# Ongoing Challenges in the Diagnosis of 11p15.5-Associated Imprinting Disorders

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## Abstract

The overgrowth disorder Beckwith-Wiedemann syndrome (BWS) and the growth restriction disorder Silver-Russell syndrome (SRS) have been described as ‘mirror’ syndromes, in both their clinical features and molecular causes. Clinically, their nonspecific features – focused around continuous variables of atypical growth – make it hard to set diagnostic thresholds that are pragmatic without potentially excluding some cases. Molecularly, both are imprinting disorders, classically associated with ‘opposite’ genetic and epigenetic changes to genes on chromosome 11p15, but both are associated with somatic mosaicism as well as an increasing range of alternative (epi)genetic changes to other genes, which make molecular diagnosis an increasingly complex process.

In this Current Opinion, we explore how the understanding of BWS and SRS has evolved in recent years, stretching the canonical ‘mirror’ designations in different ways for the two disorders and how this is changing clinical and molecular diagnosis. We suggest some possible directions of travel toward more timely and stratified diagnosis, so that patients can access the early interventions that are so critical for good outcome.

## Key points:

Health professionals need to consider imprinting disorders in patients with overgrowth or restricted growth where the cause has not been determined. Imprinting disorders are currently under-recognied.

While SRS and BWS are chiefly caused by molecular changes on chromosome 11, research studies are identifying an increasing range of (epi)genetic changes, particularly in people with SRS-like features.

These recent findings need assessment, to decide what (epi)genetic changes should be included in the diagnostic workup for BWS and SRS.

## 1. Introduction

The congenital growth disorders Beckwith-Wiedemann syndrome (BWS) and Silver-Russell syndrome (SRS) are imprinting disorders that have been described as ‘mirror’ syndromes, in both their clinical features and molecular causes.

The classical phenotype of BWS (OMIM #130650) is pre- and postnatal overgrowth, and may include abdominal wall defects, macroglossia, body asymmetry, neonatal hypoglycaemia, and predisposition to embryonal tumours, along with numerous further clinical signs at different frequencies [1]. Its estimated prevalence is approximately 1:10,000 liveborns[2]. It was clinically described in the 1960s but molecular causes were identified 20-30 years later (reviewed in [1]).

SRS (OMIM #180860; also SRS2: #618905; SRS3: #616489; SRS4: #618907; SRS5: #618908) is a growth restriction disorder, typically characterised by pre- and postnatal growth restriction associated with feeding difficulties, relative macrocephaly, typical facial features, body asymmetry and numerous additional features at lower frequency[3]. These are diagnostic criteria (the Netchine-Harbison clinical scoring system [4]) optimised for use in young children and based largely on quantitative growth metrics; they do not define SRS while excluding all other diagnoses. While SRS was clinically described in the 1950s (reviewed in [3]) the first molecular causes, maternal uniparental disomy of chromosome 7 (upd7mat) and imprinting defects on chromosome 11, were described in 1995 and 2005 respectively[5 6], and further causes continue to be found. Its prevalence has been estimated at 1:50,000 to 1:10,000 (reviewed in[2 3]).

BWS and SRS are ‘mirror’[7] disorders in the obvious sense that they are associated with overgrowth and growth restriction, respectively. They are alike in being defined chiefly by qualitative thresholds applied to quantitative growth metrics such as birth weight or asymmetry, and by ‘soft’ clinical features that overlap with other conditions and evolve with age. Early diagnosis of both conditions optimises treatment and prevents complications. Molecularly they are heterogeneous, associated (particularly SRS) with an increasing diversity of genetic and epigenetic abnormalities [8]. At the same time, the increased scope and availability of genomic medicine, and the wider range of healthcare professionals referring patients for genomic testing, have made it more important to be clear what we mean by BWS and SRS, for clinical diagnosis, molecular testing, and clinical management.

In this review we aim to explore how the understanding of BWS and SRS has evolved in recent years, how this currently presents challenges for clinical and molecular diagnosis, and how some of these challenges may be addressed in the future.

