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12

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.

Diagnosis

The advent of genetics in the definition of SRS has not only shown that SRS is genetically heterogeneous, but it is also clearly variable in its clinical manifestations, even in the same genetic class. For diagnostic purposes, different algorithms have been proposed. We use the following definition: Intrauterine growth retardation without catch-up plus at least two of the following three characteristics: relative macrocephaly, typical SRS face or body asymmetry. Another clinical score which incorporates the underweight of SRS children, but neglects the typical SRS face (which may not known by the observer) has been proposed by Netchine *et al.*: the children tested positive has to have intrauterine growth retardation in association with at least three of the following five criteria: 1) postnatal growth retardation (=height <2 SD score), 2) relative macrocephaly at birth, 3) prominent forehead during early childhood, 4) body asymmetry, 5) feeding difficulties during early childhood.[4]

Differential diagnosis

Three other syndromes with severe intrauterine growth restriction, very short stature and broad high forehead may be mixed up with SRS: the 3-M syndrome, the SHORT syndrome, and Mulibrey-nanism. Children with 3-M syndrome have no relative macrocephaly, but a long philtrum and prominent full lips absent in SRS. SHORT syndrome is associated with hyperextensible joints and characteristic malformations of large appearing, but deep set eyes, not reported in SRS. Children with Mulibrey-nanism are dolichocephalic and have a depressed bridge of nose not present in SRS.[8]

History of genetic research

Most of the SRS cases are sporadic, both genders are equally affected. In the past, different strategies have been used to detect the genetic basis of SRS. Candidate approaches which involved genes known to be important for human growth like the *IGF-I receptor* gene were not successful.[9]

Reports on the association of the inheritance of both chromosomes 7 from the mother (UPD(7)mat) with intrauterine growth restriction inspired Kotzot et al. to look systematically for UPD(7)mat in SRS and in non-syndromic cases of intrauterine growth restriction. This search was successful and identified the cause of SRS in about 4–10% of cases.[10]

The characterization of structural chromosomal aberrations in SRS let to the finding of maternal duplications of 11p15 in SRS (for review: 11) whose complementary defect, the paternal duplication of 11p15, was known to cause some cases of Beckwith–Wiedemann syndrome, an epigenetic disorder with overgrowth. These data convinced Gicquel and colleagues from Paris who were involved in Beckwith–Wiedemann syndrome research for years, to screen for epigenetic mutations on 11p15 in SRS.[12] This screening elucidated the main cause of SRS, the hypomethylation of the imprinting control region 1 of the imprinting cluster on 11p15.5, present in around 44% of SRS cases.

Maternal uniparental disomy of chromosome 7 (UPD(7)mat)

Uniparental disomy is defined by the inheritance of both homologous chromosomes from one parent. In most of the cases, the origin of this defect is thought to be a trisomic zygote containing two chromosomes from the same parent. In the case of SRS, uniparental disomy of chromosome 7 (UPD(7)mat) is present in 5–10% of cases.[10] In respect to UPD, isodisomy (two identical copies of the same chromosome) or heterodisomy are possible. Isodisomy implicates the chance for the establishment of homozygosity for recessive mutations. However, the most likely explanation for the phenotype in UPD(7)mat carriers is thought to be the altered expression of imprinted genes on chromosome 7, either by diminishment of paternally expressed gene products or by excess of maternally expressed gene products. The search for imprinted candidate genes on chromosome 7 is still active, as no serious candidate has been detected so far.

The imprinted gene *GRB10* (growth factor receptor bound protein 10) is localized on 7p11.2p13. In mice, its expression is restricted to the maternal allele. Grb10 functions as a negative regulator of IGF-I and insulin signaling in mice[13,14] and its overexpression is associated with postnatal growth retardation and insulin resistance.[14,15] However, so far neither point mutations of the coding region nor

methylation defects restricted to *GRB10* have been detected.[16,17] And in addition, there are SRS cases who carry a segmental UPD(7)mat restricted to the long arm of the chromosome 7.

Hypomethylation of the imprinting control region 1 (ICR1) on 11p15

Methylation of CpG islands is the main chemical modification of DNA which alters the availability of genes for the transcription machinery in the absence of a change in the genetic code. Frequently, methylation marks cause a diminishment or abolishment of gene expression while lack of methylation promotes gene expression. A large imprinting region is located on 11p15 which contains five imprinted genes which are expressed only from one allele. The two imprinting centers 1 and 2 (ICR1, ICR2) regulate this expression pattern.[18]

The centromeric ICR2 regulates the expression of *KCNQ1/KCNQ1OT1* (potassium channel KQT-family member 1/KCNQ1 overlapping transcript 1) and *CDKN1C* (cyclin-dependent kinase inhibitor 1C p57, Kip2). Most of the mutations or epimutations causing Beckwith–Wiedemann syndrome (BWS) are located here; 50% of the genetic defects comprise hypomethylation of ICR2.

