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A REVIEW ON BECKWITH WIEDEMANN SYNDROME

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ABSTRACT

Beckwith-Wiedemann syndrome (BWS) is a disorder involving overgrowth conditions. It is also characterized by a broad spectrum of symptoms and physical conditions that changes in range and severity from person to person. In this syndrome many individuals show conditions including above-average birth weight and increased growth after birth, uncontrolled growth of one side of the body. The syndrome occurs mainly in infants. Imprinted genes tend to be grouped together or clustered together. Several im In addition to *H19* itself, this locus also produces a micro-RNA, called *miR-675*, an antisense protein coding transcript, called *H19* opposite tumor suppressor (*HOTS*), and a long inter-genic antisense transcript called 91H printed genes are found in a cluster on chromosome 11p. The broad range of potential symptoms can affect many different organs of the body. Affected individuals may not have all of the symptoms listed in article. Cytogenetically detectable abnormalities involving chromosome 11p15 are found in 1% or fewer of affected individuals. Molecular genetic testing can identify epigenetic and genomic alterations of chromosome 11p15 in individuals with BWS. Surgery may be performed during early puberty to equalize significant differences in leg length secondary to hemi-hyperplasia; craniofacial surgery may benefit individuals with facial hemi-hyperplasia (a symptom of BWS). More symptoms are mainly Macrosomia, Macroglossia, Hemihyperplasia, Omphalocele, Placental mesenchymal dysplasia, Cleft palate and others.

KEYWORDS: Beckwith-wiedemann syndrome, clinical aspects, H19 genetic details, symptoms and treatment management.

INTRODUCTION

1. BECKWITH-WIEDEMANN SYNDROME

Beckwith-Wiedemann syndrome (BWS) is a disorder involving various overgrowth conditions. It is also characterized by a broad spectrum of symptoms and some physical conditions that change in range and severity from person to person.[1,2]

1.1. Synonyms of Beckwith-Wiedemann Syndrome[2,5,6,4]

- Beckwith-Syndrome
- BWS
- Exomphalos-Macroglossia-Gigantism Syndrome
- Hypoglycemia with Macroglossia
- Omphalocele-Visceromegaly-Macroglossia Syndrome
- Wiedemann-Beckwith Syndrome
- EMG Syndrome
- Visceromegaly-Umbilical Hernia-Macroglossia Syndrome

However, in many individuals, associated features include above-average birth weight and an unusually large tongue (macroglossia), macrosomia i.e. increased growth after birth, organomegaly i.e. enlargement of certain internal organs, and also abdominal wall defects (i.e. umbilical hernia).[4,6]

BWS may also be associated with low blood sugar levels within the first few days (neonatal-hypoglycemia), or after (hyper-insulinism), ear lobes having distinctive grooves and other facial abnormalities, abnormal enlargement of one side of the body (hemihyperplasia or hemihypertrophy) resulting in the uncontrolled and abnormal growth, and a high risk of developing certain cancers in children, mainly like Wilms tumor and hepatoblastoma.[7,8] Approximately 85 % of the people with BWS have genetic changes that appear to be occur randomly. In approximately 10-15 percent of the people with this syndrome familial transmission occurs.[9]

According to researches, BWS results from various abnormalities affecting the proper expression of certain genes that control growth within a specific region of the “chromosome 11”.[10] It is disorder with growth regulation exhibiting somatic overgrowth and a predisposition to embryonal tumors. There is 1 out of 13,700 cases of BWS.[10]

2. HISTORY

In Germany, in 1964, a familial form of omphalocele with macroglossia was reported by Hans-Rudolf Wiedemann. In 1969, Professor J. Bruce Beckwith from Loma Linda University, California, described a similar series of patients.[10,11]

Originally, Professor Wiedemann termed EMG syndrome to describe the combination of congenital exomphalos, macroglossia, and gigantism. Over time, this constellation was renamed Beckwith-Wiedemann syndrome (BWS). Beckwith-Wiedemann syndrome is the most common overgrowth syndrome in infants.[13,15]

3. PATHOPHYSIOLOGY

Despite the fact that the causes of Beckwith-Wiedemann syndrome remain unclear, approximately 80% of the patients demonstrate genotypic abnormalities of the distal region of chromosome 11p.[16]

The first identified example of the imprinting in mammals was 11p (i.e., the process by which the 2 alleles of a gene are expressed differentially)[17]. For example, the maternal allele of band 11p15.5 is normally imprinted. However, designate the silent allele as the imprinted gene.[17]

