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Beckwith-Wiedemann Syndrome

Synonyms: Wiedemann-Beckwith Syndrome, Beckwith-Wiedemann Spectrum (BWSp)

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Summary

Clinical characteristics

Beckwith-Wiedemann syndrome (BWS) is a growth disorder variably characterized by macroglossia, hemihyperplasia, omphalocele, neonatal hypoglycemia, macrosomia, embryonal tumors (e.g., Wilms tumor, hepatoblastoma, neuroblastoma, and rhabdomyosarcoma), visceromegaly, adrenocortical cytomegaly, kidney abnormalities (e.g., medullary dysplasia, nephrocalcinosis, and medullary sponge kidney), and ear creases / posterior helical ear pits. BWS is considered a clinical spectrum, in which affected individuals may have many or only one or two of the characteristic clinical features. Although most individuals with BWS show rapid growth in late fetal development and early childhood, growth rate usually slows by age seven to eight years. Adult heights are typically within the normal range. Hemihyperplasia (also known as lateralized overgrowth) is often appreciated at birth and may become more or less evident over time. Hemihyperplasia may affect segmental regions of the body or selected organs and tissues. Hemihyperplasia may be limited to one side of the body (ipsilateral) or involve opposite sides of the body (contralateral). Macroglossia is generally present at birth and can obstruct breathing or interfere with feeding in infants. Neonatal hypoglycemia occurs in approximately 50% of infants with BWS; most episodes are mild and transient. However, in some cases, persistent hypoglycemia due to hyperinsulinism may require consultation with an endocrinologist for therapeutic intervention. With respect to the increased risk for embryonal tumor development, the risk for Wilms tumor appears to be concentrated in the first seven years of life, whereas the risk for developing hepatoblastoma is concentrated in the first three to four years of life. Cognitive and neurobehavioral development is usually normal. After childhood, prognosis is generally favorable, although some adults experience issues requiring medical management (e.g., for renal or skeletal concerns).

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Diagnosis/testing

The clinical diagnosis of BWS can be established in a proband who has two tier 1 characteristic clinical findings OR one tier 1 and one tier 2 clinical finding.

A diagnosis can also be established in a proband with at least one tier 1 or tier 2 clinical finding AND either:

- A constitutional epigenetic or genomic alteration leading to an abnormal methylation pattern at 11p15.5 known to be associated with BWS; OR
- A copy number variant of chromosome 11p15.5 known to be associated with BWS; OR
- A heterozygous BWS-causing pathogenic variant in *CDKN1C*.

Management

Treatment of manifestations: Hypoglycemia is treated with oral feeding if it is mild or with glucose supplementation. Hyperinsulinism is treated with standard pharmacotherapy per endocrinologist; partial pancreatectomy may be considered in those with persistent hypoglycemia who are unresponsive to pharmacologic treatment. Feeding and/or respiratory support (sometimes requiring intubation at birth or tracheostomy for severe respiratory insufficiency) may be needed for those with macroglossia and/or upper airway obstruction. Tongue reduction surgery may be considered for this and other indications. Standard treatment is recommended for omphalocele per pediatric surgeon. A shoe lift may be considered in those with a leg length discrepancy. Epiphysiodesis prior to epiphyseal closure in early puberty may be considered in instances with leg length discrepancy >2 cm; alternatively, leg lengthening of the shorter leg may be considered. For those with hemihyperplasia of the face, referral to a craniofacial center for assessment and potential treatments may be considered. If present, standard treatment is recommended for speech delay/impediment, neoplasia, congenital heart defects, and hypercalciuria / kidney anomalies.

Surveillance:

- **Tumor surveillance.** Perspectives on screening for malignant tumors in childhood differ based on local, national, and international practices. In North America, proactive tumor screening is recommended when the risk of tumor development exceeds 1%. In many European countries, proactive tumor screening protocols are typically undertaken when the risk of tumor development exceeds 5% and are based on molecular mechanism. For most BWS molecular subtypes, tumor screening consists of abdominal ultrasound with views of the liver, adrenal glands, and kidneys every three months until age four years followed by kidney ultrasound only every three months from age four to seven years. Serum alpha-fetoprotein (AFP) levels are performed every three months until age four years. Physical exam by a pediatrician, geneticist, or pediatric oncologist twice a year is also recommended. Proposed screening for neuroblastoma in children with a heterozygous pathogenic variant in *CDKN1C* includes abdominal ultrasound, urine vanillylmandelic acid and homovanillic acid, and chest radiograph every three months until age six years, then every six months until age ten years.
- **Non-tumor surveillance** includes measurement of growth parameters, assessment for signs/symptoms of sleep apnea, and monitoring of developmental progress / educational needs at each visit; pre-feed serum glucose level per endocrinologist recommendations in neonates and infants with a history of hypoglycemia/hyperinsulinism or random serum glucose level in neonates and infants with signs/symptoms consistent with hypoglycemia; consideration of blood pressure measurements and measurement of urinary calcium-to-creatinine ratio to screen for occult nephrocalcinosis annually or biannually; consideration of kidney ultrasound to identify findings such as nephrocalcinosis and medullary sponge kidney annually between age eight years and mid-adolescence and periodically in adulthood; assessment of hemihyperplasia and leg length discrepancy at each visit at least until skeletal maturity; dental evaluation with low threshold for orthodontic evaluation as clinically indicated.

Genetic counseling

BWS is associated with abnormal expression of imprinted genes in the BWS critical region. Reliable recurrence risk assessment requires identification of the genetic mechanism in the proband that underlies the abnormal expression of imprinted genes in the BWS critical region. While the majority of families have a recurrence risk of less than 1%, certain underlying genetic mechanisms (e.g., *CDKN1C* pathogenic variants and copy number variants involving 11p15) may be associated with a recurrence risk as high as 50% depending on the sex of the transmitting parent and the specific alteration. In families with recurrence of BWS, maternally inherited *CDKN1C* pathogenic variants account for approximately 40% of genetic alterations and paternally or maternally inherited copy number variants account for approximately 9% of genetic alterations. Of note, some individuals with BWS have methylation alterations in the 11p15 imprinted domain as well as in other imprinted loci. For these individuals review of the maternal history should be undertaken for unexplained spontaneous abortion, hydatidiform moles, or a sib with BWS or another imprinting disorder (e.g., Silver-Russell syndrome); in such cases, a homozygous or heterozygous pathogenic variant in maternal effect gene in the mother's genome may confer a significant recurrence risk.

Prenatal testing and preimplantation genetic testing: If a genomic variant involving chromosome 11p15.5 (i.e., a cytogenetically visible duplication, inversion, or translocation), copy number variant of 11p15.5, or a *CDKN1C* pathogenic variant has been identified in the proband, prenatal testing via analysis of fetal DNA from samples obtained by chorionic villus sampling (CVS) or amniocentesis is possible. Preimplantation genetic testing is possible for a familial *CDKN1C* pathogenic variant and may be possible for some familial genomic variants. For evaluation of fetal methylation status, DNA extracted from amniotic fluid is currently felt to provide the most reliable tissue source, although false negative findings have been reported. Tissue obtained via CVS for prenatal testing for methylation status does not yield reliable results. Genetic counseling should emphasize the potential limitations of prenatal testing for epigenetic alterations.

Diagnosis

The phenotypic presentation of Beckwith-Wiedemann syndrome (BWS) is highly variable, and no consensus clinical diagnostic criteria are universally accepted at this time. Clinical diagnostic scoring systems have been proposed and can assist with guiding diagnostic considerations, genetic testing, and management [Weksberg et al 2010, Brioude et al 2018, Duffy et al 2019a]. However, a cautious approach should be adopted especially given the implications for tumor surveillance. That is, children with a "mild" clinical presentation, those whose algorithm scores do not meet the threshold for a BWS clinical diagnosis, and/or those with nondiagnostic genetic testing results may still be at increased risk for tumor development.

Suggestive Findings

Beckwith-Wiedemann syndrome (BWS) **should be suspected** in a proband who has one or more of the following findings, which are divided into tiers based on their relevance for the diagnosis of BWS.

Tier 1 findings. The features listed below, whether as a single finding or as a combination of findings, are highly suggestive of the diagnosis:

- Macroglossia
- Omphalocele (also sometimes referred to as exomphalos)
- Embryonal tumor, such as Wilms tumor (unilateral or bilateral), hepatoblastoma, or nephroblastomatosis
- Hemihyperplasia (lateralized overgrowth) of one or more body segments
- Macrosomia, defined as pre- and/or postnatal overgrowth, often using a cutoff of >90th or >97th centile, depending on the study
- Hyperinsulinemic hypoglycemia

- Cytomegaly of the adrenal cortex, which is considered pathognomonic for BWS
- Other pathologic findings, including placental mesenchymal dysplasia and pancreatic adenomatosis
- Family history of ≥1 family members with clinical features suggestive of BWS

Tier 2 findings, listed below, are less specific than tier 1 findings:

- Visceromegaly, typically from an imaging study such as ultrasound, involving ≥1 intra-abdominal organs, such as the liver, kidneys, and/or adrenal glands
- Unilateral or bilateral earlobe creases and/or posterior helical ear pits
- Characteristic facies (See Clinical Characteristics, **Craniofacial features.**)
- Kidney anomalies, such as structural malformations, nephrocalcinosis, or medullary sponge kidney
- Large umbilical hernia that requires surgical correction
- Other embryonal tumors, including rhabdomyoscarcoma, neuroblastoma, or adrenal tumors (pheochromocytoma, adrenocortical carcinoma)
- Transient hypoglycemia requiring medical intervention

Tier 3 findings. These findings are supportive of the diagnosis, particularly if there are tier 1 or tier 2 findings as well:

- Small umbilical hernia or diastasis recti
- Polyhydramnios and/or placentomegaly during pregnancy
- Premature birth
- Nevus simplex, typically on the forehead, glabella, and/or back of the neck AND/OR hemangioma (cutaneous or within organs such as the liver)
- Isolated transient hypoglycemia that does not require medical intervention
- Structural cardiac anomalies or cardiomegaly
- History of assisted reproductive technology (ART) to achieve the proband's pregnancy OR history of subfertility in a parent
- Monozygotic twinning that includes the proband

Establishing the Diagnosis

Clinical diagnosis. The clinical diagnosis of BWS **can be established** in a proband who has two tier 1 characteristic clinical findings OR one tier 1 and one tier 2 clinical finding.

Molecular diagnosis. A diagnosis of BWS **can be established** in a proband with at least one tier 1 or tier 2 clinical finding AND either:

- A constitutional epigenetic or genomic alteration leading to an abnormal methylation pattern at 11p15.5 known to be associated with BWS; OR
- A copy number variant of chromosome 11p15.5 known to be associated with BWS; OR
- A heterozygous BWS-causing pathogenic (or likely pathogenic) variant in *CDKN1C*.

Note: (1) A molecular diagnosis of a constitutional BWS-associated 11p15.5 (epi)genomic alteration in the absence of clinical features associated with BWS does not automatically merit a BWS clinical diagnosis. However, this molecular finding confers an increased risk for tumor development [Scott et al 2008]. Notably, Wilms tumor can be the initial presentation of subtle cases of BWS that were not clinically recognized prior to the tumor diagnosis [MacFarland et al 2018, Fiala et al 2020]. Until further data are available regarding the risk for embryonal tumor development, individuals with constitutional 11p15 (epi)genomic alterations should undergo standard tumor surveillance even in the absence of BWS-associated clinical findings (see Management). (2) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for

clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (3) Identification of a heterozygous *CDKN1C* variant of uncertain significance does not establish or rule out the diagnosis.

BWS is associated with abnormal regulation of gene transcription in two imprinted domains on chromosome 11p15.5 (also known as the BWS critical region). Regulation may be disrupted by any one of numerous mechanisms; a simplified description of known etiologic mechanisms is given here to clarify the testing pipelines described in Genetic Testing. See Molecular Pathogenesis for a detailed description of the regulation of gene expression in this genomic region.

The BWS critical region includes two domains: imprinting center 1 (IC1) regulates the expression of *IGF2* and *H19* in domain 1; imprinting center 2 (IC2) regulates the expression of *CDKN1C*, *KCNQ10T1*, and *KCNQ1* in domain 2 (see Figure 1). Genomic imprinting is a phenomenon whereby the DNA of the two alleles of a gene is differentially modified so that only one parental allele – parent specific for each gene – is normally expressed. As shown in Figure 1a, differential methylation of IC1 (sometimes also referred to as differentially methylated region 1, DMR1, or *H19*-DMR) and IC2 (sometimes also referred to as DMR2 or *LIT1*-DMR) is associated with expression of specific genes on the paternal and maternal alleles in unaffected individuals.

