

# BECKWITH-WIEDEMANN SYNDROME (BWS)

## PATERNAL UNIPARENTAL ISODISOMY (PUPD)

**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 is “paternal uniparental isodisomy” (pUPD)?

Paternal uniparental isodisomy (pUPD) refers to a genetic change in which a child receives an extra piece of the father’s chromosome. Normally, a baby will receive one copy of each chromosome from their mother and one copy of each chromosome from their father. In pUPD, there are some cells with two copies of the father’s chromosome 11p15 region and these cells no longer have a copy of the 11p15 region from the mother’s chromosome. In pUPD, both IC1 and IC2 are affected and result in an increase in “grow” signals and decrease in “don’t grow” signals.

### What is the tumor risk associated with pUPD? How do we manage this risk?

Patients with pUPD have an intermediate to high tumor risk (13.8% – 17.3% risk) (Brioude, Lacoste et al. 2013, Maas, Vansenne et al. 2016, Mussa, Molinatto et al. 2016). The most frequently seen tumors in pUPD patients are Wilms tumor (kidney tumor) and hepatoblastoma (liver tumor). We manage this risk by screening patients with pUPD 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:

Brioude, F., A. Lacoste, I. Netchine, M. P. Vazquez, F. Auber, G. Audry, M. Gauthier-Villars, L. Brugieres, C. Gicquel, Y. Le Bouc and S. Rossignol (2013). "Beckwith-Wiedemann syndrome: growth pattern and tumor risk according to molecular mechanism, and guidelines for tumor surveillance." *Horm Res Paediatr* **80**(6): 457-465.

Maas, S. M., F. Vansenne, D. J. Kadouch, A. Ibrahim, J. Bliet, S. Hopman, M. M. Mannens, J. H. Merks, E. R. Maher and R. C. Hennekam (2016). "Phenotype, cancer risk, and surveillance in Beckwith-Wiedemann syndrome depending on molecular genetic subgroups." *Am J Med Genet A* **170**(9): 2248-2260.

Mussa, A., C. Molinatto, G. Baldassarre, E. Riberi, S. Russo, L. Larizza, A. Riccio and G. B. Ferrero (2016). "Cancer Risk in Beckwith-Wiedemann Syndrome: A Systematic Review and Meta-Analysis Outlining a Novel (Epi)Genotype Specific Histotype Targeted Screening Protocol." *J Pediatr* **176**: 142-149 e141.

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.