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Multipronged study of schizophrenia-associated syndrome receives $3.1 million NIH grant

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A research team at Emory University is embarking on a multipronged study of 3q29 deletion syndrome, a genetic mutation associated with a 40-fold increased risk for schizophrenia and a range of other neuropsychiatric conditions including mild to moderate intellectual disability, autism and anxiety. The research is funded by a $3.1 million grant from the National Institute of Mental Health of the National Institutes of Health.

The researchers will produce the first neuronal model of the schizophrenia-associated syndrome, which results from the deletion of a region of 22 genes. By uncovering the specific biological processes disrupted by the mutation, they hope to provide a molecular window into the key developmental processes relevant to schizophrenia and other neuropsychiatric conditions. They also will integrate their research with other targets identified in genetic studies of schizophrenia, autism, and intellectual disability, potentially leading to new ways to treat affected patients.

Co-principal investigators for the project at Emory University School of Medicine are Jennifer Mulle, PhD, assistant professor of human genetics and Gary Basell, PhD, professor and chair of cell biology. Other project collaborators are in the Emory Department of Psychiatry and Behavioral Sciences, Emory Department of Pediatrics, Emory Department of Psychology, and the Marcus Autism Center.

Although the 3q29 deletion has a low frequency in the population (1 in 30,000), the Emory team has already established an international 3q29 deletion registry that includes over 100 carriers (ranging in age from 1.5 to 34 years), which is the largest cohort ever assembled.

"Because no other research team has worked on this syndrome, the mechanisms are not well understood," says Mulle. "Our team of geneticists, molecular biologists and psychiatrists has deep expertise in evaluating neuropsychiatric phenotypes, which will allow us to create a set of rich

behavioral and clinical variables associated with the biomaterials available through our 3q29 registry."

"In addition to advancing fundamental research, we hope to help families learn more about the syndrome and its behavioral and clinical manifestations, and potentially understand better ways to treat it."

The research team will first identify and quantify the behavioral and clinical symptoms of the deletion in children and adults along four dimensions: anxiety, cognitive ability, autism spectrum, and psychosis and prodromal (precursor) symptoms.

They also will create a publicly available banked repository of biomaterials from 3q29 deletion carriers at the Rutgers University Cell and DNA Repository. These materials will include blood cells and DNA and allow further molecular study of 3q29 deletion syndrome.

Finally, they will develop a neuronal model of 3q29 deletion syndrome using induced pluripotent stem cells (iPSCs). iPSC technology allows researchers to take blood or skin cells and reprogram them into a specific cell type, such as neurons, which can then be deeply characterized with an array of molecular tools.

iPSCs will first be used to produce two sets of cell lines from control subjects (healthy individuals) with and without the deleted 3q29 region. The researchers will use CRISPR technology to perform the gene deletion so that the two cell lines will be otherwise identical (isogenic). CRISPR allows researchers to remove or add genes in a specific location in the genome. These iPSCs will be differentiated into neurons, and molecular and cellular phenotypes in the neuronal cell lines will be compared to iPSC neurons derived from 3q29 deletion carriers with confirmed psychosis or prodromal features.

The 3q29 deletion was first described in 2005 in six individuals and was expanded in 2008 with the description of nine more patients. In 2010, Mulle and her colleagues were the first to identify enrichment of the 3q29 deletion in schizophrenia cases compared to controls, and this association has since been replicated. A recent analysis by Mulle in 25,314 schizophrenia cases and 62,432 controls shows an extremely high effect size for schizophrenia. The

3q29 deletion may be the single-largest molecular risk factor for schizophrenia, surpassing even the well-known 22q11.2 deletion.

"Rare variants have the potential to transform our understanding of disease," says MPI Bassell. "A rare genetic variant can reveal a general mechanism of disease and open a path to effective treatments. In order to unravel the biology of complex diseases, initial gene discovery must be followed by detailed functional studies, which is what our project aims to do. By combining the power of iPSC technology with DNA from affected individuals in the registry, our team hopes to define the core neurodevelopmental factors associated with the 3q29 deletion. We can ultimately translate this into a "disease in a dish" platform that can be used for screening compounds to restore functionality."

Source:

http://news.emory.edu/stories/2017/03/mulle_schizophrenia_gene_research/index.html