

## Beckwith-Wiedemann Syndrome: *H19* Methylation

**Test Code:** ZP

**Turnaround time:** 3 weeks

**CPT Codes:** 81401 x1

### Condition Description

Beckwith-Wiedemann syndrome (BWS) is a growth disorder and clinical features commonly include: macrosomia (large body size), macroglossia (enlarged tongue), visceromegaly, omphalocele, neonatal hypoglycemia, ear creases/pits, adrenocortical cytomegaly, and renal abnormalities (e.g., medullary dysplasia, nephrocalcinosis, medullary sponge kidney, and nephromegaly). Polyhydramnios may be identified during pregnancy. Infants with BWS have an approximately 20% mortality rate, mainly caused by complications of prematurity, omphalocele, and/or hypoglycemia. Macroglossia and macrosomia are generally present at birth but may have postnatal onset. The growth rate slows around seven to eight years of age. Hemihyperplasia may affect segmental regions of the body or selected organs and tissues. In addition, individuals with BWS are at an increased risk of developing embryonal tumors (e.g., Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma). Development and intelligence are typically unaffected, with the exception of mild speech delay in some individuals with severe macroglossia.

Defects in imprinted gene expression at 11p15 are associated with BWS [1]. Greater than 70% of cases are found to have alterations in DNA methylation at two distinct differentially methylated regions (DMRs) at 11p15. DMR1 is located within the telomeric domain (also known as ICR1) and controls the expression of two genes, *IGF2* and *H19*. DMR2 is located within the centromeric domain (also known as ICR2) and controls the expression of *KCNQ1*, *CDKN1C*, *SLC22A1L* and the *TSSC3* genes. Alterations in DNA methylation at either of these DMRs causes aberrant expression of these imprinted genes leading to Beckwith-Wiedemann Syndrome.

BWS is typically sporadic, though inheritance has also been reported in an autosomal dominant pattern, due to other mutations. No single explanation can account for the phenotypic heterogeneity seen in patients with BWS. The recurrence risk due to methylation defects is estimated to be low.

References:

1. Weksberg R, Smith AC, Squire J, Sadowski P. Hum Mol Genet. 2003; 12: R61-68.
2. Gaston V, Le Bouc Y, Soupre V, Burglen L et al. Eur J Hum Genet. 2001; 6:409-418.
3. Coffee, B, Muralidharan, K, Highsmith, WE, Lapunzina, P, and Warren, ST. Genet. Med. 2006; 8(10): 628-634.

### Genes

[H19](#)

### Indications

This test is indicated for:

- Individuals with a clinical diagnosis of Beckwith-Wiedemann syndrome.
- Individuals with isolated segmental hemihyperplasia.

### Methodology

Methylation-specific MLPA (MS-MLPA) is used to test for BWS. One advantage of MS-MLPA is that in addition to detecting DNA methylation abnormalities (epimutations), similar to Southern blot and quantitative methylation sensitive PCR, it also detects deletions and duplications (CNVs) of the 11p15 region. CNVs are estimated to be present in ~10% of patients with BWS. The presence of a CNV can increase the recurrence risk from that of the general population up to a 50% risk. Both methylation and CNVs will be reported from this analysis.

### Detection

Hypermethylation of DMR1 (*H19* gene) is expected to detect an additional 2-13% of individuals with BWS.

### Reference Range

For DMR1 (*H19* gene), an increase in DNA methylation of greater than two standard deviations above the mean of normal is consistent with BWS. See Coffee et al. for explanation of reference range [3].

### Specimen Requirements

**Submit only 1 of the following specimen types**

**Type: Whole Blood (EDTA)**

**Specimen Requirements:**

EDTA (Purple Top)

Infants and Young Children ( 2 years of age to 10 years old): 3-5 ml

Older Children & Adults: 5-10 ml

Autopsy: 2-3 ml unclotted cord or cardiac blood

**Specimen Collection and Shipping:**

Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

**Type: DNA, Isolated****Specimen Requirements:**

Microtainer

3µg

Isolation using the Perkin Elmer™ Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

**Specimen Collection and Shipping:**

Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

**Related Tests**

- Chromosome analysis (CA, CB) and array CGH is available for children with growth disorders and congenital anomalies with or without mental retardation.
- Methylation for DMR1 (*H19* gene) combined with methylation for DMR2 (*Lit1* gene) is offered as a separate panel when no previous studies have been performed.