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Clinical landscape of citrin deficiency: A global perspective on a multifaceted condition

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Abstract

Citrin deficiency is an autosomal recessive disorder caused by a defect of citrin resulting from mutations in *SLC25A13*. The clinical manifestation is very variable and comprises three types: neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD: OMIM 605814), post-NICCD including failure to thrive and dyslipidemia caused by citrin deficiency, and adult-onset type II citrullinemia (CTLN2: OMIM 603471). Frequently, NICCD can run with a mild clinical course and manifestations may resolve in the post-NICCD. However, a subset of patients may develop CTLN2 when they become more than 18 years old, and this condition is potentially life-threatening. Since a combination of diet with low-carbohydrate and high-fat content supplemented with medium-chain triglycerides is expected to ameliorate most manifestations and to prevent the progression to CTLN2, early detection and intervention are important and may improve long-term outcome in patients. Moreover, infusion of high sugar solution and/or glycerol may be life-threatening in patients with citrin deficiency, particularly CTLN2. The disease is highly prevalent in East Asian countries but is more and more recognized as a global entity. Since newborn screening for citrin deficiency has only been introduced in a few countries, the diagnosis still mainly relies on clinical suspicion followed by genetic testing or selective metabolic screening. This paper aims at describing (1) the different stages of the disease focusing on clinical aspects; (2) the current published clinical situation in East Asia, Europe, and North America; (3) current efforts in increasing awareness by establishing management guidelines and patient registries, hereby illustrating the ongoing development of a global network for this rare disease.

KEYWORDS

citrin, CTLN2, global network, NICCD, patient registry, *SLC25A13*

The authors would like to dedicate this work to Prof. Takeyori Saheki, a pioneer in the description of citrin deficiency and beyond.

1 | INTRODUCTION TO THE DISEASE, BIOCHEMISTRY, AND PATHOPHYSIOLOGY

In 1993, Japanese researchers first reported about adult patients with a condition clinically and biochemically resembling classical citrullinemia type 1 caused by a defect in the urea cycle enzyme argininosuccinate synthetase 1 but lacking genetic variants in the respective *ASS1* gene.[1] The same authors reported this condition, named citrullinemia type 2 or CTLN2, to be characterized by decreased hepatic argininosuccinate synthetase 1 (ASS1) with normal kinetic properties and thermal stability accompanied by near normal levels of *ASS1* mRNA in liver, normal translational activity, and no gross structural abnormalities.[1] Finally, Kobayashi et al. identified the primary cause of CTLN2 as not derived from the *ASS1* gene locus and succeeded in cloning the causative gene *SLC25A13*,[2] for which they designated the term "citrin."

Based on this historical perspective, citrin deficiency is now known as an autosomal recessive disorder caused by mutations in *SLC25A13* encoding for the inner mitochondrial membrane protein citrin, which is a part of the malate–aspartate shuttle and closely linked to several biochemical pathways including glycolysis and gluconeogenesis,[2] de novo lipogenesis and beta-oxidation, the tricarboxylic acid (TCA) cycle, and the urea cycle. The disease is characterized by age-dependent, variable clinical manifestations: neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD; OMIM 605814), failure to thrive and dyslipidemia caused by citrin deficiency (FTTDCD), and adult-onset type II citrullinemia (CTLN2; OMIM 603471).[3–5]

Neonates or infants with citrin deficiency present with intrahepatic cholestasis and diverse metabolic abnormalities, including citrullinemia, galactosemia, hypoglycemia, and sometimes hyperammonemia, which, other than in CTLN2, is probably presumed to be secondary to liver dysfunction. This condition is classified as NICCD. In most patients, clinical manifestations of NICCD improve or even resolve spontaneously by the age of 12–24 months. However, some patients in the post-NICCD period may continue to present symptoms such as failure to thrive, dyslipidemia, recurrent episodes of hypoglycemia, fatigue, abdominal pain due to pancreatitis, a condition classified as FTTDCD.[4] Besides, patients may also have a silent remission period until after adolescence, however, 10%–20% of them may then evolve into a very severe or even fatal metabolic condition, CTLN2. This most severe form of citrin deficiency is characterized by citrullinemia and hyperammonemia, severe liver steatosis, cognitive impairment with sudden episodes of unconsciousness due to brain edema, and other organ manifestations including pancreatitis, which can even occur without other features of CTLN2.[6,7]

Citrin is a Ca^{2+}-binding aspartate/glutamate carrier located at the inner mitochondrial membrane and is expressed ubiquitously and most prominently in liver, kidney, heart, and small intestine.[2,8] The role of citrin as part of the malate–aspartate nicotinamide adenine dinucleotide (NADH) shuttle is to transfer cytosolic reducing equivalents produced during hepatic glycolysis into the mitochondria.[2] Hence, a defect of citrin will result in an impaired function of the malate–aspartate NADH shuttle leading to excessively increased cytosolic NADH, decreased mitochondrial NADH, and reduced availability of cytosolic aspartate as one of the substrates of ASS1.[9] There is aralar, another aspartate/glutamate carrier encoded by *SLC25A12* and with essentially the same role as citrin, which however can unfortunately not compensate a defect of citrin due to its different expression profile lacking functionality in liver.[10]

Consequently, the elevated cytosolic NADH/NAD^+ ratio has a cascading impact on several neighboring metabolic pathways. This leads to hindered hepatic utilization of glucose in glycolysis and of lactate in gluconeogenesis,[4] compromised functionality of the TCA cycle due to mitochondrial NADH depletion and impaired beta-oxidation due to reduced abundance of peroxisome proliferator activated receptor alpha. These factors collectively contribute to a substantial energy deficit within hepatocytes, resulting in inadequate or delayed production of blood ketones during hypoglycemia, although this is not always the case and patients may even be grossly ketotic when presenting with acute hypoglycemia.

