Beckwith-Wiedemann syndrome (BWS) is a growth disorder characterized by large body size (macrosomia), defects in the closure of the abdominal wall during development, an enlarged tongue (macroglossia), asymmetric overgrowth (hemihyperplasia), neonatal hypoglycemia and ear creases/pits. Patients with BWS also show a significantly increased incidence of childhood tumours, especially Wilms tumor. BWS has an incidence of ~1 in 14,000. In 85% of cases BWS has occurred sporadically; in 15% of cases, BWS is transmitted in an autosomal dominant fashion, demonstrating preferential maternal transmission with incomplete penetrance and variable expression.

**GENETICS**

BWS is a complex multigenic disorder caused by alterations in growth regulatory genes on chromosome 11p15 that are subject to imprinting. Most autosomal genes are expressed from both the paternally and maternally derived alleles; however imprinted genes are expressed in a parent of origin specific manner. Several imprinted genes on chromosome 11p15.5 have been implicated in BWS:

- **KCNQ1**: normally paternally expressed and maternally methylated. Loss of maternal methylation results in biallelic expression of KCNQ1.
- **H19**: normally maternally expressed, paternally methylated. Gain of maternal methylation results in loss of expression of H19.

Another cause of BWS is uniparental disomy (UPD) which occurs when both copies of chromosome 11 are derived from the same parent. Patients with BWS and paternal UPD have two paternally derived copies of 11p15.5 and no maternal contribution for this region. In these patients, there are methylation defects at both KvDMR1 and H19.

Microdeletions and microduplications have also been seen in patients with BWS involving either the region with KCNQ1 or H19. Parent of origin specific chromosome rearrangements involving 11p15.5 may also cause BWS.

**ETIOLOGIC HETEROGENEITY IN BWS**

<table>
<thead>
<tr>
<th>Changes associated with BWS</th>
<th>Copy number</th>
<th>Methylation Status of KCNQ1OT1</th>
<th>Freq.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypomethylation KvDMR</td>
<td>Normal</td>
<td>Normal</td>
<td>Hypo</td>
</tr>
<tr>
<td>Hypermethylation H19DMR</td>
<td>Normal</td>
<td>Hyper</td>
<td>Normal</td>
</tr>
<tr>
<td>Paternal UPD11p15.5</td>
<td>Normal</td>
<td>Hyper</td>
<td>Hypo</td>
</tr>
<tr>
<td>Paternal duplication 11p15.5</td>
<td>Abnormal</td>
<td>Hyper*</td>
<td>Hypo*</td>
</tr>
<tr>
<td>Maternal microdeletion H19</td>
<td>Abnormal</td>
<td>Hyper</td>
<td>Normal</td>
</tr>
<tr>
<td>Maternal microdeletion KCNQ1</td>
<td>Abnormal</td>
<td>Normal</td>
<td>Hypo</td>
</tr>
</tbody>
</table>

*depends on the extent of the duplication

**TEST METHODS**

**Methylation status:** Methylation-specific Multiplex-Ligation-dependent Probe Amplification (MS-MLPA) is used to determine the methylation status of KvDMR1 (within KCNQ1) & H19DMR.

**Gene Dosage Analysis:** MLPA is used to determine the relative copy numbers of several genes in the 11p15.5 region.

**Parental gene dosage analysis for UPD:** A PCR-based microsatellite dosage assay is used to compare the quantity of genetic material from each parent in 11p15.5 region. Parental samples are required.

**TEST SENSITIVITY**

There are several molecular alterations associated with BWS. See chart below for the frequency of these changes.

Some patients with BWS who have UPD or KvDMR loss of methylation may yield a negative result due to low-level mosaicism.

**WHO SHOULD BE TESTED?**

- Individuals suspected of having BWS.
- Fetuses at risk of having BWS (e.g. omphalocoele and normal karyotype).

**For More Information**

Beckwith-Wiedemann Children’s Foundation - [http://www.beckwithwiedemannsyndrome.org](http://www.beckwithwiedemannsyndrome.org)

GeneTests online clinical information resource - [http://www.genetests.org/profiles/bws](http://www.genetests.org/profiles/bws)

To locate a genetics center near you, please visit the Canadian Association of Genetic Counsellors website at [www.cagc-acgg.ca](http://www.cagc-acgg.ca) or the National Society of Genetic Counselors website at [www.nsgc.org](http://www.nsgc.org)

1. Some cases of BWS warrant a cytogenetic analysis to rule out chromosome translocations (seen in <1% of BWS patients)
2. Parental samples are required to confirm paternal UPD in cases where a dosage discrepancy is suspected in the patient.
3. A negative molecular test result does not rule out the diagnosis of BWS. BWS patients may have CDKN1C mutations (5% of sporadic and 40% of familial cases) [please contact us to arrange this testing]. Or they may have somatic mosaicism or other epigenetic alterations, not currently assessed in the Molecular Genetics Laboratory, and may be referred to a research lab for further investigation.
4. These tests were developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.