In more than 80% of individuals with BWS, genetic testing can detect one of five alterations [Weksberg et al 2003, Weksberg et al 2005]. It is important to note that some affected individuals do not have a genetic alteration identified through genetic testing due to somatic mosaicism or to limitations in the current genetic testing platforms. For example, small deletions may be missed by routine microarray analysis for which high-density microarrays focused on the BWS critical region may be required [Baker et al 2021, Sobel Naveh et al 2022].

- A schematic of the following four molecular alterations is shown in Figure 1:
  - Loss of methylation of IC2 (at the transcriptional start site [TSS] of the *KCNQ1OT1* differentially methylated region [DMR]) [on the maternal chromosome] (See Figure 1b.)
  - Gain of methylation of IC1 (*H19*/*IGF2*:IG [intergenic] DMR) on the maternal chromosome (See Figure 1c.)
  - Paternal uniparental disomy (UPD) of 11p15.5 (See Figure 1d.)
  - A heterozygous pathogenic variant on the maternal *CDKN1C* allele (See Figure 1e.)
- Genomic variants involving chromosome 11p15.5 including cytogenetically visible duplications, inversions or translocations, or copy number variants including small duplications or deletions of 11p15.5 are not represented in Figure 1.

Note: Methylation changes may be associated with any of the primary genomic variants above except for pathogenic variants on the maternal *CDKN1C* allele [Baskin et al 2014, Brioude et al 2018].

Figure 2 summarizes the percentage of individuals with BWS by genetic mechanism.

Genetic Testing

Children who have milder or atypical phenotypes (e.g., ear pits and umbilical hernia) may have mosaic pathogenic BWS-causing alterations but may still be at increased risk (compared to the general population) of developing tumors associated with BWS. This is in part because cells with BWS-associated molecular changes may be present in organs "at risk" for tumor development (e.g., liver or kidneys) but not in tissues that influence external clinical presentation. Therefore, the index of suspicion should be high when evaluating children with minimal clinical features in the BWS phenotypic spectrum, with strong consideration of the use of genetic testing to confirm the diagnosis. Individuals with minimal features of BWS and normal genetic testing may still be at increased risk of developing childhood tumors.

Sample types. Genetic testing frequently is performed on a peripheral blood sample. If genetic testing of a blood sample is normal in the context of clinical findings suggestive of BWS, molecular genetic testing of a different

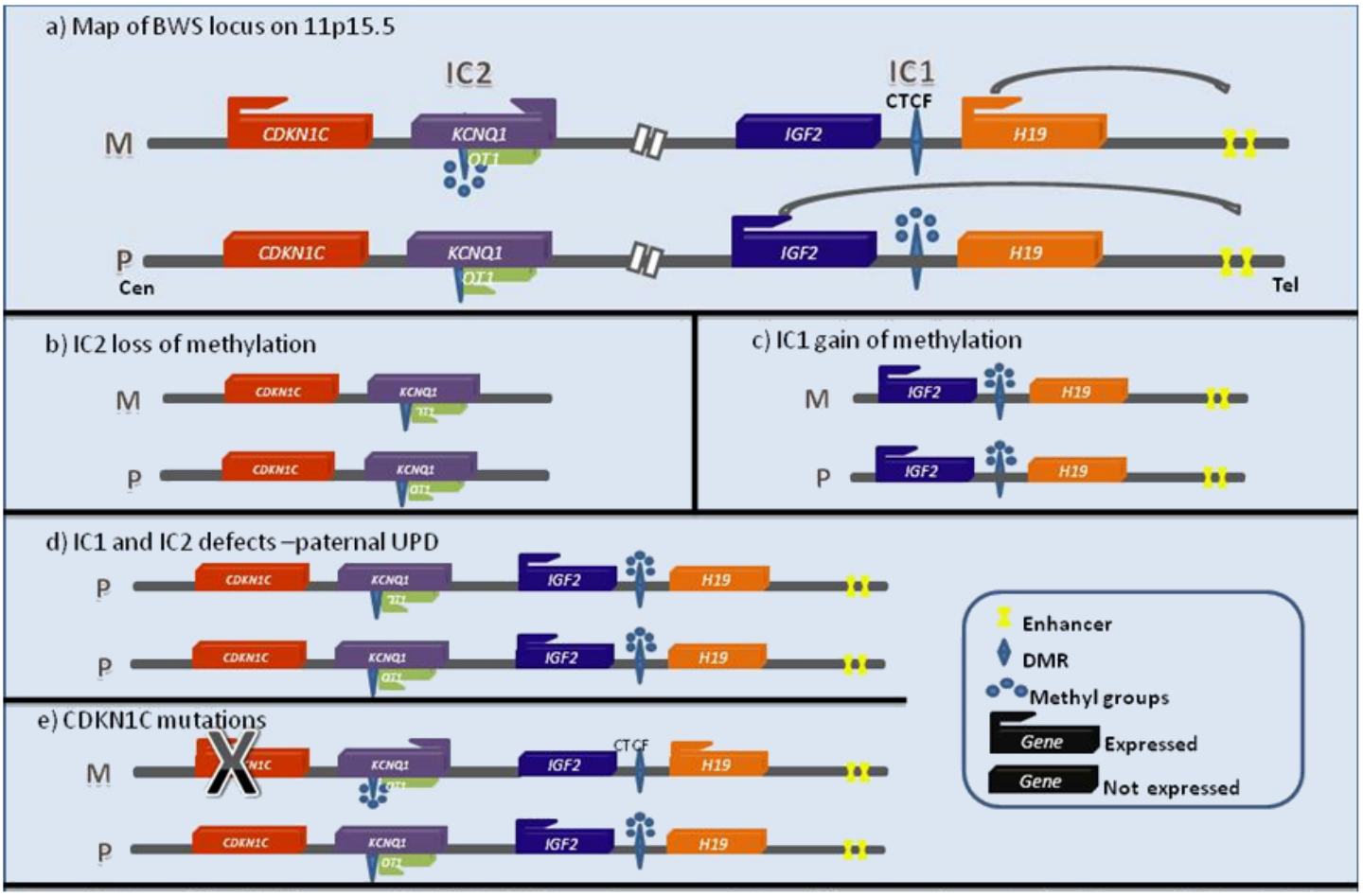

Figure 1. Map of the BWS locus on 11p15.5

a) A schematic representation of the normal parent of origin-specific imprinted allelic expression. Note: b) and c) show the altered region only. The image is not drawn to scale.

Cen = centromere; DMR = differentially methylated region; IC = imprinting center; M = maternal; OT1 = KCNQ1 antisense transcript, KCNQ1OT1; P = paternal; Tel = telomere

Republished with permission from Choufani et al [2010]

tissue may provide a positive test result. Tissue samples obtained from affected regions (e.g., skin biopsy from larger limb in a person with hemihyperplasia, excised tongue tissue from reduction glossectomy [Alders et al 2014, Duffy et al 2019a]) have a higher likelihood of detecting an alteration; however, samples such as buccal swabs or those obtained opportunistically (e.g., skin sample from incision site) may also provide positive genetic testing results. Consideration should be given to obtaining tissue samples during surgical intervention to support genetic testing.

Genetic testing approaches can include **DNA methylation studies**, **single-gene testing**, **copy number analysis for (sequences within) 11p15.5**, **chromosomal microarray**, **karyotype**, and use of **multigene panels** that include genes in the BWS critical region (see Figure 3).

- **DNA methylation studies** of IC1 and IC2 should be performed simultaneously.
  - Methylation alterations at both IC1 and IC2 suggest uniparental disomy (UPD).
  - For recurrence risk purposes, further genetic studies can be undertaken to define the mechanism that leads to the methylation abnormality (see Genetic Counseling).

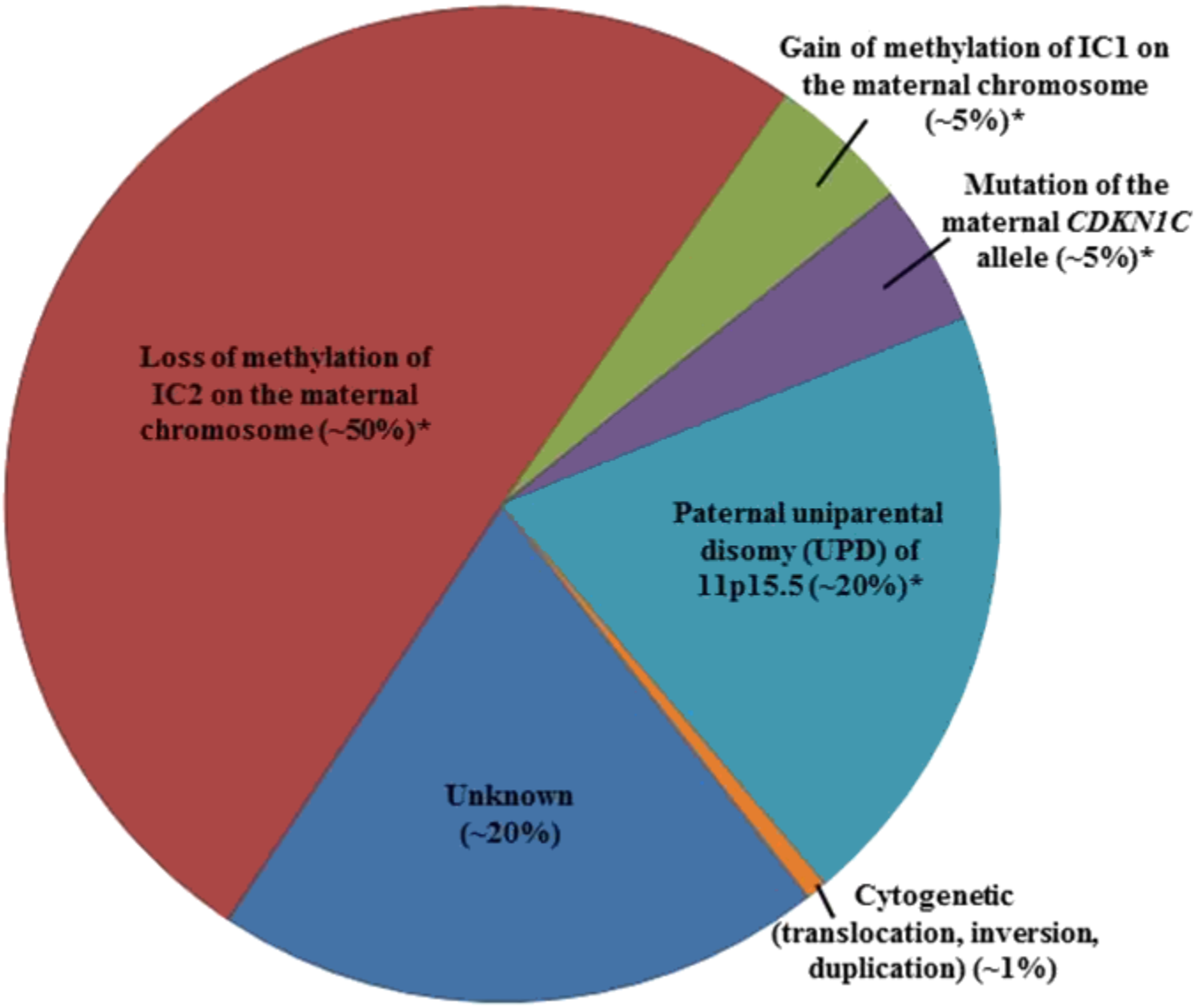

Figure 2. Causes of Beckwith-Wiedemann syndrome by genetic mechanism

* These molecular subgroups, defined by DNA methylation abnormalities, may also be the result of an underlying genomic alteration. Such genomic aberrations are most common for hypermethylation of IC1 and least common for hypomethylation at IC2. Genomic aberrations, limited to the BWS critical region on chromosome 11p15.5, can be detected by MS-MLPA or various sequencing technologies. Some deletions/duplications may be detected by CMA.

