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Innovations

The Genetics of Autism

It has been more than 50 years since autism was first identified, but its cause remains a mystery. Some experts believe the disorder is increasing in incidence, but others believe the number of diagnosed cases is on the rise—and increasing from 10–17 percent per year—because of advances in autism awareness, diagnosis, and/or classification. Currently, two to six children per 1,000 in the United States have an autism spectrum disorder. The spectrum includes severely mentally retarded individuals with epilepsy and no speech, classic autism, Asperger syndrome, and the even milder, broader autism phenotype. Rare, but severe, disorders included in the definition are Rett syndrome and childhood disintegrative disorder. Together, approximately 1.5 million Americans live with some form of autism. Recent research suggests that 425,000 children under 18 in the US have an autism spectrum disorder; 114,000 of these are under age 5.

Autism researchers are moving to better understand the causes of the neuropsychiatric disorder by using newly available tools to delve into the underlying genetics. Currently leading a major discovery project is the not-for-profit autism advocacy group, the National Alliance for Autism Research (NAAR) based in Princeton, NJ, with 45 employees nationwide. NAAR got its start 10 years ago through funding provided by parents of children with autism. According to Andy Shih, PhD, Chief Science Officer at NAAR, "Our mission is to support and fund biomedical research in autism so that we can develop a better understanding of disease mechanisms that will hopefully one day enable delivery of targeted treatment and eventually cure."

In summer 2004, the first phase of the NAAR Autism Genome Project (AGP), developed and facilitated by Dr. Shih, was launched with the goal of identifying autism susceptibility genes. The project is a partnership between NAAR and four institutes of the National Institutes of Health (NIH). The project brings together four well-known autism research teams: The Autism Genetics Cooperative (AGC); the International Molecular Genetic Study of Autism Consortium (IMGSAC); the Center Program for Excellence in Autism Research, funded by the NICHD; and the Autism Genetics Resource Exchange (AGRE), a gene bank and research consortium formed by the autism advocacy organization, Cure Autism Now (CAN). "The NAAR AGP has put the entire autism genetics research field together on one page, working together to solve a common problem," says Shih. Together, the consortium includes 170 researchers from about 50 research institutions in Europe and North America and is the largest research collaboration devoted to the genetic study of autism.

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Looking for Susceptibility Genes

Although NAAR and the international consortium it helped form for the AGP study are not exactly sure what genes they are looking for, they are convinced of a genetic contribution to the disorder. "Earlier twin studies done over the past couple of decades showed that autism has a very strong genetic component," says Shih. Because of that, it has often been called the most heritable of all neuropsychiatric disorders. Research shows that a family with one child with autism has a 5 to 10 percent chance of having another child with the disorder. Conversely, the risk is only 0.1 to 0.2 percent for having a child with autism if the family has no other children with the condition.

"Autism is genotypically and phenotypically enormously complex and heterogeneous," he says. "We see a spectrum of deficits in the communications, motor skills, and social domains." Because of that Shih and colleagues do not believe autism is a single gene disorder where you can work through Mendelian genetics and positional cloning to eventually narrow in on the particular gene. Instead, the AGP is a gene discovery study. "Autism has a multigenic base meaning it involves perhaps up to 20 interacting genes and there is also probably an element of environmental influences as well in its etiology," explains Shih.

Previous autism genetics studies used relatively small data sets, approximately 100s of families. The largest genetic study prior to the AGP involved about 350. "The results from these studies were not terribly compelling," says Shih. He explains that previous research points the way to where gene clusters for autism may be located, but he comments that the level of confidence in these regions harboring real links to the disorders are not high. "You get a few peaks in the genome from the scans which are suggestive of regions that are harboring the genes, but there is no broad consensus where those peaks are, never mind what the specific genes are and how they might interact," says Shih. Genes located on chromosomes 2, 7, 15, and 16, as well as the female X chromosome, have been suggested, among others.

6,000 Sample Data Set

Much like other voluntary health organizations, NAAR had been funding small pilot programs and fellowships into autism research. "But given the huge scientific challenges presented with autism — heterogeneity and the genetic complexity — we recognized about 4–5 years ago that in order to enable the kind of breakthrough needed by the field, unless we have a large sample set, it would be unlikely we can subset the population into groups with more simplified clinical presentations—phenotypes—that would allow more-effective genetic analysis," says Shih.

In 2003, NAAR and the National Institutes of Health announced the AGP. In July 2004, the work began thanks to $2 million in NAAR funding and $2.5 million from the NIH. In its first phase, essentially a basic, although large-scale, genotyping and linkage study, AGP assembled more than 6,000 genetic samples from 1,500 families affected by autism. Each family included two children with an autism spectrum disorder and their parents. "This first phase, this gigantic genome scan, will hopefully provide us with a higher level of confidence in the regions we've identified before and maybe even identify regions that had not previously been identified," says Shih.

Each sample will be analyzed with two technologies: a genome scan with Santa Clara, CA-based Affymetrix's GeneChip Mapping 10K Array (performed on-site by Translation Genomics Research Institute in Phoenix, AZ) and a second scan based on microsatellite technology to be conducted by NIH's Center for Inherited Disease Research (CIDR) located at Johns Hopkins. The hope is that the 10K Array will let researchers study more than 10,000 single-nucleotide polymorphisms (SNPs)—single-base-pair genetic changes—in each sample to identify possible DNA mutations associated with autism. The older microsatellite technology, by comparison, is limited to studying about 400 markers. For decades and until very recently, this was the tool of choice for gene hunting. Historically, however, it has been difficult and complex to use this for in-depth analysis. "But there is no clear consensus whether SNP or the microsatellite approach is best when used for complex disease genome scans," says Shih, explaining why both technologies will be used. Other genome analysis tools provided by Illumina (San Diego, CA) and deCODE (Reykjavik, Iceland) were also considered with the Affymetrix GeneChip.

Second Phase

"We are deep into planning of the second phase now, which is essentially a functional genomics phase we call the Autism Gene Discovery Initiative," says Shih. NAAR and NIH will begin by forming an international funding consortium. The second phase of the project will require about $15 million to $20 million over the next 5 years and will be provided to the scientists to identify the genes associated with a certain phenotype or risk for autism.

Once the genomic intervals have been identified, researchers will have both an idea where the genes for autism are with the aim of finding unique anomalies in people with autism. "The real challenge will come in phase II once this consortium has identified the intervals from the scan and started to drill down. That is when it will require a fusion of classical mammalian genetics, progressive thinking about population statistical genetics, high-throughput, cutting-edge technology, and obviously a collaborative effort in terms of analysis and interpretation of data," says Shih. "There have been a lot of theories about the genetic etiology of autism. Certainly mutations within open-reading frames is a possibility, but there may also be mutations in the regulatory regions that will control the level of expression, the timing of expression," he theorizes. "There is additional complexity associated with microdeletion and insertion on some chromosomes."

Interested researchers will abide by NIH's peer-reviewed competitive process to receive funding for second-phase research. Shih admits that the AGP consortium is probably the most competitive just because of the sheer size of the collaboration and sample set involved. Additional private/public funding partnerships, including the Canadian Institute of Health Research, the Department of Health in Ireland, and the UK Medical Research Council, are already in on the project. Says Shih, "NAAR is looking at the AGP as a way to unite the field through quality science."

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