During reviewing the literature, one must bear in mind that this inconsistent and confused nomenclature. Imprinting has been associated with structural changes in DNA near the gene, such as lack of acetylation or methylation. Many 11p genes are imprinted, including *p57* (a cation-independent cyclase), *IGF-2* (gene for insulin like growth factor-2 [IGF-2]), the gene for insulin, and *H19*.[19]

H19 is a particularly interesting gene because this gene is transcribed but not translated. *H19* messenger RNA (mRNA) appears critical for the proper imprinting of the nearby insulin and *IGF-2* genes because deletion of *H19* or transposition from its usual position relative to *IGF-2* disrupts normal imprinting of genes.[20] Evidence reveals that *H19* mRNA binds with IGF-2 mRNA binding protein, which may be one mechanism by which it directly affects the IGF-2 production.[20]

There is a complex mode of inheritance in BWS. Reported results includes autosomal dominance with some variable expressivity, contiguous gene duplication at band 11p, micro-deletions, and genomic imprinting (resulting from a defective or absent copy of maternally

derived allele).[20] Not overall, the overgrowth associated with this syndrome appears to be most often as the result of the enhanced IGF-2 action within prenatal and postnatal tissues.[20]

4. CAUSES

Imprinted genes tend to be grouped together or clustered together. Several imprinted genes are found in a cluster on chromosome 11p15.5. The cluster is mainly divided into two functional regions known as (IC1 and IC2) (which are imprinting centers). There are many specified imprinted genes which are regulated by these imprinting centers that can play an important role in the development of this syndrome.[20,21]

These genes involves the *H19* gene (a gene that signals not to grow), the *IGF2* (insulin-like growth factor II) gene, the *KCNQ10T1* (*LIT1*) gene, and the *CDKN1C* (p57 [KIP2]) gene (a signal not to grow).[21] Increased methylation at imprinting center 1 (IC1) occurs in 2-7% of people with BWS and leads to loss of *H19* expression and increased *IGF2* expression. Imprinting center 2 (IC2) is associated with KvDMR, a chemical switch found on the *KCNQ1* gene.[21]

In about 50% of people, loss of methylation at KvDMR1 occurs with BWS and leads to loss of imprinting and enhanced expression of the paternally-expressed *KCNQ10T1* (long QT intronic transcript 1 [*LIT1*]) gene, and also loss of expression of *CDKN1C*. *H19* is a long non-coding RNA thought which play a important role in inhibiting growth. i.e. *IGF2* is a growth factor. *KCNQ10T1* is a non coding RNA and *CDKN1C* is a tumor suppressor and also cell cycle regulator.[23]

Some specific causes of BWS are associated with some specific symptoms (genotype-phenotype correlation). Research indicates that the conditions like omphalocele and macroglossia are more common in individuals with defects of IC2 or a mutation of the*CDKN1C* gene. Individuals with defects of IC1 or uniparental paternal disomy (UPD) appear to be at the greater risk of developing an associated cancer such as Wilms tumor.[24]

Children mainly with uniparental paternal disomy(UPD) are also at a high risk of developing hemi-hypertrophy. Many research is necessary to understand how the specific causes of BWS correlate with the various symptoms of this disorder.[25] In some rare cases, Beckwith-Wiedemann syndrome results as changes in the structure of the chromosome 11p. Some of these chromosomal abnormalities are inherited from the parent, while others occur as a

random events in the earliest stages of development before birth or also during the formation of reproductive cells (i.e. eggs and sperm).[22.23]

4.1. THE COMPLEXITY OF THE *H19* GENE LOCUS

Recently various work done to better characterize the *H19* locus have revealed that this locus is housing several overlapping transcriptions on the DNA strands that can be produce different transcriptional products. The most extensively studied is the H19 RNA itself, which is transcribed by the RNA polymerase II and been processed by capping, splicing and polyadenylation, although it does not code for any protein product. Although the majority of the transcriptional output of the *H19* locus is non-coding RNAs, recently, it has become clear that it can also code for a protein product.[22,23]

In addition to *H19* itself, this locus also produces a micro-RNA, called *miR-675*, an antisense protein coding transcript, called *H19* opposite tumor suppressor (*HOTS*), and a long inter-genic antisense transcript called 91H.[1-3] However, longer-range chromatin interactions at the mouse *IGF2 or H19* locus reveals a novel paternally expressed, long non-coding RNA, called *PIHit*, which is the liver-specific capped and unpoly-adenylated transcript with heterogeneous size, but it is located in a poorly characterized and intergenic region between *H19* and *IGF2*.[24]

