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# Silver-Russell Syndrome and Beckwith-Wiedemann Syndrome: Opposite Phenotypes with Heterogeneous Molecular Etiology

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**Key Words**
Beckwith-Wiedemann syndrome · Growth-affecting disorder · Imprinted genes · Silver-Russell syndrome · Scoring systems · Uniparental disomy

**Abstract**
Silver-Russell syndrome (SRS) and Beckwith-Wiedemann syndrome (BWS) are 2 clinically opposite growth-affecting disorders belonging to the group of congenital imprinting disorders. The expression of both syndromes usually depends on the parental origin of the chromosome in which the imprinted genes reside. SRS is characterized by severe intrauterine and postnatal growth retardation with various additional clinical features such as hemihypertrophy, relative macrocephaly, fifth finger clinodactyly, and triangular facies. BWS is an overgrowth syndrome with many additional clinical features such as macroglossia, organomegaly, and an increased risk of childhood tumors. Both SRS and BWS are clinically and genetically heterogeneous, and for clinical diagnosis, different diagnostic scoring systems have been developed. Six diagnostic scoring systems for SRS and 4 for BWS have been previously published. However, neither syndrome has common consensus diagnostic criteria yet. Most cases of SRS and BWS are associated with opposite epigenetic or genetic abnormalities in the 11p15 chromosomal region leading to opposite imbalances in the expression of imprinted genes. SRS is also caused by maternal uniparental disomy 7, which is usually identified in 5–10% of the cases, and is therefore the first imprinting disorder that affects 2 different chromosomes. In this review, we describe in detail the clinical diagnostic criteria and scoring systems as well as molecular causes in both SRS and BWS.



Silver-Russell syndrome (SRS; OMIM 180860) and Beckwith-Wiedemann syndrome (BWS; OMIM 130650) are 2 clinically opposite growth-affecting congenital imprinting disorders. The expression of both syndromes usually depends on the parental origin of the chromosome in which the imprinted genes reside. This phenomenon is called genomic imprinting. SRS was first described by Silver et al. [1953] and Russell [1954] and is characterized by severe intrauterine and postnatal growth retardation with various additional clinical features such as hemihypertrophy, relative macrocephaly, fifth finger clinodactyly, and triangular facies. BWS is an overgrowth syndrome with many additional clinical features such as macroglossia, organomegaly, and an increased risk of

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**Table 1.** Clinical diagnostic criteria for SRS and BWS are given based on published diagnostic scoring systems

| | Scoring system |
|---|---|
| *SRS* | |
| Birth weight and/or length ≤–2 SD[a] | 1–6 |
| Height ≤–2 SD at or after 2 years of age[a] | 1–6 |
| Relative macrocephaly at birth[a] | 2–6 |
| Body, face, and/or limb asymmetry[a] | 1–6 |
| Classic facial phenotype | |
| prominent forehead, triangular face, downturned corners of the mouth and micrognathia, or protruding forehead only[a] | 1–4, 6 |
| Feeding difficulties[a] | 4, 6 |
| Normal cognitive development | 3 |
| Clinodactyly | 1, 3 |
| Genital anomalies (e.g., cryptorchidism, hypospadias) | 3 |
| Other (e.g., brachymesophalangy, syndactylous toes, inguinal hernia, pigmentary changes) | 3 |
| *BWS* | |
| Major criteria[b] | |
| Abdominal wall defect, exomphalos[c] (1.5 points), and/or diastasis recti | 7–10 |
| Macroglossia[c] (2.5 points) | 7–10 |
| Macrosomia (pre- and postnatal height >97th percentile) | 7–10 |
| Visceromegaly of intra-abdominal organ(s): for example, liver, kidney, spleen, pancreas, and adrenal glands | 7, 9, 10 |
| Minor criteria | |
| Neonatal hypoglycemia[c] (0.5 points) | 7–10 |
| Anterior ear lobe creases and/or posterior helical pits (bilateral or unilateral)[d] | 7–9 |
| Facial nevus flammeus | 7, 9, 10 |
| Hemihyperplasia[c, d] (0.5 points) | 7, 9, 10 |
| Other: pregnancy-related findings (polyhydramnios, enlarged placenta and/or thickened umbilical cord, premature onset of labor and delivery), renal abnormalities, embryonal tumor of childhood, cardiomegaly, characteristic facies, advanced bone age | 9 |

There are 6 scoring systems for SRS: 1 = Lai et al., 1994; 2 = Price et al., 1999; 3 = Bartholdi et al., 2009; 4 = Netchine et al., 2007; 5 = Dias et al., 2013, and 6 = Azzi et al., 2015, and 4 for BWS: 7 = Elliott and Maher, 1994; 8 = DeBaun et al., 1998; 9 = Weksberg et al., 2010, and 10 = Ibrahim et al., 2014. Numbers signify the scoring systems which highlighted this feature.

[a] Most sensitive scoring system for SRS – the so-called Netchine-Harbinson clinical scoring system [Azzi et al., 2015].

[b] Weksberg et al. [2010] gave more major findings: embryonal tumor of childhood, cytomegaly of adrenal cortex, renal abnormalities, positive family history of BWS, and cleft palate.