The telomeric ICR1 controls the expression of the genes *H19* and *IGF2* in a reciprocal manner (Fig. 1). In around 44% of SRS cases, a hypomethylation of the ICR1 on the paternal allele can be detected in blood lymphocytes. Interestingly, a small percentage of BWS cases (2–4%) carry the complementary defect, a hypermethylation of the same telomeric ICR1.

The normal methylation of ICR1 on the paternal allele blocks the binding of the protein CTCF (CCCTC-binding factor, a zinc finger protein). CTCF has seven binding sites on the maternal ICR1 (which is not methylated) where it inhibits the *IGF2* expression while promoting the expression of *H19* which encodes a 2.3 kb untranslated RNA. The *H19* RNA can be processed into the evolutionary conserved microRNA miR-675.[19,20] Hypothetically, this microRNA could have pleiotropic functions in the regulation of the expression of other growth-related genes.

Hypomethylation of the paternal ICR1 found in SRS results in a maternal allele-like methylation pattern which enables CTCF binding on the wrong allele and is thought to prevent sufficient *IGF2* expression (Fig. 2). The majority of ICR1 hypomethylation found in SRS is gradual; rarely hypomethylation is found to be total. This has led to the hypothesis of a mosaic distribution of this epimutation.[12] The origin of the DNA hypomethylation in SRS is still unknown.

Multilocus hypomethylation (MLH) is defined as hypomethylation at further imprinted loci in addition to the disease-specific locus. This disturbance has recently been detected in blood lymphocytes of up to 7% of SRS cases with 11p15 hypomethylation.[21–24] The meaning of this observation involving paternal and maternal alleles is still unclear, the clinical presentation was not altered by MLH.

Biological and endocrine consequences of the different epimutations

The hypothesis of an insufficient expression of IGF2 expression in the presence of hypomethylation of the paternal ICR1 on 11p15 in SRS has been tested by determination of IGF2-mRNA content in human

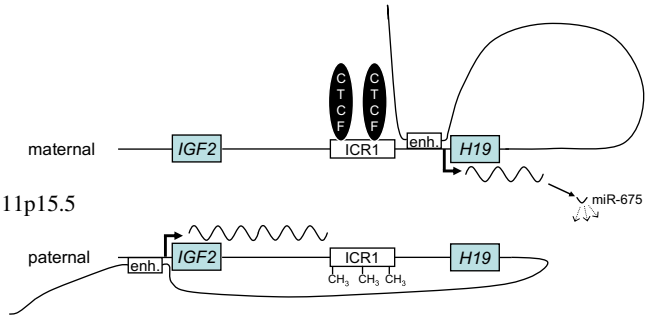

Fig. 1. Schema of the epigenetic regulation of the *IGF2/H19* locus.

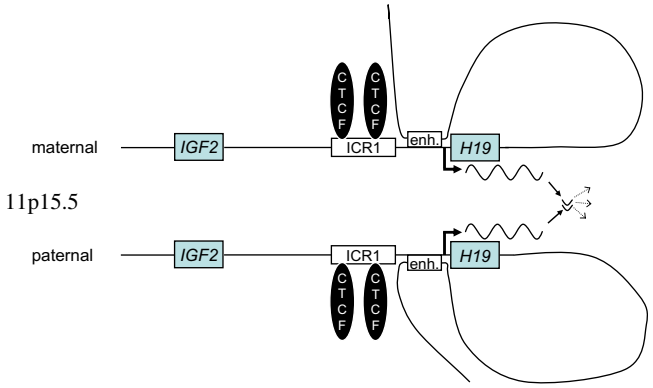

Fig. 2. Schema of the proposed deregulation of the *IGF2/H19* locus in SRS.

fibroblasts. Expression was found to be reduced in two SRS individuals in comparison to two matched controls.[12] These data still needs to be confirmed by other studies.

IGF-II serum levels in SRS patients with ICR1 hypomethylation are normal.[4,25] Serum IGF-II should mainly reflect liver synthesis where IGF2 gene expression is not imprinted. IGF-II released from non-hepatic tissues in the fetus (placenta) and child may have important auto- or paracrine actions which are diminished in SRS.

In contrast to IGF-II serum levels, which are normal, we found inadequately high-normal IGF-I serum levels and high IGFBP-3 serum levels in prepubertal children with SRS and 11p15 epimutations.[5] The levels of these two growth factors were clearly higher than in non-syndromic children born SGA who were used for comparison. The meaning of these findings is still unknown. Interestingly, these endocrine changes were not present in UPD7 cases or in the idiopathic cases with SRS.

