Beckwith-Wiedemann Syndrome [1]

What is Beckwith-Wiedemann syndrome?

Beckwith-Wiedemann syndrome (BWS) is a growth regulation disorder. The most common features of BWS include macrosomia (large body size), macroglossia (large tongue), abdominal wall defects, an increased risk for childhood tumors, kidney abnormalities, hypoglycemia (low blood sugar) in the newborn period, and unusual ear creases or pits. Children with BWS may also have hemihyperplasia, in which some parts of the body are larger on one side than on the other.

The major features of BWS, macrosomia and macroglossia, are often present at birth. Abdominal wall defects such as omphalocele, which causes the inside of the abdomen to protrude through the navel, are also present at birth and may require surgery before an infant leaves the hospital. Mothers of children with BWS may have pregnancy complications, including premature delivery and polyhydramnios, meaning excess amniotic fluid. An unusually large placenta and long umbilical cord may also be present.

The increased growth rate generally slows during childhood. Intellectual development is usually normal, and adults with BWS typically do not experience any medical problems related to their condition.

What causes BWS?

The genetic mechanisms that cause gene mutations (alterations) resulting in BWS are complex. BWS is classified as an imprinting disorder. To understand imprinting, it is important to note that everyone inherits two copies of each gene, one from each parent. Usually, this results in both copies of the genes being expressed. However, imprinting refers to the process of deactivating one copy of a gene so that only a single copy is expressed normally. Imprinting disorders are caused by inappropriate functioning of the gene expression at imprinted sites. There can be differences in this expression as well from person to person, including both copies being expressed or neither copy is expressed. Depending on the genes affected, tumor risk can range from approximately 3% to 43%.

The most common cause of BWS is a change in DNA methylation. In about 20% of BWS, a person has inherited both copies of a specific gene from his or her father, leading to some genes having increased expression and others having decreased expression. Other causes include genetic mutations (10%) and unknown reasons for about 13% to 15% of cases.

It is important for doctors to find out the specific genetic mutation involved, since that affects the specific

increase of tumor risk and the appropriate monitoring schedule.

BWS is a genetic condition related to changes in the genes of chromosome 11 (11p15.5), in an area called the short arm. This is the area of the chromosome where two genes are located: insulin-like growth factor II (IGF-2) and cyclin-dependent kinase inhibitor (CDKN1C). In about 85% of cases, the genetic changes that cause BWS happen sporadically, meaning it occurs by chance, in families where there is no history of the condition. In about 10% to 15 % of cases, the genetic changes may be inherited. This means that the risk for BWS can be passed from generation to generation in a family.

How is BWS inherited?

The 10% to 15% of BWS that is inherited follows an autosomal dominant inheritance pattern. Normally, every cell has two copies of each gene: one inherited from the mother and one inherited from the father. In autosomal dominant inheritance, a mutation happens in only one copy of the gene. This means that a parent with a gene mutation may pass along a copy of their normal gene or a copy of the gene with the mutation. Therefore, a child who has a parent with a mutation has a 50% chance of inheriting that mutation. A brother, sister, or parent of a person who has a mutation also has a 50% chance of having the same mutation.

Options exist for couples interested in having a child when they know that one of them carries a gene mutation that increases the risk for this hereditary cancer syndrome. Preimplantation genetic diagnosis (PGD) is a medical procedure done in conjunction with in-vitro fertilization (IVF). It allows people who carry a specific known genetic mutation to have children who do not carry the mutation. A woman?s eggs are removed and fertilized in a laboratory. When the embryos reach a certain size, one cell is removed and is tested for the hereditary condition in question. The parents can then choose to transfer embryos which do not have the mutation. PGD has been in use for over a decade, and more recently has been used for several hereditary cancer predisposition syndromes. However, this is a complex procedure with financial, physical, and emotional factors for couples to consider before starting. For more information, talk with an assisted reproduction specialist at a fertility clinic.

How common is BWS?

BWS has been found across different population groups. Approximately one in 13,700 people have BWS. Some researchers believe this number could be an underestimate.

How is BWS diagnosed?

The diagnosis of BWS is clinical, meaning that it is based primarily on physical signs. BWS is suspected in children who are larger than expected for their age, especially if growth is not symmetrical, meaning the same on both sides. An enlarged tongue and abdominal wall defect, primarily omphalocele, are also considered to be common features. There are many other features that may be seen in some children with BWS. However, not every child with BWS will have every feature. Features are listed as major (common) or minor (less common). It is generally agreed that at least one major feature and two minor features are required for a diagnosis of BWS:

<u>Major Features</u>

- Macrosomia (large body size)
- Macroglossia (large tongue)
- Omphalocele (abdomen protrudes through navel)
- Hemihyperplasia, meaning some parts of the body are larger on one side
- Ear lobe creases or pits
- Visceromegaly, which is the enlargement of one or more abdominal organ

- Embryonal tumor (Wilms tumor [2], hepatoblastoma [3], neuroblastoma [4], rhabdomyosarcoma [5])
- Adrenocortical tumor (adrenal gland tumor [6])
- Kidney abnormalities
- Cleft palate, which is a gap in the roof of the mouth
- Family history of BWS

