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BRIEF COMMUNICATION

Lysinuric protein intolerance with homozygous *SLC7A7* mutation caused by maternal uniparental isodisomy of chromosome 14

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Abstract

Lysinuric protein intolerance (LPI) is caused by mutations in the *SLC7A7* gene at 14q11.2. Its clinical presentation includes failure to thrive, protein intolerance due to a secondary urea cycle defect, interstitial lung disease, renal tubulopathy, and immune disorders. Maternal uniparental disomy 14 (UPD14mat) is the most common cause of Temple syndrome (TS14), which is characterized by severe intrauterine and postnatal growth failure. Here, we describe a severe form of LPI accompanied by TS14 in an 11-month-old girl, which presented as profound failure to thrive and delayed development. LPI was diagnosed by the detection of a homozygous mutation of c.713 C>T (p.Ser238Phe) in *SLC7A7*, which was eventually found to co-occur with UPD14mat. Despite receiving a protein-restricted diet with citrulline and lysine supplementation, the severe failure to thrive has persisted at follow-up of the patient at 4 years of age.

Lysinuric protein intolerance (LPI; OMIM #222700) is a rare autosomal recessive aminoaciduria resulting from biallelic mutations in the *SLC7A7* gene. *SLC7A7* is located at 14q11.2, which encodes the transporter of cationic amino acids, lysine, arginine, and ornithine, in the kidney and small intestine [1, 2]. LPI has been sporadically reported worldwide, with a higher prevalence in Finland, Southern Italy, and Japan [2–4]. Only one case has been reported in Korea [5]. The clinical features of LPI are extremely variable, ranging from nearly normal growth with minimal protein intolerance to severe multisystemic involvement with failure to thrive, hepatosplenomegaly, pulmonary alveolar proteinosis, renal tubulopathy, and immunologic disorders [6].

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Maternal uniparental disomy 14 (UPD14mat), the most common cause of Temple syndrome (TS14, OMIM #616222), is associated with the lack of expression of paternally inherited genes in the imprinted locus 14q32.2 [7, 8]. TS14 is characterized by intrauterine growth retardation, postnatal growth failure, motor delay, Prader–Willi syndrome-like marked hypotonia and small hands and feet, Silver–Russell syndrome-like relative macrocephaly, prominent forehead and feeding difficulties in infancy, as well as early onset of puberty, and severe short final stature.

Here, we report the first case of combined LPI and TS14 with UPD14mat carrying an *SLC7A7* mutation, manifesting as severe feeding intolerance, growth failure, and profoundly delayed development. The patient was naturally conceived and the second child of unrelated healthy Korean parents. The paternal age and maternal age at the time of the patient's birth were 35- and 36-years-old, respectively. She was born at 39 weeks and 2 days of gestation with a birth weight of 2 kg (−3.72 standard deviation score [SDS]), a height of 48 cm (−2.10 SDS), and a head circumference of 33 cm (−0.70 SDS). At the age of 4 months, her parents sought medical attention for apparent failure to thrive and increased frequency of vomiting after attempts to increase caloric intake. At 11 months of age, her height was 60 cm (−4.78 SDS), weight was 4.1 kg (−5.96 SDS), and head circumference was 41 cm (−2.43 SDS). The physical examination was notable for frontal bossing, a large anterior fontanelle, thin hair, a flat nasal bridge, a protruded

