should be composed of paediatric subspecialists such as an endocrinologist (co-ordinator), gastroenterologist, dietician, clinical geneticist, craniofacial team, orthopaedic surgeon, neurologist, speech and language therapist and psychologist. (A+++)

## **[H2] Early feeding and nutritional support**

The typical neonate with SRS has length SDS below weight SDS; but after birth, due to poor appetite, feeding difficulties and gastrointestinal problems, weight SDS drops below the length SDS <sup>4,17,73,81</sup>. Over time, progressive failure to thrive can result in a calorie-related length deficit <sup>4,15,82</sup>.

Feeding difficulties and failure to thrive are considerably more frequent in patients with SRS than in children with SGA but not SRS <sup>4,17</sup>. Failure to thrive in children with SRS is probably due to a combination of factors, including feeding difficulties (poor appetite, oromotor issues and the resulting low caloric intake) as well as functional and structural gastrointestinal problems. Digestive problems or malnutrition occur in over 70% of patients with SRS <sup>82</sup>, including severe gastrooesophageal reflux in 55%, which often results in persistent vomiting after the age of 1 year. Constipation is also common, particularly after age 2 <sup>82</sup>. Cyproheptadine used as an appetite stimulant improves weight gain in other paediatric

conditions<sup>83,84</sup>; however, specific studies of its use in SRS are needed before it can be recommended in these patients.

The main therapeutic goals for the first 2 years of life in patients with SRS are nutritional support, prevention of hypoglycaemia and recovery of any calorie-related length or height deficit, which should be addressed before initiation of GH therapy (see following sections on prevention of hypoglycaemia and GH therapy). However, careful monitoring is needed, especially during non-volitional feeding, because rapid catch-up weight gain in children born SGA has been associated with an increased risk of metabolic and cardiovascular disease in later life<sup>85</sup>.

Children with SRS have an abnormal body composition with low muscle mass, and are typically light for their length or height<sup>3,15,86,87</sup>. From our experience, the target for healthy nutritional status is narrow, and is dependent on individual innate muscle mass and even slight overnourishment (for example, weight >90% of ideal weight for length or height) can rapidly increase relative fat mass. Suggested targets for children aged 2–4 years preparing for GH therapy are: weight 75–85% of the 50<sup>th</sup> centile weight for length or height and/or BMI 12–14 kg/m<sup>2</sup>, using height measurements on the longer side if notable leg length discrepancy is found (see following section on GH therapy). A weight below 70% of the ideal weight for length or height compromises growth velocity, despite GH treatment. For children older than 4 years, the optimal target BMI will depend on their muscle mass. Two groups of patients are exceptions to this observation. Firstly, in patients with 11p15 LOM who have a very low muscle mass and considerable asymmetry, a lower BMI may be adequate (11–12 kg/m<sup>2</sup>). Secondly, in patients with upd(7)mat with near normal muscle mass, a higher BMI may be adequate (14–15 kg/m<sup>2</sup>).

## **Recommendations**

- 5.1 For nutritional goals in the first years of life, we recommend nutritional repletion\* with awareness of possible hazards of rapid postnatal catch-up leading to subsequent increased metabolic risk. (A+++)
- 5.2 Ask for and/or screen early for gut dysmotility (gastrooesophageal reflux, delayed gastric emptying and constipation) in all children. (A+++)
- 5.3 Diagnose and treat any oromotor and/or sensory issues that affect oral intake of food. (A+++)
- 5.4 In patients with severe feeding failure who are unresponsive to standard care, anatomical or functional disorders of the gastrointestinal tract, such as malrotation, should be excluded. (A+++)



- 5.5 Avoid enteral feeding by nasogastric or gastrostomy tube in a child capable of eating where there is adequate nutritional repletion. (A+++)
- 5.6 In cases of extreme feeding difficulties or gastroesophageal reflux, consider enteral feeding by gastrostomy tube (with or without fundoplication) or low-profile transgastric jejunostomy as a last resort to protect against hypoglycaemia and/or malnutrition. (A+++)
- 5.7 In the case of enteral feeding, prevent excessive weight gain in both volitionally and nonvolitionally fed children. (A++)

\*Low muscle mass makes typical BMI targets excessive in this population. Targets currently used in some centres include: Waterlow score 75–85%<sup>88</sup>; weight-for-length SDS -2 to -1 in first year of life; BMI target SDS between -2 to -1 after first year of life.

## **[H2] Prevention of hypoglycaemia**

Young children with SRS, particularly under age 5, have a disproportionately large brain-for-body size, low muscle and liver mass, and feeding difficulties, all of which increase their risk of fasting hypoglycaemia and its potential neurocognitive consequences. The incidence of hypoglycaemia in these children is approximately 27%<sup>20</sup>, with a high frequency of spontaneous, asymptomatic nocturnal hypoglycaemia<sup>89</sup>.

Monitoring of urinary ketones levels is usually effective in pre-empting hypoglycaemia related to fasting, activity or illness. This measurement can be used to determine the 'safe fasting time' for a child, which will change with age. Night time hypoglycaemia can be prevented by adding either high molecular weight glucose polymer (for infants under 10 months) or uncooked corn starch (for older infants and children particularly at risk) to the last evening feed. Dental hygiene is important as complex carbohydrates can promote cavities<sup>90</sup>. Severe, non-fasting and non-ketotic hypoglycaemia should always be identified and investigated further.

For episodes of preoperative fasting or febrile illness, intravenous glucose (10% dextrose) might be required. Children with SRS might need longer periods of gut rest than SGA children without SRS before oral or enteral feeding because of their gut dysmotility and intrinsic feeding defects. Before discharge, it is advisable to achieve an absence of ketonuria following at least 12 h of feeding, without intravenous support. When hypoglycaemia remains a problem, early GH therapy should be considered<sup>91,92</sup> (see following section on GH therapy).

## **Recommendations**

- 6.1 Monitoring for ketonuria at home is useful to determine which children need intervention for impending hypoglycaemia. (A++)\*
- 6.2 Develop a plan with the child's local paediatrician and emergency room for rapid admission and intravenous dextrose treatment when the child is ill. (A++)
- 6.3 Admit children with SRS to hospital early in the course of an illness associated with ketonuria or hypoglycaemia and do not discharge them until they are metabolically stable and can be adequately fed. (A++)
- 6.4 Glucagon is not recommended to correct hypoglycaemia, because of poor glycogen stores and limited ability for gluconeogenesis. (A+++)
- 6.5 Provide parents with an emergency guidance plan for illnesses. (A+++)
- 6.6 Teach parents how to recognize signs of hypoglycaemia, measure ketones, determine the 'safe fasting time' for their child, prevent hypoglycaemia using complex carbohydrates and avoid fasting outside a controlled environment. (A+++)
- 6.7 In severe cases of fasting hypoglycaemia, where other causes have been excluded and if other alternatives are ineffective, consider:
  - Early start of GH therapy to support glucose sources (increase in muscle mass and gluconeogenesis) (A++)
  - Placement of a gastrostomy tube or jejunostomy tube. (A++)

\*Children with a history of hypoglycaemia who do not have an appropriate ketone response will require formal fasting studies.

## **[H2] Surgery and anaesthesia**

Any surgery should be carefully planned due to the increased risk of fasting hypoglycaemia in patients with SRS<sup>93</sup>. As a result of their diminished weight-for-height ratio, low BMI and large head, young patients with SRS are at risk of hypothermia in a cool operating room<sup>94</sup>. Many children with SRS also have abnormal tooth distribution and a small mandible, which affects airway visualization and intubation<sup>95</sup>. Finally, young children with SRS who are malnourished might not heal well following surgery<sup>96</sup>.