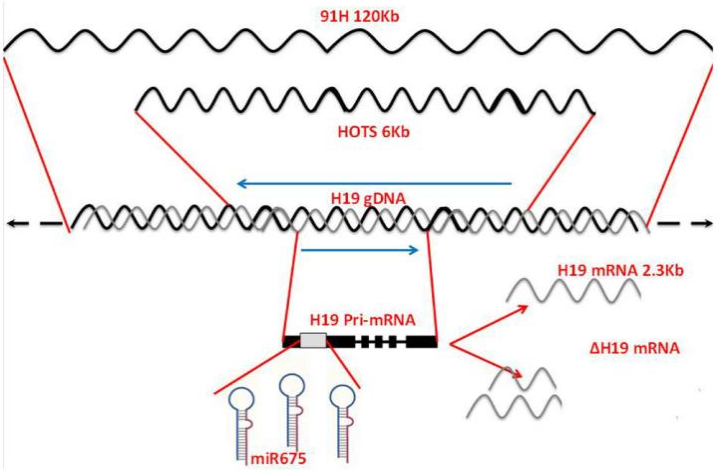

Fig .4.1 showing the h19 chromosomal complexation.

5. SIGN AND SYMPTOMS

The symptoms of BWS change greatly from person to person. Diagnosis of BWS can be challenging because the patients are often mosaic (with the genetic changes occurring in some cells or parts of the body but not others), although the external appearance is not

necessarily predictive of internal effects. This results in few individuals appearing mildly affected, while others seen more significantly affected.[27] The broad range of potential symptoms (clinical spectrum) can affect many different organs of the body. Affected individuals may not have all of the symptoms listed below. There are many clinical features of BWS becomes less evident with increasing age and many adults mainly experience normal growth and appearance. Intelligence is been usually unaffected in BWS, until associated with prolonged, untreated neonatal hypoglycemia or a chromosomal duplication.[27,28]

Some infants with BWS are born prematurely, but still have an excess birth weight (large for gestational age). Many infants with BWS are more than the 97th percentile in weight for gestational age. Overgrowth continues during childhood (macrosomia) and decreased around 7 or 8 years of age. Uncontrolled growth of one side or structure of the body (hemihyperplasia or hemihypertrophy) may occur, resulting in unequal (asymmetric) growth. Hemihyperplasia refers specifically to an increase in number of cells (proliferation) resulting in asymmetric overgrowth. A similar term, hemi-hypertrophy, which is overgrowth due to abnormally large cell size.[28,29]

Abdominal wall defects involve an exomphalos (also known as omphalocele), in which a part of an infant's intestines and abdominal organs protrude or stick out through the belly button. The intestines and other organs are covered by a thin membrane. Less severe defects can include protrusion of part of the intestines through an abnormal opening in the muscular wall of the abdomen near the umbilical cord (umbilical hernia) and separation of the left and right muscles (rectus muscles) of the abdominal wall or weakness. The internal organs of affected individuals can become abnormally enlarged. Any or all of the following organs may be affected just like that liver, spleen, pancreas, kidneys, or also adrenal glands.[29,30]

Some infants with BWS may have low blood sugar level (neonatal hypoglycemia or hyper-insulinism) due to overgrowth and increased secretion of the hormone insulin by pancreatic islets. Insulin functions to help regulate glucose level of blood by promoting the movement of glucose into the cells. Most infants with neonatal hypoglycemia associated with BWS have mild and transient symptoms. However, without proper detection and appropriate treatment, neurological complications may result.[24]

Children with BWS can be have an enlarged tongue (macroglossia), which can cause difficulties in speaking, feeding, and breathing. In addition to an enlargement of the tongue

(macroglossia), BWS may be characterized by other abnormalities of the facial (craniofacial) and skull region. Such features may include distinctive slit-like linear grooves or creases in the ear lobes and indentations on the back rims of the ears (pits), prominent eyes with relative improper development of the bony cavity of the eyes (i.e. intra-orbital hypoplasia), and/or a prominent back region of the skull (occiput). Some infants may have flat, pale red or reddish purple facial lesions at birth, mainly on the eyelids and forehead, which consist of abnormal clusters of small blood vessels (i.e. capillary nevus flammeus). Such lesions typically can be less apparent during the first year of life of infants. The children with hemihyperplasia or hemihypertrophy, can show one side of the face appear larger than the other. Due to the mosaic nature of BWS, some children have eyes with multiple colors. In addition, in some affected children, there may be improper contact of the teeth of the lower jaw and upper jaw (i.e. malocclusion) and abnormal protrusion of the lower jaw (i.e. mandibular prognathism). These features may occur secondary to abnormal enlargement of the tongue.

