Autism Speaks Top 10 Autism Research Achievements of 2011

Leading Autism Advocacy Organization Documents Progress to Discover Causes and Treatments for Autism Spectrum Disorders

NEW YORK, N.Y. (December 20, 2011)

De Novo Genetic Changes Provide New Clues for Autism
Four studies show spontaneous mutations in DNA may contribute substantially to autism occurrence

This year, four separate studies shed new light and confirmed earlier findings that in some – perhaps many – cases, genetic mutations associated with autism arise in an egg or sperm or very early in embryonic development. As such, they are not present in the genetic makeup of either parent. Together, the four studies identify hundreds of places in the human genome where spontaneous, or "de novo," mutations could increase the risk of ASD, possibly by altering early brain development.

Though rare, de novo mutations may contribute to the development of autism in a substantial number of families with just one child on the spectrum, the researchers agreed. Some went further, noting that de novo mutations might explain why advanced parental age at the time of conception appears to increase the risk that a child will develop an autism spectrum disorder (ASD). Other studies have suggested that de novo genetic mutations in eggs and sperm become more common with age.

In addition to emphasizing the diversity of genetic contributions to ASD, these studies set the groundwork for finding new candidate genes and gene networks and for the potential development of treatments specific to certain subtypes of autism.

In years past, most autism gene research focused on inherited mutations – present in one or both parents. Increasingly, however, researchers are looking at de novo variations in genes involved in the formation and function of brain cell networks. The four new studies strongly suggest that this new focus is the right direction and offer further clues on the particular areas of the genome that should be targeted by future investigation. The findings were made possible, in part, by technological advances that enabled a shift from looking at large mutations to very small DNA changes.

The three largest studies, published simultaneously in the journal *Neuron*, analyzed DNA samples from children and parents in the Simons Simplex Collection, a newly assembled repository of over 1,000 U.S. and Canadian families with only one child on the autism spectrum. Using DNA chip, or microarray, technology, the researchers scanned for genetic mutations known as copy number variants (CNVs). CNVs can range from tiny deletions in the genetic code to extra copies of a large DNA sequence.

Among other findings, their results confirmed previous smaller studies that found higher rates of spontaneous CNVs in children with ASD than in their non-affected siblings. The researchers also found that many of these non-inherited mutations affect genes or gene networks involved in brain development and have been implicated in past studies of autism and other mental disorders.

For example, they found a strong link between autism and CNVs in a region of the genome associated with Williams-Beuren syndrome, a developmental disorder marked by extreme sociability. While people with Williams-Buren syndrome are missing copies of DNA in this region, some people with autism have extra copies.

Overall, the researchers estimate there may be several hundred locations on the human genome where de novo mutations could increase the risk of ASD, further highlighting the complexity and variety of autism's causes.

The fourth study (http://www.nature.com/ng/journal/v43/n6/full/ng.835.html) looked for spontaneous mutations in 20 people with autism. This study likewise used DNA from the Simons Simplex Collection, but rather than test broadly for CNVs, the researchers used a genetic sequencing technology that targets only the protein-coding parts of the genome. The researchers found four spontaneous gene mutations that likely play a causal role in the development of autism. The researchers also noted that the four participants who carried these genetic mutations had particularly severe core symptoms of autism – suggesting that these particular genes warrant further investigation and may be associated with promising treatment targets.

Together, the four studies are the first set of experiments to offer a detailed genetic analysis of the Simons Simplex Collection, one of the largest databases focusing on families with only one child on the autism spectrum. This collection uniquely complements other large autism databases such as Autism Speaks' Autism Genetic Resource Exchange (AGRE), which focuses on families with more than one child on the spectrum.

Gilman SR, Iossifov I, Levy D, et al. Rare de novo variants associated with autism implicate a large functional network of genes involved in formation and function of synapses. Neuron. 2011 Jun 9;70(5):898-907.

Levy D, Ronemus M, Yamrom B, et al. Rare de novo and transmitted copy-number variation in autistic spectrum disorders. Neuron. 2011 Jun 9;70(5):886-97.

O'Roak BJ, Deriziotis P, Lee C, et al. Exome sequencing in sporadic autism spectrum disorders identified severe de novo mutations. Nat Genet. 2011 Jun;43(6):585-9. [Epub 2011 May 15.]

Sanders SJ, Ercan-Sencicek AG, Hus V, et al. Multiple recurrent de novo CNVs, including duplications of the 7q11.23 Williams syndrome region, are strongly associated with autism. *Neuron*. June 9, 2011;70(5):863-85.