

## Whole Genome CGH+SNP Array and Methylation Analysis for Prader-Willi Syndrome (PWS)

### Clinical Features:

Prader-Willi syndrome is characterized by central hypotonia and feeding difficulties during infancy followed by excessive eating, rapid weight gain, and central obesity in early childhood. Children with PWS exhibit characteristic facial features including bitemporal narrowing, almond-shaped palpebral fissures, and a down-turned mouth. Additional diagnostic characteristics of PWS include global developmental delay, mild to moderate intellectual disability, distinctive behaviors, short stature, hypopigmentation relative to other family members, small hands and feet, and hypogonadism manifesting as genital hypoplasia, incomplete/delayed puberty and, in the majority of cases, infertility.<sup>1,2</sup> The neurobehavioral phenotype in individuals with PWS includes hyperphagia, temper tantrums, aggression, specific repetitive and ritualistic behavior, stealing and lying, skin picking, mood and sleep disturbances.<sup>3,4</sup> Consensus diagnostic criteria were first established in 1993 and revised in 2001 to aid in the recognition of the disorder.<sup>5,6</sup>

Individuals with PWS who have deletions of the PWCR have an increased risk for depression, a higher performance IQ, and greater incidence of hypopigmentation compared to those with maternal UPD or imprinting errors. Individuals with maternal UPD have been reported to have a higher incidence of psychosis and autistic behaviors but a higher verbal IQ compared to those with PWCR deletions.<sup>3,10,11</sup>

### Inheritance Pattern/Genetics:

PWS is an imprinting disorder caused by one of three known mechanisms that result in absence of expression of specific genes on the paternally derived chromosome 15 within bands 15q11.2-q13.1. Although the clinical features are distinct from those in Angelman syndrome, both are caused by abnormal genomic imprinting status of the same proximal 15q genomic region, which contains several highly homologous low-copy repeats that confer susceptibility to recurrent deletions. In addition, genes in this region undergo epigenetic silencing by methylation, such that some genes are only expressed on the paternal chromosome and others on the maternal chromosome.

In PWS the paternal chromosome-specific expression of genes in 15q11.2-15q13.1 (called the Prader Willi syndrome chromosome region or PWCR) is compromised in one of three ways. The most common cause of PWS (70%-75% of patients) is a recurrent deletion extending from 15q11.2 to 15q13.1 on the paternally inherited chromosome. Maternal uniparental disomy accounts for 25-30% of PWS cases, while approximately 1-3% of patients have an imprinting error that establishes a maternal chromosome-specific methylation pattern despite the

presence of both parental chromosomes.<sup>1, 2</sup> Imprinting errors leading to abnormal methylation can be caused by a microdeletion within the imprinting center in 15q11.2 (8-15% of patients with an imprinting defect) or by an unknown mechanism that inappropriately silences genes regardless of the parental origin of the chromosome.<sup>7</sup> The majority of cases are de novo with a recurrence risk of <1%; however, the recurrence is 50% for an inherited imprinting center deletion.

Whole-genome CGH+SNP array can detect the common 15q11.2-15q13.1 deletion, maternal UPD, and imprinting center deletions (but not other types of imprinting errors). Together, these three causes account for > 95% of patients with PWS.

### Test Methods:

The parent-specific methylation imprint of the PWCR can be determined by the methylation multiplex ligation-dependent probe amplification (MS-MLPA) assay. Methylation analysis is available as a first-line test for patients with a suspected diagnosis of PWS or can be performed as reflex testing following normal array results for individuals with a high suspicion of PWS to identify UPD or imprinting errors. GeneDx does not offer imprinting center sequence analysis. However, patients with abnormal methylation studies but normal whole-genome CGH+SNP array are assumed to have an imprinting error.

Whole-genome CGH+SNP array is also available to identify copy number variants (CNVs) in the unique sequence of the genome and can therefore also identify other genomic imbalances that may produce a PWS-like phenotype (e.g., 1p36 deletion or 6q16 deletion).

### Test Sensitivity:

MS-MLPA can detect imprinting abnormalities in greater than 99% of individuals with PWS. Whole-genome CGH+SNP array can detect the common 15q11.2-15q13.1 deletion, maternal UPD, and imprinting center deletions (but not other types of imprinting errors). Together, these three causes account for > 95% of patients with PWS.

### References:

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