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Silver-Russell Syndrome

Synonym: Russell-Silver Syndrome

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Summary

Clinical characteristics

Silver-Russell Syndrome (SRS) is typically characterized by gestational growth restriction resulting in affected individuals being born small for gestational age, with relative macrocephaly at birth (head circumference ≥1.5 standard deviations [SD] above birth weight and/or length), prominent forehead with frontal bossing, and frequently body asymmetry. This is typically followed by postnatal growth failure, and in some cases progressive limb length discrepancy and feeding difficulties. Additional clinical features include triangular facies, fifth finger clinodactyly, and micrognathia with narrow chin. Except for the limb length asymmetry, growth failure is proportionate and head growth typically normal. The average adult height in untreated individuals is ~3.1±1.4 SD below the mean. The Netchine-Harbison Clinical Scoring System (NH-CSS) is a sensitive diagnostic scoring system. Clinical diagnosis can be established in an individual who meets at least four of the NH-CSS clinical criteria – prominent forehead/frontal bossing and relative macrocephaly at birth plus two additional findings – and in whom other disorders have been ruled out.

Diagnosis/testing

SRS is a genetically heterogeneous condition. Genetic testing confirms clinical diagnosis in approximately 60% of affected individuals. Hypomethylation of the imprinting control region 1 (ICR1) at 11p15.5 causes SRS in 35%-67% of individuals, and maternal uniparental disomy of chromosome 7 (upd(7)mat) causes SRS in 7%-10% of individuals. There are a small number of individuals with SRS who have duplications, deletions, or translocations involving the imprinting centers at 11p15.5 or duplications, deletions, or translocations involving chromosome 7. Rarely, affected individuals with pathogenic variants in *CDKN1C*, *IGF2*, *PLAG1*, and *HMGA2* have been described. However, approximately 30%-40% of individuals who meet NH-CSS clinical criteria for SRS have negative molecular and/or cytogenetic testing.

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Management

Treatment of manifestations: Multidisciplinary follow up and early specific intervention are necessary for optimal management of affected individuals, including early referral to an endocrinologist. Treatment may include growth hormone therapy. Hypoglycemia should be prevented or aggressively managed. Strategies for feeding issues include nutritional and caloric supplementation, medication for gastroesophageal reflux, therapy for oral motor problems and oral aversion, cyproheptadine for appetite stimulation, and enteral tube feeding as needed. Lower limb length discrepancy exceeding 2 cm requires intervention. In the majority of affected older children, distraction osteogenesis is recommended. Severe micrognathia or cleft palate should be managed by a multidisciplinary craniofacial team. Males with cryptorchidism or hypospadias should be referred to a urologist. Males with micropenis and females with internal genitourinary anomalies benefit from a referral to a multidisciplinary disorders of sex development (DSD) center. Physical, occupational, speech, and language therapy with an individualized education plan are used to treat developmental delays. Psychological counseling can be used as needed to address psychosocial and body image issues.

Surveillance: Monitoring of growth velocity, blood glucose concentration, and urine ketones for hypoglycemia in infants and as needed in older children; evaluation of nutritional status and oral intake at each visit as well as managing tube feedings if needed; limb length assessment at each well child visit in early childhood for evidence of asymmetric growth; evaluation for scoliosis, signs of precocious puberty, genitourinary issues, dental crowding and malocclusion, and speech-language development at each visit.

Agents/circumstances to avoid: Prolonged fasting in infants and young children because of the risk for hypoglycemia; elective surgery whenever possible due to risk of hypoglycemia, hypothermia, difficult healing, and difficult intubation.

Genetic counseling

Risk to family members: In most families, a proband with SRS represents a simplex case (a single affected family member) and has SRS as a result of an apparent *de novo* epigenetic or genetic alteration. While the majority of families are presumed to have a very low recurrence risk, SRS can occur as the result of a genetic alteration associated with up to a 50% recurrence risk depending on the nature of the genetic alteration and the sex of the transmitting parent. Rare familial cases of SRS have been reported with several underlying mechanisms, including maternally inherited 11p15 duplications, maternally inherited *CDKN1C* gain-of-function pathogenic variants, paternally inherited *IGF2* loss-of-function pathogenic variants, paternally inherited small deletions close to the boundaries of the ICR1, and paternally or maternally inherited deletions and intragenic pathogenic variants involving *PLAG1* or *HMGA2*. Reliable SRS recurrence risk assessment therefore requires identification of the causative genetic mechanism in the proband.

Prenatal testing: Reliable prenatal testing for loss of paternal methylation at the 11p1.5 ICR1 *H19*/*IGF2* region is not possible. Prenatal testing for the following SRS-related genetic mechanisms is possible provided the genetic mechanism has been demonstrated to be causative in an affected family member: upd(7)mat, SRS-related chromosomal abnormalities, intragenic *CDKN1C*, *IGF2*, *HMGA2*, or *PLAG1* pathogenic variants, and deletions involving *HMGA2* or *PLAG1*. The prenatal finding of a genetic alteration consistent with SRS cannot be used to reliably predict clinical outcome because children with SRS demonstrate varying responses to growth hormone, variable late catch-up growth, and variable developmental outcomes.

Diagnosis

Consensus clinical diagnostic criteria for Silver-Russell syndrome (SRS) have been published [Azzi et al 2015].

Suggestive Findings

SRS **should be suspected in** a proband with at least four of the following NH-CSS clinical criteria [Azzi et al 2015]:

- Small for gestational age (birth weight and/or length two or more standard deviations [SD] below the mean for gestational age)
- Postnatal growth failure (length/height two or more SD below the mean for age and sex at age 24 months)
- Relative macrocephaly at birth (head circumference more than 1.5 SD above birth weight and/or length)
- Frontal bossing or prominent forehead (forehead projecting beyond the facial plane on a side view at age one to three years)
- Body asymmetry (limb length discrepancy ≥0.5 cm, or <0.5 cm with ≥2 other asymmetric body parts)
- Feeding difficulties, or body mass index two or more SD below the mean at age two years, or current use of a feeding tube or cyproheptadine for appetite stimulation

Rarely, individuals meeting three of the six criteria have had positive molecular confirmation of SRS.

Establishing the Diagnosis

The clinical diagnosis of SRS **can be established in** a proband based on clinical diagnostic criteria [Azzi et al 2015], or the molecular diagnosis can be **established** in a proband with suggestive findings and abnormal molecular genetic testing consistent with one of several molecular mechanisms (see Table 1 and Molecular Pathogenesis).

Note: Molecular genetic testing is recommended in all individuals with suspected SRS to provide accurate recurrence risk information.

Clinical Diagnosis

SRS is an etiologically heterogeneous condition. In the international consensus statement for the diagnosis and management of SRS [Wakeling et al 2017], the NH-CSS was selected as the most sensitive of several compared clinical diagnostic scoring systems [Netchine et al 2007, Azzi et al 2015].

The clinical diagnosis of SRS can be established in a proband with at least four of the six NH-CSS clinical diagnostic criteria (see Suggestive Findings).

- Two of the criteria must be relative macrocephaly at birth and frontal bossing or prominent forehead.
- Other disorders with growth restriction must be ruled out either based on clinical features or molecular testing [Wakeling et al 2017] (see Differential Diagnosis).

Note: In older children and adults, frontal bossing or a prominent forehead may disappear. Therefore, a clinical diagnosis of SRS in older children and adults may require assessment of profile photographs from age two years or younger.

Molecular Diagnosis

The molecular diagnosis of SRS can be established in a proband with one of the following identified on molecular genetic testing (see Table 1 and Molecular Pathogenesis):

- **Abnormal methylation of chromosome 11p15.5.** SRS is associated with abnormal regulation of gene transcription in two imprinted domains on chromosome 11p15.5. Regulation may be disrupted by any one of numerous mechanisms (see Molecular Pathogenesis).
- **Maternal uniparental disomy of chromosome 7 (upd(7)mat),** which can occur by different mechanisms (see Molecular Pathogenesis).

- **Pathogenic gain-of-function variants in *CDKN1C***
- **Pathogenic loss-of-function variants in *IGF2*, *PLAG1*, or *HMGA2***

An international expert consensus algorithm for the molecular investigation of SRS has been published [Wakeling et al 2017], including first-tier, second-tier, and other molecular diagnostic testing approaches (see Figure 1). Third-tier testing using comprehensive genomic approaches has been proposed by the authors of this *GeneReview* and adapted from Wakeling et al [2017].

- **First-tier testing.** Methylation analysis of 11p15.5 imprinting control regions (ICR1/ICR2) and upd(7)mat studies performed simultaneously.

  Note: (1) Detection of an abnormality is dependent on the mechanism of disease and testing methodology used (see Table 1). (2) Mosaicism has been reported; therefore, testing alternative tissues (e.g., buccal cells or skin fibroblasts) should be considered if testing of peripheral blood is normal.

- **Second-tier testing.** If methylation analysis of 11p15.5 ICR1/ICR2 and upd(7)mat studies are normal, **a multigene panel** that includes sequence analysis of *IGF2*, *CDKN1C*, *PLAG1*, *HMGA2*, and other genes of interest (see Differential Diagnosis) may be considered.

