INNOVATE
EVIDENCE-BASED MENTAL HEALTH RESEARCH

Triggers of Neurodegenerative Disorders

Gene mutations can be thought of as "typos" in the human code. Some are harmless and are responsible for the diversity in our population, but others can cause disorders such as Cystic Fibrosis and Fragile X syndrome. Drs. Paul and Randi Hagerman discovered one such disorder in 2000. This disorder, FXTAS, or fragile-X associated tremor/ataxia syndrome, is now known to be one of the most common single-gene neurodegenerative inclusion disorders.

Dr. Paul Hagerman was one of five researchers awarded a BRAIN-STIM grant from the UC Davis Office of Research and the Behavioral Health Center of Excellence to support innovative research that may lead to extramural funding from the White House BRAIN Initiative. Hagerman's project aims to understand why neurodegenerative diseases, like FXTAS, occur on the molecular level using new imaging techniques that only now are available.

What is FXTAS?

Individuals with FXTAS are carriers for a gene mutation on the X chromosome. Genes are made up of long strands of DNA, which is composed of molecules labeled A, T, C, and G. These molecules make up the genetic "code" and when errors like repetition or deletion occur within the code, mutations can occur. The gene mutation that causes fragile X and FXTAS is due to a CGG repeat. The number of CGG repeats an individual has will determine whether they present fragile X syndrome or FXTAS.

FXTAS is found in 1 in 3000 males and 1 in 5200 females in the general population. About 1 in 300 to 500 males and 1 in 100-150 females are carriers for this gene mutation, which has been found to lead to early menopause and increased prevalence for premature ovarian failure.

Fragile X syndrome is present from birth, but symptoms of FXTAS are generally not seen until after age 50. Symptoms of FXTAS include tremors, instability, and difficulty with coordinated muscle movements like walking. These symptoms are often misdiagnosed as other neurodegenerative disorders such as Alzheimer's and Parkinson's disease, which have mechanisms and features that overlap with FXTAS. Hagerman states that, "once we are better able to understand why FXTAS and other neurodegenerative diseases occur we can start developing disease targeted treatments."

"This project holds the promise of providing critical insights into the causal pathways from gene to brain and then to disease symptoms, paving the way for the identification of possible targets for therapy. The rapid progression of FXTAS and its devastating consequences for the affected individual have created an urgent need for a new research agenda. This funding will support this new agenda, accelerate the translational process, and provide hope for the many families struggling with the consequences of this disorder."

– Leonard Abbeduto, Ph.D., Director, MIND Institute

Microscopy Techniques bring Clarity

Through the BRAIN-STIM award Hagerman's lab will use cutting-edge microscopy techniques, such as CLARITY and STED, to view mechanisms that produce the neurodegenerative disorder, FXTAS.

CLARITY is a microscopy technique that reveals whole brain structures by making them more transparent. It is used to provide a global perspective while looking at fiber relationships and patterns of cells. STED is another microscopy technique that will be used to increase precision at the sub-cellular level through super-high resolution techniques. Both CLARITY and STED will be used to look at processes and structures that could play a role in FXTAS development.

Therapeutic Interventions

Screening for FXTAS has not become routine, but is common if there is a question of diagnosis and is performed though a blood test. "The goal is to develop therapeutic approaches to effectively treat neurodevelopmental and neurodegenerative diseases," Hagerman stated in a recent interview. When there is dysregulation within the cell, release of certain signaling proteins is triggered. If left unchecked, these signaling proteins can cause the cells to die. Identification and detailed mapping of the neural inclusions seen in FXTAS will foster a greater understanding of the connectivity and mechanism of the disease. With the knowledge that this research will generate, Hagerman sees potential for identifying strategies for intervention.

Award ignites Innovation

Awards like BRAIN-STIM are valuable because they give researchers the ability to move forward on developing innovative approaches that precede or bridge traditional research funding. Hagerman's research is necessary for understanding how and why neurodegenerative and neurodevelopmental disorders occur. Overlap between FXTAS and diseases such as Alzheimer's, Huntington's, Parkinson's, and ALS may lead to disease-targeted treatments for disorders that affect countless individuals each year.

Resources

UC Davis MIND Institute:
ucdmc.ucdavis.edu/mindinstitute/

Department of Biochemistry and Molecular Medicine, School of Medicine, UC Davis:
ucdmc.ucdavis.edu/biochem/

Behavioral Health Center of Excellence at UC Davis

UC Davis launched the Behavioral Health Center of Excellence in October 2014 to advance mental health research and policy with initial funding from the Mental Health Services Act. The Innovate series highlights the Center's $4.3 million Research Pilot Award program.

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