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Original Article

Clinical and Genetic Characteristics of Korean Patients Diagnosed with Chronic Enteropathy Associated with *SLCO2A1* Gene: A KASID Multicenter Study

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Background/Aims: Chronic enteropathy associated with *SLCO2A1* gene (CEAS), an inherited disease characterized by nonspecific intestinal ulcers, has emerged in the Japanese population via loss-of-function mutations in the *SLCO2A1* gene. We aimed to investigate the clinical and genetic characteristics of Korean patients diagnosed with CEAS.

Methods: From July 2018 to July 2021, we performed Sanger sequencing of the *SLCO2A1* gene in 46 patients with chronic intestinal ulcers. CEAS was confirmed based on known *SLCO2A1* mutations. We summarized the clinical characteristics of patients with confirmed CEAS.

Results: Fourteen out of 46 patients (30.4%) had genetically confirmed CEAS, and two *SLCO2A1* variants were detected (splicing site variant c.940+1G>A and nonsense mutation [p.R603X] in *SLCO2A1*). Twelve patients (85.7%) were females and the median age at diagnosis of CEAS was 44.5 years. All patients presented with abdominal pain, and 13 patients (92.9%) presented with anemia (median hemoglobin, 9.6 g/dL). Ten patients (71.4%) had hypoalbuminemia (median, 2.7 g/dL). The most commonly involved site was the ileum (13/14, 92.9%). Manifestations of primary hypertrophic osteoarthropathy (PHO), such as digital clubbing, pachydermia, and periostosis were observed in five patients (28.6%) and two male patients and one female patient satisfied all major PHO diagnostic criteria.

Conclusions: The clinical and genetic characteristics of Korean patients with confirmed CEAS were similar to those reported in the literature. CEAS should be considered in the differential diagnosis for patients with unexplained chronic nonspecific ulcers of the small intestine. **(Gut Liver 2022;16:942-951)**

Key Words: *SLCO2A1*; Chronic enteropathy associated with *SLCO2A1* gene; Korea

INTRODUCTION

Cases of nonspecific ulceration of the small intestine have been reported since the 1960s.[1,2] Since 2015, chronic multiple ulceration of the small intestine with nonspecific histology causing chronic blood and protein loss has been called "chronic nonspecific multiple ulcers of the small intestine (CNSU)" or "cryptogenic multifocal ulcerous

stenosing enteritis (CMUSE)."[3-6] The possibility of this unexplained chronic enteropathy being an inheriting genetic disorder has been raised after the report that this enteropathy tends to segregate in the offsprings of consanguineous parents.[7]

In 2015, Umeno *et al.*[8] identified loss-of-function *SLCO2A1* (OMIM: 601460) mutations as the cause of inherited CNSU. Therefore, the label "chronic enteropathy associated with *SLCO2A1* gene (CEAS)" was proposed. Previously, it has been known that homozygous or compound heterozygous mutations of *SLCO2A1* cause primary hypertrophic osteoarthropathy (PHO), characterized by digital clubbing, periostosis, and pachydermia.[9] Some CEAS patients have also been reported to present with PHO.[10,11] In 2017, Hosoe *et al.*[10] reported 22 CEAS cases, demonstrating genetic profiles and features of CEAS patients in Japan. In 2018, Umeno *et al.*[11] reported the identification of recessive *SLCO2A1* mutations at 11 sites along with the features of 46 CEAS patients in Japan. Yamaguchi *et al.*[12] suggested that the lower immunohistochemical expression of *SLCO2A1* protein in intestinal tissues might be useful in differentiating between CEAS and other inflammatory bowel diseases including Crohn's disease (CD) and intestinal Behçet's disease.

In Korea, Chung *et al.*[5] previously reported 20 patients diagnosed with CMUSE before the emergence of the entity of CEAS. In 2018, a male Korean diagnosed with CEAS was reported as the first non-Japanese patient with the disease.[13] CEAS has now been reported in Japan, Korea, and China.[14] In particular, Huang *et al.*[15] identified four new *SLCO2A1* variants.

Still, there is a lack of data on CEAS in the Korean population, and thus we aimed to investigate the clinical and genetic characteristics of CEAS among Koreans.

