A 'gene of prejudice' could help explain variations in human personality and demystify autism

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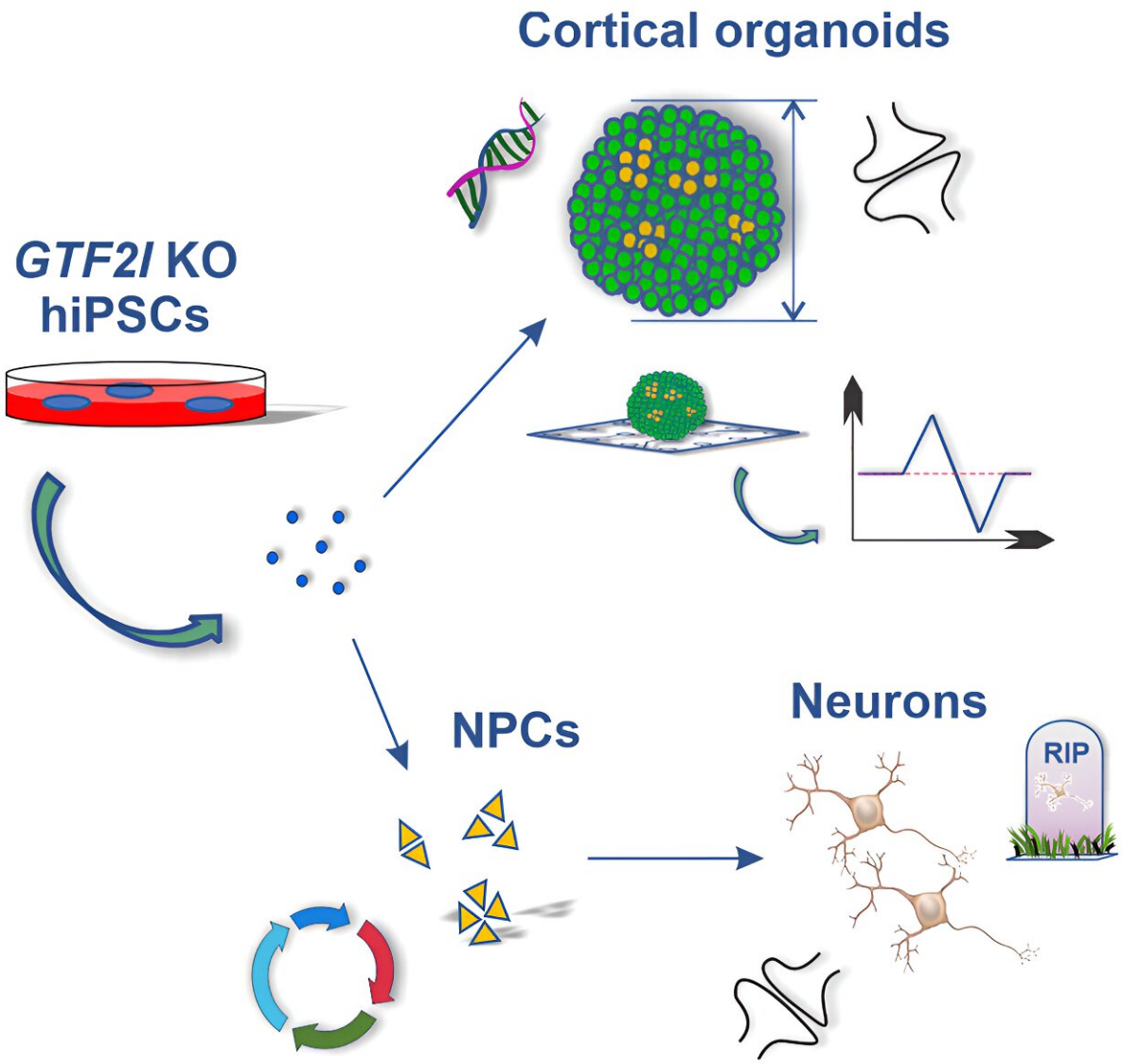

Credit: *Cell Reports* (2024). DOI: 10.1016/j.celrep.2024.113867

Individuals with the neurodevelopmental disorder Williams syndrome have a gregarious "cocktail party" personality, while those with the opposite genetic alteration, in contrast, tend to have autistic traits and are prone to struggle socially.