Studies on genotype-phenotype correlations demonstrated characteristic differences between the three cohorts which are now discernible: the UPD(7)mat cases, the 11p15 epimutation carriers and the idiopathic cases which are only defined according to the clinical phenotype.[4,5] 11p15 epimutation carriers display the more severe phenotype of SRS with lower birth weight, birth length and lower BMI than in SRS cases without 11p15 epimutation. In addition, frequency of body asymmetry and the facial phenotype were higher in the presence of 11p15 epimutations as well as the degree of severity of relative macrocephaly. In contrast, UPD(7)mat carriers frequently exhibit a mild form of SRS with sometimes only mild growth restriction and absence of macrocephaly. However, there are several case reports where 11p15 epimutations were not associated with the characteristic phenotype of SRS.[26,27] Therefore, children who do not fulfil the above clinical SRS criteria completely should not automatically excluded from molecular testing.

Recombinant GH is nowadays an accepted growth promoting drug for children born small for gestational age (SGA) including children with SRS.[5] Reports on the effectiveness of GH therapy in SRS, however, are scarce. Although these children are very short and underweight, start of puberty is not retarded. The differences of the endocrine phenotype based on the different epimutations suggest that response to growth hormone treatment may also different.

Genetic testing and genetic counselling in SRS

The molecular confirmation of the clinical diagnosis of SRS is up to date possible in ~50% of patients.

SRS patients should be tested for imprinted loci on the short and on the long arm of chromosome 7 both as cases of segmental UPD(7)mat have been described. We suggest to use methylation-specific PCR approaches for both 7p and 7q loci because they allow the detection of UPD(7)mat for diagnostic purposes and the detection of so far unknown isolated imprinting defects on chromosome 7. If

a positive result is obtained, microsatellite typing of the patient and his parents is indicated to confirm UPD(7)mat.

All currently known UPD(7)mat are the result of a chromosomal nondisjunction event followed by a trisomic rescue, in these cases the recurrence risk is not increased for relatives.

Almost 50% of SRS patients carry an ICR1 hypomethylation on 11p15. Several testing procedures have been reported for methylation analysis of the 11p15 loci. The advantage of the methylation-specific multiplex ligation dependent probe amplification (MS-MLPA) approach is that copy number variation and aberrant methylation at different loci in 11p15 can be detected in one tube. Thus, methylation defects at both ICRs in 11p15 as well as duplications and UPDs of this region will be identified. Whereas the MS-MLPA patterns for aberrant methylation are unambiguous and generally do not need confirmation by a second test, duplications/deletions and UPDs should be verified by microsatellite typing with 11p15 markers.

Recurrence risk is probably not increased in respect to ICR1 hypomethylation due to their de-novo occurrence, but three single families with familial ICR1 hypomethylation were reported.[28]

After exclusion of 11p15 (epi)mutations and UPD(7)mat, molecular karyotyping can help to identify submicroscopic imbalances. Indeed, the frequency of chromosomal imbalances in SRS is unknown but based on two studies on this subject we estimate that these chromosomal aberrations account for ~1% of SRS patients.[29,30]

Conclusions

The advent of epigenetics in SRS enables the genetic confirmation of the clinical diagnosis in around 50% of cases. Like in the other epigenetic disorders known in humans, the biology of SRS is far from being understood although the involvement of the epigenetic regulation of the gene expressing the main human growth factor, the IGF-II, implies one possible pathogenetic mechanism of the growth disturbance in SRS. More research is urgently needed to elucidate origins and biological consequences of the epimuations found in SRS. Growth promoting therapy with recombinant growth hormone is effective in the short-term, relevant studies on the long-term are missing.

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Conflict of interest

None declared.

Practice points

- Silver–Russell syndrome (SRS) occurs in most of the cases sporadically and is heterogeneous.
- Clinical diagnosis is based on the variable association of intrauterine growth retardation, lack of catch-up growth, underweight, relative macrocephaly, typical triangular face and body asymmetry.
- Main genetic defects found are at the epigenetic level: hypomethylation of the imprinting control region 1 on 11p15 (44% of cases) is associated with a severe phenotype, maternal uniparental disomy of chromosome 7 (5–10% of cases) comes with a mild phenotype.
- Hypomethylation of the imprinting control region 1 on 11p15 is thought to decrease the expression of IGF-II, the main fetal growth factor.
- IGF-II serum levels are normal in SRS.
- Short stature is treated by use of pharmacological doses of recombinant GH.

Research agenda

- The genetic basis in 40–50% of SRS cases is still unknown.
- The origin of hypomethylation and the biological consequences at the cellular level have to be elucidated.
- Reports on multilocus hypomethylation (MLH) in some SRS cases need confirmation.
- Relevant studies on the long-term efficacy of growth promoting therapy with recombinant GH are missing.

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