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Silver–Russell Syndrome: From Molecular Pathogenesis to Clinical Management

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Silver–Russell syndrome (SRS) is a rare imprinting disorder characterized by prenatal and postnatal growth retardation, relative macrocephaly, prominent forehead, body asymmetry, and feeding difficulties. The estimated incidence ranges from 1 in 30,000 to 1 in 100,000 live births. Diagnosis is primarily clinical, supported by the Netchine–Harbison Clinical Scoring System (NH-CSS), while molecular confirmation is achieved in approximately 60% of cases. The two major genetic mechanisms are loss of methylation (LOM) at chromosome 11p15 and maternal uniparental disomy for chromosome 7 (upd(7)mat); rarer causes include abnormalities involving chromosomes 14q32, 20, and 16, or mutations in CDKN1C or IGF2. Management focuses on optimizing nutrition, preventing hypoglycemia, and addressing growth failure. Growth hormone (GH) therapy effectively improves height, body composition, and appetite in most patients, though partial IGF-1 resistance may occur, particularly in 11p15 LOM. Puberty often begins early and progresses rapidly, contributing to compromised final height; combined GH and GnRH analogue therapy may be beneficial in selected cases. Long-term follow-up is required to monitor metabolic outcomes and support individualized care based on molecular subtype. A multidisciplinary approach remains essential to address the complex endocrine, nutritional, and developmental challenges of SRS throughout childhood and adolescence.

Key words: Silver-Russell syndrome, Imprinting disorder, Uniparental disomy, Growth hormone

REVIEW ARTICLE

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INTRODUCTION

Silver–Russell syndrome (SRS, also referred to as Russell–Silver syndrome; OMIM #180860) is a rare but well-defined growth disorder characterized by both prenatal and postnatal growth retardation. The condition was independently reported by Silver et al. [1] and Russell [2], who described children presenting with low birth weight, short stature after birth, distinctive facial features, and body asymmetry. Nearly all affected infants are born small for gestational age (SGA). Affected individuals typically present with relative macrocephaly — defined as a head circumference at least 1.5 standard deviations (SD) above the birth weight and/or length — and a prominent forehead with frontal bossing, often accompanied by body asymmetry [3]. Following birth, most patients continue to exhibit postnatal growth failure, sometimes with progressive discrepancies in limb length and feeding difficulties. Additional recognizable clinical traits include a triangular facial appearance, clinodactyly of the fifth finger, and micrognathia with a narrow chin [4]. In the absence of treatment, the average adult height in individuals with SRS is approximately -3.1 SD below the population mean. The clinical presentation of SRS varies widely—from severe forms with marked growth restriction and dysmorphic features to mild cases with subtle findings. Because of this broad phenotypic spectrum, many affected individuals, especially those with extreme or attenuated features, are likely underdiagnosed or misclassified. Diagnosis often depends heavily on the clinician's experience, particularly since characteristic fea-

tures tend to become less apparent in adulthood.

Globally, the estimated incidence of SRS varies between 1 in 30,000 and 1 in 100,000 live births. A molecularly confirmed study from Estonia in 2015 suggested an incidence of approximately 1 in 70,000 [5], although this may underestimate the true prevalence due to underdiagnosis. Overall, SRS likely occurs more frequently than previously assumed, but the exact incidence remains uncertain. To address diagnostic uncertainty, several scoring systems have been developed, each using defined clinical criteria that improve the detection rate of molecular abnormalities.

DIAGNOSIS

Clinical diagnosis

Molecular analyses can confirm the diagnosis in approximately 60% of affected individuals, therefore, SRS remains primarily a clinical diagnosis, established through a combination of characteristic phenotypic findings. Identification of the molecular subtype enables more precise classification of patients and may facilitate individualized management strategies [6]. Nevertheless, in a considerable subset of clinically typical cases, molecular results are negative. To improve diagnostic consistency, multiple clinical scoring systems have been proposed over time, each reflecting the inherent difficulty of achieving a confident diagnosis [7,8].

The Netchine–Harbison Clinical Scoring System (NH-CSS) provides a validated and sensitive diagnostic framework [8]. The NH-CSS demonstrated superior diagnostic sensitivity (98%) compared with previously published scoring systems and exhibited the highest negative predictive value (89%), indicating that individuals who meet fewer than four of the six criteria are very unlikely to have SRS (Table 1).