In this paper, we describe the current clinical landscape of citrin deficiency considering a global perspective on this multifaceted condition as follows: the different stages of the disease focusing on clinical aspects; the current published clinical situation in East Asia, Europe, North America; current efforts in building a worldwide framework entailing management guidelines, patient registries for documentation of the natural disease course, and preparation of clinical trials, thus illustrating the ongoing clinical and scientific developments for this rare disease.

2 | CLINICAL PRESENTATION AND COURSE OF THE DISEASE

The three distinct phases of citrin deficiency (NICCD, post-NICCD including FTTDCD and CTLN2) are illustrated in Figure 1. In this figure, we are presenting the vital status (alive or deceased) of citrin deficiency patients, collected from the nationwide study in Japan[11] and a

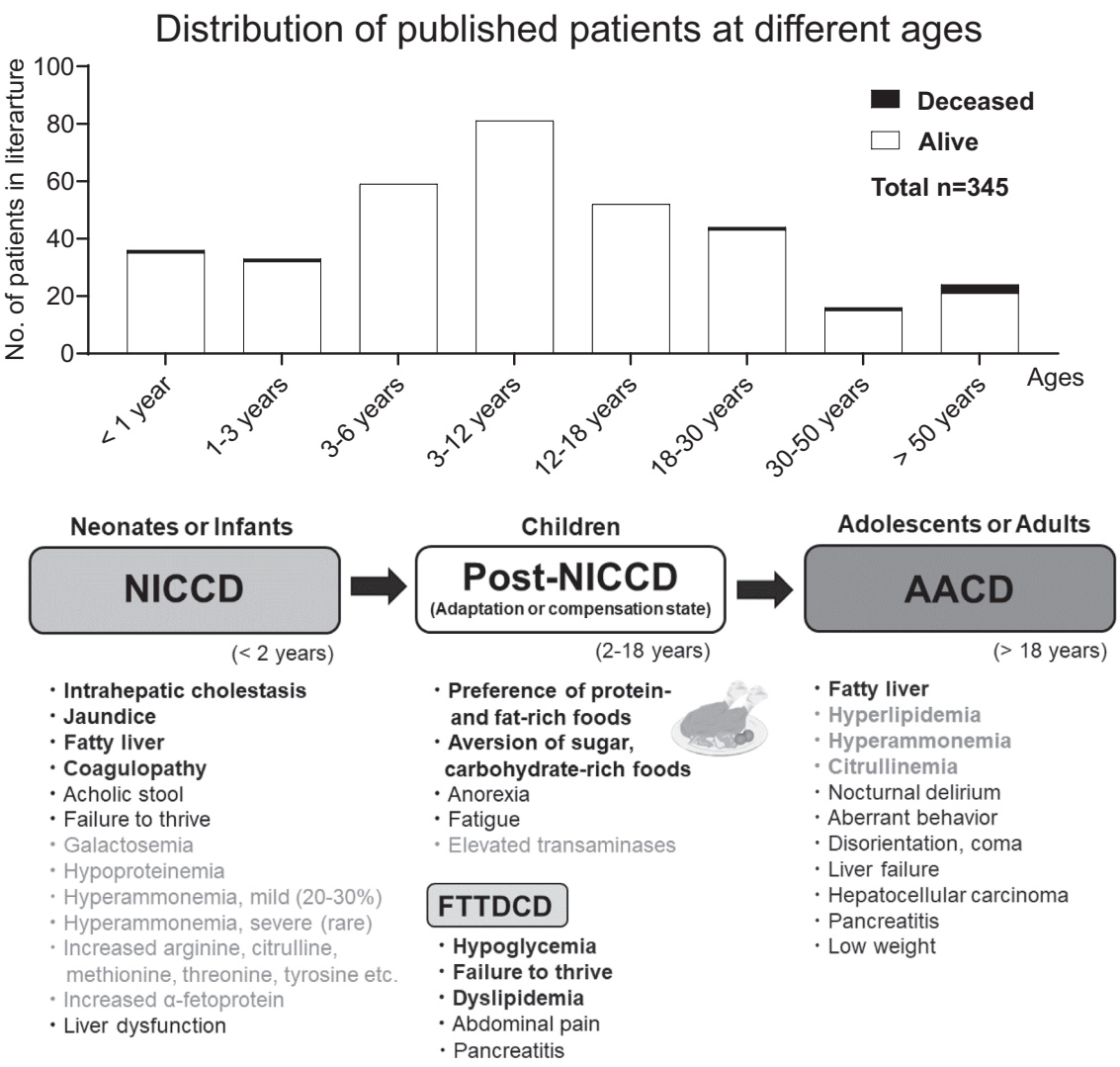

FIGURE 1 Clinical manifestations and current vital status (alive or deceased) of citrin deficiency patients (NICCD, post-NICCD, AACD) ($n = 345$). Seven patients passed away during our study and literature review. Bold: frequent clinical manifestations; light gray: laboratory manifestations; normal font: other clinical manifestations.

review of current literature[7,12–54] to provide insights into the severity of this condition.