## 2. What are the molecular causes of BWS and SRS?

The classic ‘mirror’ clinical phenotypes of BWS and SRS are mirrored, in the majority of patients, by ‘opposite’ DNA changes on chromosome 11[1 3 9], which for the most part do not affect the DNA sequence itself, but how the DNA is expressed.

Chromosome 11p15.5 contains two adjacent clusters of imprinted genes: within each cluster an imprinting centre (IC) is a regulatory DNA sequence methylated on one parental allele, which mediates parent of origin-specific expression of gene products that regulate growth in prenatal and early life (Figure 1).

Under normal conditions, the growth factor *IGF2* is expressed from paternally-inherited DNA, under the control of IC1 which is methylated on the paternal allele, while the growth repressor *CDKN1C* is normally expressed from maternally-inherited DNA, under the control of IC2 which is methylated on the maternal allele (reviewed in [10]). In principle, any genetic or epigenetic error resulting in overexpression of *IGF2* or reduced expression of *CDKN1C* (or both) could cause BWS[11-17], while any causing under-expression of *IGF2* or overexpression of *CDKN1C* (or both) could cause SRS[3 6 18-20]. This can include copy number variants (CNV), uniparental disomy (UPD), methylation disturbance, or coding changes in key genes. In practice, while almost all the molecular alterations in Figure 1 have indeed been seen, the majority of affected individuals have a subset of molecular causes.

The most frequent change in SRS (>50% of cases) is loss of methylation (LOM) of IC1[6], associated with reduced expression of *IGF2*. The most prevalent change in BWS (>60% of cases) is IC2 LOM[16], associated with reduced expression of *CDKN1C[21]*. Epigenetic changes to 11p15.5 are quantitative rather than qualitative: that is, they are almost always seen in mosaic rather than complete form, affecting a proportion of cells but not all cells in the affected person. Mosaicism is particularly a feature of DNA methylation disturbance and UPD in BWS and SRS.

A small minority of patients referred for SRS diagnosis are found to have a molecular change associated with BWS, and vice-versa. These ‘discrepant’ diagnoses include individuals with asymmetry, where it can be hard to judge clinically which somatic tissues are abnormal, or those with multi-locus imprinting disorder causing phenotype modification [22].

BWS and SRS can involve loci beyond chr11p15.5:

(i) While about 25% of BWS is caused by mosaic paternal uniparental disomy involving chr11p15, approximately 5-10% of these are in fact have mosaic paternal uniparental diploidy; that is, a proportion of their cells have a complete biallelic chromosomal complement from the father with no contribution from the mother[23]. Paternal uniploidy has features overlapping BWS but with variable developmental delay and altered tumour susceptibility. Maternal uniploidy has been described in very few cases of SRS[24].

(ii) About 20% of BWS patients with IC2 LOM, and 10-20% of SRS cases with IC1 LOM, have additional LOM at other imprinted loci across the genome, an epigenetic anomaly called multi-locus imprinting disturbance (MLID)[25]. The term MLID describes an epigenetic state of affairs; the imprinted loci affected and the resultant phenotype vary between patients. While most cases are currently recognised because of a ‘primary presentation’ – the clinical features align with a specific imprinting disorder – in at least some cases, the additional imprinting changes modify the phenotype. MLID is inherently mosaic; complete paternalisation of imprinting at all germline imprinted loci is seen in complete or biparental hydatidiform mole, and is incompatible with life[26 27]. Some cases of MLID are genetic in origin, caused by either trans-acting variants in affected individuals or their mothers [28 29]; other cases may be related to conception via assisted reproductive technology[30] or unknown other factors.

