Neuroscience Today, Neurology Tomorrow

Research Reports and Clinical Perspective

The longest 9 months of a neurologist's life may well be the 9 months of pregnancy as we try not to anticipate the consequences of genetic, metabolic, and congenital defects that are part of our professional knowledge base. If we had one wish, it might well be to eliminate all such developmental and perinatal events in the future. For now, however, autism and mental retardation remain among the most poorly understood of all neurological disorders. In this installment of Neuroscience Today, Neurology Tomorrow, we review two remarkable studies that represent important first steps in our quest to prevent and treat these disorders. We are given a pleasant surprise: Rett syndrome may not be irreversible. We are also shown that many paths lead to autism spectrum disorders but so too may these one day represent opportunities for prevention and treatment. Please send us news of your research, and comments on this month's column to clinicalneurologynews@elsevier.com.

BY RICHARD J. CASELLI, M.D.

Rett Syndrome Reversibility

Mutations in the X-linked MECP2 gene that cause the characteristic symptoms of the severe autism spectrum disorder Rett syndrome are reversible in a mouse model of the disease, reported Jacky Guy of Edinburgh University and her colleagues.

The researchers created mice in which the mouse version of the gene, Mecp2, is silenced. In another set of mice, the researchers inserted a transgene that could activate the silenced Mecp2 gene in the presence of the estrogen analogue tamoxifen. When 17 male mice with both genetic modifications were initially given five daily injections of tamoxifen 3-4 weeks after birth, the abrupt reactivation of the Mecp2 gene caused neurologic symptoms to develop in 9 mice, which died soon after the series of injections. But the other eight mice did not develop any detectable symptoms, survived as long as wild-type mice, and bred normally (Science 2007;315:1143-7).

In a similar set of male mice, gradual activation of the Mecp2 gene with weekly tamoxifen injections (later followed by three daily booster injections) eliminated toxicity. Tamoxifen treatment rescued five of six symptomatic mice to a point at which they showed only mild symptoms and survived much longer than the maximum-recorded life span of mice with a silenced Mecp2 gene (17 weeks). The mouse that died had less Mecp2 gene activation, "which may explain failure to rescue," Ms. Guy and her associates wrote.

Rett syndrome affects females almost exclusively as a result of the random inactivation of one X-linked MECP2 gene allele during female development, causing the mosaic expression of mutant and wild-type MECP2 gene alleles in the brain. Therefore, the researchers performed the same experiments in female mice that were heterozygous for the silenced Mecp2 gene (with or without the transgene that could activate the Mecp2 gene in the presence of tamoxifen). Tamoxifen caused these mice to revert progressively to a phenotype that was identical or very similar to wild-type, whereas those that were not created to activate the Mecp2 gene in the presence of tamoxifen did not have any improvement in symptoms. During electrophysiologic testing, hippocampal long-term potentiation was significantly reduced in heterozygous female mice in which one copy of the Mecp2 gene was silenced. This defect was abolished with tamoxifen treatment in females that were created to activate the Mecp2 gene in response to the drug.

"The restoration of neuronal function by late expression of MeCP2 suggests that the molecular preconditions for normal MeCP2 activity are preserved in its absence," the investigators wrote.

"The experiments do not suggest an immediate therapeutic approach to Rett syndrome, but they establish the principle of reversibility in a mouse model and, therefore, raise the possibility that neurological defects seen in this and related human disorders are not irrevocable."

Dr. Caselli's comment: Rett Syndrome, an X-linked form of mental retardation, falls at the severe end of the autism spectrum of disorders, and affects 1 in 10,000 girls. Although it has been linked to mutations of the MECP2 gene, it has been poorly understood. The study of Ms. Guy and her colleagues represents a major breakthrough, and offers the first tangible ray of hope that effective therapy may one foreseeable day be possible. They show that neurons develop normally in the face of a MECP2 mutation, and that the effects of the mutation, clinically and physiologically, are reversible with gene activation (that is safer and more effective if done gradually) even after symptoms are established. This is a most welcome surprise, but accomplishing this in human patients remains a major challenge. The authors are to be commended for not overstating the proximity of therapy, but their elegant demonstration that a dysfunctional brain can be rescued, that it is not too late, is itself nothing short of miraculous.

