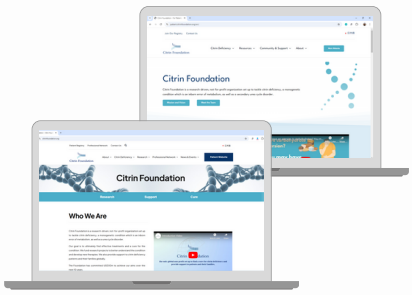
CITRIN FOUNDATION QUARTERLY NEWSLETTER

PATIENT ENGAGEMENT UPDATES

Website revamp

The Citrin Foundation team has redesigned our main website and patient website to enhance usability and accessibility. Whether seeking valuable resources, connecting with experts, or learning more about citrin deficiency, our improved platform is designed to meet all our patient's needs.



Clinician Directory

We are excited to announce the launch of our Clinician Directory, now available on both our main and patient websites. This dedicated page has been designed to connect patients with experienced clinicians in their area who specialise in citrin deficiency. Our goal is to ensure that patients receive accurate diagnoses and tailored care. By bridging the gap between patients and specialists, we hope to improve access to the support and expertise needed for managing citrin deficiency effectively.

Adult Patients Profiling Survey

The Foundation has developed an in-depth survey specifically for adult patients with citrin deficiency. This survey aims to gain a deeper understanding of the daily symptoms and challenges patients face, with a focus on the impact of the condition on the quality of life of patients. We have already initiated this project with some adult patients late last year and are eager to expand participation. If you know of any adult patients that may be interested in contributing to this important initiative, please reach out to us at patients@citrinfoundation.org.

PROFESSIONAL UPDATES

JIMD Special Issue

We are thrilled to announce the publication of an invited review by **Professor Sir John E. Walker** at the University of Cambridge, titled *"My Path to Citrin Deficiency"*, featured in the *Journal of Inherited Metabolic Disease* (JIMD, Vol. 47, No. 6). Professor Walker reflected on his Nobel Prize-winning research into ATP synthase and the mechanisms of ATP production, and how it indirectly led to the discovery of the citrin protein and its role in mitochondrial function. His pioneering work laid the foundation for all subsequent research into citrin deficiency. This exceptional review is part of a special themed issue focusing on ureagenesis defects, including citrin deficiency, and features other outstanding contributions from our collaborators, including:

- "Citrin Deficiency—The East-side Story" (Häberle, 2024)
- "The Therapeutic Landscape of Citrin Deficiency" (Vuković et al., 2024)
- "Clinical landscape of citrin deficiency: A global perspective on a multifaceted condition" (Kido et al., 2024)
- "Improved sensitivity and specificity for citrin deficiency using selected amino acids and acylcarnitines in the newborn screening" (Kido et al., 2023)

Together, these works advance global understanding and awareness of citrin deficiency. We invite you to explore this milestone issue and celebrate these remarkable achievements.

New Research Publication

We are pleased to announce a new research publication in *Molecular Metabolism* titled "Distinct roles for the domains of the mitochondrial aspartate/glutamate carrier citrin in organellar localization and substrate transport" funded by the Citrin Foundation. This groundbreaking study, led by **Drs. Sotiria Tavoulari, Denis Lacabanne, Gonçalo Pereira, and Professor Edmund Kunji** at the University of Cambridge, sheds light on the function of citrin protein, and the defects elicited by missense pathogenic mutations. Key findings reveal for the first time that calcium binding to the N-terminal domain does not regulate substrate transport as previously thought. Furthermore, calcium binding does not affect protein stability, dimerization, or mitochondrial import, while mutations in this domain cause mitochondrial import defects. Conversely, most missense mutations in the carrier domain had minimal or no impact on mitochondrial localization but significantly impaired transport activity. These insights advance our understanding of citrin deficiency pathogenesis and lay the foundation for improved diagnostics, prognostics, and potential therapies. We extend our heartfelt congratulations to the authors for their outstanding work.

