MicroarrayDx: Whole-Genome Chromosomal Microarray (CMA) For Copy Number Abnormalities and Uniparental Disomy

Routine chromosomal analysis for constitutional developmental disorders has shifted from G-banded karyotype analysis to chromosomal microarray (CMA) as a first-tier test.[1,2] The clinical sensitivity of CMA in patients with developmental delay, intellectual disability, and/or congenital anomalies is at least 10% higher than that associated with karyotyping and subtelomere FISH. CMA can detect pathogenic copy number variation (CNV) in up to 15% of individuals with intellectual disability and developmental delay when a karyotype is normal.[3,4,5] In addition, 7% of individuals with non-syndromic autism and as many as 27% of individuals with autism spectrum disorders and additional congenital anomalies carry pathogenic CNVs detectable by CMA.[6,7,8] A variety of CNVs are also reported to cause epilepsy.[9] The addition of probes containing single nucleotide polymorphisms (SNP) to a microarray allows for the detection of regions of homozygosity (ROH), which may result from uniparental disomy (UPD). While relatively rare, some cases of UPD are relevant to disorders of imprinting as well as to recessive disorders caused by inheritance of a variant within an ROH block.[10,11]

Test Indications

(1) Primary screening test for diagnosis of persons with dysmorphic features, birth defects, intellectual disability/developmental delay, autism spectrum disorder, multiple congenital anomalies, seizures or any suspicion of chromosomal imbalance.
(2) Suspected whole-chromosome or segmental UPD related to an imprinting disorder or to an autosomal recessive disorder.
(3) Determine breakpoints of chromosomal rearrangements previously detected by conventional cytogenetic methods or technologies that do not provide genome-wide coverage.

Test Method and Sensitivity

The MicroarrayDx whole-genome CMA contains 2.67 million probes placed throughout the genome that are spaced on average 880 bases apart in genic regions and approximately 1700 bases apart in non-genic regions. There are 1.9 million non-polymorphic probes for detection of copy number variants (CNVs). The array can identify deletions >25 kb including at least 25 consecutive probes and duplications >50 kb including at least 50 consecutive probes. In addition, this CMA contains 750,000 SNP probes spread throughout the genome, which provide information about regions of homozygosity (ROH) including uniparental disomy (UPD) and identity by descent (parental consanguinity) on all autosomes. Autosomal ROH is reported when at least one region of homozygosity of >10 Mb or two regions that are each >8 Mb are identified. Any additional ROH calls >5 Mb are included in the report.

Limitations

CMA cannot detect balanced chromosomal rearrangements (inversions, balanced insertions, and balanced translocations), low-level mosaicism (<20%), and rearrangements in repeat sequences (e.g., short arms of acrocentric chromosomes and heterochromatic regions). CMA also cannot identify pure uniparental heterodisomy (i.e., can only identify uniparental isodisomy, mixed hetero- and isodisomy, or segmental isodisomy). Technical limitations and inherent sequence properties may effectively reduce the resolution for some genes or regions. Erroneous results may occur in the setting of suboptimal DNA quality.

Parental Testing Policy

GeneDx recommends parental testing to evaluate the inheritance of an abnormality (familial or de novo) and also to clarify the clinical significance of copy number changes. GeneDx uses FISH, MLPA, quantitative PCR (qPCR), or targeted array, as appropriate, for parental analysis. For clinically well-characterized genomic imbalances,

parental analysis is available as a separate test for an additional cost (see Known Familial Copy Number Variant(s)). For genomic imbalances of unclear significance where parental information may inform the classification of the copy number variant, GeneDx offers free parental analysis if clinical information on the parents is provided.

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