[c] Ibrahim et al. [2014] used logistic regression and identified clinical features of BWS with the best predictive value and scored some features differently. Exact scores (points) are given in parentheses.

[d] Weksberg et al. [2010] classified this feature under major criteria.

childhood tumors (1,000-fold); however, the clinical presentation can be highly variable [Weksberg et al., 2010]. The population incidence of BWS has been estimated 1 in 10,000–15,000 [Rump et al., 2005]. In a retrospective analysis of the prevalence of imprinting disorders in Estonia, we found the birth prevalence for SRS with known molecular abnormalities to be 1 in 54,537 [Yakoreva et al., 2015]. Still, the exact frequency of both syndromes is currently unknown, and they are probably underdiagnosed due to the broad range of clinical features. As both SRS and BWS are clinically and genetically heterogeneous, the following chapters describe in detail the clinical diagnostic criteria and the molecular causes in both syndromes.

## Clinical Symptoms and Diagnostic Criteria for SRS

SRS is a well-recognized syndrome with a clinical spectrum that can vary from a very severe SRS phenotype [Donnai et al., 1989] to individuals with very mild features presenting only asymmetry or hemihypoplasia [Bliek et al., 2006; Zeschnigk et al., 2008; Eggermann et al., 2009]. As a result, the clinical diagnosis of SRS is not always easy and depends on the experience of the clinician.

For clinical diagnosis, different diagnostic scoring systems have been developed. The first diagnostic scoring system was published by Lai et al. [1994], followed by 5 others [Price et al., 1999; Netchine et al., 2007; Bartholdi et al., 2009; Dias et al., 2013; Azzi et al., 2015]. In all of them, the highlighted clinical symptoms are growth related: birth weight and/or length ≤–2 SD, height ≤–2 SD at 2 years of age or later, relative macrocephaly at least at birth [except Lai et al., 1994], and body and/or limb asymmetry (table 1). Still, it should be taken into account that not all patients have intrauterine growth restriction (IUGR), as it has been shown that overall 78% of patients had a birth weight ≤–2 SD with a wide range [Wakeling et al., 2010]. Asymmetry can affect the trunk, face, and/or limbs. Bartholdi et al. [2009] scored all subunits separately giving 3 points (maximum) for asymmetry as a very important feature.

Most of the diagnostic scoring systems also point out a distinctive facial phenotype: prominent forehead, triangular face, downturned corners of the mouth and micrognathia, or protruding forehead only (fig. 1a, b) [Lai et al., 1994; Price et al., 1999; Netchine et al., 2007; Bartholdi et al., 2009]. Facial dysmorphism and asymmetry are considered typical features of SRS [Price et al., 1999], although the range of phenotypic variance is very wide.

Feeding difficulties have been shown as the most common feature occurring in 86% of SRS cases [Wakeling et al., 2010], but only 2 scoring systems include this feature [Netchine et al., 2007; Azzi et al., 2015]. Feeding difficulties can manifest as a lack of interest in sucking or absence

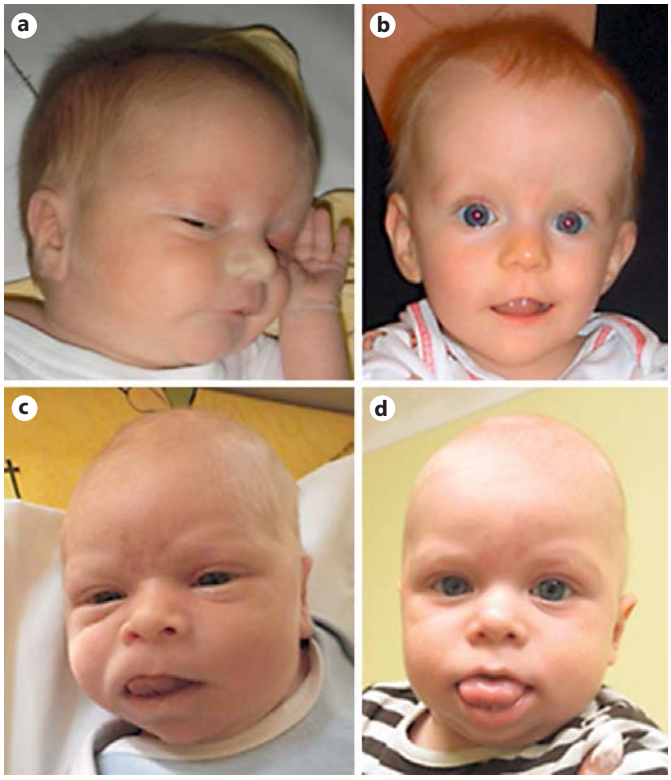


**Fig. 1. a** Facial view of a 1-week-old female patient with SRS caused by methylation abnormality at ICR1 in the 11p15 region. **b** The same SRS patient at the age of 7 months. Note the prominent forehead, triangular face, facial asymmetry, and micrognathia. **c** Facial view of a 1-week-old male with BWS caused by methylation abnormality at ICR2 in the 11p15 region. **d** The same BWS patient at the age of 5 months. Note the macroglossia, prominent eyes, facial nevus flammeus, and full lower face.

of hunger but also as gastroesophageal reflux, esophagitis, and food aversion (present in 34, 25, and 32% of patients, respectively) [Anderson et al., 2002].