Although some of the later presenting patients have no record of neonatal or infantile cholestasis, patients usually begin exhibiting clinical signs or symptoms within the first 6 months of life and receive their diagnosis by 1 year of age (Figure 2). This condition, NICCD, typically presents with several features, including low birth weight, growth restriction, intrahepatic cholestasis, diffuse fatty liver, hepatomegaly, parenchymal cellular infiltration associated with hepatic fibrosis, hypoglycemia, hypoproteinemia, hyperammonemia (rarely severe), coagulopathy, and liver dysfunction. Fortunately, NICCD is generally not life-threatening, and patients often see their manifestations resolve by the age of 1, sometimes without the need for medical intervention. The nationwide study on Japanese NICCD patients ($n = 192$)[11] demonstrated an increased incidence of cholestasis (79%), elevated transaminases (71%), hypoproteinemia (39%), prolonged prothrombin time (34%), fatty liver (33%), hyperlipidemia (24%), and hypoglycemia (30%). Growth impairment, such as poor weight gain (32%), was a significant complication, although only a minority of patients exhibited marked short stature (<−2.0 SD) (15%). Additionally, hepatomegaly (22%), anemia (17%), hyperammonemia (>100 μmol/L) (11%), and seizure (5%) were observed in only a smaller subset of NICCD patients.

The post-NICCD period is mainly characterized by apparently asymptomatic individuals with often a strong preference for protein- and/or lipid-rich foods and an aversion to carbohydrate-rich foods. Variable symptoms namely hypoglycemia, growth restriction, fatigue, anorexia, pancreatitis, and impaired quality of life might be observed at this disease stage and in fact persist in a