A clinical diagnosis can be made when a patient meets at least four of the six NH-CSS criteria, which must include relative macrocephaly and prominent forehead/frontal bossing at

Table 1. Adapted Netchine–Harbison Clinical criteria for Silver–Russell syndrome

Clinical Feature	Operational Definition
Small for gestational age (SGA)	Birth weight and/or length ≤ –2 SD for gestational age.
Postnatal growth retardation	Height at age 2 ± 1 year ≤ –2 SD, or at least 2 SD below mid-parental target height.
Relative macrocephaly at birth	Head circumference at birth ≥ 1.5 SD above birth weight and/or birth length SD score.
Prominent forehead	Forehead clearly projecting beyond the facial plane on lateral view during early childhood (ages 1–3 years).
Body asymmetry	Limb length discrepancy (LLD) ≥ 0.5 cm or arm asymmetry, or LLD < 0.5 cm with at least two other asymmetric body parts (excluding face).
Feeding difficulties and/or low BMI	BMI ≤ –2 SD at 2 years of age, or current need for nutritional support (e.g., feeding tube or appetite stimulant such as cyproheptadine).

Table 2. Genetic subtypes and testing strategies in Silver–Russell syndrome
(adapted from Saal HM et al., GeneReviews®, 2025)[36].

Analytical Method	Chromosomal Region / Gene Involved	Detected Alterations	Approximate Detection Rate in SRS
Methylation testing	Chr 11p15	Hypomethylation of *H19/IGF2* imprinting control region (paternal allele)	~35%–65%
		Somatic mosaicism or partial upd(11)mat	Rare
		Maternal duplication of 11p15.5	Uncertain frequency
	Chr 7	Maternal uniparental disomy [upd(7)mat]	~5%–10%
		Segmental deletions/duplications or mosaic trisomy 7	Rare
Chromosomal microarray (SNP-based)	Chr 11p15	Maternal 11p15 duplication or somatic mosaicism for upd(11)mat	Rare
	Chr 7	Deletions, duplications of 7p, or mosaic trisomy 7	Rare
		upd(7)mat (maternal isodisomy)	~5%–10%
STR marker analysis	Chr 11p15	Somatic mosaicism for upd(11)mat	Rare
	Chr 7	upd(7)mat or maternal mosaic trisomy 7	~5%–10%
Karyotype	Chr 11p15	Structural rearrangement (e.g., inversion or translocation)	Rare
Gene sequencing/deletion–duplication testing	*CDKN1C* (maternal transmission)	Gain-of-function mutation	Rare
	IGF2 (paternal transmission)	Loss-of-function mutation	Rare
	PLAG1, HMGA2	Pathogenic variants or copy-number changes	Rare

birth, along with two or more additional features, provided that other potential syndromic causes have been excluded [8].

Molecular diagnosis

A positive molecular finding serves as a valuable means of confirming the clinical diagnosis and allows for classification into defined molecular subtypes, which can subsequently inform personalized management strategies. Nevertheless, molecular testing is often requested for individuals who display only limited or atypical features of Silver–Russell syndrome, resulting in low diagnostic yield and unnecessary financial burden for both patients and healthcare systems [4]. To date, an identifiable molecular etiology is found in roughly 60% of clinically diagnosed patients. The two major pathogenic mechanisms include loss of methylation (LOM) at chromosome 11p15 (30%–60% of cases) and maternal uniparental disomy for chromosome 7 (upd(7)mat) (approximately 5%–10% of cases) [9,10]. In the remaining patients, the molecular basis is still unclear (Table 2).

Chromosome 11p15

Both SRS and the overgrowth disorder Beckwith–Wiedemann syndrome (BWS) arise from epigenetic and structural abnormalities involving chromosome 11p15.5, a region that contains two distinct imprinted domains. The telomeric domain, which plays a major role in the pathogenesis of SRS, is regulated by the paternally methylated H19/IGF2 intergenic differentially methylated region (H19/IGF2 IG DMR) — previously referred to as IC1, ICR1, or the H19 DMR [11,12]. In contrast, the centromeric domain includes the KCNQ1OT1 TSS-DMR, also known as IC2, ICR2, LIT1, or KvDMR1 [13]. The paternally expressed IGF2 encodes a growth factor essential for fetal development and somatic growth, whereas the maternally expressed H19 produces a long noncoding RNA (lncRNA) whose biological function remains incompletely understood. When hypomethylation occurs at the H19/IGF2 IG DMR, it leads to decreased paternal expression of IGF2 and up-regulation of maternal H19, ultimately resulting in growth restriction, a hallmark of SRS.

Numerous copy-number variants (CNVs) have also been identified within the 11p15.5 locus; the resulting phenotype depends on the size, genomic content, and parental origin of each CNV [14]. Accurate diagnosis therefore requires quantitative assessment of CpG methylation within the H19/IGF2 IG DMR.

This can be achieved through bisulfite-based assays or enzymatic techniques, such as methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) and, less commonly, Southern blotting [15]. Among these, MS-MLPA is the most widely used clinical test, as it is DNA-efficient, cost-effective, and capable of simultaneously evaluating both copy number and methylation status [16].