BWS = Beckwith-Wiedemann syndrome; CMA = chromosomal microarray; IC1 = imprinting center 1; IC2 = imprinting center 2; MS-MLPA = methylation-specific multiplex ligation-dependent probe amplification

- **Single-gene testing.** Sequence analysis followed by gene-targeted deletion/duplication analysis of *CDKN1C* should be considered in familial cases, in individuals with BWS and midline anomalies (cleft palate, posterior fossa abnormalities, omphalocele, or hypospadias [Gardiner et al 2012, Brioude et al 2015]), or in individuals for whom a strong clinical suspicion for BWS exists but no detectable chromosome 11p15.5 cytogenetic abnormalities, copy number variants, methylation abnormalities, or UPD have been identified.
- **Chromosomal microarray (CMA)** using oligonucleotide arrays can detect only large deletions or duplications in a proband. CMA may be considered first in a proband with intellectual disability. The

ability to size the deletion depends on the type of microarray used and the density of probes in the 11p15.5 region [Keren et al 2013, Baskin et al 2014, Russo et al 2016]. High-density SNP array analysis can be used to detect smaller genetic changes, including duplications, deletions, and segmental paternal UPD as well as genome-wide UPD (see Genetically Related Disorders).

- **Karyotype.** A karyotype may be considered to test for an inversion or translocation involving 11p15.5. This accounts for fewer than 1% of individuals with BWS.
- **A multigene panel** that includes *CDKN1C* and other genes of interest (see Differential Diagnosis and Genetically Related Disorders) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Genetic Testing Used in Beckwith-Wiedemann Syndrome

Method	Pathogenic Variants/Alterations Detected	Proportion of BWS Alterations Detected [1]
Methylation analysis [2, 3]	Loss of methylation at IC2 (maternal) [4]	50% [5]
	Gain of methylation at IC1 (maternal)	5% [5]
	Loss of methylation at IC2 AND gain of methylation at IC1 (paternal UPD)	20% [5]
Sequence analysis / gene-targeted deletion/ duplication analysis [6, 7]	Heterozygous maternal *CDKN1C* pathogenic variants [8]	5% in persons w/no family history of BWS [9]
		~40% in persons w/positive family history of BWS [9]
Karyotype	Cytogenetic duplication, inversion, or translocation of 11p15.5	<1% [10]

Table 1. continued from previous page.

Method	Pathogenic Variants/Alterations Detected	Proportion of BWS Alterations Detected [1]
Chromosomal array (SNP based)	Small chromosomal deletions & duplications, paternal UPD [11]	See footnote 12; ~20% [11]

SNP = single nucleotide polymorphism; UPD = uniparental disomy

1. Proportion of affected individuals as classified by gene/locus, phenotype, population group, and/or test method, in individuals fulfilling clinical diagnostic criteria for BWS. Note: Frequencies may vary in different populations [Sasaki et al 2007].

2. Assays developed to be methylation sensitive (e.g., methylation-specific multiplex ligation-dependent probe amplification [MS-MLPA], quantitative PCR [MS-qPCR], Southern blotting) allow detection of epigenetic and genomic alterations of 11p15.5. Methylation-sensitive assays can discern microdeletions and microduplications, DNA methylation alterations, and uniparental disomy (UPD). Interpretation of methylation data should take into account results of karyotype analysis because karyotypic abnormalities that alter the relative dosage of parental contributions (e.g., paternal duplication) are associated with abnormal methylation status. Other methods to confirm UPD at 11p15.5 include short tandem repeat (STR) analysis or SNP analysis [Keren et al 2013].

3. Altered methylation at imprinted loci outside of 11p15.5 can be detected in approximately 30%-50% of individuals with BWS and loss of methylation at IC2. This condition is termed multilocus imprinting disturbance (MLID) and is more common in females (4:1 female-to-male ratio) [Sanchez-Delgado et al 2016, Fontana et al 2018, Tannorella et al 2022] (see Differential Diagnosis).

4. If the affected individual is found to have altered methylation at imprinted loci outside of 11p15.5, they may have MLID, for which further genetic testing may be entertained (see Differential Diagnosis).

5. Bliek et al [2001], Weksberg et al [2001]

6. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, partial-, whole-, or multigene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

8. Some pathogenic variants may be missed on targeted sequencing and/or deletion/duplication testing and newer sequencing technologies (e.g., whole-genome sequencing) may be able to detect these.

9. The detection rate for *CDKN1C* sequencing varies by family history [Hatada et al 1997, Lee et al 1997, O'Keefe et al 1997, Lam et al 1999, Algar et al 2000, Li et al 2001, Brioude et al 2015].

10. Slavotinek et al [1997], Li et al [1998]

11. Paternal UPD occurs by postzygotic somatic recombination and can, therefore, be identified by proband-only SNP array analysis.

12. Many small chromosomal deletions, small chromosomal duplications, and UPDs are not detected by current microarray testing on the proband. These require high-density SNP arrays for detection.

Clinical Characteristics

Clinical Description

Beckwith-Wiedemann syndrome (BWS) is a growth disorder variably characterized by neonatal hypoglycemia (persistent hypoglycemia or transient hypoglycemia due to hyperinsulinemia), macrosomia, macroglossia, hemihyperplasia, omphalocele, embryonal tumors (e.g., Wilms tumor, hepatoblastoma, neuroblastoma, and rhabdomyosarcoma), visceromegaly, adrenocortical cytomegaly, kidney abnormalities (e.g., medullary dysplasia, nephrocalcinosis, and medullary sponge kidney), and ear creases / posterior helical ear pits. BWS is considered a clinical spectrum, in which affected individuals may have many or only one or two of the characteristic clinical features.

General incidence figures for the clinical findings in Beckwith-Wiedemann syndrome (BWS) are summarized in Table 2; however, specific figures vary widely in published reports, in part due to ascertainment bias and the mosaic nature of the condition in many affected individuals.

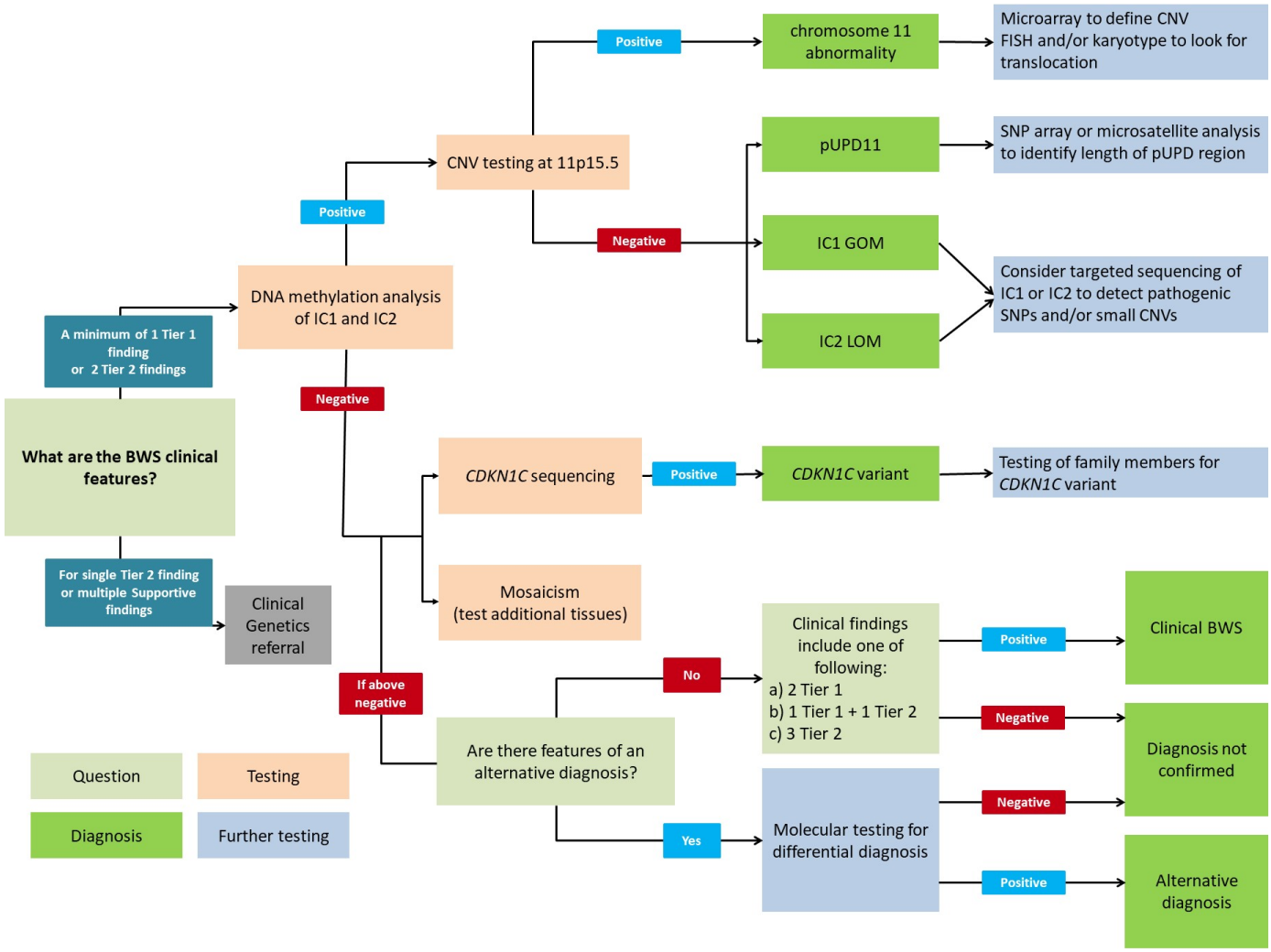

Figure 3. Flowchart for molecular diagnosis of Beckwith-Wiedemann syndrome

Recommended first-line testing (highlighted in orange) analyzes methylation at H19/IGF2:IG DMR (IC1) and KCNQ1OT1:TSS DMR (IC2) and copy number variation (CNV). These tests can yield positive molecular diagnoses of chromosome 11 abnormalities, paternal uniparental disomy of chromosome 11 (pUPD), IC1 gain of methylation (IC1 GOM), and IC2 loss of methylation (IC2 LOM) (highlighted in dark green). Further testing (highlighted in blue) can determine chromosomal abnormalities more precisely. If DNA methylation testing is normal, *CDKN1C* sequencing and/or additional tests for rare chromosomal translocations are recommended. Normal test results can also be due to tissue mosaicism (in which the genetic alteration may not be found due to absence of the molecular change in the tissue sampled), and additional tissue samples can be tested.

Adapted from Wang et al [2020]

Table 2. Beckwith-Wiedemann Syndrome: Frequency of Select Features

Feature	Approximate % of Persons w/ Feature [1]	Comment
Macroglossia	90%	
Macrosomia	45%-65% (as high as 90%)	Defined as pre- &/or postnatal overgrowth, often using a cutoff of >90th or >97th centile, depending on study
Anterior earlobe creases / posterior helical ear pits	63%	The more common preauricular ear pits are not typically assoc w/BWS.
Prenatal polyhydramnios	53%	
Facial nevus simplex	52%	Also referred to as nevus flammeus
Kidney anomalies	52%	
Neonatal hypoglycemia	30%-60%	May be exacerbated by prematurity
Omphalocele	44%	
Umbilical hernia / diastasis recti	22%-44%	
Hemihyperplasia	37%-65%	Also referred to as lateralized overgrowth
Nephromegaly on imaging	38%	Organomegaly may also incl hepatomegaly (37%) & splenomegaly (16%).
Embryonal tumor	8%	Risk is correlated w/molecular alteration. Tumor risks vary from 2.6% to 28% (see Table 3).
Cardiac anomalies	13%	
Cleft palate	3%	

Adapted from Brioude et al [2018] and Wang et al [2020]
1. Data were collected retrospectively and potentially with significant ascertainment bias. Updated prospective and filtered data (e.g., macrosomia in the context of parental growth parameters, molecular subgroups) will need to be collected.

Prenatal and perinatal. The incidence of polyhydramnios, premature birth, and fetal macrosomia may be as high as 50%. Other common features include a long umbilical cord and an enlarged placenta that averages almost twice the normal weight for gestational age. Placental mesenchymal dysplasia has been reported in some babies subsequently found to have features of BWS [Brioude et al 2018].

Infants with BWS are at increased risk for mortality mainly as a result of complications of prematurity, macroglossia, hypoglycemia, and, rarely, cardiomyopathy. However, the previously reported mortality rate of 20% is likely an overestimate given the recent improvements in syndrome recognition and treatment.