## **Recommendations**

- 7.1 Review issues related to SRS with the anaesthetist and surgeon in advance. (A+++)
- 7.2 Consider admission the night before surgery for early administration of intravenous

- dextrose before surgery to avoid ketonuria and hypoglycaemia. (A++)
- 7.3 Schedule first on the surgical list where possible. (A++)
  - 7.4 Monitor blood glucose and administer intravenous dextrose during and after surgery. Do not discharge until ketonuria is absent and the child can sustain themselves on oral or enteral feeding. (A++)
  - 7.5 Follow the intraoperative temperature maintenance protocol appropriate for the patient's size, not age. (A+++)
  - 7.6 Delay elective surgery until the child is adequately nourished. (B+)
  - 7.7 Be aware of the high risk of malnutrition after surgery and follow appropriate guidelines. (A+)

## **[H2] Growth hormone treatment**

Data on adult height in untreated patients with SRS are limited; however, SRS is associated with a significant reduction in adult height (around -3 SDS; supplementary table 4 online and <sup>3</sup>). SRS is an indication for growth-promoting GH treatment under the SGA registered licence. It is worth noting that SRS was the only syndrome to be included in the clinical trials of GH in short children born SGA that led to the US FDA and [the European Medicines Agency \(EMA\)](#) SGA indications for GH therapy in 2001 and 2003, respectively <sup>97-101</sup>. Therefore, the results of these clinical trials validate the use of GH for SRS patients.

Overall, clinical trials of GH treatment in patients with SGA (in which patients with SRS were included) demonstrated a satisfactory growth response and an increase in predicted adult height of 7–11 cm at pharmacological doses of GH <sup>97-100,102</sup>. However, the response in patients with SRS was not investigated until a Dutch longitudinal study analysed the response to GH in 62 children with a clinical diagnosis of SRS using the NH-CSS compared with 227 short, non-syndromic children born SGA. Overall, the study showed a similar response to GH in patients with SRS compared with non-SRS children born SGA (mean total height gains of 1.30 SDS and 1.26 SDS, respectively); however, the final adult height attained in patients with SRS was lower (mean adult height -2.17 SDS versus -1.65 SDS for non-SRS children born SGA) <sup>87</sup>. Although the mean height at the start of GH treatment in patients with SRS was statistically significantly lower than in those without SRS, it was shown that patients with all SRS subtypes benefited from GH treatment, with a trend towards increased height gain in patients with upd(7)mat or clinical SRS. In addition, some interim <sup>102,100</sup> and long-term <sup>103,104</sup> studies have focused on the response to GH specifically in patients with SRS, albeit without a control group of non-SRS short children born SGA. Strong predictors of the short-term and long-term responses to GH were age and height SDS at the start of GH treatment (both inversely related) <sup>103-105</sup>. However, the study of Rakover et al <sup>105</sup> of

33 patients with SRS lacked data on adult height. Mean total height gain ranged from +1.2 to +1.4 SDS for GH doses of 35–70 µg/kg per day which is similar to that achieved in patients with non-syndromic SGA<sup>97,103,104</sup>. In 2007, an SGA consensus statement advocated early treatment with GH for children born SGA, including those with SRS, who had severe growth retardation (height SDS ≤2.5; age 2–4 years; dose 35–70 µg/kg per day<sup>106</sup>).

Additional potential benefits of GH treatment are increases in appetite, lean body mass and muscle power, which can result in improved mobility<sup>86,107</sup>. In patients with Prader–Willi syndrome, another imprinting disorder, GH treatment was started in infancy and resulted in increased lean body mass and motor development, as well as decreased fat mass<sup>108,109</sup>; consequently GH treatment is now recommended from infancy in this condition. SRS children under age 2 typically present with low muscle mass and hypotonia, like Prader-Willi syndrome patients<sup>15</sup> and could also benefit from early GH treatment. Further studies are necessary to investigate this in patients with SRS.

Classic GH deficiency is neither a common nor a relevant cause of short stature in SRS, nor is it predictive of the response to GH treatment in children born SGA<sup>103,105,110</sup>. Furthermore, given the risk of hypoglycaemia associated with fasting required for GH testing, testing children with SRS might carry added risks.

For most children with SRS, an increase in height velocity of ≥3 cm per year is the lower limit of an effective response range<sup>106</sup>. The growth response depends on the patient's age, GH dose, height deficit, rate of weight gain and confounding problems such as intercurrent illness and scoliosis.

Levels of insulin-like growth factor 1 (IGF-1) in response to GH treatment in patients with SRS are difficult to interpret. Children with 11p15 LOM have significantly higher IGF-1 levels than children with upd(7)mat and other children born SGA, which suggest an element of IGF-1 resistance in patients with 11p15 LOM<sup>73,111</sup>. Basal serum levels of IGF-1 in the upper quartile of the normal age-related range or higher can be expected in children with SRS, especially those with 11p15 LOM<sup>73</sup>. In children with 11p15 LOM, serum levels of insulin-like growth factor-binding protein 3 (IGFBP-3) are also elevated<sup>111</sup>. IGF-1 levels might rise significantly above the reference range in children with SRS on standard doses of GH<sup>87,111</sup>. Further studies are needed to understand how best to use IGF-1 and IGFBP-3 serum levels to monitor GH dose in children with SRS and IGF-1 resistance.

Comprehensive reviews on the use of GH in children born SGA have concluded that GH treatment seems to be safe and effective<sup>112</sup>. Adverse effects due to GH treatment are no more frequent in children with SRS than in those with non-syndromic SGA<sup>87,113</sup> and no specific precautions are advised.

## Recommendations

- 8.1 Defer GH treatment until caloric deficits are addressed. (A++)
- 8.2 Avoid GH stimulation testing. (A++)
- 8.3 Goals of GH treatment are to improve body composition (especially lean body mass), psychomotor development and appetite, to reduce the risk of hypoglycaemia, and to optimise linear growth. (A++)
- 8.4 Treat with GH as soon as possible; starting at age 2–4 years is adequate for the majority of patients; however, due consideration should be given to the exceptions listed below\*. (A++)
- 8.5 Start GH at a dose of approximately 35 µg/kg per day. Use the lowest dose that results in catch-up growth. (A+++)
- 8.6 Terminate GH therapy when height velocity is <2 cm per year over a 6-month period and bone age >14 years (female patients) or >17 years (male patients). (A++)
- 8.7 If response to GH is poor, re-evaluate the underlying diagnosis, GH dose, IGF-1 response, adherence to therapy and other confounding systemic problems. (A+++)
- 8.8 Monitor circulating levels of IGF-1 and IGFBP-3 at least yearly during GH treatment. (A++)

\*GH treatment does not have a specific indication for SRS and is prescribed under the SGA indication (height SDS <-2.5; age >2–4 years; dose 35–70 µg/kg per day)<sup>106</sup>. Exemptions from the current SGA licensed indication used in some centres include starting GH therapy below the age of 2 years in case of: severe fasting hypoglycaemia; severe malnutrition, despite nutritional support, which will lead to gastrostomy if no improvement is seen; and severe muscular hypotonia

## [H2] Bone age advancement and puberty

The published literature on the natural history of bone age progression in patients with SRS is limited. Early bone age delay is followed by rapid advancement typically around 8–9 years<sup>3,81,113</sup> but sometimes much younger especially in non-volitionally overfed children. Onset of puberty is usually within the normal range (8 to 13 years in girls and 9 to 14 years in boys)<sup>114</sup> but at the younger end of the spectrum<sup>3,73,87,115</sup>. Adrenarche can be early and aggressive in comparison with children born with non-SRS SGA, particularly in those with 11p15 LOM<sup>116</sup>.

