

# Three cases of tufting enteropathy and review of literature

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## ABSTRACT

**Background.** Congenital tufting enteropathy (CTE) is a rare autosomal recessive enteropathy characterized by intractable watery diarrhea independent of feeding, electrolyte imbalances and severe malnutrition. The aim of this case series is to highlight the characteristic yet easily overlooked histological features of tufting enteropathy, especially in cases where initial biopsies may be reported as nonspecific, and to emphasize the importance of clinicopathological correlation and genetic confirmation.

**Case Presentation.** Here we report 3 patients with tufting enteropathy who have the characteristic histological findings and demonstrate the use of EpCAM (epithelial cell adhesion molecule) immunohistochemistry. One case was diagnosed by histopathological examination, while the other 2 were diagnosed by genetic analysis.

**Conclusions.** These cases illustrate that the histopathological features of CTE, though subtle, are usually present from the outset and can be recognized when specifically sought. Correlation with genetic testing is essential for confirmation, but increased awareness of the characteristic epithelial tufts may reduce diagnostic delay and improve patient management.

**Key words:** congenital diarrhea, EpCAM, intestinal epithelial dysplasia, pediatric, tufting enteropathy.

Congenital tufting enteropathy (CTE) was first described in 1994<sup>1</sup> and its incidence is estimated at 1/50,000-100,000 live births in Western Europe.<sup>2</sup> For this rare disease, approximately 200 cases have been reported (details are summarized in Table I).<sup>3-10</sup> Biallelic inactivation of epithelial cell adhesion molecule gene (*EPCAM*), which is located on chromosome 2p21, was identified as the cause of CTE in 2008.<sup>11</sup> More recently, variants in *SPINT2* (serine peptidase inhibitor kunitz-type 2) have also been implicated in the syndromic form of this disease, which causes an indirect loss of epithelial cell adhesion molecule (EpCAM) protein due to proteolysis by activation of matriptase.<sup>12</sup> Of all the cases reported in English

literature, approximately 74% have *EPCAM* variants, while 26% show variants in *SPINT2*.<sup>13</sup>

Variants in or loss of *EPCAM* lead to many defects, the most important being the disruption of the cell-cell junction which leads to defective barrier function. Disruption of the intestinal epithelial homeostasis, defective enterocyte function and impaired cell-matrix interactions have also been found in CTE patients.<sup>3</sup> Clinically, these patients usually present in the first few months of life with intractable diarrhea and nutrient malabsorption, resulting in impaired growth.<sup>11</sup> In addition to primary intestinal symptoms, patients, especially those who have the syndromic form associated with *SPINT2* variants<sup>13,14</sup> can have extra-intestinal symptoms,

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**Table I.** Summary of clinical features, genes and histologic findings reported in literature

Study	Number of cases	Year	Symptoms	Genetic variants	Histological findings	Outcome
Reifen et al <sup>1</sup>	3	1994	Diarrhea, vomiting	N/A*	N/A	1 died
Patey et al <sup>4</sup>	6	1997	Diarrhea	N/A	Villous atrophy, focal epithelial tufts, decreased number of IELs	Unknown
Goulet et al <sup>10</sup>	10	1998	Diarrhea	N/A	Villous atrophy, epithelial tufting	Unknown
Bird et al <sup>5</sup>	3	2007	Diarrhea, choanal atresia; eye, hematologic and hair abnormalities	N/A	Villous atrophy, crypt hyperplasia, chronic inflammation, tufting of surface enterocytes	Unknown
Sivagnanam et al <sup>11</sup>	5	2008	Diarrhea	EPCAM in 4/5 cases	Crowding of epithelial cells and tufting	Unknown
Sivagnanam et al <sup>6</sup>	1	2010	Diarrhea, cholestatic liver disease	SPINT2	N/A	Alive
Salomon et al <sup>14</sup>	57	2014	Diarrhea, superficial punctuated keratitis, choanal atresia, other atresia, dermatological anomalies, and bone malformations	EPCAM in 41 cases, SPINT2 in 12 cases	Villous atrophy, crowding epithelium/ tufts, abnormal crypts	8 died
Ranganathan et al <sup>7</sup>	17	2014	Diarrhea	N/A	Focal epithelial tufts and vacuolation	Alive
Pathak et al <sup>12</sup>	17	2019	Diarrhea	EPCAM	N/A	Alive
Holt-Danborg et al <sup>8</sup>	3	2019	Diarrhea, Choanal atresia, enterocutaneous fistula, atrial septal defect, cleft lip and palate, and toe abnormalities	SPINT2	Partial villous atrophy, normal brush border, focal epithelial tufts	Alive
Ayyildiz Civan et al <sup>9</sup>	6	2021	Diarrhea	EPCAM	Total villous atrophy, mild inflammation	3 died
Ozler et al <sup>19</sup>	2	2020	Diarrhea, tenosynovitis	EPCAM	Partial villous atrophy, crypt hyperplasia, focal tufting in surface epithelium, normal number of IELs	Alive (after long term follow up)

