

Microarray, Genomic, Fetal

PRENATAL TESTING BY ARRAY COMPARATIVE GENOMIC HYBRIDIZATION (ACGH): USEFUL FOR CLARIFYING ABNORMAL FETAL CHROMOSOME RESULTS, DETECTING SUBMICROSCOPIC GAINS/LOSSES, AND ORDERING GENETIC TESTING AFTER AN ABNORMAL ULTRASOUND RESULT.

Test Highlights

- Microarray chips contain DNA sequences representing specific regions of the human genome. Fetal DNA is extracted from amniotic fluid, chorionic villi, or cell cultures and hybridized to the chip. This allows the laboratory to detect and characterize unbalanced chromosomal abnormalities (gains or losses of genetic material) at a higher level of resolution than is possible using conventional cytogenetics.
- Prenatal genomic microarray can be used to further characterize cytogenetic abnormalities identified by conventional cytogenetic methods. For example, it can refine the breakpoints of an observed unbalanced chromosomal rearrangement, define a marker chromosome, more accurately size deletions and duplications, and identify gains/losses associated with de novo, apparently balanced translocations or inversions.
- The array contains high-density coverage at clinically relevant deletion/duplication syndrome loci and at the subtelomere and pericentromeric regions, as well as genome-wide coverage with an average probe spacing of 100kb.
- Abnormalities seen on clinical specimens will be verified using conventional cytogenetics, validated locus-specific fluorescence in situ hybridization (FISH) probes, or another validated laboratory method.

Clinical Background

Many abnormal phenotypes are associated with chromosomal imbalances. Conventional cytogenetic techniques are limited in their ability to detect or characterize subtle or cryptic abnormalities, especially in prenatal samples. These subtle or submicroscopic abnormalities may be identified using aCGH microarray analysis. Array CGH can detect deletions and duplications at loci associated with known microdeletion/microduplication syndromes, subtelomeric regions, and pericentromeric regions, as well as imbalances that may be unique to the patient. Array CGH can also identify the origin of marker chromosomes. The identification of specific abnormalities may be helpful in diagnosis, planning for special needs at birth, and postnatal treatment.

Indications for Ordering

- Clarification of an abnormal fetal karyotype requiring further characterization.
- Follow-up of de novo, apparently balanced rearrangements.
- Suspicion of an imbalance in a specific genomic region that is best evaluated by microarray.
- Fetal tissue/villi from a miscarriage or stillbirth (products of conception).
- Abnormal ultrasound findings with a normal karyotype.
- Family history of a known or suspected chromosomal abnormality that is best evaluated by microarray.
- Identification of a mosaic chromosome imbalance, such as a marker chromosome.

Additional Ordering Notes

- All samples **must have** a clinical indication for testing (please, no ICD-9 codes). A completed Patient History for Cytogenetic (Chromosome) Studies Form, which can be found at http://www.aruplab.com/Testing-Information/resources/consent_forms/history_cytogenetic.pdf, must accompany each sample. The name of a contact person (e.g., physician or genetic counselor) and his or her phone number is also required.
- The laboratory can provide the best interpretation of the test results when all relevant clinical information is available. Therefore, please provide as much clinical information as possible.
- If prenatal microarray is being ordered to clarify a fetal karyotype performed at another laboratory, the abnormal chromosome report must be included with the sample.
- Sample Requirements:
 - Amniotic fluid (direct): 15–20 cc (array only). If ordering chromosomes concurrently, please provide 25–30 cc for both tests.
 - Chorionic villus sample (CVS): 10–15 mg villi (array only). If ordering chromosomes concurrently, please provide 15–20 mg for both tests.
 - Products of conception (POC): 15–20 mg tissue.
 - Parental blood samples: 5–10 cc whole blood in a sodium heparin (green-top) tube.
- Parental blood samples are requested to be sent at the time of test order to clarify prenatal findings, identify familial rearrangements or familial variants, rule out maternal cell contamination (maternal sample only), and minimize turnaround time in positive or ambiguous cases.

Interpretation

- Data are analyzed using Genoglyphix software (Signature Genomic Laboratories, LLC) and depicted as ratio plots indicating linear clone positions for each chromosome.
- FISH, conventional cytogenetics, or other validated laboratory method will be used to confirm any abnormality on clinical specimens, and results will be interpreted using standard array CGH nomenclature.
- A written summary and interpretation of the microarray findings, including the results of parental samples (if applicable), will also be provided.

Limitations

- Array CGH will only detect imbalances (gain or loss of DNA) in the genome. Mutations, small genomic abnormalities between or within probes, and balanced rearrangements, such as translocations and inversions, will not be detected.
- Many intragenic alterations, such as point mutations and very small deletions or duplications, will not be detected using aCGH. If a specific molecular diagnosis is suspected, other molecular techniques (e.g., gene scanning or PCR-based assays) may be required. This type of testing is more sensitive than genomic microarray for detecting small changes within specific genes but is highly specific for the genetic site or gene of interest; it is also infeasible to apply other molecular techniques on a whole-genome basis at this time.
- The failure of the array to detect an imbalance at any specific locus does not exclude the diagnosis of any disorder associated with that locus.
- This technique will not detect point mutations, nor will it detect copy number changes in regions not represented on the array.
- This technique is not meant to detect low-level mosaicism.

Methodology

- The technique involves DNA preparation, labeling, hybridization, array scanning, analysis, and interpretation.
- DNA is prepared from direct or cultured samples for testing by the array. A sample suitable for FISH analysis for possible confirmation testing is also created.
- The DNA is labeled with a fluorescent dye and compared with control DNA, which is labeled with a different fluorescent dye.
- The sample and control DNA are then combined and hybridized to a microarray slide.
- Relative concentrations of sample to control DNA are assessed to determine whether there is a gain or loss of each DNA sequence represented on the array.
- Abnormalities seen on clinical specimens will be verified using conventional cytogenetics, validated locus-specific fluorescence in situ hybridization (FISH) probes, or another validated laboratory method.

Related Tests

- Chromosome Analysis, Amniotic Fluid (CY) ([2002293](#))
- Chromosome Analysis, Chorionic Villus (CY) ([2002291](#))
- Chromosome Analysis, Products of Conception (CY) ([2002288](#))

Reference

1. South ST, Lamb AN. Detecting genomic imbalances in prenatal diagnosis: main hurdles and recent advances. *Expert Opin Med Diagn* 2009;3:227–35.

Test Information

2002366

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For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.