Prenatal Chromosomal Microarray (CMA) For Copy Number Abnormalities and Uniparental Disomy in Fetuses with Ultrasound Anomalies

Comparative Genomic Hybridization (CGH) and Single Nucleotide Polymorphism (SNP) Array

Clinical Utility:

The sensitivity of chromosomal microarray (CMA) in a prenatal setting has recently been shown by a large multicenter study to be 5.8% greater than conventional cytogenetics in fetuses with ultrasound abnormalities. Furthermore, in pregnancies due to advanced maternal age or abnormal maternal serum screen, an additional 1.7% of cases were found to have a clinically relevant copy number change not detected by karyotyping.[1] The American College of Obstetricians & Gynecology and the Society for Maternal Fetal Medicine have recommended CMA specifically for fetuses with abnormal ultrasound findings.[2-4] Additionally, their joint Committee Opinion states that CMA can be performed in fetuses without abnormal ultrasound findings if the mother is undergoing invasive prenatal diagnostic testing and that CMA should not be restricted to women aged 35 years and older.[2] GeneDx offers two chromosomal microarrays for prenatal testing: a targeted CMA and a whole-genome CMA. Both CMAs utilize a combined CGH and SNP array platform for detection of copy number changes and uniparental disomy, respectively. The table below summarizes the two chromosomal microarrays offered at GeneDx.

The prenatal targeted CMA contains 42,000 oligonucleotide probes placed throughout the genome and within 100 common or novel microdeletion and microduplication syndromes as well as those involving subtelomeric regions and any other intrachromosomal region greater than 1.5 Mb. Several genes associated with Mendelian disorders that are detectable prenatally are covered at the exon-level for detection of possible intragenic deletions or duplications. In addition, this array contains 18,000 SNP probes covering only those chromosomes known to contain imprinted genes (specifically, chromosomes 6, 7, 11, 14, 15, and 20) and can provide information regarding some types of uniparental disomy (UPD) (see test limitations).

The whole-genome CMA contains 118,000 oligonucleotide probes placed throughout the genome and within more than 220 targeted regions for detection of copy number variants (CNVs). This CMA detects, on average, CNVs of greater than 200 kb across the entire genome and between 500 bp to 15 kb in targeted regions. Approximately 60 genes associated with neurodevelopmental disorders have enhanced coverage for detection of pathogenic partial gene copy number variants. In addition, this CMA contains 66,000 SNP probes throughout the genome and can provide information about some types of UPD on all chromosomes. Regions of homozygousity (ROH) is reported if there is at least one region $\geq$10 Mb or two regions each $\geq$ 8 Mb, suggesting identity by descent.

GeneDx recommends parental testing when a proband is found to have a genomic imbalance. Parental analysis is used to evaluate the inheritance of an abnormality (familial or de novo) and may also clarify the clinical significance of copy number changes. GeneDx uses fluorescence in situ hybridization (FISH), quantitative PCR (qPCR), multiplex ligation-dependent probe amplification (MLPA), targeted microarray, or G-band chromosome analysis, as appropriate, for parental analysis. For clinically well-characterized genomic imbalances, parental analysis is available as a separate test for an additional cost. For genomic imbalances of unclear significance, GeneDx offers free parental analysis if clinical information on the parents is provided.

Test Methods and Sensitivities:

Prenatal Targeted Chromosomal Microarray (CMA):

Screens for 100 common or novel microdeletion and microduplication syndromes, any other genomic imbalances greater than 1.5 Mb, and uniparental disomy of chromosomes 6, 7, 11, 14, 15, or 20.

Array Design for Prenatal Targeted Chromosomal Microarray (CMA):
60,000 probes (copy number + SNP)
Detects CNVs of 100 kb in 100 targeted regions and 1.5 Mb in the rest of the genome.
Includes exon-level coverage of some genes associated with Mendelian disorders that are prenatally detectable.
Maternal cell contamination studies are performed concurrently.
Result Confirmation: FISH, qPCR, MLPA or array

Prenatal Whole-Genome Chromosomal Microarray (CMA):

Detects genomic imbalance greater than 200 kb throughout the entire genome and stretches of homozygosity, suggestive of uniparental disomy or identity-by-descent (i.e. parental consanguinity). Regions of homozygousity (ROH) is reported if there is at least one region $\geq$10 Mb or two regions each $\geq$ 8 Mb, suggesting identity by descent.

Array Design for Prenatal Whole-Genome Chromosomal Microarray (CMA):
180,000 probes (copy number + SNP)
Detects CNVs of 500 bp to 15 kb in >220 targeted regions and >200 kb in the rest of the genome.
Includes enhanced coverage for detection of pathogenic partial gene copy number variants in approximately 60 genes associated with neurodevelopmental disorders.
Maternal cell contamination studies are performed concurrently.
Result Confirmation: FISH, qPCR, MLPA or array

Test limitations:

CMA cannot detect balanced chromosomal rearrangements (inversions, balanced insertions, and reciprocal translocations), polyploidy, low-level mosaicism (<20%), and rearrangements in repeat sequences (e.g., short arms of acrocentric chromosomes and some heterochromatic regions). CMA cannot identify pure uniparental heterodisomy (i.e., can only identify uniparental isodisomy or segmental heterodisomy). Normal findings at a specific locus do not rule out the diagnosis of a genetic disorder associated with that locus since another abnormality may be present but undetectable by CMA. Test result interpretation may be confounded by the detection of copy number variants (CNV) present in the general population. The targeted SNP coverage in the prenatal targeted CMA limits detection of homozygosity in the entire genome; therefore, consanguinity will not be reported. Test result interpretation may be confounded by the present of significant maternal-cell contamination.

References:

1. Wapner, R.A. (2012) AJOG 206(1) Supplement:S2 .
2. ACOG Committee Opinion No. 581. Obstet & Gynecol 122:1374-1377, 2013.
3. Vialard F et al. Fetal Diagn Ther 25:277-284, 2009.
4. Rickman L et al. Eur J Med Genet 48:232-240, 2005)