Our experience is that in patients with SRS and early adrenarche, the onset of central puberty might be earlier and the tempo faster than expected. In the last decades, population studies analysing the timing of normal puberty observed a mean age of puberty onset of 9.7 to 10 years in girls <sup>114</sup>. As a group, girls with SRS seem to start central puberty at a mean age of 9.1 years (I. Netchine, unpublished work). This early puberty further accelerates bone age maturation, which leads to an attenuated pubertal growth spurt and compromised adult height. Children with upd(7)mat are more likely to progress to central puberty even younger (mean starting age 8.5 years in girls and 9.5 years in boys) (I. Netchine, unpublished work). A rapid increase in BMI might also exacerbate the tendency to early adrenarche and central puberty <sup>117-119</sup>.

The window for effective GH treatment seems to be shorter in SRS patients than non-SRS SGA patients. In a recent study comparing a cohort of patients with SRS and a cohort of patients born SGA non-SRS, puberty started significantly earlier in the former (at 10.2 years versus 11.2 years in girls with SRS and non-SRS SGA, respectively, and at 11.4 years versus 12.0 years in boys with SRS and non-SRS SGA, respectively) <sup>87</sup>. Furthermore, a steeper decline in height SDS from the onset of puberty until adult height was seen, which contributed to a lower adult height and a larger distance to target height than in non-SRS SGA patients. However, in 17 patients with SRS in this study, puberty was postponed for two years with gonadotropin-releasing hormone analogue (GnRHa) due to a low predicted adult height. [The effect](#) of GnRHa on final height has been analysed previously by the same authors in a cohort of SGA patients, including SRS patients<sup>120,121</sup>. This analysis suggested that the combination of GnRHa, started at the initiation of puberty and continued for at least 2 years, along with GH treatment, improves adult height in patients born SGA with a poor adult height prognosis. A retrospective study of GnRHa treatment specifically in patients with SRS did not detect an effect of GnRHa on adult height, but this therapy was used in only 16 of 37 patients and was not standardised <sup>104</sup>. Further studies are required to specifically look at its effects in patients with SRS.

Aromatase catalyses the rate-limiting step in the conversion of androstenedione to oestrone and testosterone to oestradiol. In patients with adrenarche with advancing bone age, but without central puberty, third-generation aromatase inhibitors (such as anastrozole) might be helpful in preventing rapid bone maturation, but are currently not indicated for growth disorders <sup>122</sup>. An 18-month double-blind clinical trial is currently underway to study the efficacy and tolerance of treatment with anastrozole to slow bone maturation related to pathological adrenarche in patients with SRS and Prader–Willi syndrome <sup>123</sup>.

## Recommendations

- 9.1 Monitor for signs of premature adrenarche, relatively early and accelerated central puberty, and insulin resistance. (A+++)
- 9.2 Monitor and anticipate acceleration of bone age especially from mid childhood. (A++)
- 9.3 Consider personalised treatment with GnRHa for at least 2 years in children with evidence of central puberty (starting no later than 12 years in girls and 13 years in boys) to preserve adult height potential. (A++)

### [H2] Long-term metabolic complications

Individuals born with a low birth weight are at increased risk of adult health problems including coronary heart disease<sup>124-126</sup>, hypertension, dyslipidaemia, insulin resistance and obesity (the metabolic syndrome)<sup>127-130</sup>. Studies of children born SGA indicate that those who have rapid or disproportionate catch-up in weight are at particularly high risk<sup>119,131,132</sup>.

Insulin resistance in young, pre-pubertal, children with SRS can be atypical and difficult to detect in the fasting state; however, impaired glucose tolerance can be confirmed on formal oral glucose tolerance testing<sup>133,134</sup>. Insulin resistance becomes more classic in the pubertal or post-pubertal age groups with elevation in fasting levels of glucose and insulin, and possibly the development of type 2 diabetes mellitus<sup>135,136</sup>.

Overall, GH therapy seems to have positive metabolic effects in children born SGA<sup>137</sup>, although specific data on such effects in SRS are lacking. Many studies of long-term GH treatment in children born SGA have shown positive outcomes, including increased lean body mass, reduced fat mass, decreased blood pressure and improvement in lipid profile<sup>107,120,137,138</sup>, which might last after discontinuation of therapy<sup>138,139</sup>.

In a study of 110 children born SGA treated with GH, those with the highest baseline levels of IGF-1 were the least insulin sensitive. Gains in height and IGF-1 response were positively associated with insulin secretion<sup>140</sup>. In SRS, children with 11p15 LOM seem to be at a higher metabolic risk due to poor muscle mass and raised levels of IGF-1 than children who have upd(7)mat and other children born SGA<sup>15,16,73,87</sup>. Further research is, therefore, required on the long-term effects of GH therapy on body composition and metabolic parameters in SRS and its various genotypes.

## Recommendations

- 10.1 Avoid excessive or rapid weight gain to prevent increased insulin resistance, which is associated with early and rapidly advancing adrenarche, early central puberty, and, in girls, a future risk of developing polycystic ovary syndrome. (A++)
- 10.2 Raise awareness among gastroenterologists, dieticians, neonatologists, paediatricians and primary health-care providers of the importance of not overfeeding this group of children. (A+++)
- 10.3 Advise parents, grandparents and care-givers about the risk of insulin resistance associated with intrauterine growth retardation and overfeeding. (A+++)
- 10.4 Screen for physical and biochemical indicators of insulin resistance during GH treatment, especially in children with low muscle mass and high baseline levels of IGF-1. (A+)
- 10.5 In patients with clinical signs of insulin resistance, consider formal assessment of insulin sensitivity with a 2-h oral glucose tolerance test including insulin and C-peptide levels (A++)
- 10.6 Advocate a healthy diet and lifestyle in older children and young adults with particular emphasis on protein calorie balance and regular exercise to avoid disproportionate weight gain, particularly after discontinuation of GH treatment. (A+++)

## **[H2] Neurocognitive problems**

Motor and speech delay are common in children with SRS<sup>4,16-18,20</sup> (Table 2). Motor delay might be related to reduced muscle bulk and fairly large head size. Verbal dyspraxia and more global developmental delay or learning difficulties, usually mild, have been described in some children with SRS, particularly those with upd(7)mat<sup>12,15,16,20,141</sup>. Autistic spectrum disorder has also been reported more frequently in this subgroup than in the other subgroups of SRS<sup>15</sup>. Myoclonus-dystonia in patients with upd(7)mat is probably associated with altered expression of the paternally-expressed *SGCE* on chromosome 7q21<sup>20,40,142,143</sup>.

## **Recommendations**

- 11.1 Refer infants and children with SRS for a developmental assessment when necessary to ensure appropriate intervention as early as possible. (A+++)
- 11.2 In patients with upd(7)mat, check for symptoms of myoclonus-dystonia at each clinical appointment and refer early to a paediatric neurologist if required. (A+++)
- 11.3 Monitor children with upd(7)mat for signs of verbal or oromotor dyspraxia and/or signs of autistic spectrum disorders. (A+++)
- 11.4 Inform parents about increased risk of speech, oromotor and learning disabilities (especially in those with upd(7)mat). (A+++)



11.5 Follow school-age children for any learning difficulties, psychosocial challenges and/or cognitive delay, to enable appropriate intervention. (A+++)

## **[H2] Orthopaedic problems**

Orthopaedic problems seen in association with SRS include limb or body asymmetry, scoliosis, hip dysplasia and hand and/or foot anomalies (table 2).