However, hypomethylation in SRS is often partial, and low-level changes may escape detection. Furthermore, methylation levels can differ among tissues—for example, between blood leukocytes, buccal epithelial cells, and skin fibroblasts—which may account for false-negative molecular results when only blood is analyzed [17].

Although MS-MLPA can identify CNVs, genome-wide array analysis remains valuable for defining the exact size and gene composition of such rearrangements.

Chromosome 7

Cytogenetic analyses have revealed several structural abnormalities of chromosome 7 in individuals with SRS, including duplications of 7p11.2–p13 and small marker chromosomes [18]. The first molecular evidence linking chromosome 7 to SRS came from the discovery of maternal upd(7)mat, identified in approximately 10% of affected patients [19]. Microsatellite analyses in nearly all upd(7)mat cases supported a trisomic rescue mechanism as the origin. Because of this trisomic origin, it has been proposed that mosaic trisomy 7 may contribute to SRS pathogenesis. In cases of UPD, homozygosity for pre-existing recessive variants can also result in abnormal phenotypes. Indeed, upd(7)mat was first reported in a growth-restricted patient with cystic fibrosis, in whom both alleles of the CFTR mutation were inherited from the mother [20]. Nonetheless, the lack of a shared isodisomic region among SRS cases excludes a single recessive gene as the primary cause of the syndrome. The prevailing explanation for the SRS phenotype in upd(7)mat carriers is a disturbed expression of imprinted genes on chromosome 7. Upd(7)mat is consistently associated with growth retardation and SRS-like features, whereas paternal upd(7) does not produce this phenotype [19,20]. It is therefore hypothesized that reduced activity of paternally expressed genes, or alternatively overexpression of maternally expressed factors, underlies the growth restriction observed in SRS. Research has focused primarily on two candidate regions on chromosome 7: 7p11.2–p13 and 7q32 [21]. Duplications of the 7p11.2–p13 segment have been identified in SRS cases, and this region contains several growth-regulatory genes, including GRB10, IGFBP1, IGFBP3, PHKG1, EGFR, and GHRHR [22]. Among these, GRB10, a maternally expressed

imprinted gene with a key role in growth regulation, has been considered a strong candidate. However, point mutations or methylation defects in GRB10 have not been detected despite extensive screening, and duplications not involving this gene do not produce SRS features. Another locus of interest, 7q31, has been implicated through the identification of patients with segmental upd(7q) and intrauterine growth restriction. This region contains several imprinted genes (*MEST/PEG1*, *CPA4*, *COPG2*) and non-coding RNAs (*MESTIT*, *CIT1/COPG2IT1*), although no pathogenic variants or isolated imprinting defects have yet been confirmed [22]. Finally, while intrauterine growth restriction is also reported in upds of other chromosomes and may arise from confined placental mosaicism.

SRS like syndromes

Chromosome 14q32

Abnormalities involving the imprinted locus on chromosome 14q32 — including maternal uniparental disomy of chromosome 14 (upd(14)mat), paternal microdeletions, and hypomethylation of the DLK1/GTL2 intergenic DMR (also known as MEG3-DMR or 14q32-DMR) — lead to Temple syndrome [23].

This condition shows considerable clinical overlap with SRS, sharing features such as being born small for gestational age, postnatal growth failure, hypotonia, delayed motor milestones, and early puberty.

Among patients clinically diagnosed with SRS, a small number have been reclassified as having Temple syndrome, including 1 of 127, 2 of 85, and 1 of 26 individuals in reported cohorts.

However, the true frequency of 14q32 epigenetic abnormalities in patients fulfilling NH-CSS diagnostic criteria for SRS is still uncertain.

Chromosome 20 and 16

Maternal uniparental disomy of chromosomes 20 and 16 (upd(20)mat and upd(16)mat) has occasionally been identified in patients evaluated for prenatal and postnatal growth restriction or suspected SRS [20,24]. But their phenotypes lack core SRS characteristics such as relative macrocephaly and asymmetry.

CDKN1C and IGF2 gene

CDKN1C and IGF2, both located on chromosome 11p15, are key genes involved in the growth regulation abnormalities observed in SRS and BWS [25]. A maternally inherited gain-of-function mutation in CDKN1C has been identified in a multigenerational family with SRS, whereas a paternally inherited loss-of-function mutation in IGF2 was reported in another familial case. To date, however, no additional pathogenic variants in either gene have been found in sporadic or familial SRS cases. Therefore, sequence analysis of CDKN1C and IGF2 may be warranted mainly in familial SRS where the inheritance pattern supports such testing, although coding mutations in these genes remain rare.