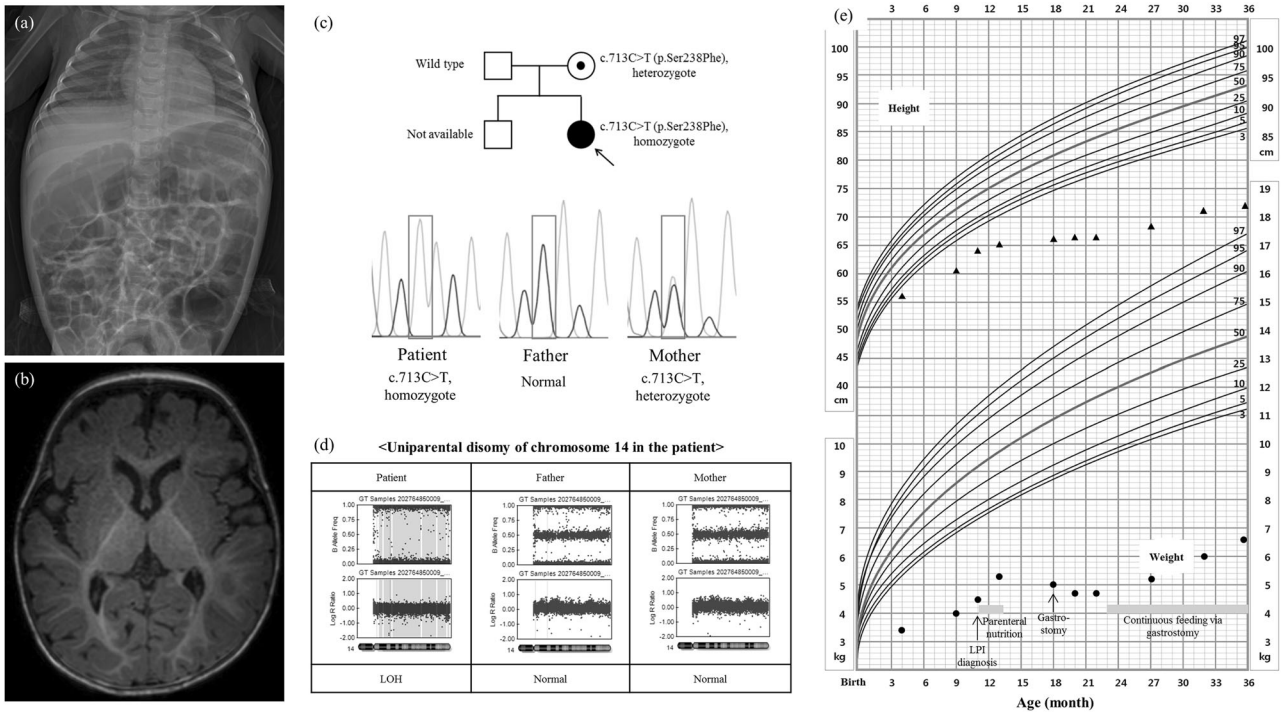

Fig. 1 Radiologic findings, genetic analysis, and growth chart of the patient. **a** Diffuse air distension of bowel loops was observed on simple X-ray. **b** Brain magnetic-resonance imaging obtained at 9 months of age showed no focal lesions in the brain parenchyma and mild myelination delay. **c** Genetic mutational analysis showed pathogenic homozygote mutations of *SLC7A7*. The familial segregation study showed the heterozygous mutation only in the mother, with wild-type alleles in the father. **d** The analysis revealed a loss of heterozygosity spanning the entire chromosome 14. **e** The patient's growth chart plotted by Korea Center for Disease Control and Prevention chart percentiles. Regardless of a low-protein diet, supplementation with citrulline and lysine, and continuous enteral feeding to improve caloric intake, the patient failed to achieve catch-up growth due to recurrent abdominal distension, vomiting, and diarrhea

abdomen without organomegaly, and small hands and feet. She was hypotonic, and though she grasped her rattle and smiled in response to faces, she could not hold her head steady. Initial laboratory tests revealed normocytic anemia (hemoglobin 9.5 g/dL) and mildly elevated aspartate transaminase and alanine transaminase (95 IU/L and 46 IU/L). Serum lactate dehydrogenase (1138 IU/L) and ferritin levels (3831 ng/mL) were also elevated. Her plasma ammonia level was 57 μmol/L (reference range, 11–32). A simple X-ray revealed normal lungs with gaseous distension of the abdomen (Fig. 1a). The abdominal ultrasound demonstrated slightly heterogeneous echogenicity of the liver, without a focal lesion. Cerebral magnetic resonance imaging results showed mild myelination delay considering the patient's age (Fig. 1b). Her karyotype was 46, XX and the methylation specific-multiplex ligation-dependent probe amplification analyses on chromosome 11p15 and 15q11.2-q13 were normal.

The results of plasma amino acid analysis were within normal range, except for a slightly elevated citrulline level and a decreased ornithine level. The patient's urinary orotic acid level was 228 mmol/mol creatinine (reference range, 0.0–4.6 mmol/mol creatinine) with markedly elevated urinary excretion of arginine, citrulline, glutamine, lysine, and ornithine (Table 1). The diagnosis of LPI was confirmed by the detection of the homozygous mutation of c.713 C>T (p.Ser238Phe) in the *SLC7A7* gene, which has previously been reported in Japanese patients [9]. The familial segregation study showed the heterozygous mutation only in the mother, with wild-type alleles in the father (Fig. 1c). Single-nucleotide polymorphism microarray (aSNP) was performed to detect UPD14, revealing a loss of heterozygosity encompassing the entire chromosome 14, on which the *SLC7A7* gene is located (Fig. 1d). No deletions or duplications were observed. The Sanger sequencing and aSNP revealed the presence of maternal isodisomy of chromosome 14 (UPiD14mat) in our patient. Whole-exome sequencing to exclude the possibility of another genetic disorder causing developmental delay did not reveal a pathogenic, clinically relevant variant except for the *SLC7A7* mutation.

