Title: “The Potential Role of the NHE9 Gene in Autism”

Host: Dale Connelly
Specialist: Rajini Rao, Ph.D.
Professor, Department of Physiology

Dale: “From the Johns Hopkins University Brain Science Institute.”

Dr. Rao: “The issue with autism is that its prevalence is increasing at a sort of staggering rate, it's currently 1 in 88 in the US and its even higher among boys where it's diagnosed at 1 in 50. So it is really becoming a major public health concern.”

Dale: “Dr. Rajini (Rudge-nee) Rao is a professor of physiology at the Johns Hopkins School of Medicine. She and her team have discovered how variants in a gene linked to autism could lead to successful genetic testing or targeted drug treatment.

Today on Brain Talk, the role the gene NHE9 could play in autism.

Dr. Rao says ‘autism is one of the neurological disorders a person is most likely to inherit. But,’ she explains, ‘from a genetic perspective, autism is also the most complex...’”

Dr. Rao: “We have 100s of candidate genes that have been identified by trawling through massive banks of genetic and clinical data bases but in spite of all this clear genetic link there still is a problem pinpointing what variants specifically contributes to autism, remains a really big challenge.”

Dale: “The gene … known as NHE9 … is suspected of involvement in many other brain disorders including addiction, epilepsy, and ADHD.

Dr. Rao’s study was able to determine how this gene might affect healthy signaling between neurons. NHE9 acts as a transporter. It shuttles charged particles in and out of tiny compartments called endosomes, which deliver cargo to different parts of the cell.”

Dr. Rao: “In this study what we first showed was that NHE9 alters the acidity inside the endosomes. And by doing so it affected not just the fate of the cargo but also the rate of its delivery and the direction, essentially where it went. And we could see right away that this could potentially impact events at the surface of the cell where nerves talk to one another, so it could impact the delivery of neurotransmitters like glutamate that influence synaptic signaling.”

Dale: “In a second part of the study, Dr. Rao and her team built a model of the NHE9 protein. They looked at which genetic variations, common to autistics, had an effect on the NHE9 protein. The team then examined how a weakened NHE9 protein might affect cells known as glia. Glia mop up neurotransmitters that are released as a form of communication in the spaces between nerve cells, known as synapses.”
Dr. Rao: “So they mop it up…which ends the signal. We chose to study these types of glia cells because we knew patients had elevated levels of glutamate in their brains, suggesting they couldn’t clear it effectively from the synapses. These elevated levels are quite harmful because they can spark seizures.”

Dale: “Seizures are common in people with autism. Dr. Rao found that the mutated NHE9 gene affected the ability of the glial cells to remove this excess glutamate. Which shows that a mutation of the NHE9 gene likely plays a role in autism.”

Dr. Rao: “That’s where we are right now, there are a couple of ways in which we can take this forward in the form of therapy, we can look for drugs that we know have a mild alkalinizing affect, and this would counter the excess acidity that is caused by defects in the NHE9 protein.”

Dale: “The other possibility is developing a screening method that can evaluate gene variations in autistic people. For more information on autism and the brain, go to brainscienceinstitute.org.

From Johns Hopkins University I’m Dale Connelly and this is Brain Talk.”

Learn more about Dr. Rao
Read “Researchers Ferret Out Function Of Autism Gene” | a Johns Hopkins press release
Read “Functional evaluation of autism-associated mutations in NHE9” | a research publication in Nature; Sept 25, 2013