

Rare diseases offer insights into autism spectrum disorders

Preliminary laboratory studies suggest new biological targets for intervention.

At the November 2008 annual symposium of the Autism Consortium—a research collaboration of 14 institutions in Boston—several speakers discussed progress in a promising avenue of basic research: using rare single-gene disorders to better understand the brain basis of autism spectrum disorders.

Although the research is still preliminary, the studies suggest that—at least in mice or fruit flies—it is possible to reverse the molecular abnormalities caused by certain genetic mutations, thereby alleviating or even eliminating particular symptoms.

Of course, it's a long leap from mice and fruit flies to people. (Researchers have been curing cancer in mice for decades.) But the recent findings in single-gene disorders have caused a significant shift in the way that researchers think about autism spectrum disorders.

Rare but relevant disorders

Collectively, single-gene disorders account for only 10% to 15% of all cases of autism spectrum disorders. It's easier, however, to study the biological effects of a single gene than it is to study the effects of multiple genes acting together. For that reason, molecular biologists are using these rare disorders to understand what causes the communication difficulties, impeded development, and other symptoms of autism spectrum disorders.

Rett syndrome. This disorder, caused by mutations in the MECP2 gene, leads to physical and mental problems that first appear between 6 months and 18 months. All patients with Rett syndrome suffer from symptoms of an autism spectrum disorder, such as hampered development and repetitive behaviors. Rett syndrome may also cause tremors and breathing problems.

In 2007, researchers at Edinburgh University published a paper about

their success in reversing symptoms in mice. They first “silenced” the MECP2 gene to breed mice that developed neurological symptoms similar to those in people with Rett syndrome. When the mice reached adulthood, the investigators used a drug to reactivate functioning of the MECP2 gene. After drug treatment, symptoms subsided and the mice appeared normal.

Tuberous sclerosis complex. This disorder is caused by mutations in either the TSC1 or TSC2 gene. It is characterized by tumor formation, especially in the brain or eyes, but may also cause mental retardation, epilepsy, and other problems. Anywhere from 25% to 60% of children with this complex develop an autism spectrum disorder.

The TSC1 and TSC2 genes code for proteins known as negative regulators that suppress production of other proteins. One such protein, mTOR, becomes overactive and interferes with normal brain function.

In 2008, researchers used rapamycin (Sirolimus), an immune system suppressant that prevents the rejection of transplanted organs, to suppress mTOR signaling in mice genetically engineered to exhibit the symptoms of tuberous sclerosis complex. After treatment with rapamycin, the mice performed better on tests of learning and memory. The study demonstrated, in principle, that a drug could reverse some symptoms of a genetic mutation—even when the mutation remained.

Fragile X syndrome. This disorder, caused by mutations in the FMR1 gene, results in mental retardation, epilepsy, and other problems. About 15% to 30% of patients develop symptoms of an autism spectrum disorder.

In 2005, researchers at the Albert Einstein College of Medicine tested lithium and other inhibitors of the neurotransmitter glutamate in a fruit fly model of fragile X syndrome. The

researchers first deactivated the FMR1 gene in flies to simulate learning and memory problems—exhibited as lethargic and inept courtship behavior. Then they tested various glutamate inhibitors, given during the larval stage or after the flies reached adulthood. When given during development, the glutamate inhibitors eliminated the learning and memory problems in flies. When given to adult flies, the drugs reduced the deficits.

In 2007, researchers at the Massachusetts Institute of Technology used a different approach to reverse symptoms of fragile X syndrome in mice. They created “double-mutant” mice, bred with both the FMR1 defect and another mutation that inactivated a brain chemical known as PAK. The double-mutant mice behaved close to normal, showing—in principle—that PAK may provide a new target for therapy.

Future directions

This basic science, while promising, is still in the early stages. A particularly daunting challenge is finding a safe delivery mechanism (sometimes called a vector) for gene therapy in people.

But the investigations into single-gene diseases have given researchers new ways to evaluate the molecular basis of autism spectrum disorders. And for the first time, it seems possible that—one day—they may find ways to alleviate the devastating effects of neurodevelopmental disorders. ♥

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For more references, please see www.health.harvard.edu/mentalextra.

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