'Language Gene' Has a Partner

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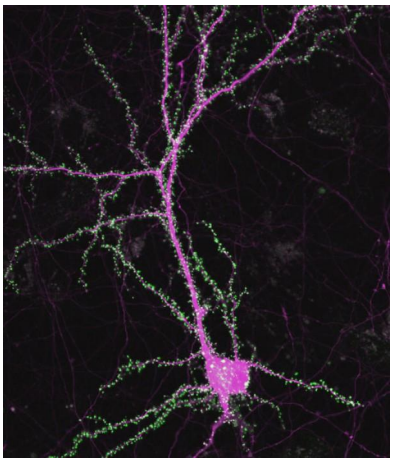

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Speak easy. The language gene *FOXP2* may work through a protein partner that stimulates the formation of excitatory connections (green) in nerve cells (magenta).

1.Few genes have made the headlines as much as *FOXP2*. The first gene associated with language disorders, it was later implicated in the evolution of human speech. Girls make more of the FOXP2 protein, which may help explain their precociousness in learning to talk. Now, neuroscientists have figured out how one of its molecular partners helps *Foxp2* exert its effects.

2. The findings may eventually lead to new therapies for inherited speech disorders, says Richard Huganir, the neurobiologist at Johns Hopkins University School of Medicine in Baltimore, Maryland, who led the work. *Foxp2* controls the activity of a gene called *Srpx2*, he notes, which helps some of the brain's nerve cells beef up their connections to other nerve cells. By establishing what *SRPX2* does, researchers can look for defective copies of it in people suffering from problems talking or learning to talk.

3. Until 2001, scientists were not sure how genes influenced language. Then Simon Fisher, a neurogeneticist now at the Max Planck Institute for Psycholinguistics in Nijmegen, the Netherlands, and his colleagues fingered *FOXP2* as the culprit in a family with several members who had trouble with pronunciation, putting words together, and understanding speech. These people cannot move their tongue and lips precisely enough to talk clearly, so even family members often can't figure out what they are saying. It "opened a molecular window on the neural basis of speech and language," Fisher says.

4. A few years later, other researchers showed that the *FOXP2* gene in humans differed from the chimp version by only two bases, the "letters" that make up DNA. That small difference may have affected *Foxp2* performance such that animal calls could eventually transform into the human gift of gab. In 2009, a team put the human version of the gene in mice and observed that the rodents produced more frequent and complex alarm calls, suggesting these

mutations may have been involved in the evolution of more complex speech. But how *Foxp2* works has largely remained a mystery.

5. Huganir didn't start out trying to solve this mystery. He was testing 400 proteins to see if they helped or hindered the development of specialized junctions between nerve cells, called synapses, which allow nerve cells to communicate with one another. A single neuron can have up to 10,000 synapses, or connections to other neurons, Huganir says. Of the 10 proteins he identified, one that strongly promoted synapse formation was *Srpx2*, a gene other researchers had linked to epilepsy and language problems.

6. Huganir and his colleagues examined *Srpx2* activity in isolated nerve cells, determining that it stimulated the formation of "excitatory" connections, ones where a "turn on" message was conveyed to the receiving nerve cell. *Srpx2* also enhanced the number of excitatory connections in the part of the brain in developing mice that is the equivalent of the human language center, the researchers report online today in *Science*. Because *Foxp2* regulates the activity of several genes, including *Srpx2*, Huganir and his team took a closer look at how *Foxp2* affected this gene. When *Foxp2* is around, *Srpx2* makes fewer excitatory synapses, they report. It may be that the right balance of excitatory synapses and other connections may be necessary for complex vocalizations, Huganir suggests.

7. As a final test, the researchers looked to see how changing the activity of the *Srpx2* gene affected alarm calls of baby mice. Mice pups separated from their moms call for help with squeals too high-pitched for humans to hear. When the researchers artificially inhibited *Srpx2*'s activity, the mice squealed less. But the pups squealed normally again when gene activity was restored, Huganir and his colleagues report.

8. The work "shows that *Foxp2* affects synapse formation through *Srpx2*," says Svante Pääbo, a paleogeneticist at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, who has studied *Foxp2* in primates and in mice. "It is the first target gene of *Foxp2* that has a clear function with respect to neuronal function."

9. Huganir says his team still doesn't know whether *FOXP2* affects nerve cells that relate to language processing or nerve cells that control muscles involved in talking. Still, he says the link to synapse formation via *SRPX2* "is an important clue how *FOXP2* could be regulating language development."

http://news.sciencemag.org/biology/2013/10/language-gene-has-partner