MATERIALS AND METHODS

1. Subjects and clinical data

This study was approved by the institutional review boards of all participating institutions including Asan Medical Center (IRB numbers: 2012-0637 and 2019-1295) and informed consents were obtained from study participants. From July 2018 to July 2021, from five academic centers in Korea, we enrolled the patients who had unexplained chronic intestinal ulceration or who had a previous diagnosis of CMUSE as per the diagnostic criteria proposed by Perlemuter *et al.*[16] A total of 46 patients together with their venous blood samples were collected. We performed genetic analyses as described below. We collected clinical data, including sex, age at diagnosis, age at symptom onset, interval from symptom onset to diagnosis, family history of CEAS, history of taking nonsteroidal anti-inflammatory drugs, symptoms, history of bowel resection, laboratory data, and tuberculosis test results including tests for latent tuberculosis (tuberculin skin test, interferon-gamma release assay, and tuberculosis-specific ELISPOT assay) and intestinal tuberculosis (acid-fast bacilli stain, *Mycobacterium tuberculosis* culture and polymerase chain reaction of intestinal biopsy tissue) at diagnosis of CEAS. Characteristics of gastrointestinal involvement of CEAS were also captured. Gastrointestinal involvement of CEAS was any active ulcerative lesion or obvious scarred ulcer observed by radiography or endoscopy. Involvement of the terminal ileum was determined as the involvement of ileum within 30 cm from the ileocecal valve.[17] We also captured data on PHO manifestations, such as digital clubbing, pachydermia, arthralgia of large joints, and periostosis.[18] The major PHO diagnostic criteria are digital clubbing, periostosis, and pachydermia,[19] and we checked whether these were present. Periostosis were evaluated by hand X-ray.

2. Genomic DNA preparation and Sanger sequencing

Genomic DNA was extracted from peripheral blood using Qiacube (Qiagen, Hilden, Germany) according to the manufacturer's instructions. *SLCO2A1* was amplified with 13 pairs of intronic primers flanking all 14 coding exons.[11] The amplification conditions involved one cycle of 95°C for 7 minutes, followed by 30 cycles of 95°C for 30 seconds, 56°C for 30 seconds, 72°C for 1 minute and one cycle of 72°C for 7 minutes. Polymerase chain reaction products were confirmed with agarose gel electrophoresis and cleaned via treatment with Exo-SAP® (10:1 U ratio; mixture of exonuclease I and shrimp alkaline phosphatase, Affymetrix, Cleveland, OH, USA) with incubation at 37°C, 15 minutes; 80°C, 15 minutes; and 4°C at hold. Sequencing was performed using an ABI 3730XL sequencer (Cosmogenetech, Seoul, Korea). CEAS was confirmed if any known pathogenic mutation reported by Umeno *et al.*[11] was identified.

3. Statistical analysis

For the description and summary of clinical characteristics, categorical variables are expressed as numbers with percentages. Continuous variables are expressed as medians with interquartile ranges (IQRs).

RESULTS

1. Clinical features

Out of 46 patients, 14 patients (30.4%) were confirmed

as CEAS based on Sanger sequencing and their medical records. Twelve of 14 CEAS patients (85.7%) were females (Table 1). The median age at CEAS diagnosis was 44.5 years (IQR, 30.2 to 50.2 years). The median age at symptom onset (n=12) was 18.0 years (IQR, 11.7 to 32.5 years), with a median diagnostic delay of 13.5 years (IQR, 10.7 to 19.2 years). Five patients (35.7%) had a family history of CEAS. Four patients (28.6%) had a history of taking nonsteroidal anti-inflammatory drugs. Only one patient (7.1% [Patient 11]) showed a positive result in interferon-gamma release assay. All patients presented with abdominal pain. Half of the patients (7/14, 50.0%) presented with loose stool, and three patients (21.4%) presented with weight loss and gastrointestinal bleeding. The most commonly affected site was the ileum (13/14, 92.9%)—the terminal ileum was saved in three patients (21.4%)—, followed by the jejunum (5/14, 35.7%) and the duodenum (5/14, 35.7%).

Table 1. Clinical Characteristics of Patients Diagnosed with Chronic Enteropathy Associated with *SLCO2A1* Gene

Characteristics	Value (n=14)
Female sex, No. (%)	12 (85.7)
Age at diagnosis, median (IQR), yr	44.5 (30.2–50.2)
Age at symptom onset, median (IQR), yr	18.0 (11.7–32.5)
Interval from symptom onset to diagnosis, median (IQR), yr	13.5 (10.7–19.2)
Family history of CEAS, No. (%)	5 (35.7)
History of taking NSAIDs, No. (%)	4 (28.6)
Positive for tuberculosis tests, No. (%)*	1 (7.1)
Symptoms, No. (%)	
Abdominal pain	14 (100.0)
Loose stool	7 (50.0)
Weight loss	3 (21.4)
GI bleeding	3 (21.4)
History of bowel resection, No. (%)	7 (50.0)
Involved GI tract, No. (%)	
Esophagus	0
Stomach	2 (14.3)
Duodenum	5 (35.7)
Jejunum	6 (42.9)
Ileum	13 (92.9)
Terminal ileum-saved	3 (21.4)
Colon	2 (14.3)
Clinical manifestations of PHO, No. (%)	
Digital clubbing	5 (35.7)
Pachydermia	3 (21.4)
Periostosis	4 (28.6)
Joint pain	4 (28.6)
Laboratory data, median (IQR)	
Hemoglobin, g/dL	9.6 (7.9–10.0)
Protein, g/dL	5.2 (4.6–6.0)
Albumin, g/dL	2.7 (2.1–3.0)
ESR, mm/hr	7.0 (3.0–8.0)
CRP, mg/dL	0.4 (0.1–0.8)
Fecal calprotectin, μg/g	789 (211–1,297)