There is a variety of renal abnormalities have occurred in individuals with BWS, including abnormally enlarged kidneys (i.e. nephromegaly), renal medullary dysplasia i.e. incomplete development of the innermost tissues of the kidney and the formation of calcium deposition in the kidney (i.e. nephrocalcinosis), which could potentially impair and affect kidney function. Additional abnormalities include duplication of the series of tubes and ducts through which the kidneys reabsorb water and sodium (duplicated collecting system), widening of some of the small tubes and collecting ducts (medullary sponge kidney), and the occurence of small pouches (i.e. diverticula) on the kidneys.[15,16,18]

Children with BWS may have an high risk of developing certain childhood cancers, like Wilms tumor (or nephroblastoma), which is a malignancy of the kidney, and tumors involving the liver (i.e. hepatoblastoma). Less commonly, other malignancies have been reported (e.g., neuroblastoma, rhabdomyosarcoma). The risk of malignancy is greatest before the age of 8.

6. EPIDEMIOLOGY

In United States, frequency is determined at 1 in 15,000 live births.

- The International Worldwide frequency is determined at 1 in 13,700 live births in other developed countries. Cases are also maximum in infants produced with in vitro fertilization.[19,20]

- The most common is mental retardation. Strict maintenance of euglycemia decreases the risk of nervous tissue damage.
- No race predilection is observed.
- No sex predilection is noted.
- Beckwith-Wiedemann syndrome is a congenital type of disorder. Also the Wilms tumor is the most common cancer in children with Beckwith-Wiedemann syndrome, occurring in about 5-7% of all children with Beckwith-Wiedemann syndrome.[8,15]
- Wilms tumor develops in most children before 4 years of age. However, children with Beckwith-Wiedemann syndrome can develop tumors like Wilms tumor when they are as old as 7-8 years.
- 95% of all Wilms tumor cases have been diagnosed mainly in the age group of 8%.
- Approximately 85% of people with BWS have no family history of this syndrome. For these people, BWS is caused by epigenetic changes and genetic variation (changes) that appear to occur randomly. More rarely, the disorder appears to be inherited.[20]
- The incidence is supposed to occur in 1 in 13,700 individuals in the general population. Because people those are mildly affected may go undiagnosed, it is difficult to determine the true frequency of BWS in the general population in world.

7. CLINICAL ASPECTS

This syndrome is considered a clinical spectrum, in which the affected individuals may have many of these features or may have only one or two clinical findings. Early death may occur from such complications of prematurity, hypoglycemia, cardio-myopathy, macroglossia, or tumors.[23]

However, the previously reported mortality of 20% is likely an overestimate given better recognition of the disorder along with enhanced treatment options. Macroglossia and macrosomia are generally present at birth but may have postnatal onset. Growth rate slows around age seven to eight years. Hemi-hyperplasia can affect the selected organs and tissues or segmental regions of the body.[23]

The imprinting center 1 (i.e. ICR) that resides between the *IGF2* and *H19* loci is normally differentially methylated, leading to the *IGF2* expression from the paternal chromosome together with silencing of *H19* expression, loss of *H19* expression (*H19* epimutation). This

gain of methylation leads also to predisposition to develop the cancers such as Wilm's tumor, hepatoblastoma and other childhood tumors.[23]

However, *IGF2*, other than *H19*, is the key factor in the development of BWS, since in many cases of BWS, normal methylation and expression of *H19* is accompanied by *IGF2* bi-allelic expression. However, in 2%–7% of BWS patients, both alleles are methylated, leading to *IGF2* loss of imprinting.[10]

8. DIAGNOSIS AND MANAGEMENT

8.1. DIAGNOSTIC TESTING

A provisional diagnosis of BWS based on clinical assessment may be confirmed by molecular/cytogenetic testing. Cytogenetically detectable abnormalities involving chromosome 11p15 are found in 1% or fewer of affected individuals. Molecular genetic testing can identify epigenetic and genomic alterations of chromosome 11p15 in individuals with BWS:

- Loss of methylation on the maternal chromosome at imprinting center 2 (IC2) in 50% of affected individuals;
- Paternal uniparental disomy for chromosome 11p15 in 20%; and
- Also can be gain of methylation on the maternal chromosome at imprinting center 1 (IC1) in 5%.
- Methylation alterations are associated with deletions or duplications in this region with have high heritability.

