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Genetic defect keeps verbal cues from hitting the mark

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A genetic defect that profoundly affects speech in humans also disrupts the ability of songbirds to sing effective courtship tunes. This defect in a gene called FoxP2 renders the brain circuitry insensitive to feel-good chemicals that serve as a reward for speaking the correct syllable or hitting the right note, a recent study shows.

The research, which was conducted in adult zebrafinches, gives insight into how this genetic mutation impairs a network of nerve cells to cause the stuttering and stammering typical of people with FoxP2 mutations. It appears Nov. 21 in an early online edition of the journal *Neuron*.

"Our results integrate a lot of different observations that have accrued on the FoxP2 mutation and cast a different perspective on what this mutation is doing," said Richard Mooney, Ph.D., the George Barth Geller professor of neurobiology at Duke University School of Medicine and a member of the Duke Institute for Brain Sciences. "FoxP2 mutations do not simply result in a cognitive or learning deficit, but also produce an ongoing motor deficit. Individuals with these mutations can still learn and can still improve; it is just harder for them to reliably hit the right mark."

About 15 years ago, researchers discovered a British family with many members suffering from severe speech and language deficits. Geneticists eventually pinned down the culprit—a gene called forkhead box transcription factor or FoxP2—that was mutated in all the affected individuals. The discovery led many to believe FoxP2 was a "language

gene" that granted humans the ability to speak. But further studies showed that the gene wasn't unique to humans, and in fact was conserved among all vertebrates, including songbirds.

Though the gene is present in every cell, it is "active," or turned on, mostly in brain cells, particularly ones residing in a region deep within the brain known as the basal ganglia. This region is dysfunctional in Tourette syndrome, known for its vocal tics and outbursts, and is also shrunk in individuals with FoxP2 mutations.

To explore the complex circuitry involved in these deficits, Mooney and his former graduate student Malavika Murugan, Ph.D., decided to replicate the human mutation in this region of the brain in songbirds. Zebrafinches start learning how to sing 30 days after they hatch, listening to a male tutor and then practicing thousands of times a day until, 60 days later, they are able to make a very good copy of the tutor's song. As good as that copy is at day 90, the male finch's song gets even more precise when he "directs" it to a female as part of courtship.

To investigate the role of FoxP2 in the generation of this directed song, Murugan introduced specifically targeted sequences of RNA to suppress FoxP2 activity in the basal ganglia of male zebrafinches. The birds were placed in a glass cage that revealed a female sitting on the other side. Murugan then recorded sonograms of their song to capture the subtle vocal variations indistinguishable to the human ear when they produced directed songs at the female.

Murugan found that though the genetically manipulated males had already learned how to sing, their ability to hit the right note repeatedly in the presence of a female—a behavior critical to attracting a mate—was subpar. This indicates that in songbirds, FoxP2 has an ongoing role in vocal control separate from a role in learning, a distinction that has not been possible to make in humans with FOXP2

mutations.

Having deduced the behavior associated with this genetic mutation, the researchers then identified underlying neural deficits by recording brain activity in birds with normal and altered FoxP2 genes. In one set of experiments, Murugan sent an electrical signal into the input side of the basal ganglia pathway and then used an electrode on the output side to measure how quickly the signal traveled from one side to the other. Surprisingly, the signal moved more quickly through the basal ganglia of FoxP2 mutant songbirds than it did in songbirds with the functional gene.

Murugan also found that dopamine, an important brain chemical involved in brain signaling and the reinforcement of learned behaviors like singing or playing sports, could influence how fast basal ganglia signals propagated in birds with normal but not mutant forms of FoxP2.

"This switch between undirected and directed song is actually dependent on the influx of this neurotransmitter called dopamine," said Murugan, first author of the study. "So what we think is happening is knocking down FoxP2 makes the male incapable of reducing song variability in the presence of a female. An adult male sees the female, there is an influx of dopamine, but because the system is insensitive, the dopamine has no effect and the adult male continues to sing a variable tune." In juveniles, the inability to constrain variability and to respond to dopamine could also account for poor learning.

Though the researchers are cautious not to draw too many parallels between their findings in birds and the deficits in humans, they think their study does highlight the value of songbirds in studying human behaviors and disease.

"Birds are one of the few non-human animals that learn to vocalize," said

Mooney. "They produce songs for courtship that they culturally transmit from one generation to the next. Their brains might be a thousandth the size of ours, but in this one dimension, vocal learning, they are our equal."

Provided by Duke University