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Chromosomal Microarray Testing for Children With Unexplained Neurodevelopmental Disorders

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Children with neurodevelopmental disorders, including developmental delay, intellectual disability, autism spectrum disorder (ASD), or congenital anomalies may have genetic abnormalities that traditionally were detected using **G-banded karyotype** analysis. Karyotyping identifies clinically relevant genetic abnormalities in approximately 5% of children with these disorders.¹ However, Karyotyping has now been replaced by chromosomal microarray analysis (CMA), which detects unbalanced chromosomal rearrangements like G-banded karyotyping but also detects smaller chromosome abnormalities, increasing the diagnostic yield to approximately 20% of patients.^{1,2} Because of its greater sensitivity, CMA tests should now be considered by any clinician evaluating a child with otherwise unexplained developmental delay, intellectual disability, ASD, or congenital anomalies (**Audio**) (Figure).

How It Works

A microarray is a device that looks like a microscope slide and contains DNA sequences specific to the type of variation that is being examined. The most common microarrays used for clinical CMA testing include thousands to millions of pieces of DNA sequences that span the length of every human chromosome. Microarrays may also incorporate DNA sequences targeted to detect specific genes or chromosomal regions known to cause an abnormal phenotype.

G-banded chromosome analysis is performed by microscopic evaluation of each chromosome from **metaphase** cells prepared from a patient sample and is therefore somewhat subjective. In contrast, CMA uses computer algorithms to determine the relative amount of patient DNA bound to the microarray by comparison to a control DNA sample and is therefore less dependent on human factors. CMA can detect losses (deletions) or gains (duplications) of specific chromosomal regions across the genome at high resolution. Although G-banding analysis is estimated to reliably detect imbalances in regions of DNA that are greater than 5 to 10 megabases (millions of base pairs, Mbp) in length, CMA is designed to detect genome-wide imbalances of greater than 400 kilobases (thousands of base pairs, kb; a 10-fold increase in resolution for the detection of clinically relevant

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chromosome abnormalities).^{1,3}CMA also facilitates precise delineation of the break point (site of the chromosome break) and gene content in detected structural abnormalities, which allows each chromosomal imbalance to be evaluated for the number of genes included, whether any of those genes have been previously implicated in disease and if there are any expected phenotypes described for imbalances of that chromosomal region.

Because of CMA's enhanced resolution, new terminology and nomenclature have been introduced. Copy-number variants (CNVs) are losses or gains of chromosomal regions that are greater than 1 kb in length (Audio). CNVs are described using the chromosomal band(s) involved and genome sequence coordinates based on DNA sequences included on the microarray. CNVs can be nonrecurrent (having imbalances with breakpoints at different positions across the genome, meaning it is unlikely that these imbalances would be observed in more than 1 individual or family) and recurrent (imbalances mediated by highly similar DNA sequences that flank a unique DNA region and result in deletions or duplications of the intervening unique region, predisposing susceptible chromosome regions [hotspots] to recurrent imbalances and resulting in unrelated individuals with the same deletion or duplication). The most common recurrent CNV disorder is 22q11.2 deletion syndrome (formerly DiGeorge or velocardiofacial syndrome), which has a prevalence of 1 in 4000 live births⁴; other examples include Prader-Willi syndrome and Angelman syndrome, both involving deletion of portions of chromosome 15.

Important Care Considerations

CMA is now the recommended first-line genomic test for children with neurodevelopmental disorders, including ASD, irrespective of having concomitant congenital anomalies. Precise genomic information from CMA testing can detect a genetic cause for a child's clinical presentation and may help tailor further evaluations and target clinical management. For example, those with 22q11.2 deletion syndrome can exhibit clinical features including developmental or learning disabilities, ASD, conotruncal cardiac anomalies, dysmorphic facial features, palatal defects, hypernasal speech, immunodeficiency, hypocalcemia, and psychiatric illness.⁴ Once 22q11.2 deletion is diagnosed, specific medical assessments for children⁴ and adults,⁵ such as having immunologic evaluations (age 5 years) and monitoring calcium levels throughout the lifespan, have been defined to help manage clinical care. In addition, because patients with 22q11.2 deletions have a 25% to 30% lifetime risk for schizophrenia, specific guidelines exist for monitoring change from baseline symptoms that may suggest a treatable psychiatric illness⁵ (Audio).

CMA limitations include the inability to detect rare balanced translocation where the break point might disrupt the coding region of a gene and inactivate it. CMA cannot determine the precise mechanism of a gain or loss, which may affect the recurrence risk relevant to future counselling for the same CNV disorder in other family members. In addition, most microarrays used for routine clinical CMA cannot detect single gene-level deletions or duplications unless the gene was specifically targeted in the array design (Audio). However, continued development of whole exome- and genome sequence-based analyses and new algorithms to identify copy-number variants from this data will likely overcome these limitations. It is anticipated that clinical genetic testing will become a sequencing-based test

that can detect copy-number and sequence variants in a single assay. CMA testing can also detect abnormalities not previously described and of unclear clinical meaning.

Value

The average cost for routine karyotype analysis, formerly preferred for cytogenetic testing, is approximately \$800. CMA costs more ($\approx$ \$1500) but is worth the greater expense because of its greater diagnostic yield (Audio).⁶CMA's greater potential for making a genetic diagnosis may yield more information that is actionable for medical management. This additional information may also help to avoid costs attributable to exploratory testing, which typically occurs when seeking a diagnosis for neurodevelopmental abnormalities. Several insurance companies now have guidelines for CMA coverage.

Evidence Base

The International Standards for Cytogenomic Array Consortium¹(part of the Clinical Genome Resource Project) recommend use of CMA over G-banded karyotyping because of the greater amount of information obtained by CMA. Guidelines from the American College of Medical Genetics and Genomics⁷ and the American Academy of Pediatrics⁸ followed, and CMA is widely considered to be a first-line test for those with unexplained neurodevelopmental disorders, including ASD or congenital anomalies (grade C).

Bottom Line

CMA offers a powerful approach for detecting pathogenic copy-number changes in the genome. CMA should be offered when evaluating individuals diagnosed with otherwise unexplained developmental delay, intellectual disability, ASD, or congenital anomalies. CMA can be critical in these patient populations for providing etiologic diagnoses and to aid in directing medical management.

Audio, CME, and Additional Resources

Listen to the accompanying audio program for more information about chromosomal microarray. Take the CME at <http://jamanetwork.com/learning/article-quiz/10.1001/jama.2016.18845>. Learn more at jamagenetics.com.

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Figure.

Comparison of G-Banded Karyotyping vs Chromosomal Microarray Analysis

Abbreviations: bp, base pairs; kb, thousands of base pairs; Mb, megabase(s).