



# CITRIN FOUNDATION

## QUARTERLY NEWSLETTER

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2023 brought great strides for the Foundation on all fronts including research, raising awareness, and patient support for citrin deficiency (CD), culminating in our Second In-person Global Symposium in September last year.

Throughout the past year, the Foundation has made good progress in our research efforts by deepening collaborations with our existing consortium and working with new collaborators. Our existing research projects are making good progress. Our clinical strategy has also yielded good results where we have identified global CD clinical cohorts of over 1,100 patients. Furthermore, we have redoubled our efforts to provide holistic support to our patients through a range of new resources and opportunities for patients and families.

As we embark on the new year, our commitment to making a lasting difference in the lives of those affected by citrin deficiency remains unwavering. We look forward to making further progress in the development of novel therapies and laying the important groundwork for future clinical trials, including the establishment of a global patient registry. Your continued support is the driving force behind our achievements, and we look forward to the challenges and triumphs that lie ahead.

## RECAP OF 2023

### GLOBAL IN-PERSON SYMPOSIUM

The highlight of 2023 was our Second In-person Global Symposium in Cambridge, UK, where many of you were present. It was a great gathering for our research, clinical and patient community where many great ideas were discussed, and friendships were formed as we were united by our shared goals and visions. Please click [here](#) if you are interested to learn more about it.



### RESEARCH PROGRESS

#### New Research Initiatives

##### Global Omics Study

A particularly exciting development in 2023 was the initiation of the Global Omics Study - a pivotal, multi-site clinical study with over 15 centers from over 5 countries participating, aiming to identify novel biomarkers specific to CD. These biomarkers will be crucial for future clinical efforts in developing new therapies.

## **The development of mRNA therapy with Moderna**

The Foundation is working with Moderna Therapeutics and our collaborators to investigate *in vitro* pre-clinical studies to evaluate the basic effectiveness and properties of Moderna's latest version of lipid nanoparticle (LNP)-mRNA encoding wild type citrin protein in suitable cellular models. If these experiments yield positive results, the plan is to test the same mRNA therapy in animal models in the future to pave the way for eventual clinical trials in patients.

## **Generation and characterization of a citrin-KO rat model**

As part of the Foundation's ongoing efforts to create better pre-clinical research models to recapitulate human CD, we have developed a citrin-KO rat model. Studies at the University Children's Hospital Zürich and University of Cambridge are underway to characterize and validate the model.

## **Studies in CTLN2 patient liver samples**

The Foundation has initiated a joint study in collaboration with Shinshu University (Prof. Masahide Yazaki), University Children's Hospital Zürich (Prof. Johannes Häberle), and the Autonomous University of Madrid (Prof. Jorgina Satrustegui) to employ updated methodologies to study the liver samples of CTLN2 patients and investigate the possible decline in ASS protein expression in these patients.

## **Adult Metabolic Study**

This clinical study, a collaborative effort involving the Foundation, the University of Helsinki (Prof. Hannele Yki-Järvinen), the University of California Berkely (Prof. Marc Hellerstein), and the University of Oxford (Prof. Leanne Hodson), 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 please contact us at [patients@citrinfoundation.org](mailto:patients@citrinfoundation.org).

## **Other Research Projects Funded or Started in 2023**

- Modulating NAD<sup>+</sup> availability in a rodent model of citrin deficiency (Prof. Joseph Baur, University of Pennsylvania)
- Metabolic alterations in primary hepatocytes from mouse CD model and effects of redox manipulations – pilot studies (Prof. Marc Hellerstein, University of California Berkeley)
- Metabolic alterations *in vivo* in liver of rodent CD double knockout-out model and effects of redox manipulations (Prof. Marc Hellerstein, University of California Berkeley)
- Development of a human cellular model and targeting liver glycerol-3-phosphate phosphatase for citrin deficiency (Prof. Marc Prentki and Dr. S.R. Murthy Madiraju, Montreal Diabetes Research Center, CRCHUM)

