SPECIAL REPORT SUBARTICLE

The year in review

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The ten **notable papers** picked by SFARI staff describe superb contributions that span the breadth of autism research from molecules to behavior. We recognize that ten other articles might have been selected without loss of enthusiasm or excitement. It has indeed been an extraordinary year and we invite your comments on our selections.

I would like to thank the **SFARI staff** — writers, editors, research directors and research administrators. Together with the National Institutes of Health and non-profit organizations such as Autism Speaks, the Nancy Lurie Marks Family Foundation and the Autism Science Foundation, they have helped move the field forward at an unprecedented pace. Few of the advances described in our annual review would have been possible just a few years ago.

The notable papers describe new findings in human genetics, gene and protein networks, stem cell biology, potential therapeutics, epidemiology and clinical description of the autism spectrum.

Here are a few thoughts.

It is now clear that certain **copy number variants** (CNVs) are autism risk factors. Each one is rare, but together they account for a significant fraction of ‘idiopathic’ (non-syndromic) autism. This is a still-unfolding story as techniques for CNV detection evolve from comparative genomic hybridization to **DNA sequencing**.

We will know more in the coming year about the genetic landscape of autism spectrum disorders. More than 300 genes may be involved, so it is essential to develop sophisticated analyses of gene and protein networks that may bring some order to these vast amounts of data.

Arrows already point to proteins that may regulate the balance between synaptic excitation and

inhibition, and also to proteins that influence the expression of synaptic plasticity, the ability of **synapses** — the junctions between neurons — to modulate their strength in response to experience. It will be important to document how these changes contribute to the function of neural circuits that mediate components of social cognition and behavior.

The elegant study of **fragile X syndrome** and tuberous sclerosis complex **by Auerbach, Osterweil and Bear** offers important lessons regarding potential therapeutics. The two disorders share aspects of intellectual disability and autism-like behaviors. Both are associated with changes in protein synthesis in dendrites and changes in long-term synaptic depression. Both are regulated by mGluR5, a receptor that mediates excitatory signaling. It seemed plausible that an effective therapy in one condition would have a positive effect on the other.

No such luck. On close examination, the **TSC2** gene and the **FMR1** gene were found to have opposite effects on dendritic mRNA and protein levels and on long-term depression. What's more, drugs that enhance the action of mGluR5 have opposite effects on dendritic mRNA and protein levels in TSC and FMR1 mouse models. Opposite effects are also seen with mGluR5 antagonists.

This means that a useful therapy in one condition would likely exacerbate the deficit in the other. There are double negatives (inhibition of inhibitors) and triple negatives in this story, but it is worth the effort. Basically, FMR1 serves as a brake on mRNA and TSC1/2 stimulates mRNA production. Genetic variants lead to the opposite effects. Both effects are regulated in part by mGluR5.

The implications for idiopathic autism are clear. Biomarkers must be discovered that can stratify the population. Potential therapies that only benefit a subset of individuals in the heterogeneous autism population should not be discarded.

The past year illustrates once again how fundamental neuroscience and clinical research converge to the great benefit of those on the autism spectrum.

In the coming year, I hope that we will move closer to the identification of specific protein targets, specific neural circuits, and specific times in development that are particularly vulnerable to the action of autism risk factors.