Limb asymmetry can affect the arms, legs or both. In seven patients with clinically-diagnosed SRS, limb length discrepancy was not significantly affected by GH treatment<sup>144</sup>. Limb lengthening surgery performed to equalize limb lengths in patients with SRS has shown positive results<sup>145</sup>.

Scoliosis has been reported in 9–36% of individuals with SRS<sup>20,146,147</sup>. The causal relationship to leg length asymmetry is not clear<sup>146,147</sup>. Associated back pain has been reported inconsistently<sup>5,146</sup>. GH therapy might be associated with worsening of existing scoliosis; however, causality has not been established<sup>148</sup>. A study in a large group of children with Prader–Willi syndrome (another imprinting disorder, whose clinical features include like SRS growth failure, infant hypotonia, early feeding difficulties and an increased risk of scoliosis) has clearly shown that GH therapy does not influence onset and progression of scoliosis<sup>149</sup> but specific studies are required to determine whether GH therapy modifies scoliosis risk in SRS.

## **Recommendations**

12.1 Where necessary, refer to a paediatric orthopaedic surgeon for collaborative management of body asymmetry, limb length discrepancy and scoliosis. (A+++)

12.2 Routinely examine all patients with SRS for scoliosis. (A+++)

12.3 Before initiation of GH therapy, refer patients with scoliosis to the orthopaedic team and monitor while receiving GH. (A+++)

12.4 Evaluate leg length asymmetry regularly and consider orthopaedic management if necessary. (A++)

## **[H2] Maxillofacial abnormalities**

SRS is characterized by craniofacial disproportion, which results in a triangular-shaped face<sup>95</sup>. Delayed dental eruption, microdontia, absence of secondary teeth and blunted condyles have all been reported in patients with SRS<sup>150,151</sup>.

In our experience, the upper jaw arch is frequently narrow and crowded, but in the lower arch crowding might be severe, with displacement of lower incisors into a lingual position. Micrognathia is frequent, with lack of mandibular growth, which results in a small, pointed chin and an overbite. Children with notable facial asymmetry might have a crossbite that impairs normal chewing. Velopharyngeal insufficiency with or without a submucous cleft is quite common in patients with 11p15 LOM SRS <sup>20</sup>. Otitis media is frequent in young children with SRS <sup>7</sup> and seems to be improved by orthodontic treatment <sup>152</sup>.

Orthodontic intervention in children with SRS can help normalize oropharyngeal function and facial appearance. An experienced craniofacial team, including orthodontists, plastic surgeons and ear, nose and throat surgeons is ideal. Multiple orthodontic techniques have been used successfully <sup>153</sup>. Currently, rapid palatal expansion is the most effective technique to change the shape of the face <sup>154</sup>.

Many patients with SRS report excessive daytime fatigue, snoring and/or disrupted sleep. However, data are very limited regarding sleep problems, including sleep disordered breathing, in association with SRS. A retrospective study identified mild sleep disordered breathing in 74% of patients with SRS, (not exacerbated with GH therapy) <sup>155</sup>. Further studies are necessary.

## **Recommendations**

- 13.1 Develop a referral relationship with a maxillofacial team or orthodontist who has experience caring for patients with SRS. (A++)
- 13.2 Refer patients to the maxillofacial team for assessment after eruption of primary dentition when necessary. (A++)
- 13.3 Encourage early orthodontic intervention and compliance with follow-up. (A+)
- 13.4 Screen for symptoms of sleep disordered breathing (such as snoring, apnoeas, excessive daytime fatigue, disrupted sleep and agitation). (A++)
- 13.5 Refer patients with suspected sleep disordered breathing to the appropriate specialist for evaluation of obstructive sleep apnoea. (A++)

## **[H2] Other congenital anomalies**

Congenital anomalies have been described in a minority of patients with SRS, particularly those with 11p15 LOM (supplementary table 1 online). Genital abnormalities, including cryptorchidism and hypospadias, occur frequently in boys<sup>16,20</sup>. Mayer–Rokitansky–Kuster–Hauser syndrome in female patients is characterised by congenital hypoplasia or aplasia of the uterus and upper part of the vagina<sup>16,18,156,157</sup>. Structural renal anomalies<sup>18,20</sup> and congenital heart defects<sup>4,18,20,158</sup> have also been reported.

## **Recommendations**

- 14.1 Investigate genital abnormalities in boys. (A+++)
- 14.2 Investigate girls with primary amenorrhoea for Mayer–Rokitansky–Kuster–Hauser syndrome. (A+++)

## **[H2] Adulthood**

Very little information exists in the literature regarding the long-term natural history of SRS. The majority of individuals with SRS are not routinely followed up, and the small numbers of adults reported have few medical problems. However, it is well recognised that being SGA at birth with accelerated gain in weight for length, particularly during early life, increases the risk of metabolic problems in adulthood<sup>119,132,159</sup> (see previous discussion). Medical problems reported in **adults** with 11p15 LOM include hypertension, dilated cardiomyopathy, type 2 diabetes mellitus, hypercholesterolaemia, fatty liver infiltration, elevated glucose levels and raised HbA<sub>1c</sub><sup>135,136,160</sup> but these reports might not be representative of the population as a whole.

## **Recommendations**

- 15.1 Consider medical follow-up of adolescents and young adult patients with SRS or develop collaboration with a general or internal medicine team for follow-up. (A+++)
- 15.2 Avoid losing contact with adult patients with SRS, to facilitate their participation in and potential benefit from future clinical research. (A+++)

## **[H1] Genetic counselling**

Accurate genetic counselling depends on the underlying molecular cause. 11p15 LOM is associated with a low recurrence and offspring risk, although empirical figures are not

available. Only three sibships with 11p15 LOM are reported in the literature <sup>13,20</sup>, and the underlying mechanism is unknown in all three.

The potential for a familial *trans*-acting gene mutation suggests that the recurrence risk in patients with SRS and MLID; may potentially be higher than other SRS cases; however, evidence to support this supposition does not yet exist.

Rare familial cases of SRS have been reported with underlying mechanisms including: maternally inherited 11p15 duplication <sup>24,26</sup> (supplementary table 2 online); maternally inherited *CDKN1C* gain-of-function mutations <sup>60</sup>; and paternally inherited *IGF2* loss-of-function mutations <sup>61</sup>. In these families, the risk of recurrence might be as high as 50%. Investigation for underlying CNVs in patients with 11p15 LOM is, therefore, important. upd(7)mat is associated with a low recurrence and offspring risk (if the karyotype of the patient is normal)<sup>50</sup>. Data are limited regarding the risk of parents of children with clinically diagnosed SRS having another child with SRS; however, the overall risk is probably low. Similarly, the offspring risk for individuals with clinically diagnosed SRS is likely to be low.

## **Recommendation**

16.1 Genetic counselling should be performed by a health professional experienced in the field of imprinting disorders. As the recurrence risk associated with CNVs is dependent on their size, location and parental origin, these should be taken into consideration during counselling for the family. (A+++)

## **[H1] Conclusions**

Children with SRS and their families face challenges from birth to adulthood. In addition to the problems associated with being born SGA, clinicians treating patients with SRS need to be aware of syndrome-specific management issues. These include substantial feeding difficulties, severe postnatal growth failure with no catch-up, recurrent hypoglycaemia, premature adrenarche, fairly early and rapid puberty, insulin resistance, body asymmetry, orthodontic issues, sleep disordered breathing and the potential for other congenital anomalies.