## **New Research Publications**

In terms of publications, three manuscripts originating from Foundation-sponsored projects were successfully accepted for publication:

- Nicotinamide riboside rescues dysregulated glycolysis and fatty acid  $\beta$ -oxidation in a human hepatic cell model of citrin deficiency ([Yau et al. 2023](#))
- Exogenous aralar/slc25a12 can replace citrin/slc25a13 as malate aspartate shuttle component in liver ([González-Moreno et al. 2023](#))
- Improved sensitivity and specificity for citrin deficiency using selected amino acids and acylcarnitines in the newborn screening ([Kido et al. 2023](#))

## Citrin Foundation Study Abroad Award

The Foundation proudly launched the Citrin Foundation Study Abroad Award last year. The first inaugural recipient, A/Prof. Jun Kido, successfully completed his 8-month fellowship with Prof. Johannes Häberle at the University Children's Hospital Zürich where he worked on the generation and biochemical study of induced pluripotent stem cells (iPSCs) derived from CD patients, among other things.



## CLINICAL STRATEGY PROGRESS

### Clinical Cohorts

The Foundation has significantly expanded our clinical cohort in the past year to over 1,100 patients, by identifying more than 450 patients from various cohorts globally in countries such as Taiwan, Korea and Vietnam. One such cohort of over 300 patients is at the National Children Hospital Hanoi under the care of A/Prof. Nguyen Pham Anh Hoa, who has become our close collaborator.



### Establishment of Strategic Centers

#### *CD Center of Excellence at Kumamoto*

The Citrin Deficiency Center of Excellence at Kumamoto University led by Prof. Kimitoshi Nakamura and sponsored by our Foundation has made great progress towards the goal of uncovering more CD patients, improving newborn screening and genetic diagnosis, standardizing diagnosis and management guidelines for CD, and developing a CD patient registry. It has also acted as a leader for clinical studies in Japan and Asia.

#### *Urea Cycle Disorders (UCD) Translational Research Center at Zürich*

The Foundation has announced the significant initiative of the establishment of the UCD Translational Research Center at University Children's Hospital Zürich, University of Zürich, to be led by Prof. Johannes Häberle. This Center will focus on translational research and clinical studies for UCD, with CD as a model disease.

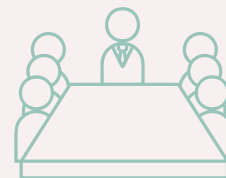


### Ureagenesis Test

After successful pilot studies assessing the safety and diagnostic utility of the ureagenesis test in some CD patients, conducted in collaboration with Prof. Johannes Häberle, who developed the test with his team, we are expanding the scope of these studies to larger patient cohorts.

### Advisory Board Expansion

In 2023, Prof. Fumio Endo was appointed as a Special Advisor to the Foundation. We are very grateful for his substantial contributions so far.



## RAISING GLOBAL AWARENESS

### Conferences and External Events

Throughout 2023, the Foundation actively engaged and presented in numerous international meetings to raise awareness of CD within the IEM community and to share the work we do:

- 44th Society for Inherited Metabolic Disorders (SIMD) Annual Meeting in Salt Lake City, Utah
- 6th Asian Congress on Inherited Metabolic Disease (ACIMD) in Bangkok, Thailand
- 64th Annual Meeting of the Japanese Society for Inherited Metabolic Diseases (JSIMD) in Osaka, Japan

In August last year, the Foundation also organized a talk in partnership with Boston Children’s Hospital’s Metabolism Grand Rounds, inviting Prof. Johannes Häberle to speak about citrin deficiency.

More recently, the Foundation released a global awareness video that has been shared widely on our various social media channels. You may watch the [full video](#) on our YouTube Channel.

### Expert Talks

In 2023, the Foundation hosted two talks by leading experts in their respective fields that are relevant to our aims and help broaden the scope of our professional network.