(iii) SRS is associated with genetic and epigenetic changes independent of chr11:

1. about 5% of cases have upd7mat; while this is not associated with a specific gene at present, the imprinted *MEST* locus on 7q32 is implicated in rare cases of segmental upd7mat (reviewed in [3]). There are subtle clinical differences in this subgroup including an increased risk of autism and tremor[31].
2. the imprinted locus on chr14q32 shows disturbance (UPD, CNV or LOM) in Temple syndrome (TS14), an imprinting disorder with some phenotypic overlap with SRS.[32-34]
3. in individuals with SRS-like features, other UPD have been found, including upd20mat[35 36], upd6mat[37], upd15mat[38] (normally associated with PWS), and upd16mat[39] (though this may represent evidence of trisomy 16 rescue).
4. children with SRS-like features have CNV and SNV affecting genes in growth pathways, including *CDKN1C* and *IGF2* on chr11[9 40 41], as well as *PLAG1* and *HMGA2* which regulate the IGF2 pathway[42], and a growing list of other genes.[43-45]

iv) BWS has not been directly associated with other imprinted loci in the literature. This is partly because historically diagnosis of BWS is strongly associated with chromosome 11 and therefore when other loci are identified a new diagnostic label is applied, (whereas in SRS, upd7mat was the first identified cause before the more common LOM at 11p15 was discovered, which set a precedent). However, just as in the cases reported with SRS features associated with imprinting errors at other loci, some features of BWS are seen in patients with aberrations at other imprinted loci:

1. the imprinted locus on chr14q32 shows ‘mirror’ disturbances to cases with TS14 (e.g. upd14pat, CNV or GOM) in the condition Kagami-Ogata syndrome. Some of the features, including macrosomia, abdominal wall defects and an increased hepatoblastoma risk, have overlap with BWS [46]
2. occasional cases of paternal UPD 7 and overgrowth have been reported [47 48] and it is reasonable to consider that opposite changes to those resulting in SRS-like growth restriction on other chromosomes may produce an opposite growth phenotype
3. Single gene mutations in non-chromosome 11 genes have not been reported as such in BWS but mutations in genes such as *GPC3* which cause Simpson-Golabi-Behmel syndrome have considerable overlap with BWS including overgrowth, macroglossia and abdominal wall defects [49].

To summarise, while the molecular causes of BWS and SRS can be thought of as ‘mirror-image’ changes on chr11p15, this view is nuanced by the disparities between the proportions of different anomalies, as well as abnormalities of imprinted and non-imprinted loci on other chromosomes and historical conventions on terminology.

## 3. Why is accurate diagnosis important in BWS and SRS?

The fundamental benefits of accurate diagnosis are the same for people with BWS and SRS: an end to the anxiety of not-knowing, prediction of future challenges and needs, and access to clinical management, genetic counselling and peer support. These benefits take slightly different forms for BWS and SRS.

### 3.1 BWS

Accurate and timely diagnosis of BWS is important, partly to inform management of immediate clinical issues such as hyperinsulinism or macroglossia, but particularly to trigger surveillance for childhood neoplasia in some (but not all) patients[1]. For patients at risk of neoplasia, screening is so important that it warrants a low clinical threshold for referral, in order to identify patients who might have few other management needs.

Different (epi)genetic lesions in BWS are relatively associated with different patterns of clinical features[50]. IC1 gain of methylation (GOM) and upd11pat are associated with increased risk of overgrowth, asymmetry, and also embryonal tumours such as Wilms tumour[51]. In some cases, mosaicism is so confined that the presenting clinical feature is lateralised overgrowth, or an embryonic tumour, without other features of BWS[52]. IC2 LOM is associated with conception by assisted reproductive technology, monozygotic twinning, and MLID[25 53-55], but less associated with certain classical features of BWS, including high birth weight (affected individuals may have normal or even low birth weight) and tumour predisposition (such that tumour surveillance is not recommended in current consensus guidelines). *CDKN1C* mutation is associated with heritable BWS, with maternal transmission and variable expressivity, but not with asymmetry [13 56].

Approximately 20% of people with clear clinical features of BWS have no detectable molecular abnormality. Because of the risk that such individuals have a molecular abnormality not accessible to genetic testing, they are managed as if at high risk of neoplasia.

BWS can be molecularly diagnosed in individuals with almost no classical clinical features of the syndrome; it has been re-designated Beckwith-Wiedemann Spectrum (BWSp) to reflect this[1]. At the ‘clinical’ end of the spectrum are individuals with phenotypic features of BWS but no positive molecular diagnosis; at the ‘atypical’ end are those with fewer clinical features – such as isolated lateral overgrowth, or an embryonal tumour – but a confirmed molecular diagnosis that guides their management.

