Researchers Win Contract to Study Stem Cells from Early-Onset Alzheimer’s Disease Patients

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**Miller School researchers Margaret Pericak-Vance, Ph.D., and Derek Dykxhoorn, Ph.D., have won a three-year, $721,423 U.S. Department of Defense contract to ascertain and analyze induced pluripotent stem cells (iPSCs) from early-onset Alzheimer’s Disease patients with specific Alzheimer’s-linked genetic mutations.**

Pericak-Vance, the Dr. John T. Macdonald Foundation Professor of Human Genomics and Director of the Hussman Institute for Human Genomics (HIHG), and Dykxhoorn, associate professor in the John T. Macdonald Department of Human Genetics and Director of the Center for Molecular Genetics in HIHG, will serve as co-principal investigators, in collaboration with Dr. Richard Mayeux of Columbia University.

They will lead a HIHG research team that will develop a screening tool to identify significant differences between the iPSCs in individuals with Alzheimer’s Disease (AD) versus individuals without dementia. The results of this screen will likely point to the production of beta amyloid levels in the culture supernatant, which has been linked to AD, along with other cellular phenotypes such as expression of phosphorylated tau.

AD is pathologically characterized by the presence of extracellular plaques and intracellular neurofibrillary tangles in the brain. Beta amyloid is a key protein found in AD-associated plaques and occurs in individuals expressing certain genetic mutations, such as certain ApoE alleles. Increased release of beta amyloid may cause beta amyloid peptide deposits.

Pericak-Vance has been a leader in genetic characterization of AD risk for more than three decades. She was the first to discover the pivotal role of ApoE in AD risk in 1993, and subsequent analyses worldwide have confirmed those findings.

“This project is the result of decades of work to identify genetic risk variants and to characterize their biological function,” said Pericak-Vance. “I knew that even in diseases with the clinical and biological complexity of Alzheimer’s, we would move that foundational work toward translational research targeting prevention and treatment. Now, it’s happening.”

Since day one of the Human Genome Project though its completion in April 2003, the mapping of the human genome has promised to pave the way to an era of discovery in personalized medicine with the potential to transform health care. Recently, the concept of precision medicine with strategies to prevent and treat human disease tailored for the individual has accelerated, thanks to the development of powerful methods and tools for extracting and analyzing large genomic datasets. These tools and methods are now being leveraged by HIHG investigators to translate laboratory results into clinical practice, with the goal of improving diagnosis and treatment of human disease.

The development of induced pluripotent stem cells allows for the derivation of patient-specific stem cells that can then be differentiated into practically any cell type of interest. This current study has been greatly facilitated by the recent development of an iPSC core facility under Dykxhoorn’s direction.

“This new facility will allow this cutting-edge technology to support research studies across a wide variety of disorders by providing investigators with patient-specific stem cells that can then be used to derive disease-relevant primary cells for analysis,” said Dykxhoorn. “These cells will be of particular importance for disorders in which these primary cell types are not readily available.”

Using iPSCs from blood collected from Caucasian and Hispanic families with early-onset AD and variants identified by the screening tool, the HIHG team will conduct gene expression of AD-associated genes to confirm that the AD-associated variant alters expression of the gene, resulting in the accumulation of beta amyloid and tau as well as axonal growth and branching. With AD-specific iPSC derived neurons, the team will be able to describe the function of the associated genetic variants in the pathogenesis of AD.