Normal cognitive development is one of the key features of methylation abnormalities in the 11p15.5 region, but this is not absolute. Developmental delay has been reported in 34% of SRS patients, but this is usually mild and may not be apparent before late childhood [Wakeling et al., 2010]. Speech delay is more common in maternal uniparental disomy 7 (mUPD7) patients [Hannula et al., 2001a; Wakeling et al., 2010]. The different etiological causes of SRS are given in table 2. Behavioral problems are uncommon, but mild hyperactivity is described in some cases [Wakeling et al., 2010].

Fifth finger clinodactyly is a common feature among SRS patients and occurs in more than half of the cases, but other congenital anomalies such as genital anomalies, limb defects, congenital heart defect, and cleft palate are seldom described [Wakeling et al., 2010].

Different authors have shown that patients with mUPD7 have a milder phenotype in comparison with the cases of methylation abnormalities of the 11p15.5 region [Hannula et al., 2001a; Wakeling et al., 2010; Wakeling, 2011]. Severe feeding difficulties, speech delay and excessive sweating were common, but typical facial features and asymmetry were observed less frequently [Wakeling et al., 2010]. Still, it is not possible to differentiate these subgroups based on clinical grounds only [Kotzot, 2008; Bartholdi et al., 2009; Wakeling et al., 2010]. Some authors have shown that 15% of mUPD7 patients have an increased risk of developing myoclonus-dystonia [Guettard et al., 2008; Wakeling et al., 2010].

It has been shown that genetic testing should also be considered in cases of 'SRS-like' phenotypes, for example, mild IUGR and postnatal growth retardation associated with a prominent forehead and triangular face or asymmetry as the only clinical signs. The lack of IUGR in patients with an SRS-like phenotype should not automatically result in exclusion from molecular testing [Bliek et al., 2006; Eggermann et al., 2009]. Wakeling et al. [2010] have also shown that only 78% of SRS children with confirmed molecular abnormalities had IUGR, particularly with imprinting center 1 (ICR1) hypomethylation.

The oldest reported case of SRS is a 69-year-old male who was originally reported by Russell [1954]; he developed type 2 diabetes, osteopenia, testosterone deficiency, and hypercholesterolemia [Searle and Johnson, 2016]. Two previous reports have also noticed the development of diabetes in adult SRS patients [Price et al., 1999; Bliek et al., 2006].

In summary, the most sensitive scoring system is the recently published so-called Netchine-Harbinson clinical scoring system, which detected 98% of patients with SRS with known molecular abnormalities [Azzi et al., 2015].

## Clinical Symptoms and Diagnostic Criteria for BWS

In 1994, Elliott and Maher were the first to summarize the clinical features of 91 BWS cases and describe the first diagnostic scoring system for BWS. Later, 3 additional diagnostic scoring systems were developed [Elliott and Maher, 1994; DeBaun and Tucker, 1998; Weksberg et al., 2010; Ibrahim et al., 2014]. In case of BWS clinical diagnosis, most of the authors divide clinical symptoms into 2 categories: major and minor criteria (table 1). For the clinical diagnosis of BWS, 3 major or 2 major and 1–3

**Table 2.** The etiological causes of SRS and BWS, prevalence among diagnosed cases and references

| Etiological causes | Prevalence among diagnosed SRS cases | Prevalence among diagnosed BWS cases |
|---|---|---|
| UPD7 | maternal 5–10% [Kotzot et al., 1995; Eggermann et al., 1997; Preece et al., 1997; Netchine et al., 2007; Abu-Amero et al., 2008; Binder et al., 2008] | – |
| Methylation abnormality at ICR1 in the 11p15 region | hypomethylation in 37–63% [Netchine et al., 2007; Binder et al., 2008; Bartholdi et al., 2009; Bruce et al., 2009; Abu-Amero et al., 2010; Turner et al., 2010; Vals et al., 2015b] | hypermethylation 5–10% [Gaston et al., 2001; Cooper et al., 2005, 2007; Sasaki et al., 2007] |
| Methylation abnormality at ICR2 in the 11p15 region | few cases with the hypomethylation of both ICRs [Begemann et al., 2011] | hypomethylation in 50–60% [Gaston et al., 2001; Cooper et al., 2005; Weksberg et al., 2010; Begemann et al., 2012b] |
| Duplication in the 11p15 region (may involve ICR1 and/or ICR2) | maternal 1–2% [Eggermann et al., 2010a, 2014b] | paternal microdeletions involving ICR1 (~5%) and microduplications of ICR2 (<1%) [Niemitz et al., 2004; Sparago et al., 2004; Bliek et al., 2009b; Demars et al., 2011; Begemann et al., 2012b; Vals et al., 2015a] |
| Other chromosomal aberrations (including cryptic) | 2% (the most frequent are 1q21 microdeletion, 12q24 microdeletion, ring chromosome 15, and deletion 15qter) [Bruce et al., 2010; Spengler et al., 2012; Fuke et al., 2013; Fokstuen and Kotzot, 2014; Azzi et al., 2015] | rare cases, maternally inherited balanced translocations/inversions [Begemann et al., 2012b] |
| UPD11 | maternal single case [Bullman et al., 2008] | paternal 20–27% [Henry et al., 1991; Gaston et al., 2001; Cooper et al., 2005, 2007] |
| *CDKN1C* gene mutations | gain-of-function mutation, single case [Brioude et al., 2013] | loss-of-function mutations 8–10%, familial 50–68%, and sporadic cases 5–31% [Cooper et al., 2005; Weksberg et al., 2010; Eggermann et al., 2014a; Brioude et al., 2015] |
| *HMGA2* gene mutations | single case [De Crescenzo et al., 2015] | – |
| Structural mutations in the *H19/IGF2* enhancer region | rare cases [Grønskov et al., 2011] | – |
| Paternally inherited *IGF2* nonsense mutation | 4 cases [Begemann et al., 2015] | – |
| Unknown etiology | 30–40% [Binder et al., 2008; Wakeling, 2011; Azzi et al., 2015] | 13–15% [Weksberg et al., 2010] |

