Consortium recommends microarray testing as new standard for pediatric genetic diagnosis

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An international consortium of genetics experts has issued a consensus statement recommending chromosomal microarray (CMA) as the new standard practice for genetic evaluation of children with unexplained developmental delay, autism or birth defects.

The statement and a related research review are published in the May 14, 2010 issue of the American Journal of Human Genetics.

"CMA gives us a huge improvement in the diagnostic yield of genetic testing and in our ability to counsel parents about why their child has developmental disability or multiple congenital anomalies," says David Ledbetter, PhD, Woodruff professor and director of the Division of Medical Genetics at Emory University School of Medicine. Ledbetter heads the International Standard Cytogenomic Array Consortium (ISCA), a group of clinical genetics laboratories and genomics experts focused on standardizing the collection of cytogenetic data.

"Our consortium statement should help set the new standard of care for genetic evaluation of children with unexplained developmental delays and other birth defects, and should be a major step forward in using modern genomic technology in a clinical setting," Ledbetter says.

Clinical genetic testing is a standard diagnostic practice for testing children with unexplained developmental delay/intellectual disability,

autism spectrum disorders and multiple congenital anomalies. These disorders account for the largest proportion of genetic testing because of their high prevalence in the population. Developmental delay/intellectual disability is present in about three percent of the population, and autism spectrum disorders affect approximately one in 150 people.

Previous guidelines have recommended testing with G-banded karyotyping, a type of chromosome testing that was first developed in the early 1970s. These tests allow geneticists to visualize and analyze chromosomes for imbalances, including deletions and duplications of genetic regions (copy number variations) that can be inherited or represent new mutations during sperm or egg development. Some copy number variations are common and benign, while others are associated with disease or developmental disorders.

The human genome project allowed geneticists to develop chromosomal microarray (CMA), also referred to as molecular karyotyping. Various forms of CMA have been used by an increasing number of geneticists, pediatric neurologists and developmental pediatricians over the past several years to evaluate children with developmental disorders. However, uniform best practice guidelines have not yet been issued by professional societies for the routine use of CMA as a first tier test.

"A karyotype to scan for chromosome problems is already a well accepted standard of care for these patients," says the article's first author, David Miller, MD, PhD, of the Division of Genetics and Department of Laboratory Medicine at Children's Hospital Boston. "CMA is a more powerful chromosome scan, so we believe it makes even more sense to do a CMA test in the majority of patients."

The ISCA conducted a literature review of 33 studies, including 21,698 patients tested with CMA, and compared CMA to G-banded karyotyping. They found that CMA consistently has a diagnostic yield of

15 to 20 percent, compared to approximately five percent with G-banded karyotyping. The higher yield of CMA is due primarily to its higher sensitivity for submicroscopic copy number variations.

The ISCA organized two workshops, beginning in 2008, to analyze the research data and develop the consensus opinion. Sufficient research data now exists, the consortium reports, to support CMA as the first frontline test in the evaluation of any child with unexplained, non-syndromic developmental delay, intellectual disability or autism. CMA should replace the G-banded karyotype, which has been the standard for 30 to 40 years, the group recommends.

"We hope that our statement, which represents many different institutions and many different clinicians and laboratory experts, will provide other professional organizations the background scientific data to endorse the conclusions of our group or to make their own evaluation of the data and clinical utility," says Ledbetter.

A third ISCA workshop this June in Bethesda, Md., will include clinicians, clinical labs, genomics and bioinformatics experts, as well as representatives from the top vendors developing chromosomal microarray technology and software for analysis.

Using a Grand Opportunities "GO" grant from the American Recovery and Reinvestment Act (ARRA) through the NIH, the ISCA has been developing a central public database of chromosomal microarray data from clinical labs. That database, which will be housed at the National Center for Biotechnology Information (NCBI) at NIH, is expected to include approximately 200,000 patient samples over the next two years that will be used to develop standard guidelines for interpretation of CMA tests.

The database also will be used to develop additional summary

recommendations and allow the ISCA to work with vendors to make interpretation guidelines and software tools available to all clinical testing labs and to clinicians who want to better understand and interpret the laboratory data from their patients.

The ISCA now has a membership of more than 100 clinical cytogenetics laboratories that will contribute genotype and phenotype data to the central database at NCBI. The consortium will continue to collect and analyze data from the pediatric population and compare it to normal copy number variation data from other large databases and continue to refine maps of pathogenic vs. benign copy number variation in the human genome.

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