Molecular network identified underlying autism spectrum disorders

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Quinn, an autistic boy, and the line of toys he made before falling asleep. Repeatedly stacking or lining up objects is a behavior commonly associated with autism. Credit: Wikipedia.

Researchers in the United States have identified a molecular network that comprises many of the genes previously shown to contribute to autism spectrum disorders. The findings provide a map of some of the crucial protein interactions that contribute to autism and will help

uncover novel candidate genes for the disease. The results are published in *Molecular Systems Biology*.

"The study of autism disorders is extremely challenging due to the large number of clinical mutations that occur in hundreds of different human genes associated with autism," says Michael Snyder, Professor at the Stanford Center for Genomics and Personalized Medicine and the lead author of the study. "We therefore wanted to see to what extent shared molecular pathways are perturbed by the diverse set of mutations linked to autism in the hope of distilling tractable information that would benefit future studies."

The researchers generated their interactome - the whole set of interactions within a cell - using the BioGrid database of protein and genetic interactions. "We have identified a specific module within this interactome that comprises 119 proteins and which shows a very strong enrichment for autism genes," remarks Snyder.

Gene expression data and genome sequencing were used to identify the protein interaction module with members strongly enriched for known autism genes. The sequencing of the genomes of 25 patients confirmed the involvement of the module in autism; the candidate genes for autism present in the module were also found in a larger group of more than 500 patients that were analyzed by exome sequencing. The expression of genes in the module was examined using the Allen Human Brain Atlas. The researchers revealed the role of the corpus callosum and oligodendrocyte cells in the brain as important contributors to autism spectrum disorders using genome sequencing, RNA sequencing, antibody staining and functional genomic evidence.

"Much of today's research on autism is focused on the study of neurons and now our study has also revealed that oligodendrocytes are also implicated in this disease," says Jingjing Li, Postdoctoral Fellow at the

Stanford Center for Genomics and Personalized Medicine who helped to spearhead the work. "In the future, we need to study how the interplay between different types of brain cells or different regions of the brain contribute to this disease."

"The module we identified which is enriched in autism genes had two distinct components," says Snyder. "One of these components was expressed throughout different regions of the brain. The second component had enhanced molecular expression in the corpus callosum. Both components of the network interacted extensively with each other."

The working hypothesis of the scientists, which is consistent with other recent findings, is that disruptions in parts of the corpus callosum interfere with the circuitry that connects the two hemispheres of the brain. This likely gives rise to the different phenotypes of autism that result due to impairment of signaling between the two halves of the brain.

"Our study highlights the importance of building integrative models to study complex human diseases," says Snyder. "The use of biological networks allowed us to superimpose clinical mutations for autism onto specific disease-related pathways. This helps finding the needles in the haystack worthy of further investigation and provides a framework to uncover functional models for other diseases."

More information: Integrated systems analysis reveals a molecular network underlying autism spectrum disorders, *Molecular Systems Biology*, DOI: 10.15252/msb.20145487

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