  Note: (1) The genes included in various multigene panels and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Other testing options**
  - **SNP chromosomal microarray (CMA).** Some individuals ultimately diagnosed with SRS will have a SNP CMA due to their significant growth abnormalities at birth or later or based on speech or other developmental delays. While this is not a first- or second-tier testing recommendation for individuals suspected to have SRS, CMA will identify chromosomal deletions, duplications, or isodisomy, including of chromosomes 7 or 11, that may establish the diagnosis of SRS (see Table 1).
  - **Methylation analysis of chromosomes 11 and 16** to detect SRS due to upd(11)mat and upd(16)mat (see Differential Diagnosis). Methylation analysis of chromosomes 11 and 16 should be considered in individuals with clinical features of SRS who do not have hypomethylation of 11p15.5 ICR1/ICR2 or upd(7)mat [Luk et al 2016a, Pignata et al 2021].

- **Third-tier testing.** When the diagnosis of SRS is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Silver-Russell Syndrome

Method	Pathogenic Variants/Alterations Detected		Proportion of SRS Alterations Detected [1]
Methylation analysis [2]	Chr 11	Loss of methylation at *H19/IGF2* (paternal) [3]	~35%-67% [4]
		Somatic mosaicism for upd(11)mat [5, 6]	Rare
		Duplication of 11p15.5 (maternal)	Unknown [7, 8]
	Chr 7	upd(7)mat [9]	~7%-10% [10]
		Deletions, duplications, mosaic trisomy 7	Rare [11]
Chromosomal microarray analysis (SNP based)	Chr 11	Duplication of 11p15.5 (maternal)	Unknown [7, 8]
		Somatic mosaicism for upd(11)mat [5, 6]	Rare [12]
	Chr 7	Deletions, duplications of 7p, mosaic trisomy 7	Rare [11, 13, 14]
		upd(7)mat	Maternal isodisomy 7 only [15]
STR marker analysis	Chr 11	Somatic mosaicism for upd(11)mat [5, 6]	Rare
	Chr 7	upd(7)mat [9], maternal mosaic trisomy 7	~7%-10% [10]
Karyotype	Inversion or translocation of 11p15.5		Rare [5, 6]
Sequence analysis [16] / gene-targeted deletion/ duplication analysis [17]	*CDKN1C* (maternal transmission)		Rare [18]
	IGF2 (paternal transmission)		Rare [19]
	PLAG1		Rare [20]
	HMGA2		Rare [21]

Table 1. continued from previous page.

Method	Pathogenic Variants/Alterations Detected	Proportion of SRS Alterations Detected [1]
Unknown		30%-40% [22]

chr = chromosome; SNP = single-nucleotide polymorphisms; STR = short tandem repeat; upd(7)mat = maternal uniparental disomy of chromosome 7; upd(11)mat = maternal uniparental disomy of chromosome 11

1. See Molecular Genetics for information on variants/alterations detected.

2. Assays developed to be methylation sensitive such as multiplex ligation probe analysis (MS-MLPA), quantitative PCR (MS-qPCR), or Southern blotting (mainly historical testing) allow detection of epigenetic and genomic alterations of 11p15.5. Methylation-sensitive assays can diagnose SRS resulting from DNA methylation alterations, deletions, and duplications, or uniparental disomy (UPD). Interpretation of methylation data should consider results of copy number testing because copy number variants that alter the relative dosage of parental contributions (e.g., paternal duplication) are associated with abnormal methylation status. Note that MLPA testing may be followed by microarray testing to define breakpoints of deletions or duplications. Other methods to confirm maternal UPD at 11p15.5 include short tandem repeat (STR) analysis or SNP analysis [Keren et al 2013].

3. A small number of individuals have hypomethylation of only *H19* or *IGF2* [Bartholdi et al 2009].

4. False negatives may occur because of mosaicism as 11p15.5 hypomethylation occurs post fertilization. Testing tissues from a second source (e.g., buccal cells or fibroblasts) should be performed.

5. Bullman et al [2008]

6. Luk et al [2016a]

7. Fisher et al [2002], Eggermann et al [2005], Schönherr et al [2007]

8. Heide et al [2018]

9. Both isodisomy and heterodisomy [Bernard et al 1999, Price et al 1999] as well as segmental maternal UPD [Hannula et al 2001, Eggermann 2008] have been reported. Mosaicism has been observed in cases of upd(7)mat and other chromosome 7 rearrangements; therefore, testing of an alternate tissue source may be appropriate [Reboul et al 2006]. Prenatal diagnosis of mosaic trisomy 7 was confirmed postnatally by microsatellite analysis [Abdelhedi et al 2014].

10. Hannula et al [2001], Kim et al [2005], Abu Amero et al [2008], Eggermann et al [2012b]

11. Courtens et al [2005], Flori et al [2005], Font-Montgomery et al [2005]

12. Luk et al [2016b] described one group of 28 individuals with SRS, of which 3.6% who had mosaic upd(11)mat.

13. A *de novo* duplication of 7p11.2-p13 on the maternal allele containing *GRB10*, *GFBP1*, and *GFBP*3 has been reported [Monk et al 2000].

14. A *de novo* deletion of 7q32.2 on the paternal allele including *MEST* has been reported [Carrera et al 2016]. Further, a small paternally inherited 79-kb deletion of 7q32.2 was detected involving *MEST* in an individual with SRS [Vincent et al 2022].

15. Note: SNP array analysis will detect maternal UPD only in those with isodisomy; 28.8% of upd(7)mat (2%-3% of all individuals with SRS) are a result of isodisomy [Chantot-Bastaraud et al 2017].

16. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, partial-, whole-, or multigene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

17. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

18. Several reports, including one four-generation family segregating a *CDKN1C* gain-of-function pathogenic variant [Brioude et al 2013, Sabir et al 2019, Binder et al 2020, Li et al 2023]. In all reported familial cases to date, there was a maternally inherited substitution of arginine at amino acid 279 (p.Arg279).

19. One family with SRS and a paternally transmitted *IGF2* loss-of-function variant has been reported by Begemann et al [2015], and a few others have been reviewed by Tümer et al [2018]. Several individuals with *IGF2* pathogenic variants have been reported [Masunaga et al 2020].

20. Heterozygous loss-of-function *PLAG1* variants were identified in affected individuals from two families and one additional individual [Abi Habib et al 2018, Inoue et al 2020].

21. Heterozygous loss-of-function *HMGA2* variants were identified in two individuals [Abi Habib et al 2018, Hübner et al 2020].

22. Approximately 40% of individuals with at least four of the six Netchine-Harbison clinical diagnostic criteria will have nondiagnostic laboratory studies.

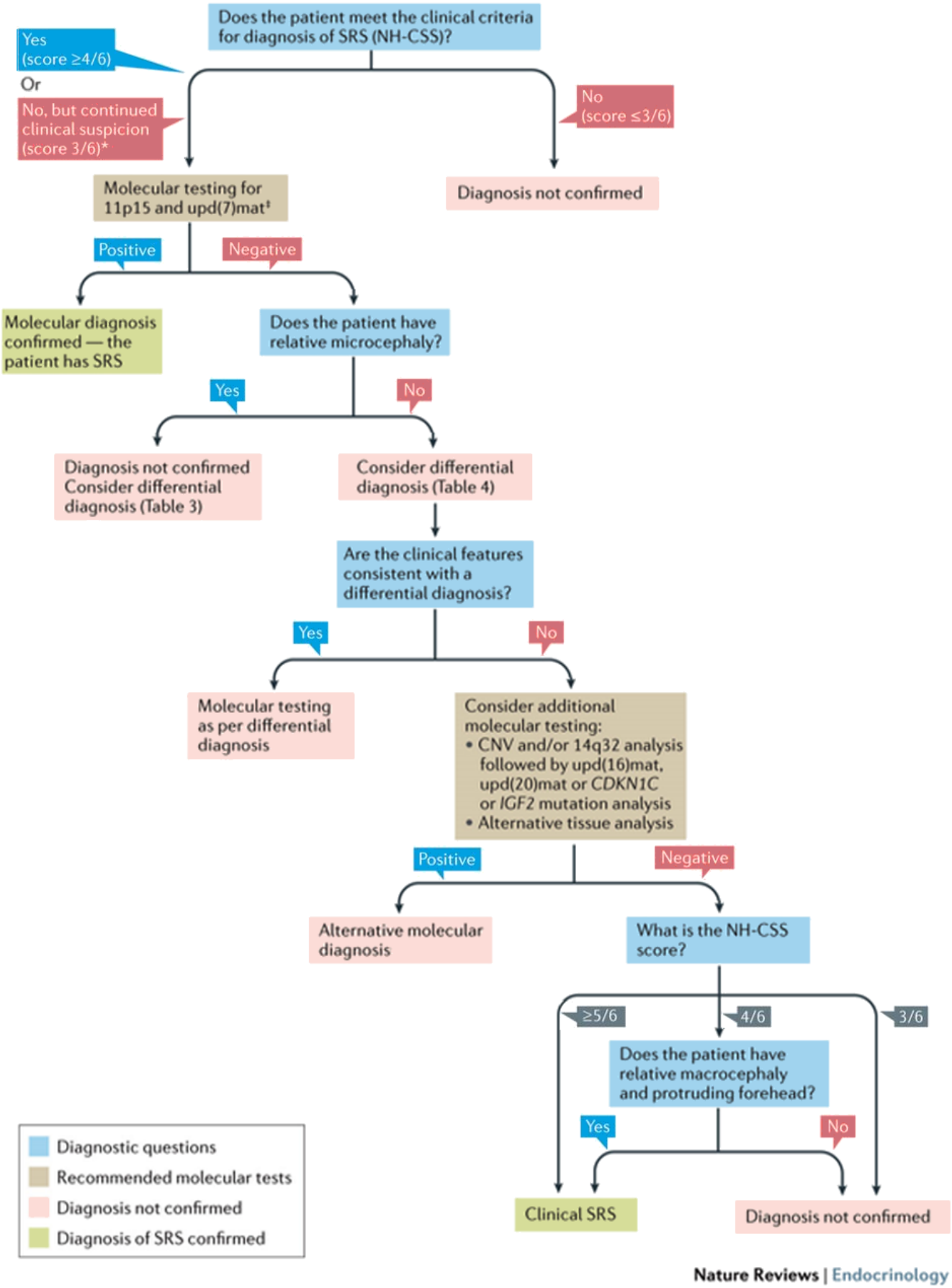

Figure 1. Flowchart for investigation and diagnosis of Silver-Russell syndrome

Adapted from Wakeling et al [2017]

