BECKWITH-WIEDEMANN SYNDROME (BWS)

MOLECULAR CAUSES AND TESTING

Beckwith-Wiedemann syndrome (BWS) is a rare disorder involving changes on a region of chromosome 11p15 that influence pre- and postnatal growth. Some of these changes act directly on the DNA itself (**genetic** changes). Other changes affect the regulation of the growth genes and whether they are turned on or turned off (**epigenetic** changes). These changes disrupt the normal balance of growth gene expression and lead to the overgrowth seen in patients with BWS.

How is growth controlled?

The regulation of growth genes is controlled by a process called **imprinting**, where the chromosome from one parent expresses some genes that the chromosome from the other parent does not. The expression of these genes is controlled by **methylation**, which is a marker on DNA, which acts as a signal to "turn on" or "turn off" the gene (similar to a light switch).

On chromosome 11p15, there are two imprinted regions that are responsible for growth, imprinting control region 1 (IC1) and imprinting control region 2 (IC2). The mother's chromosome expresses genes that signal "don't grow" and the father's chromosome expresses genes that signal "grow." Normally, these signals and the expression of these genes are balanced, which results in normal, symmetric growth. In BWS, genetic changes affect the presence of these growth genes and how they function. Epigenetic changes affect the expression of these genes, and can cause an increase in the expression of "grow" signals, or a decrease in the expression of "don't grow" signals.

What kinds of genetic changes occur in BWS?

Genetic changes affect the DNA itself and are caused by small duplications or deletions, chromosome rearrangements or inversions, or mutations. These changes can lead to extra pieces of chromosome 11p15, and these changes may be inherited (passed down from parent to child). In BWS, patients may have extra pieces of chromosome 11p15, which result from a chromosome duplication, translocation, or inversion. Mutations affecting the *CDKN1C* gene may also occur.

What kinds of epigenetic changes occur in BWS?

Epigenetic changes affect the methylation "marks" or growth signals on DNA. These signals regulate the expression of genes that control growth. The DNA itself is usually normal, and epigenetic changes are typically not inherited.

How do we test for the different molecular causes of BWS?

There are three main tests that can help determine the type of BWS:

SNP arrays (microarrays): This test looks at all of the chromosomes to determine if there are missing or extra pieces. This test will also look at each chromosome to see if there is a copy from the mother and a copy from the father.

Methylation analysis for chromosome 11p15: This test will look at the marks on the DNA at two specific imprinted regions on chromosome 11p15 (IC1 and IC2).

CDKN1C gene sequencing: This test looks for mutations in the CDKN1C gene.

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What does a negative testing result mean?

A negative result with clinical features can be classified as a clinical diagnosis of BWS. A testing result may be negative due to the genetic or epigenetic change not being present in the tissue sample tested. This can occur due to mosaicism. Mosaicism is when a genetic or epigenetic change occurs in some parts of the body but not other parts. For example, in patients with negative testing in blood, testing of an affected part of the body may be informative. In detecting mosaic epigenetic changes, the sensitivity of methylation testing depends on which technique is used.