GenomeDx: Whole-Genome Chromosomal Microarray Comparative Genomic Hybridization (CGH) and Single Nucleotide Polymorphism (SNP) Array for Copy Number and Uniparental Disomy (UPD) Analysis

Routine chromosomal analysis for constitutional developmental disorders has shifted from G-banded karyotype analysis to DNA chromosomal microarray (CMA) as a first-tier test.[1] 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 long stretches of homozygosity, which may result from uniparental disomy (UPD). While relatively rare, some cases of uniparental disomy are relevant to disorders of imprinting as well as to recessive disorders caused by inheritance of a variant within a long stretch of homozygosity.[10,11]

Test Indications:

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. Suspected whole-chromosome or segmental UPD related to an imprinting disorder or to a recessive disorder (with detection of a homozygous variant in a proband who has only one carrier parent and non-paternity is ruled out). Determine breakpoints of chromosomal rearrangements previously detected by conventional cytogenetic methods and BAC arrays.

Test Method and Sensitivity:

The GenomeDx v5 (whole-genome chromosomal array) contains 118,000 oligonucleotide probes used for detection of copy number variants (CNVs). The array detects CNVs of >200 kb, on average, across the entire unique sequence of the human genome and between 500 bp to 15 kb in more than 220 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 detect stretches of homozygosity extending 5 Mb or longer. Interpretation of results sometimes depends on whether a CNV is inherited or de novo, and analysis of parental samples is useful for accurate interpretation.

Limitations:

CMA cannot detect balanced chromosomal rearrangements (inversions, balanced insertions, and reciprocal translocations), genomic alterations in regions that are not represented on the microarray, polyploidy, low-level mosaicism (<20%), rearrangements in repeat sequences (e.g., short arms of acrocentric chromosomes and heterochromatic regions), and variants of single or small stretches of nucleotides (point variants, indels, etc). CMA cannot identify pure uniparental heterodisomy (i.e., can only identify uniparental isodisomy or segmental heterodisomy). With GenomeDx v5, regions of homozygosity (ROH) will be reported if there is at least one region ≥10Mb, or two regions each ≥8 Mb, suggesting identity by descent. The possibility of uniparental disomy (UPD) is reported when there is a terminal ROH ≥10 Mb or an interstitial ROH ≥20 Mb. 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 this cytogenetic array design. Test results are often complex and interpretation may be confounded by the detection of copy number variants (CNV) that may be present in the general population.

Parental Testing Policy:

GeneDx recommends parental testing when a patient 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 FISH, quantitative PCR (qPCR), targeted CMA 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 (see Known Familial Deletion/Duplication testing). For genomic imbalances of unclear significance, GeneDx offers free parental analysis if clinical information on the parents is provided.

References:

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