Clinical Characteristics

Clinical Description

Silver-Russell Syndrome (SRS) is characterized by intrauterine growth restriction resulting in affected individuals being born small for gestational age with relative macrocephaly (head circumference ≥1.5 standard deviations [SD] above birth weight and/or length), a prominent forehead usually with frontal bossing, and frequently body asymmetry. This is followed by postnatal growth failure and, in some individuals, progressive limb length discrepancy and severe feeding difficulties in the first few years of life. Additional clinical features include triangular facies, fifth finger clinodactyly, and micrognathia with a small chin. Except for the limb length asymmetry, growth failure is usually proportionate but with normal head growth. The average adult height in untreated individuals is ~3.1±1.4 SD below the mean.

To date, more than 1,000 individuals have been diagnosed with SRS [Wollmann et al 1995, Wakeling et al 2017, Fuke et al 2021, Lokulo-Sodipe et al 2022, Mackay et al 2022]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Silver-Russell Syndrome: Frequency of Select Features

Feature		% of Persons w/Feature	Comment
Growth abnormalities		≥80%	Incl prenatal or postnatal growth failure, relative macrocephaly, &/or body asymmetry
Feeding difficulties		84%-100%	Or BMI ≤2SD at age 24 mos; or current use of a feeding tube or cyproheptadine for appetite stimulation
Skeletal features		75%	Incl hypoplastic elbow joints, fifth finger clinodactyly, joint contractures, brachydactyly, &/or scoliosis
Body asymmetry		68%	Limb &/or facial asymmetry
Dysmorphic & skin features		≥64%	Incl triangular-shaped face, frontal bossing &/or prominent forehead, micrognathia, downturned corners of mouth, dental crowding, shoulder dimples, & café au lait macules
Craniofacial anomalies		64%	Incl Pierre Robin sequence, cleft palate, &/or dental anomalies
Developmental delays	Global delays	20%-65%	
	Speech delays	39%-50%	
Reduced muscle mass		56%	
High-pitched voice		45%	
Delayed close of anterior fontanelle		43%	
Genitourinary abnormalities		40% (in males)	Incl hypospadias &/or cryptorchidism, renal anomalies (renal anomalies seen in 10%, primarily in upd(7)mat)
Fasting hypoglycemia		24%-29%	Excessive sweating w/ or w/o hypoglycemia has been reported in up to 67% of affected persons.
Heart defects		9%	Ventricular septal defects, atrial septal defects, patent ductus arteriosus

Based on Wakeling et al [2010], Azzi et al [2015], and Wakeling [2021]

Growth. The earliest manifestation of SRS is abnormal growth. Most children are born small for gestational age with birth weight and/or length two or more SD below the mean. Although growth velocity may be within the

normal range, children with SRS rarely show significant catch-up growth. At age two years, most affected children remain two or more SD below the mean for length unless parents are tall.

In two European series of untreated adults with SRS, height ranged from 3.7 to 3.5 SD below the mean for males and 4.2 to 2.5 SD below the mean for females [Wollmann et al 1995, Binder et al 2013]. Except for limb length asymmetry, growth failure is proportionate with normal head growth. Most children diagnosed clinically as having SRS who demonstrated catch-up growth in later childhood had conditions other than SRS [Saal et al 1985].

Growth charts for European children with SRS have been published [Wollmann et al 1995]. Growth charts for North American children with the Wollmann data superimposed are available from the MAGIC Foundation.

Growth and use of growth hormone (GH). Children with any condition associated with body differences and/or short stature are often sensitive about body image. These factors can play a significant role in self-image, peer relationships, and socialization. Thus, early referral to a pediatric endocrinologist is essential for children with SRS.

The goals of GH treatment are multifaceted, including improving growth velocity, body composition (especially lean body mass), psychomotor development, and appetite, as well as reducing the risk of hypoglycemia and optimizing overall linear growth [Wakeling et al 2017]. GH therapy in children with intrauterine growth restriction of all causes has been shown to significantly improve growth and final height, especially in children who do not experience catch-up growth [Dahlgren et al 2005, Jensen et al 2014, Zanelli & Rogol 2018]. Specifically, children with SRS have benefited from GH supplementation [Toumba et al 2010, Binder et al 2013], although final heights were less in individuals with SRS because their heights were lower at the initiation of treatment [Smeets et al 2016].

Note: Many children with SRS do not achieve normal stature even with administration of human GH if rapid bone age advancement during puberty is not managed (see Management).

GH deficiency. Treatment with human GH is necessary in the presence of documented GH deficiency. However, GH deficiency is not common in SRS [Wakeling et al 2017].

- Testing for GH deficiency by fasting is contraindicated because of the risk for inducing hypoglycemia [Wakeling et al 2017].
- Treatment with GH in SRS is indicated regardless of the presence or absence of GH deficiency.

Feeding disorders and hypoglycemia. Children with SRS have little subcutaneous fat and often have a poor appetite, oral motor issues, and feeding disorders [Fuke et al 2013]. They are at risk for hypoglycemia, especially associated with prolonged fasting [Wakeling et al 2017]. In a study of children with SRS, contributing factors for hypoglycemia included reduced caloric intake, often secondary to poor appetite and feeding difficulties; reduced body mass; and, in several children, GH deficiency [Azcona & Stanhope 2005]. While most children had clinical symptoms of hypoglycemia, including diaphoresis, several were asymptomatic.

Gastrointestinal disorders are common, including gastroesophageal reflux disease, esophagitis, oral aversion, vomiting, constipation, and failure to thrive. One large study documented gastrointestinal problems including feeding disorders and/or malnutrition in 77% of children with SRS, and 55% of children had severe gastroesophageal reflux, which may have an atypical presentation without vomiting in this group [Marsaud et al 2015]. Reflux esophagitis should be suspected in children with either oral aversion or aspiration.

Gastrointestinal disorders should be treated early and adequately. It is critical that attention to growth and nutrition begin in infancy. Aggressive feeding measures are often required, including use of nasogastric tubes or, less frequently, gastrostomy tube placement (see Management).

Skeletal abnormalities include the following:

- Limb length asymmetry, caused by hypoplasia or hemihypoplasia with diminished growth of the affected side
- Fifth finger clinodactyly and/or brachydactyly. These are among the most frequently described skeletal anomalies (albeit minor) in individuals with SRS.
- Scoliosis, which has been reported in up to 36% of individuals with SRS in some studies [Abraham et al 2004]. Another study identified scoliosis or kyphosis in 21% of individuals; 18% required corrective surgery [Yamaguchi et al 2015].

Bone age advancement and puberty. Monitoring for signs of premature adrenarche, early and accelerated central puberty, and insulin resistance is very important in individuals with SRS. Personalized treatment with gonadotropin-releasing hormone (GnRH) analogs for at least two years in children with evidence of central puberty (starting no later than age 12 years in girls and age 13 years in boys) can be considered to preserve adult height potential [Wakeling et al 2017] (see Management).

Craniofacial anomalies are common. Some individuals with SRS have Pierre Robin sequence and cleft palate. Wakeling et al [2010] found cleft palate or bifid uvula, which is often associated with submucous cleft palate, in 7% of those with 11p15.5 methylation defects and none in individuals with upd(7)mat. Individuals with suspected Pierre Robin sequence should be monitored for obstructive apnea.

Dental and oral abnormalities are common. Microdontia, high-arched palate, and dental crowding secondary to relative micrognathia and small mouth have been reported [Orbak et al 2005, Wakeling et al 2010]. Overbite and dental crowding appear to be the most common orofacial manifestations [Hodge et al 2015]. Poor oral hygiene in the presence of dental crowding can lead to increased risk for dental caries.

Neurodevelopment. Children with SRS are at increased risk for developmental delays including motor, cognitive, and speech delays as well as learning disabilities.

In a review of a large cohort of children with SRS with either 11p15 methylation defects or upd(7)mat, developmental delay was seen in 34% of individuals; the majority had mild delays. Developmental delays were more commonly seen in those with maternal upd(7)mat than those with 11p15 methylation defects (65% vs 20%). Speech delays were common in both groups [Wakeling et al 2010].

A study surveying adults with SRS reported that 64.5% had motor delays and 38.7% had speech delay, with most of the subjects having attended mainstream education and 21.2% receiving special education support. For individuals older than 21 years, 40% obtained university degrees [Lokulo-Sodipe et al 2020]. In a study looking at executive function in adolescents and adults with SRS, mean full scale IQ studies were normal for individuals with SRS due to 11p15 loss or methylation and upd(7)mat (IQs were 101.75 and 101.00, respectively) and equivalent to controls [Burgevin et al 2023]. Further studies of individuals with molecularly confirmed SRS and early medical management are needed to provide a more accurate cognitive prognosis.

