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BECKWITH-WIEDEMANN SYNDROME

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.

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. omphalocele and normal karyotype).

ETIOLOGIC HETEROGENEITY IN BWS

Changes associated with BWS	Copy number	Methylation Status of H19	Methylation Status of KCNQ1OT1	Freq.
Hypomethylation KvDMR	Normal	Normal	Hypo	50-60%
Hypermethylation H19DMR	Normal	Hyper	Normal	2-7%
Paternal UPD11p15.5	Normal	Hyper	Hypo	10-20%
Paternal duplication 11p15.5	Abnormal	Hyper*	Hypo*	<1%
Maternal microdeletion H19	Abnormal	Hyper	Normal	<1%
Maternal microdeletion KCNQ1	Abnormal	Normal	Hypo	<1%

*depends on the extent of the duplication

For More Information

Beckwith-Wiedemann Children's Foundation - http://www.beckwith-weidemannsyndrome.org

GeneTests online clinical information resource - 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-accg.ca or the National Society of Genetic Counselors website at www.nsgc.org

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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.