A UNIQUE APPROACH TO SOLVING A UNIQUE UCD - CITRIN DEFICIENCY

Li Eon Kuek[1], Barbara Yu[1]

[1]Citrin Foundation, United Kingdom & Singapore

Background

Citrin deficiency (CD) continues to pose diagnostic and therapeutic challenges due to its heterogeneous clinical manifestations and limited understanding of its pathophysiology. CD results from loss of citrin, a mitochondrial aspartate–glutamate carrier, which impairs mitochondrial aspartate transport to the cytosol and disrupts the malate–aspartate shuttle, affecting multiple metabolic pathways. How this defect gives rise to diverse, age-dependent symptoms remains unclear. Emerging evidence suggests disturbances in hepatic NADH/NAD^+ balance and ATP homeostasis as possible drivers of broader metabolic dysfunction. Yet key questions remain: Why do symptoms evolve over time? What triggers the onset of adolescent and adult CD (AACD)? What mechanisms underlie hepatic steatosis and hypoglycemia? Are there compensatory pathways? What therapeutic strategies should be pursued?

Methods

Citrin Foundation is building a global ecosystem to solve CD holistically and drive progress from research to care. It provides long-term funding for coordinated scientific and clinical efforts, together with translational infrastructure. Fundamental research investigates the effects of citrin mutants on protein biogenesis, intracellular localization, transport function, and biochemical impact. New cellular, organoid, and animal models are being developed and characterized to support pre-clinical studies. Clinical studies aim to identify reliable biomarkers and assess CD's effects in patients using stable isotope flux analysis. Treatment strategies span small molecules that target disease pathways to mRNA and gene therapies under investigation. Patient-focused initiatives remain central: these include supporting patients and families, expanding identification, conducting surveys to inform future cohort studies, and engaging patients for research participation.

Results

A growing multidisciplinary consortium of researchers, clinicians, and industry partners has been established. A major strategic initiative, the UCD Translational Research Center Universität Zürich – Citrin Foundation, was recently launched. Five new cellular and five new animal models have been developed, providing platforms for mechanistic investigation and therapeutic evaluation. New patient cohorts have been identified and studied. Studies in citrin-KO hepatocyte lines show malate–aspartate shuttle dysfunction and reduced ATP production. PPARα expression is downregulated in citrin-KO HepG2 cells and patient liver biopsies, suggesting impaired hepatic β-oxidation. Clinical studies indicate a higher incidence of AACD in males than females.

Conclusions

CD remains an enigmatic disorder with significant unmet needs. By integrating fundamental research, translational studies, and patient engagement, we aim to untangle CD's biological complexity and accelerate development of diagnostics and treatments. CD can also serve as a model for solving UCDs and broader innovation. We invite you to help solve this enigmatic condition and collaborate more broadly together.