Genitourinary problems have been observed. The most common anomalies are hypospadias and cryptorchidism in males [Bruce et al 2009, Wakeling et al 2017]. Mayer-Rokitansky-Kuster-Hauser syndrome (associated with underdeveloped or absent vagina and uterus with normal appearance of the external genitalia) has been reported in females [Bruce et al 2009, Abraham et al 2015]. Renal anomalies are not common; however, horseshoe kidney and renal dysplasia have been reported [Wakeling et al 2010].

Heart defects are uncommon but have been reported and include patent ductus arteriosus, ventricular septal defects, tetralogy of Fallot, and total anomalous pulmonary venous return [Wakeling et al 2010, Ghanim et al 2013]. Routine cardiovascular evaluation is not needed unless clinically indicated.

Genotype-Phenotype Correlations

Several genotype-phenotype correlations have been observed in individuals with SRS.

Using methylation-sensitive restriction enzymes to measure the degree of methylation of *H19* within the 11p15.5 region, Bruce et al [2009] developed a scale of extreme *H19* hypomethylation, moderate *H19* hypomethylation, normal *H19* methylation, and upd(7)mat (normal *H19* methylation). They determined that children with SRS with extreme *H19* hypomethylation (i.e., ≥6 SD below the mean or <9% methylation) were more likely to have more severe skeletal manifestations (including radiohumeral dislocation, syndactyly, greater limb asymmetry, and scoliosis) than children with SRS with moderate hypomethylation and those with upd(7)mat.

A study by Wakeling et al [2010] compared clinical features of children with SRS caused by 11p15.5 imprinting control region 1 (ICR1) *IGF2*/*H19* methylation defects to those with maternal upd(7)mat. They found that fifth finger clinodactyly and congenital anomalies including cleft palate, congenital heart defects, genital anomalies in males, and renal anomalies were more frequent in children with 11p15.5 ICR1 hypomethylation than those with upd(7)mat, whereas learning difficulties and speech disorders were more frequent in children with upd(7)mat than ICR1 hypomethylation.

In another study, children with SRS due to upd(7)mat attained more linear growth (or height) with GH therapy compared to children with 11p15.5 ICR1 hypomethylation, possibly because children with 11p15.5 methylation abnormalities showed elevated levels of insulin-like growth factor 1 (IGF-1, the product of *IGF1*) and therefore a degree of IGF-1 resistance. Children with SRS due to upd(7)mat had IGF-1 response patterns similar to other children who were small for gestational age and did not have SRS [Binder et al 2008].

A series of children with SRS with 11p15.5 loss of methylation (LOM), upd(7)mat, and SRS with no identified epigenetic or genetic variants showed genotype-phenotype correlations comparable to children with SRS reported in earlier publications. There were more individuals who were small for gestational age in the 11p15.5 LOM group and SRS group with no identified epigenetic/genetic etiology compared to those with upd(7)mat. Triangular face and frontal bossing were more common in individuals with 11p15.5 LOM and no epigenetic/genetic etiology cases compared to those with upd(7)mat. Facial and limb asymmetry were more common in individuals with 11p15.5 LOM compared to the upd(7)mat and SRS with no epigenetic/genetic abnormalities groups [Luk et al 2016b].

Another study comparing individuals with SRS due to 11p15.5 LOM to individuals with SRS due to upd(7)mat showed similar body weight at diagnosis (3 and 3.2 SD below the mean, respectively), but heights were greater in individuals with 11p15.5 LOM (3.0 SD below the mean) compared to those with upd(7)mat (3.8 SD below the mean). Asymmetry was seen in 76% of individuals with 11p15.5 LOM vs 50% of individuals with upd(7)mat. Most cases in both groups had normal neurocognitive development (86% of individuals with 11p15.5 LOM and 80% of individuals with upd(7)mat). Triangular facies were reported in 89% of individuals with 11p15.5 LOM vs 50% of those with upd(7)mat. Also of note, clinodactyly was more frequently reported in individuals with 11p11.5 LOM (68%) compared to those with upd(7)mat (20%). Genital anomalies were seen in 19% of individuals with 11p15.5 LOM and none of the individuals with upd(7)mat [Lin et al 2021].

Penetrance

Penetrance for SRS is estimated to be 100% for males and females. Sex-limited penetrance is observed in individuals with *CDKN1C*- or *IGF2*-related SRS.

Prevalence

The prevalence of SRS is unknown and was previously estimated at 1:30,000-100,000 (A Toutain, Orphanet). A retrospective study conducted in Estonia estimated the minimum prevalence of SRS at birth as 1:15,886 [Yakoreva et al 2019].

Genetically Related (Allelic) Disorders

Table 3 includes other phenotypes associated with genetic alterations in genes and chromosomal regions involved in Silver-Russell syndrome (SRS).

Table 3. Allelic Disorders

Phenotype	Molecular Alteration(s) [1]
Beckwith-Wiedemann syndrome (BWS)	• Abnormal regulation of gene transcription in the imprinted domain on chr 11p15.5 (i.e., the BWS critical region) • Maternally inherited loss-of-function pathogenic variant in *CDKN1C*
Isolated hemihyperplasia	Molecular alterations of chr 11p15 incl: • Loss of methylation at the ICR2 • Gain of methylation at the ICR1 [1] • Paternal UPD of chr 11p15 [2]
Isolated hemihypoplasia	Somatic mosaicism for loss of methylation at paternal ICR1 [3]
Isolated Wilms tumor	Constitutional alterations of chr 11p15.5 incl: • Hypermethylation at the ICR1 • Paternal UPD of chr 11p15.5 • Genomic abnormalities incl deletions & insertions [4]
IMAGe syndrome	Maternally inherited gain-of-function pathogenic variant in *CDKN1C*

chr = chromosome; ICR = imprinting control region; UPD = uniparental disomy
1. Martin et al [2005]
2. Shuman et al [2002]
3. Zeschnigk et al [2008], Eggermann et al [2009]
4. Scott et al [2008]

Differential Diagnosis

Intrauterine growth restriction and short stature. The differential diagnosis of Silver-Russell syndrome (SRS) includes any condition that can cause intrauterine growth restriction and short stature. The presence of disproportionate short stature excludes the diagnosis of SRS and suggests a diagnosis of skeletal dysplasia. A skeletal survey can be performed to exclude a skeletal dysplasia that may mimic SRS.

Note: Bone age may be delayed in children with SRS; however, delayed bone age is a nonspecific finding frequently seen in children with intrauterine growth restriction of many etiologies.

Microcephaly. Individuals with SRS have a normal head circumference or relative macrocephaly. The presence of significant microcephaly should prompt a search for an alternative etiology.

Disorders with intrauterine growth restriction and poor postnatal growth of interest in the differential diagnosis of SRS are listed in Tables 4a and 4b.

Table 4a. Monogenic Disorders with IUGR and Poor Postnatal Growth to Consider in the Differential Diagnosis of Silver-Russell Syndrome

Gene(s)	Disorder	MOI	Characteristic Features of Disorder	
			Overlapping w/SRS (in addition to IUGR & poor postnatal growth)	Distinguishing from SRS
BLM	Bloom syndrome	AR	Café au lait macules	• Abnormal sister chromatid exchange • Microcephaly
BRCA1 *BRCA2* *BRIP1* *ERCC4* *FAAP100* *FANCA* *FANCB* *FANCC* *FANCD2* *FANCE* *FANCF* *FANCG* *FANCI* *FANCL* *FANCM* *MAD2L2* *PALB2* *RAD51* *RAD51C* *RFWD3* *SLX4* *UBE2T* *XRCC2*	Fanconi anemia	AR AD XL	Café au lait macules	• ↑ chromosome breakage • Absent thumb(s) or thumb hypoplasia • Microcephaly • Radial anomalies • ↑ malignancy risk
CCDC8 *CUL7* *OBSL1*	Three M syndrome	AR	• Fifth finger clinodactyly • Relatively large head • Triangular facies	• Short broad neck • No limb or facial asymmetry
CDC45 *CDC6* *CDT1* *GMNN* *MCM5* *ORC1* *ORC4* *ORC6*	Meier-Gorlin syndrome (OMIM PS224690)	AR AD	• Frontal bossing • Small mouth	• Absent patellae • Microcephaly • Microtia
CDKN1C	IMAGe syndrome	AD [1]	• Frontal bossing • Genital abnormalities	• Adrenal hypoplasia • Adrenal insufficiency • Metaphyseal dysplasia
DDX11	Warsaw syndrome	AR	Fifth finger clinodactyly	• ↑ chromosome breakage • Hearing loss • Microcephaly
IGF1R	Insulin growth factor 1 resistance (incl deletion of 15q26.1) [2]	AR AD	• Clinodactyly • Dental anomalies	• Global DD • Microcephaly • Synophrys
NBN	Nijmegen breakage syndrome	AR		• Chromosome instability • Microcephaly • Sloping forehead

Table 4a. continued from previous page.