Newly Funded Research Project

mRNA therapy for citrin deficiency

We are pleased to announce a new project funded by the Foundation with **Dr. Julien Baruteau** (University College London Great Ormond Street Institute of Child Health) as the Principal Investigator. This study will 1) characterize a novel mouse model of citrin deficiency and 2) show extensive proof of concept of LNP-mRNA therapy in the mouse model with mild and advanced liver disease, with and without hyperammonemia. If successful, this project will pioneer the translation of mRNA therapy for patients.

CONFERENCES AND EVENTS

Malaysia Webinar

The Foundation hosted a webinar on Citrin Deficiency in Malaysia, where there is a cohort of over 50 patients in Kuala Lumpur Hospital alone. The webinar brought together professionals from all over the country to learn more about the condition.

Barbara Yu opened the session with an introduction to our Foundation, our mission and activities. This was followed by a presentation by **Dr. Huey Yin Leong**, Clinical Geneticist & Inherited Metabolic Disease Specialist at Kuala Lumpur Hospital which provided an insightful overview of the cohort in Malaysia and highlighted the challenges and progress in the awareness, diagnosis and management of the condition in the country.

Leading expert in the field, **Professor Kimihiko Oishi**, Chair of the Department of Paediatrics at Jikei University School of Medicine, Japan, delivered a presentation on clinical presentations and effective management strategies for various phenotypes. The session wrapped up with a dynamic Q&A and discussion.

We would like to extend our gratitude to our speakers and attendees for their valuable contributions and look forward to working more closely with the patient cohort in Malaysia.

65th Annual Meeting of the Japanese Society for Inherited Metabolic Diseases (JSIMD), November 2024, Tokyo, Japan

From November 7th to 9th, the Citrin Foundation participated in the 65th Annual Meeting of the Japanese Society for Inherited Metabolic Diseases (JSIMD).

A highlight of the meeting was the Citrin Deficiency Symposium hosted by the Foundation on November 8th. The topic of the symposium was *"Advancements in Novel Therapies and New Cellular Models for Citrin Deficiency"*. Chaired by **Professor Kimitoshi Nakamura** (Kumamoto University) and **Professor Kimihiko Oishi** (Jikei University School of Medicine), the well-attended session opened with an overview presentation by the Foundation's Co-Founder and President, **Barbara Yu**. The session featured **Professor Joseph Baur** (University of Pennsylvania), who presented on the "Roles of NAD+ Concentration and Redox State in a Mouse Model of Citrin Deficiency". **Dr. Julien Baruteau** (University College London Great Ormond Street Institute of Child Health) delivered a presentation on "Messenger RNA therapy: application for Citrin Deficiency". Finally, **Professor Jun Kido** (Kumamoto University) shared insights on "New cellular models for better understanding of therapeutic interventions in Citrin Deficiency".

The Foundation also organized a citrin deficiency luncheon, bringing together scientists, clinicians, and close collaborators interested in advancing citrin deficiency research. This gathering provided a space to exchange new ideas and strengthen relationships with key partners. The Foundation's annual participation in the JSIMD meeting fosters international collaborations and crucially strengthens our deep ties with Japan—a region central to our mission.

Happy New Year from the Foundation

As we welcome 2025, we want to express our gratitude for all of your continued support and engagement in the work we are doing. Your collaboration and dedication have been instrumental in propelling us forward on our mission.

Looking ahead, we are excited to continue on this meaningful journey together in 2025. One of this year's highlights will be hosting our 3rd Citrin Foundation Global Symposium, to be held in Cambridge, UK, this summer.

Thank you for being a part of the Foundation's journey to finding a cure for citrin deficiency. We welcome suggestions on how we can improve our resources as well as ideas for new projects to explore so that we can support you better. If you would like to get in touch, please email us at patients@citrinfoundation.org. We look forward to continuing to support you and your family.

https://patient.citrinfoundation.org/en/