IQR, interquartile range; CEAS, chronic enteropathy associated with *SLCO2A1* gene; NSAIDs, nonsteroidal anti-inflammatory drugs; GI, gastrointestinal; PHO, primary hypertrophic osteoarthropathy; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.
*Tuberculosis tests included a tuberculin skin test, interferon-gamma release assay, tuberculosis-specific ELISPOT assay, and acid-fast bacilli stain, *Mycobacterium tuberculosis* culture and polymerase chain reaction of intestinal biopsy tissue.

Regarding the laboratory findings, 13 patients (92.9%) had anemia, and the median hemoglobin level was 9.6 g/dL (IQR, 7.9 to 10.0 g/dL). A total of 10 patients (71.4%) had hypoalbuminemia and the median serum albumin level was 2.7 g/dL (IQR, 2.1 to 3.0 g/dL). The median erythrocyte sedimentation rate was 7 mm/hr (IQR, 3 to 8 mm/hr), and the median serum C-reactive protein level was 0.4 mg/dL (IQR, 0.1 to 0.8 mg/dL). The median fecal calprotectin level was 789 μg/g (IQR, 211 to 1,297 μg/g).

Five patients (35.7%) had at least one major sign of PHO, except for three female patients who had only nonspecific joint pain. Three patients (two male patients [Patient 6 and Patient 13] and one female patient [Patient 10]) exhibited all three major PHO manifestations.

2. Sanger sequencing of *SLCO2A1* for suspected CEAS

Six *SLCO2A1* mutations were identified in 14 patients confirmed as CEAS (Supplementary Table 1), among which two variants were predicted to be pathogenic: one splicing site variant c.940+1G>A and one nonsense mutation (p.R603X) (Fig. 1). Six patients (42.9%) had homozygous mutations and the remaining eight patients (57.1%) had compound heterozygote mutations (Table 2, Supplementary Table 1). The remaining four polymorphisms that were presumed nonpathogenic are summarized in Supplementary Table 2. They consisted of three synonymous (p.S70S, p.R280R, and p.N599N) and one missense (p.A396T) mutations in the *in silico* prediction model (PolyPhen-2, MutationTaster, https://www.mutationtaster.org/).

Among the remaining 32 patients without CEAS, additional two mutations (p.G427_P430del in one patient and pI553V in another patient) were found (Supplementary Table 3). As a whole, heterozygous and homozygous p.S70S mutations (c.210G>A) were identified in 17 and eight of 46 patients, respectively. Heterozygous and homozygous p.R280R mutations (c.840A>G) were identified in 23 and four of 46 patients, respectively. Heterozygous and homozygous p.N599N mutations (c.2071C>T) were identified in 12 and two of 46 patients, respectively. Additionally, heterozygous and homozygous p.A396T mutations (c.1186G>A) were identified in 19 and three of 46 patients, respectively.