minor clinical diagnostic features are needed. Most BWS patients have 3 major features, including anterior abdominal wall defects, macroglossia, pre- or postnatal overgrowth, and/or organomegaly. Growth parameters typically show height and weight around the 97th percentile with a head circumference closer to the 50th percentile [Weksberg et al., 2010]. However, it is known now that a macrosomia at birth is present only in approximately half of the cases [Mussa et al., 2016b]. Adults with BWS are usually in the normal range [Weng et al., 1995]. Abnormal growth manifests also as macroglossia and/or hemihyperplasia. Macroglossia is the most common feature of BWS, found in 90–97% of patients [Elliott et al., 1994; Gaston et al., 2001; Ibrahim et al., 2014].

Other minor features are neonatal hypoglycemia, hemihyperplasia, and characteristic facial features. A rec-

ognizable facial phenotype consists of prominent eyes, facial nevus flammeus, full lower face and anterior ear lobe creases and/or posterior helical pits in addition to macroglossia (fig. 1c, d). The craniofacial dysmorphic features are most apparent before the age of 3 years, and after the age of 5 years often only minor dysmorphism is present [Elliott and Maher, 1994]. In adolescence, it is difficult to recognize BWS by facial phenotype only [Vals et al., 2015a]. Hypoglycemia is reported in 30–50% of babies with BWS and likely caused by islet cell hyperplasia and hyperinsulinism [Weksberg et al., 2010].

The risk for embryonal malignancies in BWS is a major concern and is reported in 4–21% of patients [DeBaun et al., 1998; Rump et al., 2005; Tan and Amor, 2006; Ibrahim et al., 2014; Mussa et al., 2016a]. The most common tumor is Wilms tumor, followed by hepatoblastoma, neuroblastoma, and adrenocortical carcinoma. Most of the tumors occur during the first 8–10 years and very seldom are reported later [DeBaun and Tucker, 1998; DeBaun et al., 1998; Tan and Amor, 2006; Mussa et al., 2016a]. Asymmetry of the limbs (hemihyperplasia), nephromegaly, and nephrogenic rests are the clinical features associated with an increased relative risk of cancer [Beckwith, 1998; DeBaun and Tucker, 1998; DeBaun et al., 1998; Coppes et al., 1999]. Constitutional 11p15 abnormalities have been identified in 3% of individuals with sporadic Wilms tumor without features of growth disorders [Scott et al., 2008].

Patients with BWS have an increased frequency of malformations, including abdominal wall defects (omphalocele or exomphalos, umbilical hernia and diastasis recti) and visceromegaly (single or combination of organs: liver, spleen, pancreas, kidneys, and adrenals). Fetal adrenocortical cytomegaly is a pathognomic finding of BWS [Weksberg et al., 2010]. Nephrourological anomalies are present in 28–61% of BWS cases and include a range of phenotypic expressions: nephromegaly, cortical/pyramidal hyperechogenicity, and kidney malformations [DeBaun et al., 1998; Mussa et al., 2016a]. Cardiac anomalies are described in 20% of children with BWS [Pettenati et al., 1986].

There is a certain degree of clinical variability depending on the etiology of BWS. The different etiological causes of BWS are given in table 2. Hemihypertrophy is strongly associated with UPD11, and exomphalos is associated with an imprinting center 2 (ICR2) defect or *CDKN1C* mutation, but not UPD11 or ICR1 defect [Engel et al., 2000; Cooper et al., 2005; Mussa et al., 2016b]. Renal defects were typical in patients with UPD11 or ICR1 defect, and uretheral malformations in ICR1 gain of methylation cases. Ear anomalies and nevus flammeus were associated with ICR2 or *CDKN1C* genotype. Macroglossia was less common among UPD11 patients [Mussa et al., 2016b]. A characteristic growth pattern was found in each etiological group of BWS; neonatal macrosomia was almost constant in ICR1 gain of methylation, postnatal overgrowth in ICR2 loss of methylation, and hemihyperplasia more common in UPD11 [Mussa et al., 2016b]. Risk of neoplasia is significantly higher in UPD11 and ICR1 defect cases. The risk of Wilms tumor in the ICR2 loss-of-methylation defect appears to be minimal [Cooper et al., 2005; Mussa et al., 2016b]. Hepatoblastoma occurred only in UPD11 cases. Cancer risk was lower in ICR2 defect or *CDKN1C* gene mutation, intermediate in UPD11, and very high in ICR1 cases [Mussa et al., 2016b].

