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Today HCU Network America and HCU Network Australia announce the recipient of their first Homocystinuria due to severe methylenetetrahydrofolate reductase (MTHFR) and cobalamin G (cblG) Deficiency research grant, awarding ETH Zurich, to identify potential treatment for severe MTHFR and cblG. The research, led by Dr. Ferdinand von Meyenn, aims to replicate the characteristics of these disorders using cerebral organoids, providing essential insight into the mechanism of this metabolic function. In addition, potential therapies will be screened to determine if a new molecule is capable of rescuing disease related complications that are typically still present despite current treatment methods. Dr. von Meyenn is an Assistant Professor at ETH Zurich in Switzerland at the Laboratory of Nutrition and Metabolic Epigenetics.

Homocystinuria due to severe MTHFR is one of the most common types of remethylation disorders and arises from mutations in the MTHFR gene, resulting in nonfunctional MTHFR protein. It disrupts the remethylation of homocysteine to methionine because the non-functional protein does not provide an essential methyl donor.

Current treatment consists of betaine anhydrous supplementation. Even though current treatment strategies help reduce mortality and morbidity, they cannot reverse the symptoms associated with reduced cerebral function.

Cobalamin G deficiency is an inborn error of metabolism which disrupts the utilization of vitamin B12 to convert homocysteine to methionine in the remethylation pathway. Typically, patients present during their first year of life with metabolic crisis, anemia, failure to thrive, seizures or developmental delay. Patients have elevated plasma homocysteine and low methionine levels. Unlike combined cobalamin disorders such as cblC, patients do not have elevated levels of methylmalonic acid; making early detection on newborn screening tests impossible for this group of rare disorders. Unless there is a family history for this disorder, patients are not diagnosed until they become symptomatic. The disease prevalence is unknown for this disorder.

The current treatment consists of hydroxocobalamin injections (a very specific form of B12) and betaine anhydrous. If a patient is symptomatic at the time of diagnosis, treatment will not reverse the side effects. Many patients despite current treatment standards still become symptomatic.

According to the principal investigator, Dr. Ferdinand von Meyenn, “the project supported by the HCU Network America and HCU Network Australia aims to understand and find treatments for two rare disorders, MTHFR and Cobalamin G deficiencies, which usually start in infancy and lack efficient treatments. We plan to use lab-grown mini-brains (cerebral organoids) made from special cells to better understand the diseases. These mini-brains will also help to test new treatments since they have been useful in studying other brain development disorders.

The mini-brains will be checked to see if they show similar problems as seen in patients, like growth defects, changes in brain tissue, and other specific issues. The project will also use these mini-brains to test existing and new drugs to see if they can help with these disorders. This includes drugs like folate and its derivatives, and other potential treatments. The goal is to create a lab-based platform to test many treatments for MTHFR and Cobalamin G deficiencies effectively and thereby help identify novel treatments for the affected children to help them live a better life.”

HCU Network America Board Member and Chair of Severe MTHFR steering committee, Grace Talbert said: "The idea of research for severe MTHFR seemed so farfetched when my daughter, Carson, was diagnosed 3 years ago. I am so proud of the families who rallied around the globe to make this research possible. I am thankful for Dr. von Meyenn and his innovative idea to research this rare condition. I'm beyond thrilled for how this may shape the understanding and treatments for severe MTHFR. For the first time since my daughter was diagnosed, I am feeling hopeful for her future and for all the children diagnosed with severe MTHFR."

Family representative from HCU Network Australia Renske Dijkhuis said: "We're very grateful for the enormous amount of support we have received from our community and beyond, to be able to help raise funds for this research grant!"

Board member for HCU Network America and Remethylation Grant Program Lead, Brittany Parke said "I am especially grateful to Dr. von Meyenn to expand this project to include coblamain G in addition to his original submission for severe MTHFR research. This information will propel future research and help our community better understand these complex and rare disorders. It was too fantastic of a project to pass up the opportunity to fund a second project for the cblG community."

HCU Network America and HCU Network Australia thank their community of supporters whose contributions made this grant possible.

Not pictured by request, the Hudelson Family.

About HCU Network America:
HCU Network America is a 501c (3) non-profit organization founded in 2016 dedicated to helping patients and their families affected by Homocystinuria (HCU) and related disorders. The mission of the organization is to inform and provide resources for patients and families, create connections, influence state and federal policy, and support advancement of diagnosis and treatment for HCU and related disorders.

About HCU Network Australia:
HCU Network Australia is a Health Promotion Charity established in 2014, with the vision "to be a driving force in the journey to a cure, improving quality of life along the way." Our aim is to improve individual outcomes through education, research and support.