Beckwith-Wiedemann syndrome

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**Identity**

**Alias**
Exomphalos-macroglossia-gigantism triad

**Inheritance**
Incidence of 7/10^4; given the variable expression of the symptoms, the actual frequency is likely to be higher; generally there is sporadic occurrence of the syndrome (85%); inheritance is mostly maternal (imprinting) with a more severe phenotype after maternal transmission.

**Clinics**

**Note**
Clinically and genetically heterogeneous; three distinct regions on 11p15 have been associated with BWS (BWSCR1/2/3); BWSCR2 seems to be particularly associated with hemihypertrophy.

**Phenotype and clinics**
Multiple features that occur variably; most prominent is the EMG triad (exomphalos-macroglossia-gigantism): apart from the abdominal wall defects and pre- and postnatal growth abnormalities, earlobe pits or creases, facial nevus flammeus, hypoglycemia, renal abnormalities and hemihypertrophy (unilateral overgrowth) are frequently seen.

Patient with Beckwith-Wiedemann syndrome. The face shows the enlarged tongue (macroglossia), the ear the typical earlobe creases - Marcel Mannens.
Neoplastic risk
The increased risk for childhood solid tumours is 7.5% (thousand fold increase); tumours most frequently seen are nephroblastoma (Wilms tumour), adrenocortical carcinoma, rhabdomyosarcoma and hepatoblastoma; clinical risk factors are hemihypertrophy and nephromegaly; genetic risk factors are uniparental disomy (UPD) and H19/IGF2 imprinting defects.

Treatment
In general surgical correction of the abdominal wall defects and macroglossia; monitoring the glycaemia during the first 3 days and early treatment of hypoglycaemia (deleterious for central nervous system) is of importance to avoid further complications; frequent screening for tumour development.

Prognosis
Clinical features tend to become less with ageing; tumour risk decreases strongly after the 4-7th year of birth.

Cytogenetics

Inborn conditions
Paternal duplications of chromosome region 11p15, maternal translocations involving chromosome region 11p15.3-p15.5.

Cytogenetics of cancer
Apart from chromosome 11 aberrations, multiple chromosomes are involved in tumour development; promising prognostic indicators in Wilms tumour might be chromosome 1p and 16q aberrations; other molecular abnormalities associated with an adverse outcome in Wilms tumour are 22q allele loss or P53 aberrations.

Other findings
Note
In 10-20% of BWS cases, uniparental disomy of chromosome region 11p15 is seen, mostly in a mosaic form.

Genes involved and proteins

H19
Alias: D11S813E, D11S878E, ASM, ASM1
Location: 11p15.5
Note
Imprinted, maternally expressed, untranslated mRNA.
DNA/RNA
Description: The human H19 gene is 2.7 kb long and includes 4 small introns; maternally expressed, paternal imprint.

Protein
Description: Untranslated.
Expression: Highly expressed in endodermal and mesodermal embryonic tissues; in adult brain, only in the pons and globus pallidus; in adult tissues, expression is primarily confined to skeletal and cardiac muscle; other tissues are down-regulated postnatal but re-expressed in tumours that express the gene during embryogenesis.
Function: Putative tumour suppressor; proposed regulatory function for IGF2 expression (under debate).

Mutations
Germinal: Hypermethylated in 10-20% of sporadic BWS cases; familial transmission unclear yet; loss of imprinting (LOI) can be induced in deletion mouse models.
Somatic: Hypermethylated in 10-20% of sporadic BWS cases mostly somatic events due to UPD in mosaic form; LOI in tumours.

IGF2 (insulin-like growth factor 2 (somatomedin A))
Alias: IGF-II, somatomedin A, Hs.75963
Location: 11p15.5
DNA/RNA
Transcription: 1356 bp mRNA, paternally expressed, maternal imprint.

Protein
Description: 180 amino acids, 20.14 kDa (unprocessed).
Expression: IGF2 has the highest levels of expression in tissues that are affected by prenatal overgrowth in BWS; the main source of expression is liver; expression depends on promoter usage; P1 is exclusively active in adult liver, whereas P3 and P4 exert their action in liver prenatal; P2 is only active in certain tumour cell lines.
Localisation: Secreted.
Function: Embryonal growth factor, mitogen.
Homology: Belongs to the insulin/IGF/relaxin family.

Mutations
Germinal: Hypomethylated; LOI in sporadic BWS cases; familial transmission unclear yet; BWS phenotype can be induced in igf2 overexpressing mouse models.
Somatic: Hypomethylated, LOI in sporadic BWS cases; mostly somatic events due to UPD in mosaic form; LOI in tumours.

CDKN1C (cyclin-dependent kinase inhibitor 1C)
Alias: KIP2, P57KIP2, P57, CDKN5
Location: 11p15.5
DNA/RNA
Description: 1511 bp messenger, preferentially maternally expressed (paternal imprint).

Protein
Description: 316 amino acids; 32,177 kDa, CDK inhibitory domain, PAPA repeat, conserved C-terminal domain.
Expression: It is expressed in the heart, brain, lung, skeletal muscle, kidney, pancreas and testis; high levels are seen in the placenta, low levels in liver.
Localisation: Nuclear.
Function
Summary: Cyclin-dependent kinase inhibitor 1C is a tight-binding inhibitor of several G1 cyclin/Cdk complexes and a negative regulator of cell proliferation; mutations of CDKN1C are implicated in sporadic cancers and Beckwith-Wiedemann syndrome suggesting that it is a tumour suppressor candidate; in BWS however, no evidence for tumour association was found.
Homology: p21CIP1 CdK inhibitor gene family.
Mutations
Germinal: Mostly maternal, nucleotide substitutions, small deletions.
Somatic: CDKN1C mutations are described in tumour formation; mouse mutation-models reveal part of the BWS phenotype in particular the abdominal-wall defects.

KCNQ1OT1 (KCNQ1 overlapping transcript)
Alias: KCNQ1 overlapping transcript 1, LIT1, KvDMR1, KvLQT1-AS, Long QT intronic transcript 1
Location: 11p15.5
DNA/RNA
Description: Maternally imprinted gene, > 80 kb RNA.
Transcription: Intronic transcript 1, embedded in intron 9 (and 10) of KCNQ1, in opposite orientation; expressed in most human tissues and from the paternal allele, the maternal allele being imprinted through a specific methylation of a CpG island; abnormally expressed in patients with Beckwith-Wiedemann syndrome, independently of IGF2 imprinting; no abnormal imprinting in Wilms tumour.
Protein
Description: 517 amino acids, 60,048 kDa; KRABA domain; similarities to a KRABB domain; SCAN box; nuclear localisation signal KKKR; 2 x 2 zinc-fingers.
Expression: Widely expressed at low levels; expression is highest in testis; splice variants of ZNF215 show tissue specific expression.
Localisation: Nuclear.
Function: Putative transcription factor; ZNF215 was cloned from a region associated with hemihypertrophy, cardiac abnormalities, Wilms tumour and minor BWS features; as such the gene might be responsible for a distinct phenotype in BWS.
Homology: Belongs to the Krueppel family of C2H2-type zinc finger proteins.
Mutations
Germinal: Various amino acids substitutions found in BWS / hemihypertrophy patients; causal relationship with phenotype unclear.
Somatic: In tumours no mutations found so far.

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