IEL: intraepithelial lymphocyte, N/A: not available.

such as superficial punctuated keratitis, corneal erosions<sup>15</sup>, cataracts<sup>16</sup>, skeletal dysplasia, cholestatic liver disease, chronic arthritis, bone and dermatological abnormalities.<sup>3</sup> Typical histopathological findings of CTE are partial or total villous atrophy, crypt hyperplasia without inflammation and focal epithelial tufts. The tufts consist of tightly packed enterocytes at villous tips and basement membrane abnormalities which results in teardrop-like

configurations.<sup>3</sup> However, cases reported in the literature are clinically heterogenous, with varying severity and not all cases display the typical histopathological findings, which poses a diagnostic challenge.<sup>17</sup> BerEP4 immunohistochemistry (monoclonal antibody to EpCAM) can be helpful in the diagnosis of cases that do not have the typical morphological findings. In addition to intestinal epithelial cells, loss of BerEP4 can also be seen in hepatocytes

and bile duct epithelium in liver biopsies of patients with tufting enteropathy.<sup>18</sup>

Although large series of tufting enteropathy have been published, most emphasize the genetic basis or clinical spectrum.<sup>14-16</sup> Our series draws attention to the diagnostic challenge that these cases pose and highlights the fact that the characteristic histological findings of tufting enteropathy can usually be detected if carefully sought, which may shorten diagnostic delay.

## Case Presentations

### Case 1

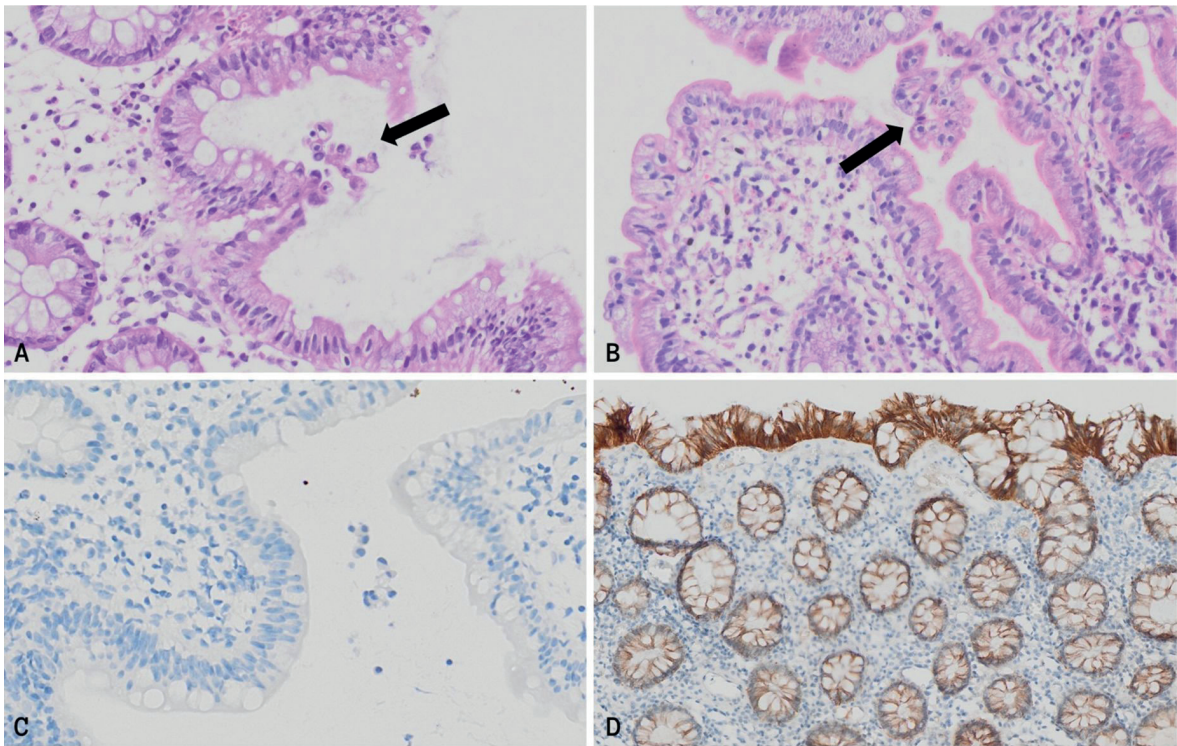
A 2-month-old girl was admitted to the pediatric intensive care unit with prerenal acute kidney failure due to profuse watery diarrhea that had been resistant to treatment. The family pedigree showed that the parents were consanguineous (second-degree cousins). There were two family members reported to have had similar symptoms during childhood, including the father's younger brother who died in early infancy. Unfortunately, no reliable information on their age, sex, clinical features, or outcome was available. The patient had symptoms of watery diarrhea that occurred 8 to 9 times a day. Before admission to our center, she was hospitalized for two weeks at another hospital and had received antibiotic treatment. Breastfeeding was discontinued due to a preliminary diagnosis of cow's milk protein allergy. The patient was fed with an enteral nutrition formula however oral intake was completely discontinued after a few days due to worsening of symptoms.