Growth parameters. Prenatal and/or postnatal generalized overgrowth is observed in 45%-65% of individuals diagnosed with BWS [Wang et al 2020]. Overgrowth is often defined as a length/height and/or weight that is >90th or >97th centile, or >2 standard deviations above the mean for age and sex, depending on the study. Although most individuals with BWS show rapid growth in early childhood, adult height typically remains at the upper range of normal. Growth rate usually appears to slow around age seven to eight years.

- Growth parameters should be assessed in the context of parental/familial growth parameters (e.g., a child's height at the 85th centile may reflect overgrowth when parental heights plot at ~10th centile).
- Growth parameters obtained in the neonatal period following a premature delivery may not be indicative of subsequent growth patterns.
- Macrocephaly is not a typical feature of BWS.

Hemihyperplasia* (also referred to as lateralized overgrowth, hemihypertrophy*, asymmetric overgrowth, or segmental overgrowth) can often be appreciated at birth; however, it may become more or less evident as the child grows. When asymmetry is present, it is important to distinguish if the asymmetry represents hemihyperplasia or hemihypoplasia (hemiatrophy), which suggests a condition other than BWS. It can be difficult to distinguish mild hemihyperplasia from asymmetry that is considered normal within the general population, such as leg length discrepancies of 1 cm or less. Girth differences can be confounded by placement of the measuring tape, choice of body landmarks, etc., and there are currently no specific recommendations regarding standardized measurements. Diagnostic imaging studies such as CT or MRI may be helpful in defining the tissues involved [Mussa et al 2021].

- Hemihyperplasia may affect segmental regions of the body or selected organs and tissues.
- Hemihyperplasia is typically characterized by overgrowth of muscle tissue leading to differences in bulk but can be associated with bone overgrowth as well.
- When several body segments are involved, hemihyperplasia may be limited to one side of the body (ipsilateral) or involve opposite sides of the body (contralateral).
- Asymmetric growth can remain relatively stable throughout childhood. However, progressive asymmetric growth has also been observed, and this is likely related to mosaicism in the specific tissue (i.e., the percent of cells with the 11p15.5 alteration).
- Referral to an orthopedist for periodic monitoring of leg length discrepancy may include imaging to assess rate of growth and the potential development of scoliosis (see Management).

*Note: Hemihyperplasia refers to an abnormality of cell proliferation leading to asymmetric overgrowth; in BWS, hemihyperplasia, referring to increased cell number, has replaced the term hemihypertrophy, which refers to increased cell size.

Craniofacial features

- **Macroglossia** (present in ~90%) is generally present at birth, though postnatal development has also been observed [Mussa et al 2016c]. Macroglossia typically consists of an increased size of the tongue in terms of length, width, and/or thickness. When assessing for macroglossia, it is important to ensure that the tongue tissue itself is enlarged. Hypotonia can lead to the appearance of a large tongue, as the tongue sometimes is not retained in the mouth.
  - Macroglossia can occasionally obstruct breathing in neonates, who may require respiratory support, tongue reduction, or in some cases tracheostomy.
  - Macroglossia may also interfere with feeding in neonates and infants.
  - Many affected individuals do not require surgical intervention for macroglossia (see Management, Treatment of Manifestations) depending on the degree of macroglossia and growth velocity. Additionally, growth of the oral cavity may eventually accommodate the enlarged tongue size.
  - Indications and timing for surgical correction of macroglossia (reduction glossectomy) vary across different centers. Indications for reduction glossectomy can include airway obstruction leading to sleep apnea, feeding issues, anterior open bite malocclusion, prognathism, and aesthetic concerns [Cielo et al 2018, Cohen et al 2020, Geisler et al 2022].
- **Cleft palate** is a rare finding in affected individuals (see Phenotype Correlations by Molecular Mechanism).
- **Ear findings** may be unilateral or bilateral.
  - Ear lobe creases are typically on the anterior aspect of the lobe; ear lobe creases that develop in adulthood are not considered to be a feature of BWS.
  - Ear pits associated with BWS are located on the posterior aspect of the helix.
- **Characteristic facies** may include infraorbital creases, midface retrusion, thin vermilion of the upper lip, and prominent jaw (which may become evident in childhood).

Endocrine abnormalities

- **Hypoglycemia.** Neonatal hypoglycemia is well documented and occurs in approximately 50% of infants with BWS [Mussa et al 2016a]. If hypoglycemia is severe and undetected or untreated, it poses a significant risk for developmental sequelae.
  - Most episodes of hypoglycemia are mild and transient and resolve in 72 hours or less.
  - In more severe situations, hypoglycemia can persist beyond 72 hours because of hyperinsulinism (defined as increased insulin secretion and/or action at the time of hypoglycemia). Monitoring for hypoglycemia with pre-feed glucose / insulin checks and referral to an endocrinologist for possible fasting studies is recommended if hypoglycemia is persistent (see Management).
  - Delayed onset of hypoglycemia (i.e., in the first month of life) is occasionally observed.
- **Hypothyroidism** has been described but is not common.

Anterior abdominal wall defects including omphalocele, umbilical hernia, and diastasis recti are common. Large umbilical hernias may or may not include the bowel and/or require surgical repair.

Neoplasia. Children with BWS are at increased risk for a variety of tumors, in particular Wilms tumor and hepatoblastoma, but also neuroblastoma, rhabdomyosarcoma, and adrenocortical carcinoma. A wide variety of other tumors, both malignant and benign, may also be seen [Cöktü et al 2020].

- The increased risk for Wilms tumor appears to be concentrated in the first seven years of life [Mussa et al 2019b]. However, Wilms tumor has been reported in children with BWS who are older than age seven years [Gazzin et al 2019].
- The risk for developing hepatoblastoma is concentrated in the first three to four years of life [Mussa et al 2019a].
- The risk of developing a specific tumor in children with BWS is associated with the underlying molecular mechanism and certain phenotypic features (e.g., hemihyperplasia, nephromegaly) [Choufani et al 2013, Maas et al 2016, Mussa et al 2016b, Brzezinksi et al 2021, Duffy et al 2021] (see also Phenotype Correlations by Molecular Mechanism).

Table 3 provides the frequency of select tumors by molecular subtype. Potential limitations of these data include retrospective data collection as well as potential ascertainment bias. In addition, misclassification of BWS subgroups can arise using current clinical testing by methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) [Brzezinski et al 2017]. In the future, prospective studies and improved molecular diagnostics could impact the tumor risks noted below.

Table 3. Beckwith-Wiedemann Syndrome: Frequency of Select Tumors by Molecular Mechanism

Tumor type	Molecular Mechanism [1]	Estimated Tumor Risk
Overall risk for all types of tumors	Loss of methylation at IC2 (maternal)	2.6%
	Gain of methylation at IC1 (maternal)	28.1%
	Paternal UPD	16%
	Heterozygous maternal *CDKN1C* pathogenic variants	5.6%
	Classic BWS phenotype w/normal molecular genetic testing	6.2%

Table 3. continued from previous page.

Tumor type	Molecular Mechanism [1]	Estimated Tumor Risk
Wilms tumor	Loss of methylation at IC2 (maternal)	0.2%
	Gain of methylation at IC1 (maternal)	24%
	Paternal UPD	7.9%
	Heterozygous maternal *CDKN1C* pathogenic variants	Not increased [2]
	Classic BWS phenotype w/normal molecular genetic testing	4.1%
Hepatoblastoma	Loss of methylation at IC2 (maternal)	0.7%
	Gain of methylation at IC1 (maternal)	Unknown; rare
	Paternal UPD	3.5%
	Heterozygous maternal *CDKN1C* pathogenic variants	Not increased [2]
	Classic BWS phenotype w/normal molecular genetic testing	0.3%
Neuroblastoma	Paternal UPD	1.4%
	Heterozygous maternal *CDKN1C* pathogenic variants	4.2%
Adrenocortical carcinoma	Paternal UPD	1.1%

Adapted from Brioude et al [2018] Supplementary Table 3 (which also includes risks below 1% for neuroblastoma, rhabdomyosarcoma, and adrenocortical carcinoma)
BWS = Beckwith-Wiedemann syndrome; IC1 = imprinting center 2; IC2 = imprinting center 2; UPD = uniparental disomy
1. Molecular test results undertaken on blood sampling should be used cautiously when applied to tumor risk determination given that tissue-specific mosaicism is known to impact test results and molecular changes may vary by the tissue tested [Brzezinski et al 2017, Duffy et al 2021].
2. The risks for Wilms tumor and for hepatoblastoma are not increased compared to the general population.

Perspectives on screening for malignant tumors in childhood differ based on local, national, and international practices. In North America, proactive tumor screening is commonly recommended when the risk of tumor development exceeds 1%; however, in many European countries, proactive tumor screening protocols are typically undertaken when the risk of tumor development exceeds 5% [Brzezinski et al 2017, Kalish et al 2017, Brioude et al 2018, Duffy et al 2021, Mussa et al 2021] (see Management, Tables 8 and 9).

Other renal issues

- **Kidney abnormalities** outside of malignancy can include medullary dysplasia, duplicated collecting system, nephrocalcinosis, medullary sponge kidney, cystic changes, and diverticula [Mussa et al 2012].
- **Hypercalciuria** can be found in children with BWS even in the absence of renal abnormalities. Of 18 individuals with BWS, 4/18 (22%) had hypercalciuria (as compared to 7%-10% in the general population), and 2/18 (11%) had nephrocalcinosis on imaging (as compared to 7%-10% in the general population) [Goldman et al 2003].

Cognitive and neurobehavioral development is usually normal in children with BWS unless there is a chromosome abnormality, brain malformation, or history of hypoxia or significant untreated hypoglycemia. Neurobehavioral issues such as autism spectrum disorder have been reported with increased frequency in children with BWS ascertained by parental report [Kent et al 2008]. A 2022 study showed that some preschool children with BWS demonstrated psychosocial concerns similar to those reported in children with other chronic

health concerns. Additionally, some children with BWS had language comprehension concerns and/or gross motor development [Butti et al 2022], although large body size may transiently impact early gross motor development. Further studies, including longitudinal neurodevelopmental assessments and review of family history for similar issues, are needed to accurately assess whether neurobehavioral and cognitive development is impacted in people with BWS.

Cardiovascular. Much of the information regarding cardiovascular findings in BWS is anecdotal. Cardiomegaly was reported in approximately 20% of affected individuals prior to molecular testing and may be detected in infancy if a chest x-ray is performed, but typically resolves without treatment.

- Cardiomyopathy has been reported but is rare.
- Long QT syndrome has been reported in a child with BWS who had a balanced translocation between chromosomes 11 and 17 that interrupted *KCNQ1* [Kaltenbach et al 2013].

Hearing loss is rarely reported in individuals with BWS and is either sensorineural [Kantaputra et al 2013] or conductive due to stapedial fixation [Hopsu et al 2003].

Note: Although parents of children with BWS occasionally raise concerns regarding hearing loss and hypotonia, it is difficult to ascertain whether these and other issues occur with a greater frequency in individuals with BWS compared to the general population.

Brain abnormalities involving the posterior fossa have been rarely reported [Gardiner et al 2012, Brioude et al 2015].

Hematologic. Neonatal polycythemia may occasionally be observed but typically does not require treatment and is self-limited.

Skin. Infantile hemangiomas of the skin and intra-abdominal organs (for example, in the liver) have been noted in some individuals with BWS. However, management is not specific for BWS.

Adulthood. After childhood, prognosis is generally favorable with respect to health and quality of life. However, health concerns (e.g., renal medullary dysplasia, urolithiasis, subfertility in males) may present in older individuals, often stemming from pediatric issues (i.e., azoospermia may result from late surgical correction of cryptorchidism) [Gazzin et al 2019]. In addition, both benign tumors (mammary fibroepithelioma, non-functional adrenal adenoma, hepatic angioma, uterine myoma) and malignant tumors (early T-cell precursor acute lymphoblastic leukemia, intratubular germ cell neoplasia, testicular Sertoli cell tumor) diagnosed outside of early childhood (i.e., after age 7-8 years) were noted in one small study, including one case of hepatoblastoma at age 22 years [Gazzin et al 2019]. As with pediatric presentation, adult health issues in BWS may be associated with specific molecular subtypes, but further study is needed.