Now, thanks to new findings by researchers at the Sanford Stem Cell Institute at University of California San Diego, scientists have a better understanding of why. The research, published in *Cell Reports*, may help explain variations in human personality and could even lead to the development of a treatment that makes it easier for some individuals with autism to better function in society.

Often referred to as "the opposite of autism," Williams syndrome is a rare genetic condition caused by the deletion of about 25 genes in the 7q11.23 chromosomal region. This alteration produces a constellation of symptoms like heart disease and developmental delay. It characteristically features a strikingly engaging personality with high sociability, talkativeness, and a vocabulary that masks a typically below-average IQ.

The social strengths of Williams syndrome, however, are a double-edged sword. Individuals with this seemingly paradoxical condition know no strangers, making them particularly vulnerable to abuse and bullying.

Instead of a deletion of genes in the 7q11.23 chromosomal region, some people's DNA features a duplication, resulting in behaviors that are, in turn, quite the opposite of those exhibited by individuals with Williams

syndrome. Those with this opposing rare genetic alteration—known as 7q11.23 duplication syndrome—customarily experience symptoms including autism, social phobia, and selective mutism.

While the broader genetic region underlying Williams syndrome has previously been studied, scientists at UC San Diego hypothesized that one gene in particular—GTF2I—is predominantly responsible for the social variation seen in the disorder.

"I like to describe this gene as the gene of prejudice," said Alysson Muotri, Ph.D. director of the UC San Diego Integrated Space Stem Cell Orbital Research Center and lead author on the paper. "Without it, everyone in the world is your friend."

To learn more about its role, researchers used human pluripotent stem cells to create mini organs that mimic the human brain during fetal development—minus GFT2I. At 2 months of age, these so-called brain organoids were smaller than ones with GTF2I. Indeed, loss of the gene, they found, resulted in increased cell death, decreased electrical activity, and defects in synapses, the electrochemical connections that allow neurons to communicate with each other.

Researchers still don't fully understand why the alteration of the GTF2I gene affects the brain like it does. The team hypothesizes that increased cell death reduces the number of cells in the brain—and thus, its electrical activity. It's also possible that the gene helps repair synapses, meaning that those without it have a greater number of such that go unrepaired.

For some with autism, hope for a better treatment

Hundreds of genes have been tied to autism, but GTF2I "is the only gene we are aware of that regulates socialization more directly," Muotri said.

The new research suggests that when it comes to sociality, the gene is the main player in fetal brain development. Indeed, individuals without either Williams or 7q11.23 duplication syndromes—that is to say, most of us—have a balanced gene dosage of GTF2I, and are neither hyper- nor hypo-social.

The findings from the new study align with previous work that has demonstrated hypersociability in animals who lack GTF2I. For example, fruit flies who don't have the gene prefer to eat together, without the usually obligatory "social bubble," and mice who've had the gene deleted are friendlier than most. Moreover, incredibly, alterations to a gene that controls the function of GTF2I—potentially turning it off—may be at least partially responsible for the loving, friendly disposition of domesticated dogs compared to wild wolves.

Thanks to the findings of Muotri's team, hope may be on the horizon for those with GFT2I-linked autism. The research has paved the way for the potential development of a drug that regulates its expression, facilitating social interaction for affected individuals. Such treatment may also help those who have a normal GFT2I gene that was "turned off" by the epigenome, biochemical regulators that modify how our genes are expressed during development and across the lifespan.

The team's work also sheds light on the evolution of human sociality, Muotri contends. Chimpanzees—the closest evolutionary relative of humans—are social but only to an extent, preferring to deal with just a few other chimps at once. Humans, on the other hand, "create large communities in which we trust each other without really knowing each other," he said. Case in point: "When you enter a plane, you don't ask to see the pilot's license," he said.

GFT2I is "most likely among the genes that help humans achieve that safe balance, where we trust the community but sometimes don't trust

each other to the same degree," he added. "There's a fine-tuning of socialization in humans you don't see in other species."

What results is the ability to effectively collaborate—and such collaboration, Muotri asserts, has been key to humanity's greatest achievements: "It's when we cooperate that we can put a man on the moon. It's when we cooperate that we can decode the human genome. Because we work together."

More information: Jason W. Adams et al, Loss of GTF2I promotes neuronal apoptosis and synaptic reduction in human cellular models of neurodevelopment, *Cell Reports* (2024). DOI: 10.1016/j.celrep.2024.113867

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