Macrocephaly and Overgrowth Syndromes Panel: Sequencing and CNV Analysis

Test Code: MM261
Turnaround time: 6 weeks
CPT Codes: 81321 x1, 81401 x1, 81403 x1, 81404 x1, 81406 x1

Condition Description

Macrocephaly is defined as a head circumference, which is 2 standard deviations larger than the average when matched for age and sex. It refers to an abnormally large head inclusive of the scalp, cranial bone, and intracranial contents. Macrocephaly can arise due to a true enlargement of the brain (megalencephaly) or other conditions such as hydrocephalus and be either syndromic or non-syndromic. The genetic subtypes of macrocephaly include familial forms of macrocephaly, autism, syndromic associations such as PTEN hamartoma syndrome, Noonan syndrome, Sotos syndrome, and metabolic disorders such as glutaric aciduria type 1 and D-2-hydroxyglutaric aciduria.

Reference:

Genes

AKT1, AKT2, AKT3, CDKN1C, CUL4B, DNMT3A, EZH2, GLI3, GNAQ, GPC3, MED12, MTOR, NFIX, NSD1, PHF6, PIK3CA, PIK3R2, PTEN, RNF135, UPF3B

Indications

This test is indicated for:

- Patients with a clinical diagnosis of macrocephaly or other overgrowth syndrome.

Methodology

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

**Copy Number Analysis:** Comparative analysis of the NGS read depth (coverage) of the targeted regions of genes on this panel was performed to detect copy number variants (CNV). The accuracy of the detected variants is highly dependent on the size of the event, the sequence context and the coverage obtained for the targeted region. Due to these variables and limitations a minimum validated CNV size cannot be determined; however, single exon deletions and duplications are expected to be below the detection limit of this analysis.

Detection

**Next Generation Sequencing:** Clinical Sensitivity: Unknown. Pathogenic variants in the promoter region, some pathogenic variants in the introns and other regulatory element mutations cannot be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype.

Analytical sensitivity for sequence variant detection is ~99%.

**Copy Number Analysis:** The sensitivity and specificity of this method for CNV detection is highly dependent on the size of the event, sequence context and depth of coverage for the region involved. The assay is highly sensitive for CNVs of 500 base pairs or larger and those containing at least 3 exons. Smaller (< 500 base pairs) CNVs and those that involving only 1 or 2 exons may or may not be detected depending on the sequence context, size of exon(s) involved and depth of coverage.

Specimen Requirements

Related Tests

- Macrocephaly and Overgrowth Syndromes: Sequencing and Beckwith-Wiedemann Syndrome Methylation Panel
- Macrocephaly and Overgrowth Syndrome: Deletion/Duplication Panel