# Scientists Find Promising Therapies for Fragile X and Down Syndromes

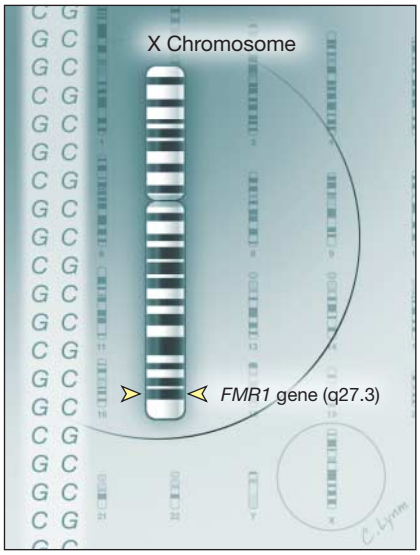
Bridget M. Kuehn

CLINICIANS HAVE LONG VIEWED the intellectual disabilities associated with developmental disorders, such as fragile X and Down syndromes, as irreversible or untreatable. However, emerging data suggest that a number of potential drug therapies targeting the molecular pathways involved in these disorders may one day help to improve cognition, memory, and behavior in patients with these genetic conditions.

Advances in the understanding of the genetic and molecular basis of developmental disorders, as well as the creation of mouse models for these conditions, have led scientists studying them to some surprising insights. Even later in life, mice with Down syndrome or fragile X syndrome (FXS) that are given targeted treatment can experience improvements in cognitive function. Findings from such animal studies have paved the way to human trials to assess some of these potential therapies, with some experimental therapies for FXS already entering late-stage clinical trials.

These developments have led to a "sea change" in the way developmental disorders are viewed by scientists and clinicians, said Mark F. Bear, PhD, professor of neuroscience at the Massachusetts Institute of Technology in Cambridge and a Howard Hughes Medical Institute investigator.

Bear explained that the genes linked to intellectual disorders cause such devastating and complex consequences for patients with these conditions that many concluded the damage was permanent. "The consequences can be so diverse, it is hard to imagine that small molecules could have an effect," he said. "But that's what we are finding."




**Therapies targeting cognitive and neurological deficits associated with fragile X syndrome are under study, based on genetic and molecular discoveries about the disorder.**

## FXS TRIALS

The discovery in 1991 that FXS is caused by the loss of the fragile X mental retardation 1 (*FMR1*) gene provided the clue scientists needed to begin to investigate the mechanism underlying the disorder's cognitive deficits and how such deficits might be treated.

Within a few years of this gene discovery, researchers described the protein the gene encodes, the fragile X mental retardation protein (FMRP), and created a mouse model in which the *FMR1* gene is knocked out (Krueger DD and Bear MF. *Annu Rev Med*. doi:10.1146/annurev-med-061109-134644 [published online ahead of print November 19, 2010]). Further study revealed that FMRP regulates the synthesis of proteins in the synapses between brain neurons. In healthy individuals, it accomplishes this by balancing the activity of metabotropic glutamate receptors (mGluR), which help trigger protein synthesis at the synapse. But when mutations in the *FMRI* gene cause a loss or reduction of FMRP, the result is excessive activity of mGluR5.

Based on the findings, Bear and his colleagues developed a theory that dysregulation of mGluR signaling caused the neurological deficits seen in the disorder (Bear MF et al. *Trends Neurosci*. 2004;27[7]:370-377). Robert Riddle, PhD, program director of the neurogenetics cluster at the National Institute of Neurological Disorders and Stroke, credited Bear's work for helping to kickstart the search for FXS therapeutics.

Animal studies then showed that knocking down the excessive activity of mGluR5 in particular could ameliorate some of the cognitive and neurological deficits seen in mice lacking FMRP, even if the treatment occurred later in the mouse's life. Importantly, the benefit of inhibiting mGluR has been demonstrated in FXS models in such evolutionarily distinct species as mice and fruit flies, noted Bear.

"It's an evolutionarily conserved relationship," he said. "We have a very strong rationale for the human studies."

Clinical trials have progressed quickly because multiple pharmaceutical companies had already developed drugs that target mGluR receptors. Bear cofounded Seaside Therapeutics to pursue development of a mGluR inhibiting drug for FXS, and the company

licensed an mGluR5 inhibitor from Merck & Co and began clinical testing. Since then, Novartis and Roche have begun clinical studies on other mGluR inhibitors.

