Biostatistics approach to genetics yields new clues to roots of autism

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Results from a statistical analysis shows a cluster of SNPs — single nucleotide polymorphisms — in one section of a single gene, indicating the location of a mutation likely linked to autism.

(Medical Xpress)—A study is only as good as the tools used to analyze it. One of those tools is statistics, and while biologists and chemists set up and run the experiments, statisticians are at work tinkering with the math that makes sense of all the data. Researchers at The Rockefeller University have recently developed a novel statistical method for genetic screens, which takes advantage of recent increases in computing power. Applying it to autism, they have uncovered genes that had not been suggested in previous analyses.

By crunching data from the genomes of hundreds of individuals with various degrees of autism, the researchers identified several functionally related genetic variations that they say are likely to be linked to autism or to the underlying pathology of neuronal development that may cause it.

The work suggests that beginning treatment in infants at the first symptoms, around the age of 12 months, could change the course of the disease. Catching the disorder early, the researchers say, could prevent the permanent "pruning" of neurons, which occurs during the first two years of life, from cementing autistic symptoms in place. The researchers also say that their data-scouring methodology may be used to help identify previously unknown genetic causes of other diseases, even in cases where data has already been exhaustively analyzed.

The research, led by Knut Wittkowski, biostatistician in the Center for Clinical and Translational Science at The Rockefeller University Hospital, is a twist on a traditional data-mining technique known as a genome-wide association study. By comparing DNA from groups of people with a certain illness to those without it, the technique identifies genetic variations that are associated with the disease. Conventional analyses look for individual mutations called SNPs—single-nucleotide polymorphisms. But looking for individual blips in the genetic code did not prove a reliable way to identify risk factors for early-onset diseases like autism. Wittkowski's method looks not just at individual SNPs, but at combinations of several SNPs—the equivalent of looking at whole words rather than just the single letters that form them.

Wittkowski applied this "multivariate" approach to data from studies of autism as well as studies of childhood absence epilepsy, a condition that turns out to have a similar genetic profile.

First, looking at a study of 185 cases of childhood epilepsy, Wittkowski's team found that mutations in genes that control axonal

guidance and calcium signaling—both of which are important early in the developing brain when neurons are forming the appropriate connections—led to increased chances of having the disorder. This prompted the researchers to take a closer look at data from one of the largest studies of autism in the country, containing genome sequences of some 2,700 individuals. By using their more powerful statistical approach, the researchers found clusters of mechanistically related genes where previous studies had merely suggested a few isolated SNPs. Their work implicated the Ras pathway—a calcium-dependent signaling network that spurs neuronal growth—as playing a key role in autism.

If confirmed by clinical research, the data points to the possibility that early pharmaceutical intervention could make a significant difference in the development of the disease."Our results suggest that the drugs currently used to treat childhood epilepsy—ion channel modulators—might have a beneficial effect on individuals with autism, if given at the right time, between 9 and 24 months of age," says Wittkowski.

"The implications of the paper are not restricted to autism," Wittkowski says. "Our approach is likely to 'revive' genome-wide association studies as a strategy to identify genetic risk factors and to develop novel treatment options for a wide range of diseases, just as people had hoped for when the genetic code was deciphered a decade ago."

More information: "A novel computational biostatistics approach implies impaired dephosphorylation of growth factor receptors as associated with severity of autism." K M Wittkowski, V. Sonakya, B. Bigio, M. K. Tonn, F. Shic, M. Ascano Jr., C. Nasca and G. Gold-Von Simson. *Translational Psychiatry* (2014) 4, e354; DOI: 10.1038/tp.2013.124
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