RESEARCH SUMMARY

JORDAN'S GUARDIAN ANGELS

Jordan's syndrome is a neurodevelopmental disorder caused by variants, or mutations, in genes that encode parts of a protein complex called Protein Phosphatase 2A (PP2A). These genes include PPP2R5D, PPP2R5C, and PPP2R1A. This protein complex is a cellular machine that helps control biochemical processes in many different tissues of the body, including the brain. PP2A does this by acting as an on/off switch for other proteins involved in metabolism and cell growth. As a result, genetic variants associated with Jordan's syndrome that impair the function of the PP2A complex may cause a spectrum of neurodevelopmental delays as well as low muscle tone, seizures, autism spectrum disorder, and ophthalmologic, skeletal, endocrine, cardiac, and genital anomalies. Because the PP2A complex is involved in so many processes in the body, it has also been implicated in Alzheimer's disease and cancer.

COLUMBIA UNIVERSITY

DR. WENDY CHUNG, MD, PHD

Dr. Chung's team in New York is taking on the role of describing the clinical characteristics of individuals with PPP2R5D variants. They have been enrolling PPP2R5D families through the research registry Simon's Searchlight to be able to learn more about Jordan's syndrome. What genetic variants do individuals have in the PPP2R5D gene? What are most common features of Jordan's syndrome? These questions and more are vital to understanding the scope and spectrum of the condition so that doctors, researchers, and families now more about what to expect.

UC DAVIS

DR. KYLE FINK, PHD AND DR. JAN NOLTA, PHD

Dr. Nolta is the director of the Stem Cell Core facility at the UC Davis School of Medicine, where they are working on creating stem cells from skin samples of individuals with Jordan's syndrome and enabling them to be grown into brain cells or even mini-brains in a dish. Also at UC Davis, Dr. Fink's team is working on testing several therapeutic strategies that involve binding proteins to certain parts of a cell's genetic material. This technique allows the amount of healthy versus variant PPP2R5D to be selectively increased or decreased.

UNIVERSITY OF SOUTH ALABAMA

DR. RICHARD HONKANEN, PHD

Dr. Honkanen's team is working on using a DNA-editing technique called CRISPR to create human brain cells in a dish that express different variants of PPP2R5D. Then they will observe how each genetic variant affects cellular processes on the molecular level compared to cells with unvaried PPP2R5D. To do this, they will measure the levels of gene transcripts, proteins and on/off signals called phosphorylation that the cells create.

KU LEUVEN

DR. VEERLE JANSSENS, PHD

Dr. Janssens' team in Belgium is working on growing human brain cells in a dish and expressing different PPP2R5D and PPP2R1A variants in these cells as well as in mice. Then, they will study how different variants affect the growth and function of the cells and try to understand what the biochemical effects of these variants are on brain cells.

SEATTLE CHILDREN'S HOSPITAL

DR. GHAYDA MIRZAA, MD

Dr. Mirzaa's team is working on trying to identify the specific mechanisms by which PPP2R5D variants affect brain growth and neuronal function using stem cells from individuals with Jordan's syndrome. They have identified that PPP2R5D regulates a molecular assembly line involved in cell growth. We know that this assembly line, or pathway, is disrupted, it can cause brain overgrowth, intellectual disability, and autism spectrum disorder in children. Therefore, Dr. Mirzaa's team will take PPP2R5D-variant brain cells they have grown in a dish, expose them to a variety of different drugs known to affect this assembly line, and see if there are any interesting effects on cell growth and function.

UNIVERSITY OF IOWA

DR. STEFAN STRACK, PHD

Dr. Strack's team has also created three PPP2R5D mouse models. These mice are unique in that their PPP2R5D genes are "conditional", meaning they may start out with a normal PPP2R5D gene and then it becomes variant as the mouse develops, or they start out with a variant gene that becomes normal later in their development. This technology will allow the Strack lab to identify what developmental periods are most critical in the development of Jordan's syndrome and whether Jordan's syndrome may be reversible or amenable to drug therapies.

VANDERBILT UNIVERSITY

DR. BRIAN WADZINSKI, PHD

Dr. Wadzinski's team is working to better understand the structure, function, and regulation of PPP2R5D enzymes by creating antibodies and nanobodies that bind to PPP2R5D. These antibodies and nanobodies are made using help from alpacas! Their goal is to use the information they learn about how PPP2R5D works to identify a potential drug that restores normal function to variant forms of the enzyme and then test that drug in mouse models.

UNIVERSITY OF ROCHESTER

DR. HOUHUI XIA, PHD

Dr. Xia's team is using a technology called electrophysiology to measure the brain activity of mice with PPP2R5D variants created by the Strack lab. They will also create brain cells in a dish with different PPP2R5D variants and measure the electrical activity of those individual neurons. They hope to better understand how communication between brain cells is changed by PPP2R5D variants and what brain regions are most involved.

UNIVERSITY OF WISCONSIN-MADISON

DR. YONGNA XING, PHD

Dr. Xing's team at UW-Madison is working on understanding how PP2R5D variants affect the structure and function of the PP2A complex using multidisciplinary approaches, including cryo-EM structural biology. Specifically, they are building on their previous work with the PP2A complex to understand the biophysical mechanisms by which the PP2A complex is created, recycled, controlled by diverse regulatory proteins, and incorporates different subunits, including PPP2R5D.