SPECIAL REPORT

Hot topics in autism research in 2022

BY **SPECTRUM**

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Evolution of organoids:

This year saw the debut of ever-more complex techniques to grow and analyze brain organoids and other 3D tissue cultures.

Human cortical organoids, for example, can **form functional connections** in the brains of newborn rats and influence the animals' behaviors and sensations, one team reported in October, setting the stage to study circuit flaws. Organoids grown from **delicate single neural rosettes** can capture the intricacies of neural tube development, according to work published in December. A technique to sequence gene expression within organoids, described this past July, makes it newly possible to determine **which cell types are affected** by autism-linked genetic variants, and how. And organoids with mutations in autism-linked genes can also **serve as useful drug screens**, scientists announced at Neuroscience 2022 in November.

Assembloids — conglomerations of organoids that model how two brain areas grow in tandem — can **replicate the connectivity differences** seen in people with 22q13.3 deletion syndrome and mouse models of the condition, another team announced at Neuroscience 2022. And applying the gene-editing tool CRISPR to assembloids can reveal which autism-linked genes help direct the **development and migration of interneurons**, a November preprint reported.

Beyond brain organoids and assembloids, growing multiple mouse stem-cell lines together in one dish can even give rise to "**embryoids**," researchers announced in October. These models contain structures that mimic the heart and central nervous system, and they may pave the way to probe

prenatal development in lab-grown human embryos.

Working together — common and rare variants:

At least six large-scale genetic studies this year revealed how common and rare variants jointly influence autism's occurrence and heterogeneity.

These variants work additively in some cases to increase a person's likelihood of having autism, though they may contribute differently to the condition's traits, the studies showed. For instance, autistic people with a **high number of common variants** linked to the condition tend to have few co-occurring developmental disabilities, according to one study from June, and people who carry rare de novo mutations tend to have fewer common variants, according to another published at the same time. But autistic children with language delays inherit more common variants than autistic children with typical language development do, according to **unpublished work** presented at the **2022 American Society of Human Genetics** conference in October.

Instead of working additively, common variants and a rare autism-linked deletion within the 16p chromosomal region have similar effects on the expression of other genes in the region, an October **study** showed, suggesting that the accumulated effects of many common variants can sometimes equal that of a rare variant.

Two additional studies published in August expanded the list of genes associated with autism and other developmental conditions, and shed light on the **role of rare inherited variants**.

Getting at the mechanism behind autism's sex bias:

Autism's sex bias is one of the condition's biggest mysteries: Why, researchers continue to ask, are boys and men nearly four times as likely to be diagnosed with autism as girls and women?

A combination of factors is likely at play, but **biological differences** are central to the discrepancy, findings from 2022 suggest. For example, the **X chromosome** can harbor mutations that increase a person's likelihood of autism and have an outsized effect on boys, one study from October found. Compared with boys, girls are also less affected by **common inherited variants** linked to autism, another study reported in June. And in the womb, boys, unlike girls, tend to have patterns of **cortical gene expression** that line up with what is seen in the brains of autistic adults, according to work presented at Neuroscience 2022 in November.

It's not all biology, though, according to a June study that credits autism's sex bias primarily to **how it is diagnosed**. That team found an equal ratio of autistic girls to autistic boys when they corrected for differences in how boys and girls tend to perform on certain tasks during different periods of development.

New translational efforts:

Despite our advances in understanding the biology of autism, few efforts to translate those findings into treatments have succeeded. Some industry players took steps to change that in 2022.

A few companies are taking on what has long been a challenge for the field: designing treatments for idiopathic autism that won't be thwarted by the condition's heterogeneity. Swiss-based **Stalicla** is hoping to make an end-run around that obstacle by using biological measures to define subgroups of autistic people and then designing specific treatments for each, *Spectrum* reported in June. **Iama Therapeutics**, an Italian start-up *Spectrum* profiled in October, is instead betting on a single treatment with a known mechanism and then trying to identify the population of autistic children who would respond best to it.

Therapeutics designed for people with rare genetic conditions linked to autism largely avoid the heterogeneity problem and have also made strides in 2022. Multiple clinical trials for drugs that boost expression of a key gene linked to **Angelman syndrome**, for example, are **in the works**. And a treatment for Dravet syndrome, a genetic condition that can cause fatal epilepsy, **reduced seizures** in children with the syndrome in a clinical trial this year. Strong relationships between **researchers and family groups** often buoy these trials; in some cases, researchers are studying their **own child's rare condition**, as *Spectrum* reported in a profile in July.

Profound autism:

In December 2021, a committee organized by *The Lancet* formally recommended a term for autistic people who require round-the-clock, life-long support: **profound autism**. The label sparked a conversation that held the attention of advocacy and research communities throughout 2022.

The committee intended "to call attention to the fact that these kids and adults exist, and that they do need different services," co-chair Catherine Lord told *Spectrum*. Many welcomed the approach — including the Autism Science Foundation, which rolled out **$35,000 in new grants** to study profound autism — but others saw it as potentially **isolating some autistic people** from the larger community.

In February, an **open letter** with more than two dozen signatures called the term "highly problematic." A November editorial on *Spectrum* by Autism Science Foundation president Alison Singer, **arguing in favor** of the term, garnered both **support and resistance**. Many in favor see the label as an opportunity to include more autistic people with high support needs in research. But its creation is not in keeping with the neurodiversity paradigm, shirking the expertise of autistic people, argued developmental psychologist **Sue Fletcher-Watson** in **a response** to the editorial.

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