Beckwith-Wiedemann Syndrome

Beckwith-Wiedemann syndrome (BWS) is characterized by overgrowth, congenital malformations, and increased risk for embryonic tumors. Clinical features include:

- Macrosomia
- Macroglossia
- Omphalocele
- Visceromegaly
- Neonatal hypoglycemia
- Embryonic tumors (Wilms tumor, hepatoblastoma, neuroblastoma)
- Ear creases/pits
- Hemihyperplasia

Approximately 70% of BWS cases are found to have alterations in DNA methylation at two distinct, differentially methylated regions (DMRs) at 11p15. Segmental paternal uniparental disomy of chromosome 11p15.5 occurs in ~10-20% of BWS cases. DMR1 is located within the telomeric domain (also known as ICR1) and controls the expression of two genes: *IGF2* and *H19*. Hypermethylation of DMR1 occurs in ~2-7% of BWS cases.

DMR2 is located within the centromeric domain (also known as ICR2) and controls the expression of *Lit1, CDKN1C*, and several other genes in the region. Alterations in DNA methylation at either of the DMRs cause aberrant expression of these imprinted genes, leading to BWS. Hypomethylation of DMR2 occurs in ~50% of BWS cases.

Testing Methodology

EGL Genetics uses methylation-specific MLPA (MS-MLPA) to test for hypomethylation of DMR2 and hypermethylation of DMR1, indicative of BWS. One advantage of MS-MLPA is that in addition to detecting DNA methylation abnormalities (epimutations), similar to Southern blot and quantitative methylation sensitive PCR, it also detects copy number variations (CNVs; deletions and duplications) of the 11p15 region, which are estimated to be present in ~10% of patients with BWS. The presence of a CNV can increase the recurrence risk up to 50%, from that of the general population.
**Russell-Silver Syndrome**

Russell-Silver syndrome (RSS) is characterized by intrauterine growth restriction (IUGR) and subsequent postnatal growth deficiency. Other clinical features include:

- Proportionate short stature
- Normal head circumference
- Limb and/or facial asymmetry
- 5th finger clinodactyly
- Triangular faces with prominent forehead and narrow chin

RSS is a genetically heterogeneous condition, associated with gene expression defects on chromosome 7 and 11. At 11p15, there is a differentially methylated region (DMR1) which controls the expression of two genes: IGFB2 and H19. Hypomethylation at DMR1 on the maternal chromosome 11 leads to decreased expression of IGFB2 and causes RSS in 20-35% of clinically diagnosed cases.

In an additional 10% of clinically diagnosed RSS cases, maternal uniparental disomy of chromosome 7 (matUPD7) is also identified, and is believed to result in alterations of imprinted gene expression on chromosome 7; however, a single causative gene for RSS has not been identified.

**Testing Methodology**

EGL Genetics uses methylation-specific MLPA (MS-MLPA) to test for hypomethylation of DMR1 at 11p15. One advantage of MS-MLPA is that it not only detects DNA methylation abnormalities (epimutations), similar to Southern blot and quantitative methylation sensitive PCR, but it will also detect copy number variations (CNVs; deletions and duplications) of the 11p15 region. The presence of a CNV can increase the recurrence risk up to 50%, from that of the general population.

To test for matUPD7, EGL Genetics uses methylation-specific PCR (MS-PCR), which targets two differentially methylated regions on chromosome 7 to detect both methylated (maternal) and unmethylated (paternal) alleles. Parental samples are not required for matUPD7 testing. EGL Genetics offers a RSS panel, which includes H19 methylation and matUPD7 analysis; both may be ordered individually.

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For more information about EGL Genetics:

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