Familial Versus Sporadic Autism

Sporadic autism spectrum disorder is associated with a significantly higher frequency of de novo copy number mutations than the less common familial type of the disorder, reported Jonathan Sebat, Ph.D., of Cold Spring Harbor (N.Y.) Laboratory, and his colleagues.

The researchers performed whole-genome scans of a sample of patients, control subjects, and their biologic parents with an 85,000-probe microarray. The sample consisted of 118 families containing a single child with autism, 47 families with multiple affected siblings, and 99 control families with no cases of autism; there was a complete parent-child "trio" for 195 patients and 196 healthy control individuals. They excluded cases of syndromic autism and known cytogenetic abnormalities (Science 2007 March 15 [Epub doi:10.1126/science.1138659]).

A total of 17 different copy number variants (CNVs)—gains or losses of large chunks of DNA sequence—were confirmed to be de novo in 14 patients and 2 control individuals. Most of the mutations had never been seen before, and only the largest ones had been reported previously in the literature. Spontaneous CNVs were found significantly more often among patients with autism spectrum disorder (14 of 195) than in unaffected individuals (2 of 196). These also occurred in a significantly higher percentage of sporadic (10%, 12 of 118) than familial cases (2%, 2 of 77).

The limited resolution of genome microarray scans likely means that the researchers could not "detect the vast majority of CNVs. Much smaller deletions or even point mutations can produce the same consequences as the larger, more easily detectable events," they wrote.

"The strong association of de novo CNVs with ASD is consistent with such mutations being a primary cause in most cases rather than merely contributory," the investigators wrote. The normally high male:female ratio for ASD was lower among patients with de novo CNVs (9 males and 5 females, 1.8:1) than it was in the overall sample (163 males and 32 females, 5:1), which "suggests that de novo CNVs that are detectable by our method have increased penetrance, and thus contribute to disease more equally in females and males."

Five de novo mutation events in particular occurred in single genes that are known to be associated with fetal brain development, mental retardation, epilepsy, or spinocerebellar ataxia type 2. These five genes are among the top 3% of human genes in length, which "may simply reflect that large genes, by virtue of their size alone, are more likely to be affected by random rearrangements."

None of the de novo CNVs were observed more than twice and most were seen only once. "Lack of recurrence may in fact reflect an underlying reality that autistic behavior can result from many different genetic defects," the investigators wrote.

Dr. Caselli's comment: Gene array analyses of sporadic cases of autism and mental retardation are the newest and most powerful flashlights illuminating the dark of these poorly understood but often tragic disorders. Dr. Sebat and his colleagues show that there is a significant association with one form of genetic disorder, gene copy number variants, and autism, and this is true for both boys and girls despite the greater prevalence of autism in boys. The findings also imply that many genes may contribute to autism, and the largest genes may be among the most susceptible simply by the fact that their greater size provides greater opportunity for error. Similar genetic associations have been identified in other forms of mental retardation (for example, Neurology 2007;68:743-50). Autism and mental retardation may be the end product of multiple forms of genetic disturbance that cumulatively add up to a similar phenotype. If so, then further questions arise whether it is truly a cumulative effect, or whether certain strategic genetic errors are to blame. Why do some people carry some of the same genetic changes and yet remain asymptomatic? What predisposes to such mutations? And as was shown for MECP2, might any of these be reversible? With this first ray of light, we realize how much more there is to be learned. ■

Clinical perspective by Dr. Caselli, *chair of neurology at the Mayo Clinic, Scottsdale, Ariz., and professor of neurology at the Mayo Medical School, Rochester, Minn.*

Research reports by Jeff Evans, senior writer.

NIH Launched an Online Genetics Site for Parents

The National Institutes of Health has launched "Health Information Rx Program" to encourage physicians to refer parents of newborns diagnosed with genetic conditions to Genetics Home Reference, a free, patient-friendly Web site with information on more than 500 genetic topics. The Web site also provides information on newborn genetic screening for expectant mothers. Program details are availabe from the Web site: ghr.nlm.nih.gov. ■

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