Phenotype Correlations by Molecular Mechanism

While general phenotypic correlations by molecular mechanism are provided below, specific clinical outcomes in any individual with BWS cannot be precisely predicted based on the molecular alteration. The remaining variability in individuals with BWS may be due to somatic mosaicism, genetic background, and/or other unidentified factors. For information on tumor risk based on molecular mechanism, see Table 3.

Table 4. Associated Findings in Individuals with BWS by Molecular Mechanism

Molecular Mechanism	Associated Findings	Comments
Loss of methylation at IC2 (maternal)	Lower risk for tumor development overall (~3%)	Higher risk for hepatoblastoma than for WT
	Hemihyperplasia may be observed.	
	Positive family history in those w/genomic alterations at IC2	Rare
	Omphalocele	
	Brain malformations involving posterior fossa	Rare
	Female monozygotic twinning discordant for BWS	Male monozygotic twinning is far less frequent & is assoc w/range of molecular alterations.
	History of subfertility / use of ART to achieve pregnancy [1]	In parents of affected person
Gain of methylation at IC1 (maternal)	One of the highest risks for WT	
	Hemihyperplasia may be observed.	
	Positive family history in those w/deletion of IC1	
Paternal UPD	One of the highest risks for WT & hepatoblastoma	
	More commonly assoc w/hemihyperplasia	Particularly when paternal UPD is mosaic
	Severe BWS phenotype	When due to high levels of somatic mosaicism of paternal UPD
Heterozygous maternal *CDKN1C* pathogenic variants	Assoc w/neuroblastoma & single cases of ganglioneuroblastoma, ganglioneuroma, acute lymphocytic leukemia in children, & melanoma in an adult [2]	Given that leukemia & melanoma occur with some frequency in persons who do not have BWS, it is difficult to determine whether these single cases represent a coincidental occurrence of 2 unrelated conditions or if the malignancy was indeed related to BWS.
	Most commonly assoc w/positive family history of BWS	
	Cleft palate	Hatada et al [1997], Li et al [2001]
	Omphalocele	
	Brain malformations involving posterior fossa	Rare
Duplications of 11p15 detectable by cytogenetic analysis [3]	Developmental delay	If duplication affects *KCNQ1*, EKG & echocardiogram is recommended.

ART = assisted reproductive technology; BWS = Beckwith-Wiedemann syndrome; IC1 = imprinting center 2; IC2 = imprinting center 2; UPD = uniparental disomy; WT = Wilms tumor

1. Carli et al [2022]

2. Brioude et al [2015], Cardoso et al [2022]

3. Typically with unbalanced rearrangements

Nomenclature

BWS was originally called EMG, based on the three clinical findings of *e*xomphalos, *m*acroglossia, and *g*igantism.

In terms of syndromic nomenclature, it is well accepted that clinical diagnoses of many genetic disorders caused by germline pathogenic variants can be challenging when there is a wide range of clinical expressivity. This is particularly true for disorders associated with somatic mosaicism of pathogenic variants. Utilization of a dyadic approach to nomenclature as proposed by Sapp et al [2019] and Biesecker et al [2021] will provide increased clarity for diagnostic classification. Examples could include: 11p15.5 IC1-related BWS, 11p15.5 UPD-related BWS, and 11p15.5 IC2-related BWS.

Prevalence

The reported prevalence of ~1:10,000 [Mussa et al 2013] to ~1:13,700 [Thorburn et al 1970] likely represents an underestimate given the existence of undiagnosed individuals with milder phenotypes.

Genetically Related (Allelic) Disorders

Molecular alterations at 11p15 including loss of methylation at imprinting center 2 (IC2), gain of methylation at imprinting center 1 (IC1) [Martin et al 2005], and 11p15 paternal uniparental disomy [Shuman et al 2002] have been reported in individuals who have **apparently isolated hemihyperplasia (lateralized overgrowth)**. Some cases of apparently isolated hemihyperplasia represent one end of the clinical spectrum of BWS; however, other cases of isolated hemihyperplasia are likely caused by somatic mosaicism in genes outside of the 11p15 region.

Isolated Wilms tumor can be associated with constitutional alterations of chromosome 11p15 including hypermethylation at IC1, paternal uniparental disomy (UPD) of 11p15, loss of methylation at IC2 (rare), and genomic abnormalities of 11p15, including deletions and insertions [Scott et al 2008].

Somatic mosaicism for loss of methylation at the paternal IC1 is associated with **Silver-Russell syndrome** and/or **isolated hemihypoplasia** [Zeschnigk et al 2008, Eggermann 2009, Eggermann et al 2015].

CDKN1C. A maternally inherited pathogenic variant in *CDKN1C* leading to increased stability of cyclin-dependent kinase inhibitor 1C was reported in one family with Silver-Russell syndrome [Brioude et al 2013], and maternally inherited gain-of-function heterozygous pathogenic variants in *CDKN1C* cause IMAGe syndrome [Arboleda et al 2012, Milani et al 2014].

Mosaic genome-wide paternal uniparental isodisomy (UPiD), a sporadic overgrowth disorder, can also be considered in the differential diagnosis of BWS. Like BWS, mosaic genome-wide paternal UPiD is associated with large size for gestational age, placentomegaly, polyhydramnios, macroglossia, hypoglycemia due to hyperinsulinism, umbilical hernia, hepatomegaly, hemangioma, and a high tumor risk (kidney, liver, adrenal gland) [Inbar-Feigenberg et al 2013, Kalish et al 2013, Postema et al 2019]. In contrast to BWS, mosaic genome-wide paternal UPiD can be associated with features of multiple imprinting disorders as well as a higher rate of developmental delay and a more severe presentation. Chimeric genome-wide paternal UPiD has also been reported with similar features to mosaic genome-wide paternal UPiD; in chimeric genome-wide paternal UPiD, there may be mixed cell populations in the internal and external genitalia, including the gonads, which could lead to an increased risk for germ cell tumors [Sheppard et al 2019].

Differential Diagnosis

Overgrowth. Beckwith-Wiedemann syndrome (BWS) is often considered in the differential diagnosis of children presenting with overgrowth (see Table 5). It is important to note the existence of as-yet unclassified overgrowth syndromes that need to be differentiated from BWS.

Of note: In children considered to have BWS and developmental delay who have a normal chromosome study, no history of hypoxia or hypoglycemia, and normal brain imaging, other causes of developmental delay need to be considered.

Table 5. Overgrowth Disorders to Consider in the Differential Diagnosis of Beckwith-Wiedemann Syndrome

Gene(s) / Genetic Mechanism	Disorder	MOI	Features of DiffDx Disorder	
			Overlapping w/BWS	Distinguishing from BWS
Multilocus imprinting disturbances	Multilocus imprinting disorder	See footnote 1.	Variable (e.g., overgrowth, macroglossia, ear findings, nevus simplex, neonatal hypoglycemia)	Discordance between (epi)genotype & phenotypic findings (i.e., clinical features of BWS & Angelman syndrome); assoc w/features of TNDM, SRS, & BWS.
Mosaic or chimeric genome-wide paternal uniparental isodisomy	Mosaic or chimeric genome-wide paternal uniparental isodisomy	Sporadic	See Genetically Related Disorders.	See Genetically Related Disorders.
GPC3 *GPC4*	Simpson-Golabi-Behmel syndrome type 1	XL	Macrosomia, visceromegaly, macroglossia, kidney anomalies, ↑ risk for embryonal tumors	Variable DD, facial features (coarse features, downslanted palpebral fissures, widely spaced eyes, macrostomia, midline groove in vermilion of lower lip), cleft lip, structural & conduction cardiac abnormalities, skeletal abnormalities incl polydactyly
DIS3L2	Perlman syndrome (OMIM 267000)	AR	Macrosomia, high incidence of Wilms tumor	Facial features (micrognathia, low-set ears, depressed nasal bridge, inverted V shape to vermilion of upper lip), high neonatal mortality, significant ID (common)
EZH2	Weaver syndrome (See *EZH2*-Related Overgrowth.)	AD [2]	Macrosomia, umbilical hernia	Learning disability / ID, camptodactyly, ↑ risk of neuroblastoma
NSD1	Sotos syndrome	AD [2]	Macrosomia	Facial features (dolichocephaly, frontal bossing, downslanted palpebral fissures, pointed chin), sparse hair in frontoparietal distribution, ID, macrocephaly
DNMT3A	Tatton-Brown-Rahman syndrome	AD [2]	Macrosomia, cardiac anomalies	Macrocephaly, obesity, ID, ASD, behavioral/psychiatric issues, distinctive facies w/prominent central incisors, joint hypermobility, scoliosis, seizures, ↑ risk of myeloid leukemia
HRAS	Costello syndrome	AD [2]	Can be similar to BWS in neonatal period (when affected infants present w/ macrosomia).	Cardiac abnormalities (incl structural defects, hypertrophic cardiomyopathy, or arrhythmias), failure to thrive, DD, coarse facial features

AD = autosomal dominant; AR = autosomal recessive; ASD = autism spectrum disorder; BWS = Beckwith-Wiedemann syndrome; DD = developmental delay; DiffDx = differential diagnosis; ID = intellectual disability; MOI = mode of inheritance; SRS = Silver-Russell syndrome; TNDM = transient neonatal diabetes mellitus; XL = X-linked

1. Multilocus imprinting disorder can be associated with pathogenic variants in maternal effect genes (e.g., *NLRP2*, *NLRP5*, *NLRP7*, *PADI6*) [Eggermann et al 2022; Pignata et al 2022].

2. Most probands have the disorder as the result of a *de novo* pathogenic variant.

Hemihyperplasia or segmental overgrowth can occur as an isolated finding or may be associated with other syndromes such as Klippel-Trenaunay-Weber syndrome (OMIM 149000) and the disorders summarized in

Table 6. Asymmetries, such as of the face, legs, or chest, should be evaluated to exclude plagiocephaly, congenital hip dislocation, and chest wall deformities.

Table 6. Disorders with Hemihyperplasia or Lateralized Overgrowth to Consider in the Differential Diagnosis of Beckwith-Wiedemann Syndrome

Gene(s) / Genetic Mechanism	Disorder	MOI	Features of DiffDx Disorder	
			Overlapping w/BWS	Distinguishing from BWS
Genetically heterogeneous [1]	Silver-Russell syndrome (SRS)	See footnote 2.	Growth asymmetry of regions of the body (e.g., ≥1 limbs)	Most clinical features that are characteristic of SRS (e.g., growth failure) are not seen in BWS. In addition, SRS is not assoc w/↑ risk for embryonal tumors.
AKT1	Proteus syndrome	See footnote 3.	Asymmetric overgrowth, vascular malformations incl cutaneous capillary malformations	Progressive segmental or patchy overgrowth most commonly affecting skeleton, skin, adipose, & CNS; modest or no manifestations at birth; progression through childhood, causing severe overgrowth & disfigurement & range of tumors
NF1	Neurofibromatosis 1	AD	Asymmetric overgrowth	Multiple café au lait macules, intertriginous freckling, cutaneous neurofibromas, Lisch nodules
PIK3CA	*PIK3CA*-related overgrowth spectrum (PROS) (incl CLOVES syndrome, MCAP syndrome, & Klippel-Trenaunay syndrome)	See footnote 3.	Hemihyperplasia, vascular malformations	Variable presentations; see PROS for comprehensive clinical descriptions, recommendations for testing (often requires tissues other than blood), & mgmt.
PTEN	*PTEN* hamartoma tumor syndrome (incl Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, *PTEN*-related Proteus syndrome, & *PTEN*-related Proteus-like syndrome)	AD	Asymmetric overgrowth	Variable presentations; see *PTEN* hamartoma tumor syndrome for comprehensive clinical descriptions.

AD = autosomal dominant; AR = autosomal recessive; CLOVES syndrome = congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal syndrome; CNS = central nervous system; DD = developmental delay; DiffDx = differential diagnosis; ID = intellectual disability; MCAP syndrome = megalencephaly-capillary malformation syndrome; MOI = mode of inheritance; XL = X-linked

1. Hypomethylation of the imprinted control region 1 (ICR1) at 11p15.5 causes SRS in 35%-50% of individuals, and maternal uniparental disomy (mUPD7) causes SRS in 7%-10% of individuals. A small number of affected individuals have duplications, deletions, or translocations involving the imprinting centers at 11p15.5 or duplications, deletions, or translocations involving chromosome 7. Rarely, affected individuals with pathogenic variants in *CDKN1C*, *IGF2*, *PLAG1*, and *HMGA2* have been described.

