

Cytogenomic SNP Microarray (CMASNP)

DETECTS UNBALANCED CHROMOSOMAL ABNORMALITIES (LOSS AND/OR GAIN OF DNA) AND LONG CONTIGUOUS STRETCHES OF HOMOZYGOSITY IN POSTNATAL CONSTITUTIONAL CASES WITH UNEXPLAINED ABNORMAL PHENOTYPES (E.G., INTELLECTUAL DISABILITY, DEVELOPMENTAL DELAY, DYSMORPHIC FEATURES, CONGENITAL ANOMALIES, AND AUTISM)

Test Highlights

- This array platform contains DNA sequences representing specific regions of the human genome designed to detect both copy-number variation (loss or gain of DNA) and loss of heterozygosity (LOH).
- This platform offers excellent performance and exceeds current guidelines for specificity, sensitivity, and resolution across the genome.
- This test is designed to identify hundreds of common microdeletion/microduplication syndromes, subtelomeric deletions or duplications, and LOH at thousands of loci throughout the genome.
- Patient DNA is hybridized to the chip in order to:
 - Identify unbalanced chromosomal abnormalities (copy-number variants [CNVs]) undetectable by conventional chromosome analysis
 - Further characterize cytogenetic abnormalities identified by conventional cytogenetic methods
 - Detect areas of the genome that have long contiguous stretches of homozygosity (LCSH)
- The very high probe density present on this chip provides the broadest coverage of RefSeq genes on a single array, with average probe spacing of one probe per 880 bp over all genes and increased density over disease-causing OMIM, cancer, and ISCA constitutional genes.
- The large number of single-nucleotide polymorphisms (SNPs) also present on the array allows detection of gene-level, copy-neutral LOH, uniparental disomy (UPD), and regions “identical-by-descent,” which may indicate increased risk of a recessive condition.
- Fluorescence in situ hybridization (FISH) or routine chromosome studies on parental blood specimens may be recommended in order to identify familial rearrangements or variants detected by microarray.

Clinical Background

- Many abnormal phenotypes are associated with chromosomal imbalances. Conventional cytogenetic techniques are limited in their ability to detect or characterize subtle or cryptic

abnormalities and cannot detect LCSH that may be suggestive of UPD or an increased risk of a recessive condition.

- Since these abnormalities can be identified using microarray-SNP analysis, array-based testing is now recommended as a first-tier test for the indication of intellectual disability, developmental delay, dysmorphic features, congenital anomalies, and autism.
- The identification of specific abnormalities by array may be helpful in diagnosis and/or medical management of the patient.

Indications for Ordering

- Individuals with an unexplained abnormal phenotype, such as:
 - Autism/autism spectrum disorder (ASD)/pervasive developmental disorder (PDD)
 - Developmental delay/intellectual disability, with or without dysmorphic features
 - Multiple congenital anomalies
 - Heart defects
 - Epilepsy/seizures
- Screening for microdeletions and microduplications associated with known syndromes/clinical phenotypes
- Screening for unique microdeletions and microduplications not associated with known syndromes
- Identification of LCSH that may be suggestive of UPD or increased risk of a recessive disorder
- Further characterization of a chromosomal abnormality, including marker chromosomes, ring chromosomes, apparent terminal deletions, unbalanced translocations, or subsequent analysis of an apparently balanced de novo rearrangement seen in patients with abnormal phenotypes

Additional Ordering Notes

- **All samples must have a clinical indication for testing.** Please complete the Patient History for Genomic Microarray Form, which can be found at <http://www.aruplab.com/Lab-Tests/Genetics/Genomic-Microarray-Patient-Form-ARUP-IBCA.pdf>, and submit it to the laboratory along with the patient sample.
- Sample requirements: 3 mL (minimum 1 mL in newborns) whole blood in sodium heparin (green-top) tube, shipped at room temperature.

- High-quality DNA from blood may also be accepted. A minimum of 1 µg of DNA (concentration between 100 ng/µl and 400 ng/µl) will be required, with an OD260/280 ratio of 1.8 to 2.0 and an OD260/230 ratio of >1.5.
- Unacceptable conditions: clotted or frozen specimens; DNA must not be degraded.

Interpretation

- A written summary and interpretation of the microarray findings are provided.
- Gains and losses are reported based on genomic content.
- Duplications smaller than 400 kb and deletions smaller than 50 kb may not be investigated or reported. CNVs devoid of relevant gene content or reported as common findings in the general population may not be reported.
- Regions of homozygosity are reported when a single LCSH is greater than 8 Mb to 15 Mb (dependent upon chromosomal location and likelihood of imprinting disorder), or when the total autosomal LCSH proportion is greater than 3% (only autosomal LCSH greater than 3 Mb are considered for this estimate).
- Test results are often complex; a copy-number change of uncertain clinical significance may be detected.

Limitations

- This technique will detect only copy-number imbalances and LCSH in the nuclear genome. It will not detect balanced rearrangements, such as translocations, inversions, and balanced insertions. Additionally, base-pair mutations, imbalances of the mitochondrial genome, genomic imbalances below the resolution of this array platform, and aberrations in regions of the genome not represented on the array platform may not be detected. Low-level mosaicism may also not be detected.
- As this array accurately detects copy-number changes below the resolution of FISH technologies, parental testing may not be available by alternative methodologies.

Methodology

- The technique involves DNA preparation, amplification, purification, labeling, hybridization, washing, array scanning, analysis, and interpretation.
- Copy-number changes are calculated based on hybridization

signal intensity data from the experimental sample relative to data derived from phenotypically normal individuals.

- This cytogenomic-SNP test is run on the Affymetrix® CytoScan™ HD array, which interrogates the entire genome using more than 2.6 million markers for copy-number analysis and approximately 750,000 SNPs.
- Data is analyzed using Affymetrix Chromosome Analysis Suite software (ChAS).

Related Tests

- Chromosome Analysis Peripheral Blood with Reflex to Microarray (2005763)
- Conventional cytogenetic analysis (karyotyping) will detect large additions, deletions, and rearrangements, including balanced translocations and inversions. Conventional cytogenetics generally cannot detect duplications and deletions smaller than approximately 5 Mb to 10 Mb (5,000 kb to 10,000 kb) in size (the average size of a chromosomal band) or larger changes that do not alter the karyotype banding pattern. Other molecular techniques (e.g., gene-scanning or PCR-based assays) are more sensitive than genomic microarray for detecting many intragenic alterations, such as point mutations and very small deletions or duplications, but are highly specific and restrictive for the genetic site or gene of interest.

References

1. Miller DT, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet.* 2010;86(5):749–64.
2. Kearney HM, et al. American College of Medical Genetics recommendations for the design and performance expectations for clinical genomic copy number microarrays intended for use in the postnatal setting for detection of constitutional abnormalities. *Genet Med.* 2011;13(7):676–9.
3. Kearney HM, et al. American College of Medical Genetics standards and guidelines for interpretation and reporting of postnatal constitutional copy number variants. *Genet Med.* 13(7):680–5.

Test Information

2003414 Cytogenomic SNP Microarray

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.

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