Developmental delay occurs very seldom and is associated with cytogenetically detectable duplications involving the paternal copy of chromosome 11p15 [Waziri et al., 1983; Slavotinek et al., 1997].

Ibrahim et al. [2014] developed the latest clinical diagnostic scoring system for BWS. They used logistic regression and identified clinical features of BWS with the best predictive value for a positive methylation abnormality. Furthermore, in comparison to previous clinical scoring systems, they developed a weighted scoring system to prioritize patients presenting with the most common features of BWS. Since macroglossia and exomphalos had the highest regression coefficient estimates, these were weighted with the highest scores, 2.5 and 1.5 points, respectively. However, neonatal hypoglycemia and hemihypertrophy scored with 0.5 points only. In their new scoring system, the probability of a molecular abnormality ranges from 7.8% for a score of 0 to 98.2% for a score of 8 [Ibrahim et al., 2014].

In summary, the BWS phenotype can vary significantly from a very mild phenotype to intrauterine, neonatal, or pediatric death [Weksberg et al., 2010]. The overall mortality rate of BWS is about 10% with most deaths occurring early secondary to congenital malformations or prematurity [Elliott and Maher, 1994].

### Molecular Basis for SRS

The etiology of SRS is heterogeneous. Several candidate genes and genetic regions have been described in relation to SRS. The first identified molecular cause of SRS was mUPD7 [Kotzot et al., 1995], which is usually present in 5–10% of all cases (table 2) [Kotzot et al., 1995; Eggermann et al., 1997; Preece et al., 1997; Netchine et al., 2007;

Abu-Amero et al., 2008; Binder et al., 2008]. It is very probable that the SRS features associated with mUPD7 arise from altered expression of imprinted genes in chromosome 7. There are several imprinted regions in chromosome 7, among them *GRB10* in 7p12 and the *MEST* imprinted region in 7q32.2, in which epigenetic change most likely may cause the SRS phenotype [Monk et al., 2000, 2002; Hannula et al., 2001b; Carrera et al., 2016]. Still, the precise genomic region in chromosome 7 responsible for the SRS phenotype has not yet been identified.

Gicquel et al. [2005] were the first to show the relaxation of paternal imprinting and biallelic expression of *H19* and downregulation of maternally imprinted insulin-like growth factor 2 *(IGF2)* in the 11p15 region. Now it is well known that hypomethylation of the ICR1 in 11p15 is the major epigenetic alteration causing SRS [Bliek et al., 2006]. The 11p15 region contains 2 clusters of imprinted genes. The maternally expressed *H19* and the paternally expressed *IGF2* gene are controlled by telomeric ICR1. The genes within the second imprinted domain *(CDKN1C* and *KCNQ1)* are regulated by centromeric ICR2, which is mainly involved in the etiology of BWS [Weksberg et al., 2010]. Hypomethylation of ICR1 is found in 37–63% of SRS cases depending on the clinical criteria used for defining cases [Netchine et al., 2007; Binder et al., 2008; Bartholdi et al., 2009; Bruce et al., 2009; Abu-Amero et al., 2010; Turner et al., 2010; Vals et al., 2015b]. A mosaic distribution of the 11p15 epimutation is present in nearly all SRS patients, and this is due to a postfertilization error. Clinically, this mosaicism is reflected by hemihypoplasia [Eggermann et al., 2010a].

In SRS, methylation defects in the imprinted region in 11p15 were considered to be restricted to the telomeric ICR1. Still, a few cases have been published which showed hypomethylation of both 11p15 ICRs, but the molecular cause for that remained unclear [Begemann et al., 2011]. Recently, some patients with severe IUGR and an SRS-like phenotype, which is caused by a paternally inherited *IGF2* nonsense mutation, have been published [Begemann et al., 2015]. In some families, the SRS or severe growth retardation was caused by chromosomal structural mutations in the *H19/IGF2* enhancer region [Grønskov et al., 2011]. Therefore, it is suggested that IGF2P0 methylation analysis should be included in standard molecular testing for SRS as in some SRS cases with normal H19-ICR methylation, IGF2P0 hypomethylation is found instead [Bartholdi et al., 2009; Grønskov et al., 2011].

The third possible cause of SRS is a maternal duplication in 11p15 with a 1–2% frequency [Eggermann et al., 2010a, 2014b]. Most reported duplications involve ICR1 and ICR2 and are usually caused by unbalanced translocations, but duplication of the entire ICR2 as well as a partial duplication of ICR1 can also cause SRS [Fisher et al., 2002; Eggermann et al., 2005, 2010b; Schönherr et al., 2007; South et al., 2008; Bliek et al., 2009b; Cardarelli et al., 2010; Bonaldi et al., 2011; Demars et al., 2011; Begemann et al., 2012b; Chiesa et al., 2012; Hu et al., 2013; Brown et al., 2014; Vals et al., 2015a]. The identification of an SRS patient with a duplication restricted to ICR2 suggests that both ICRs on 11p15 are involved in the etiology of SRS [Schönherr et al., 2007].

matUPD11 as well as *CDKN1C* gene mutations have only been reported once as a cause of SRS [Bullman et al., 2008; Brioude et al., 2013].