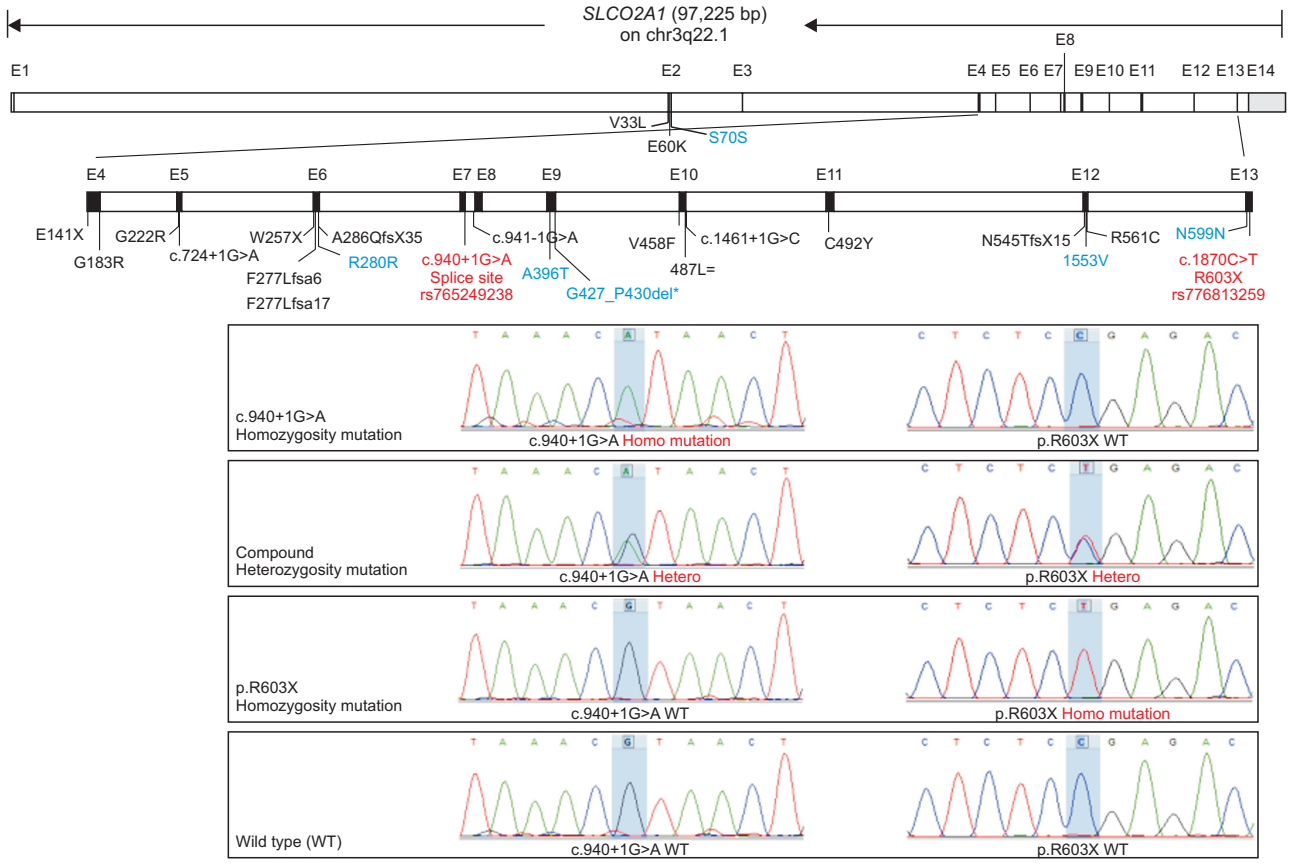

Fig. 1. Gene map and sequence-based chromatogram of *SLCO2A1* mutations. Red-colored loci: two pathogenic *SLCO2A1* mutations (splicing site variant c.940+1G>A and nonsense mutation [p.R603X]) identified in this study and previously reported by Umeno *et al.*[11] Blue-colored loci: six presumed nonpathogenic mutations identified among the 46 patients in this study. Black-colored loci: all other variants reported by Umeno *et al.*[11] and Huang *et al.*[15] *p.Glu427_Pro430del, which was identified in one Korean patient, is considered to be likely pathogenic in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/). This patient had a heterozygous mutation and no other variants. The impact of this variant on the pathogenesis of chronic enteropathy associated with *SLCO2A1* gene is expected to be minimal.

Table 2. Identification of Pathogenic Mutations in *SLCO2A1* Gene among 14 Patients

Gene	dbSNP	Nucleotide change	Amino acid change	Mutant allele frequency*	gnomAD frequency†	Clinical significance
SLCO2A1	rs765249238	c.940+1G>A	Splice site	0.43	3.26E-04	Pathogenic‡
	rs776813259	c.1807C>T	p.R603X	0.57	2.76E-04	Pathogenic‡

*Mutant allele frequency in 14 cases in this study; †Genome Aggregation Database (gnomAD) East Asian frequency (GRCh37); ‡ClinVar.

3. Characteristics of individual patients

The clinical characteristics of 14 CEAS patients are summarized in Supplementary Table 1.

Patient 1 was a 39-year-old woman with a homozygous *SLCO2A1* mutation (c.940+1G>A) whose symptoms began at 21. Nonspecific ulcers and strictures were detected in the jejunum and the ileum except for the terminal ileum (Fig. 2A). She had digital clubbing and periostosis on hand X-ray. Before her CEAS diagnosis, she had been treated for CD with 5-aminosalicylic acid (5-ASA), corticosteroids, and immunomodulator. All of these medications failed and were thus stopped.

Patient 2 was a 45-year-old woman with a heterozygous compound *SLCO2A1* mutation (c.940+1G>A and c.1807C>T) whose symptoms began at 32. Endoscopic and radiologic examinations showed multiple ileal strictures. She complained of bilateral knee arthralgia and had digital clubbing. Before the CEAS diagnosis, she had been treated with 5-ASA, corticosteroids, and immunomodulator for presumed CD, but her symptoms did not improve. She underwent ileal resection at 38 because of multifocal strictures.

