Schizophrenia linked to genetic structural abnormality in adolescent brain

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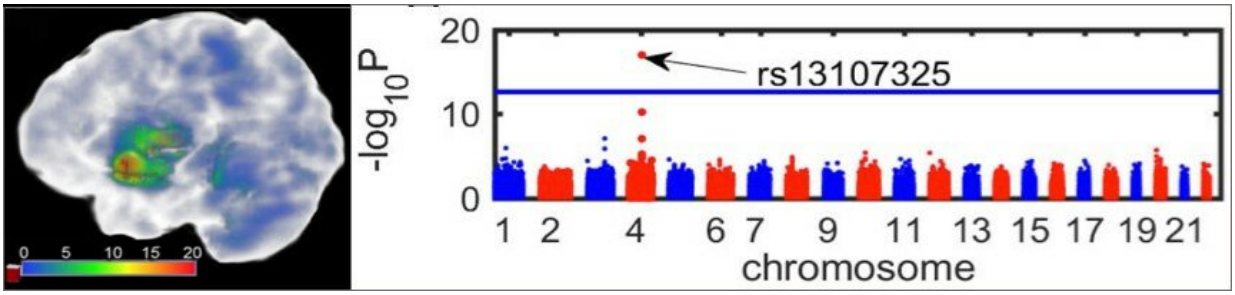

The left picture is a three-dimensional spatial distribution of the association between a risk gene mutation site and the volume of gray matter in schizophrenia; the deeper the red, the higher the statistical significance, followed by yellow and green, and the lowest statistical significance is blue. The right image is the most prominent Manhattan map showing the correlation between gray matter volume in the brain area (putamen) and genome-wide variation sites. The results were arranged according to chromosome number. Credit: University of Warwick

Schizophrenia could be caused by a genetic mutation that causes a structural abnormality in the brain during adolescence. Therefore testing for the gene SLC39A8, and brain scans for schizophrenia could predict whether or not someone will develop it—researchers at the University of Warwick have found.

Abnormal brain development in adolescence is associated with adult

mental illness. Researchers from the University of Warwick have discovered how genes that are directly associated with mental illness become pathogenic.

Feng Jianfeng's research team, from the Department of Computer Science, have analyzed over 10,000 genetic imaging data collected from more than 20 universities in 6 countries.

By whole-brain and whole-genome association study, they have found that a genetic mutation—that was associated with higher risk for schizophrenia, was significantly correlated to the enlargement of putamen volume in adolescent brains.

The study has found a new pathway of genetic risk disrupting the development of adolescent brain and thereby further increasing the risk of mental illness, which will hopefully help reveal the pathogenesis of schizophrenia and provide new possibilities for the theoretical study of prior intervention before the emergence of clinical symptoms.

Prevention and treatment of psychiatric disorders are global challenges. It is reported that mental illness has become one of the biggest challenges of the medical system, exceeding that of cardiovascular and cerebrovascular diseases and malignant tumor.

The clinical symptoms of various mental diseases may be caused by abnormal brain development in adolescence. However, previous study has accumulated 20,000 genetic imaging data worldwide had failed to identify any genetic variant that is associated with both higher risk for psychiatric disorders and grey matter volume of brain structure.

The team focused on brain structural images of 14-year-old healthy adolescents. Instead of applying the classic anatomical atlas of brain regions, the current research had chosen to run a holistic exploratory

analysis at a voxel-wise and genome-wide level, and found for the first time that grey matter volume of putamen in adolescents is associated with a genetic variation that had already been associated with risk for schizophrenia by the International Psychiatric Genetics Research Group.

Based on the statistical results of large-scale genomic association analysis, the research team conducted summary data-based Mendelian randomization analysis, inferring a new pathway from gene and brain to mental diseases: a genetic mutation (SNP rs13107325 on a zinc-transporter gene SLC39A8) elevates the risk of schizophrenia in adulthood by interrupting the development of putamen volume in adolescent brains.

Another difficulty resolved by the current study is that the voxel-wise and genome-wide association study significantly increased the computation by 40,000 times compared with previous genome-wide association study of candidate brain structures. To meet this computational challenge, the research team developed a new algorithm that speeds up the association analysis by 10,000 times, which enabled 16,000,000 associations to be calculated within 100 hours, and validated the findings using multiple independent samples.

Professor Feng Jianfeng, team leader from the University of Warwick comments: "Thanks to our international network for collaborations on brain science, the current multi-center genetic imaging data analysis becomes possible. The study has integrated more than 10,000 cases of image genetics data from over 20 universities and research institutes from six countries, including IMAGEN in EU, SYS in Canada, UK Biobank, 3C of France and LIBD of US."

Luo Qiang, member of the research team comments: "One of the major difficulties this kind of research needs to overcome is that genetic control of brain changes with age. Previous studies have not strictly

controlled the confounding effect of age on the gene-brain association, and this confounding effect may blur such association."

More information: Association of a schizophrenia-risk nonsynonymous variant with putamen volume: A voxel-wise and genome-wide association study, *JAMA Psychiatry*, 2019.

Provided by University of Warwick