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An evolutionary approach reveals new clues toward understanding the roots of schizophrenia

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Is mental illness simply the evolutionary toll humans have to pay in return for our unique and superior cognitive abilities when compared to all other species? But if so, why have often debilitating illnesses like schizophrenia persisted throughout human evolutionary history when the affects can be quite negative on an individual's chances of survival or reproductive success?

In a new study appearing in *Molecular Biology and Evolution*, Mount Sinai researcher Joel Dudley has led a new study that suggests that the very changes specific to human evolution may have come at a cost, contributing to the genetic architecture underlying schizophrenia traits in modern humans.

"We were intrigued by the fact that unlike many other mental traits, schizophrenia traits have not been observed in species other than humans, and schizophrenia has interesting and complex relationships with human intelligence," said Dr. Joel Dudley, who led the study along with Dr. Panos Roussos. "The rapid increase in genomic data sequenced from large schizophrenia patient cohorts enabled us to investigate the molecular evolutionary history of schizophrenia in sophisticated new ways."

The team examined a link between these regions, and human-specific evolution, in genomic segments called human accelerated regions, or

HARs. HARs are short signposts in the genome that are conserved among non-human species but experienced faster mutation rates in humans. Thus, these regions, which are thought to control the level of gene expression, but not mutate the gene itself, may be an underexplored area of mental illness research.

The team's research is the first study to sift through the human genome and identify a shared pattern between the location of HARs and recently identified schizophrenia gene loci. To perform their work, they utilized a recently completed, largest schizophrenia study of its kind, the Psychiatric Genomics Consortium (PGC), which included 36,989 schizophrenia cases and 113,075 controls. It is the largest genome-wide association study ever performed on any psychiatric disease.

They found that the schizophrenic loci were most strongly associated in genomic regions near the HARs that are conserved in non-human primates, and these HAR-associated schizophrenic loci are found to be under stronger evolutionary selective pressure when compared with other schizophrenic loci. Furthermore, these regions controlled genes that were expressed only in the prefrontal cortex of the brain, indicating that HARs may play an important role in regulating genes found to be linked to schizophrenia. They specifically found the greatest correlation between HAR-associated schizophrenic loci and genes controlling the expression of the neurotransmitter GABA, brain development, synaptic formations, adhesion and signaling molecules.

Their new evolutionary approach provides new insights into schizophrenia, and genomic targets to prioritize future studies and drug development targets. In addition, there are important new avenues to explore the roles of HARs in other mental diseases such as autism or bipolar disorder.