Patients 3 and 4 were sisters, aged 48 and 44 years, respectively, at the time of CEAS diagnosis. Genetic testing

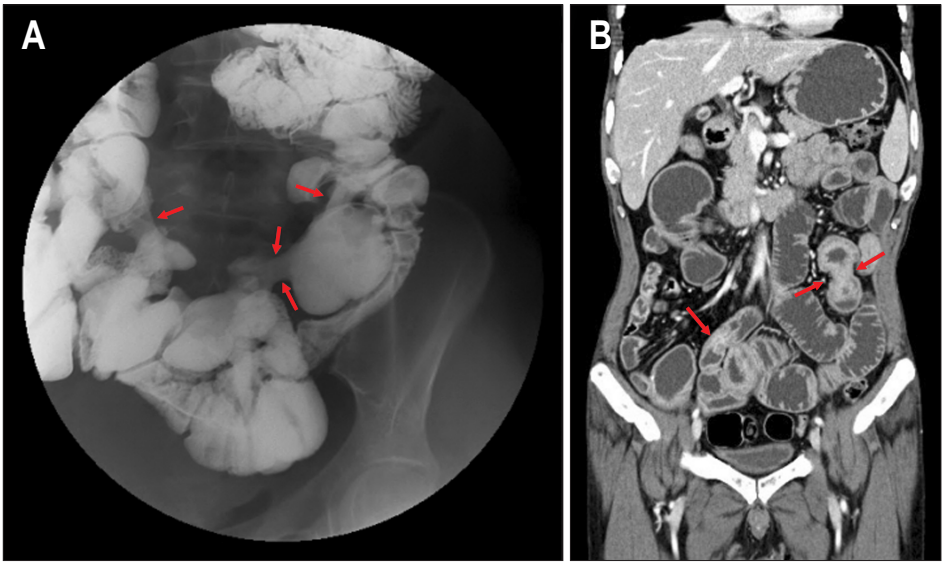

Fig. 2. Radiographic findings of patients diagnosed with chronic enteropathy associated with *SLCO2A1* gene. (A) Small bowel follow-through showing multifocal strictures (arrows) with upstream bowel dilatation at the pelvic ileal loops (Patient 1). (B) Computed tomographic enterography showing focal wall thickening causing luminal narrowing at the ileum (arrows) (Patient 6).

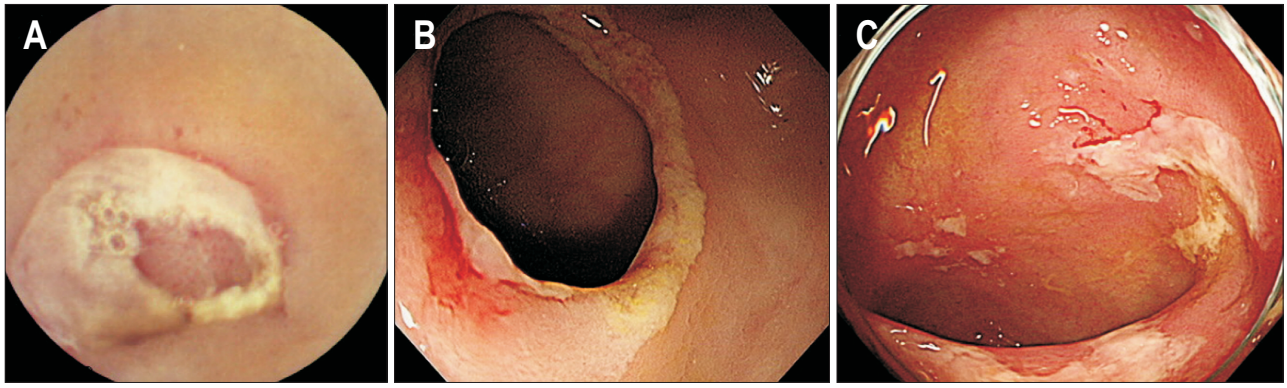

Fig. 3. Endoscopic findings of patients diagnosed with chronic enteropathy associated with *SLCO2A1* gene. (A) Capsule endoscopy showing a circular ulcer at the ileum (Patient 5). (B) Shallow circular ulcer at the colon (Patient 6). (C) Shallow geographic ulcerative lesions at the terminal ileum (Patient 10).

showed homozygous *SLCO2A1* mutations (c.1807C>T). Symptoms started at 37 (Patient 3) and 34 (Patient 4), respectively. Active ulcers or ulcer scars were documented in the stomach, duodenum, ileum, and colon in Patient 3 and in the stomach, duodenum, and ileum in Patient 4.

