LETTER

Reply to Walsh *et al*

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We appreciate the informative letter by Walsh *et al* with regards to our recent article.¹ We are interested in the clinical course of the male patient with an *FLNA* variant who developed severe complications, including gastrointestinal tract, in his adolescence although he had lived relatively well until then.

The brothers in our article, Patient I and Patient II, with in-frame exon skipping due to a 4-bp deletion in *FLNA* also developed gastrointestinal complications in their later life, and we would like to describe additional information on their clinical courses.

Patient I, an elder brother, suffered from the intractable diarrhea since the neonatal period. When he presented hematogenous diarrhea with abdominal pain at 4 years of age, colonoscopy revealed cobblestone appearance and longitudinal ulcers in his terminal ileum, which are the characteristic findings of Crohn's disease. Histopathological features of biopsy specimen exhibited increased lymphocyte infiltration of the lamina propria and crypt architectural distortion, but no granuloma formation was observed. At the age of 9, his gastrointestinal symptoms, including hematochezia, diarrhea, and abdominal pain, worsened and colonoscopy showed the exacerbation of intestinal inflammation with multiple ulcers. After initiation of treatment for Crohn's disease, including elemental diet, mesalazine, and azathioprine, his gastrointestinal symptoms improved.

Patient II, the younger brother, had never showed any symptoms of chronic intestinal inflammation when we reported him in the original article at the age of 10. However, at the age of 12, he presented hematogenous diarrhea with abdominal pain and colonoscopy revealed a small solitary ulcer in his terminal ileum. Recently, our follow-up colonoscopy revealed multiple ulcer lesions in the distal jejunum. This endoscopic finding as well as his clinical symptoms suggested the diagnosis of Crohn's disease, although like Patient I, pathological examination failed to detect the findings of intestinal granuloma. Treatments of elemental diet and mesalazine have been started because of progressive gastrointestinal symptoms.

The *FLNA* gene encodes filamin A, a widely expressed actin-binding protein that is involved in the integration of actin cytoskeleton and the modulation of cell shape and migration. *FLNA* gene mutations cause multiple organ abnormalities, including cardiac valvular disease,

periventricular nodular heterotopia, chronic idiopathic intestinal pseudo-obstruction, or Ehlers-Danlos syndrome.² These abnormalities seem to be associated with development and function of the affected organs, which exist from birth. On the other hand, chronic intestinal inflammation, which had never been reported in previous patients with *FLNA* mutations, occurred in our patients several years after birth.

Widely accepted causes of chronic intestinal inflammation are inappropriate responses by dysregulated immune system to intestinal microbiota and disruption of intestinal barrier function.³ Moreover, heredity is also known to play a role in this intestinal immune dysregulation and defect in intestinal barrier structure and function.⁴ Although further investigations are needed to confirm it, *FLNA* mutations may be associated with impairment of immune system or barrier function to microbes in digestive tract and may cause susceptibility to intestinal inflammation.

This letter and that of Walsh *et al* provide a shared insight that patients with *FLNA* mutations can develop intestinal complications later in life and should be actively monitored for their lifetime.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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