### 3.2 SRS

The growth of children is affected by a very wide range of mendelian, polygenic, medical or social factors, and it is reasonable to imagine that a genetic or environmental insult would be more likely to restrict growth than enhance it. The majority of babies born small for gestational age subsequently catch up in childhood. Only some, including those with SRS, do not catch up, and require clinical intervention. A diagnosis of SRS differentiates this patient group from other growth-restricted individuals who may or may not need intervention[3]. Moreover, among people with molecularly diagnosed SRS there is an increased prevalence of noncommunicable conditions such as hypertension or type 2 diabetes in adulthood[57]. Because of this, clinical diagnosis of SRS triggers multidisciplinary management to optimise growth and wellbeing, and also molecular testing to stratify prognosis and management.

IC1 LOM is associated with asymmetry, probably in relation to mosaicism, with severe pre- and postnatal growth restriction and characteristic facial features in infancy[4 31]. The facial features tend to ameliorate over time, such that clinical referral thresholds for children are not suitable for adults [57]. upd7mat is associated with less severe growth restriction than chr11 anomalies at birth, but with some neurological features including an increased risk of developmental delay due to additional imprinted genes on chr7[31].

Temple syndrome has considerable clinical overlap with SRS in early childhood, such that a small percentage of children referred for SRS testing are diagnosed with TS14; however, newborns with TS14 have less severe growth restriction but greater likelihood of hypotonia[32 58]. Feeding difficulties early on can be less of a presenting feature. In mid-childhood they have a greater risk of premature puberty and truncal obesity; some of these features also overlap with Prader-Willi syndrome[59]. In practice, the age of presentation may influence the clinical features to the point where the referring clinician may suspect SRS (or PWS) rather than TS14, which is less well recognised.

DNA methylation disturbances have been identified in a wider range of imprinted loci, including chr 6, 15, 16 and 20; these loci are associated with a range of imprinting disorders with partially overlapping clinical histories[35 37 38 60].

Genomic analyses of children with SRS features have now implicated numerous genes, but all in very rare cases. *IGF2* inactivating mutations and dominant-negative mutations of *CDKN1C* are heritable but modified by parent of origin[9 40 41]. *PLAG1* and *HMGA2* lie on the IGF2 pathway and show CNV and SNV in rare cases[42]. The key growth phenotypes of SRS – prenatal and postnatal growth restriction – are also associated with numerous differential diagnoses of SRS, accompanied by different clinical features such as intellectual disability, relative microcephaly, dysmorphisms, skeletal dysplasia, or, in the case of chromosome breakage syndromes, tumour susceptibility [3 43-45] Genomic diagnosis in these cases is beneficial for genetic counselling of recurrence risk, and may be essential for stratified treatment, such as the contraindication for Growth Hormone in chromosome breakage syndromes [3].

## 4. What are the current challenges for diagnosis?

The main challenges are setting a reasonable clinical threshold for testing when the symptoms of both conditions are often non-specific and involve determining when growth (a continuous variable) is abnormal enough to initiate testing. When this is coupled to the range of genetic testing that is required to comprehensively make and/or exclude a diagnosis, it is not easy to formulate clear rules.

Since the majority of SRS and BWS cases involve chr11p15, first-line diagnosis of both requires gene dosage and DNA methylation analysis in parallel of IC1 and IC2. Many laboratories worldwide do this using methylation-specific MLPA of blood-derived DNA, a robust and economical commercial test which in principle can diagnose almost all aetiologies of BWS, and most SRS cases involving chr11. Further molecular testing may be required if first-line testing is negative, or to definitively identify the molecular change in some cases when first-line testing is positive[61].

4.1 Clinical heterogeneity is plainly inherent to BWS and SRS, because of their molecular heterogeneity and in particular the contribution of mosaicsm. This brings two potential challenges: first, if clinical thresholds for testing are stringent, they exclude individuals with atypical presentations; second, if clinical referral criteria directly dictate the testing requested, some individuals do not receive testing of all relevant loci.