Soon after receiving the diagnosis of LPI, the patient started a low-protein diet (1.5 g/kg/day) with oral citrulline (100 mg/kg/day with meals) and lysine (150 mg/kg/day) supplementation. During the 3-year follow-up period, there were no episodes of acute metabolic derangement. However, inadequate caloric intake persisted through age 4 years due to recurrent flatus, abdominal distension, and vomiting

Table 1 The results of plasma and urine amino acid analyses at diagnosis and during follow-up

	Plasma amino acid level (μmol/L)								Urine amino acid level (μmol/g creatinine)	
	11 months (diagnosis)	1 year 4 months	1 year 7 months	1 year 10 months	2 years 3 months	2 years 8 months	3 years 1 month	Reference range	11 months	Reference range
								2–24 months / 3–18 years		
Alanine	213	342	242	322	413	237	727	143–439 / 153–547	2498	767–6090
Arginine	24	12	18	61	22	19	47	12–133 / 10–140	13278	38–165
Citrulline	69	21	35	26	49	27	59	3–35 / 1–46	1182	22–180
Glutamic acid	78	62	54	68	82	90	86	10–133 / 5–150	70	50–590
Glutamine	736	572	636	637	796	1073	1420	246–1182 / 254–823	4436	670–1562
Glycine	208	205	267	316	330	269	354	81–436 / 127–341	5657	3023–11148
Isoleucine	43	24	19	23	10	22	39	31–86 / 22–107	38	38–342
Leucine	75	44	34	44	19	25	54	47–155 / 49–216	228	70–570
Lysine	115	23	39	28	34	30	38	52–196 / 48–284	36134	189–850
Methionine	25	16	18	12	12	11	29	9–42 / 7–47	158	174–1090
Ornithine	19	9	17	10	11	10	11	22–103 / 10–163	1520	55–364
Phenylalanine	32	35	38	46	23	29	60	31–75 / 29–91	336	175–1340
Threonine	153	91	68	49	38	65	107	24–174 / 35–226	774	252–1528
Tryptophan	36	27	17	17	6	9	39	23–71 / 0–79	275	0–93
Valine	207	100	66	103	55	95	156	64–294 / 74–321	160	99–316

after feeding. This produced severe malnutrition with a global decrease in almost all plasma essential amino acid levels (Table 1). Her weight and developmental status did not improve despite efforts to increase caloric intake, such as continuous gastric tube feeding (Fig. 1e). Her renal and pulmonary function remained normal.

The three possible mechanisms can be considered to explain UPiDmat of whole chromosome [10, 11]. The first is trisomy rescue by elimination of the paternal chromosome after fertilization by a disomic oocyte, which had a meosis II nondisjunction without meiotic recombination. Advanced maternal age is a major risk factor for chromosome nondisjunction. The second is monosomy rescue after fertilization of a sperm with nullisomy. The third is gamete complementation, which related to the fertilization of a nullisomic sperm by a disomic oocyte. We do not know the underlying mechanism of UPiDmat of our patient. However, it would be associated with advanced parental ages.

Failure to thrive and short stature are hallmarks of both LPI and TS14. Poor growth in LPI has been considered a postnatal condition caused by protein malnutrition, but a subnormal or low-normal final height is usually achieved through adequate nutritional support [12]. In addition, both intrauterine and postnatal mild to moderate growth failure are observed in most TS14 patients, but early puberty results in severe adult short stature in some cases [7, 8]. The birth height SDS and childhood height SDS of our patient were −2.10 and −6.06, respectively. The profound growth failure in our patient was caused by both TS14 and LPI, but the secondary malnutrition, manifested as recurrent abdominal distension and vomiting, and growth hormone deficiency might be responsible for her profound growth failure as well [13–15]. In the situation of malnutrition, the diagnosis of growth hormone deficiency may be uncertain due to reduced IGF-1 levels and variable stimulated growth hormone concentrations [16]. Therefore, growth hormone provocation testing could be considered in the future when the patient's nutritional status improves. However, the efficacy of growth hormone would be limited due to severe malnutrition.

The gastrointestinal symptoms in LPI patients are usually associated with an acute hyperammonemic crisis. However, our patient showed persistent malabsorption with gaseous abdominal distension and vomiting without an episode of hyperammonemia. Altered arginine and nitric oxide concentrations in the enterocyte may have been responsible, because the dibasic amino acids, especially L-arginine, have a secretory effect on the enterocytes in its high concentrations [17].

Our patient presented with intrauterine growth retardation without catch-up growth after birth and showed persistent failure to thrive, hypotonia, delayed development, facial dysmorphism, and small hands and feet. Based on analysis of markedly elevated urinary excretion of dibasic amino acids, Sanger sequencing of the *SLC7A7* gene, and aSNP analysis, we diagnosed LPI with UPiD14mat, which is the first case to our knowledge. In conclusion, our study underlines the importance of performing parental segregation studies, even in patients with a recessive disease and previously reported mutations, especially when the mutation is found to be homozygotic. Imprinting disorders such as UPD may underlie and contribute to the severity of the recessive disease.

