Prenatal Diagnosis

Advances Over FISH

The technology, which has also been called chromosomal microarray, was first used to analyze gains and losses in chromosomal material in tumors and tumor cell lines. It is now a valuable tool in the postnatal testing of individuals with birth defects.

Between one-half and two-thirds of children with serious developmental abnormalities go undiagnosed and have a normal karyotype, so from a postnatal perspective, this new test has been welcomed at Johns Hopkins University and the Kennedy Krieger Institute, both in Baltimore, as well as at other institutions. Having a diagnosis facilitates the most appropriate therapy and allows parents to plan for the prenatal period. The obstetrician will use array-CGH instead of FISH in order to cast a wider net—one that can catch a deletion on chromosome 22, as well as other possible deletions which may cause the heart defect.

Right now, the available array-CGH platforms can detect more than 40 syndromic chromosomal disorders. Just as with FISH, a normal result rules out only those conditions that correspond to the deletions or duplications that are covered on the array.

How Array-CGH Works

Array-CGH involves labeling the patient’s DNA in one fluorescent dye, labeling DNA from a normal control with a different fluorescent dye, allowing the DNA from both to mix, and then applying the mixture to a slide that contains small segments of DNA from known chromosomal regions. The slide serves as the platform or the array. The mixture of the patient’s DNA and the normal control DNA is allowed to match up, or hybridize, with the complementary DNA segments on the slide.

If we see on a prenatal ultrasound that a fetus has cardiac problems, for example, we might suspect the DiGeorge syndrome. The obstetrician today would probably perform an amniocentesis and order both a karyotype and FISH with a specific probe for the DiGeorge syndrome, which is caused by a deletion on chromosome 22, just as he or she would do in the postnatal period for a child with the syndrome’s more obvious phenotypic features.

In the near future, the obstetrician facing this prenatal situation will likely proceed differently than he or she would in the postnatal period. The obstetrician will use array-CGH instead of FISH in order to cast a wider net—one that can catch a deletion on chromosome 22, as well as other possible deletions which may cause the heart defect.

Array-CGH is far from perfect in evaluating chromosomal material. It can only detect instances where there is a significant addition or deletion of genetic material. And, of course, it can only evaluate those genes encoded on the array.

As with every other prenatal diagnostic tool developed to date, the future use of this new technique involves many questions, including which variants are normal as opposed to abnormal, the technique’s potential role as a screening tool, and other often vexing ambiguities and issues. However, its use in prenatal diagnosis will build upon a body of national experience in the postnatal setting.

To familiarize us with the new technology and discuss its role in prenatal diagnosis, I have invited Dr. Karin J. Blakemore to serve as the guest professor of this month’s Master Class. Dr. Blakemore is the director of maternal-fetal medicine and the Prenatal Genetics Service at Johns Hopkins University School of Medicine in Baltimore—an institution that is gearing up to use array-CGH as part of its armamentarium for prenatal diagnosis.

She is joined by her colleague Denise Batista, Ph.D., who is an assistant professor in the Johns Hopkins department of pathology and codirector of the university’s prenatal cytogenetics laboratory. Dr. Batista also serves as the director of the cytogenetics laboratory at the Kennedy Krieger Institute in Baltimore.

Dr. Reeces, who specializes in maternal-fetal medicine, is Vice President for Medical Affairs, University of Maryland, as well as the John Z. and Akiko K. Bowers Distinguished Professor and dean of the school of medicine. He is the medical editor of this column.
The Near Future

The clinicians and cytogeneticists who are using and offering array-CGH are on a learning curve. Experts seem to have been caught off guard in ensuring that we knew what variants are associated with the normal phenotype, and on other issues as well.

At Johns Hopkins University and the Kennedy Krieger Institute, we have postnatal experience to draw upon as we bring prenatal array-CGH to cases in which we have been able to give a specific syndromic diagnosis to approximate 5%-8%, depending on the array platform we utilize. In about 12%, we have found variants that we cannot yet explain.

Until we learn more, we plan to limit prenatal array-CGH to cases in which there is a known abnormality on ultrasonography, and may be lost during the culture process. On the other hand, experts believe the role of array-CGH is to enhance our current approach to prenatal testing, and in this sense, it is an exciting development.

Key Points for Array-CGH

- Detects: Unbalanced rearrangements, aneuploidy, gains and losses of regions represented in the array.
- Won't detect: Balanced reciprocal translocations, point mutations, or small changes in the genes.
- Pick-up rate: Estimated as 5%-10% from postnatal studies of developmental delay/dysmorphic children.
- Confirmation: By FISH probes.
- Parental studies: Necessary to sort out normal variants versus abnormal.
- Copy number variants: Might find copy number variants of unknown significance.
- Difference between commercial and home-brew arrays available with different genome coverage.

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Array-CGH also cannot detect point mutations, or small changes in the genes, like those that cause hemophilia or sickle cell disease. It is designed to detect the syndromes caused by duplications or deletions of larger amounts of chromosomal material.

Chromosomal mosaicism, in which only some cells show a particular abnormality, may or may not be more readily detected by array-CGH than by standard techniques.

On one hand, mosaicism may be more readily detected with array-CGH than with standard karyotype analysis because abnormal cells often do not divide as well and may be lost during the culture process that is part of the standard karyotyping methodology. On the other hand, experts believe that we may not detect mosaicism below a certain level—below the level, some say, at which the abnormality affects fewer than 15%-30% of cells.

Array-CGH will also inevitably detect normal variants (benign duplications and deletions that are not associated with any abnormal phenotype). Some variants will be difficult to explain. This has been true for karyotyping as well, and just as we have in the past, we will want to minimize parents’ anxiety over the unknowns.

When we find variants of uncertain significance, we may perform additional studies, checking their blood samples for the same.

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The question of whether array-CGH could replace a karyotype in prenatal testing is an interesting one. For now, there are too many questions and issues (mosaicism and normal variants, for instance) to do away with karyotyping. We believe the role of array-CGH is to enhance our current approach to prenatal testing, and in this sense, it is an exciting development.

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