Apart from patients with duplication 11p15, microdeletion 12q14, ring chromosome 15, and deletion 15qter, at least 30 patients with various other chromosomal rearrangements have been reported. The chromosomal aberrations most frequently associated with the clinical diagnosis of SRS are ring chromosome 15 and terminal deletions of 15q, including the *IGF1R* gene, located at 15q26.3 with a role in pre- and postnatal growth and brain development [for review, see Fokstuen and Kotzot, 2014]. SRS patients share clinical features with the 12q14 microdeletion syndrome. De Crescenzo et al. [2015] recently identified a novel heterozygous 7-bp intronic deletion in the *HMGA2* gene, located in the 12q14 chromosomal region, in the proband and her mother with typical features of SRS. Some studies have shown that a small proportion of the SRS patients may have cryptic chromosomal rearrangements, which are detectable with chromosomal microarray analysis only, but these abnormalities account for less than 2% of the cases [Bruce et al., 2010; Spengler et al., 2012; Fuke et al., 2013; Fokstuen and Kotzot, 2014; Azzi et al., 2015]. A clinical overlap with Temple syndrome, mUPD16, mUPD20, and 1q21 microdeletion is also described [Spengler et al., 2012; Fuke et al., 2013; Fokstuen and Kotzot, 2014; Azzi et al., 2015].

In ~30–40% of all cases with an SRS phenotype, the underlying molecular defect remains presently unknown and diagnosis is purely clinical [Binder et al., 2008; Wakeling, 2011; Azzi et al., 2015].

### Molecular Basis for BWS

In nearly 70% of BWS patients, an altered expression or mutations of 11p15 encoded factors can be observed with preponderance of an ICR2 hypomethylation ac-

counting for 50–60% of the cases (table 2) [Gaston et al., 2001; Cooper et al., 2005; Weksberg et al., 2010; Begemann et al., 2012b]. The centromeric ICR2 in the 11p15 region controls the *KCNQ1* (potassium channel KQT-family member) cluster, the maternally expressed *KCNQ1* and *CDKN1C*, and the paternally expressed *KCNQ1QT1* gene. DNA methylation defects involving ICR1 usually cause SRS (loss of methylation in 37–63% of the cases) but can also cause BWS (gain of methylation in 5–10% of the cases) [Gaston et al., 2001; Cooper et al., 2005, 2007; Sasaki et al., 2007]. Some of these methylation alterations have been associated with genomic alterations [Niemitz et al., 2004; Sparago et al., 2004; Prawitt et al., 2005]. Methylation changes that occur in conjunction with genomic alterations are important because of their heritability [Weksberg et al., 2010].

Similarly to SRS, the hypomethylation of both 11p15 ICRs has also been described in BWS [Azzi et al., 2009; Bliek et al., 2009a]. Azzi et al. [2009] suggested that epigenetic mosaicism may vary between different tissues, and tissue-specific distribution of this mosaicism may explain the clinical expression of either SRS or BWS.

The paternal UPD11 is the third important cause of BWS and accounts for 20–27% of BWS cases [Henry et al., 1991; Gaston et al., 2001; Cooper et al., 2005, 2007].

In BWS patients without methylation abnormalities in the 11p15 region, the *CDKN1C* gene point mutations are frequent and can occur in 8% of BWS patients [Cooper et al., 2005]. Later, it was shown that loss-of-function mutations in the imprinted *CDKN1C* gene are associated with BWS and gain-of-function mutation with SRS [for review, see Eggermann et al., 2014a]. In familial BWS cases, the occurrence of *CDKN1C* gene mutations is especially high, as it is found in 50–68% of the cases. In 5–31% of sporadic cases, the *CDKN1C* point mutation is detected as the cause of BWS [Eggermann et al., 2014a; Brioude et al., 2015].

Few cases of duplications or deletions involving the ICR1 and/or ICR2 in the 11p15 region have been reported as a cause of BWS [Bliek et al., 2009b; Demars et al., 2011; Begemann et al., 2012b; Vals et al., 2015a]. Microdeletions involving ICR1 are identified in ~5% and microduplications of ICR2 occur very seldom, in <1% of BWS cases [Niemitz et al., 2004; Sparago et al., 2004]. In rare cases, the unbalanced duplication of 11p15 can be inherited due to a familial balanced chromosomal translocation [Slavotinek et al., 1997; Delicado et al., 2005]. It is important to know that the clinical outcome in carriers of these microduplications or microdeletions is influenced by the size, the breakpoint positions, and the parental inheritance of the imbalance reflecting the imprinting status of the affected genes. An extended review about copy number variations in the 11p15.5 imprinting control regions based on the location and the type of imbalance in both the BWS and SRS patients is given by Begemann et al. [2012b].

A few families with a maternally inherited point mutation in ICR1 causing ICR1 hypermethylation by altering an OCT-binding motif have also been identified [Demars et al., 2010; Poole et al., 2012].