Minor Features

- Polyhydramnios (excessive amniotic fluid)
- Prematurity (low birth weight)
- Hypoglycemia (low blood sugar)
- Advanced bone age
- Heart problems
- Diastatsis recti, which is the separation of the right and left sides of the main abdominal muscle
- Hemangioma, a noncancerous tumor made up of blood vessels
- Facial nevus flammeus, a hemangioma of the skin, also called a ?port-wine stain?
- Characteristic facial features
- Identical twins

Early diagnosis of BWS is important because children with BWS are at a higher risk for developing certain tumors; including Wilms tumor and hepatoblastoma (see below).

Genetic testing for gene mutations associated with BWS is available, but it is complex. It is recommended that all families considering genetic testing for BWS meet with a clinical geneticist, a medical doctor who has training in genetics, and genetic counselor that can explain the tests and coordinate testing. The genetic testing methods that are currently available may be able to identify up to 80% of genetic mutations causing BWS.

What are the estimated cancer risks associated with BWS?

Several different tumor types, both cancerous and benign (noncancerous), have been reported in children with BWS. The estimated risk for a tumor in a child with BWS is about 7.5%. Tumors are very rare after age 10, and the risk for an individual tumor decreases over time until the risk is similar to that of the general population. The cancer risk is highest in children with BWS who have hemihyperplasia and organomegaly, meaning the enlargement of organs, especially nephromegaly, the enlargement of the kidneys, than in children with isolated hemihypertrophy. In fact, it is estimated that those with hemihyperplasia may have a much higher risk, up to four times greater, than patients with BWS without hemihyperplasia.

The most common tumor types are:

- Wilms tumor (kidney tumor; about 40% of cases)
- Hepatoblastoma (liver tumor)
- Adrenocortical carcinoma (about 20% of cases)
- Neuroblastoma
- Rhabdomyosarcoma

What are the screening options for BWS?

Screening recommendations for people with BWS are aimed primarily at detecting hepatoblastoma and Wilms tumor. Current suggested screenings for people who are known or suspected to have BWS include:

- Baseline magnetic resonance imaging [7] (MRI) or computed tomography [8] (CT or CAT) scan of the

abdomen at the time of diagnosis
- Abdominal ultrasound [9] to screen for hepatoblastoma and Wilms tumor every three months, until age 4. After age 4, imaging may be limited to just a kidney ultrasound until age 8
- Serum alpha-fetoprotein blood test every six weeks, or every three months at the minimum, until age 4
- Regular physical examination, including abdominal exam; schedule determined by your doctor

If a child has an identical twin that doesn?t have signs of BWS, the twin should still be screened with ultrasounds and serum alpha-fetoprotein blood tests, as noted above.

Additionally, screening for hypoglycemia is important in infancy. Children with BWS may also need to be evaluated by a craniofacial team, doctors who specialize in treating head and face conditions, to determine if surgery may be required to decrease tongue size. Support may be needed to assist with feeding difficulties in infancy and speech development in childhood. Children with significant hemihyperplasia may need to be evaluated by an orthopedist (bone doctor).

Screening recommendations may change over time as new technologies are developed and more is learned about BWS. It is important to talk with your doctor about appropriate screening tests.

Learn more about what to expect when having common tests, procedures, and scans [10].

Questions to ask the doctor

If you are concerned about the risk for cancer in your child, talk to your doctor. Consider asking the following questions of your doctor:

- What is my child?s risk of developing cancer?
- What can I do to reduce my child?s risk of cancer?
- What are my options for cancer screening?

If you are concerned about your family history and think that you, your child, or other family members could have BWS, consider asking the following questions:

- Does our family history increase my child?s risk of developing a cancerous or benign tumor?
- Could my family have BWS?
- Should I meet with a genetic counselor?
- Should I consider genetic testing [11]?

More Information

The Genetics of Cancer [12]

Genetic Testing [11]

What to Expect When You Meet With a Genetic Counselor [13]

Collecting Your Family Cancer History [14]

Sharing Genetic Test Results with Your Family [15]

Additional resources

National Cancer Institute
www.cancer.gov

[16]

American Cancer Society
www.cancer.org [17]

CancerCare
www.cancercare.org [18]

To find a genetic counselor in your area, ask your doctor or visit the following websites:

National Society of Genetic Counselors
www.nsgc.org [19]

National Cancer Institute: Cancer Genetics Services Directory
www.cancer.gov/cancertopics/genetics/directory [20]

Links:
[1] http://www.cancer.net/cancer-types/beckwith-wiedemann-syndrome
[2] http://www.cancer.net/node/31257
[3] http://www.cancer.net/node/31274
[4] http://www.cancer.net/node/31395
[5] http://www.cancer.net/node/31380
[6] http://www.cancer.net/node/31341
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[19] http://www.nsgc.org/
[20] http://www.cancer.gov/cancertopics/genetics/directory