Citrin Foundation

Introduction to Citrin Foundation

RESEARCH **SUPPORT** **CURE**

Section 1: Introduction to Citrin Foundation

Citrin Foundation is a research-driven, patient-centric, non-profit organization set up in 2016 to tackle citrin deficiency. Our goal is to find effective treatments and ultimately a cure for the condition. We also provide support to citrin deficiency patients and their families globally.

The Foundation has committed to investing USD30 million, entirely provided by our co-founders, for the next decade to achieve our aims. We fund research projects by offering generous grants to clinicians and researchers who wish to better understand the condition, uncover more patients, and to develop new therapies.

Mission & Vision

There are two cornerstones to the Foundation's mission: finding a cure for citrin deficiency and providing life-long support to CD patients. We believe that a multi-disciplinary, innovative and long-term approach will deliver breakthrough treatments and address the well-being of CD patients holistically. We seek to work with leading scientists, researchers, and clinicians in related fields globally to solve this medical problem together.

We have developed the following list of objectives to achieve this:

- Identify patients with Citrin Deficiency (CD) worldwide
- Study the natural course of disease in large patient cohorts
- Improve the diagnosis of CD
- Understand the basic science and pathogenesis of the disease
- Explore the benefits of existing therapies
- Develop new therapies
- Support affected patients and their families

Section 2: What is Citrin Deficiency?

Citrin deficiency (CD) is an autosomal recessive liver disease caused by mutations in the SLC25A13 gene encoding for the mitochondrial aspartate-glutamate carrier, citrin. CD manifests as several age-dependent phenotypes; 1) neonatal intrahepatic cholestasis caused by CD (NICCD) 2) the silent or adaptation period 3) failure to thrive and dyslipidemia caused by CD (FTTDCD) and 4) adolescent and adult CD (AACD) (formerly known as CTLN2). Multiple key metabolic pathways in the liver are affected by CD such as the malate-aspartate shuttle, glycolysis, gluconeogenesis, *de novo* lipogenesis and the urea cycle. The recommended management for CD is dietary management with protein and fat-rich food, and avoidance of excessive carbohydrates. While there is currently no cure for CD, medium-chain triglycerides (MCT) are the most widely used treatment and may improve some clinical symptoms by rapidly supplying energy to the liver and restoring redox balance.

Management

Below are the general treatment options for patients with citrin deficiency.
Treatment should be adjusted accordingly as the condition and its severity may be very different for each patient.

Diet Management

- Maintain a low carbohydrate, high-protein, high-fat diet. Based on the 2019 Citrin Deficiency Guidelines published by the Japan Society of Inherited Metabolic Disorders, the recommended PFC ratio for citrin deficiency patients is Protein: 15% – 25%, Fat: 40% – 50%, Carbohydrate: 30% – 40%.
- Try to consume a variety of sources of fat and avoid relying on animal fat by actively opting for more healthy options such as vegetable-derived fat like olive oil.
- For patients of any age, it is very important to eat frequently by having breakfast, lunch, dinner, and consuming snacks in between meals.

MCT Supplements

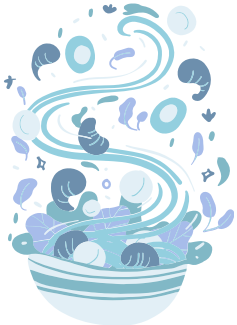
MCT (medium-chain triglycerides) is different from usual fat as it directly provides energy to the liver. This is important for citrin deficiency patients as they have an energy deficiency in the liver. As MCT is not commonly found in foods, citrin deficiency patients are recommended to take MCT oil as a supplement. MCT-enriched formula / MCT-supplemented breast milk (please consult your doctor for dosage) is recommended for NICCD patients.

Post-NICCD:

- It is best to take MCT oil with your meals, in divided portions throughout the day.
- One recommended dose for MCT after the age of one is 1g/kg/day, with a maximum daily dose of 40g. If patients are unable to tolerate this dose due to stomach discomfort, they may lower the dose accordingly.

Some suggested methods of consuming MCT oil are as follows:

- Blend it in your smoothies or drinks
- Mix it in your salad or add it to boiled vegetables
- Add it to your soup and stir it well
- Having it as a dip with bread



Section 3: Research Funding and Ongoing Projects

We believe that having a global consortium of scientific researchers and clinicians collaborating in an open, non-competitive, and synergistic manner will allow us to achieve our goals.

Research Grants

We are looking to expand the scope and number of research projects funded by our Foundation to accelerate the scientific development and understanding of citrin deficiency. Clinical, translational, and basic science proposals will be considered, with innovative and/or interdisciplinary grants being encouraged. Our Foundation will also work with biotech and pharmaceutical companies to develop potential therapies for this condition.

Our capacity to provide funding does not rely on any external factors or targets, so those who are successful in their grant applications will have a real shot at producing ground-breaking research. Our grant applications are open to applicants throughout the year, and we support projects for up to three years with average grant amounts ranging between USD200,000 to USD500,000.