Gene(s)	Disorder	MOI	Characteristic Features of Disorder	
			Overlapping w/SRS (in addition to IUGR & poor postnatal growth)	Distinguishing from SRS
PCNT	Microcephalic osteo dysplastic primordial dwarfism type II	AR	High-pitched voice	• Disproportionate short stature w/ mesomelic shortening • Microcephaly • Skeletal anomalies • Dysmorphic facial features
SRCAP	Floating-Harbor syndrome	AD	• Clinodactyly • High-pitched voice • Male genital anomalies	• Wide mouth • Prominent nose • Clavicular abnormalities • Cone-shaped epiphyses • Broad thumbs & great toes

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; IUGR = intrauterine growth restriction; MOI = mode of inheritance; XL = X-linked

1. Typically a *CDKN1C* pathogenic variant causing IMAGe syndrome is inherited in an autosomal dominant manner; however, only maternal transmission of the pathogenic variant results in IMAGe syndrome.

2. Bruce et al [2009], Ocaranza et al [2017]

Chromosomal abnormalities. Many conditions caused by a chromosome imbalance can be associated with small size for gestational age and poor postnatal growth, leading to a misdiagnosis of SRS. A chromosomal microarray, preferably using a SNP-based platform, can be helpful for identifying deletions and duplications as well as regions of homozygosity, giving potential clues to chromosomal uniparental disomy and rare recessive disorders in cases of consanguinity [Grote et al 2014]. Uniparental disomy of several chromosomes have been reported to cause an SRS-like phenotype, including chromosomes 6, 14 (Temple syndrome), 16, and 20 [Sachwitz et al 2016, Wakeling et al 2017, Geoffron et al 2018].

Table 4b. Chromosomal Abnormalities Associated with IUGR and Poor Postnatal Growth to Consider in the Differential Diagnosis of Silver-Russell Syndrome

Chromosomal Abnormality	Characteristic Features of Disorder	
	Overlapping w/SRS (in addition to IUGR & poor postnatal growth)	Distinguishing from SRS
Diploid/triploid mixoploidy [1]	Limb asymmetry	• Global DD • Microcephaly
Maternal UPD of chr 6	• Triangular face • Frontal bossing • Clinodactyly	• No asymmetry • No relative macrocephaly • No postnatal growth restriction; catch-up growth seen in many persons
Temple syndrome (maternal UPD of chr 14), paternal chr 14 deletion, or LOM at 14q32) (OMIM 616222)	Many features overlap w/SRS.	• Challenging to distinguish on clinical basis • Later in life, affected persons are overweight w/truncal obesity.

Table 4b. continued from previous page.

Chromosomal Abnormality	Characteristic Features of Disorder	
	Overlapping w/SRS (in addition to IUGR & poor postnatal growth)	Distinguishing from SRS
Maternal UPD of chr 20 [2] or deletion of chr 20q13.2 (loss of paternally expressed *GNAS*)	• Triangular face • Feeding difficulties • Clinodactyly • Cryptorchidism	• Hypotonia • No relative macrocephaly • No asymmetry

chr = chromosome; DD = developmental delay; IUGR = intrauterine growth restriction; LOM = loss of methylation; UPD = uniparental disomy
1. Graham et al [1981]
2. Tannorella et al [2021]

Fetal alcohol syndrome can also be considered in the differential diagnosis of SRS. Like SRS, fetal alcohol syndrome is associated with small size for gestational age, poor postnatal growth, and fifth finger clinodactyly. Unlike SRS, fetal alcohol syndrome is also associated with microcephaly, hypoplastic philtrum, short palpebral fissures, and a history of in utero exposure to alcohol.

Multilocus imprinting disturbances (MLID). Individuals with MLID may present with single or multiple imprinting disorders (e.g., SRS, Beckwith-Wiedemann syndrome [BWS]) [Grosvenor et al 2022] or may be phenotypically normal. Although a genetic etiology has not been identified in many children with MLID, 20%-30% of mothers of children with MLID and significant reproductive issues may have trans-acting, compound heterozygous, or homozygous pathogenic variants in maternal effect genes encoding subcortical maternal complex (SCMC) proteins [Eggermann et al 2022, Tannorella et al 2022]. SCMC proteins are involved with early embryonic development and maturation of oocytes. Pathogenic variants in the SCMC genes (*NLRP2*, *NLRP5*, *NLRP7*, *PADI6*, and *KHDC3L*) can result in reproductive failure, molar pregnancies, and children with imprinting disorders [Eggermann et al 2022]. One individual with MLID and paternal uniparental disomy (UPD) of chromosome 20 has been reported [Choufani et al 2021].

For individuals with methylation alterations in the 11p15 imprinted domain as well as other imprinted loci, review of the maternal history should be undertaken for findings such as recurrent pregnancy loss or molar pregnancy. In these situations, consideration should be given to testing for pathogenic variants in maternal effect genes that lead to SRS. If a pathogenic variant in a maternal effect gene is detected in the proband and mother, information regarding the increased risk for reproductive complications such as preeclampsia, recurrent pregnancy loss, and molar pregnancy as well as the significant risk for having children with imprinting disorders should be addressed through genetic counseling [Elbracht et al 2020, Eggermann et al 2022, Tannorella et al 2022].

Eleven individuals with SRS tested using MS-MLPA assays were found to have MLID with methylation disturbances at up to nine imprinted differentially methylated regions (iDMRs) per person. In addition to imprinting control region 1 (ICR1), the most frequent loci involved were ICR2 and *MEST*. When both ICR1 and ICR2 iDMRs at 11p15.5 exhibited loss of methylation (LOM), the phenotype depended on the locus that was more severely affected, as seen in the five individuals with SRS/MLID with LOM at both iDMRs [Bilo et al 2023].

Note: It is not yet clear if oligogenic or multifactorial causes are relevant in MLID. While it appears that some heterozygous variants in SCMC genes may be disease causing, such cases may also be associated with unidentified pathogenic variants in the second allele or pathogenic variants in other SCMC genes. In addition, the potential interaction of pathogenic variants with interventions such as assisted reproductive technology will be an important area of future work.

Management

International consensus management guidelines for Silver-Russell Syndrome (SRS) have been published [Wakeling et al 2017].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with SRS, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Silver-Russell Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Growth	Assessment & plotting of growth on age-appropriate growth curves	See MAGIC Foundation for SRS-specific growth charts.
Endocrine	Eval by endocrinologist for GH deficiency, hypoglycemia, & precocious or early-onset puberty	Referral to endocrinologist is recommended as soon as diagnosis of SRS is suspected or made.
GI & feeding difficulties	Consultation w/pediatric gastroenterologist & dietician/nutritionist	• For children suspected of having GERD, eval for esophagitis incl video swallow studies, gastric emptying studies, pH probe, & endoscopy are recommended. • Intestinal malrotation has been reported & needs to be ruled out in those w/feeding disorders, constipation, & delayed gastric emptying.
Skeletal anomalies	Physical exam for eval of possible limb length asymmetry & scoliosis.	
Craniofacial disorders	• Physical exam for cleft palate & bifid uvula w/submucous cleft palate • Referral to craniofacial center for further eval & mgmt	
Genitourinary	Eval of possible hypospadias &/or cryptorchidism	
Cardiac	Clinical exam for cardiac murmur or other signs/symptoms of congenital heart disease	Baseline echocardiogram or referral to cardiologist as clinically indicated
Neurodevelopment	Eval of neurocognitive development, speech, language, & muscle tone	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of SRS to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

GERD = gastroesophageal reflux disease; GH = growth hormone; MOI = mode of inheritance; SRS = Silver-Russell syndrome

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for SRS. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists including an endocrinologist, gastroenterologist, dietician, clinical geneticist and genetic counselor, craniofacial team, orthopedic surgeon, neurologist, speech-language therapist, and psychologist (see Table 6).

Table 6. Silver-Russell Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Growth abnormalities	Early referral to endocrinologist & consideration of GH therapy [1]	Mgmt is best undertaken in center w/experience w/growth disorders.
Hypoglycemia	Hypoglycemia should be prevented & aggressively managed if present.	• Frequent feeding, avoidance of prolonged fasting between feeds (≤4 hours in infants), & complex carbohydrates are recommended. • Monitoring for urinary ketones after prolonged fasting (incl when infants start sleeping through the night) or w/excess physical activity or illness is recommended.
Endocrine (other)	Early referral to endocrinologist for signs of premature adrenarche, early & accelerated central puberty, & insulin resistance	Personalized treatment w/GnRH analogs for at least 2 yrs in children w/evidence of central puberty (starting no later than age 12 yrs in girls & age 13 yrs in boys) can be considered to preserve adult height potential. [2, 3]
GI & feeding difficulties	Early referral to GI specialist &/or dietician to initiate early treatment	• Measures incl nutritional & caloric supplements; treatment of GERD; speech &/or occupational therapy for oral motor problems & oral aversion; appetite stimulants such as cyproheptadine; enteral feeding w/gastrostomy or jejunostomy tube for extreme cases of feeding aversion &/or GERD w/ or w/o fundoplication • With non-volitional feeding, too rapid & excessive weight gain must be avoided.
Skeletal abnormalities	Early referral to orthopedic surgeon for mgmt of limb length discrepancy & scoliosis	• Initial treatment of limb length discrepancy can incl use of a shoe lift. In older children, limb lengthening w/distraction osteogenesis is a commonly used procedure. When single-segment limb lengthening is sufficient, limb lengthening w/femoral internal distracters is generally done prior to completion of growth but close to final attainment of height. For young children w/leg length discrepancy >4 cm, lengthening is done in the lower segment (tibia) w/ external fixators. [4] • Scoliosis & kyphosis should be monitored & early bracing is recommended. Many individuals will need corrective surgery. [5]
Craniofacial anomalies	Early referral to craniofacial expert for severe micrognathia, cleft palate, &/or complex dental anomalies	• Dental hygiene & dental crowding is managed routinely by pediatric dentist &/or orthodontist. • Early dental care, orthodontia for dental crowding, & maxillofacial surgery may be needed in older children once growth is completed.
Genitourinary anomalies	Early referral to urologist for children w/ hypospadias &/or cryptorchidism.	Males w/micropenis & females w/internal genitourinary anomalies (e.g., Mayer-Rokitansky-Kuster-Hauser syndrome) benefit from referral to multidisciplinary DSD center.