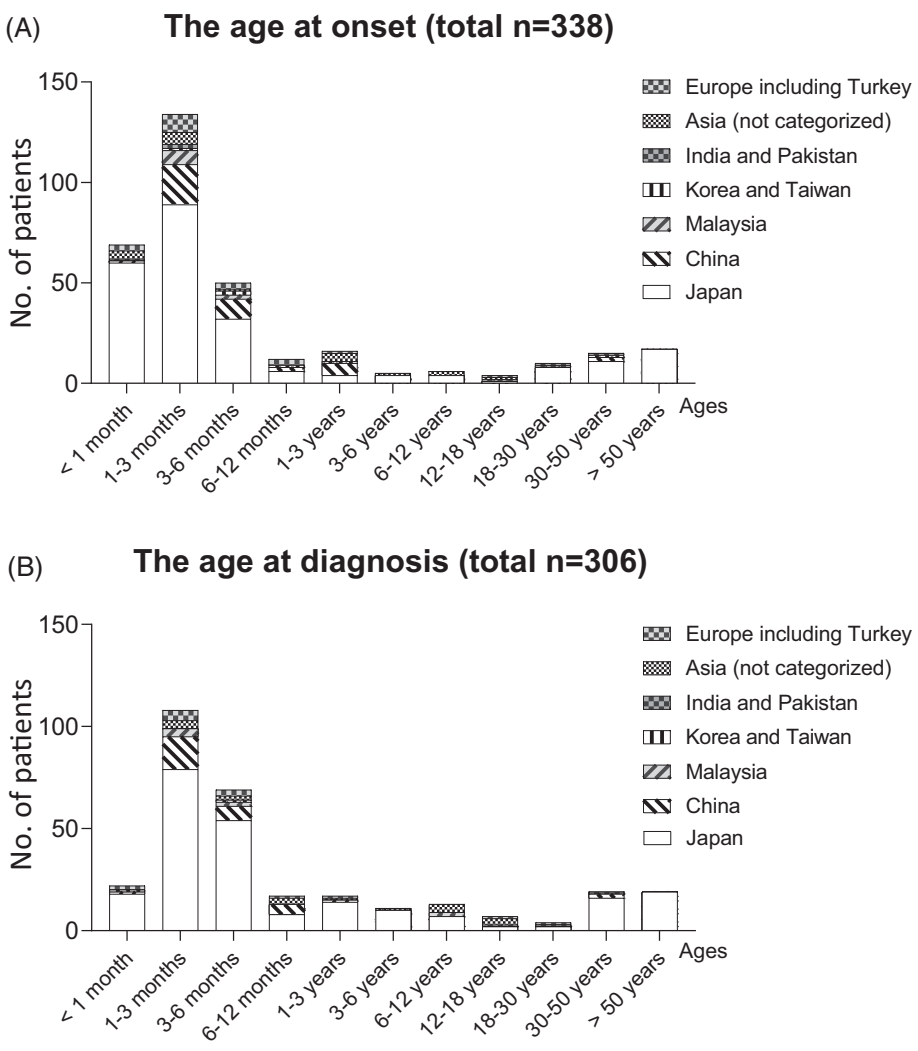

FIGURE 2 Current status of patients with citrin deficiency regarding (A) the age at onset ($n = 338$) and (B) the age at diagnosis ($n = 306$). Japan[11] (A: $n = 213$, B: $n = 209$). Japan (other studies) (A: $n = 23$, B: $n = 20$). China (A: $n = 41$, B: $n = 32$). Malaysia (A: $n = 9$, B: $n = 8$). Korea or Taiwan (A: $n = 6$, B: $n = 2$). India or Pakistan (A: $n = 6$, B: $n = 3$). Asia (not categorized) (A: $n = 19$, B: $n = 18$). Europe including Turkey (A: $n = 21$, B: $n = 14$).

small subset of post-NICCD patients. Notably, these symptoms align with the transition of certain post-NICCD patients toward FTTDCD, a condition that may be characterized by hypoglycemia, failure to thrive and dyslipidemia. In the largest so far reported cohort, most post-NICCD patients ($n = 13$) had not previously experienced manifestations related to NICCD.[11]

The end-stage of citrin deficiency manifests as the abrupt onset of CTLN2 at around 20 years of age, affecting a significant number of patients who were previously in either NICCD or post-NICCD states. CTLN2 is characterized by the development of symptomatic hyperammonemia and neuropsychiatric manifestations including aggression, delusions, disorientation, drowsiness, flapping tremor, hyperactivity, irritability, loss of memory, nocturnal delirium, seizures, and coma. External factors, including alcohol consumption, sugar intake,[55] specific medication like acetaminophen and rabeprozole,[56] glycerol infusion,[57] and surgical procedures may exacerbate these manifestations. It is important to avoid administration of high sugar solutions and glycerol for patients with undiagnosed liver cirrhosis or liver disease because CTLN2 patients with hepatic encephalopathy have died after infusion of high sugar solutions and/or glycerol.[55,57] This fatal outcome is caused by sugar and glycerol induced increases of the cytosolic NADH/NAD^+ ratio leading to accumulation of cytosolic NADH and subsequently impairment of hepatic cellular function.[58]

In the Japanese nationwide study, some CTLN2 patients ($n = 17$) developed hyperammonemic coma (83%), liver cirrhosis (18%), ascites (18%), liver tumor (18%), and pancreatitis (18%), symptoms which were not presented during the NICCD state. Moreover, hyperlipidemia and fatty liver were likely to persist.[56,59,60]

An interesting aspect in the Japanese nationwide study concerned the sex of patients: in NICCD, there was a nearly equal distribution between males and females (73:80). In contrast, CTLN2 displayed a male-to-female ratio of 2.4 to 1 (120:50),[61] indicating that males tend to exhibit lower resistance to CTLN2 phenotype than

females, possibly due to male preference for carbohydrate-rich food and alcohol.[61]

In general, the prognosis of patients with citrin deficiency is favorable unless there is development of CTLN2. In the Japanese cohort,[11] out of 222 patients, three unfortunately passed away, primarily due to unrelated causes, and one patient succumbed to pancreatitis. Even the majority of CTLN2 patients (11 out of 17) were fully employed with no significant neurological disability, registering at grades 0 or 1 on the modified Rankin Scale. However, two CTLN2 patients developed severe disability (grade 5). It is important to realize that CTLN2 or "citrullinemia type 2" is very different from "citrullinemia type 1" in terms of pathophysiology and therapy. For instance, citrin deficiency must not be treated with high dose glucose infusions, which are in contrast part of standard emergency treatment for all other urea cycle disorders (UCDs). As there have been tragic events caused by this terminology-related confusion,[62] the authors of this paper therefore suggest avoiding the term "citrullinemia type 2" (or its abbreviation CTLN2), but instead using "adolescent and adult citrin deficiency" (AACD) for this phase of the disease, as it is practiced in this paper from now on.

At present, the majority of known patients were diagnosed based on their clinical manifestation. If numbers of known patients and published rates of incidence of citrin deficiency are compared, an underdiagnosis of the condition becomes obvious. This leads to the role of newborn screening (NBS) for this condition, which is discussed in the next section.

3 | NBS AND OTHER DIAGNOSTIC STRATEGIES

To improve the diagnostic rate and hereby the prognosis of affected patients,[63] several NBS programs included citrin deficiency as target disease mainly in East Asia such as Taiwan, China, and Japan.[63–70] In most of these NBS programs, citrulline levels in dried blood spots (DBS) were used as marker despite its low sensitivity and specificity. Recently, a new scoring system using threshold levels for arginine (≥9 μmol/L), citrulline (≥39 μmol/L), isoleucine + leucine (≥99 μmol/L), tyrosine (≥96 μmol/L), and C0/C5-DC ratio (≥327) in DBS demonstrated an improved detection rate for newborns who later developed NICCD. Moreover, this method can be implemented in existing NBS programs at no additional costs.[71]