Additionally, a few cases of the mosaic genome-wide paternal UPD (also known as androgenic/biparental mosaicism) that may explain unusual BWS phenotypes have been described [Gogiel et al., 2013].

In ~13–15% of all cases with a BWS phenotype, the underlying molecular defect is unknown [Weksberg et al., 2010], and other genomic loci are likely to be involved in the etiology of BWS [Bliek et al., 2009c].

### Clinical Overlap of SRS and BWS with Other Methylation Abnormalities and Multilocus Methylation Defects

During the recent years, many patients with disturbed methylation at multiple imprinted loci have been reported in the literature. This group of conditions has been named multilocus methylation defects (MLMD). MLMD was first reported in patients with transient neonatal diabetes mellitus [Mackay et al., 2008]. Different MLMD are now found in 20–26% of BWS patients with ICR2 hypomethylation [Rossignol et al., 2006; Azzi et al., 2009; Bliek et al., 2009c; Eggermann et al., 2014b] and in 10–20% of SRS patients with ICR1 hypomethylation [Azzi et al., 2009; Turner et al., 2010; Poole et al., 2013; Eggermann et al., 2014b]. Moreover, the International Clinical Imprinting Consortium performed comprehensive methylation analysis of imprinted genes in a research cohort of 285 patients with clinical features of imprinting disorders, with or without a positive molecular diagnosis [Poole et al., 2013]. They found that 22% of patients with diagnosed epimutations had methylation defects of additional imprinted loci, and among patients with clinical features of an imprinting disorder but no molecular diagnosis, methylation anomalies were diagnosed in 8%, including missed and unexpected molecular diagnoses. Vals et al. [2015b] also detected the hypomethylation of *PLAGL1* (6q24) and *IGF2R* (6q25) genes without 11p15 imprinting disorder and clinical features of 6q24-related transient neonatal diabetes mellitus in one patient with the highest BWS clinical scoring.

Clinically, there is no difference between SRS or BWS patients carrying MLMD and patients with 'isolated imprinting defects' in ICR1 or ICR2 in 11p15, respectively [Eggermann et al., 2012]. Moreover, MLMD carriers with the same aberrant methylation patterns in lymphocytes may present with either BWS or SRS [Azzi et al., 2009]. These observations broaden the phenotypic and epigenetic definitions of imprinting disorders and show the importance of comprehensive molecular testing for patient diagnosis and management [Poole et al., 2013].

Therefore, it is very important to widen the epigenetic investigations if methylation disorders are suspected and to include molecular tests for multiple imprinted loci. MLMD testing can be carried out using multilocus methylation-specific single nucleotide primer extension assay, which allows the simultaneous characterization of 10 imprinted loci in 5 chromosomes (*PLAGL1,* 6q24; *IGF2R,* 6q25; *GRB10,* 7p12; *MEST,* 7q32; *ICR1, ICR2*, and *IGF2P0*, 11p15.5; *MEG3* and *IG-DMR*, 14q32; *SNRPN,* 15q11.2). A detailed description of this method was published by different authors [Gonzalgo and Liang, 2007; Begemann et al., 2012a]. Another alternative is to test different imprinted loci separately using, for example, methylation analysis for 11p15 and 15q11q13, and UPD (6, 7, and 14) methylation-specific multiplex ligation-dependent probe amplification testing.

Genome-wide DNA methylation analysis should be considered in patients with growth disturbances in whom imprinting disorder is suspected, as imprinting disorders frequently share common symptoms.

## The Management of SRS and BWS

Children with SRS and BWS should be followed by a team of different specialists including pediatric endocrinologists, dieticians, clinical geneticists and surgeons (including orthopedic surgeons). In both syndromes, body asymmetry can occur. Ongoing follow-up by an orthopedic surgeon should be organized for leg-length discrepancies >1–2 cm [Weksberg et al., 2010].

Tanner and Ham [1969] first reported the use of a growth hormone (GH) in the treatment of SRS. Later, several authors showed the positive effect of using early GH treatment for increasing eventual height in SRS patients [Wollmann et al., 1995; Toumba et al., 2010; Binder et al., 2013; Smeets et al., 2016]. Mean adult height in untreated SRS was 151.2 ± 7.8 cm in males and 139.9 ± 9.0 cm in females, based on the growth studies of 386 cases [Wollmann et al., 1995]. Another study showed that GH-treated SRS patients reached an adult height of –2.12 ± 0.98 SD gaining 1.22 SD in comparison to baseline; adult height SD of the untreated SRS patients was –3.13 ± 1.37 SD [Binder et al., 2013]. Smeets et al. [2016] recently showed that children with SRS have a similar height gain during GH treatment as non-SRS subjects. All (epi)genetic SRS subtypes benefit from GH treatment with a trend towards mUPD7 and idiopathic SRS having the greatest height gain.

Many BWS children will require surgery for omphalocele in the neonatal period, and this is generally well tolerated. Hypoglycemia also occurs in the majority of BWS patients, but this is usually mild and transient. Still, sometimes hypoglycemia should be treated to avoid neurological damage [Elliott and Maher, 1994; Weksberg et al., 2010].

