

Autism Speaks - 2008 Science Achievements



Mark Daly, Ph.D., Harvard

The year started out with a bang when Mark Daly, Ph.D. (from the Autism Consortium) and Steve Scherer, Ph.D. (from the Autism Speaks-funded Autism Genome Project) almost simultaneously reported that DNA deletions and duplications on chromosome 16 explain the cause of 1-2 percent of the cases of autism. Individuals who have deletions in this chromosomal region have a high likelihood of developing autism. There are about 25 genes in this region of chromosome 16, related to brain function. The search is now on for which of those genes might be causing autism.

Taken together with other known genetic disorders that cause autism, we now can account for the genetic cause of about 10-15 percent of cases of autism.



*Dan Geschwind, M.D., Ph.D.
Professor, UCLA*

Three leading scientists (Dan Geschwind, M.D., Ph.D., Matthew State, M.D., Ph.D., and Aravinda Chakravarti, Ph.D.) reported new evidence that a gene called Contactin Associated Protein-Like 2 (CNTNAP2) is a risk gene for autism, most likely influencing the development of neural circuitry for language development in males. Previous research had shown that a rare mutation in CNTNAP2 is associated with seizures, language delay, and autism. Children with this rare mutation typically have onset of seizures between 14-20 months of age, followed by regression in language, learning ability, and social skills.

It's remarkable to consider that only a decade ago, we didn't even know where to look for genes related to autism. Now, scientists have identified several specific autism risk genes. This has been helped as scientists from around the world are pooling together their genetic data in large collaborative studies. The Autism Genetic Resource Exchange and THE Autism Genome Project –both large genetic data bases funded by Autism Speaks – have played a central role in these discoveries.

The genetics research of the last ten years is beginning to shed light on the biochemical basis of autism. Specifically, several findings suggest that autism and related developmental disorders that often result in autism, such as Rett Syndrome, are caused by abnormalities in the connections between neurons (synapses). There are several ways synaptic functioning can be affected. The goal is to eventually be able to intervene and correct the biochemical abnormalities so that synaptic functioning can return to normal.

One of the exciting findings reported last year did just that in a mouse model of tuberous sclerosis - a genetic disorder caused by mutations in the TSC1 or TSC2 gene that results in mental retardation, autism, and seizures. By inactivating this gene in mice, it was possible to mimic the TSC syndrome and the mice involved had learning and memory problems. Alcino Silva, Ph.D. and colleagues at UCLA showed that these learning deficits are related to hyperactivity of a biochemical pathway in the

hippocampus, a brain structure involved in learning and memory. They then introduced a treatment that inhibited this pathway which eliminated the learning deficits in the mouse. This example of “recovery” from a genetic condition represents a true paradigm shift in our thinking about developmental disorders. It was previously thought that it would not be possible to reverse a developmental syndrome. These results suggest that the pathology is reversible – the brain circuits affected do not atrophy but rather remain in an immature state, and they can be later activated in such a way to repair the syndrome's consequences. This report, and others documenting similar results for Fragile X and Rett Syndrome, suggest that potentially functional brain circuitry is lying dormant that can be corrected through biochemical manipulation.

Last year, Autism Speaks funded Adrian Bird, Ph.D. from the UK to extend this type of research in a mouse model of Rett syndrome. Although the translation from a mouse model to a treatment for humans will be extremely challenging, these findings are motivating scientists world-wide to pursue this goal.

There is currently no molecular marker or biological test that is capable of identifying autism at an early age. Last year, however, Anthony Bailey, M.D. and his co-workers in the United Kingdom reported a potential biomarker for autism that can be measured from a blood spot. The biomarker is secreted amyloid precursor protein-alpha (sAPP). In their study, they found that 60% of children with autism showed elevated sAPP.



*Judy Van de Water, Ph.D.,
University of California,
Davis*

Another potential early biomarker was reported by Judy Van de Water, Ph.D. and Lisa Croen, Ph.D, who measured maternal antibody reactivity to the fetus during mid-pregnancy in mothers who had participated in a prenatal screening program in California. They found that mothers whose children developed autism had higher levels of this immune marker during pregnancy.



*Deborah Fein, Ph.D.,
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Connecticut*

Earlier detection and treatment will certainly result in better outcomes for individuals with autism. In 2008, the first peer-reviewed scientific articles were published on the topics of recovery from autism and prevention of the disorder through early intervention. Debby Fein, Ph.D., a member of Autism Speaks Scientific Advisory Board, has been documenting cases of recovery from autism for the past few years. Dr. Fein reviews evidence that between 3-25% of children are no longer diagnosed with autism and have normal cognitive, adaptive and social abilities. Early indicators here include increased IQ, improved receptive language & imitation skills and decreased autism symptoms. In most cases, the changes are thought to be the result of behavioral intervention. A second article describes a model of prevention of autism via early detection and early intervention.

The model describes how environmental enrichment through early intervention can mitigate the influences of genetic and environmental risk factors and alter the trajectory of brain development such that a subgroup of children never develops the full blown syndrome of autism.

As new methods for autism detection and treatment become available, it is essential that we consider how these new findings are going to be disseminated to the practicing clinician. Discovery of a biomarker for early detection or a new medical treatment for autism will only have impact if clinicians in the community are aware of this information and use it. For example, in 2008, it was reported that rates of mortality in individuals with autism are twice that of the general population. Epilepsy and infectious disease were found to be the most common cause of mortality. This suggests that mortality in autism could be reduced with appropriate access to care and physician training.

The last decade has witnessed a dramatic increase in the number of scientists who are turning their creative minds and efforts toward discovering the causes of, and effective treatments for, autism. Many of these scientists are young people who are just starting their careers and rely on Autism Speaks to fund their fellowships and research. As a science, autism research is now becoming mature enough to yield what promises to be truly ground-breaking discoveries.