The typical laboratory findings in NICCD comprise elevated transaminases together with cholestatic parameters and elevated blood amino acid concentrations mainly of arginine, citrulline, methionine, threonine, and tyrosine.[11] A peculiar finding is that of an increased galactose in blood or urine due to inhibition of UDP-galactose-epimerase, and this may even already have been picked up in NBS programs that use galactose as target parameter. All the laboratory signs associated with NICCD very often improve spontaneously or even normalize entirely by the age of 24 months. Most patients with NICCD develop some degree of fatty liver, which can be severe in single cases. Liver histology in NICCD patients demonstrated a mixture of two types of hepatocytes with macrovesicular or microvesicular fat droplets, cholestasis, and hemosiderin deposition in periportal hepatocytes and macrophages.[72] In the adaptation period, most patients do not show any laboratory abnormalities apart from elevated transaminases in few cases. During this period, only a minority of patients present clinically and are then classified as FTTDCD, which can be accompanied by hypoglycemia and dyslipidemia.[73] In AACD, only arginine and citrulline levels are increased in the amino acid profile.[11] Very prominent, however, are the signs of hepatic manifestation in this phase, which is characterized by liver disease progression and presence of bridging fibrosis and perisinusoidal fibrosis. Such hepatic alterations can then advance into end stage liver disease resembling advanced nonalcoholic fatty liver disease (NAFLD).[60] Besides, AACD patients are reported to show high serum pancreatic secretory trypsin inhibitor (PSTI) concentrations, a marker known as serine protease inhibitor Kazal type 1 (SPINK1). *PSTI/SPINK1* gene expression is associated with the onset of pancreatitis,[74] and elevated serum PSTI levels are thought to be indicative of continuously damaged pancreatic acinar cells.[75]

For confirmation, pathogenic *SLC25A13* variants on both alleles should be identified for a definite diagnosis of citrin deficiency. However, if only a single *SLC25A13* variant is detected in a patient with a strong suspicion due to clinical presentation, an elevated serum PSTI could be helpful in distinguishing citrin deficiency from conventional NAFLD.[60] Finally, western blotting of citrin protein using patient skin fibroblasts or lymphocytes may be used in cases of inconclusive molecular genetic testing.[15,76]

4 | THE GENETIC BACKGROUND AND FREQUENCY OF CITRIN DEFICIENCY: GLOBAL ASPECTS

Following the initial identification of citrin deficiency in patients from Japan, other East Asian countries also reported a similar prevalence, leading to an increasing number of patient series from this region of the world.[15,16,19,27,37,47,55–57,59,60,77,78] In 2007, the first patient of European ancestry was documented,[79] and subsequently, additional publications emerged from various

European countries, the United States, and the Middle East.[7,15,16,19,27,37,43,44,47] In light of this, we provide a summary of the current epidemiological data, categorized by age at onset (Figure 2A) and age at diagnosis (Figure 2B).

As per manuscript preparation, a total of 651 *SLC25A13* variants have been documented in ClinVar database.[80] Among these variants, 146 have been classified as pathogenic/likely pathogenic, including

TABLE 1 Frequency of *SLC25A13* variants in CD patients of Vietnam, China, Taiwan, Korea, and Japan cohort.

Variant		Allele frequency					
Nucleic acid	**Amino acid**	**Vietnam**	**China**	**Taiwan**	**Korea**	**Japan**	**Total**
c.852_855delTATG	p.Met285Profs*2	91.78% (536/584)	58.33% (616/1056)	55.56% (20/36)	30.30% (20/66)	25.90% (173/668)	56.64% (1365/2410)
c.1177+1G>A	p.Ala340_Arg392del	0.51% (3/584)	1.33% (14/1056)	2.78% (1/36)	12.12% (8/66)	28.29% (189/668)	8.92% (215/2410)
IVS16ins3kb	p.Ala584Valfs*2	3.60% (21/584)	10.04% (106/1056)	ND	33.33% (22/66)	3.29% (22/668)	7.10% (171/2410)
c.1638_1660dup	p.Ala554Glyfs*17	0.68% (4/584)	8.52% (90/1056)	13.89% (5/36)	3.03% (2/66)	2.99% (20/668)	5.02% (121/2410)
c.615+5G>A	p.Ala206Valfs*7	1.37% (8/584)	7.58% (80/1056)	19.44% (7/36)	ND	0.15% (1/668)	3.98% (96/2410)
c.1311+1G>A	p.Val411_Cys437del	ND	ND	ND	ND	7.19% (48/668)	1.99% (48/2410)
c.674C>A	p.Ser225*	ND	ND	ND	9.09% (6/66)	4.49% (30/668)	1.49% (36/2410)
c.1399C>T	p.Arg467*	0.51% (3/584)	1.52% (16/1056)	ND	1.52% (1/66)	ND	0.83% (20/2410)
IVS4ins6kb	p.Glu110fs*127	ND	1.52% (16/1056)	ND	NT	ND	0.66% (16/2410)
c.1592G>A	p.Gly531Asp	ND	ND	ND	3.03% (2/66)	1.05% (7/668)	0.37% (9/2410)
c.955C>T	p.Arg319*	ND	0.76% (8/1056)	ND	ND	ND	0.33% (8/2410)
c.1048G>A	p.Asp350Asn	ND	0.76% (8/1056)	ND	ND	ND	0.33% (8/2410)
c.1078C>T	p.Arg360*	ND	0.57% (6/1056)	ND	ND	0.30% (2/668)	0.33% (8/2410)
c.1799dup	p.Tyr600*	ND	ND	ND	ND	1.20% (8/668)	0.33% (8/2410)
c.1801G>T	p.Glu601*	ND	ND	ND	ND	1.20% (8/668)	0.33% (8/2410)
c.550C>T	p.Arg184*	ND	0.57% (6/1056)	ND	ND	0.15% (1/668)	0.29% (7/2410)
c.1813C>T	p.Arg605*	ND	ND	ND	3.03% (2/66)	0.75% (5/668)	0.29% (7/2410)
c.1092_1095del	p.Phe365Trpfs*407	ND	0.57% (6/1056)	ND	ND	ND	0.25% (6/2410)
c.2T>C	p.Met1Thr	0.68% (4/584)	0.57% (6/1056)	ND	ND	ND	0.17% (4/2410)
c.1801G>A	p.Glu601Lys	ND	ND	ND	ND	0.30% (2/668)	0.08% (2/2410)
Other variants		5	28	1	3	6	42
Subject number		$n = 292$	$n = 528$	$n = 18$	$n = 33$	$n = 334$	$n = 1205$

