

BECKWITH-WIEDEMANN SYNDROME (BWS)

IC2 LOSS OF METHYLATION

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 that 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 does “IC2 loss of methylation” mean?

Loss of methylation (or **hypomethylation**) at imprinting control region 2 (IC2) is an epigenetic change that causes a decrease in the expression of genes that signal “don’t grow.” This causes an imbalance between the “don’t grow” and “grow” genes and results in overgrowth. The IC2 region may also be referred to as ICR2, *LIT1*, DMR2, or KvDMR. This epigenetic change is typically not inherited (meaning that it is not usually passed down from parent to child).

What is the tumor risk associated with IC2 BWS? How do we manage this risk?

Patients with IC2 loss of methylation have a lower tumor risk (2.5% – 3.1% risk) (Brioude, Lacoste et al. 2013, Maas, Vansenne et al. 2016, Mussa, Molinatto et al. 2016). The most common type of tumor to develop is hepatoblastoma. Wilms tumor is rare in IC2 patients, though cases have been reported. Other more rare types of tumors can occur in IC2 loss of methylation patients. We manage this risk by screening patients with IC2 for tumors. The American Association for Cancer Research (AACR) guidelines recommend tumor screening for all patients with BWS beginning at birth or at the time of diagnosis (Kalish, Doros et al. 2017). This screening includes:

Ultrasound Screening

- Full abdominal ultrasound every 3 months until age 4 years
- Renal ultrasound every 3 months from age 4 – 7 years

Alpha-fetoprotein (AFP) Screening

- AFP measurements every 3 months until age 4 years

References:

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