NEWS

Mystery gene uncovered in autism studies may steer neurons

BY **JESSICA WRIGHT**

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It's been more than 30 years since **Vann Bennett** walked out of a Baltimore slaughterhouse carrying buckets slopping with pig brains. Bennett, then a young researcher at Johns Hopkins University in Baltimore, usually biked around the gritty city. He convinced a friend to lend him a car for the unsavory errand and watched as the slaughterhouse employees harvested and handed him the still-warm brains.

All this because Bennett needed the brains to find an elusive set of proteins called ankyrins. Three years earlier, Bennett had discovered ankyrins in blood cells[1]. Ankyrins are microscopic scaffolds that strengthen the cell's outer shell and tether important proteins in place.

At the time, the prevailing wisdom held that ankyrins were unique to blood cells. But crude studies with antibodies suggested that the brain is rich with a similar protein, which Bennett later dubbed ankyrin B.

"This was the brain version [of a blood protein] and we really wanted to understand the brain properties," says Bennett, now a professor of cell biology at Duke University in Durham, North Carolina. "In the 1980s this was revolutionary."

Since then, Bennett has worked to understand ankyrin B's role in the brain and elsewhere. In 2003, it was linked to a type of cardiac arrhythmia, or irregular heartbeat[2]. But for the most part, ankyrin B — and ANK2, the gene that encodes it — has gone largely unnoticed by neuroscientists.

Last month, however, all that changed, when two studies zeroed in on ANK2 as a top autism candidate[3, 4].

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“One of the strengths of [sequencing studies] is finding genes like this that would never have been candidates, but follow-up is hard,” says **Stephan Sanders**, assistant professor of psychiatry at the University of California, San Francisco. With little prior information on ANK2’s possible role in autism, Sanders and others took to searching **PubMed**, the vast repository of published biomedical studies.

They might be relieved to learn that Bennett and others have already created systems to probe ANK2’s role in the brain.

“I wasn’t surprised” to find that ANK2 is involved in autism, says **Matthew Rasband**, professor of neuroscience at the Baylor College of Medicine in Houston, Texas, who is systematically deleting ANK2 from different cell types in the mouse brain. “It was more like I was astonished and amazed, especially because we have all the tools sitting in the lab ready to figure out what these proteins are doing.”

Hot gene:

Researchers first found a harmful mutation in ANK2 in someone with autism in 2012[5]. Then, last year, a second mutation in someone with autism solidified its role in the disorder[6]. Last month, it became one of only four genes to make the shortlist of ‘high-confidence’ autism candidates from **two massive sequencing studies**.

Still, the gene has been slow to get autism researchers’ attention. In the only direct effort to understand its link to autism, researchers reported last year that its expression peaks slightly during mid-fetal development[6]. This developmental period is emerging as a crucial time for autism risk. ANK2's expression closely matches that of many other autism genes, including **SCN2A**.

“This means that it may be a so-called 'hot gene,' meaning that it organizes the other genes in the network, or that it’s interacting with a lot of them,” says **Jeremy Willsey**, a postdoctoral scholar in **Matthew State**’s laboratory at the University of California, San Francisco, who led the study.

SCN2A encodes a calcium channel, which binds to **ANK3**, another member of the ankyrin family. ANK3 has been linked to schizophrenia and bipolar disorder[7].

The most intriguing clues for ANK2’s link to autism come from mice lacking the gene, which Bennett made in 1991[8]. The mice die immediately after birth, and neurons in the fetal brain don't reach as far across the brain as those of control mice. Most strikingly, the mice lack a brain structure called the corpus callosum, which connects the brain’s hemispheres.

About one-third of people who lack a corpus callosum **also have autism**. And a **popular theory** holds that weak long-range connections and too many short-range ones underlie autism.

“It is very intriguing,” says **Silvia De Rubeis**, a postdoctoral fellow in **Joseph Buxbaum’s** laboratory at the Icahn School of Medicine at Mount Sinai in New York and a co-author on last month’s sequencing studies. “It’s a molecule that makes sense with everything else.”

Brain star:

Work from Bennett's lab is starting to reveal how ANK2 mutations might lead to these problems with connectivity.

In 1993, Bennett found that although every cell in the body makes ankyrin B, neurons make a version that is twice as big as the others[9]. This is intriguing, because many autism candidate genes **are unusually long**.

Last year, his team found that unlike others in its family, ANK2 may not bind to the outer membrane of neurons[10]. In a study in press at the *Journal of Cell Biology*, they report that it instead shuttles cellular cargo from one end of the neuron to the other.

Without this transport, neurons can't extend their projections to distant locations in the brain, says Bennett. “I had no idea that it would actually be involved in intracellular transport. That was nothing I could have imagined," he says.

ANK2’s link to autism may go beyond neurons, too. In mouse brains, for example, astrocytes, star-shaped cells that provide structural support to the brain, express more ANK2 than do all other cell types[11]. In a study published this month in *Nature Neuroscience*, Rasband’s team found that ANK2 also functions in Schwann cells, which coat neuronal projections to insulate them and enhance their conductivity[12].

Rasband has found that removing ANK2 from different cell types in the brain leads to different effects. Because mice missing the gene in only some cells survive, he plans to see if any of the mice have autism-like behaviors.

Bennett also intends to engineer mice missing the part of ankyrin B that is only expressed in neurons.

Even if it’s taken 30 years to get here, he says, he has always known ANK2 must play a crucial role in some brain disorder. "It’s actually a little surprising it’s taken so long.”

References:

1: Bennett V. *et al. Nature* **299**, 126-131 (1982) **PubMed**

2: Mohler P.J. *et al. Nature* **421**, 634-639 (2003) **PubMed**

3: Iossifov I. *et al. Nature* **515**, 216-221 (2014) **PubMed**

4: De Rubeis S. *et al. Nature* **515**, 209-215 (2014) **PubMed**

5: Iossifov I. *et al. Neuron* **74**, 285-299 (2012) **PubMed**

6: Willsey A.J. *et al. Cell* **155**, 997-1007 (2013) **PubMed**

7: Smith K.R. *et al. Neuron* **84**, 399-415 (2014) **PubMed**

8: Kordeli E. and V. Bennett **114**, 1243-1259 (1991) **PubMed**

9: Chan W. *et al. J. Cell. Biol.* **123**, 1463-1473 (1993) **PubMed**

10: He M. *et al. J. Biol. Chem.* **288**, 14769-14779 (2013) **PubMed**

11: Cahoy J.D. *et al. J. Neurosci.* **28**, 264-278 (2008) **PubMed**

12: Chang K.J. *et al. Nat. Neurosci.* **17**, 1673-1681 (2014) **PubMed**