CDKN1C MUTATIONS

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.

How do mutations in CDKN1C cause BWS?

Mutations in CDKN1C are genetic changes on chromosome 11 that can cause BWS. The CDKN1C gene is a “don’t grow” gene that is normally expressed on the mother’s chromosome. When CDKN1C is mutated (mutations are random changes in the DNA code of a gene), the gene can stop working properly or in some cases, not work at all. Because the “don’t grow” signal is broken, the only active signal in the cell is the “grow” signal from the father’s chromosome. This results in cell overgrowth.

What is the tumor risk associated with CDKN1C mutations in BWS? How do we manage this risk?

Patients with CDKN1C mutations have an intermediate tumor risk (6.9% – 8.8%) (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). In patients with CDKN1C mutations specifically, however, neuroblastoma (a tumor affecting the nervous system) has also been seen in ~2.8% of patients (Maas et al., 2016). We manage this risk by screening patients with CDKN1C mutations 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, Kamihara, Bourdeaut 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
Neuroblastoma Screening

• Urine VMA/HVA every 3 months until age 6 years
• Chest x-ray every 3 months until age 6 years
• Urine VMA/HVA and Chest x-ray every 6 months from 6 – 10 years

References:

Patient family education materials provide educational information to help individuals and families. You should not rely on this information as professional medical advice or to replace any relationship with your physician or healthcare provider.