Presented here are the first international consensus guidelines for the diagnosis and management of SRS, based on published evidence and expert opinion. A summary of all 72 recommendations, including a flow chart for the investigation and diagnosis of SRS, is available as supplementary information online.

These management recommendations apply to all patients clinically diagnosed with SRS, both with and without a molecularly confirmed diagnosis. However, identification of the underlying molecular subtype can guide treatment with regard to specific risk factors. Management should involve a multi-disciplinary approach and close parental guidance. A practical checklist for use in routine clinical follow up of these patients is proposed in Table 5.

As there are limited published data specific to SRS, many questions remain (Box 2). International collaboration and further research is urgently needed to better inform the investigation and management of patients with SRS in the future.

### **Competing interests**

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## Further information

AFIF-SSR-PAG: <http://www.silver-russell.fr>

AISRS: <http://www.aisrs.it/>

ALICE ABSL: <http://www.alice.be/>

BKMF: <http://bkmf.de/en/>

CGF: <http://www.childgrowthfoundation.org>

MAGIC Foundation: <https://www.magicfoundation.org>

European Network for Human Congenital Imprinting Disorders: <http://www.imprinting-disorders.eu>

## **Box 1: Definitions**

### **Small for gestational age (SGA)**

Weight and/or length less than -2 SDS for gestational age at birth, based on accurate anthropometry at birth (including weight, length and head circumference) and reference data from a relevant population <sup>106</sup>.

### **Intrauterine growth retardation (IUGR)**

Also known as intrauterine growth restriction, this diagnosis is based on at least two ultrasonography measurements at least 2 weeks apart, with fetal weight below 10<sup>th</sup> percentile for gestational age. IUGR might or might not result in a baby born SGA <sup>161</sup>.

### **Silver–Russell syndrome (SRS)**

A distinct syndromic growth disorder in which prenatal and postnatal growth failure are associated with other characteristic features, including relative macrocephaly at birth, protruding forehead in early life, body asymmetry and substantial feeding difficulties. Almost all children with SRS are born SGA. Postnatal catch-up growth is not seen in the vast majority of children with SRS.

## Box 2: Future research directions for SRS

### Clinical

- Incidence and/or prevalence
- Frequency of associated features (for example, scoliosis, sleep disordered breathing, developmental delay, behavioural issues)
- Frequency and associated phenotype of molecular subtypes
  - 11p15, upd(7)mat
  - MLID
  - 14q32 abnormalities, UPD(20)mat, UPD(16)mat
- Clinical overlap with other imprinting disorders

### Molecular

- Development of testing methodology
- Identification of additional molecular causes in patients with clinically diagnosed SRS
- Prenatal testing: methodology, ethical implications

### Management

- Use of cyproheptadine as appetite stimulant
- Optimal timing of GH use
- Interpretation of IGF-1 levels
- Role of aromatase inhibitors to control bone age advancement
- GnRH analogue inhibition of central puberty
- Control of postnatal weight gain
- Limb lengthening

### SRS in adulthood

- Natural history, including risk of metabolic syndrome
- Quality of life indicators
- Reproductive issues (ART, recurrence risk associated with MLID)

Abbreviations: ART, assisted reproductive technology; GH, growth hormone; GnRH, gonadotropin-releasing hormone; IGF1, insulin-like growth factor 1; MLID, multi-locus imprinting disturbance



**Table 1: Netchine-Harbison clinical scoring system**

Clinical criteria	Definition
SGA (birth weight and/or birth length)	$\leq -2$ SDS for gestational age
Postnatal growth failure	Height at 24±1 months $\leq -2$ SDS or height $\leq -2$ SDS below mid-parental target height
Relative macrocephaly at birth	Head circumference at birth $\geq 1.5$ SDS above birth weight and/or length SDS
Protruding forehead*	Forehead projecting beyond the facial plane on a side view as a toddler (1–3 years)
Body asymmetry	LLD of $\geq 0.5$ cm or arm asymmetry or LLD $< 0.5$ cm with at least two other asymmetrical body parts (one non-face)
Feeding difficulties and/or low BMI	BMI $\leq -2$ SDS at 24 months or current use of a feeding tube or cyproheptadine for appetite stimulation

Clinical diagnosis is considered if patient scores at least four out of six from these criteria. **If all molecular test are normal and differential diagnoses have been ruled out, patients scoring at least four of six criteria, including both prominent forehead and relative macrocephaly should be diagnosed as clinical SRS.** \*Protruding forehead is equivalent to 'prominent forehead'<sup>162</sup>. Abbreviations: LLD, leg length discrepancy; SDS, SD score; SGA, small for gestational age.

**Table 2: Additional clinical features of SRS**

<b>Clinical feature</b>	<b>Frequency % (total no. patients)</b>	<b>Reference</b>
Triangular face	94 (164)	16-18
5th finger clinodactyly	75 (319)	4,15-18,20
Shoulder dimples	66 (61)	15
Micrognathia	62 (115)	16,18,20
Low muscle mass	56 (103)	15,16
Excessive sweating	54 (106)	16,20
Low-set and/or posteriorly rotated ears	49 (266)	15-17,20
Down-turned mouth	48 (176)	15,16,18,20
High pitched or squeaky voice	45 (26)	16
Prominent heels	44 (61)	15
Delayed closure of fontanelle	43 (47)	18,20
Male genital abnormalities	40 (85)	15,16,18,20
Speech delay	40 (189)	16,17,20
Irregular or crowded teeth	37 (195)	16-18,20
Motor delay	37 (254)	4,16-18,20
Syndactyly of toes	30 (264)	15-17,20
Hypoglycaemia	22 (103)	4,20
Scoliosis and/or kyphosis	18 (227)	16,20,147

**Table 3- Differential diagnosis of SRS in patients with relative microcephaly**

Feature	Syndrome (OMIM number)					
	<b>Bloom syndrome (#210900)</b>	<b>Nijmegen breakage syndrome (#251260)</b>	<b>MOPD II (#210720)</b>	<b>Meier–Gorlin syndrome (#224690, #61380, #613803, #613804, #613805)</b>	<b>IGF1R mutation or deletion (#147370, #612626)</b>	<b>IGF1 mutation (#147440)</b>
Birth weight SDS	Mean -4.6	Mean -1.6	Mean -3.9	Mean -3.8	-1.5 to -4.9	-2.5 to -4.5
Adult height range (cm)	Male patients: 128-164 Female patients: 115-160	Male patients: 161-172 Female patients: 150-165	Mean 96	Male patients: 136-157 Female patients: 127-150	IGF1R mutation: 1 female patient - 140 2 male patients - 133 and 170	1 male patient: 117
Cognitive function	Usually normal	At pre-school age IQ normal or borderline; progressive deterioration to moderate mental retardation	Variable: none / mild ID (majority), occasionally severe ID	90% normal IQ, occasionally mild or moderate ID	Variable: normal (~50%), mild ID (25%), moderate or severe ID (25%)	Severe ID
Facial features	Narrow face with underdeveloped malar area and mandible, fairly prominent nose, sun sensitive telangiectasia in malar distribution	Receding forehead, prominent mid-face, small mandible, up-slanting palpebral fissures, long nose and philtrum, large ears	Prominent, long, broad nose with hypoplastic tip, low insertion of columella, prominent eyes in infancy, micrognathia	Microtia, narrow, beaked nose with low insertion of columella, small mouth, retrognathia	IGF1R mutation: often normal; triangular face, micrognathia.  15q26-qter deletion: micrognathia	No consistent features reported
Other features	Patchy areas of hypopigmented and hyperpigmented skin, feeding difficulties, high tumour risk (44% develop cancer by age 25), hypogonadism, type 2 diabetes mellitus, immunodeficiency, chromosomal instability with increased frequency of sister chromatid exchange	Severe, progressive microcephaly, immunodeficiency, cancer predisposition, chromosomal instability and rearrangements, café au lait spots, premature ovarian failure	Mean OFC at birth -4.6 SDS, progressive microcephaly, mesomelic limb shortening, progressive metaphyseal bone dysplasia, hip dysplasia, acanthosis nigricans, insulin resistance, cryptorchidism, intracranial aneurysm, dental anomalies, squeaky voice	Patellar hypoplasia, pulmonary emphysema, cryptorchidism, mammary hypoplasia (post-pubertal 100%), hypoplastic labiae	IGF1R mutation: pectus excavatum, 5 <sup>th</sup> finger clinodactyly, short fingers  15q26-qter deletion: fifth finger clinodactyly, short fingers, talipes, congenital heart disease, renal anomalies	Sensorineural deafness
Inheritance or molecular abnormality	Autosomal recessive  Mutations in <i>RECQL3</i>  High prevalence in Ashkenazi Jewish population	Autosomal recessive  Mutations in <i>NBN</i>  High prevalence in Slavic population	Autosomal recessive  Mutations in <i>PCNT</i>	Autosomal recessive  Mutations in <i>ORC1, ORC4, ORC6, CDT1, CDC6</i>	IGF1R mutation: majority autosomal dominant; compound heterozygosity reported in 2 cases	Autosomal recessive  Mutations in <i>IGF1</i>