2. SRS typically has a low recurrence risk; however, accurate assessment of recurrence risk requires identification of the causative genetic mechanism in the affected family member.

3. Not known to be inherited; most identified pathogenic variants are somatic (mosaic).

Multilocus imprinting disturbances (MLID). Individuals with MLID may present with single or multiple imprinting disorders (e.g., BWS, Silver-Russell syndrome [SRS]) [Grosvenor et al 2022] or may be phenotypically

normal. Although a genetic etiology has not been identified in many children with MLID, 20%-30% of mothers of children with MLID and significant reproductive issues may have trans-acting, compound heterozygous or homozygous pathogenic variants in maternal effect genes encoding subcortical maternal complex (SCMC) proteins [Eggermann et al 2022, Tannorella et al 2022]. SCMC proteins are involved with early embryonic development and maturation of oocytes. Pathogenic variants in the SCMC genes (*NLRP2*, *NLRP5*, *NLRP7*, *PADI6*, and *KHDC3L*) can result in reproductive failure, molar pregnancies, and children with imprinting disorders [Eggermann et al 2022]. One individual with MLID and paternal uniparental disomy for chromosome 20 has been reported [Choufani et al 2021].

For individuals with methylation alterations in the 11p15 imprinted domain as well as in other imprinted loci, review of the maternal history should be undertaken for findings such as recurrent pregnancy loss or molar pregnancy. In these situations, consideration should be given to testing for pathogenic variants in maternal effect genes that lead to BWS. If a pathogenic variant in a maternal effect gene is detected in the proband and mother, information regarding the increased risk for reproductive complications such as preeclampsia, recurrent pregnancy loss, and molar pregnancy as well as the significant risk for having children with imprinting disorders should be addressed through genetic counseling [Elbracht et al 2020, Eggermann et al 2022, Tannorella et al 2022].

Note: It is not yet clear if oligogenic or multifactorial causes are relevant in MLID. While it appears that some heterozygous variants in SCMC genes may be disease causing, such cases may also be associated with unidentified pathogenic variants in the second allele or other SCMC genes. In addition, the potential interaction of pathogenic variants with interventions such as assisted reproductive technology will be an important area of future work.

Management

Clinical practice guidelines for Beckwith-Wiedemann syndrome have been published and most frequently focus on the issue of tumor screening protocols (see Kalish et al [2017] and Brioude et al [2018]).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Beckwith-Wiedemann syndrome, the evaluations summarized in Table 7 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 7. Beckwith-Wiedemann Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Constitutional	Measurement of weight, length/height, & head circumference	To assess for macrosomia or overgrowth
Endocrinologic	Measurement of pre-feed blood glucose level in neonates	To assess for hypoglycemia [1]; consider consultation w/ endocrinologist
ENT/Mouth	Assessment for macroglossia & cleft palate	Consider referral to plastic surgeon, ENT, or craniofacial team & feeding specialist if macroglossia is a concern & for those w/cleft palate.
	Dental/orthodontic assessment	In older children, particularly those who have a history of macroglossia

Table 7. continued from previous page.

System/Concern	Evaluation	Comment
Respiratory	Assessment of airway sufficiency	Particularly in neonates & infants; most airway issues are related to macroglossia, which may either improve over time or require treatment.
	Consider sleep study	To assess for obstructive sleep apnea, which may be assoc w/ macroglossia
Gastrointestinal	Assessment for abdominal wall abnormalities, incl omphalocele & umbilical hernia	
	Baseline abdominal ultrasound [2]	To assess for organomegaly & tumors
	Serum AFP level	To evaluate for hepatoblastoma (see Surveillance) [3, 4]; it is important to utilize normal ranges for BWS based on specific age categories to guide result interpretation, esp in premature & young infants. [5]
Renal	Renal imaging can be achieved through baseline complete abdominal ultrasound (See **Gastrointestinal** in this table.)	To assess for kidney anomalies, nephromegaly, & Wilms tumor
		If there is evidence of calcium deposits on renal ultrasound, consider urine calcium-to-creatinine ratio, CT of kidneys, & referral to nephrologist.
Musculoskeletal	Clinical eval for hemihyperplasia	To incl assessment of: • Gross motor skills • PT (if delay in gross motor skills) &/or orthopedic referral if leg length discrepancy >1 cm
Hearing	Audiologic eval	Assess for hearing loss in neonates or in those w/speech delay.
Cardiovascular	Clinical eval for signs/symptoms of cardiomyopathy or congenital heart defects	Comprehensive cardiac eval incl EKG & echocardiography is recommended when a cardiac abnormality is suspected clinically or if genomic alteration is detected that deletes or duplicates part of *KCNQ1* (see Phenotype Correlations by Molecular Mechanism).
Development	Assessment of speech-language skills	Esp in those w/history of macroglossia
	Assessment of development	If significant delay is identified, consider brain MRI to assess for malformations of posterior fossa.
Genetic counseling	By genetics professionals [6]	To inform affected persons & their families re nature, MOI, & implications of BWS to facilitate medical & personal decision making

Table 7. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support, if needed.	

AFP = alpha-fetoprotein; MOI = mode of inheritance; PT = physical therapy
1. Transient hypoglycemia typically resolves in the first few days of life; evaluation for hyperinsulinism is recommended for those who have hypoglycemia that persists for longer than 72 hours.
2. Renal ultrasound alone is insufficient, as it will not evaluate for liver or other abdominal tumors.
3. Perspectives on obtaining and monitoring serum AFP levels to screen for hepatoblastoma differ based on local, national, and international practices [Kalish et al 2017, Brioude et al 2018].
4. Current data suggest that those who undergo serial serum AFP screening for hepatoblastoma have an earlier stage at diagnosis and a better overall prognosis compared to those who do not undergo serum AFP screening [Trobaugh-Lotrario et al 2014, Duffy et al 2017].
5. Duffy et al [2019b]
6. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 8. Beckwith-Wiedemann Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Hypoglycemia [1]	• Oral feeding if hypoglycemia is mild • Prompt treatment w/glucose supplementation, most typically IV D10 or D25 solutions if hypoglycemia is more severe, w/goal of keeping glucose levels in 3.9-5.5 mmol/L (70-100 mg/dL) range • Consult endocrinologist for escalated treatment & eval if hypoglycemia is severe.	To keep glucose levels in 3.9-5.5 mmol/L (70-100 mg/dL) range [2]
Hyperinsulinism	Standard medical treatment per endocrinologist	• This may incl using medications such as diazoxide or somatostatin analogs. • Newer medications may incl mTOR inhibitors or glucagon-like peptide receptor antagonists. [3]
	Partial pancreatectomy may be considered in those w/persistent hypoglycemia who are unresponsive to pharmacologic treatment.	
Cleft palate	Standard treatment ideally per craniofacial team, incl plastic surgeons, orthodontists, & speech-language pathologists familiar w/natural history of BWS	The use of special nipples or short-term nasogastric tube feeding is often required.

Table 8. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Macroglossia [4]	Feeding &/or respiratory support for those w/feeding &/or breathing issues	• Long nipples may be considered, like those used for infants w/cleft palate. • Supplemental feeding tube may be considered in those w/severe feeding difficulties.
	Tongue reduction surgery may be considered. [5]	Surgery is typically undertaken in infancy or early childhood & referral to an experienced, multidisciplinary center is recommended. [6]
Anterior overbite & prognathism	Standard treatment per orthodontist & craniofacial team	
Speech delay/ impediment	Speech therapy	
Respiratory insufficiency	Intubation at birth may be required for those w/ macroglossia.	Until causes of airway obstruction (incl macroglossia) are determined & treatment plan is defined.
	Tracheostomy may be considered in those w/severe respiratory insufficiency & evidence of upper airway obstruction.	
Omphalocele	Standard treatment by pediatric surgeon	
Leg length discrepancy	Shoe lift may be considered in those w/leg length discrepancy	Leg length discrepancy <2 cm typically does not require surgical intervention
	Epiphysiodesis prior to epiphyseal closure in early puberty may be considered in instances w/leg length discrepancy >2 cm; alternatively, leg lengthening of shorter leg may be considered. [7]	To equate final leg lengths
Hemihyperplasia of upper limb	Typically does not require any intervention	
Hemihyperplasia of face	Referral for assessment & discussion of treatment options	Typically at craniofacial center
Neoplasia	Standard treatment per pediatric oncologist	For cases where molecular mechanism has not been identified, tissue samples obtained at time of surgery (i.e., skin, tumor, & unaffected organ tissue) can be used for genetic testing to provide information for mgmt and genetic counseling (see Establishing the Diagnosis).
Hypercalciuria / kidney anomalies	Standard treatment per nephrologist	
Congenital heart defects	Standard treatment per cardiologist	
Hearing loss	Hearing aids may be helpful per otolaryngologist.	
Developmental delay	Standard treatment such as infant stimulation programs, OT/PT, & IEPs	Consider referral to neurodevelopmental specialist.

Table 8. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family/Community	• Ensure appropriate genetic counseling / social work involvement to connect families w/resources & support. • Coordinate care to manage multiple subspecialty appointments if indicated.	

IEP = individualized education program; OT = occupational therapy; PT = physical therapy
1. Because onset of hypoglycemia is occasionally delayed for several days, or even months, parents should be informed of the symptoms of hypoglycemia so that they can seek appropriate medical attention.
2. Brioude et al [2018]
3. Guemes et al [2016]
4. Tongue growth does slow over time and jaw growth can accelerate to accommodate the enlarged tongue.
5. Surgical reduction approaches may vary depending on the nature of macroglossia (e.g., if asymmetry is present, etc.), tongue function concerns, and/or the preferential approach of the surgical team. Indications for tongue reduction surgery vary but may include airway obstruction, orthodontic issues, and/or social/aesthetic issues. Residual aesthetic and speech issues may require further assessment and alternate treatment approaches [Naujokat et al 2019, Geisler et al 2022].
6. In those who do not have a known molecular genetic cause for BWS, genetic testing can be undertaken on tissue available from surgical reduction during tongue reduction surgery.
7. De Pellegrin et al [2021]

Surveillance

Perspectives on screening for malignant tumors in childhood differ based on local, national, and international practices. In North America proactive tumor screening is often recommended when the risk of tumor development exceeds 1% [Brzezinski et al 2017, Kalish et al 2017, Brioude et al 2018, Duffy et al 2021, Mussa et al 2021]. In many European countries, proactive tumor screening protocols are typically undertaken when the risk of tumor development exceeds 5%, and as such, tumor screening is based on the risk associated with specific molecular mechanism (see Table 3) [Brioude et al 2018]. Table 9 summarizes typical tumor screening protocols in North America. Surveillance has been shown to improve outcomes, including earlier detection of tumors [Mussa et al 2019b].

For general screening guidelines outside of tumor surveillance, see Table 10.

Table 9. Beckwith-Wiedemann Syndrome: Tumor Surveillance Protocols [1, 2]

Assessment	Frequency	Comment
Abdominal ultrasound w/views of liver, adrenal glands, & kidneys	Every 3 mos until age 4 yrs [3]	To screen primarily for hepatoblastoma & Wilms tumor but also for adrenocortical carcinoma & abdominal neuroblastoma
Renal ultrasound only	Every 3 mos from age 4-7 yrs	To screen for Wilms tumor
Serum AFP level	Every 3 mos until age 4 yrs	To screen for hepatoblastoma [4, 5]
		If AFP is elevated, & imaging reveals no suspicious lesion, follow-up measurement of serum AFP concentration plus baseline liver function tests 4-6 wks later can be used to determine the trend in serum AFP concentrations over time. [6]
		If the concentration is not decreasing, it is appropriate to undertake an exhaustive search for an underlying tumor.
Physical exam by pediatrician, geneticist, or pediatric oncologist	2x/yr	Incl ongoing education about tumor signs/symptoms & to aid in compliance
Proposed screening for neuroblastoma in children w/heterozygous pathogenic variant in *CDKN1C*		

Table 9. continued from previous page.