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Family/Community	• Ensure appropriate social work involvement to connect families w/ local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics (enrollment for children & adults w/lower IQ & developmental disabilities).

DSD = disorders of sex development; GH = growth hormone; GI = gastrointestinal; GnRH = gonadotropin-releasing hormone
1. Children with SRS have benefited from GH supplementation [Toumba et al 2010, Binder et al 2013]. Smeets et al [2016] found that height gain in children with SRS treated with GH was similar to that in children who did not have SRS, although final heights were less in individuals with SRS because their heights were lower at the initiation of treatment. A study by Rizzo et al [2001] demonstrated significant increase in height in children with SRS treated with GH but without a change in body or limb asymmetry.
2. Wakeling et al [2017]
3. Many children with SRS do not achieve normal stature even with administration of human GH if rapid bone age advancement during puberty is not managed.
4. Goldman et al [2013]
5. Yamaguchi et al [2015]

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Referral to a psychologist for neuropsychological testing should also be considered for children with developmental concerns. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.

    - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
    - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction. Physical therapy is recommended to maximize mobility and to reduce the risk for or severity of later-onset orthopedic complications (e.g., contractures).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Surveillance

Surveillance guidelines for children with SRS are outlined in Wakeling et al [2017].

Table 7. Silver-Russell Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Growth	Measurement of growth parameters w/special attention to growth velocity & weight gain	At each visit

Table 7. continued from previous page.

System/Concern	Evaluation	Frequency
Endocrine	• Monitor for ketotic hypoglycemia (urine ketones & blood glucose) during infancy & in older children w/macrocephaly, lean body habitus, & poor appetite. • Monitor urine ketones to prevent hypoglycemia in infants when frequency of feeding is being ↓ & in children who are acutely ill w/↓ feeding or fever & in older children at time of ↑ physical activity. • Monitor for early signs of puberty incl early adrenarche due to risk of rapid bone age advancement & reduced final height despite GH therapy.	
GI & feeding difficulties	• Eval of nutritional status & safety of oral intake • Monitor & manage nasogastric feeding or gastrostomy tube, if needed. • Monitor for constipation.	
Skeletal	• Exam & measurement of limb length discrepancy. Measurement of infant lengths & both legs recorded, & longer limb entered on a growth curve. For measuring height in older children, an appropriate-sized lift sufficient to level the hips should be placed under the foot of the shorter lower extremity. • Eval of scoliosis	
Development	• Monitor developmental progress & educational needs. • Monitor speech articulation & language.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility & self-help skills	
Genitourinary	Monitor for cryptorchidism	At each visit in infancy
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

GH = growth hormone; GI = gastrointestinal; OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Avoid prolonged fasting in infants and young children because of the risk of inducing hypoglycemia. For this reason, testing for GH deficiency by fasting is contraindicated [Wakeling et al 2017].

Avoid elective surgery whenever possible. If surgery is unavoidable, physicians must be aware of the risk for hypoglycemia, hypothermia, difficult healing, and difficult intubation (due to abnormal tooth distribution and micrognathia, which can affect airway visualization and the intubation process).

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The

following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

The following recurrence risk information pertains to individuals who have Silver-Russell syndrome (SRS) without other imprinting disorders, such as multilocus imprinting disturbances (MLID) (see Differential Diagnosis for more information on MLID).

In most families, a proband with SRS represents a simplex case (a single affected family member) and has SRS as a result of an apparent *de novo* epigenetic or genetic alteration. While the majority of families are presumed to have a very low recurrence risk, SRS can occur as the result of a predisposing genetic alteration associated with up to a 50% recurrence risk depending on the nature of the genetic alteration and the sex of the transmitting parent. Reliable SRS recurrence risk assessment therefore requires identification of the causative genetic mechanism in the proband.

Chromosome 11p15.5-Related SRS – Risk to Family Members

Parents of a proband

- The majority of individuals with chromosome 11p15.5-related SRS have the disorder as the result of 11p15.5 hypomethylation at the paternal imprinting control region 1 (ICR1) that occurred as a postzygotic event.
- Rarely, a parent of an individual with 11p15.5-related SRS has a predisposing genetic alteration that results in an SRS-causing genetic alteration when transmitted to offspring. Rare familial cases of chromosome 11p15.5-related SRS have been reported due to predisposing genetic alterations including the following:
  - Maternally inherited 11p15 duplication
  - Maternally inherited *CDKN1C* gain−of-function pathogenic variant
  - Paternally inherited *IGF2* loss−of−function pathogenic variant
  - Paternally inherited small deletion close to the boundaries of the ICR1
- To allow reliable recurrence risk counseling, the following testing is recommended:
  - **Proband with hypomethylation at the ICR1 on the paternal chromosome.** In the proband, SNP chromosomal microarray (CMA) to detect underlying copy number variants (CNVs) and cytogenetic analysis to detect larger duplications in the 11p15.5 region, which may involve translocations and inversions. If a genetic alteration is identified in the proband, the parents of the proband should undergo testing (i.e., SNP CMA or cytogenetic analysis) capable of detecting the genetic alteration identified in the proband.
  - **Proband with a *CDKN1C* or *IGF2* pathogenic variant.** Molecular genetic testing of the parents for the pathogenic variant identified in the proband. If the genetic alteration identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered: the proband has a *de novo* pathogenic variant, or the proband inherited a genetic alteration pathogenic variant from a parent with germline (or somatic and germline) mosaicism. (Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ [gonadal] cells only.)
- The family history of some individuals diagnosed with *CDKN1C*- or *IGF2*-related SRS may appear to be negative because of sex-limited penetrance. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that the respective parent is not heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If neither parent of the proband is found to have a predisposing genetic alteration, the risk to sibs is presumed to be low (empiric data are not available) but still increased compared to the general population because of the possibility of parental germline mosaicism for a predisposing genetic alteration (paternal germline mosaicism for an *IGF2* pathogenic variant has been reported) and the possibility that a parent has a pathogenic variant in a gene associated with MLID (see Differential Diagnosis, **MLID**).
- If a parent has a CNV involving the 11p15.5 region, the risk to sibs is variable and can be as high as 50% depending on the size of the affected fragment [Abi Habib et al 2017, Wakeling et al 2017, Heide et al 2018].
  - Abi Habib et al [2017] reported a familial case with hypomethylation caused by a paternally transmitted deletion close to the boundaries of the 11p15.5 ICR1 with the father and his children affected. They estimated that such deletions are present in approximately 1% of individuals with SRS due to ICR1 hypomethylation.
  - Heide et al [2018] reported a maternally inherited 11p15.5 duplication.
- If a parent has a translocation or inversion involving the 11p15.5 region, the risk to sibs is increased and depends on the specific chromosomal rearrangement and other variables.
- If the mother of the proband has a *CDKN1C* gain-of-function pathogenic variant or the father of the proband has an *IGF2* loss-of-function pathogenic variant, the recurrence risk of SRS in sibs is 50%.

Offspring of a proband. The risk to offspring depends on the genetic mechanism underlying chromosome 11p15.5-related SRS in the proband:

- If no underlying 11p15.5 genetic alteration is identified in the proband, the risk to offspring of SRS is presumed to be low, as the imprint is normally reset in the germline (empiric data are not available). There is also a low recurrence risk associated with the possibility of unidentified molecular alterations or MLID (see Differential Diagnosis, **MLID**).
- If the proband has a CNV or chromosomal rearrangement, the risk to offspring of SRS may be as high as 50% depending on the sex of the proband and the specific genetic alteration.
- If the proband has a pathogenic variant in *CDKN1C* or *IGF2*, offspring have a 50% chance of inheriting the pathogenic variant; the risk of SRS in offspring depends on the involved gene and the sex of the proband.
  - Offspring who inherit a *CDKN1C* gain-of-function pathogenic variant from a female proband will have SRS; offspring who inherit a *CDKN1C* gain-of-function pathogenic variant from a male proband will not have SRS.
  - Offspring who inherit an *IGF2* loss−of−function pathogenic variant from a male proband will have SRS; offspring who inherit an *IGF2* loss−of−function pathogenic variant from a female proband will not have SRS.
- If the proband has somatic mosaicism for maternal uniparental disomy of chromosome 11 (upd(11)mat), the risk to offspring of SRS is presumed to be low, as the imprint is normally reset in the germline.

