AUTISM SPECTRUM DISORDERS

A forward screen in mice finds a hit in humans with autism spectrum disorder

El Hayek, L. et al. *eLife* <https://doi.org/10.7554/eLife.56883> (2020)

Autism spectrum disorder (ASD) is a complex condition to study. “Autism is so heterogeneous – genetically and phenotypically,” says Maria Chahrour, a researcher at the University of Texas Southwestern Medical Center. “We all as a field have struggled to find disease genes.” Even as the sequences of more and more patients are collected, much about ASD and its causes remain unknown.

“You can start thinking of this as a collection of individually rare disorders,” says Chahrour. Her lab studies the complex genetics of ASD and how the different genes involved might be grouped together to find effective therapies for cohorts of patients. She looks at lots of patient genomes, but her lab recently joined up with that of immunologist Bruce Beutler, a colleague at UT Southwestern, to add another approach. One that instead starts with mice.

“We had this sort of out-of-the-box idea to use forward genetics in mice to try to find candidates for genes that might be underlying autism in human patients,” says Chahrour.

The Beutler lab had developed a pipeline for random mutagenesis in mice that can quickly resolve what’s been mutated. “By the time we’re done with our screen, they’re done mapping the gene, so we get our hit,” she says.

There are several autism-like phenotypes that could be screened for in mice, but those that involve social behavior or learning and memory can be tedious and time-consuming to determine. Chahrour and her lab decided to record ultrasonic vocalizations (USVs), which can be quantified relatively quickly and used as a marker of abnormal brain development. Through the screen, they found pups with abnormal vocalizations, linked to a mutation in the chromatin regulator *Kdm5a*. Knockout mice developed for targeted validation recapitulated the USV phenotype, displayed repetitive behaviors, and had deficits in social, learning, and memory phenotypes. An initial neuronal analysis revealed decreases in dendritic spine density, complexity, and length as well.

All signs pointed to a promising candidate, but the ultimate test of a forward

genetic screen is whether mutations in mice turn up in people too. Via the GeneDx and GeneMatcher projects, Chahrour found patients with *KDM5A* mutations, most of whom have a complete lack of speech. “That’s a distinguishing feature,” says Chahrour. The results suggest *KDM5A* mutations represent a genetic subtype of ASD. Those patients have been enrolled in Chahrour’s human studies, in which the lab creates cell lines with the mutation for further study. The lab is also looking for more patients to determine how common *KDM5A* mutations are. Meanwhile, functional studies with the *Kdm5a* knockout mice continue, as do forward screens to find additional candidates. “We expect that there’s going to be many more genes to discover, and we think this is an efficient way to discover them,” says Chahrour. “It’s very much ongoing.”

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Published online: 15 January 2021
<https://doi.org/10.1038/s41684-021-00713-2>

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