Assessment	Frequency	Comment
Abdominal ultrasound	Every 3 mos until age 6 yrs, then every 6 mos until age 10 yrs	This screening has been variably incorporated into screening protocols given the relatively low yield, high rates of false positive test results, & lack of evidence regarding diagnostic, mgmt, & outcome benefits. Therefore, initiation of this tumor screening protocol should be preceded by discussion between the provider & family re risks vs benefits of the protocol.
Urine vanillylmandelic acid & homovanillic acid		
Chest radiograph		

1. For alternate tumor surveillance recommendations utilized in many European countries, see Brioude et al [2018] and Mussa et al [2021].
2. The tumor screening protocol does NOT take into account the underlying molecular mechanism for BWS (see Table 3), with the exception of a different proposed screening protocol for neuroblastoma in individuals with a heterozygous pathogenic variant in *CDKN1C*.
3. This avoids confusion about whether to perform renal ultrasound only or abdominal ultrasound based on age.
4. AFP serum concentration may be elevated in children with BWS in the first year of life.
5. Most cases of hepatoblastoma will occur in the first year of life, with the oldest known case of hepatoblastoma in BWS detected at age 30 months [Kalish et al 2017].
6. Increased frequency of serum AFP testing will depend on significant increases in the AFP level as defined by the AACR guidelines [Kalish et al 2017].

Table 10. Beckwith-Wiedemann Syndrome: Recommended General (Non-Tumor) Surveillance

System/Concern	Evaluation	Frequency
Growth	Measurement of growth parameters	At each visit
Endocrine	Pre-feed serum glucose level	Per endocrinologist recommendations in neonates & infants w/history of hypoglycemia or hyperinsulinism, particularly in those who are being treated for hyperinsulinism
	Random serum glucose level	In neonates & infants w/signs/symptoms consistent w/hypoglycemia
Respiratory	Monitor for signs/symptoms of sleep apnea [1]	At each visit
Renal	Consideration of renal ultrasound to identify findings such as nephrocalcinosis & medullary sponge kidney	Annually between age 8 yrs & mid-adolescence & periodically in adulthood
	Consideration of blood pressure measurements & measurement of urinary calcium-to-creatinine ratio to screen for occult nephrocalcinosis	Annually or biannually
Development	Monitor developmental progress & educational needs.	At each visit
Musculoskeletal	Assessment of hemihyperplasia & leg length discrepancy	At each visit until skeletal maturity
Dental	Dental, w/low threshold for orthodontic, eval	Every 6 mos after eruption of teeth
Hearing	Audiology eval	As clinically indicated
Family/Community	Assess family need for social work support, care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

1. Consider a sleep study to assess for obstructive sleep apnea in symptomatic individuals.

Evaluation of Relatives at Risk

It is appropriate to evaluate the newborn sib of an individual with BWS in order to identify as early as possible those who would benefit from initiation of preventive measures. Evaluations can include:

- Genetic testing if a maternal *CDKN1C* pathogenic variant or familial duplication, deletion, or cytogenetically visible alteration of 11p15 is known;
- Monitoring of an at-risk newborn sib for hypoglycemia, even in the absence of obvious clinical findings on prenatal investigation;
- Careful evaluation of the apparently unaffected twin of discordant monozygotic twins (MZ), including clinical examination and molecular testing, preferably of multiple tissues, if available. There should be strong consideration of tumor surveillance for the apparently unaffected MZ twin given the possibility of shared fetal circulation and the potential for resulting somatic mosaicism [Weksberg et al 2002, Cohen et al 2019].

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

The following recurrence risk information pertains to individuals who have Beckwith-Wiedemann syndrome (BWS) without other imprinting disorders, such as multilocus imprinting disturbances (MLID). See Differential Diagnosis for more information on MLID.

BWS without MLID is associated with abnormal expression of imprinted genes in the BWS critical region. Abnormal expression of imprinted genes can be caused by an epigenetic or genomic alteration leading to an abnormal methylation pattern at 11p15.5, a copy number variant of chromosome 11p15.5, or a heterozygous maternally inherited *CDKN1C* pathogenic variant. Reliable recurrence risk assessment requires identification of the genetic mechanism in the proband that underlies the abnormal expression of imprinted genes in the BWS critical region. While the majority of families have a recurrence risk of less than 1%, certain underlying genetic mechanisms involve a recurrence risk as high as 50%. In families with recurrence of BWS, maternally inherited *CDKN1C* pathogenic variants account for approximately 40% of genetic alterations, and paternally or maternally inherited copy number variants including small duplications or deletions of 11p15.5 account for approximately 9% of genetic alterations [Baskin et al 2014].

Risk to Family Members

Parents of a proband

- Most individuals with BWS do not have an affected parent.
- Recommendations for the clinical evaluation of the parents of a child with BWS and no known family history of BWS include a medical and family history focused on BWS-associated medical issues in early childhood. Infant and childhood photographs of the parents may be useful. Although physical examination may be of limited value in adulthood, ear pits/creases may still be present. Anterior ear lobe

creases are not uncommon in the general population; however, posterior ear pits are rarely reported outside of the association with BWS.

- If the proband has BWS associated with MLID, the maternal history should also be reviewed with respect to potential recurrent pregnancy loss or other adverse outcomes that could indicate a maternal effect gene abnormality. Pathogenic variants in maternal effect genes are associated with an increased risk for reproductive complications such as preeclampsia, recurrent pregnancy loss, and molar pregnancy as well as the risk for having children with imprinting disorders [Elbracht et al 2020, Eggermann et al 2022].
- Clarification of the genetic status of the parents of the proband is recommended to allow reliable recurrence risk assessment. Testing recommendations for the parents are based on the genetic alteration identified in the proband. If the genetic alteration identified in the proband is a:
  - Cytogenetically visible duplication, inversion, or translocation involving chromosome 11p15.5, then chromosome analysis (karyotyping) should be offered to both parents;
  - Copy number variant (e.g., a small 11p15.5 duplication or deletion), then microarray (SNP based) should be offered to both parents;
  - Heterozygous *CDKN1C* pathogenic variant, then targeted testing for the *CDKN1C* pathogenic variant identified in the proband should be offered to the mother of the proband;
  - Paternal uniparental disomy (UPD) of 11p15.5, then parental testing is not indicated/recommended/required, as paternal UPD of 11p15.5 is typically due to postzygotic somatic recombination;
  - Loss of methylation of imprinting center 2 (IC2) or gain of methylation of imprinting center 1 (IC1), then maternal history should be reviewed for findings suggestive of a variant in a maternal effect gene.
- If the proband has neither a genomic variant (i.e., a copy number variant at 11p15.5 or a cytogenetically visible chromosome alternation) nor a *CDKN1C* pathogenic variant and the family history is uninformative (no maternal history of unexplained spontaneous abortion, hydatidiform moles, or a sib with BWS or another imprinting disorder [e.g., Silver-Russell syndrome]), parental testing is typically not indicated.
- Note: If the family history suggests possible MLID, further consideration for genetic testing for pathogenic variants in maternal effect genes should be entertained (see Differential Diagnosis).

Sibs of a proband. See Table 11.

Table 11. Risk to Sibs of a Proband with Beckwith-Wiedemann Syndrome

Genetic Alteration Identified in the Proband		Recurrence Risk to Sibs of the Proband
Abnormal methylation at 11p15.5	LOM at IC2 or GOM at IC1	Empirically low unless there is a maternal history of unexplained spontaneous abortion, hydatidiform moles, or a sib w/BWS or another imprinting disorder (e.g., SRS); in such cases, a homozygous or heterozygous pathogenic variant in maternal effect genes in the mother's genome may confer a significant recurrence risk (see Differential Diagnosis, **MLID**). [1]
	Genomic variant involving chromosome 11p15.5; incl: • Cytogenetically visible duplication, inversion, or translocation • CNV (e.g., small 11p15.5 duplication or deletion)	If a parent has the same genomic abnormality or is a carrier of a balanced chromosome rearrangement, the recurrence risk may be as high as 50% depending on the sex of the transmitting parent & the specific alteration.
	Paternal UPD of 11p15.5	Empirically low but not quantified [2]
	No underlying 11p15.5 genetic alteration identified in the proband	
Heterozygous *CDKN1C* pathogenic variant		If the mother of the proband is heterozygous for the *CDKN1C* pathogenic variant identified in the proband, the recurrence risk for BWS in sibs is 50%. [3]
		If the mother is not heterozygous for the *CDKN1C* pathogenic variant identified in the proband, the risk to sibs of BWS is presumed to be low, but increased over that of the general population because of the possibility of maternal germline mosaicism. [4]
No BWS-causing genetic alteration identified in the proband (~20% of probands w/BWS do not have a molecular diagnosis.)		A genetic alteration may not be identified in the proband due to somatic mosaicism or to limitations in current genetic testing platforms. In the absence of a suggestive family history, the recurrence risk to sibs is empirically low but not quantified.

BWS = Beckwith-Wiedemann syndrome; CNV = copy number variant; GOM = gain of methylation; IC1 = imprinting center 1; IC2 = imprinting center 2; LOM = loss of methylation; MLID = multilocus imprinting disturbances; SRS = Silver-Russell syndrome; UPD = uniparental disomy

1. Tannorella et al [2022]

2. Brioude et al [2018]

3. If the father is heterozygous for the *CDKN1C* pathogenic variant, sibs have a 50% likelihood of inheriting the variant. The BWS recurrence risk in sibs who inherit a paternal *CDKN1C* pathogenic variant is increased but the exact risk is unknown. Unexpectedly, one instance of paternal transmission of a *CDKN1C* pathogenic variant from a clinically unaffected father has also been reported [Lee et al 1997, Li et al 2001].

4. Brioude et al [2015]

Offspring of a proband. See Table 12.

Table 12. Risk to Offspring of a Proband with Beckwith-Wiedemann Syndrome

Genetic Alteration Identified in the Proband		Recurrence Risk to Offspring of the Proband
Abnormal methylation at 11p15.5	LOM at IC2 or GOM at IC1	Likely low unless the proband is female and presents with a history of unexplained spontaneous abortion, hydatidiform moles, or a sib w/BWS or another imprinting disorder (e.g., SRS);

Table 12. continued from previous page.

Genetic Alteration Identified in the Proband		Recurrence Risk to Offspring of the Proband
		in such cases, a homozygous or heterozygous pathogenic variant in maternal effect genes in the proband's genome may confer a significant recurrence risk (see Differential Diagnosis, **MLID**).
	Genomic variant involving chromosome 11p15.5; incl: • Cytogenetically visible duplication, inversion, or translocations • CNV (e.g., small 11p15.5 duplication or deletion)	• The recurrence risk may be as high as 50% depending on the sex of the proband and the specific alteration. Small deletions at IC1 & rarely small duplications at IC2 have been reported in familial cases. [1] • Rare familial cases of SRS (see Genetically Related Disorders) have been reported in persons w/small 11p15.5 IC1 deletions & maternally inherited 11p15 duplications. Therefore, the offspring of a proband w/either of these genetic alterations may be at risk for SRS depending on the specific alteration & the sex of the proband.
	Paternal UPD of 11p15.5	Likely very low; however, empiric data are not yet available.
	No underlying 11p15.5 genetic alteration identified in the proband	Presumed to be low in the absence of a genomic abnormality, as the imprint normally is reset in the germline; empiric data are not yet available. [2] There remains a low risk for unidentified molecular alterations or MLID (see Differential Diagnosis, **MLID**).
Heterozygous *CDKN1C* pathogenic variant		If the proband is female, the recurrence risk for BWS in offspring is 50%.
		If the proband is male, the recurrence risk for BWS in offspring is low, but there have been too few cases reported to generate a risk figure.
No BWS-causing genetic alteration identified in the proband (~20% of probands w/BWS do not have a molecular diagnosis.)		The recurrence risk is likely low as the proband may have somatic mosaicism for paternal UPD. However, the risk may be increased if the proband has a pathogenic variant that is not detected by current genetic testing platforms or (in a female proband) a pathogenic variant(s) in an SCMC gene.

BWS = Beckwith-Wiedemann syndrome; CNV = copy number variant; LOM = loss of methylation; MLID = multilocus imprinting disturbances; SCMC = subcortical maternal complex; SRS = Silver-Russell syndrome; UPD = uniparental disomy

1. Tannorella et al [2022]

2. Niemitz et al [2004]

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has a BWS-related genetic alteration or chromosome rearrangement, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and genetic counseling regarding prenatal testing is before pregnancy. Decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or who carry genomic alterations that increase the

risk of BWS in offspring (e.g., an unaffected female who has inherited a balanced 11p15 translocation from her father).
- If pathogenic variants in maternal effect genes are detected in the proband and mother, information regarding the increased risk for reproductive complications such as preeclampsia, recurrent pregnancy loss, and molar pregnancy as well as the risk for having children with imprinting disorders should be included in genetic counseling [Elbracht et al 2020, Eggermann et al 2022].

