NEWS

Network of protein variants suggests new autism genes

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Isoform interactions: Proteins encoded by autism candidate genes (red nodes) interact with many more proteins (blue and yellow lines) than previously thought (gray lines).

Researchers have created a network of various forms of many proteins linked to autism, revealing new molecular interactions that may play a role in the disorder. The unpublished work was presented in a poster last week at the **Salk Institute, Fondation IPSEN and *Nature* Symposium on Biological Complexity** in La Jolla, California.

In recent years, genetic studies have revealed **dozens of genes linked to autism**. Scientists are searching for common molecular pathways and other ways of making sense of this huge assortment.

In the new study, **Lilia Iakoucheva** and her colleagues at the University of California, San Diego, used computer modeling to construct a network of protein interactions.

These networks are typically constructed based on the default versions of proteins. The new study represents the first network based on the various forms of proteins that exist in the body.

The researchers selected 191 autism candidate genes and identified more than 400 alternative versions, or isoforms, of the proteins encoded by these genes in the brain. Isoforms are produced by mixing, matching and reorganizing different subunits of a gene as it is translated into a protein.

In collaboration with **Marc Vidal**'s lab at the Dana-Farber Cancer Institute in Boston, the researchers introduced pairs of proteins in yeast cells to see which ones interact directly. They paired each autism-linked protein isoform with each of a list of 15,000 protein-coding regions listed in a database**.**

The result, dubbed the Autism-Centered Interactome Network, includes many direct, pairwise interactions between proteins that have not previously been reported, expanding the set of these so-called binary interactions by 53 percent.

For example, the analysis identifies new partners for the autism candidate genes **FOXP2** and **A2BP1**.

The isoform network overlaps with a network of genes, identified in a 2011 paper, that are **over- or under-expressed** in the brains of people with autism compared with control brains.

"They basically validate the previous gene expression networks," says **Daniel Geschwind**, chair of human genetics at the University of California, Los Angeles School of Medicine, who led the 2011 study. The convergence in data suggests that the field is on the right track, he says.

The researchers also analyzed interactions between isoforms encoded by genes located within spontaneous, or *de novo*, **copy number variations** (CNVs) — duplications or deletions of relatively long stretches of DNA — implicated in autism.

The researchers found that genes from 26 different CNVs interact with each other. For example, there are interactions between proteins encoded by the 22q11.21-22 and **16p11.2** chromosomal regions.

Some of the newly identified genes may be important in autism even if they haven't popped up other in studies, the researchers say.

"These new genes may not necessarily carry genetic mutations within them, but they may serve as therapeutic targets," says Iakoucheva.

For example, the analysis pinpointed a gene called BZRAP1 as a bridge between networks of signaling, regulatory and structural genes related to autism.

A 2009 study of **inherited CNVs linked to autism** also fingered BZRAP1, but the new results suggest it might be worthy of more intense focus.

The team is studying how *de novo* mutations identified by sequencing the exomes, or protein-coding region of the genome, of people with autism may disrupt the interactions between proteins.

*For more reports from the Salk Institute, Fondation IPSEN and Nature Symposium on Biological Complexity please **click here**.*