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# A better genetic test for autism

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A large study from Children's Hospital Boston and the Boston-based Autism Consortium finds that a genetic test that samples the entire genome, known as chromosomal microarray analysis, has about three times the detection rate for genetic changes related to autism spectrum disorders (ASDs) than standard tests. Publishing in the April issue of *Pediatrics* (and online March 15), the authors urge that CMA become part of the first-line genetic work-up for ASDs.

Expectant parents who have family members with ASDs, as well as families who already have an affected child, often request genetic testing. However, there is still only limited knowledge about actual causative genes. The currently recommended tests (karyotyping to look for chromosomal abnormalities and testing for Fragile X, the single largest known genetic cause of ASDs) often come up negative. Chromosomal microarray analysis (CMA) is a genome-wide assay that examines the chromosomes for tiny, sub-microscopic deletions or duplications of DNA sequences, known as copy-number variants.

CMA offers about 100-fold greater resolution than standard karyotyping. However, since it is new, it is often considered a second-tier test. Depending on where a person lives, or what insurance they have, CMA may not be covered by health insurance. "Based on our findings, CMA should be considered as part of the initial clinical diagnostic evaluation of patients with ASDs," says Bai-Lin Wu, PhD, Director of Children's DNA Diagnostic Lab in the Department of Laboratory Medicine, which has offered CMA to families since 2006.

The research team, led by co-senior authors Wu (heading the Children's team), and David Miller, MD, PhD, of Children's Division of Genetics and Department of Laboratory Medicine (heading the Autism Consortium team), assessed the diagnostic value of CMA in the largest cohort to date -- 933 patients with a clinical diagnosis of ASD (by DSM-IV-TR criteria) who received clinical genetic testing in 2006, 2007 and 2008.

Half were Children's patients who had their samples submitted to the hospital's DNA Diagnostic Laboratory, and the others were recruited through the Autism Consortium, a research and clinical collaboration of five Boston-area medical centers. Nearly half of the patients were diagnosed with autistic disorder, nearly half with PDD-NOS (pervasive developmental disorder - not otherwise specified) and about 3 percent with Asperger disorder. Ages ranged from 13 months to 22 years.

Testing included the two currently used tests (G-banded karyotype and fragile X), as well as CMA. When the researchers compared the tests' diagnostic yield, they found:

- Karyotyping yielded abnormal results in 2.23 percent of patients
- Fragile X testing was abnormal in 0.46 percent
- CMA results were judged to be abnormal in 7.3 percent of patients when the entire length of the chromosomes (the whole genome) was sampled.

Extrapolating from these results, the researchers estimate that without CMA, genetic diagnosis will be missed in at least 5 percent of ASD cases. CMA performed best in certain subgroups, such as girls with autistic disorder, and past studies indicate that it also has a higher yield

in patients with intellectual disability (who constituted only 12 percent of this sample).

"CMA clearly detects more abnormalities than other genetic tests that have been the standard of care for many years," says Miller. "We're hoping this evidence will convince insurance companies to cover this testing universally."

In all, roughly 15 percent of people with autism have a known genetic cause. Establishing a clear genetic diagnosis helps families obtain early intervention and services for autism, and helps parents predict the possibility of having another child with autism.

In addition, by pinpointing bits of chromosomes that are deleted or duplicated, CMA can help researchers zero in on specific causative genes within that stretch of DNA. They can also begin to classify patients according to the type of deletion or duplication they have, and try to find specific treatment approaches for each sub-type of autism.

"Just in the last two years, a number of studies have revealed the clinical importance of ever smaller chromosome deletions and duplications found with advanced microarray technology," says Wu. "These new, highly-efficient tests can help in the evaluation or confirmation of autism spectrum disorders and other developmental disorders, leading to early diagnosis and intervention and a significantly improved developmental outcome."

Two known chromosome locations - on chromosome 16 (16p11.2) and chromosome 15 (15q13.2q13.3) accounted for 17 percent of abnormal CMA findings. Both chromosome abnormalities were initially linked with ASDs by Children's Hospital Boston and collaborators in The New England Journal of Medicine and the Journal of Medical Genetics, respectively, in 2008. Children's now offers specific tests targeting both

of these "hot spots."

However, the researchers note that most copy-number changes were unique or identified in only a small number of patients, so their implications need further study. Many of them are presumed to be related to ASDs because they involve important genes, cover a large region of the chromosome, or because the child is the first person in that family to have the change.

"Some deletions and duplications are rare and specific to one individual or one family," says Miller. "Learning about them is going to be an evolving process. There won't be one single test that finds all genetic changes related to autism, until we completely understand the entire genome."

**More information:** Shen Y; et al. Clinical genetic testing for patients with autism spectrum disorders. *Pediatrics* 2010 Apr; 125(4):e1-e17. (Published online March 15)

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