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SLCO2A1 gene is the causal gene for both primary hypertrophic osteoarthropathy and hereditary chronic enteropathy

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To the editor

We read with great interest the article by Yuan L et al. [1] regarding the safety and efficacy of a selective cyclooxygenase (COX)-2 inhibitor for the treatment of primary hypertrophic osteoarthropathy (PHO). In this study, a total of 27 patients including 7 patients with *HPGD* (15-hydroxyprostaglandin dehydrogenase) gene mutations and 20 patients with *SLCO2A1* (solute carrier organic anion transporter family member 2A1) gene mutations were treated with etoricoxib and followed up for nine months. The authors stated that the major symptoms such as joint swelling, digital clubbing, and pachydermia were improved in most patients. They also reported that no severe adverse event occurred throughout the study period.

PHO is classified into two subtypes by causal gene: *HPGD* gene relevant PHO type I [PHOAR1 (PHO autosomal recessive 1)] and *SLCO2A1* gene relevant PHO type II [PHOAR2 (PHO autosomal recessive 2)]. Because urinary levels of prostaglandin E2 (PGE2) are characteristics in patients with either subtype [1,2], the major symptoms of digital clubbing, periostosis, and pachydermia in PHO are explained by excessive PGE2 caused by its impaired degradation. On the other hand, PHOAR1 and PHOAR2 have some differences in clinical features. For example, PHOAR2 has a marked male predominance and sometimes shows severe anemia [3]. Moreover, urinary levels of PGE2 metabolites in PHOAR2 were significantly higher than those in PHOAR1 [1].

We have recently shown that loss-of-function mutations in the *SLCO2A1* gene cause hereditary enteropathy referred to as “chronic enteropathy associated with *SLCO2A1* gene” (CEAS) [4]. CEAS is characterized by persistent blood and protein loss due to the development of multiple small intestinal ulcers. It is inherited by an autosomal recessive manner, but it has female predominance [5]. We also reported that as well as PHOAR2, the urine levels of PGE metabolites in CEAS patients are significantly higher than those of healthy control [4]. Although PGE2 has been known to play a protective role against gastrointestinal mucosal damage [6], multiple intestinal ulcers occur in CEAS. Moreover, the gastrointestinal lesions of CEAS are endoscopically similar to those of nonsteroidal anti-inflammatory drug (NSAID)-induced enteropathy. Furthermore, the lesions mimic those of cryptogenic multifocal ulcerous stenosing enteritis (CMUSE) caused by the *PLA2G4A* gene mutations, in which a decrease in intracellular PGE2 production results in multiple ulcers of the small intestine. We thus hypothesize that decrease in intracellular PGE2 by impaired PGE2 transport is causative of small intestinal ulcers of CEAS.

As described above, CEAS and PHOAR2 share a causative gene and their clinical features are profoundly influenced by other modifiers. Taken together with the facts that CEAS predominantly occurs in females and PHOAR2 occurs in males, sex-related modifier genes or hormones should be considered.

To date, we found five Japanese male patients with CEAS, who manifested all three major symptoms of PHO [5]. Wang Q et al. [7] also reported two male patients with PHO, who presented anaemia and hypoalbuminemia presumably due to small intestinal ulcers. Since CEAS and PHOAR2 share a common causal gene, we presume that patients with PHOAR2 are prone to intestinal ulcerations. Yuan L et al. [1] reported that five patients (18.5%) showed a positive faecal occult blood test and these patients were suspected to have gastrointestinal ulcers. In our previous prospective trial with the use of capsule endoscopy, 16.7% of the healthy volunteers showed some small intestinal mucosal injuries after two weeks of a selective COX-2 inhibitor administration [8]. Therefore, we recommend small intestinal scrutiny by capsule endoscopy and scheduled blood tests when patients with PHOAR2 were treated by selective COX-2 inhibitors. Otherwise, the patients may not be candidates for the treatment by the medication.

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Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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