Sequence analysis of *CDKN1C* identifies a heterozygous maternally inherited pathogenic variant in approximately 40% offamilial cases and 5%-10% of cases with no family history of BWS.[21]

BWS may be diagnosed or confirmed very shortly after the birth based on the clinical evaluation, detection of characteristic physical findings (e.g., increased weight and length, macroglossia, abdominal wall defects and careful methylation testing and chromosomal (cytogenetic) analysis of the BWS region (i.e., chromosome 11p15.[29,32,30]

In some cases, certain procedures may be performed before birth (prenatally). For example, ultrasound imaging may allow assessment of organ size and overall size of the developing fetus and potentially reveal other findings that may be suggestive of BWS, such as increased

amniotic fluid surrounding the fetus (hydramnios), enlarged placenta, omphalocele, enlarged abdominal circumference, and/or other abnormalities. If BWS is suspected, prenatal testing is available.[33,32,30]

8.1.1. MAJOR FINDINGS ASSOCIATED WITH BWS

- Macrosomia (i.e. traditionally defined as weight and length/height >97th centile).
- Macroglossia.
- Hemihyperplasia (i.e. asymmetric overgrowth of one or more regions of the body).
- Omphalocele (it is also called exomphalos) or umbilical hernia.
- Embryonal tumor (e.g., Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma) in childhood.[35,36]
- One or more intra-abdominal organs including liver, spleen, kidneys, adrenal glands, and/or pancreas involved by Visceromegaly.
- Cytomegaly of the fetal adrenal cortex (i.e. pathognomonic).
- Renal abnormalities including structural abnormalities, nephromegaly, nephrocalcinosis, and/or later development of medullary sponge kidney.
- Anterior linear ear lobe creases or posterior helical ear pits.
- Placental mesenchymal dysplasia.
- Cleft palate (most rare in BWS).
- Cardiomyopathy (most rare in BWS).
- Positive family history (≥1 family members with a clinical diagnosis of BWS or a history or a features suggestive of BWS).[40,39,38,36]

8.1.2. MINOR FINDINGS ASSOCIATED WITH BWS

- Pregnancy-related findings including polyhydramnios and prematurity
- Neonatal hypoglycemia
- Vascular lesions including nevus simplex (typically appearing on the forehead, glabella, and/or back of the neck) or hemangiomas (cutaneous or extracutaneous)
- Characteristic facies including midface retrusion and infraorbital creases
- Structural cardiac anomalies or cardiomegaly.
- Advanced bone age (most common in overgrowth/endocrine disorders)[40,39,38]

An enhanced frequency of *female monozygotic twins* discordant for BWS has been reported. Loss of methylation at IC2 seen in these females. In contrast, the less frequently observed male monozygotic twins show a broad spectrum of BWS-associated molecular alterations.[48]

8.1.3. SUB-FERTILITY OR ASSISTED REPRODUCTIVE TECHNOLOGIES

It seems to be associated with an increased risk of BWS cases with loss of methylation at IC2. No specific aspect of sub-fertility or its treatment has been specifically associated with the enhanced risk of epigenetic defects associated with BWS after ART.[45,43]

9. MANAGEMENT AND TREATMENT

Treatment manifestations

Treatment of hypoglycemia to reduce the risk of central nervous system complications; abdominal wall repair for omphalocele; endotracheal intubation for a compromised airway and use of specialized nipples or nasogastric tube feedings to manage feeding difficulties results as macroglossia. Children with macroglossia may benefit from tongue reduction surgery in infancy or early and from speech therapy early childhood.[44,45,46]

Surgery may be performed during early puberty to equalize significant differences in leg length secondary to hemi-hyperplasia; craniofacial surgery may benefit individuals with facial hemihyperplasia.[47,46]

Neoplasias can be treated using standard pediatric oncology protocols. pediatric nephrologist can treat and assessed the Nephrocalcinosis and other renal findings. Referral of children with structural GI tract anomalies to the relevant specialist; standard management for cardiac problems; standard interventions for children with developmental delay.[47]

Prevention of secondary complications

Prompt evaluation and standard treatment for suspected urinary tract infections to prevent secondary renal damage.[48,49]

Surveillance

Monitor for the hypoglycemia, especially in the neonatal period; screen for embryonal tumors by abdominal ultrasound examination every three months until age eight years; monitor serum alpha-fetoprotein (AFP) concentration every two to three months in the first four years of life for early detection of hepatoblastoma.[50] Annual renal ultrasound examination foraffected individuals between age eight years and mid-adolescence to identify those with nephrocalcinosis or medullary sponge kidney disease; consideration of annual or biannual measurement of urinary calcium/creatinine ratio.[50.51]