TABLE 1 (Continued)

Variant		Allele frequency					
Nucleic acid	**Amino acid**	**Vietnam**	**China**	**Taiwan**	**Korea**	**Japan**	**Total**
References		Nguyen et al.[84]	Lin et al.[83]	Tsai et al.[13] Song et al.[18] Hu et al.[48] Lee et al.[81] Lin et al.[82] Yeh et al.[86]	Oh et al.[85]	Tabata et al.[77]	

Note: Order of variants according to total reported frequency. IVS16ins3kb: c.1750_1751[insNM_138459.3:2672_24;1750+72_72_1751-4dup] (Tabata et al.[77]), IVS4ins6kb: Genbank accession no. KF425758 (Song et al.[100]).
Abbreviations: CD, citrin deficiency; ND, not detected; NT, not tested.

35 deletion/insertion mutations, 34 nonsense mutations, 31 splice site mutations, 13 missense mutations, 1 silent mutation, and 32 large deletion/duplication mutations. Table 1 provides an overview of reported mutations and their variant frequency in cohorts from Vietnam, China, Taiwan, Korea, and Japan.[13,18,48,77,81–86] Specific *SLC25A13* variants are notably prevalent within these patient cohorts, such as c.852_855delTATG, c.1177+1G>A, IVS16ins3kb, and c.1638_1660dup, which appear to be widely distributed and common among all East Asian countries.

The overall high prevalence of citrin deficiency is underlined by the known carrier frequencies in East Asian populations, which can be as high as 1:31 in Vietnam or 1:47 in China (Table 2).[87–93] In Japan, the frequency of homozygotes or compound heterozygotes for *SLC25A13* pathogenic variants is estimated at 1:17 000 based on the carrier frequency of 1:65.[9,77] Interestingly, this number is in accordance with the observed frequency of NICCD,[94] but quite different from the observed frequency of AACD (1:100 000–1:230 000),[95] suggesting that not all patients will develop the most severe disease form and/or that certain individuals within the adult population are not yet diagnosed. Importantly, some parents were described as being affected by bi-allelic pathogenic variants in *SLC25A13*, however without displaying any manifestations.[96] For instance, it has been reported that an asymptomatic father shared the same *SLC25A13* genotype as his son, who was diagnosed with NICCD.[31] Hence, it is crucial to conduct thorough investigations and provide counseling to family members of citrin deficiency patients, regardless of whether they exhibit manifestations.

Currently, new cases of citrin deficiency are documented in various parts of the world, underscoring the global nature of this disorder. This pan-ethnicity is partly explained by migration, spreading citrin deficiency to different regions of East Asia as well as worldwide.[97] For instance, c.852_855delTATG variant was identified in more than 50% of citrin deficiency carriers in South China,[83] and was also prevalent in Southern Asia, including Vietnam,[84] Taiwan,[82] and Thailand.[90] Nonetheless, its frequency is gradually decreased when moving toward the North, whereas c.1750_1751[insNM_138459.3:2672_24;1750+72_72_1751-4dup] variant demonstrated the inverse tendency.[35,42–44] In contrast, the variant c.1177+1G>A was exclusively identified in Japan[77,89,91,98] and South Korea.[77,85,89] The carrier frequencies for *SLC25A13* variants suggest that the Korean population is mixed mainly with populations from Northeast Asia.[99] In contrast to South Asia, the frequency of the variant c.1750_1751[insNM_138459.3:2672_24;1750+72_72_1751-4-dup] was similar to the frequency of c.852_855delTATG in South Korea[77,85,89] and northern parts of China,[83,89,100,101] however, uncommon for Japan.[77,89,91,98] This phenomenon can be attributed to the historical migration patterns, where the influence of ancestors from Northeast Asia played a more significant role in the movement toward Southeast Asia than the reverse.[99] This increased migration from North to South may account for the reduced prevalence of the c.852_855delTATG variant in Northeast Asia compared to Southeast Asia.