Possible imprinting risks associated with assisted reproductive technology (ART). Offspring born following pregnancies conceived naturally following an extended period of subfertility and/or with the use of ART have an increased risk for imprinting disorders [Cortessis et al 2018]. The risk for BWS in live births from ART conception in one study was tenfold higher than from natural conception [Mussa et al 2017].

Monozygotic twinning. Monozygotic twins clinically discordant for BWS (usually females) have been shown to also be discordant for loss of methylation at IC2 in skin fibroblasts but variably concordant in blood cells, probably as a result of shared fetal circulation [Weksberg et al 2002]. Male monozygotic twins are much less frequently observed and demonstrate additional molecular findings including UPD for 11p15 and gain of methylation at IC1. One study demonstrated that in monozygotic twins where the proband with BWS has a higher score on the diagnostic algorithm used, the "unaffected" twin may or may not manifest any BWS-related clinical features [Cohen et al 2019]. This is thought to be due to asymmetric levels of mosaicism, with the majority of embryonic cells with the BWS-related molecular alteration being localized in the embryo with more severe features of BWS. As no recurrences are reported in the sibs of these twins, the recurrence risk is not known.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Positive family history

- **Primary genomic variants.** If a pathogenic genomic variant involving chromosome 11p15.5 (i.e., a cytogenetically visible duplication, inversion, or translocation), a pathogenic copy number variant of 11p15.5, or a *CDKN1C* pathogenic variant has been identified in the proband, prenatal testing via analysis of fetal DNA from samples obtained by chorionic villus sampling (CVS) or amniocentesis is possible. Preimplantation genetic testing is possible for a familial *CDKN1C* pathogenic variant and may be possible for some familial genomic variants.
- **Methylation changes.** DNA extracted from amniotic fluid is currently felt to provide the most reliable tissue source for evaluating fetal methylation status, although false negative findings have been reported [Eggermann et al 2015]. Cultured amniocytes may demonstrate clonal findings that are not representative of the fetal status, similar to postnatal testing issues related to somatic mosaicism. Similarly, tissue obtained via CVS for prenatal testing for methylation status does not yield reliable results; a false positive test has been reported [Eggermann et al 2015]. This latter issue reflects the timing of methylation establishment in early placental development. Likewise, preimplantation genetic testing may be possible for a pathogenic familial genomic alteration but not for evaluation of methylation status. Genetic counseling regarding the potential limitations of prenatal testing for epigenetic alterations should be undertaken [Eggermann et al 2015].

For all pregnancies at increased risk for BWS, whether or not the genetic mechanism is known:

- Maternal serum alpha-fetoprotein (AFP) concentration may be elevated at 16 weeks' gestation in the presence of omphalocele.
- Ultrasound examination can be performed at 19-20 weeks' gestation and again at 25-32 weeks' gestation to assess growth parameters that may become advanced for gestational age late in the second trimester and to detect abdominal wall defects, organomegaly, kidney anomalies, cleft palate, cardiac abnormalities, and macroglossia.

Note: (1) If ultrasound examination does not show malformations or abnormalities of fetal growth, a residual risk for recurrence of BWS remains, given the variability in clinical presentation. (2) Even in the absence of obvious clinical findings on prenatal investigation, the newborn should be monitored for hypoglycemia.

Negative family history. In pregnancies in which there is no family history of BWS but an abnormality such as apparently isolated omphalocele is detected on ultrasound examination, additional investigations that should be considered [Porter et al 2009, Wilkins-Haug et al 2009] include:

- Molecular genetic testing for methylation alterations in amniocytes, and if no methylation alteration is identified, testing for a *CDKN1C* pathogenic variant;
- Chromosomal microarray for copy number variants involving chromosome 11p15 and/or cytogenetic testing to evaluate for duplications, inversions, or translocations involving 11p15;
- Serial ultrasound examinations to assess fetal growth and to detect other abnormalities characteristic of BWS.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements. Molecular genetic testing can be offered if there is a high index of suspicion for BWS.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Associazione Italiana Sindrome di Beckwith-Wiedemann ODV (AIBWS-Onlus)**
  Italy
  Phone: 39 345.3121850
  Email: info@aibws.org
  www.aibws.org
- **Beckwith-Wiedemann Children's Foundation International**
  www.beckwithwiedemann.org
- **MedlinePlus**
  Beckwith-Wiedemann syndrome

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Beckwith-Wiedemann Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

CDKN1C	11p15.4	Cyclin-dependent kinase inhibitor 1C	CDKN1C database	CDKN1C	CDKN1C
H19	11p15.5	Unknown	H19 @ LOVD	H19	H19
IGF2	11p15.5	Insulin-like growth factor II	LOVD - Growth Consortium (IGF2)	IGF2	IGF2
KCNQ1	11p15.5-p15.4	Potassium voltage-gated channel subfamily KQT member 1	KCNQ1 @ LOVD KCNQ1 @ ZAC-GGM	KCNQ1	KCNQ1
KCNQ1OT1	11p15.5	Unknown	KCNQ1OT1 @ LOVD	KCNQ1OT1	KCNQ1OT1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Beckwith-Wiedemann Syndrome (View All in OMIM)

103280	H19, IMPRINTED MATERNALLY EXPRESSED NONCODING TRANSCRIPT; H19
130650	BECKWITH-WIEDEMANN SYNDROME; BWS
147470	INSULIN-LIKE GROWTH FACTOR II; IGF2
600856	CYCLIN-DEPENDENT KINASE INHIBITOR 1C; CDKN1C
604115	KCNQ1-OPPOSITE STRAND/ANTISENSE TRANSCRIPT 1; KCNQ1OT1
607542	POTASSIUM CHANNEL, VOLTAGE-GATED, KQT-LIKE SUBFAMILY, MEMBER 1; KCNQ1
616186	H19/IGF2-IMPRINTING CONTROL REGION

Molecular Pathogenesis

Imprinting is an epigenetic process whereby the DNA of the two alleles of a gene is differentially modified so that only one parental allele (parent specific for each gene) is normally expressed and the other allele is not expressed or is silenced [Barlow 1994]. Imprinted genes cluster to distinct domains in the genome and an imprinting center (IC) controls resetting of a group of closely linked imprinted genes during transmission through the germline [Nicholls 1994].

- Gain of methylation or hypermethylation: increased level of DNA methylation compared to control samples. For imprinted regions this may be associated with methylation of a normally unmethylated allele.
- Loss of methylation or hypomethylation: decreased level of DNA methylation compared to control samples. For imprinted regions, this may be associated with loss of methylation of a normally methylated allele.

An **imprinting center (IC)** is a region of DNA that can regulate the expression of neighboring imprinted genes on the same allele (in *cis*) over large distances. ICs are usually characterized by differential DNA methylation and differential histone modifications and may also be referred to as imprinting control regions (ICRs) or differentially methylated regions (DMRs).

Many different molecular alterations in the 11p15 region occur in association with Beckwith-Wiedemann syndrome (BWS). Several imprinted genes, including growth factors and tumor suppressor genes, that are located in the 11p15 region have been implicated in the pathogenesis of this condition:

- ***IGF2*** is an imprinted gene encoding a paternally expressed embryonic growth factor. Disruption of *IGF2* imprinting resulting in biallelic expression has been observed in some individuals with BWS as well as in

multiple types of tumors, including Wilms tumor. Mice with a pathogenic variant in the paternally derived *Igf2* allele are small at birth, whereas the same pathogenic variant on the maternally inherited allele does not affect fetal growth. Overexpression of *Igf2* or disruption of the *Igf2* receptor has also been shown to cause overgrowth in mice.

- ***H19*** is an imprinted gene encoding a maternally expressed and biologically active noncoding mRNA that may function as a tumor suppressor. Approximately 50% of individuals with BWS exhibit biallelic *IGF2* expression in their tissues, demonstrating uncoupled expression of *IGF2* and *H19*; that is, most retain normal maternal monoallelic expression of *H19*. Less commonly, changes in *H19* expression or methylation are reported in individuals with BWS [Joyce et al 1997, Sparago et al 2004].
- ***CDKN1C*** encodes the protein $p57^{KIP2}$, a member of the cyclin-dependent kinase inhibitor family that acts to negatively regulate cell proliferation. This gene is both a putative tumor suppressor gene and a potential negative regulator of fetal growth. Both of these functions and the preferential maternal expression (incomplete repression of transcription of the paternal allele) of this gene support its causal role in BWS. Pathogenic variants in this gene have been reported in approximately 5% of affected individuals. *CDKN1C* pathogenic variants are found more frequently in individuals with omphalocele, cleft palate, and a positive family history. However, not all instances of vertical transmission of BWS can currently be ascribed to pathogenic variants in *CDKN1C* [Hatada et al 1997, Lee et al 1997, Cardoso et al 2022].
- ***KCNQ1*.** The protein encoded by *KCNQ1* forms part of a potassium channel and has also been implicated in at least two cardiac arrhythmia syndromes, Romano-Ward syndrome and Jervell and Lange-Nielsen syndrome. This gene is maternally expressed in most tissues (excluding the heart) and has four alternatively spliced transcripts, two of which are untranslated.
- ***KCNQ1OT1*** is an antisense transcript that originates in intron 10 of *KCNQ1*. Loss of imprinting occurs in the 5' differentially methylated promoter region (IC2) of *KCNQ1OT1* in 50% of individuals with BWS [Bliek et al 2001, Weksberg et al 2001].

Imprinting centers 1 and 2 (IC1 and IC2) within the 11p15.5 region control gene expression across large chromosomal domains:

- **IC1** is the telomeric imprinting center on chromosome 11p15.5 that maps upstream of the *H19* promoter and regulates *H19* and *IGF2* expression. IC1 may also be referred to as ICR1, DMR1, or H19DMR. It is normally methylated on the paternally derived allele and unmethylated on the maternally derived allele.
- **IC2** is the centromeric imprinting center that regulates expression of several genes, including *KCNQ1OT1*, *KCNQ1*, and *CDKN1C*. It may also be referred to as ICR2, DMR2, or KvDMR1. It is normally methylated on the maternally derived allele and unmethylated on the paternally derived allele.

Overall, there are two imprinted domains in the BWS critical region (see Figure 1a).

Domain 1 is telomeric and contains the imprinted genes *H19* and *IGF2*. *H19* and *IGF2* are reciprocally expressed imprinted genes, with *H19* expressed from the maternally derived allele and *IGF2* expressed from the paternally derived allele. The expression of this domain is regulated by IC1 (see above). IC1 is normally methylated on the paternally derived allele and unmethylated on the maternally derived allele. Regulation of transcription is accomplished by binding of the zinc-finger insulator protein CTCF to its consensus sequence within IC1. CTCF only binds to unmethylated sequence (maternally derived allele) and interferes with downstream enhancers interacting with the *IGF2* promoters [Hark et al 2000].

Domain 2 is centromeric and contains the imprinted genes *CDKN1C*, *KCNQ1*, and *KCNQ1OT1*. Regulation of this domain is controlled by IC2. IC2 is located in intron 10 of *KCNQ1*. IC2 contains the promoter for *KCNQ1OT1*, a noncoding RNA with regulatory function [Smilinich et al 1999, Pandey et al 2008]. Although the exact regulation of this region is not clear, it is known that loss of methylation at IC2 on the maternally derived chromosome results in biallelic expression of the normally paternally derived

expressed *KCNQ1OT1*. Additionally, it has been shown that individuals with BWS and loss of methylation at IC2 on the maternally derived chromosome have reduced *CDKN1C* expression [Diaz-Meyer et al 2003].

Uniparental disomy (UPD). In BWS, somatic mosaicism for 11p15 UPD is found in 20% of affected individuals. The UPD appears to consistently arise from a somatic recombination event resulting in paternal disomy. Most UPD cases demonstrate segmental mosaicism for paternal UPD for 11p15, suggesting that the underlying mechanism is a postzygotic somatic recombination event. Therefore, UPD may not be detected if a low level of mosaicism occurs in the tissue sampled, and testing other tissues (e.g., skin fibroblasts, tumor biopsy) should be considered.

Chapter Notes

Acknowledgments

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