Patients 5 and 7 were sisters, and Patient 6 was their uncle. They had confirmed heterozygous compound *SLCO2A1* mutations (c.940+1G>A and c.1807C>T). At 16, Patient 5 received capsule endoscopic evaluation due to abdominal pain, anemia, and hypoalbuminemia. Capsule endoscopy showed multifocal ileal ulcers and stenosis (Fig. 3A), but capsule endoscope was retained at an ileal stenotic segment. Patient 5 was diagnosed with CD and treated with 5-ASA, corticosteroids, and immunomodulator, but did not show improvement. Therefore, she underwent ileal resection for retained capsule, but abdominal pain continued. She was finally diagnosed with CEAS at 19.

Patient 6 was a 54-year-old man at diagnosis whose symptoms began at 11. He underwent three ileal resections for obstruction at the ages of 42, 48, and 52 years. At 54 years of age, he underwent another ileal resection due to small bowel perforation. Investigations showed multifocal strictures and ulcers in the duodenum, jejunum, ileum, and colon (Figs 2B, 3B). He had digital clubbing, pachydermia, and periostosis. He was treated with 5-ASA, corticosteroids, immunomodulator, anti-tumor necrosis factor (TNF) agent, and vedolizumab for presumed CD. However, 5-ASA, immunomodulator, and anti-TNF agent failed to improve his symptoms. He is currently being treated with vedolizumab, but intestinal inflammation and strictures persist.

Patient 7, the younger sister of Patient 5, was 16-year-old and had abdominal pain and loose stool since 12. Capsule endoscopy showed shallow ulcers and inflammatory lesions in the distal ileum.

Patient 8 was a 34-year-old woman with a heterozy-

gous compound *SLCO2A1* mutation (c.940+1G>A and c.1807C>T) whose symptoms began at 11. Investigations showed ulcerations and strictures involving the jejunum and ileum. Before CEAS diagnosis, she underwent four small bowel resections due to multifocal ulcers and strictures between the ages of 15 and 25. She had been treated with 5-ASA, corticosteroids, immunomodulator, and anti-TNF agent for presumed CD, none of which were effective in improving her symptoms.

Patient 9 was a 21-year-old woman with a heterozygous compound *SLCO2A1* mutation (c.940+1G>A and c.1807C>T). She presented with abdominal pain at 12. Investigations showed terminal ileal ulcer scars and ileal wall thickening. She had been treated with 5-ASA, corticosteroids, immunomodulator, and anti-TNF agent for presumed CD before the CEAS diagnosis. However, the medications were ineffective and were thus stopped.

Patient 10 was a 52-year-old woman diagnosed with CEAS via the confirmation of a homozygous *SLCO2A1* mutation (c.1807C>T). Examinations showed superficial ulcerative ileal lesions and scars (Fig. 3C). She had digital clubbing, facial pachydermia, and hand periostosis. She had been treated with 5-ASA, corticosteroids, immunomodulator, anti-TNF agent, and ustekinumab for presumed CD. Her disease did not respond to 5-ASA, corticosteroids, immunomodulator, and anti-TNF agent. She is currently on ustekinumab therapy, but endoscopy and magnetic resonance enterography are still showing active bowel lesions.

Patient 11 was a 51-year-old woman with a heterozygous compound *SLCO2A1* mutation (c.940+1G>A and c.1807C>T). She had been complaining of abdominal pain for 11 years. Examinations showed jejunal and ileal ulcers and strictures. She underwent bowel resection for capsule endoscope retention.

Patient 12 was a 63-year-old woman with a homozygous *SLCO2A1* mutation (c.940+1G>A). Examinations showed hyperemic inflammatory changes of the duodenum and luminal narrowing with shallow geographic ulcers in the jejunum and ileum.

Patient 13 was a 29-year-old man with a heterozygous compound *SLCO2A1* mutation (c.940+1G>A and c.1807C>T) whose symptoms started at 15. Multifocal inflammatory and stenotic lesions were found in the duodenum, jejunum, and ileum, but not the terminal ileum. He underwent small bowel resections for strictures and obstruction involving the duodenum and jejunum at 15, 16, 17, 23, and 24 years of age. He had digital clubbing, pachydermia, and periostosis. Before the CEAS diagnosis, the patient received 5-ASA and corticosteroids but did not experience improvements.

Patient 14 was a 45-year-old woman with a homozygous *SLCO2A1* mutation (c.1807C>T). She underwent three bowel resections between the ages of 22 and 36 years. Endoscopic and radiographic examinations showed ileal ulcerative lesions and inflammation. Before the diagnosis of CEAS, she had been treated with 5-ASA, corticosteroids, immunomodulator, anti-TNF agent, and vedolizumab for presumed CD, which were ineffective.

