High-resolution molecular karyotyping to detect genetic disorders

Constitutional SNP array karyotyping
Chromosome constitutional microarray analysis

Moderate to severe mental retardation occurs in approximately 1 percent of the population and has many causes, with one third to one-half of cases being idiopathic. Unbalanced chromosome abnormalities are the most common cause of mental retardation, accounting for approximately 10 percent of cases; however, the ability of traditional karyotype analysis and fluorescence in situ hybridization (FISH) to identify a pathogenetic chromosome abnormality is limited by the band resolution achieved in the study and by the need for some clinical information to choose the proper FISH probes to utilize. Since the resolution of conventional cytogenetic analysis is 5-10Mb (5-10 million base pairs), any rearrangement smaller than this would be missed. In addition to mental retardation and developmental delay, unbalanced chromosome abnormalities and aneuploidy are also identified in patients with autism/autism spectrum disorder, dysmorphic features and multiple congenital anomalies. Chromosome microarray analysis (CMA) utilizes a "DNA chip" that provides a genome-wide assessment of copy number changes (deletions and duplications) at a resolution far greater than what is achievable with other cytogenetic methodologies.

Clinical Utility

Note: This test requires insurance preauthorization. The Laboratory will not accept the specimen without preauthorization. Also note that CMA is generally performed in the outpatient setting.

The Beaumont experience with CMA has demonstrated a pathogenetic copy number in nearly 25 percent of the all children who had a previously "normal" karyotype. In addition to intellectual disability, CMA has been shown to detect a submicroscopic rearrangement in 7 percent of children with nonsyndromic autism, 27 percent of children with syndromic autism spectrum disorder, and 17 percent of neonates with birth defects. Thus, SNP chromosome microarray analysis should be considered as a front-line test to evaluate patients with a suspected genetic disorders.

Test limitations CMA cannot detect:

1. balanced chromosome rearrangements such as translocations, balanced insertions, or inversions
2. low-level mosaicism
3. an abnormality in a region not represented on the array

Patients *(Newborns, children and adults)*

- developmental delay/intellectual disability
- dysmorphic features
- multiple congenital anomalies
- autism/autism spectrum disorder
- seizures
- behavior problems
- possible microdeletion/ microduplication syndrome not amenable to FISH testing

References
1. Jacquement ML *et al* (2006): J Med Genet 43, 843-849.
2. Shaffer LG and Bejjani BA (2006): Cytogenet Genome Res 115:303-309.
3. Marshall CR *et al* (2008): Am J Hum Genet 82, 477-488.
4. Shevell MI *et al* (2008): AM J Med Genet 147B: 1101-1108.
5. Lu XY *et al* (2008): Pediatrics 122: 1310-1318; Sagoo GS et al (2009): Genet Med 11(3): 139-146.

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Principle of the test

The Beaumont CMA test utilizes the Affymetrix CytoScan HD Single Nucleotide Polymorphism (SNP) array which provides the broadest coverage and highest performance for detecting both copy number altering and copy number neutral aberrations. CytoScan HD Array has greater than 99 percent sensitivity and can reliably detect 25-50 kb copy number changes across the genome. With more than 2 million copy number markers (akin to performing over two million simultaneous FISH experiments), including 750,000 SNPs, the Beaumont CytoScan Array offers high-density resolution of the entire genome, extending throughout promoter and miRNA regions for relevant aberration detection and reporting. The Beaumont SNP array can also provide genotype information that allows for detection of copy number neutral aberrations such as uniparental disomy and consanguinity which can provide evidence for candidate recessive disorders. SNP array analysis is similar to the previously offered oligonucleotide array; however, it has comparatively superior sensitivity with resolution as good as 880 base pairs between each marker

Specimen collection

One green-top (Sodium Heparin) tube (5-7mL). Collect 5-7 mL peripheral blood (minimum: 3.0 mL). Gently invert tube to mix specimen.

Rejection criteria:

- improperly labeled specimens
- frozen specimens
- cracked or compromised specimen tubes
- specimens received greater than 72 hours past the time of collection

Test code: GSNPC

Specimen storage

Room temperature (20-25°C or 68-77°F): 24 hours

Refrigerated (2-8°C or 36-46°F): 72 hours

Frozen (-20°C/-4°F or below): Unacceptable

Physician office /draw site specimen preparation

Do not freeze specimen. Store peripheral blood at room temperature (20-25°C or 68-77°F) prior to courier pickup. For delays in transport (greater than 24 hours from the time of collection), refrigerate (2-8°C or 36-46°F) specimen.

Transport

Preparation for courier

Room temperature (20-25°C or 68-77°F): 24 hours

Refrigerated (2-8°C or 36-46°F): 72 hours

Frozen (-20°C/-4°F or below): Unacceptable

FedEx shipping instructions

Transport 5-7 mL whole blood (minimum: 3 mL) at room temperature. If the specimen will not be received at the testing laboratory within 48 hours of collection, transport refrigerated. Do not fix or freeze the specimen. A pathology report for the patient must be provided.

Advantages of SNP array karyotyping for analysis

- one assay - whole genome copy number and UPD status
- permits evaluation of specific gene content involved in genomic imbalance to permit genotype:phenotype correlations
- chromosomal arm resolution is increased by several thousand fold when compared to FISH
- detects abnormalities missed by other techniques – including uniparental disomy
- detects atypical deletions missed by FISH
- can identify genomically complex chromosome abnormalities and genomic imbalance in an individual with a previously diagnosed "balanced" chromosome abnormality

- test performed Monday through Friday
- results available within seven to 14 days
- additional time may be needed for reflex testing of abnormal results
- positive or negative for chromosome abnormality; a comprehensive interpretative report will be provided

For more information or questions about SNP Array, please contact Mark Micale, Ph.D. at 248-898-9063, or a Customer Service Agent at 800-551-0488.