Chromosomally Microarray Analysis (CMA)

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**CLINICAL APPLICATION**

Chromosomally Microarray Analysis (CMA) testing is now available through PAML for the clinical diagnosis of unbalanced chromosomal aberrations (gains and losses) and uniparental disomy (UPD) in patients with:

- Developmental delay/intellectual disability (DD/ID)
- Multiple congenital anomalies (MCA)
- Autism spectrum disorders (ASD)
- Growth retardation, speech delay and other indications

CMA is a complimentary assay to conventional karyotyping for cases in which an unbalanced chromosomal abnormality such as sub-microscopic microdeletion or microduplication of genomic regions are suspected. CMA is also recommended for patients whose clinical features do not conform to well-characterized genetic syndromes. Identifying genomic imbalances in these patients can help by providing a definitive diagnosis and potential interventional and preventative treatments based on published data on other patients with similar genomic imbalances. The whole genome CMA provides a shot-gun approach that eliminates costly and stepwise screening of individual genes and loci. CMA findings can also help by identifying additional medical specialties that are needed for optimal patient care and treatment.

**CLINICAL BACKGROUND**

The entire human genome packaged in 46 chromosomes is approximately 3000 megabase pairs (Mbp of DNA in length). Cytogenetic analysis (karyotyping) can detect balanced and unbalanced rearrangements at resolutions above the five million to ten million base pair (5–10 Mbp) level of resolution. In recent years, microarray comparative genomic hybridization (CMA) has been instrumental in increasing the diagnostic yield approximately four to five–fold over metaphase chromosome analysis. In separate studies CMA has been shown to detect pathogenic rearrangements in 15% to 20% (range from 12.2% to 28.9%) of patients with DD/ID, ASD, multiple anomalies, growth retardation, and other indications. FISH assays, while limited to a specific locus of the genome for any given assay, increases the resolution exponentially and can identify rearrangements of a locus of interest for a known syndrome at 150,000 to 200,000 base pair (150–200 Kb) resolution and above. In contrast, CMA is not limited to a few loci; CMA can detect gains or losses of genomic material as small as 10,000 to 150,000 base pairs (10–150 Kb) throughout the genome in a single assay. The addition of CMA can complement conventional metaphase cyogenetic and FISH analysis.

**RESULT INTERPRETATION**

Chromosome imbalance or copy number variations (CNVs) observed through CMA testing are classified into three categories: 1) Pathogenic, 2) Benign, and 3) Results of uncertain significance.

Pathogenic results include copy number variations that are known to, or are most likely to, explain a patient’s phenotype. The pathogenic category includes CNVs that are consistent with microdeletion and microduplication syndromes or which include gene(s) known to cause a particular phenotype due to either haploinsufficiency or copy number gain.

Benign category includes CNVs that are considered benign polymorphisms in the general population. Those polymorphisms are described in published studies that support their benign nature. Since CMA testing detects benign CNVs in nearly all individuals, benign CNVs are generally not included on the clinical report. Thus, a normal CMA test report indicates that no clinically significant copy number changes were detected.

Results of uncertain significance, which are a byproduct of our evolving understanding of CNVs in humans, are occasionally encountered. This is due to lack of sufficient scientific data to confidently support a categorization into either the pathogenic or benign categories. Testing parental samples can be a useful tool to help assess the clinical significance of CMA results.

If CNVs are inherited from a phenotypically normal carrier parent, the CNV is likely not responsible for the abnormal phenotype in the patient. If a CNV of uncertain clinical significance is a new mutation not inherited from either parent, the likelihood that the CNV is contributing to the patient’s phenotype is increased. As a member of the International Standards for Cytogenomic Array Consortium, we work closely with more than 160 international laboratories to develop standards and guidelines for accurate interpretation of these CNVs in the clinical setting.

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**Quick Facts**

- Detects unbalanced chromosomal aberrations (gains and losses).
- More than 2.6 million unique SNP and CNV oligonucleotide probes spanning the whole genome.
- Affymetrix Cytoscan HD Oligonucleotide array.
- Combination of Single Nucleotide Polymorphism and Copy Number Variant probes.
- Improved diagnostic yield four to five–fold over conventional cytogenetics.
- Suitable for patients with DD/ID, MCA, ASD.
- Detects Uniparental disomy (UPD).
- Not to replace karyotyping or FISH when balanced rearrangements chromosome aneuploidy or microdeletion syndromes are suspected.

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TEST TECHNOLOGY

PAML's Chromosome Microarray assay utilizes an Affymetrix SNP oligonucleotide array. This array is composed of 2.6 million unique oligonucleotide strands of DNA arranged on a glass slide that correspond to well-characterized areas of human genome (microarray chip).

Patient DNA is hybridized to the array and the resulting pattern is compared to the DNA content of normal control individuals. Variations in the hybridization profiles are analyzed to detect unbalanced gain and loss of genetic material (deletions, duplications and other unbalanced structural abnormalities).

In addition, through the use of single nucleotide polymorphism (SNP) probes, copy number neutral rearrangements resulting in loss of heterozygosity (LOH) and uniparental disomy (UPD) are also detected.

Combination of SNP and copy number variant (CNV) probes in the same array leads to a much better detection rate for low level mosaicism.

COMMENTS

Metaphase cytogenetic analysis must be performed for patients who may be carriers of balanced chromosomal rearrangement (reciprocal translocations, inversions or insertions) or low-level mosaicism.

Not to replace karyotyping or FISH when balanced rearrangements chromosome aneuploidy or microdeletion syndromes are suspected.

Chromosomal microarrays are not recommended in cases in which whole chromosome aneuploidy is suspected such as trisomy of chromosomes 13, 18 and 21 or sex chromosomes aberrations such as Turner syndrome (45,X) or Klinefelter syndrome (47,XXY).

FISH probes are routinely used for diagnostic evaluation of well delineated microdeletion and microduplication genetic syndromes such as 22q11 syndrome (DiGeorge/VCFS) or Williams syndrome.

SELECTED REFERENCES