Chromosome 7-Related SRS – Risk to Family Members

Parents of a proband

- In most individuals with SRS caused by maternal uniparental disomy of chromosome 7 (upd(7)mat), the genetic alteration occurred as a *de novo* event.
- Rarely, a parent of a proband with upd(7)mat has a predisposing genetic alteration. Such predisposing genetic alterations include the following:
  - CNV in the critical imprinted region on chromosome 7 (e.g., paternally inherited deletion or maternally inherited duplication involving 7q32 [*MEST*])

- A translocation involving chromosome 7
- To allow reliable recurrence risk counseling, the following testing is recommended for the proband and parents of the proband:
  - **Proband.** SNP CMA (to detect underlying CNVs) and cytogenetic analysis (to detect translocations and other rearrangements involving chromosome 7)
  - **Parents of the proband.** If a genetic alteration is identified in the proband, the parents of the proband should undergo testing (i.e., SNP CMA and/or cytogenetic analysis) capable of detecting the genetic alteration identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If neither parent of the proband is found to have a predisposing genetic alteration, the risk to sibs is presumed to be low but still increased compared to the general population because of the possibility of parental germline mosaicism for a predisposing genetic alteration and the possibility that a parent has a pathogenic variant in a gene associated with MLID (see Differential Diagnosis, **MLID**).
- If the father of the proband has a deletion involving 7q32 (*MEST*) or the mother of the proband has a duplication involving 7q32 (*MEST*), the recurrence risk to sibs may be 50%.
- If a parent has a translocation involving chromosome 7, the risk to sibs is increased and depends on the specific chromosome rearrangement and the other variables. Behnecke et al [2012] described upd(7)mat associated with a familial translocation involving chromosome 7.

Offspring of a proband. The risk for recurrence in sibs of the proband is presumed to be low if a predisposing genetic alteration has been ruled out.

HMGA2- and *PLAG1*-Related SRS – Risk to Family Members

Parents of a proband

- Some individuals with *HMGA2*- or *PLAG1*-related SRS have the disorder as the result of a deletion or intragenic pathogenic variant inherited from a heterozygous parent.
- Some individuals with *HMGA2*- or *PLAG1*-related SRS have the disorder as the result of a deletion or intragenic pathogenic variant that occurred *de novo* in the proband or was inherited from a parent with germline (or somatic and germline) mosaicism.
- To allow reliable recurrence risk counseling, the following testing is recommended:
  - **Proband with an intragenic *HMGA2* or *PLAG1* pathogenic variant.** Molecular genetic testing of the parents for the pathogenic variant identified in the proband
  - **Proband with a deletion involving *HMGA2* or *PLAG1*.** SNP CMA of the parents for the deletion identified in the proband
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* genetic alteration.
  - The proband inherited a genetic alteration from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is known to have an *HMGA2* or *PLAG1* intragenic pathogenic variant or a deletion involving *HMGA2* or *PLAG1*, the risk to the sibs of inheriting the pathogenic variant is 50%.
  - Familial SRS recurrence due to *HMGA2* and *PLAG1* genetic alterations has been reported [Abi Habib et al 2018, Hübner et al 2020, Vado et al 2020, Dong et al 2023].

- Both maternal and paternal transmission of genetic alterations involving *PLAG1* and *HMGA2* have been reported.

- If the *HMGA2* or *PLAG1* genetic alteration identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk of SRS in sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *HMGA2*- or *PLAG1*-related SRS has a 50% chance of inheriting the genetic alteration; a child who inherits an intragenic *HMGA2* or *PLAG1* pathogenic variant or a deletion involving *HMGA2* or *PLAG1* will have SRS.

Proband with No SRS-Causing Genetic Alteration Identified – Risk to Family Members

The recurrence risk to sibs of a proband and offspring of a proband is likely low. However, the risk may be increased if the proband has a genetic alteration that is not detected by current genetic testing platforms or a pathogenic variant in an MLID-related gene (see Differential Diagnosis, **MLID**).

Related Genetic Counseling Issues

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Loss of paternal methylation at the 11p1.5 ICR1 *H19/IGF2* regions. Reliable prenatal testing for loss of paternal methylation at the 11p1.5 ICR1 *H19/IGF2* region is not possible, since studies show that differentially methylated regions are not firmly established by the gestational age at which chorionic villus sampling (CVS) is performed (10-12 weeks' gestation) [Paganini et al 2015]. Additionally, there are no validated studies establishing reliable testing for differential methylation patterns in amniocytes. Since the majority of epigenetic pathogenic variants can be mosaic, reliable prenatal testing becomes even more challenging [Eggermann et al 2016].

Maternal uniparental disomy. Upd(7)mat can be diagnosed prenatally. Maternal isodisomy 7 can be diagnosed with a SNP CMA. Maternal heterodisomy 7 can be diagnosed by analyzing fetal SNP CMA and comparing it to SNP CMA of both parents.

Chromosomal abnormalities. If a causative chromosomal abnormality (e.g., an unbalanced translocation involving 11p15.5, a paternal deletion, or a maternal duplication of chromosome 11p15.5 including *CDKN1C*) or a maternal duplication or paternal deletion involving 7q32.2 that includes *MEST* has been identified in the proband, prenatal testing with SNP CMA on fetal cells obtained by CVS or amniocentesis is possible. Preimplantation genetic testing can also be offered with a known chromosome anomaly depending on the size of the duplication or deletion.

Intragenic *CDKN1C*, *IGF2*, *HMGA2*, or *PLAG1* pathogenic variant or deletion involving *HMGA2* or *PLAG1*. A known maternally inherited *CDKN1C* gain-of-function pathogenic variant, paternally inherited *IGF2* loss–of–function pathogenic variant, or parental intragenic pathogenic variant or deletion involving *HMGA2* or *PLAG1* can be diagnosed using preimplantation genetic testing or prenatally with samples obtained from CVS or amniocentesis [Eggermann et al 2016, Abi Habib et al 2018].

Note: The preimplantation genetic diagnosis or prenatal finding of a genetic alteration consistent with SRS cannot be used to reliably predict clinical outcome [Eggermann et al 2016]: children with SRS demonstrate varying responses to growth hormone, variable late catch-up growth, and variable developmental outcomes.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Genetic and Rare Diseases Information Center (GARD)**
  Phone: 888-205-2311
  Silver-Russell syndrome
- **L'AISRS, Associazione Italiana Sindrome di Russell-Silver**
  Italy
  www.aisrs.it
- **L'ASBL ALICE: Association Libre d'Informations sur la Croissance des Enfants Silver Russell**
  Belgium
  www.alice.be
- **L'Association Française des Familles touchées par le syndrome de Silver Russell (SSR)**
  France
  www.silver-russell.fr
- **Magic Foundation**
  Phone: 800-362-4423
  Email: contactus@magicfoundation.org
  Russell Silver Syndrome
- **National Organization for Rare Disorders (NORD)**
  Russell-Silver Syndrome
- **Silver Russell Syndrome Global Alliance**
  www.silverrussellsyndrome.org
- **Bundesverband Kleinwüchsige Menschen (BKMF)**
  Leinestrasse 2
  28199 Bremen
  Germany
  Phone: 49-421-336169-0
  Email: info@bkmf.de
  www.bkmf.de
- **Child Growth Foundation**
  United Kingdom
  Phone: 0208 995 0257

Email: nfo@childgrowthfoundation.org
www.childgrowthfoundation.org

- **Human Growth Foundation**
  www.hgfound.org
- **Little People of America**
  Phone: 888-LPA-2001; 714-368-3689
  Fax: 707-721-1896
  Email: info@lpaonline.org
  lpaonline.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Silver-Russell Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CDKN1C	11p15.4	Cyclin-dependent kinase inhibitor 1C	CDKN1C database	CDKN1C	CDKN1C
H19	11p15.5	Unknown	H19 @ LOVD	H19	H19
HMGA2	12q14.3	High mobility group protein HMGI-C	HMGA2 database	HMGA2	HMGA2
IGF2	11p15.5	Insulin-like growth factor II	LOVD - Growth Consortium (IGF2)	IGF2	IGF2
PLAG1	8q12.1	Zinc finger protein PLAG1	PLAG1 database	PLAG1	PLAG1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Silver-Russell Syndrome (View All in OMIM)

103280	H19, IMPRINTED MATERNALLY EXPRESSED NONCODING TRANSCRIPT; H19
147470	INSULIN-LIKE GROWTH FACTOR II; IGF2
180860	SILVER-RUSSELL SYNDROME 1; SRS1
600698	HIGH MOBILITY GROUP AT-HOOK 2; HMGA2
600856	CYCLIN-DEPENDENT KINASE INHIBITOR 1C; CDKN1C
603026	PLAG1 ZINC FINGER PROTEIN; PLAG1
618905	SILVER-RUSSELL SYNDROME 2; SRS2
618907	SILVER-RUSSELL SYNDROME 4; SRS4
618908	SILVER-RUSSELL SYNDROME 5; SRS5

Molecular Pathogenesis

Chromosome 11p15.5-Related Silver-Russell Syndrome (SRS)

Imprinted genes often occur in clusters that include a regulatory imprinting control region (ICR). The importance of imprinted genes at chromosome 11p15.5 for fetal growth is known [DeChiara et al 1990, Fitzpatrick et al 2002, Eggermann et al 2009]. At one of the 11p15.5 imprinted clusters, parent-specific differential methylation of imprinting control region 1 (ICR1) regulates reciprocal expression of *IGF2*, which encodes a growth factor crucial for fetal development, and the noncoding transcript *H19*. In SRS, hypomethylation of the ICR1 leads to biallelic *H19* expression and biallelic silencing of *IGF2*, resulting in growth restriction; this accounts for approximately 35%-67% of affected individuals [Gicquel et al 2005, Abu-Amero et al 2010, Wakeling et al 2017].

See Figure 2 for an outline of the molecular changes associated with 11p15.5-related SRS.

Abnormal methylation at 11p15.5 can occur through several mechanisms:

- **Hypomethylation** at the ICR1 on the paternal chromosome is detected in 35%-67% of individuals with SRS. Because the ICR1 regulates methylation of *IGF2* and *H19*, differential analysis showed that in most cases both genes are hypomethylated.

