Prader Willi and Angelman Syndrome PCR Tests

The UNC Hospitals Molecular Genetics Laboratory offers a PCR test for defects of the gene region on chromosome 15 associated with Prader Willi and Angelman syndromes.

Molecular basis of the diseases: Prader-Willi and Angelman syndromes involve an imprinted region on chromosome 15 where genes are differentially methylated and therefore differentially expressed depending on the parental origin of the chromosome. Besides an imprinting error, gene deletion or uniparental disomy are other mechanisms for loss of gene expression. Prader-Willi syndrome results from absence (or lack of expression) of genes that are normally expressed from the paternal allele, whereas Angelman syndrome is caused by absence (or lack of expression) of genes normally expressed from the maternal allele. These are referred to as "reciprocal syndromes".

Prader-Willi syndrome (PWS) is a common syndromal cause of obesity. Incidence is estimated to be 1:20,000. In infancy PWS manifests with profound hypotonia, mild prenatal growth retardation, poor feeding and failure to thrive. Starting at about 12 to 18 months of age, patients exhibit uncontrolled overeating, and obesity becomes a major diagnostic feature and a major health problem. Other common clinical features include short stature, mild mental retardation, gross motor delay, characteristic facial features and behavioral problems. Deletions in the paternally inherited chromosome 15q11q13 account for approximately 70% of PWS cases. Maternal uniparental disomy (UPD) and imprinting defects in the 15q region are other causes of PWS that are detectable by the new PCR assay.

Angelman syndrome (AS) is characterized by severe motor and intellectual retardation, ataxia, absence of speech, hyperactivity, hypotonia and frequent smiling with episodes of unprovoked laughter. Incidence is estimated at 1:20,000. The majority of cases (70-75%) are caused by deletions within the maternally inherited chromosome 15q11q13. Paternal UPD and imprinting defects of 15q account for a small proportion of cases (about 10%). Another 10% are caused by mutation of the ubiquitin ligase gene UBE3A on 15q. In some AS cases, the molecular defect has not yet been identified.

Laboratory Testing and Reporting: The preferred sample is EDTA anticoagulated blood (lavender-top) which may be refrigerated up to 48 hours before analysis by methylation-specific PCR and capillary gel electrophoresis. Results of testing for the methylated (maternal) SNRPN allele and the unmethylated (paternal; expressed) SNRPN allele located on 15q11q13 are interpreted by a pathologist. Amplification of maternal alleles only (lack of paternal alleles) is consistent with PWS. Amplification of paternal alleles only (lack of maternal alleles) is consistent with AS. Amplification of both alleles is normal but does not rule out either diagnosis. The test detects approximately 99% of patients with PWS and about 80% of those with AS. It detects deletion, UPD and imprinting defects within the PWS/AS region on chromosome 15, but it does not distinguish between these different molecular aberrations. Our UNC Cytogenetics Lab

performs FISH to determine whether deletion is the operative mechanism, and karyotype to screen for other syndromes with overlapping clinical features.

References:

1. Muralidhar B, Butler MG. Methylation PCR Analysis of Prader-Willi Syndrome, Angelman Syndrome, and Control Subjects. American Journal of Medical Genetics 1998, 80:263-265
2. On-line Mendelian Inheritance In Man (OMIM) http://www.ncbi.nlm.nih.gov/omim/ Prader-Willi Syndrome OMIM #176270, Angelman Syndrome OMIM #105830

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