BECKWITH-WIEDEMANN SPECTRUM (BWSp)

Mosacism

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

BWS is a mosaic disorder, which means that some cells in the body may be affected and others may not. This results in a range of features. Because of this, BWS was redefined as the Beckwith-Wiedemann spectrum (BWSp). This spectrum describes a range of features due to changes on chromosome 11p15, from isolated lateralized overgrowth to classical BWS.

What is mosaicism?

Mosaicism refers to the presence of different types of cells within an individual. This results in some cells having a normal number of chromosomes and/or normal gene expression and other cells having a genetic or epigenetic change. The distribution of normal cells and affected cells (the cells with changes) can differ between parts of the body, and some parts of the body may have all normal cells or all affected cells, while other parts of the body can have both normal and affected cells. The ratio of affected to normal cells is usually expressed as a percentage.

These mosaic changes occur after fertilization (when egg and sperm come together), and the amount of affected cells and parts of the body with affected cells depend on when the genetic or epigenetic change occurred during fetal development. For example, a patient who had the change occur earlier in development will likely have a higher percentage of affected cells and have more areas of the body with affected cells compared to a patient who had the change occur later in development.

How does mosaicism affect patients with BWSp?

In patients with BWSp, affected cells have abnormal gene expression, which leads to overgrowth. The distribution of normal and affected cells results in a range of clinical features observed between patients, depending on where in the body the patient the affected cells are. For example, patients with lateralized overgrowth have more affected cells in the larger limb compared to their other limb.

How does mosaicism affect BWSp genetic testing?

Mosaic changes can occur in some parts of the body, but not other parts. As a result, some patients with BWSp may have negative BWS genetic testing in a blood sample, because the changes are not present in the blood. Testing an affected part of the body can help detect the genetic or epigenetic change present in a patient. In detecting mosaic epigenetic changes, the sensitivity of methylation testing depends on which technique is used.

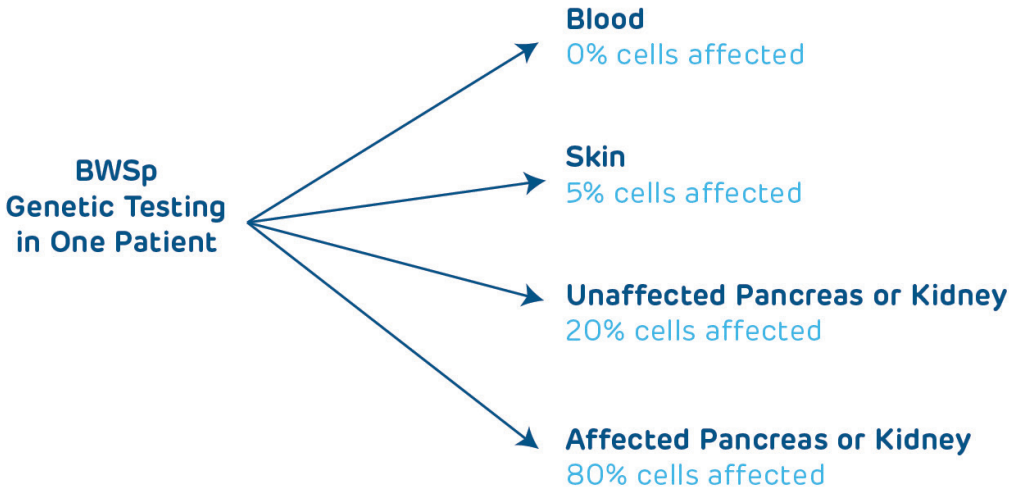
What tissues can be tested to detect mosaicism in BWSp?

In patients suspected to have BWSp with negative blood testing results, testing an affected part of the body can help identify the molecular type of the patient. Affected parts of the body may include:

- Skin biopsy from larger limb in patients with lateralized overgrowth
- Pancreas samples from patients with hyperinsulinism requiring partial pancreatectomies
- Tumor samples from patients with tumors commonly developed in BWSp
    - Example: kidney samples from a patient with Wilms tumor

Why test multiple tissues in patients?

Testing multiple available tissue samples from a patient can help detect the degree of mosaicism and identify which tissue(s) may be affected. For example, the distribution of affected cells can differ between tissues in a patient:



Regardless of clinical features, any patient with an identified BWSp molecular change in chromosome 11p15 is considered to be part of the Beckwith-Wiedemann spectrum (BWSp).

References:

Brioude, F., Kalish, J.M., Mussa, A., Foster, A.C., Bliek, J., Ferrero, G.B.,...Maher, E.R. (2018). Expert Consensus Document: Clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome: an international consensus statement. *Nat Rev Endocrinol*, 14, 229-249. doi:10.1038/nendo.2017.166.