- **Principles of gene regulation and its potential modulation in citrin deficiency** by Dr. Julian Sale, University of Cambridge
- **mRNA Therapies - Therapeutic strategies beyond Vaccines** by Prof. Uğur Şahin, Founder and CEO of BioNTech

## PATIENT ENGAGEMENT

### Membership Update

In the past year, our global patient membership has grown significantly to over 300 patients worldwide, with 96 new patients joining our community. Our professional network has also grown with professionals joining from Turkey, Malaysia, Japan, Indonesia, Vietnam, the UK, and the US.

### Resources and Support

Last year also marked a surge in the Foundation’s capabilities to support our patients as we dedicated efforts to create a number of valuable resources for our membership:

- Food-related resources including seasonal recipes, practical snack ideas and special event flyers
- Emergency card template
- Age-specific resources i.e. alcohol and peer pressure resource, revamped workplace flyer, resource for primary school children
- YouTube Channel launch with a number of videos including patient interviews and our new CD Awareness YouTube Video
- Multi-language CD patient flyers proofread by our registered members: Korean, German, Mandarin



## WHAT’S NEW THIS JANUARY?

### Advisory Board

The Foundation has appointed four new advisors who are the leading experts in their fields and who we believe will help us to further our aims. We are grateful to them for joining our efforts, and we look forward to their future contributions.

#### Dr. Nicholas Ah Mew

Dr. Nicholas Ah Mew is Director of the Inherited Metabolic Disorders Program at Children’s National Hospital and is Associate Professor of Paediatrics at The George Washington University.

### ***Prof. Marc Hellerstein***

Prof. Marc Hellerstein is a Professor of Human Nutrition at the University of California, Berkeley, where he occupies an Endowed Chair (Dr. Robert C. and Veronica Atkins Chair). He is also a Professor of Endocrinology, Metabolism and Nutrition in the Department of Medicine at the University of California in San Francisco.

### ***Dr. Robin Lachmann***

Dr. Robin Lachmann leads the Charles Dent Metabolic Unit at University College London Hospitals, one of the largest units in the world looking after adults with inherited metabolic diseases.

### ***Stephen Yang***

Stephen Yang is Head of Strategy for Immunology at Novartis where he is responsible for coordinating company-wide research, commercialisation and business development activities within the therapeutic area.

## **Upcoming Events**

### ***Citrin deficiency and eating disorders online info session, 27th March 2024***

The clinical manifestations of CD such as strong food preferences and low BMI may sometimes lead to the misdiagnosis as an eating disorder like anorexia nervosa ([Takeuchi et al. 2015](#)). With this in mind, the Foundation has reached out to the eating disorders community in North America and will be hosting an online information session on CD for eating disorders professionals. If you are interested in participating, please contact [info@citrinfoundation.org](mailto:info@citrinfoundation.org).

### ***Society for Inherited Metabolic Disorders (SIMD) 45th Annual Meeting, April 2024, North Carolina, USA***

The Foundation is set to participate in this year's SIMD meeting in Charlotte, North Carolina and will showcase a poster presentation as well as having an exhibition booth at the event. We are looking forward to working with more professionals in the USA to improve the diagnosis, management and treatment of CD.

## **Patient engagement and support**

### ***Adult patient support group***

We are excited to announce the launch of our adult patient support group. This group will provide a safe space for our adult patients to connect and offer mutual support. If you have any adult patients who may be interested in joining this group, please ask them to contact [patients@citrinfoundation.org](mailto:patients@citrinfoundation.org).

### ***International Patient Committee***

This month we officially launched our International Patient Committee and held our first committee meeting in which many exciting ideas were raised. Please stay tuned for future updates.

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.

If you would like to get in touch, please email us at [info@citrinfoundation.org](mailto:info@citrinfoundation.org) for general inquiries or [grants@citrinfoundation.org](mailto:grants@citrinfoundation.org) for grant inquiries.

***You can look forward to the next edition of our newsletter in Spring.***

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<https://citrinfoundation.org/>

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