Our Ongoing Research Projects

Citrin Foundation is currently supporting numerous projects through collaborative partnerships with leading scientists and physicians globally to better understand the pathophysiology of CD, improve the identification and diagnosis of patients, and to develop effective therapies for the condition. Below are some examples of the ongoing projects sponsored by the Foundation. For more details about our projects, please visit our website https://citrinfoundation.org/funded-research/

Basic Science Projects

- Understanding the impact of citrin pathogenic mutants on biogenesis and bioenergetics in liver
- Metabolic flux studies in a double-knockout mouse model and the effects of redox manipulation
- Targeting of liver glycerol-3-phosphate phosphatase as a potential treatment for CD

Development of New Pre-clinical Research Models

- Citrin-knockout HepaRG human hepatocyte model
- Citrin-knockout HepG2 human hepatocyte model
- CD patient-derived induced pluripotent stem cell (iPSC) hepatocyte model
- Citrin-knockout rat model
- Aralar liver-conditional citrin knockout mouse model

Improving Patient Identification and Diagnosis

- Improved newborn screening method
- Global patient registry for CD

Identifying Effective Biomarkers and Establish Functional Assays

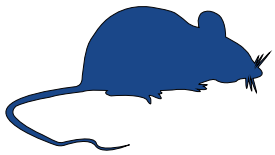
- Global omics study to identify novel biomarkers for CD
- Ureagenesis function test
- Metabolic flux studies in adult CD patients

Evaluation of Existing Therapies:

- Evaluation of MCT in CD cellular models and in patients

Development of Novel Liver-specific Therapies

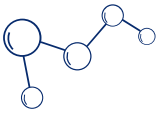
- Prime editing therapies for CD
- mRNA therapy (in collaboration with Moderna)
- Evaluation of novel small molecule compounds including nanoparticles
- Functional replacement of citrin with aralar



Pre-clinical Research Models Available

Various pre-clinical cellular and animal models are available from Citrin Foundation to aid in your research on citrin deficiency on a case-by-case basis. For mouse models, the Foundation has made the citrin/mGPD double-KO strain available for order from the Jackson Laboratories mouse repository.

Section 4: Details of Some of Our Clinical Studies



Global Multi-omics Study in Citrin Deficiency for Biomarker Identification

Currently there are no disease-specific and age-related biomarkers for CD. This Foundation-led study seeks to discover specific circulating biomarkers for CD using multi-omics analyses (metabolomics, proteomics, lipidomics, transcriptomics) of plasma samples from at least 100 patients of all ages globally. This ongoing study is a collaborative effort involving more than 10 clinical centers from multiple countries including Switzerland, USA, UK, Japan, South Korea, Taiwan, and Vietnam, with results anticipated in 2025. Prof. Johannes Häberle (University Children's Hospital Zürich) and Prof. Kimitoshi Nakamura (Kumamoto University) are global co-PIs for this landmark study.

Ureagenesis Function Test

The ureagenesis test, developed by Prof. Johannes Häberle and his team at the University Children's Hospital Zürich, accurately determines the urea cycle functions in patients by measuring the incorporation of orally ingested ammonium chloride tracer into urea. The test can better inform if the urea cycle of patients is compromised to enable better prognosis. The test has already been conducted on some CD patients and has been proven to be very safe. If you have a patient with citrin deficiency and are interested in this test, please reach out to our Foundation at patients@citrinfoundation.org.

Adult Metabolic Study

This clinical study is a collaborative effort between the Foundation, the University of Helsinki (Prof. Hannele Yki-Järvinen), the University of California Berkeley (Prof. Marc Hellerstein), and the University of Oxford (Prof. Leanne Hodson), and will use state-of-the-art stable isotope tracer methods to precisely determine the metabolic status of adult CD patients. If you or your patients are interested to learn more about this study, please contact us at patients@citrinfoundation.org.

Section 5: Resources for Patients

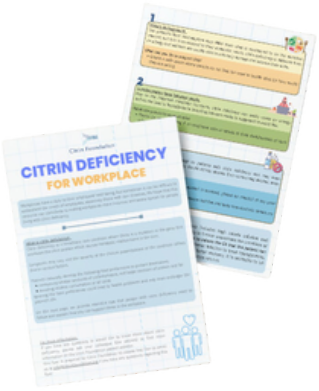
Patient Flyer

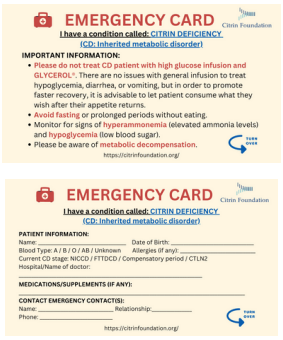
We have developed a comprehensive, downloadable resource which covers:

- Overview of the condition
- Current treatment and management
- Available support and resources
- Ways in which patients can get involved with the Foundation

Patient Website

We have created a dedicated citrin deficiency patient website which includes resources such as patient stories, diet management tips, and more.





Global Digital Community

Citrin Foundation

@citrinfdn

@citrinfoundation

Register with Us

If you are a medical practitioner who is interested in citrin deficiency and would like to be kept informed of any updates or developments, please register with us via our website at https://citrinfoundation.org to become a part of our global professional network.

Citrin Foundation

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Citrin Foundation

Find a cure, Fund research, Support Patients and Families