4.2 Epigenetic heterogeneity is understood to be a challenge for SRS but it is also likely to be the case for BWS, because clinical features of the disorders are associated to different extents with imprinting disturbance. Imprinted loci implicated in SRS and SRS-like disorders are on chromosomes 11, 7, 14, 20, 6, 15 and 16; testing must include the first three and may include the others. If testing focuses on the canonical loci on chr11 and chr7 and omits other loci, a proportion of affected children elude diagnosis. The heterogeneity of BWS lies mainly in the unknown contribution of MLID to the phenotype; but since normal diagnostics investigates only chr11, the contribution of loci outside chr11 is probably limited but remains presently unknown. The epigenetic challenge is, therefore: which loci should be included in first-line diagnosis, or in secondary testing when firstline diagnosis is negative, and which loci are so rare that they need not be tested?

4.3 Somatic mosaicism is a challenge for both BWS and SRS. In diagnostic testing, a few cell types (typically blood leukocytes) are analysed as a proxy for the whole person, and this approach may not diagnose a case with mosaicism when the mosaicism does not involve the tissue type tested. Laboratories must apply qualitative thresholds to quantitative measures of DNA methylation, which means that cases with low-level mosaicism may require orthogonal analysis to confirm a diagnosis[8 62]. Alternative tissues may be tested if standard testing gives a negative result but clinical suspicion remains, particularly in cases of asymmetry or neoplasia where low-level mosaicism for UPD or methylation anomaly may be present (eg, [62 63]). Clinically, the pattern of mosaicism probably relates to the clinical presentation of the patient. In some cases of asymmetric growth, it can be hard to assess clinically whether the larger or smaller tissues are the affected ones, such that a patient referred for BWS testing may turn out to have SRS or vice versa[22]. Finally, a normal result can neither confirm nor exclude a diagnosis of BWS or SRS, and if a strong clinical suspicion of disease persists, then a clinical diagnosis is made and the patient managed accordingly.

4.4 Genetic testing is not a challenge for most cases of BWS. DNA sequencing is required to detect SNV in *CDKN1C*, which are not detected by first-line DNA methylation testing. In some individuals, GOM at IC1 or LOM at IC2 is caused by CNVs or SNVs acting in cis[64-66], but the limited diagnostic capacity to identify such variants, located in noncoding DNA, means that recurrence counselling is seldom informed by comprehensive genetics. For individuals with a negative diagnosis, additional gene panels may be sequenced to pursue differential diagnoses of overgrowth syndromes[67 68], dependent on laboratory infrastructure, national guidelines, the clinical features of the patient, and the clinical benefit of having a positive diagnosis (reviewed in [69]).

The genetic challenge for SRS is the growing range of genetic variants identified in people with SRS-like features and growth restriction. As genomic testing becomes cheaper, more technologically agnostic and more available to mainstream referral – that is, as more practitioners request diagnosis for growth-disordered children – labs can offer increasingly extensive genetic panels for testing. Many of the disorders involved have limited overlap with SRS, and are regarded as differential diagnoses. It may be important to clinically stratify cases, to direct genetic testing toward SRS or differential diagnosis, and thereby direct interpretation of variants in substantial panels of potentially causative genes.

## 5. Where do we go from here?

We have come a long way from the days when SRS and BWS were defined using purely clinical nosology. It should be acknowledged that the key features of BWS – macrosomia, macroglossia and abdominal wall defects – are ‘harder clinical handles’ than pre- and postnatal growth failure seen in SRS; therefore, BWS has always had a higher recognised prevalence than SRS. The advent of genetic analysis for both disorders has rightly become indispensable for diagnosis and prognosis, while concomitantly broadening the clinical spectrum to the point where it reflects back the question of clinical definition itself. Do the recent clinical consensus statements[1 3] continue to indicate where the boundaries of BWS and SRS are drawn? Which molecular and clinical features should be included and excluded? If clinical and molecular definitions are not congruent, which should be dominant? We offer some suggestions for directions of travel, but stress that understanding of these disorders is changing rapidly, and our comments may soon be out of date.

