Citrin Foundation

Research Support Cure

Section 1: Introduction to Citrin Foundation

Citrin Foundation is a non-profit, research-driven, patient-centred organisation set up in 2016 to tackle citrin deficiency (CD). Our goal is to find effective treatments and ultimately a cure for the condition. We also provide support to CD 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 CD and providing life-long support to patients. We believe that a multi-disciplinary, innovative and long-term approach will deliver breakthrough treatments and address the well-being of 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 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 benefit of existing therapies
- Develop new therapies
- Support affected patients and their families
- Drive innovation in the rare disease field

Section 2: What is Citrin Deficiency?

CD is an autosomal recessive liver disease and a urea cycle disorder (UCD) caused by mutations in the SLC25A13 gene encoding for the mitochondrial aspartate-glutamate carrier, citrin. Citrin is a key component of the malate-aspartate shuttle responsible for moving reducing equivalents (NADH) from the cytosol into the mitochondria. CD disrupts the NADH/NAD+ redox balance, affecting multiple key metabolic pathways in the liver such as, glycolysis, gluconeogenesis, de novo lipogenesis, beta-oxidation, and the urea cycle.

CD manifests as several age-dependent phenotypes: 1) neonatal intrahepatic cholestasis caused by CD (NICCD) in newborns or infants; 2) the silent/adaptation period or; 3) failure to thrive and dyslipidaemia caused by CD (FTTDCD) in childhood, observed in a subset of patients; and in a small percentage of patients 4) adolescent and adult CD (AACD) (formerly known as citrullinemia type 2, CTLN2), the most severe form of CD. A hallmark in patients is a self-selected aversion to carbohydrates and sweets with a preference for high-protein and high-fat foods.

Phase	Age	Signs and symptoms	
		Common	Less frequent
Neonatal Intrahepatic Cholestasis caused by Citrin Deficiency (NICCD)	Newborn	Persistent jaundice, failure to thrive, fatty liver, hepatomegaly, cholestasis. Typically resolves after a year.	Abnormal bleeding, vitamin K deficiency, hypoproteinaemia, galactosemia
"Silent" adaptation period	> 1 year old	Strong preference for protein/fat-rich foods, aversion to carbohydrate-rich foods and sugars.	Fatigue, hypoglycaemia, fatty liver, stomach discomfort
Failure to Thrive and Dyslipidaemia caused by Citrin Deficiency (FTTDCD)		Strong preference for protein fat-rich foods, aversion to carbohydrate-rich foods and sugars. Fatigue, hypoglycaemia, gastrointestinal disorders, and growth impairment.	Pancreatitis, hyperlipidaemia, hepatoma, fatty liver
Adolescent and Adult Citrin Deficiency (AACD)	Adolescence to adulthood	Sudden onset hyperammonaemia and citrullinemia, steatohepatitis. Alcohol, Carbohydrate/sugar consumption or infections may be potential triggers.	Pancreatitis, hyperlipidaemia, hepatoma, fatty liver, low BMI

Management

Management of CD is primarily based on dietary intervention, with an emphasis on protein and fat-rich foods and avoidance of excessive carbohydrate intake. Although there is currently no curative therapy, medium-chain triglycerides (MCTs) are commonly incorporated into management and may benefit some patients.

Diet Management

According to the 2019 Citrin Deficiency Guidelines published by the Japan Society of Inherited Metabolic Disorders, the recommended macronutrient distribution (PFC ratio) for CD is 15–25% protein, 40–50% fat, and 30–40% carbohydrate.

A variety of fat sources is encouraged. While animal fats may be included, preference should be given to plant-derived fats (e.g. olive oil) to support overall nutritional balance. Regular, frequent meals, consisting of three main meals with inter-meal snacks, are recommended across all age groups.

MCT Supplements

In infants with NICCD, MCT-enriched formula or MCT-supplemented breast milk is recommended. In post-NICCD and older patients, MCT oil should be taken with meals, in divided doses throughout the day. A commonly recommended target dose after one year of age is 1 g/kg/day, with a maximum daily dose of 40 g.

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 CD. 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 typical 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. For more details about our projects, please visit our website at “Funded Research”.

Section 4: Further Reading

- J. Kido, G. Makris, S. Santra, J. Häberle, Clinical landscape of citrin deficiency: A global perspective on a multifaceted condition, J. Inherit. Metab. Dis. 47 (2024) 1144–1156. https://doi.org/10.1002/jimd.12722
- T. Vuković, L.E. Kuek, B. Yu, G. Makris, J. Häberle, The therapeutic landscape of citrin deficiency, J. Inherit. Metab. Dis. (2024). https://doi.org/10.1002/jimd.12768
- J. Kido, J. Häberle, K. Sugawara, T. Tanaka, M. Nagao, T. Sawada, Y. Wada, C. Numakura, K. Murayama, Y. Watanabe, K. Kojima-Ishii, H. Sasai, K. Kosugiyama, K. Nakamura, Clinical manifestation and long-term outcome of citrin deficiency: Report from a nationwide study in Japan, J Inherit Metab Dis (2022). https://doi.org/10.1002/jimd.12483
- J.E. Walker, My path to citrin deficiency, J. Inherit. Metab. Dis. (2024). https://doi.org/10.1002/jimd.12818
- K. Hayasaka, Metabolic basis and treatment of citrin deficiency, J Inherit Metab Dis 44 (2021) 110–117. https://doi.org/10.1002/jimd.12294

Section 5: Resources for Patients

Patient Flyer

We have developed a comprehensive, downloadable resource which covers:

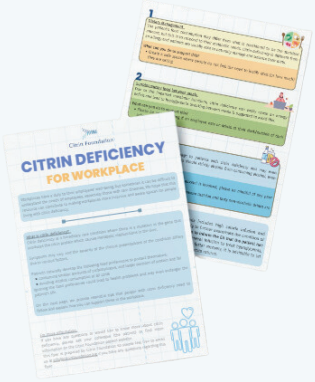
- Overview of the condition
- Dietary and Supplementary Management
- Available support and resources
- Ways in which patients can get involved with the Foundation

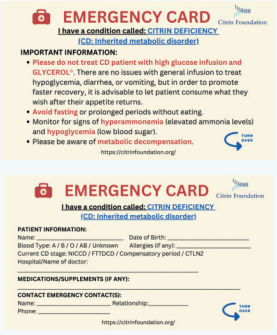
Other Available Resources

- Peer Support Group
- Age-specific Informational Flyers
- Newsletters
- Patient Emergency Card
- A Step-by-step Guide to Calculating PFC Ratios
- Recipes
- Patient Stories

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

Section 6: Get In Touch

Register with Us

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

Email Enquiries

General
For general information enquiries: info@citrinfoundation.org

Patient & Family
For patients, caregivers, or healthcare professionals seeking information, support, or guidance related to citrin deficiency: patients@citrinfoundation.org

Grants & Research
For questions related to research funding, grant applications, or ongoing funded projects: grants@citrinfoundation.org

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Find a cure, Fund research, Support Patients and Families