SNP-Microarray for postnatal constitutional disorders assay:

Test Ordering Information

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<th>Test Information (v1_030112):</th>
<th>SNP-Microarray Assay for postnatal constitutional disorders (CMGDL test code 5001)</th>
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<td>CPT Codes</td>
<td>83890, 83900, 83892, 88386</td>
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<td>For additional information</td>
<td>please refer to the CMGDL <a href="http://www.medgen.med.miami.edu">www.medgen.med.miami.edu</a></td>
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Clinical Significance and Test Indications

The CMGDL SNP-Microarray assay is a chromosomal microarray. Chromosomal microarray is increasingly utilized for genetic testing of individuals with unexplained developmental delay/intellectual disability (DD/ID), autism spectrum disorders (ASD), or multiple congenital anomalies (MCA). A 2010 review by Miller et al has defined a Consensus Statement for the use of Chromosomal Microarray testing as First-Tier Clinical Diagnostic Test for Individuals with Developmental Disabilities or Congenital Anomalies in place of G-banded karyotyping. The CMGDL SNP-Microarray assay has probes that can detect imbalances related to common microdeletion/microduplication syndromes, subtelomeric deletions or duplications at loci throughout the genome. This assay can detect imbalances that may not be well described and also further define chromosomal breakpoints in imbalances that are already known.

Test Indications:
The CMGDL SNP-Microarray assay is indicated in any patient with a suspected chromosome imbalance. In particular, this test is indicated for individuals with

- unexplained developmental delay/intellectual disability
- autism spectrum disorders
- multiple congenital anomalies including but not limited to craniofacial and oral abnormalities, birthmarks or pigment abnormalities

Other test indications include failure to thrive, seizures and congenital heart defects.

When ordered after abnormal karyotype results, the SNP-Microarray can help to better define a chromosome abnormality and identify possible genes involved.

Specimen Requirements

1.0 (minimum) to 5.0 ml of whole blood

Collection Tube: Lavender Top Tube /w EDTA

Handling: Room Temp- specimen processed within 72 hours

Turn-Around Times

14 to 28 business days.

Methodology and Assay Characteristics

This test is performed using the Illumina HumanOmni1-Quad BeadChip (Illumina, CA) array. Samples single nucleotide polymorphism (SNP) genotyping is performed to determine presence of Copy Number Variation (CNV) and/or Loss of Heterozygosity (LOH). The HumanOmni1-Quad BeadChip array is based on the Illumina Infinium technology and delivers a dense genome-wide coverage, highly comprehensive for disease-associated content. The BeadChip contains more than one million markers derived from the 1000 Genome project. The BeadChips are imaged by using the iScan Reader (Illumina, CA). The image data file obtained is then downloaded into the GenomeStudio Software (Illumina, CA) and used to perform primary data analyses, such as raw data normalization, clustering, and genotype calling. The Karyostudio (Illumina, CA) software is used to scrutinize gene content for Copy Number Variation (CNV) and/or Loss of Heterozygosity (LOH), in particular in reference to relevant clinical association. The analysis is based on the GRCh36/hg18 assembly.

CMGDL categories of clinical significance and results reporting. The CMGDL is adopting ACMG-recommended terminology to facilitate unambiguous communication of clinical significance throughout the medical community. The CMGDL will assign any CNV/LOH reported in the patient to one of three main categories of significance. Pathogenic: the CNV is documented as clinically significant in multiple peer-reviewed publications, even if penetrance and expressivity of the CNV are known to be variable. Uncertain clinical significance: at the time of reporting, insufficient evidence is available for unequivocal determination of clinical significance of a CNV. Benign: the CNV has been reported in multiple peer-reviewed publications or curated databases as a benign variant, particularly if the nature of the copy number variation has been well characterized and/or the CNV represents a common polymorphism. Note: Benign CNVs are not reported by the CMGDL.
Positive evaluation criteria for inclusion in a CMGDL clinical report:
- CNV loss of >200 kb or gain >500 kb of regions with at least one disease-causing OMIM annotated gene or within a region of clear clinical significance;
- UPD testing is recommended for patient results demonstrating a long contiguous region of homozygosity in a single chromosome of >20 Mb interstitially or >10 Mb telomERICally (15 and 8 Mb, respectively, for imprinted chromosomes)

Loss of heterozygosity is often not reported unless clinical significance is known or highly suspicious. The CMGDL has designed clinical cutoffs to limit abnormal tests that are not clinically significant, while maximizing the reporting of clinically significant results.

Test Limitations
This assay is not designed to detect balanced chromosomal changes or other CNVs (insertions or deletions) that are in regions not well covered with probes. Also, it is not used to reliably detect low level mosaicism. Small genetic changes, such as point mutations and small size deletions within a single gene, may not be detected with this technology.

Results of this test should be interpreted in the context of clinical presentation and in consultation with a licensed clinical geneticist.

Many conditions that may be detected by the SNP-Microarray assay can be caused by other genetic changes and cannot be clinically ruled out based on a normal SNP-Microarray SNP test. If a specific genetic diagnosis is suspected, please consult with a certified clinical geneticist for additional testing that may be recommended.

Detection of some CNVs, particularly deletions, may reveal carrier status for recessive disorders in the deletion interval. Comprehensive reporting of heterozygous recessive mutations is outside the scope of the intended use of the CMGDL SNP-Microarray assay and it is not be adopted by the CMGDL. Consequently, recessive carrier status of tested individuals is not be disclosed by the CMGDL on a routine bases. Any clinical concern for recessive disorders should be communicated to the CMGDL for appropriate consideration in advance of testing.

This test may identify mutations unrelated to the patient’s reason for referral that may be diagnostic of a presymptomatic or adult onset or clinically undetected condition.

This test was developed and its performance determined by the CMGDL. It has not been cleared or approved by the U.S. Food and Drug Administration. This test is used for clinical purposes. Pursuant to the requirements of CLIA ’88, this laboratory has verified the test accuracy and precision. Genetic testing using the methods applied by the CMGDL is expected to be highly accurate. However, the chance of a false positive or a false negative result, due to laboratory errors incurred during any phase of the testing, cannot be completely excluded.

Related Tests (visit our website at www.medgen.med.miami.edu)

References:
-Genome Res (2009) 16:1682-1690;
-DatabasE of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER), https://decipher.sanger.ac.uk/application/
-Database of Genomic Variants (DGV), http://projects.tcag.ca/variation/
-Database of Structural Variation, dbVAR ; http://www.ncbi.nlm.nih.gov/dbvar/
-International Standard Cytogenomic Array Consortium, https://isca.genetics.emory.edu
-UCSC Genome Bioinformatics Site, http://genome.ucsc.edu/

Clients must contact the Genetics Billing Office at (305)-243-6583 to establish a “Client Account Number” prior to forwarding specimens to the laboratory.