### 5.1 Molecular diagnosis

5.1.1 DNA methylation testing: The majority of cases of BWS and SRS have imprinting disturbance, and first-line testing focusing on imprinting is economical enough to be used with a relatively low clinical threshold for referral. In our view, first-line testing for BWS and SRS should be incorporated into a common imprinting ‘panel’ test for growth-related imprinting disorders. This would include (at the time of writing) CNV and DNA methylation of loci on chromosomes 6, 7, 11, 14, 15 and 20. A patient meeting referral criteria for any growth-related imprinting disorder (or with a clinical suspicion of MLID) could then be tested in a common pathway. This would have the following merits:

(i) Imprinting panel testing would ameliorate the risk of missing diagnoses in patients because of their age at presentation, possible mosaicism, multi-locus involvement or other genetic/environmental modifiers. The increased likelihood of early diagnosis would offset potential lowering of proportional yield. (ii) Economy of scale and efficiency should help such a test to be applied with a low threshold of clinical suspicion, and potentially early in the diagnostic process; this could therefore shorten the diagnostic odyssey and enable early intervention that could interrupt sequences of morbidity. A key example of this is in France, where widespread testing of hypotonic infants for PWS has reduced the age of diagnosis to <6 months, enabling intervention before the onset of characteristic morbidity, and transforming patient outcome (see for example [70] and references therein). (iii) Clinicians could request the ‘masking’ of some loci on the panel, to diagnose specific disorders without testing for others, if a focused approach is required. (iv) Imprinting panel testing would also detect cases with multi-locus involvement (uniploidy or MLID), where presentation is unpredictable but early intervention is advisable. Current SRS and BWS consensus guidelines do not recommend MLID testing, because of the limited evidence available at the time of their writing, but this situation remains under review. Imprinting panel testing would enable detection of MLID at the point of first-line testing, and referring clinicians would then need to assess whether additional investigations, interventions or counselling were warranted.

5.1.2. Genetic testing: Advances in genomic technology and research have enabled identification of an increasing range of UPD, SNV and CNV in children with SRS/BWS features, associated with an increasing breadth of clinical features. Most of the variants identified are very rare, and many are associated with other disorders that have varying clinical overlap with SRS. Therefore, in a patient where first-line testing is negative, the decision about whether to test further, and what genes to test, should be made in consultation between clinician and laboratory to prioritise what gene panels are most relevant.

For BWSp, *CDKN1C* analysis follows imprinting analysis, particularly for familial cases. Overgrowth gene panels may then be appropriate with the same caveat as for SRS: ie, requiring consultation between the patient, the clinician and the lab.

For either BWS or SRS where MLID is detected, genome testing could include maternal-effect variants. This is not recommended in current guidelines because of the relative novelty of MLID at the time of writing; but in principle the recurrence rate of MLID approaches 100% if the mother has variants in maternal-effect genes such as *NLRP2* or *NLRP7*, and in practice, such testing is becoming available in several nations.

### 5.2 Clinical diagnosis: What’s in a name?

Around the time when BWS and SRS were defined, the great geneticist Victor McKusick observed that ‘nosologists in all fields tend to be either ‘lumpers’ or ‘splitters’’[71]. ‘Lumping’ is the pattern-recognition involved in defining a syndrome, or in grouping patients for efficient clinical diagnosis or evidence-based management; ‘splitting’ is the stratification of affected individuals clinically and molecularly to optimise care. The clinical and molecular advances in understanding have led to different changes for BWS and SRS.