10. REFERENCES

1. Beckwith JB. Abstract, Western Society for Pediatric Research 1963Extreme cytomegaly of the adrenal fetal cortex, omphalocele, hyperplasia of kidneys and pancreas, and Leydig-cell hyperplasia: Another syndrome? Los Angeles, November 11.
2. Hennekam RCM, Krantz I, Allanson, J. Eds. Syndromes of the Head and Neck. 5th ed. Oxford University Press, New York, NY; 2010; 389-405.
3. Vanderver A, Pearl PL. Beckwith-Wiedemann Syndrome. NORD Guide to Rare Disorders. Lippincott Williams & Wilkins. Philadelphia, PA., 2003; 518.
4. Cohen MM Jr, Nori G, Weksberg R. Overgrowth Syndromes. 1st ed. Oxford University Press, New York, NY; 2002; 11-31.
5. Azzi S, Habib WA, Netchine I. Beckwith–Wiedemann and Russell–Silver Syndromes: from new molecular insights to the comprehension of imprinting regulation. Curr Opin Endocrinol Diabetes Obes 2014; 21: 30–38.
6. Kalish JM, Jiang CL, Bartolomei MS. Epigenetics and Imprinting in Human Disease. Int J Dev Biol, 2014; 58: 291–298.
7. Wiedemann HR. Complexe malformatif familial avec hernie ombilicale et macroglossie–un ‘syndrome nouveau’? J Genet Hum. 1964; 13: 223–32.
8. Beckwith JB. Macroglossia, omphalocele, adrenal cytomegaly, gigantism, and hyperplastic visceromegaly. Birth Defects. 1969; 5: 188–96
9. Beckwith-Wiedemann Syndrome. The Children’s Hospital of Philadelphia. Reviewed January 03, 2011. Available at: http://www.chop.edu/conditions-diseases/beckwith-wiedemann-syndrome Accessed February 2, 2016.
10. Beckwith-Wiedemann Syndrome. Genetics Home Reference. Reviewed June 2015. Available at: http://ghr.nlm.nih.gov/condition/beckwith-wiedemann-syndrome Accessed February 2, 2016.
11. McKusick VA., ed. Online Mendelian Inheritance in Man (OMIM). Baltimore. MD: The Johns Hopkins University; Entry No: 130650; Last Update:01/15/2015. Available at:http://www.omim.org/entry/130650 Accessed February 2, 2016.
12. Beckwith-Wiedemann Syndrome. Orphanet. Last update: December 2011. Available at:http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=116 Accessed February 2, 2016.
13. Shuman C, Beckwith JB, Smith AC, et al. Beckwith-Wiedemann Syndrome. 2000 Mar 3 [Updated 2010 Dec 14]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016.

Available from: http://www.ncbi.nlm.nih.gov/books/NBK1394/ Accessed February 2, 2016.

14. Shaffer LG, Agan N, Goldberg JD, Ledbetter DH, Longshore JW, Cassidy SB. American College of Medical Genetics statement of diagnostic testing for uniparental disomy. Available online. 2001. Accessed 8-8-16. [PMC free article] [PubMed]
15. Algar E, Brickell S, Deeble G, Amor D, Smith P. Analysis of CDKN1C in Beckwith Wiedemann syndrome. Hum Mutat., [PubMed] 2000; 15: 497–508.
16. Alsultan A, Lovell MA, Hayes KL, Allshouse MJ, Garrington TP. Simultaneous occurrence of right adrenocortical tumor and left adrenal neuroblastoma in an infant with Beckwith-Wiedemann syndrome. Pediatr Blood Cancer. [PubMed] 2008; 51: 695–8.
17. Baujat G, Rio M, Rossignol S, Sanlaville D, Lyonnet S, Le Merrer M, Munnich A, Gicquel C, Cormier-Daire V, Colleaux L. Paradoxical NSD1 mutations in Beckwith-Wiedemann syndrome and 11p15 anomalies in Sotos syndrome. Am J Hum Genet. [PMC free article] [PubMed] 2004; 74: 715–20.
18. Beckwith JB. Nephrogenic rests and the pathogenesis of Wilms tumor: developmental and clinical considerations. Am J Med Genet. [PubMed] 1998; 79: 268–73.
19. Bliek J, Maas SM, Ruijter JM, Hennekam RC, Alders M, Westerveld A, Mannens MM. Increased tumour risk for BWS patients correlates with aberrant H19 and not KCNQ1OT1 methylation: occurrence of KCNQ1OT1 hypomethylation in familial cases of BWS. Hum Mol Genet. [PubMed] 2001; 10: 467–76.
20. Choufani S, Shuman C, Weksberg R. Beckwith-Wiedemann syndrome. Am J Med Genet C Semin Med Genet., 2010; 154C: 343–54.
21. Chitayat D, Rothchild A, Ling E, Friedman JM, Couch RM, Yong SL, Baldwin VJ, Hall JG. Apparent postnatal onset of some manifestations of the Wiedemann-Beckwith syndrome. Am J Med Genet., 1990; 36: 434–9.
22. Dao D, Frank D, Qian N, O'Keefe D, Vosatka RJ, Walsh CP, Tycko B. IMPT1, an imprinted gene similar to polyspecific transporter and multi-drug resistance genes. Hum Mol Genet., 1998; 7: 597–608.
23. DeBaun MR, Niemitz EL, Feinberg AP. Association of in vitro fertilization with Beckwith-Wiedemann syndrome and epigenetic alterations of LIT1 and H19. Am J Hum Genet., 2003; 72: 156–60.
24. Dória S, Sousa M, Fernandes S, Ramalho C, Brandão O, Matias A, Barros A, Carvalho F. Gene expression pattern of IGF2, PHLDA2, PEG10 and CDKN1C imprinted genes in spontaneous miscarriages or fetal deaths. Epigenetics., 2010; 5: 444–50.