DISCUSSION

We investigated the clinical characteristics and genetic analysis results of Korean CEAS patients. Since the 1960s, when CMUSE was first reported, CMUSE has been widely diagnosed globally.[5,17,20-23] However, in Japan, the diagnostic entity named CNSU was proposed in 2014.[4] "CMUSE" and "CNSU" are commonly characterized by unexplained, intractable, and superficial ulcerative enteric lesions, usually among adolescents and young adults.[4,16] In 2011, Matsumoto *et al.*[7] found that CNSU tends to segregate in children of consanguineous parents. Finally, in 2015, Umeno *et al.*[8] identified *SLCO2A1* mutation as the probable cause of inherited chronic enteropathy among CNSU patients. *SLCO2A1* encodes a prostaglandin transporter mediating prostaglandin uptake and clearance, and loss-of-function mutations of *SLCO2A1* impair prostaglandin transport.[8] Umeno *et al.*[8] also revealed that the *SLCO2A1* protein was not detected on vascular endothelial cellular membranes in the small intestines of affected patients. Since then, Japanese studies on CEAS have been published.[10,11] In 2018 and 2019, case reports of a Korean male and a Chinese female diagnosed with CEAS were published.[13,14]

Previously, CMUSE has mostly been reported from Europe and South Korea, while CNSU has only been reported in East Asia.[24] Debate persists about whether CMUSE and CNSU are a single entity, but they seem to belong to the same disease spectrum at the least. Considering the discovery of several mutations, including *PLA2G4A* (OMIM: 600522) and *SLCO2A1*, CMUSE is believed to be associated with *PLA2G4A* mutation, and CNSU is believed to be associated with *SLCO2A1* mutations, so-called CEAS.[25-27] *PLA2G4A* mutation is thought to cause a reduced production of eicosanoids-like prostaglandins, which are important for maintaining the mucosal integrity of the intestine.[24-26] In contrast to CNSU, CMUSE tends to affect males and females equally, and more frequently involves the jejunum.[6,24] However, it is difficult to differentiate CMUSE from CNSU in the clinic. Therefore, genetic analyses could be helpful for differential diagnosis of idiopathic intestinal ulceration and stenosis as well as for understanding their

pathophysiology.[28] Genetic testing of patients previously diagnosed with CMUSE clinically and those manifesting CEAS features could help clarify the diagnosis.[24]

In this study, we diagnosed 14 CEAS patients by identifying loss-of-function *SLCO2A1* mutations. Two pathogenic *SLCO2A1* mutations (splicing site variant c.940+1G>A and nonsense mutation [p.R603X]), previously reported by Umeno *et al.*,[11] were identified in 14 patients. We also identified six novel polymorphisms among 46 patients including 14 patients diagnosed with CEAS. Of note, those six polymorphisms have not been able to confer the diagnosis of CEAS.

Of 14 CEAS patients, 12 were females. This aligns with reported male-to-female ratios ranging from 1:2.5 to 1:3.5.[8,10,11] Although our male-to-female ratio was much higher (1:6), it would be imprudent to generalize this ratio, given our small sample size.

Symptoms of CEAS tended to start in adolescence, as the median age of symptom onset was 18.0 years (range, 2 to 40 years). This is consistent with reported ages at onset of 21 and 16.5 years reported elsewhere.[10,11] Notably, CEAS was associated with a diagnostic delay (median, 13.5 years; IQR, 10.7 to 19.2 years) after symptom onset. Previous reports have cited delayed diagnoses because the nomenclature "CEAS" was only proposed in 2015.[8] Many CEAS patients have previously been diagnosed with CD or CMUSE, or have been assessed as having idiopathic disease. Five of our 14 CEAS patients had a family history of CEAS, and all of the afflicted family members were included in our study. Two of these patients were sisters; another set of sisters had an uncle with CEAS who was also enrolled in this study. The frequency of familial CEAS history (5/14, 35.7%) was higher than frequencies reported elsewhere, ranging from 22% to 27%.[8,11] All of our patients had abdominal pain which has been reported as the most common symptom; two previous studies found that abdominal pain affects 39% and 77.3% of CEAS patients, respectively.[10,11] Although 13 out of 14 patients had anemia, only three presented with gross gastrointestinal bleeding. The anemia pattern in our patients was a mixture of iron deficiency anemia and anemia caused by chronic inflammation. Anemia associated with CEAS may be due to chronic, insidious bleeding, malabsorption related to bowel inflammation, or chronic inflammation itself. CEAS has been reported to be characterized by anemia, hypoproteinemia and hypoalbuminemia, and relatively normal inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein, as observed in our study; this differs from CD, which is typically associated with elevated inflammatory markers.[29] On the other hand, in contrast to blood inflammatory markers, fecal calprotectin levels were mostly elevated among our study patients, thus reflecting intestinal inflammation.