Abbreviations: ID, intellectual disability; MOPD II, microcephalic osteodysplastic primordial dwarfism type II; OFC, occipito-frontal circumference.



**Table 4: Differential diagnosis of SRS in patients with relative normocephaly or macrocephaly**

Feature	Syndrome (#OMIM number)				
	<b>3-M syndrome (#273750)</b>	<b>Mulibrey nanism (#253250)</b>	<b>SHORT syndrome (#269880)</b>	<b>Floating harbour syndrome (#136140)</b>	<b>IMAGe syndrome (#614732)</b>
Birth weight SDS	Mean: -3.1	Mean: -2.8 (range -4.0 to 0.5)	Mean: -3.3	Mean: -2.5	-2.0 to -4.0
Adult height range (cm)	115-150	136-150	Mean 154	Female patients: 98-156 Male patients: 106-164	1 male patient: 160 1 female patient: 143
Cognitive function	Normal	Mild motor and speech delay only	Normal	Delayed speech. Intellect variable: normal to significant ID	Normal or mild ID
Facial features	Anteverted nares, full lips, mid-face hypoplasia, long philtrum	Triangular face, frontal bossing	Micrognathia, high broad forehead, triangular-shaped face, deep-set eyes, prominent nose, low-set posteriorly rotated ears, hypoplastic nasal alae, facial lipodystrophy, thin hair	Triangular face, deep-set eyes, long eyelashes, bulbous nose, wide columella, short philtrum, thin lips	Frontal bossing, low-set ears, flat nasal bridge, short nose
Other features	Prominent heels (also in upd(7)mat), short broad neck, pectus deformity, short thorax, winged scapulae, hyperlordosis, hip dysplasia, subtle radiographic changes (slender long bones, tall vertebral bodies)	Hepatomegaly, yellow spots on retina, progressive restrictive perimyocarditis, insulin resistance, high pitched voice, slender long bones with thick cortex and narrow medullar channels, shallow sella turcica, increased tumour risk (particularly Wilms and ovarian stromal tumours)	Rieger anomaly, dental delay, partial lipodystrophy, transparent skin, dimples on elbows and buttocks, herniae, fifth finger clinodactyly, hyperextensible joints, hypogonadism, high pitched voice, type 2 diabetes mellitus, nephrocalcinosis, thin gracile bones,	Delayed speech development with expressive language delay, significantly delayed bone age, broad fingertips	Congenital adrenal hypoplasia, metaphyseal and/or epiphyseal dysplasia, male genital anomalies
Inheritance or molecular abnormality	Autosomal recessive Mutations in <i>CUL7</i> , <i>OBSL1</i> , <i>CCDC8</i>	Autosomal recessive Mutations in <i>TRIM37</i> High prevalence in Finnish population	Autosomal dominant Mutations in <i>PIK3R1</i>	Autosomal dominant Mutations in <i>SRCAP</i>	Imprinted – Maternally inherited mutations in <i>CDKN1C</i>

Abbreviation: ID, intellectual disability

**Table 5: Clinical checklist for management of patients with SRS**

	At diagnosis	0-2 years	2-10 years	10-18 years
Document molecular subtype	■			
Provide support group information	■			
Genetic counselling for parents	■			
<b>Feeding and growth</b>				
Exclude feeding difficulties	■	■	□	□
Ensure nutritional repletion	■	■	■	■
Screen for gut dysmotility	■	■	□	□
Screen for oromotor or sensory issues	■	□	□	□
Avoid rapid postnatal/childhood weight gain	■	■	■	■
Measure head circumference	■	■	■	■
Measure and monitor linear growth	■	■	■	■
Calculate and monitor BMI	■	■	■	■
Screen for symptoms/signs of hypoglycaemia	■	■	□	□
Consider growth hormone treatment	■	□	■	■
Monitor IGF-1 or IGFBP3 levels (more than yearly)	■	□	■	■
Monitor clinically (with or without biochemical testing) for insulin resistance	■	N/A	■	■
<b>Adrenarche and puberty</b>				
Monitor clinically for early adrenarche	■	■	■	N/A
Anticipate early bone age advancement	■	N/A	■	■
Consider treatment of early or rapid central puberty	■	N/A	■	□
<b>Other medical</b>				
Monitor for symptoms of sleep disordered breathing	■	■	■	■
Orthodontic or dental	■	□	■	■
Ear, nose and throat	■	□	□	□
<b>Neurodevelopment</b>				
Developmental assessment	■	■	□	□
Screen for myoclonus-dystonia*	■	■	■	■
Speech and language evaluation	■	■	■	□
School progress	■	N/A	□	□
Monitor for speech, motor and cognitive difficulties	■	□	■	□
Psychosocial evaluation	■	N/A	□	□
<b>Musculoskeletal</b>				
Limb length discrepancy or asymmetry	■	□	□	□
Scoliosis	■	□	□	□
Screen for hip dysplasia	■	■	□	□

N/A not applicable;

■ Assessment recommended (unless N/A to age group)

□ Assessment may be considered, depending on the clinical features of the patient [Au: We cannot use blocks in this way. OK to replace with AR and AC, respectively?] [Ed: can we use R and C, to be defined as 'recommend assessment' and 'consider assessment' ?.

The letter A at the beginning of every acronym will reduce clarity.

\*upd(7)mat only

### Figure legends:

Figure 1: Flow chart for investigation and diagnosis of SRS. Diagnostic questions in blue boxes; recommended molecular testing in yellow boxes. Green boxes: diagnosis of SRS confirmed; pink boxes: diagnosis not confirmed. Abbreviations: CNV, copy number variant. NH-CSS, Netchine-Harbison clinical scoring system; SRS, Silver–Russell syndrome.

Figure 2A: Representation of the 11p15 region, showing both centromeric and telomeric domains. Only the imprinted genes that are implicated in the pathophysiology of Silver–Russell syndrome are represented. Blue boxes: paternally expressed genes (the growth promoter *IGF2* and the long non coding RNA (lncRNA) *KCNQ1OT1*). Pink boxes: maternally expressed genes (the growth inhibitor *CDKN1C*, the ion channel *KCNQ1* and the non-coding RNA *H19*). Circles: Differentially methylated regions (DMRs). Black circles: methylated DMRs. White circles: unmethylated imprinting control regions (ICRs).