25. Eggermann T. Silver-Russell and Beckwith-Wiedemann syndromes: opposite (epi) mutations in 11p15 result in opposite clinical pictures. Horm Res. 2009; 71 Suppl2: 30–5.
26. Eggermann T, Algar E, Lapunzina P, Mackay D, Maher ER, Mannens M, Netchine I, Prawitt D, Riccio A, Temple IK, Weksberg R. Clinical utility gene card for: Beckwith-Wiedemann Syndrome. Eur J Hum Genet., 2014; 22(3).
27. Gardiner K, Chitayat D, Choufani S, Shuman C, Blaser S, Terespolsky D, Farrell S, Reiss R, Wodak S, Pu S, Ray PN, Baskin B, Weksberg R. Brain abnormalities in patients with Beckwith-Wiedemann syndrome. Am J Med Genet A., 2012; 158A: 1388–94.
28. Gicquel C, Gaston V, Mandelbaum J, Siffroi JP, Flahault A, Le Bouc Y. In vitro fertilization may increase the risk of Beckwith-Wiedemann syndrome related to the abnormal imprinting of the KCN1OT gene. Am J Hum Genet., 2003; 72: 1338–41.
29. Greer KJ, Kirkpatrick SJ, Weksberg R, Pauli RM. Beckwith-Wiedemann syndrome in adults: observations from one family and recommendations for care. Am J Med Genet A., 2008; 146A: 1707–12.
30. Halliday J, Oke K, Breheny S, Algar E, J, Amor D. Beckwith–Wiedemann syndrome and IVF: a case – control study.Am J Hum Genet., 2004; 75: 526–8.
31. Ibrahim A, Kirby G, Hardy C, Dias RP, Tee L, Lim D, Berg J, MacDonald F, Nightingale P, Maher ER. Methylation analysis and diagnostics of Beckwith-Wiedemann syndrome in 1,000 subjects. Clin Epigenetics. Jun 4; 2014; 6(1): 11.
32. Inbar-Feigenberg M, Choufani S, Cytrynbaum C, Chen YA, Steele L, Shuman C, Ray PN, Weksberg R. Mosaicism for genome-wide paternal uniparental disomy with features of multiple imprinting disorders: diagnostic and management issues. Am J Med Genet A. Jan; 2013; 161A(1): 13–20.
33. Kaltenbach S, Capri Y, Rossignol S, Denjoy I, Soudée S, Aboura A, Baumann C, Verloes A. Beckwith-Wiedemann syndrome and long QT syndrome due to familial-balanced translocation t(11;17)(p15.5;q21.3) involving the KCNQ1 gene. Clin Genet. Jul; 2013; 84(1): 78–81.
34. Kantaputra PN, Sittiwangkul R, Sonsuwan N, Romanelli V, Tenorio J, Lapunzina P. A novel mutation in CDKN1C in sibs with Beckwith-Wiedemann syndrome and cleft palate, sensorineural hearing loss, and supernumerary flexion creases. Am J Med Genet A. Jan; 2013; 161A(1): 192–7.
35. Kimura Y, Yasuhiro K, Kimura S. Anesthetic management of two cases of Beckwith-Wiedemann syndrome. J Anesth., 2008; 22: 93–95.