So far, the results of phase 2 trials by Seaside and Novartis in adults with FXS suggest that the patients with the most severe symptoms may benefit from the drugs, Bear said. Bear's results have been presented at scientific meetings but not yet published. Novartis found improvements in stereotypic behavior, hyperactivity, and inapropriate speech in a subgroup of patients with a fully methylated *FMR1* promotor (Jacquemont S et al. *Sci Transl Med.* 2011; 3[64]:64ral). Bear explained because humans are often mosaic for the *FMR1* gene (some cells have functioning copies of the *FMR1* gene), some individuals may produce some FMRP protein. Those with more FMRP would likely have less severe symptoms, while those with the least amount of FMRP would have more severe symptoms. Both companies are proceeding with phase 3 trials, Bear said.

Other drugs that target the same or related pathways are also being tested. One of these is lithium, which acts on the same pathway as the mGluR inhibitors but is less selective, according to Bear. Another is the antibiotic minocycline, which has completed early human studies (Paribello C et al. *BMC Neurol*. 2010;10:91).

## TARGETS IN DOWN SYNDROME

Scientists studying Down syndrome also have been able to create mouse models of the disorder and have demonstrated that various drugs or drug candidates can help to improve cognitive symptoms in affected animals. The findings are leading to early clinical trials and to new strategies for studying the disorder.

"It's a beautiful example of translational research," said Mara Dierssen, MD, PhD, of the University of Cantabria in Barcelona. Dierssen chaired a symposium at the 2010 Society for Neuroscience meeting in November that highlighted how genomics, model animals, and systems-biology approaches have helped move Down syndrome researchers closer to developing therapeutics (Gardiner K et al. *J Neurosci*. 2010; 30[45]:14943-14945).

Previously, deficits associated with Down syndrome were considered intractable, noted Dierssen, so little research was directed at understanding the specific molecular pathways involved. But more information about the genetic basis of the disorder, and the creation of mouse models that recapitulate many of the symptoms of the disorder, have "given us insight on the cellular, molecular, and genetic underpinnings of the disease," she said.

One mouse model, Ts65Dn, has been particularly useful. Ts65Dn has hippocampal-related learning and memory problems similar to those seen in Down syndrome and has been used by several groups to identify several potential therapeutic targets, said Katheleen Gardiner, PhD, professor in the department of pediatrics and researcher at the Intellectual and Developmental Disabilities Research Center at the University of Colorado, in Denver. For example, Alberto Costa, MD, PhD, and colleagues at the University of Colorado in Denver found that Ts65Dn mice treated with memantine, an *N*-methyl-D-aspartate (NMDA)–receptor antagonist approved for the treatment of Alzheimer disease, had reduced deficits on memory tasks (Costa AC et al. *Neuropsychopharmacology*. 2008;33[7]:1624-1632).The scientists believe that the function of the NMDA receptors is disrupted by increased expression of several genes on chromosome 21 in Down syndrome and that memantine might help correct the dysfunction. Costa is recruiting participants for a preliminary clinical study of the drug in patients with Down syndrome (NCT01112683 at http://www.clinicaltrials.gov).

However, mouse models for Down syndrome have some serious limitations, Gardiner noted. In Down syndrome, also called trisomy 21, the condition is caused when the affected individual has part or all of an additional chromosome 21; thus, the genes involved in Down syndrome are all located on chromosome 21. But in mice, the mouse versions of the human genes found on chromosome 21 are spread across 3 chromosomes. For example, the Ts65Dn mouse model is trisomic for about only 50% of the protein-encoding genes found on human chromosome 21.

Such limitations have led some scientists to explore a systems-based approach, which they hope will allow them to zero in on the most important gene and protein interactions in the disorder. Gardiner explained that the cognitive deficits seen in patients with Down syndrome are not directly caused by the proteins encoded on chromosome 21 but rather by the effects of these proteins on other clinically important pathways. Thus, she and her colleagues comb the literature to identify pathways involved in intellectual disabilities that interact with proteins encoded by genes on chromosome 21.

"It's the biggest picture we can get," she said.

Gardiner hopes that identifying such potentially important pathways may lead to high-volume strategies for screening potential drug candidates. She and her colleagues are studying cell-based models of Down syndrome, such as induced pluripotent stem cell lines or white blood cell lines derived from patients. Such cell lines would express many of the relevant genes and could be used to develop a high-throughput system for screening large numbers of candidate drugs. For example, hundreds of drugs could be tested in white blood cell lines to determine each drug's effects on a particular pathway. Those that prove promising could be tested in induced pluripotent stem cell lines and then in mice models.