Figure 2B: Structure of the *IGF2/H19* DMR. This DMR contains short repetitive blocks of sequence and harbours seven binding sites for the zinc finger protein CTCF (green). Multiple enhancer elements (grey ovals) distal to *H19* are shared between *H19* and *IGF2*, able to increase expression of either. Binding of CTCF to the unmethylated maternal DMR blocks interactions between the *IGF2* promoter and enhancers downstream of *H19*, which results in maternal *H19* expression. Conversely, methylation of ICR1 on the paternal allele prevents CTCF binding, enabling interaction between the *IGF2* promoter and distal enhancers, and thus paternal *IGF2* expression<sup>163,164</sup>.

Figure 3: Mutations and epimutations of the imprinted region at chromosome 11p15 associated with Silver–Russell syndrome. The structure of the 11p15 region is represented as in figure 2. Paternal hypomethylation of *H19/IGF2* IG-DMR results in loss of paternal *IGF2* and gain of maternal *H19* expression, which leads to a growth restriction phenotype<sup>9</sup>. Less commonly, maternal duplication of the centromeric or both domains results in growth retardation due to increased dosage of *CDKN1C*; however, smaller CNVs should be classified with caution due to the complex regulation of the region<sup>27</sup>. Rare familial cases have been associated with a maternal *CDKN1C* gain-of-function mutation (green cross)<sup>60</sup> or a paternal *IGF2* loss-of-function mutation (red cross)<sup>61</sup>.



**Summary of Boxes & Tables:**

Box 1: Definitions

Box 2: Questions for future research

Table 1: Netchine-Harbison clinical scoring system (NH CSS)

Table 2: Frequency of features in SRS

Table 3: Differential diagnosis – relative microcephaly

Table 4: Differential diagnosis – normo-/relative macrocephaly

Table 5: Clinical checklist for management of patients with SRS

**Supplementary Information:**

Summary of recommendations

Table 1: Frequency of features in different subtypes of SRS and non-SRS SGA

Table 2: Genetic variants on chromosome 11p15

Table 3: Genetic variants on chromosome 7

Table 4: Adult height data in untreated patients with SRS

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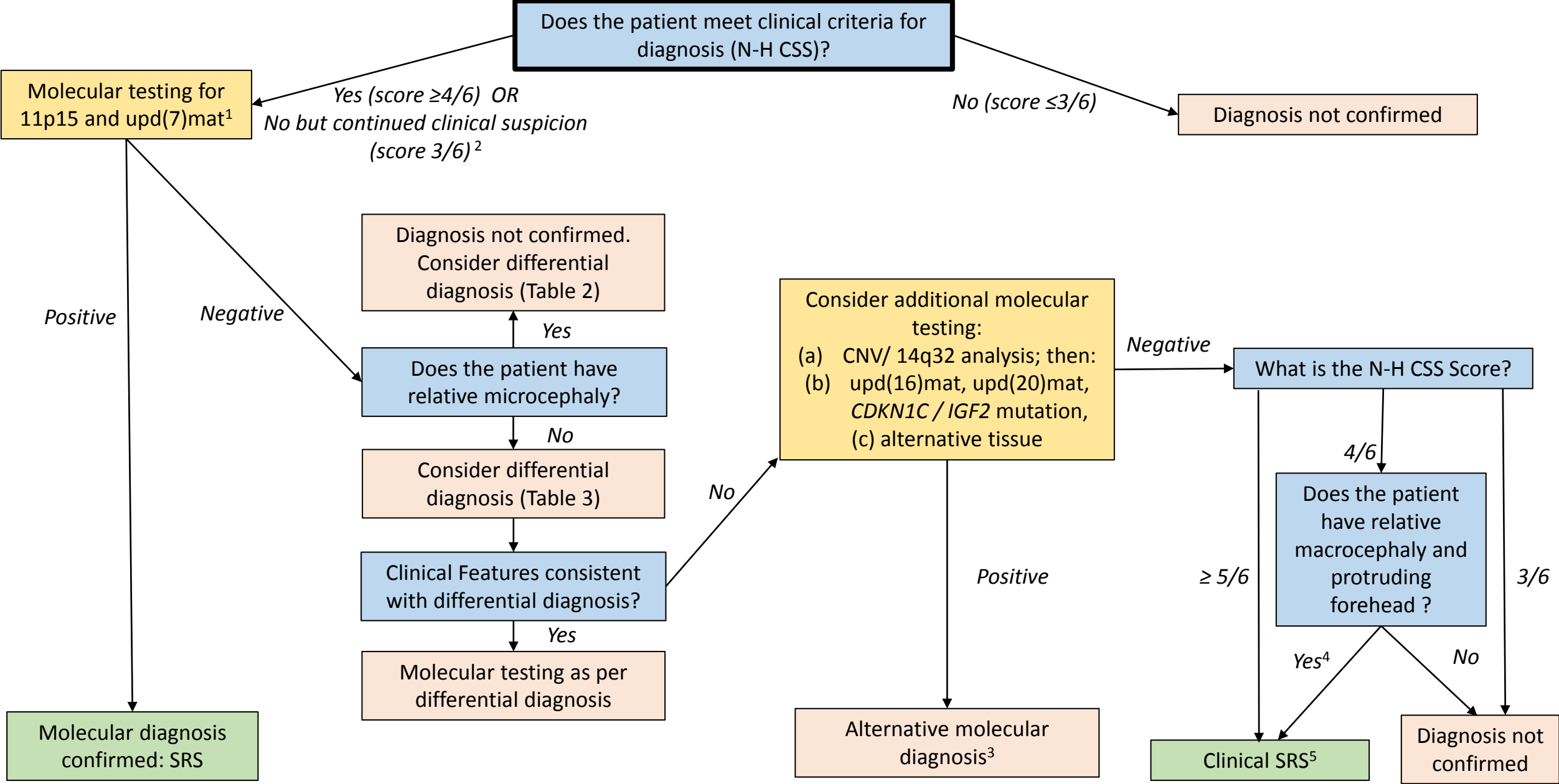
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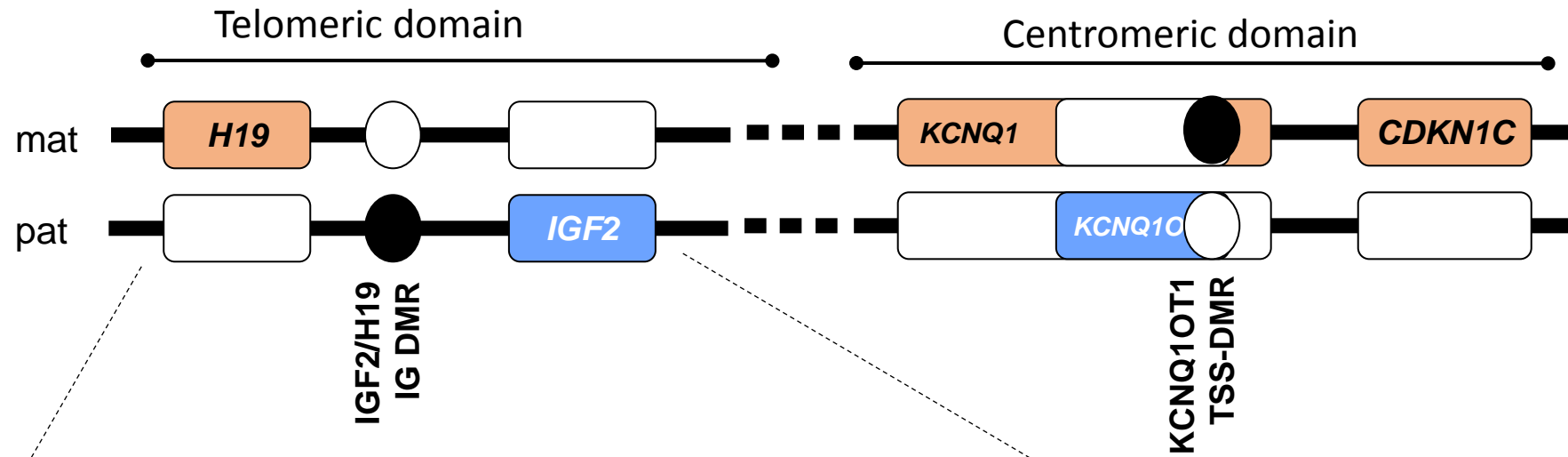
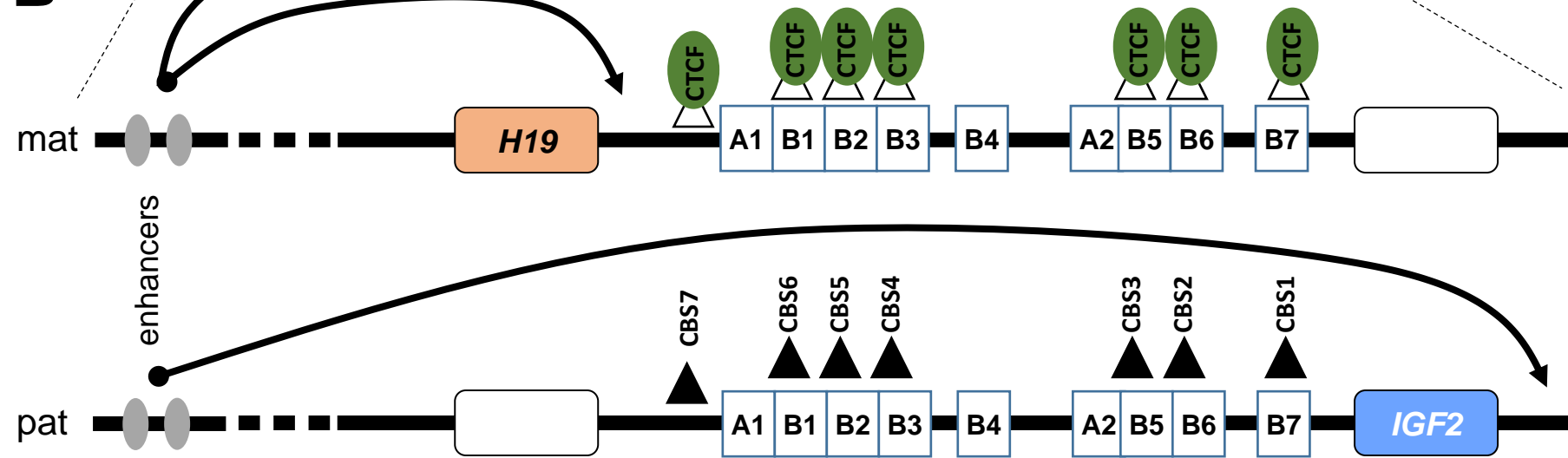
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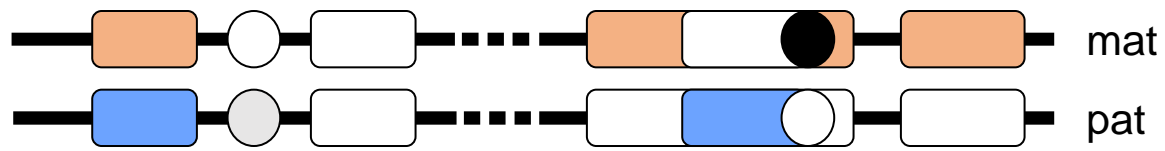