Due to the high risk of tumors, a screening by 3-month serial abdominal ultrasonography to assess kidneys, liver, pancreas and adrenal glands, is advisable in every BWS child below the age of 8–10 years [Andrews and Amparo, 1993; Weksberg et al., 2010]. A baseline MRI has been suggested to provide information for subsequent interpretation of further imaging [Beckwith, 1998]. Alpha-fetoprotein (AFP) can be measured after every 3–4 months to the age of 4 years for early detection of hepatoblastoma. If the AFP level increases, consultation with a pediatric oncologist should be performed [Tan and Amor, 2006; Weksberg et al., 2010]. As the risk for neuroblastoma is small, specific surveillance is not recommended. Still, tumor surveillance is recommended for the apparently unaffected monozygotic co-twin of a child with BWS [Weksberg et al., 2010].

Surgical tongue reduction is performed in up to 50% of all cases with BWS. Untreated macroglossia that does not regress spontaneously may lead to prognathism, open anterior bite, and dental problems [Elliott and Maher, 1994]. This is best assessed by a craniofacial team, including a plastic surgeon, speech therapist, and an orthodontist [Weksberg et al., 2010].

## Familial Recurrence of SRS and BWS

Most cases of SRS usually occur sporadically [Netchine et al., 2007; Bartholdi et al., 2009; Wakeling et al., 2010], although several families with apparently autosomal dominant transmission of SRS have also been identified [Duncan et al., 1990; Al-Fifi et al., 1996]. The most common cause for autosomal dominant transmission is 11p15 duplication [Brown et al., 2014] and in single cases *CDKN1C* [Brioude et al., 2013] or *HMGA2* gene muta-

tions [De Crescenzo et al., 2015]. Bartholdi et al. [2009] also described a family where epimutation was transmitted from an affected father to his daughter. There have also been some descriptions of the presentation of SRS and BWS in different generations of the same family caused by a duplication in the chromosomal region 11p15 [Cardarelli et al., 2010; Vals et al., 2015a].

A few familial descriptions of SRS with apparently autosomal recessive inheritance are described [Teebi, 1992; Õunap et al., 2004; Bartholdi et al., 2009]. Later, Bartholdi et al. [2009] showed that it was caused by hypomethylation of *H19* and *IGF2* in siblings of normal parents, most likely reflecting germline mosaicism of an incorrect methylation mark at the ICR1 during spermatogenesis in the fathers. Therefore, there is a low recurrence risk for epimutations in SRS [Bartholdi et al., 2009].

Most BWS cases are sporadic, but familial occurrence has been reported, in particular in cases of *CDKN1C* point mutations [Eggermann et al., 2014a], translocations involving the 11p15 region [Slavotinek et al., 1997; Smith et al., 2012], or duplication of 11p15 [Vals et al., 2015a]. In these families, BWS follows an autosomal dominant inheritance pattern with incomplete penetrance depending on the parental origin of mutation [Eggermann et al., 2014b]. In case of duplication 11p15 or *CDKN1C* gene mutations, the recurrence risk is 50% [Eggermann et al., 2014a; Vals et al., 2015a]. Gonadal mosaicism should be considered in the provision of recurrence risk when parents are not found to carry a transmissible microdeletion or mutation associated with BWS [Weksberg et al., 2010].

There is an increased risk of monozygotic twins in BWS which are nearly always phenotypically discordant [Smith et al., 2006; Bliek et al., 2009a].

## Assisted Reproductive Technology

It has been shown that the use of assisted reproductive technology (ART) has increased the frequency of imprinting disorders such as BWS and Angelman syndrome. An increased prevalence of ART in the mothers of patients with BWS (4.6%) compared with the control population (0.8%) has been found [DeBaun et al., 2003; Gicquel et al., 2003; Halliday et al., 2004]. It has also been shown that some patients with BWS born after ART show abnormal methylation at loci other than the 11p15 region. Moreover, the mosaic distribution of epimutations suggests that imprinting is lost after fertilization due to a failure to maintain methylation marks during preimplantation development [Rossignol et al., 2006].

A few cases of SRS after ART have also been reported [Källén et al., 2005; Svensson et al., 2005; Bliek et al., 2006]. These results are consistent with animal studies reporting disordered expression and epigenetic changes in imprinted genes following in vitro embryo culture. The absolute risk of an imprinting disorder after ART appears to be very small, but further data are required to determine whether the association between ART and human imprinting disorders reflects the effect of embryo culture (or some other aspect of ART) and/or a common mechanism for infertility and imprinting disorders [Maher, 2005].

## Conclusions

Clinical presentation can vary widely in both SRS and BWS, which sometimes makes the work of clinicians challenging. Neither syndrome has common published consensus diagnostic criteria yet. This is one of the main aims of the European Network of Congenital Imprinting Disorders (http://www.imprinting-disorders.eu/) in the near future to help clinicians recognize and diagnose both syndromes and select the candidates for further molecular studies in everyday practice. It is very important to test patients with a very wide range of clinical symptoms for imprinting disorders as they are usually underdiagnosed. Understanding the exact molecular causes of both syndromes will improve genetic counseling of affected families.

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The author has no conflicts of interest to disclose.

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