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Author contributions EK and BHL drafted the manuscript. All authors were involved in the diagnosis and treatment of the patient. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from the parents of the patient regarding the reporting and publication of this case report. As it was not a clinical trial and no off-label drugs were used, ethical board approval was not necessary for this case report.

References

1. Torrents D, Mykkanen J, Pineda M, Feliubadalo L, Estevez R, de Cid R, et al. Identification of SLC7A7, encoding y+LAT-1, as the lysinuric protein intolerance gene. Nat Genet. 1999;21:293–6.
2. Borsani G, Bassi MT, Sperandeo MP, De Grandi A, Buoninconti A, Riboni M, et al. SLC7A7, encoding a putative permease-related protein, is mutated in patients with lysinuric protein intolerance. Nat Genet. 1999;21:297–301.
3. Koizumi A, Shoji Y, Nozaki J, Noguchi A, E X, Dakeishi M. et al. A cluster of lysinuric protein intolerance (LPI) patients in a northern part of Iwate, Japan due to a founder effect. The mass screening group. Hum Mutat. 2000;16:270–1.
4. Sperandeo MP, Bassi MT, Riboni M, Parenti G, Buoninconti A, Manzoni M, et al. Structure of the SLC7A7 gene and mutational analysis of patients affected by lysinuric protein intolerance. Am J Hum Genet. 2000;66:92–9.
5. Ko JM, Shin CH, Yang SW, Seong MW, Park SS, Song J. The first Korean case of lysinuric protein intolerance: presented with short stature and increased somnolence. J Korean Med Sci. 2012;27:961–4.
6. Mauhin W, Habarou F, Gobin S, Servais A, Brassier A, Grisel C, et al. Update on lysinuric protein intolerance, a multi-faceted disease retrospective cohort analysis from birth to adulthood. Orphanet J rare Dis. 2017;12:3.
7. Ioannides Y, Lokulo-Sodipe K, Mackay DJ, Davies JH, Temple IK. Temple syndrome: improving the recognition of an under-diagnosed chromosome 14 imprinting disorder: an analysis of 51 published cases. J Med Genet. 2014;51:495–501.
8. Kagami M, Nagasaki K, Kosaki R, Horikawa R, Naiki Y, Saitoh S, et al. Temple syndrome: comprehensive molecular and clinical findings in 32 Japanese patients. Genet Med: Off J Am Coll Med Genet. 2017;19:1356–66.
9. Shoji Y, Noguchi A, Shoji Y, Matsumori M, Takasago Y, Takayanagi M, et al. Five novel SLC7A7 variants and y+L gene-expression pattern in cultured lymphoblasts from Japanese patients with lysinuric protein intolerance. Hum Mutat. 2002;20:375–81.
10. Niida Y, Ozaki M, Shimizu M, Ueno K, Tanaka T. Classification of uniparental isodisomy patterns that cause autosomal recessive disorders: proposed mechanisms of different proportions and parental origin in each pattern. Cytogenet genome Res. 2018;154:137–46.
11. Kotzot D, Utermann G. Uniparental disomy (UPD) other than 15: phenotypes and bibliography updated. Am J Med Genet Part A. 2005;136:287–305.
12. Palacin M, Bertran J, Chillaron J, Estevez R, Zorzano A. Lysinuric protein intolerance: mechanisms of pathophysiology. Mol Genet Metab. 2004;81(Suppl 1):S27–37.
13. Esposito V, Lettiero T, Fecarotta S, Sebastio G, Parenti G, Salerno M. Growth hormone deficiency in a patient with lysinuric protein intolerance. Eur J Pediatr. 2006;165:763–6.
14. Evelina M, Grazia M, Francesca O, Marta C, Paolo C, Rossella G, et al. Growth hormone deficiency and lysinuric protein intolerance: case report and review of the literature. JIMD Rep. 2015;19:35–41.
15. Tortora A, La Sala D, Lonardo F, Vitale M. Maternal uniparental disomy of the chromosome 14: need for growth hormone provocative tests also when a deficiency is not suspected. BMJ case Rep. 2019;12:e228662.
16. Beas F, Contreras I, Maccioni A, Arenas S. Growth hormone in infant malnutrition: the arginine test in marasmus and kwashiorkor. Br J Nutr. 1971;26:169–75.
17. Turvill JL, Mourad FH, Farthing MJ. Proabsorptive and prosecretory roles for nitric oxide in cholera toxin induced secretion. Gut. 1999;44:33–9.