BECKWITH-WIEDEMANN SYNDROME (BWS)

IC1 GAIN 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 "IC1 gain of methylation" mean?

Gain of methylation (or **hypermethylation**) at imprinting control region 1 (IC1) is an epigenetic change that causes an increase in the expression of genes that signal "grow." This increase causes an imbalance between the "don't grow" and "grow" genes and results in overgrowth. The IC1 region may also be referred to as ICR1, *H19, H19/IGF2* or DMR1. 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 IC1 BWS? How do we manage this risk?

Patients with IC1 have a high tumor risk (22.8% – 28.6%) (Brioude, Lacoste et al. 2013, Maas, Vansenne et al. 2016, Mussa, Molinatto et al. 2016). The most frequently seen tumors in BWS patients are Wilms tumor (a tumor of the kidneys) and hepatoblastoma (a tumor of the liver). Wilms tumor is seen more frequently in IC1 patients than hepatoblastoma (Maas et al., 2016). We manage this risk by screening patients with IC1 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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