5 | CITRIN DEFICIENCY IN EUROPE: THE EXPERIENCE FROM THE UNITED KINGDOM

Since in the United Kingdom (UK), the largest cohort of citrin deficiency patients in Europe has been reported, we present here the experience from this country: over 30 citrin deficiency patients have been characterized, many of whom were described in a nationwide survey of dietetic practice published in 2020.[7] The disease is most prevalent in the South Asian (predominantly Pakistani) community, which has a high degree of consanguinity. A single mutation in *SLC25A13* accounts for over two-thirds of alleles in UK citrin deficiency patients, namely c.1763G>A [p.Arg588Gln]. The c.1173T>G [p.Tyr391*]

TABLE 2 Carrier frequency of *SLC25A13* variants in Japan, China, Taiwan, Korea, Vietnam, Singapore, and Thailand cohort.

Variant		Allele frequency									
Nucleic acid	**Amino acid**	**China**	**China**	**China**	**Taiwan**	**Vietnam**	**Singapore**	**Thailand**	**Japan**	**Japan**	**Korea**
c.2T>C	p.Met1Thr	NT	NT	NT	NT	ND	ND	2.77%	NT	NT	NT
c.852_855delTATG	p.Met285Profs*2	0.79%	0.54%	0.84%	0.53%	1.47%	0.72%	0.26%	0.16%	0.15%	0.22%
c.1177+1G>A	p.Ala340_Arg392del	NT	ND	NT	ND	ND	ND	ND	0.33%	0.27%	0.16%
c.615+5G>A	p.Ala206Valfs*7	0.13%	0.12%	0.10%	0.30%	ND	0.24%	NT	ND	NT	ND
IVS16ins3kb	p.Ala584Valfs*2	0.03%	NT	0.04%	NT	ND	ND	0.29%	NT	NT	NT
c.674C>A	p.Ser225*	NT	ND	NT	ND	ND	ND	ND	0.18%	0.19%	ND
c.1664_1665insA GATTAC AGGTGGCTGC CCGGGG	p.Gln556Aspfs*15	NT	NT	NT	NT	ND	0.18%	NT	NT	NT	NT
c.1638_1660dup	p.Ala554Glyfs*17	0.04%	0.04%	0.04%	0.04%	0.15%	ND	ND	0.04%	0.04%	0.02%
c.1420G>A	p.Val474Met	NT	NT	0.04%	NT	ND	ND	NT	NT	NT	NT
c.1399C>T	p.Arg467*	NT	NT	NT	NT	0.10%	ND	NT	NT	NT	NT
c.493C>T	p.Gln165*	NT	NT	NT	NT	ND	0.06%	NT	NT	NT	NT
c.1311+1G>A	p.Val411_Cys437del	NT	ND	NT	ND	ND	ND	ND	0.04%	0.04%	ND
c.1813C>T	p.Arg605*	NT	ND	NT	ND	ND	ND	NT	ND	ND	0.04%
c.550C>T	p.Arg184*	NT	0.02%	NT	ND	ND	ND	NT	ND	NT	ND
Carrier frequency (subject number)		1:51 ($n = 3409$)	1:70 ($n = 2855$)	1:47 ($n = 2428$)	1:57 ($n = 1314$)	1:31 ($n = 985$)	1:41 ($n = 831$[a])	1:15, 1:90[b] ($n = 1537$)	1:69 ($n = 1372$)	1:74 ($n = 1315$)	1:112 ($n = 2455$)
References		Lin et al.[88]	Lu et al.[89]	Zhang et al.[92]	Lu et al.[89]	Tran et al.[93]	Bylstra et al.[87]	Wongkittichote et al.[90]	Lu et al.[89]	Yamaguchi et al.[91]	Lu et al.[89]

Abbreviations: ND, not detected; NT, not tested.

[a]758 Chinese, 23 Malay, 23 Indian, 27 others.

[b]Exclude c.2T>C; IVS16ins3kb: c.1750_1751[insNM_138459.3:2672_24;1750+72_72_1751-4dup].

and c.1465T>C [p.Cys489Arg] variants were seen in patients of white Caucasian ethnicity and some patients of East Asian origin were described with some of the variants detailed above including c.852_855delTATG. Just over a third of patients in the UK presented with NICCD although a similar proportion were diagnosed prospectively due to a positive family history of the condition. A quarter of patients were described as being diagnosed in the FTTDCD phase and only two UK patients have been confirmed as having developed AACD to date (Reference 102 and personal communication). The most common manifestations of citrin deficiency described in the UK cohort comprise a history of liver disease and abdominal pain including one patient who received a successful liver transplantation in early adulthood for confirmed pancreatitis having suffered recurrent debilitating abdominal pain episodes throughout late childhood. Most patients in the UK demonstrated the characteristic dietary preferences of citrin deficiency with protein preference and carbohydrate aversion. Fewer than half of UK patients were prescribed a specific low-carbohydrate, high-protein, high-fat diet but most of the remaining patients self-selected a diet that was lower in carbohydrate and higher in fat and protein than the normal UK diet. Some patients in the UK are prescribed an "emergency regimen" based on whole milk or soya milk with added medium-chain triglycerides (MCT) emulsion and/or protein powder. At presentation, many UK patients were shown to be underweight and short but after treatment, growth improved in several patients though most remained of comparatively short stature. UK patients homozygous for the p.Arg588Gln variant in *SLC25A13* show a wide phenotypic variation. Only a minority (in one center only 20%) of these patients showed any liver disease. Over half of these patients presented with hypoglycemia either in the context of NICCD/FTTDCD or were diagnosed through investigation for hypoglycemia with delayed/impaired ketogenesis. Some were grossly ketotic when they presented with hypoglycemia but showed delayed ketogenesis on controlled fasting. One p.Arg588Gln homozygous patient died from AACD.[102]