BWS has evolved into the Beckwith-Wiedemann spectrum, an extended ‘lump’ where both clinical and molecular features contribute to the diagnosis but where molecular diagnosis focused on chromosome 11 ‘splits’ patients particularly for tumour surveillance. Since SRS is defined as a clinical entity by the NH-CSS (the decision of the international consensus of 2016), children with different genetic changes are ‘lumped’ into this clinical diagnosis, while, conversely, children with those same genetic changes may be excluded if they do not meet diagnostic thresholds. There has been discussion of re-designating SRS as Silver-Russell Spectrum (SRSp), a larger ‘lump’ potentially including TS14, Mulchandani-Conlan-Bhoj Syndrome, upd6mat and upd16mat, and a range of genetic conditions (as referenced, for example, in Eggermann et al, 2022: [72]). The designation SRSp would have a satisfying ‘mirror’-symmetry with BWSp. However, if SRSp were to be defined dually by clinical and molecular features, then its clinical parameters might be broadened beyond usefulness for (a) referring patients for molecular testing and (b) stratifying patient groups in need of particular management.

In our view, some moves toward both lumping and splitting might be useful. Firstly, we believe that if molecular diagnosis of imprinting disorders used a common testing pathway with a shared molecular panel, referral criteria could have lower thresholds. A larger lump of patients would be tested, and access to testing would be improved for individuals who currently do not meet testing criteria. Secondly, two-part diagnostic description can combine clinical and molecular elements (eg IC1 SRS or upd11 BWS) in dyadic names.[73] This may be particularly helpful for some groups of patients: for example, individuals with a clinical diagnosis but negative molecular testing may be termed ‘clinical’ or ‘idiopathic’ to identify them with the clinical group for management purposes (for example, BWS-clinical); carriers of CNVs affecting imprinted regions, in whom the phenotype might be modified by the role of further genes in the regions; or individuals with upd11-BWSp whose only clinical feature is a Wilms’ tumour, who can be ‘lumped’ to signify their management needs.

However, using genetic names to define a condition is particularly complex in this group of conditions. For example, people with TS14 require a different emphasis regarding clinical interventions from those required with SRS- LOM 11p15.5; that may be better served by maintaining the syndromic identity than by lumping TS14 into a spectrum designation of SRS-14q. For example patients with TS14 have a particular issue with premature puberty that can be as early as 3 years of age. In addition to hypotonia, that have concern regarding weight gain in older childhood and it is probable that they require a more rigorous nutritional intervention. Different aberrations on 14q (eg upd14mat, LOM14q32, etc) have potentially different prognoses but precise genetic classifications make comprehension difficult and may mean that the key long term medical issues in TS14 such as premature puberty and metabolic imbalance seen in this group as a whole, are not recognised by taking the splitting approach to its extremes.

We believe it is time to revisit the SRS consensus guidelines, to re-validate the central axiom that the diagnosis is clinical and to decide which epigenetic and genetic changes lie within SRS and set the agenda for translational research. Our final key message is that imprinting disorders are an under-recognised cause of growth and developmental disorders. Patients with prenatal onset of overgrowth or restricted growth where the cause has not been determined should be investigated for an imprinting disorder.

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Figure 1: organisation of imprinting centres 1 and 2 on chromosome 11p15.5, and the different genetic and epigenetic changes associated with BWS and SRS.

The central diagram represents the key imprinting control regions and imprinted genes located near the telomere of chromosome 11, within chr11p15.5. IC1, which is methylated on the paternally-inherited allele, lies between the noncoding RNA H19 (expressed from the maternally inherited allele) and the growth factor gene, IGF2, expressed from paternally-inherited DNA. IC2, which is methylated on the maternally-inherited allele, lies at the promoter of the long noncoding RNA KCNQ1OT1 (paternally-expressed), which regulates in-cis the expression of the coding gene KCNQ1 and the growth repressor CDKN1C (maternal) between the noncoding RNA H19 (expressed from the maternally inherited allele).

To the left are represented the genetic and epigenetic changes associated with BWS; those associated with SRS are to the right. The approximate percentage of diagnoses is noted, along with relevant subsets of diagnoses. Additional SRS diagnoses outwith chr11p15 are indicated in italic text.

red: maternally-inherited DNA; blue: paternally-inherited DNA; grey: imprinted (silenced) genes; filled rectangles: protein-coding genes; unfilled rectangles: noncoding RNA; circles: imprinting centres, with black fill indicating methylated DNA and white fill indicating unmethylated DNA.