  Note: (1) Because 11p15.5 hypomethylation at the paternal ICR1 is usually a postzygotic event, most individuals with SRS have a somatic distribution of abnormal methylation patterns (see Table 1 for testing implications). About 1% of the individuals with 11p15.5 ICR1 hypomethylation have a deletion close to the boundaries of the ICR1 on the paternal allele [Abi Habib et al 2017]. (2) A small number of individuals with SRS have selective hypomethylation of only *H19* or only *IGF2* [Bartholdi et al 2009].

- A small number of individuals with SRS have a duplication involving the maternal 11p15.5 region. Larger duplications, which can involve translocations and inversions, are detectable by cytogenetic analysis [Fisher et al 2002, Eggermann et al 2005], and deletions and duplications are detectable by SNP microarray [Begemann et al 2012, Eggermann et al 2012a] (see Table 1).

- Rare familial cases of SRS have been reported with underlying mechanisms including the following:
  - Maternally inherited 11p15 duplication
  - Maternally inherited *CDKN1C* gain−of-function pathogenic variants
  - Paternally inherited *IGF2* loss−of−function pathogenic variants
  - Small paternally inherited deletions adjacent to the 11p15.5 ICR1.

In these families, the risk of recurrence can be as high as 50%. Investigation for underlying CNVs in individuals with 11p15.5 loss of methylation is therefore important [Abi Habib et al 2017, Wakeling et al 2017, Heide et al 2018].

Chromosome 7-Related SRS

The genetic loci responsible for maternal uniparental disomy of chromosome 7 (upd(7)mat) imprinting appear to include at least *PEG1*/*MEST*, which is an imprinted gene cluster at 7q32 [Hannula et al 2001, Eggermann et al 2012a]. A reported case with a small 79-kb deletion at 7q32.2 supports loss of the paternal copy of *MEST* as a cause of SRS [Vincent et al 2022]. Abnormal methylation at 7q32 can occur through the following several mechanisms:

- **Upd(7)mat,** reported in 7%-10% of individuals with SRS [Wakeling 2011, Singh et al 2023], can occur by the following:
  - Maternal isodisomy or heterodisomy [Bernard et al 1999, Price et al 1999]
  - Mosaicism for upd(7)mat [Reboul et al 2006]

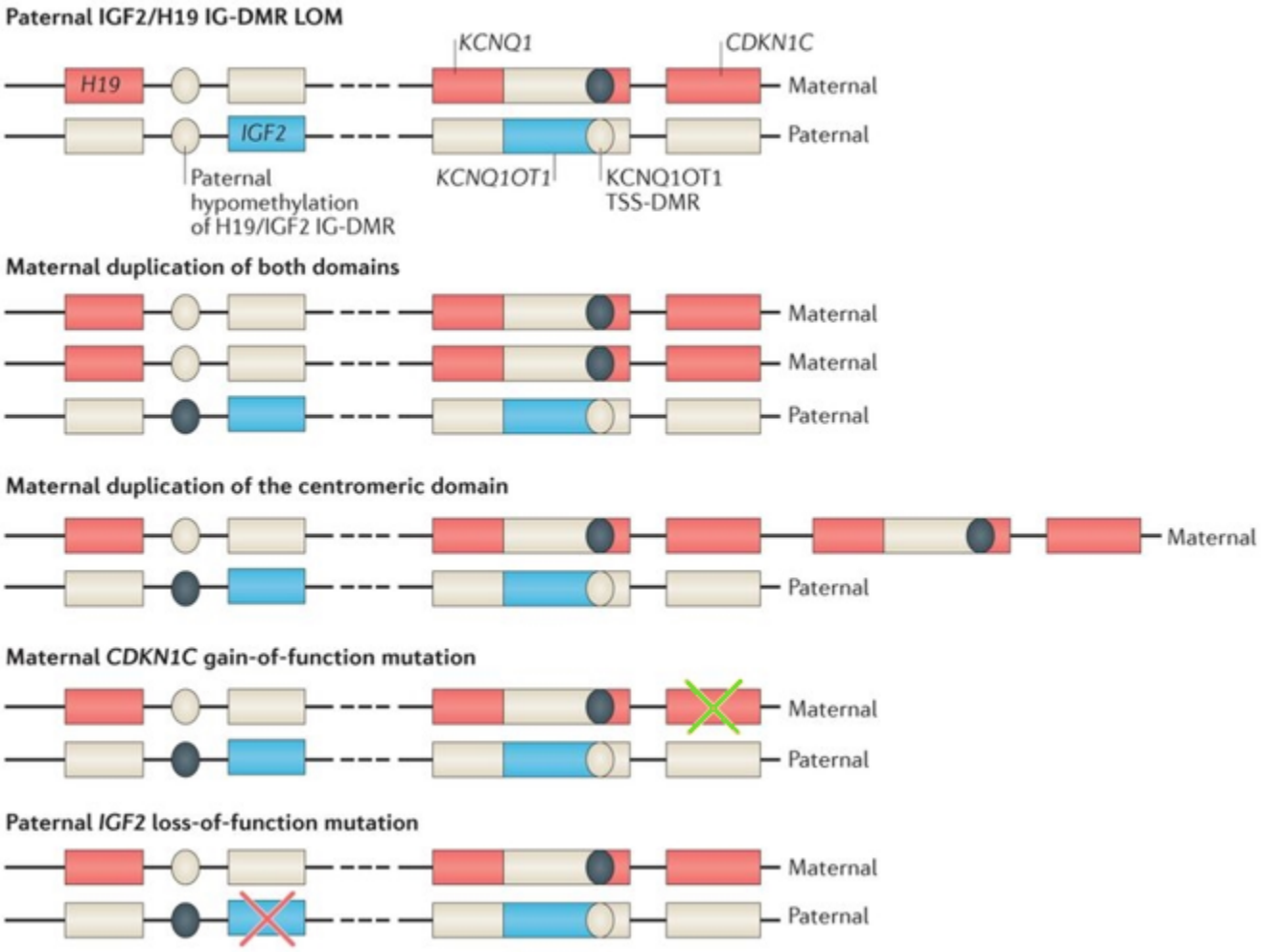

Figure 2. Paternal hypomethylation of the imprinting control region 1 (ICR1; also called *H19*/*IGF2* IG-DMR, or intergenic differentially methylated region) results in loss of paternal *IGF2* expression and gain of maternal *H19* expression, which leads to a growth restriction phenotype [Gicquel et al 2005, Wakeling et al 2017]. Rarely, maternal duplication of the centromeric or both domains increases dosage of *CDKN1C*. Rare familial cases have been associated with a maternal *CDKN1C* gain-of-function pathogenic variant (green X) [Brioude et al 2013, Wakeling et al 2017] or a paternal *IGF2* loss-of-function pathogenic variant (red X) [Begemann et al 2015, Wakeling et al 2017].

Adapted from Wakeling et al [2017]

  - Segmental upd(7)mat has been reported: one individual with upd(7)mat for 7q31-qter [Hannula et al 2001], and two individuals with upd(7)mat of most of the long arm of chromosome 7 (7q11.2-qter) [Eggermann 2008].
- **Chromosome 7 cytogenetic abnormalities,** which are rarely seen in individuals with SRS, include the following:
  - Mosaic trisomy 7 with maternal heterodisomy has been reported in two children [Flori et al 2005, Font-Montgomery et al 2005], one of whom was identified prenatally [Font-Montgomery et al 2005]
- 46,XY/46,XY and upd(7)mat mosaicism [Fuke et al 2013]
- Maternal segmental isodisomy of 86.51 Mb of chromosome 7q11q36 and absence of heterozygosity has been reported in a female with SRS who also had congenital chloride diarrhea caused by homozygous pathogenic variants in *SLC26A3*, which maps to 7q22.3-q31.1 [Lyu et al 2021].
- Several deletions of 7q32.2 including the paternal *MEST* allele [Carrera et al 2016, Vincent et al 2022]

Deletions and Intragenic Pathogenic Variants Involving *HMGA2*

Deletions of the *HMGA2* locus (12q14.3) have been reported in several individuals with SRS, including a 7.3-kb deletion that includes exons 1 and 2 [Leszinski et al 2018, Mercadante et al 2020].

Loss-of-function pathogenic variants have been identified in several individuals, five of which were identified by next-generation sequencing [Hübner et al 2020], including a deletion of exons 1-3 in a child and the affected father, a *de novo* splice variant, and a homozygous pathogenic variant (c.239C>T [p.Pro80Leu]) in two sibs with severe short stature (parents were first cousins and short for their families). Two additional individuals have also been reported by Abi Habib et al [2018].

Deletions and Intragenic Pathogenic Variants Involving *PLAG1*

A 77-kb deletion of 8q12.1 involving *PLAG1* and *CHCHD7* has been reported in a male [Baba et al 2022].

Loss-of-function pathogenic variants have been reported in several individuals. Abi Habib et al [2018] reported two *PLAG1* pathogenic variants including one in two female sibs and their affected mother. A custom next-generation sequencing panel identified a frameshift variant in a three-generation family with five affected individuals (c.551delA [p.Lys184SerfsTer45]) [Vado et al 2020]. Exome sequencing also identified a pathogenic variant (c.131del [p.Asn44ThrfsTer6]) in a child and the affected father [Dong et al 2023].

Chapter Notes

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