6 | GLOBAL EFFORT IN THE PRESENT AND FUTURE

In recent years, significant strides in understanding the pathology of citrin deficiency were made, primarily due to reports coming from regions in East Asia, where a substantial citrin deficiency patient population resides. Additionally, effective therapeutic approaches have been clinically established.[28,30,40,103] However, many aspects of citrin deficiency still require further investigation and clarification. In this context, the global landscape of citrin deficiency has the potential to undergo significant transformation through the establishment of a global network dedicated to this condition, bringing together clinicians, researchers, and patients. To illustrate some ongoing activities, we briefly describe here the efforts into management guidelines and patient registries.

While Japan has already developed treatment and diagnosis guidelines (https://jsimd.net/pdf/newborn-mass-screening-disease-practice-guideline2019.pdf), a universally accepted global directive for the diagnosis and management of citrin deficiency has yet to be established. Hence, it is imperative to formulate such guidelines through the collective efforts of the global UCDs network, possibly as an addition to the existing UCDs guidelines[104] and in line with recent textbook chapters.[105]

To better understand the natural history and to prepare for emerging therapeutic trials, patient registries are essential. In Japan, there are currently two registration systems in place for citrin deficiency: the Registration System for Metabolic & Inherited Diseases (JasMin) and the Rare Disease Data Registry of Japan.[106] While these registry systems presently serve research purposes, they are designed to create a versatile platform that can be customized to accommodate various rare disorders and facilitate collaboration among all stakeholders. Furthermore, a specialized registration system tailored specifically for citrin deficiency is under development in Japan. This planned registry system will collect annual patient data using dedicated forms. Additionally, a global, patient-driven registry system where patients or their guardians can voluntarily provide basic information, including few personal data and contact details (e.g., email address) along with a deposition of their interest to participate (or not) in planned clinical trials is currently in preparation (with involvement of the authors of this paper).

7 | CONCLUSIONS AND SUMMARY

Here, we provide an overview of citrin deficiency on a global scale, examining its clinical course and genetic basis, NBS procedures, and clinical research. While patients with citrin deficiency have been predominantly identified in East Asia, cases have also been reported in various regions worldwide. The clinical manifestations of citrin deficiency are influenced by environmental factors such as diet and lifestyle and the diversity of the condition becomes evident already in patients with NICCD.[11] Additionally, other less explored factors, including other genes associated with mitochondrial function, citrin and aralar comparative expression levels, and epigenetic

mechanisms related to citrin, might impact the clinical presentation of the disease.

The currently available NBS programs, even if using a new scoring system,[71] have limitations in their capacity to identify all affected newborns. This is thought to occur because many of these newborns have not yet displayed any signs or symptoms of NICCD and may exhibit normal NBS results at 4–6 days after birth. Consequently, there is a critical need for a reliable biomarker that can be integrated into NBS protocols, facilitating early disease detection.

Regarding treatment options, the primary strategy involves dietary management with specific ratios of low-carbohydrate, high-protein, and high-fat content (ranging from 30% to 50%, 15%–25%, and 30%–40%, respectively). Moreover, infusion of high sugar solutions or/and glycerol may be lethal in patients with AACD. Concurrently, supplementation of MCT has emerged as a universal standard for effective treatment of citrin deficiency. Nevertheless, ongoing research endeavors (e.g., gene therapy) are anticipated to lead to the development of innovative and effective therapies in the near future. These initiatives would greatly profit from the establishment of global guidelines and the creation of a patient registry for citrin deficiency, both enabling patients and clinicians to access standardized information and treatment options for this condition.

In summary, just 25 years after its initial description, significant progress has been made in understanding the diverse clinical course and biochemical and genetic basis of citrin deficiency. Consequently, substantial advancements have been accomplished or are currently underway toward enhancing patient care. This progression has been made possible through an extensive knowledge foundation driven by researchers from East Asian countries, which has now expanded to a global network of clinicians and scientists dedicated to addressing this challenging and intriguing rare metabolic condition.

AUTHOR CONTRIBUTIONS

Jun Kido and Johannes Häberle were responsible for research design. Jun Kido, Georgios Makris, Saikat Santra, and Johannes Häberle wrote the manuscript. All authors read and approved the final version of the manuscript for submission.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data used in this review are accessible through the peer-reviewed publications cited herein.

ETHICS STATEMENT

The contents of this review article were based on the results of studies approved by the ethical committee of the Faculty of Life Science, Kumamoto University (Ethics No. 1660). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients or their legal guardians for being included in the study. Animals were not used.

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