Microarray analysis improves prenatal diagnosis

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A "chip" or array that can quickly detect disorders such as Down syndrome or other diseases associated with chromosomal abnormalities proved an effective tool in prenatal diagnosis in a series of 300 cases at Baylor College of Medicine, said researchers in a report that appears in the current issue of the journal *Prenatal Diagnosis*.

In the report, a team led by Dr. Arthur Beaudet and Dr. Sau Wai Cheung at BCM, described use of array comparative genomic hybridization to analyze samples taken during amniocentesis or chorionic villus sampling for chromosomal abnormalities. Amniocentesis and chorionic villus sampling allow researchers to obtain fetal cells for testing.

"Larger studies of this test will help us decide whether it should be used as a first line measure to detect chromosome abnormalities in fetuses," said Beaudet, chair of molecular and human genetics at BCM and senior author of the report. "They will also enable us to determine whether such testing should be offered more widely to pregnant women."

Cheung is professor of molecular and human genetics at BCM and director of the College's Cytogenetics Laboratory.

"The array enables you to detect smaller deletions or duplications of genetic material that would not be seen on a regular karyotype (a depiction of the size, shape and number of chromosome and any abnormalities in them)," said Dr. Ignatia B. Van den Veyver, associate professor of obstetrics and gynecology and molecular and human

genetics at BCM and first author of the report. Each of these deletions or duplications is rare but added together, the rate of event could be as high as that seen in Down Syndrome.

In some of these cases where small amounts of DNA are lost or duplicated, children often have significant learning disabilities or health problems that could not be picked up with an ultrasound or other means of prenatal diagnosis, she said.

"This test adds information we could not detect by any other means right now in prenatal diagnosis," she said.

Array comparative genomic hybridization provides the tools to scan fetal DNA quickly and automatically to identify copy number variation, which indicates the deletion or addition of genetic material at a particular point on the genome.

The array starts with single-stranded fragments of DNA embedded on a glass slide to form the array, which is then exposed to fluorescently labeled single-stranded DNA. Half of the labeled DNA is from the fetus being tested and is labeled with one fluorescent color. The other is reference DNA, which is labeled with another color. The fluorescently labeled DNA – reference and patient – binds to DNA on the array. The color of the fragments will vary based on how much DNA from each binds to the DNA on the array. If the fetus has a DNA duplication, then the patient color on the array will be stronger. If the fetus has a deletion, the reference color will show up stronger. A specialized scanner evaluates the color differences, which are then fed into a computer for analysis.

In this study, most of the women sought prenatal testing because they were older and faced a higher risk of having children with certain chromosomal abnormalities, such as Down syndrome. Some had had

abnormal ultrasounds and needed more information, and still others had had children with a genetic abnormality previously.

The scientists found 58 copy number variations, which indicate that there is either more or less genetic material than one would expect to find at that location on the chromosome.

Forty of these variations were interpreted as benign. Thirty-nine of them were inherited from a parent who had no evidence of genetic disease. One had been seen before and had not been associated with disease.

In 15 cases when the array detected something that was significant for patient care, the finding was either suspected because the mother "carried" the change in her DNA, or because another prior test, such as a karyotype, had detected it.

Three cases were classified as uncertain. Two of these involved copy number variations, not seen before and not inherited from the parents, in fetuses with birth defects identified on the prenatal ultrasound. In one, the array findings were interpreted as likely unrelated to the birth defects and in the other they were thought to cause the defects. In the third case, there was a relatively large deletion in an area of chromosome 3, but it was also present in the mother, who had no reported medical problems.

In two cases the array comparative genome hybridization identified disorders that would have been missed otherwise and in seven cases the results added new information about risk of disease valuable in genetic counseling.

"My conclusion is, that providing there is good genetic counseling that accompanies it, the test can be offered to prospective parents who want prenatal diagnosis. There are many parents interested in having this additional diagnostic information," said Van den Veyver. "If we use an

array that is targeted and we have parental samples to confirm the meaning of detected changes, in the majority of cases, we will be able to counsel the patients about the significance of the findings."

Source: Baylor College of Medicine