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# Silver–Russell syndrome

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The Silver–Russell syndrome (SRS) is a sporadic clinically and genetically heterogeneous disorder. Diagnosis is based on the variable combination of the following characteristics: intrauterine growth retardation, short stature because of lack of catch-up growth, underweight, relative macrocephaly, typical triangular face, body asymmetry and several minor anomalies including clinodactyly V. Different diagnostic scores have been proposed. The main genetic defects detected are at the epigenetic level: hypomethylation of the imprinting control region 1 (ICR1) on 11p15 in around 44% of cases and maternal uniparental disomy of chromosome 7 (UPD(7)mat) in 5–10% of cases. Severe phenotype is frequently associated with hypomethylation of ICR1 while mild phenotype is more often seen in combination with UPD(7)mat. Origins and biological consequences of these epimuations are still obscure. For genetic testing, we recommend a methylation-specific PCR-approach for both 7p and 7q loci (confirmed by microsatellite typing) for the detection of UPD(7)mat, and the methylation-specific multiplex ligation dependent probe amplification (MS-MLPA) approach for methylation analysis of the 11p15 loci. Short stature in SRS can be treated by use of pharmacological doses of recombinant GH resulting in good short-term catch-up; sufficient information on the therapeutic effect in terms of final height is still missing.



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## Introduction

The Silver–Russell syndrome is a clinically and genetically heterogeneous disorder. The Silver–Russell syndrome was independently described by Silver et al.[1] who emphasized the short stature and "congenital hemihypertrophy" of these children and by Russell[2] who focused his report on the "intrauterine dwarfism" and the "cranio-facial dysostosis" associated with this syndrome. Despite the recent progress in the genetic characterization of this syndrome, the diagnosis still relies on the clinical phenotype.

## Clinical presentation

The children with Silver–Russell syndrome (SRS) are presented to gynecologists because of intrauterine growth restriction, to neonatologists because of severe hypotrophy and feeding problems, to general pediatricians because of failure to thrive and short stature and rarely to geneticists because of the presence of minor anomalies and a peculiar aspect. The diagnosis which is frequently delayed is based on several findings which are ranked in the frequency of their occurrence in Silver–Russell syndrome (SRS):

1. Intrauterine growth retardation
   Severe intrauterine growth retardation with a very low birth length and very low birth weight is found in the vast majority of the affected. These children are born very small for gestational age = SGA with a mean birth length of around −4.0 SD score (43 cm) and a mean birth weight of −3.7 SD score (1900 g).[3]
2. Lack of catch-up growth
   During infancy, SRS children show frequently normal growth, but no catch-up resulting in the conservation of their very short stature. Mean final height in SRS is at around −4.2 SD score (SDS) which means an adult height of 140 cm in women and 151 cm in men.[3] Syndrome specific growth charts are available.[3]
3. Underweight
   Weight development mirrors growth: these children fail to thrive and lack fat and muscle tissue from birth onwards. Gastric tube feeding is frequently indicated during the first weeks of life.[4] The underweight is chronic, a BMI above the 25th percentile is rare in adolescents with SRS.
4. Relative macrocephaly
   In contrast to the body, the growth of the cranium is undisturbed. Therefore, the head circumference is frequently normal for age. This contrasting appearance of body and head is named "relative macrocephaly" which has recently been defined as a head circumference exceeding the length/height SDS by at least 1.5 SDS.[4]
5. Typical Silver–Russell face
   This face has been described excellently by Russell[2] as a triangular shaped face with a broad prominent forehead, a very small chin and a wide shark-like mouth. The resulting triangular appearance of the face is especially evident in infants and young children.
6. Body asymmetry
   The asymmetry divides the body into two halves with different but stable growth patterns. It involves the face (scoliosis of the face), but not the cranium. Shortening and narrowing of arms and legs, fingers and toes of the same half as well as narrowing of the thorax and abdomen can be observed.[5] Sometimes asymmetry does not manifest in a difference of the length but instead of the circumference of the extremities. The relative asymmetry remains unaltered during growth.[6]
7. Minor malformations
   Minor anomalies like clinodactyly V and dysplastic ears are frequent, but less specific.[3] The same is valid for hypospadias in males with SRS.[7]

Mental development is normal. Puberty starts at normal age, but to early in respect to height in both genders.