[A technical review]

Chromosome SNP Microarray

A New High-density Allele-specific Diagnostic Platform

Analysis of submicroscopic genomic changes can detect the cause of congenital anomalies and/or learning disabilities.

Introduction

Genetic imbalances are often associated with multiple birth defects, developmental delay, growth retardation, and dysmorphic features. Standard cytogenetic analysis can identify visible chromosomal alterations, such as an extra chromosome band, but small deletions or duplications in the genome cannot be reliably detected. Submicroscopic unbalanced rearrangements have been found in approximately 3% of patients with learning disabilities and mental retardation of unknown cause using a set of FISH (fluorescence in situ hybridization) probes that can only target the ends of the chromosomes.[1]

Advances in molecular cytogenetics further improved the sensitivity of testing through the application of microarray-based comparative genomic hybridization (CGH) technology. In CGH-based microarrays, large numbers of genomic probes are immobilized on glass slides as targets for the competitive hybridization of patient and normal DNA. The tagging of each DNA source with different fluorochromes allows for identification of copy number changes in the targeted regions when the fluorescence signal is measured.[2]

Single-nucleotide Polymorphism (SNP)

Further technical advancement in copy number resolution by microarray testing, with the additional capacity to differentiate DNA sequence variation, was provided by the 262,000 SNP-based microarray. A single-nucleotide polymorphism is the smallest genetic variation that can occur within a DNA sequence. There are millions of these position-specific markers within our genome, and many have been used for years in gene mapping studies.

In general, chromosome microarrays look at the genome with different levels of resolution based on the number of targets in the array. The greater the number, the more sensitive the array will be at detecting dosage changes associated with phenotypes such as autism, developmental delay, mild mental retardation, or congenital malformations.[3,4] SNP arrays interrogate single base pair (allele) targets that have two different forms, revealing which form is present at that locus as well as the number of copies of that DNA segment. CGH-based arrays cannot detect polymorphic allele targets (only dosage), resulting in a significant advantage for the SNP array. This advantage is based both on added confirmation of dosage changes through allele comparisons and the identification of syndrome-associated "copy neutral" contiguous stretches of allele homozygosity. The presence of the latter allows for detection of uniparental disomy for all chromosomes and, when consanguinity is present, it will provide the degree as well as the resulting genomic location of regions of recessive allele risk.[5,6]

Increase in Genomic Targets

The initial 262,000 SNP microarray has been upgraded to offer a much more dense array of 1.8 million genomic targets (marker every 700 bp).[7] The ultra dense array is much more sensitive in identifying extremely small genomic variations and more statistically reliable due to the large increase in markers through which each variation is detected. Many of the current genetic research initiatives employ this array format,[4] which benefits parallel development of clinical applications. The ultra high resolution is particularly important in the study of autism, where dosage changes may be very small and in the follow-up of developmentally delayed children with apparently balanced chromosome rearrangements.[8,9] Many of these cases have ultimately been shown to have small dosage changes adjacent to the chromosome breakpoints.[10]

There are limitations with arrays for detecting mosacism; however, higher density targeting allows large imbalances to be detected at very low levels. In general, the smaller the imbalance, the higher the percentage of abnormal cells necessary to allow detection.

Since the density of the current array is so great, the majority of all genes and syndromes can be readily monitored, making a detected syndrome list unnecessary. The custom targeting of established, clinically relevant, designated regions or genes with the array software allows the detection of imbalances at the lowest threshold levels. As new research identifies additional genes/regions critical to normal development, these will be added to the custom list, and the archived patient data files may be reëxamined using the most current information.

SNP Microarray – Pediatric (Reveal®) 510002

Related Information Clinical Questionnaire for SNP Microarray; Fluorescence in situ Hybridization (FISH), Microdeletion Syndromes [510388]

Synonyms aCGH, CGH, CMA, Microarray Pediatric/Adult, Reveal® SNP Microarray – Pediatric, SNP Array, WGA

Special Instructions Pertinent medical findings must accompany the test request form. Call 800-345-4363 to request forms, or photocopy the Clinical Questionnaire for SNP Microarray. This test may also be performed on adults.

When a child tested with this assay is found to have an abnormal array of unknown clinical significance that may be clarified through parental testing, there will be no charge associated with the follow-up parental testing that is based on the child's results. All other parental follow-up testing will be charged, including (but not limited to) autism susceptibility regions, known microdeletions/microduplications, autosomal recessive deletions/duplications, and large copy-number changes with likely pathogenic significance. The child's abnormal array results will indicate whether parental testing will be performed at no charge and will include the appropriate parental follow-up test number. For parental follow-up testing for arrays not performed at LabCorp, call 800-345-4363 to speak to a genetic counselor.