Similar to previous Japanese studies,[8,10,11] in our study, the ileum was the most commonly involved site. Umeno *et al.*[11] reported sparing of the terminal ileum associated with CEAS, whereas Eda *et al.*[30] and Hu *et al.*[14] reported cases of CEAS involving the terminal ileum. In our study, 10 of 14 cases (71.4%) involved the terminal ileum. Notably, we enrolled two patients with colonic involvement. As far as we know, colonic involvement has not been reported in any previous studies on CEAS. Yanai *et al.*[29] reported that, unlike CD patients, CEAS patients had no colorectal involvement. However, two patients in our study had circular and superficial colonic ulcers, not associated with anastomosis, similar to ulcers observed in the ileum. Therefore, the presence of colonic lesions cannot exclude the diagnosis of CEAS.

As PHO shares causative mutations with CEAS, some CEAS patients may have signs of PHO. Previous reports of CD associated with PHO may have actually described CEAS patients.[31,32] Umeno *et al.*[11] and Hosoe *et al.*[10] also reported that 20% to 27% of CEAS patients had PHO and that the three major PHO manifestations—digital clubbing, periostosis, and pachydermia—were more common in males. This aligns with our finding that 35.7% of our patients had at least one major sign of PHO and that the three major PHO manifestations were more common in males (2 out of 2) than in females (1 out of 12).

In the real-world clinical practice, CEAS is often misdiagnosed as CD after excluding drug-induced enteropathy and intestinal tuberculosis. In contrast to CD, CEAS tends to affect females more frequently than males and less frequently shows colorectal involvement and systemic inflammatory symptoms or signs.[11,29] Endoscopic and radiologic findings of CEAS can be characterized as multiple, circularly aligned, sharply demarcated, geographic, and shallow ulcers or multifocal short segmental strictures mostly in the small intestine. Although a case report noted the effectiveness of azathioprine for an adolescent patient with CEAS,[30] patients in the current study who had been treated with 5-ASA, immunomodulator, or biologics did not show improvements, consistent with the knowledge that there is no effective medical therapy for CEAS. Therefore, *SLCO2A1* genetic testing can be recommended in adolescents to middle-aged patients with unexplained chronic enteropathy that mainly affects the small intestine with aforementioned characteristics on endoscopic and radiologic examinations, who show chronic anemia and hypoalbuminemia, lacks systemic inflammatory signs relative to the degree of intestinal lesions, or do not respond to treatment targeting CD.

This study had several limitations. First, not all patients had undergone capsule endoscopy or enteroscopy; therefore, information regarding the affected intestinal site may be incomplete. However, small bowel follow-through, computed tomography enterography, and magnetic resonance enterography could have been adequate for evaluating the small intestine. Second, as some patients were lost to follow-up or were referred to other hospitals, we could not obtain some necessary information, including clinical course after the CEAS diagnosis. However, our study investigated the characteristics of Korean CEAS patients at the time of diagnosis rather than their clinical course. Finally, our small sample limits generalizability. However, considering that CEAS is rare and that this study recruited 46 patients from five institutions over 3 years, our study is meaningful as the first Korean CEAS case series.

In conclusion, our findings on 14 Korean patients confirmed as CEAS are mostly consistent with previous Asian studies. Our study contributes to the understanding of CEAS, but larger-scale studies are required to elucidate the pathophysiology of CEAS and to develop medical therapies for this rare disease. Of note, gastroenterologists should not forget genetic testing as a diagnostic tool when confronted with unexplained chronic enteropathy, especially for those with chronic anemia and hypoalbuminemia.

CONFLICTS OF INTEREST

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S.J.P. is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: B.D.Y. Data collection: H.S.H., J.B., J.C.P., H.S.L., D.P., A.R.Y., S.J.P., S.N.H., S.J.K., C.K.L., B.I.L., S.W.H., S.H.P., S.J.M., S.K.Y., K.S., B.D.Y. Data analysis and interpretation: H.S.H., J.B., J.C.P., H.S.L., D.P., B.D.Y. Drafting of the manuscript: H.S.H., J.B., H.S.L., B.D.Y. Critical revision of the manuscript: H.S.H., J.B., J.C.P., H.S.L., D.P., A.R.Y., S.J.P., S.N.H., S.J.K., C.K.L., B.I.L., S.W.H., S.H.P., S.J.M., S.K.Y., K.S., B.D.Y. Study supervision and guarantor of the study: B.D.Y.

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SUPPLEMENTARY MATERIALS

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