Genomic microarray analysis for intellectual disability, developmental delay, multiple congenital anomalies, and autism spectrum disorders

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Citation

Authors' conclusions
Chromosome abnormalities are a common cause of developmental delay (DD), intellectual disability (ID), multiple congenital anomalies (MCA), and other neurodevelopmental disorders. However, traditional cytogenetic techniques (such as a karyotype analysis) will identify a chromosome abnormality in fewer than 10% of individuals with clinical features suggestive of a genetic syndrome. In addition, standard karyotype analysis identifies a chromosome abnormality in only 5% to 10% of fetuses undergoing prenatal testing because of an increased risk of a chromosome disorder. Newer microarray-based genetic tests, including array-based comparative genomic hybridization (aCGH) and single nucleotide polymorphism (SNP) microarray testing, significantly increase the detection rate in both prenatal and postnatal cases. Array CGH involves hybridizing patient DNA to a microarray containing thousands of small DNA segments (typically bacterial artificial chromosome [BAC] clones or oligonucleotide probes). By evaluating hybridization intensities, copy number variants (CNVs; segments of DNA longer than 1 kilobase that differ in copy number from a reference genome) such as deletions and duplications may be identified. Because of the large number of probes representing segments of all 23 chromosomes, aCGH provides a cytogenetic evaluation at a significantly higher resolution than a standard karyotype analysis. The array may be targeted in nature, assaying certain regions of the genome known to be associated with a specific syndrome or phenotype (often used in prenatal diagnosis) or may be genome-wide (probes at regular intervals spanning the entire genome). While the diagnostic yield of such testing varies with the number and distribution of probes, aCGH typically identifies chromosome abnormalities in approximately 10% of patients with a suspected chromosome disorder who have a normal karyotype by conventional cytogenetics. SNP microarrays, which analyze thousands of SNPs (variants in which a single base pair differs from a specified reference sequence) throughout the genome, also detect CNVs, including both deletions and duplications. SNP microarray testing involves hybridizing patient DNA to a microarray containing the SNP probes and comparing results with those obtained from a given set of control samples. In addition to identifying CNVs, SNP microarrays can detect "copy number neutral" abnormalities. Specifically, SNP microarrays may reveal the presence of uniparental disomy (UPD, when both copies of a chromosome are inherited from the same parent with no contribution from the other parent) or consanguinity (parents are related by blood). These copy number neutral abnormalities can lead to disease if a recessive gene variant is present (either UPD or consanguinity) or if an imprinted region of a chromosome is involved (UPD only). The resolution of SNP microarrays is determined by the length and spacing between probes, and by the statistical algorithms used to identify gains and losses (which differ between the various statistical software packages available for analysis). Like aCGH, SNP microarrays offer a cytogenetic evaluation at a significantly higher resolution than a standard karyotype analysis, as well as the ability to look for genomic imbalances throughout the genome in a single assay. The primary concern with both aCGH and SNP microarray testing is the identification of CNVs of unknown clinical significance. In addition, the microarrays will not detect balanced chromosome rearrangements (i.e., balanced translocations or inversions) or imbalances not covered by the probes on the microarray. The applications of these tests in both prenatal and pediatric populations include testing for aneuploidy (having extra or missing chromosomes) and deletions or duplications, and evaluating unclear or apparently balanced rearrangements.

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