Contact your local LabCorp branch supply department to order buccal swab kits using PeopleSoft N° 3177.

Storage Instructions Maintain specimen at room temperature.

Specimen Whole blood **or** LabCorp buccal swab kit. (Buccal swab collection kit contains instructions for the use of a buccal swab.)

Volume 4 mL **or** LabCorp buccal swab kit

Minimum Volume 2 mL (neonatal) (**Note:** This volume does **not** allow for repeat testing) **or** two buccal swabs

Container Green-top (heparin) tube (preferred), yellow-top (ACD) tube, or lavender-top (EDTA) tube or LabCorp buccal swab kit.

Causes for Rejection Quantity not sufficient for analysis; wet buccal swab

Use Detects chromosomal imbalance that may be present in newborns or children with developmental delay/congenital anomalies/autism; provides detection of uniparental disomy of any chromosome and the degree of consanguinity, as well as the genomic locations of recessive allele risk

Limitations This assay does not detect balanced rearrangements and low-level mosaicism.

Methodology Whole genome SNP-based copy number microarray analysis targeting 2.695 million copy number and allele-specific genome sites

Additional Information Positive evaluation criteria include: DNA copy gain/loss within known clinically significant gene region of 50 Kb or greater. DNA copy number loss >200 kb or gain >500 kb outside known clinically significant regions with at least one OMIM annotated gene or within a region of clear clinical significance. UPD testing is recommended for patient results demonstrating a long contiguous region of homozygosity in a single chromosome >20 Mb interstitially or >10 Mb telomerically (15 and 8 Mb, respectively, for imprinted chromosomes). Contiguous homozygosity >10 Mb within multiple chromosomes suggests common descent. These regions of potential recessive allele risk are designated.

Reference

Shaikh TH. Oligonucleotide arrays for high-resolution analysis of copy number alteration in mental retardation/multiple congenital anomalies. *Genet Med.* 2007 Sep; 9(9):617-625.

Chromosome Analysis With Reflex to SNP Microarray – Pediatric (Reveal®) 052300

Synonyms aCGH, CGH, Chromosome RFX Microarray Pediatric/Adult, High Resolution G-Banding, Prometaphase Analysis

Special Instructions Pertinent medical findings must accompany request. Call 800-345-4363 to request forms, or photocopy the Clinical Questionnaire for SNP Microarray. This test may also be performed on adults.

When a child tested with this assay is found to have an abnormal array of unknown clinical significance that may be clarified through parental testing, there will be no charge associated with the follow-up parental testing that is based on the child's results. All other parental follow-up testing will be charged, including (but not limited to) autism susceptibility regions, known microdeletions/microduplications, autosomal recessive deletions/duplications, and large copy-number changes with likely pathogenic significance. The child's abnormal array results will indicate whether parental testing will be performed at no charge and will include the appropriate parental follow-up test number. For parental follow-up testing for arrays not performed at LabCorp, call 800-345-4363 to speak to a genetic counselor.

Specimen Whole blood

Volume 6 mL (adults), 3 mL (pediatric)

Minimum Volume 2 mL

Container Green-top (heparin) tube

Collection Using sterile technique, collect 10 mL blood into a green-top (heparin) tube or syringe. Invert the tube several times to prevent coagulation. Specimens must be sent the same day as collected and arrive in the laboratory within 48 hours of venipuncture.

Storage Instructions Maintain specimen at room temperature. Specimen may be refrigerated if there is a delay in shipment. Do **not** freeze.

Causes for Rejection Hemolysis; clotted specimen; specimen more than 48 hours old; use of improper anticoagulant; frozen specimen

Use Detects microscopically visible chromosomal abnormalities and, if normal, array reflex detects submicroscopic imbalance associated with developmental delay/autism using 2.695 million genomic targets. The SNP microarray also provides detection of UPD (uniparental disomy) and the degree of consanguinity, as well as the genomic locations of recessive allele risk.

Methodology Culture of cells in special medium; colcemid arrest of cells in prophase stage of mitosis following cell synchronization techniques; if cytogenetic analysis is normal, high resolution microarray targeting 2.695 million copy-number and allele-specific genome sites from cultured cells will be performed.

For the most current information regarding test options, including specimen requirements and CPT codes, please consult the online Test Menu at www.LabCorp.com.

References

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7. Affymetrix. *Genome-Wide Human SNP Array 6.0.* Available at http://www.affymetrix.com/products/application/genome_wide_snp_6_ad.affx. Accessed: October 15, 2008.

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