NEWS

Autism and cancer share genetic roots, researchers find

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Bigger heads: In mice that lack PTEN in a small subset of neurons, the cerebral cortex is thicker and the dentate gyrus region of the hippocampus is larger.

Genetic research in the past few years has revealed that autism unexpectedly shares common roots with cancer. Based on these intriguing findings, some researchers are turning to rapamycin, a proven cancer drug, as a potential treatment for autism.

Of the 18 candidate genes for autism uncovered so far[1], 3 genes ? PTEN, TSC1 and TSC2 ? are part of a biochemical pathway with a long-established role in cancer.

Knocking out these genes in mouse brains causes enlarged neurons, seizures and behaviors similar to autism.

"[This] brings about an enormously optimistic idea that, for some small subset of kids with autism, treatment of this pathway with a drug might reverse some symptoms," says microbiologist **Arnold Levine** of the Institute for Advanced Studies at Princeton University.

Though the number of people with autism who have these mutations is relatively small, the research may pinpoint the brain regions affected in all types of the heterogeneous disorder.

"If autism is like the destruction of a house, then you can burn the house, knock down the beams of the house, or flood the house, but at the end of the day you have the same thing: no house," says **Luis Parada**, director of the Kent Waldrep Center for Basic Research on Nerve Growth and Regeneration at the University of Texas Southwestern Medical Center.

"Though the pathway we're modeling may only represent two percent of autistic patients," Parada

says, “it could be pointing to exactly where, in the brain, things have to go wrong."

Most cell types in the body rely upon the phosphatidylinositol-3-kinase (PI3-kinase) biochemical pathway for cell growth, survival, aging and, ultimately, programmed cell death.

Since the mid-1980s, scientists have known that dysfunction of this pathway is important in many types of human cancer. Parada likens the pathway to a river with multiple dams ? any one of which, if broken, could lead to unbridled cell growth and tumor formation.

A role for PTEN:

What turned out to be a very important dam along that river was discovered in 1997: PTEN, an enzyme that is supposed to suppress tumor formation. About 70 percent of all human cancers exhibit mutations in the PI3-kinase pathway. “More often than not it's the PTEN dam that's fallen apart," says Parada.

Interestingly, people with some germline mutations ? which are incorporated into the DNA of all of the body?s cells ? in PTEN have also been known to have enlarged heads, seizures, or autism. One 2005 study found that 3 out of 18 children with autism carry a mutation in the PTEN gene[2].

"I think that there are going to be many more people with PTEN mutations than we realize," says Levine. "Depending on your genetic background, those mutations could lead to no abnormal phenotype, or they could be significant in the brain and cause autism, or [be] significant in the breast tissue and cause breast cancer."

To investigate the effect of these PTEN mutations in the brain, Parada made mice that lack PTEN in a small subset of neurons in the cerebral cortex and a part of the hippocampus called the dentate gyrus. "If we knocked out PTEN in every cell in the brain, consequences would be so overwhelmingly dramatic that we wouldn't be able to tell what was going on," Parada says.

Those mice huddle by themselves in the corner of their cage, rather than interacting with litter mates; show an increased sensitivity to lights and other sensory stimuli; and many have sporadic seizures, much as those with autism do.

In later anatomical analysis of the brains, Parada found "unique deranged properties" in the neurons that do not have PTEN: "The neurons were much bigger, and the projections were far more complex, making many more possibilities of synaptic interaction,” he says.

His team is repeating the experiments by knocking out TSC1 and TSC2, mutations in which lead to Tuberous sclerosis complex (TSC) in humans.

Complex disorder:

TSC afflicts 1 in 6,000 people and is characterized by benign tumors all over the body, but mostly in the brain. Though these tumors are non-cancerous, people with TSC have an increased risk of getting kidney or brain cancer later in life.

Most individuals with TSC have seizures, and up to half are also diagnosed with autism spectrum disorders[3].

TSC1 and TSC2 are two more 'dams' sitting downstream of PTEN on the PI3-kinase pathway, Parada says.

If Parada?s TSC knock-out mice show similar phenotypes to the PTEN knock-outs, "that would constitute a further validation of our hypothesis that we're on to a pathway that has very important consequences for how the brain functions socially," Parada says.

The subset of individuals with mutations in the PI3-kinase pathway may find hope in rapamycin. Approved by the **US Food and Drug Administration** a decade ago to treat kidney transplant rejection, rapamycin blocks a protein complex called mTOR, which sits at the downstream end of the pathway. Rapamycin and related compounds are already established treatments for many types of cancer.

In January, researchers from the Cincinnati Children's Hospital reported that when 25 individuals were given rapamycin over one year, their tumor volume decreased by nearly 50 percent. However, 12 months after the therapy was stopped, their tumors increased to nearly their original size[4].

"There is much enthusiasm for these trials," says **David Kwiatkowski**, program leader of the Cancer Genetics Program at the Dana-Farber/Harvard Cancer Center.

In June, Kwiatkowski and colleagues from the University of California, Los Angeles, reported that giving rapamycin to TSC knock-out mice for three days cuts down the chances of death, prevents abnormal brain enlargement, and reverses learning and memory problems[5].

The team, collaborating with researchers from the University of Cambridge, is leading a clinical trial to test whether rapamycin can restore short-term memory in people with TSC.

Parada is also giving his PTEN knock-out mice rapamycin to see if it affects their non-social behaviors or brain anatomy. Parada declines to reveal details of the unpublished findings, but says the preliminary results are “promising.”

Even if the drug proves effective in people, however, some doctors are worried about the harsh side effects of suppressing the immune system.

"There's concern that it would need to be continued for the lifetime of the patient, which is not a pleasant thought," Kwiatkowski says.

References:

1. Abrahams B.S. and Geschwind D.H. *Nat. Rev. Genet.* **9**, 341-355 (2008) **PubMed ?**
2. Butler M.G. *et al. J. Med. Genet.* **42**, 318-321 (2005) **PubMed ?**
3. Wiznitzer M. J. *Child Neurol.* **19**, 675-679 (2004) **PubMed ?**
4. Bissler J.J. *et al. N. Engl. J. Med.* **358**, 140-51 (2008) **PubMed ?**
5. Ehninger D. *et al. Nat. Med.* Epub ahead of print. **PubMed ?**