Gardiner said that therapies that result from research that is currently under way are unlikely to correct all of the cognitive deficits that patients with Down syndrome experience. However, the results in mice suggest that it may be possible to develop treatments that enhance cognition and memory

enough to improve patients' abilities to live independently and to ease their families' concerns about their long-term well-being, she said.

### BUILDING A FRAMEWORK

These promising developments have been aided by basic research and translational research funded by the National Institutes of Health (NIH). "It's a good example of benefit of basic and broad research," said Riddle.

Riddle noted that working groups across the NIH's various institutes have been established and have now developed strategic plans for FXS (http://tinyurl.com/2fmjnax) and Down syndrome (http://tinyurl.com/2anrbuk).

Additionally, an increased focus on translational research at the NIH in the past 10 to 15 years is providing more resources to help scientists studying developmental disorders to advance their studies to clinical trials, Riddle said. The institutes are also working cooperatively with drug companies to evaluate promising drugs in clinical trials. For example, the National Institute of Mental Health and the National Institute of Neurological Disorders and Stroke participated in a cooperative agreement with Seaside to bring its FXS drug to trials (NCT00965432 at http://www.clinicaltrials.gov).

If the therapies under study for FXS and Down syndrome prove effective, the approach may have implications for other developmental disorders that involve intellectual impairment or autism-like symptoms. Such disorders "involve genes that sit in pathways that regulate protein synthesis at synapses," Bear said. "The treatments developed for one may apply more broadly."

The findings in Down syndrome also may have implications for even more common disorders, such as Alzheimer disease, which occurs in many patients with Down syndrome, Dierssen said. "We are getting into learning and memory phenomena and the epigenetic changes underlying activity-dependent neural plasticity that allow adults to compensate for lesions and traumas," she said.

The research is also providing insight into normal brain function, the scientists agree.

"The brain is more plastic than we ever imagined," Riddle said. □

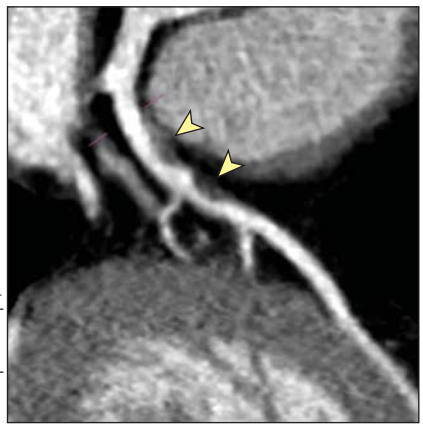
# Studies Hint at Benefits of Imaging as a Screening Tool to Detect Coronary Risk

Mike Mitka

CHICAGO—Research is producing very preliminary and somewhat optimistic evidence for using imaging as a screening technique for assessing cardiac risk in asymptomatic and symptomatic patients. But some experts caution that even if larger, more rigorous trials validate these findings, incorporating imaging into patient assessment faces great challenges because the added value to diagnosis, to treatment strategies, and to reducing hard clinical events remains unknown.

Researchers from the Medical University of South Carolina in Charleston presented findings from 2 such studies at the annual meeting of the Radiological Society of North America, held here in November. One showed the benefits of using coronary computed tomography angiography (cCTA) to risk-stratify patients with obesity and obstructive sleep apnea; the other examined the use of contrast-enhanced cCTA to identify black patients with noncalcified, and possibly vulnerable, plaque.

In the first study, researchers administered cCTA to 49 obese patients diagnosed with obstructive sleep apnea (mean age, 61 years; mean body mass index [BMI], 33) and to 46 obese patients without obstructive sleep apnea (mean age, 60 years; mean BMI, 30). The imaging showed that while the amount of calcified plaque in the coronary arteries was not significantly different between the 2 groups, patients with obstructive sleep apnea had a significantly higher prevalence of noncalcified and mixed plaque and also vessel narrowing and vessel involvement. Specifically, 88% of those with sleep apnea had narrowing in at least 1 vessel compared with 59% of patients without sleep apnea.



U. Joseph Schoepf, MD/MUSC

**Contrast-enhanced coronary computed tomography angiography can identify noncalcified plaque (arrowheads) in arteries.**

U. Joseph Schoepf, MD, lead investigator and a professor of radiology and medicine and director of cardiovascular imaging at the Medical University of South Carolina, said that the findings suggest that cCTA might be used as a screening tool to refine risk assessment for this type of obese patient because obstructive sleep apnea is not a recognized risk factor in standard stratification methods. "Imagine a physician works up a patient for cardiovascular risk using the Framingham risk score, but overlooks those patients with obstructive sleep apnea," Schoepf