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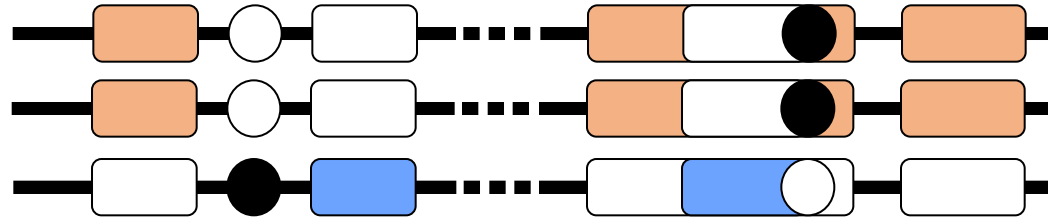


<sup>1</sup>Arrange CNV analysis BEFORE other investigations if patient has significant unexplained global developmental delay/ intellectual disability, and /or relative microcephaly. <sup>2</sup>Studies have excluded 11p15 LOM and upd(7)mat in patients with IUGR and postnatal growth retardation alone; some patients, particularly those with upd(7)mat or children under 2 years, score 3/6 (see text for details). <sup>3</sup>Insufficient evidence at present to determine relationship to SRS, with the exception of tissue mosaicism <sup>4</sup>Unless evidence of catch-up growth by 2 years . <sup>5</sup>Previously known as idiopathic SRS.

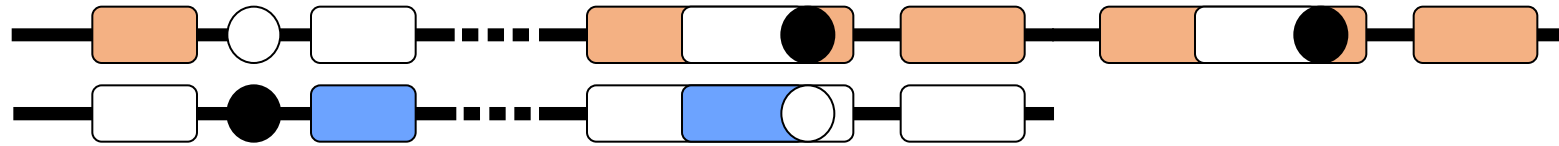
**A****B**



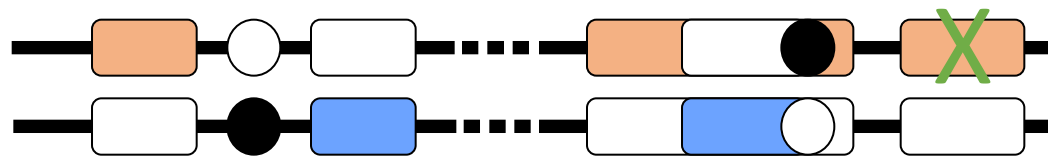
Paternal IGF2/H19 IG DMR LOM



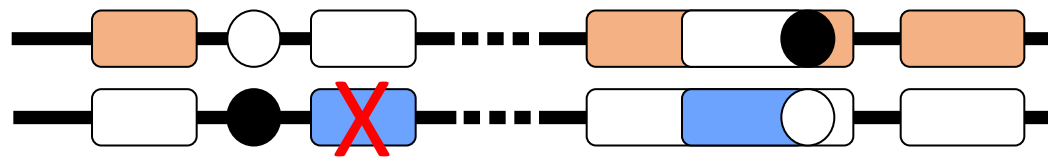
Maternal duplication of both domains



Maternal duplication of the centromeric domain



Maternal *CDKN1C* gain of function mutation



Paternal *IGF2* loss of function mutation