36. Kuroiwa M, Sakamoto J, Shimada A, Suzuki N, Hirato J, Park MJ, Sotomatsu M, Hayashi Y. Manifestation of alveolar rhabdomyosarcoma as primary cutaneous lesions in a neonate with Beckwith-Wiedemann syndrome. J Pediatr Surg., 2009; 44: e31–5.
37. Lam WW, Hatada I, Ohishi S, Mukai T, Joyce JA, Cole TR, Donnai D, Reik W, Schofield PN, Maher ER. Analysis of germline CDKN1C (p57KIP2) mutations in familial and sporadic Beckwith-Wiedemann syndrome (BWS) provides a novel genotype-phenotype correlation. J Med Genet., 1999; 36: 518–23.
38. Li M, Squire JA, Weksberg R. Molecular genetics of Wiedemann-Beckwith syndrome. Am J Med Genet., 1998; 79: 253–9.
39. Maher ER, Afnan M, Barratt CL. Epigenetic risks related to assisted reproductive technologies: epigenetics, imprinting, ART and icebergs? Hum Reprod.., 2003a; 18: 2508–11.
40. Maher ER, Brueton LA, Bowdin SC, Luharia A, Cooper W, Cole TR, Macdonald F, Sampson JR, Barratt CL, Reik W, Hawkins MM. Beckwith-Wiedemann syndrome and assisted reproduction technology (ART). J Med Genet., 2003b; 40: 62–4.
41. Mussa A, Russo S, De Crescenzo A, Freschi A, Calzari L, Maitz S, Macchiaiolo M, Molinatto C, Baldassarre G, Mariani M, Tarani L, Bedeschi MF, Milani D, Melis D, Bartuli A, Cubellis MV, Selicorni A, Cirillo Silengo M, Larizza L, Riccio A, Ferrero GB. (Epi)genotype-phenotype correlations in Beckwith-Wiedemann syndrome. Eur J Hum Genet. Feb; 2016b; 24(2): 183–90.
42. Mussa A, Russo S, Larizza L, Riccio A, Ferrero GB. (Epi)genotype-phenotype correlations in Beckwith-Wiedemann syndrome: a paradigm for genomic medicine. Clin Genet. 2015 Jul 3; Epub ahead of print.
43. Nicholls RD. New insights reveal complex mechanisms involved in genomic imprinting. Am J Hum Genet. [editorial; comment] 1994; 54: 733–40.
44. Niemitz EL, DeBaun MR, Fallon J, Murakami K, Kugoh H, Oshimura M, Feinberg AP. Microdeletion of LIT1 in familial Beckwith-Wiedemann syndrome. Am J Hum Genet., 2004; 75: 844–9.
45. Percesepe A, Bertucci E, Ferrari P, Lugli L, Ferrari F, Mazza V, Forabosco A. Familial Beckwith-Wiedemann syndrome due to CDKN1C mutation manifesting with recurring omphalocele. Prenat Diagn., 2008; 28: 447–9.
46. Pettenati MJ, Haines JL, Higgins RR, Wappner RS, Palmer CG, Weaver DD. Wiedemann-Beckwith syndrome: presentation of clinical and cytogenetic data on 22 new cases and review of the literature. Hum Genet., 1986; 74: 143–54.

47. Sidi, A.; Ohana, P.; Benjamin, S.; Shalev, M.; Ransom, J.H.; Lamm, D.; Hochberg, A.; Leibovitch, I. Phase I/II marker lesion study of intravesical BC-819 DNA plasmid in *H19* overexpressing superficial bladder cancer refractory to *Bacillus* calmette guerin. *J. Urology*, 2008; *180*: 2379–2383.
48. Hanna, N.; Ohana, P.; Konikoff, F.M.; Leichtmann, G.; Hubert, A.; Appelbaum, L.; Kopelman, Y.; Czerniak, A.; Hochberg, A. Phase 1/2a, dose-escalation, safety, pharmacokinetic, and preliminary efficacy study of intratumoral administration of BC-819 in patients with unresectable pancreatic vancer. *Cancer Gene Ther*, 2012; *19:* 374–381.
49. Mizrahi, A.; Czerniak, A.; Ohana, P.; Amiur, S.; Gallula, J.; Matouk, I.; Abu-lail, R.; Birman, T.; Hochberg, A.; Levy, T. Treatment of ovarian cancer ascites by intra-peritoneal injection of diphtheria toxin A chain-*H19* vector: A case report. *J. Med. Case Rep*, 2010; *4*: 228.
50. Yu, L.; Chen, M.; Zhao, D.; Yi, P.; Lu, L.; Han, J.; Zheng, X.; Zhou, Y.; Li, L. The *H19* gene imprinting in normal pregnancy and pre-eclampsia. *Placenta*, 2009; *30:* 443–347.
51. Vaiman, D.; Mondon, F.; Garcès-Duran, A.; Mignot, T.M.; Robert, B.; Rebourcet, R.; Jammes, H.; Chelbi, S.T.; Quetin, F.; Marceau, G. Hypoxia-activated genes from early placenta are elevated in Preeclampsia, but not in Intra-Uterine Growth Retardation. *BMC Genomics*, 2005; *6:* 111.