MANAGEMENT

Feeding difficulties

Infants with SRS are typically shorter and lighter than peers, with weight declining further after birth because of poor appetite, feeding difficulty, and gastrointestinal problems. Persistent undernutrition can lead to calorie-related growth failure. Digestive symptoms such as reflux or constipation are frequent, and nutritional management during infancy focuses on preventing hypoglycemia and restoring growth before GH therapy begins [26]. However, excessive or forced feeding requires caution, as rapid catch-up weight gain in small-for-gestational-age children increases future metabolic risk. Because of their low muscle mass and altered body composition, SRS patients need individualized nutritional targets, balancing adequate caloric intake without over nourishment [27].

Hypoglycemia

Young children with SRS are prone to fasting hypoglycemia due to reduced muscle and liver glycogen stores, large brain-to-body ratio, and feeding difficulties, particularly under age 5 years. Regular urinary ketone testing helps determine individual fasting tolerance and guide preventive feeding strategies [28]. Nighttime hypoglycemia can be avoided by adding slow-release carbohydrates such as uncooked cornstarch to the evening feed. During illness or preoperative fasting, intravenous glucose may be necessary. Because of gastrointestinal dysmotility, reintroduction of oral or enteral feeding often requires a longer recovery period than in SGA children. Glucagon is not recommended for the treatment of hypoglycemia in these patients, as their glycogen reserves are low and their capacity for gluconeogenesis is limited. If hypoglycemia persists, early initiation of GH therapy should be considered [29].

Growth hormone treatment

Data on final height in untreated individuals with SRS are

scarce, but most achieve an adult height around −3 SDS. SRS is recognized as an indication for GH therapy under the SGA indication license, and clinical trials including SRS patients supported the FDA (food and drug administration) and EMA (European medicines agency) approvals in the early 2000s [30]. Subsequent studies have shown that children with SRS exhibit a growth response to GH comparable to that of non-syndromic SGA children, with mean total height gains of approximately +1.2 to +1.4 SDS, corresponding to an improvement of 7–11 cm in predicted adult height [31]. Although final height tends to remain lower in SRS, all molecular subtypes benefit from GH therapy, particularly when started at a younger age and lower baseline height SDS.

Consensus guidelines recommend early GH therapy for children with SGA, including those with SRS, when height is ≤−2.5 SDS at 2–4 years of age and the dose is 35–70 μg/kg/day [32]. Beyond promoting linear growth, GH can enhance appetite, lean body mass, and muscle strength, similar to its effects in Prader–Willi syndrome. Although classic GH deficiency is uncommon in SRS, treatment typically increases height velocity by ≥3 cm/year. Children with 11p15 LOM often show elevated IGF-1 and IGFBP-3 levels, suggesting partial IGF-1 resistance, which complicates biochemical monitoring during therapy. Overall, GH treatment is considered safe and effective in SRS, with no higher risk of adverse effects than in non-syndromic SGA children.

Advanced skeletal maturation

Data on bone age progression in SRS are limited, but early bone age delay is typically followed by rapid advancement around 8–9 years of age, often earlier in overnourished children [33]. Puberty generally begins within the normal range but tends to occur earlier and progress faster than in non-syndromic SGA peers, particularly in those with 11p15 LOM or upd(7)mat. Accelerated bone maturation and a rapid pubertal tempo contribute to reduced pubertal growth and lower adult height. Combined therapy with GH and gonadotropin-releasing hormone analogues (GnRHa) may help improve final height in selected patients with early puberty, although results remain inconsistent [34]. Aromatase inhibitors such as anastrozole are being investigated as potential options to slow bone maturation in SRS, but their use is not yet approved for growth disorders.

Metabolic complications

Individuals born SGA have an increased risk of metabolic syndrome in adulthood, particularly when rapid or disproportionate postnatal weight gain occurs. In SRS, insulin resistance may be subtle in prepubertal children but becomes more evident during puberty, occasionally progressing to glucose intolerance or type 2 diabetes [35]. Although GH therapy generally improves body composition and lipid metabolism in SGA populations, specific data in SRS remain limited. Children with 11p15 LOM appear to have higher metabolic risk than those with upd(7)mat, likely due to reduced muscle mass and elevated IGF-1 levels. Long-term studies are needed to clarify genotype-specific metabolic effects of GH treatment in SRS.

CONCLUSION

Children with SRS encounter diverse medical and developmental challenges from infancy to adulthood. Beyond the general complications of being born SGA, key management concerns include feeding difficulties, postnatal growth failure, recurrent hypoglycemia, early adrenarche and puberty, insulin resistance, body asymmetry, dental and airway problems, and other congenital anomalies. These recommendations apply to all clinically diagnosed cases, but molecular subtype identification can help tailor management according to specific risks. Optimal care requires a multidisciplinary approach and active family involvement.

AUTHOR CONTRIBUTIONS

This study was designed and the manuscript was written by Kyungmi Jang. Jungeun Moon contributed to the revision and editing of the manuscript.

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