MedicalXpress

Genetic test for familial data improves detection genes causing complex diseases such as Alzheimer's

January 6 2017

A team of researchers at Baylor College of Medicine has developed a family-based association test that improves the detection in families of rare disease-causing variants of genes involved in complex conditions such as Alzheimer's. The method is called the rare-variant generalized disequilibrium test (RV-GDT), and it incorporates rare, as opposed to common, genetic variants into the analysis. In families in which several members are affected by a genetic condition, RV-GDT proved more powerful than other family-based methods in detecting rare genetic variants causing the condition. The results appear in the *American Journal of Human Genetics*.

"The heritability of complex diseases such as Alzheimer's hasn't been explained by common variants found in genome-wide association studies in the past," said senior author Dr. Suzanne Leal, director of the Center for Statistical Genetics and professor in the Department of Molecular and Human Genetics at Baylor. "With recent technological advances in next-generation sequencing, there is an increased interest in exploring the causes of complex disease due to rare variants, so we developed the RV-GDT to effectively determine this relationship using familial data."

To illustrate the application of the family-based RV-GDT method, Leal and colleagues analyzed whole genome sequence data from 81 families with a history of Alzheimer's disease.

The RV-GDT method is tailored for nuclear and extended families. It can analyze the whole genome of each family member, assessing associations within a family and increasing analytical power efficiently by incorporating information beyond first-degree relatives and other factors such as age, sex and body mass index to control for confounding.

By developing the rare variant GDT test, Leal and team also were able to gather statistical information on genetic variants over a genomic area of interest, which is usually a gene. The RV-GDT method avoids increased false positives, regardless of the structure of populations and pedigrees with missing genotype data.

"When you have multiple affected individuals within a family, this is most likely going to be caused by variants that have a larger effect size than those you see in the general population. The RV-GDT is a powerful method for identifying complex trait etiology in extended pedigrees," said Leal.

In their study of families with Alzheimer's disease, the research team was able to identify suggestive associations between Alzheimer's and rare variants in genes AXIN1 and TNK1 by applying the RV-GDT method.

"Although the link between TNK1 and Alzheimer's has been documented in the past for a common variant, this is the first study to implicate AXIN1 and rare variants in TNK1," said Leal. "These findings may provide new insights into the understanding of the disease and its causes and can be used for evaluating risk in the future."

As the first method to handle extended pedigrees with missing genotype data, the RV-GDT also can be applied to conditions such as type 2 diabetes, breast cancer, Parkinson's and other psychological traits that present in families.

More information: Zongxiao He et al. The Rare-Variant Generalized Disequilibrium Test for Association Analysis of Nuclear and Extended Pedigrees with Application to Alzheimer Disease WGS Data, *The American Journal of Human Genetics* (2017). DOI: 10.1016/j.ajhg.2016.12.001