On admission, the patient was found to be severely dehydrated. The birth weight of the patient was 2900 grams (-0.8 standard deviation score [SDS]). Her body weight at admission was 2600 grams (-7.2 SDS) consistent with severe growth faltering. Laboratory examination revealed metabolic acidosis with a blood pH of 7.16, bicarbonate of 9 mEq/L and creatinine of 1.52 mg/dL (normal range, 0.2-0.4 mg/dL). Stool examination revealed no reducing

substances, parasites, or amoebae. After starting intravenous fluids and stabilization, endoscopic biopsies from various parts of the stomach, small intestine, and colon were taken to shed light on the etiology of the chronic diarrhea. The preliminary diagnoses included cytomegalovirus (CMV) colitis, enteric anendocrinosis, lymphangiectasia and cow's milk protein allergy.

At initial examination, the endoscopic biopsies showed no specific findings. The diagnoses of lymphangiectasia and cow's milk protein allergy were ruled out immediately because there were no dilated lymphatic channels or an increase in eosinophils in the lamina propria. CMV and chromogranin immunohistochemistry studies were performed for the remaining diagnoses. CMV was negative in all tissues. Chromogranin revealed fewer neuroendocrine cells (1-2 NECs per crypt) than the normal number of 4-5 NECs per crypt. However, this was not enough to support the diagnosis of enteric anendocrinosis as most cases lack NECs completely or have 1 NEC per 10 crypts. After these findings, whole exome sequencing (WES) was performed to evaluate variants in *NEUROG3*. However, the WES study revealed a pathogenic homozygous *EPCAM* variant (NM\_002354.3: c.227C>G [p.Ser76Ter]) instead. The biopsies were re-evaluated in this view with additional hematoxylin and eosin (H&E) staining and immunohistochemical staining for EpCAM. In the H&E sections of the duodenum, terminal ileum and colon, focal, subtle epithelial disorganization and tear-drop formation were found (Fig. 1A-B). Immunohistochemistry revealed complete loss of EpCAM expression in the intestinal and colonic tissues, which is specific for CTE (Fig. 1C).

The patient was fed with total parenteral nutrition after the diagnosis and per oral feeding could not be achieved. At 1 year of age, despite parenteral nutrition support, the patient developed progressive feeding intolerance with vomiting and abdominal distension, followed by respiratory distress and circulatory collapse. Cardiopulmonary resuscitation



**Fig. 1.** Histopathological findings of Case 1. **A.** Endoscopic biopsy of the colon showing characteristic tear-drop formation (arrow) of shedding surface epithelium (H&E, original magnification 200x). **B.** Tear-drop formation and epithelial tufts (arrow) are seen in the duodenum (H&E, original magnification 200x). **C.** BerEP4 immunohistochemistry shows complete loss of staining (original magnification 200x). **D.** Normal colonic control tissue shows diffuse positivity with BerEP4 on the surface epithelium and colonic crypts (original magnification 100x).

was unsuccessful, and the patient could not be resuscitated. The outcome was attributed to complications of severe malnutrition and intestinal failure.

### Case 2

A 17-month-old boy was admitted to the intensive care unit with severe malnutrition and dehydration due to watery diarrhea that had been increasing since birth. The parents were first cousins and were healthy. They had another child who passed away soon after birth due to similar symptoms. The patient was born at 35 weeks of gestation, weighing 2700 grams. When he was admitted to our center at 17 months of age, he weighed 3,600 g (-9.7 SDS) and his height was 61 cm (-7.7 SDS). The patient was previously hospitalized in multiple centers and no etiology could be identified

for the intractable diarrhea. Endoscopic and colonoscopic biopsies were performed and they revealed crypt hyperplasia, villous atrophy, and an increase in intraepithelial lymphocytes. Soon after admission the clinical condition of the patient deteriorated, and he passed away. The family consented to an autopsy and molecular genetic studies. The autopsy revealed villous atrophy in the small intestine, hydrops in the gallbladder, severe malnutrition and cachexia and reactive enlargement of mesenteric lymph nodes. The duodenum sections were examined by electron microscopy. There were a few microvilli however no microvillus inclusions were identified. No definitive cause could be identified for chronic diarrhea. To rule out genetic causes, whole exome sequencing was performed. A homozygous missense variant in *EPCAM* (NM\_002354.3: c.757G>A [p.Asp253Asn]) compatible with the

disease phenotype in the affected individual was found. This case has been previously published in 2022 by Güvenoğlu et al.<sup>17</sup> The additional details regarding genetic studies can be found in their article. We reviewed the autopsy sections of this patient and performed EpCAM immunohistochemistry on the duodenal tissue. The histologic examination of the duodenum showed villous atrophy and classic teardrop formation on the surface (Fig. 2A). In addition, there was a slight increase in intraepithelial lymphocytes. The BerEP4 immunohistochemistry was negative as expected (Fig. 2B).

### Case 3

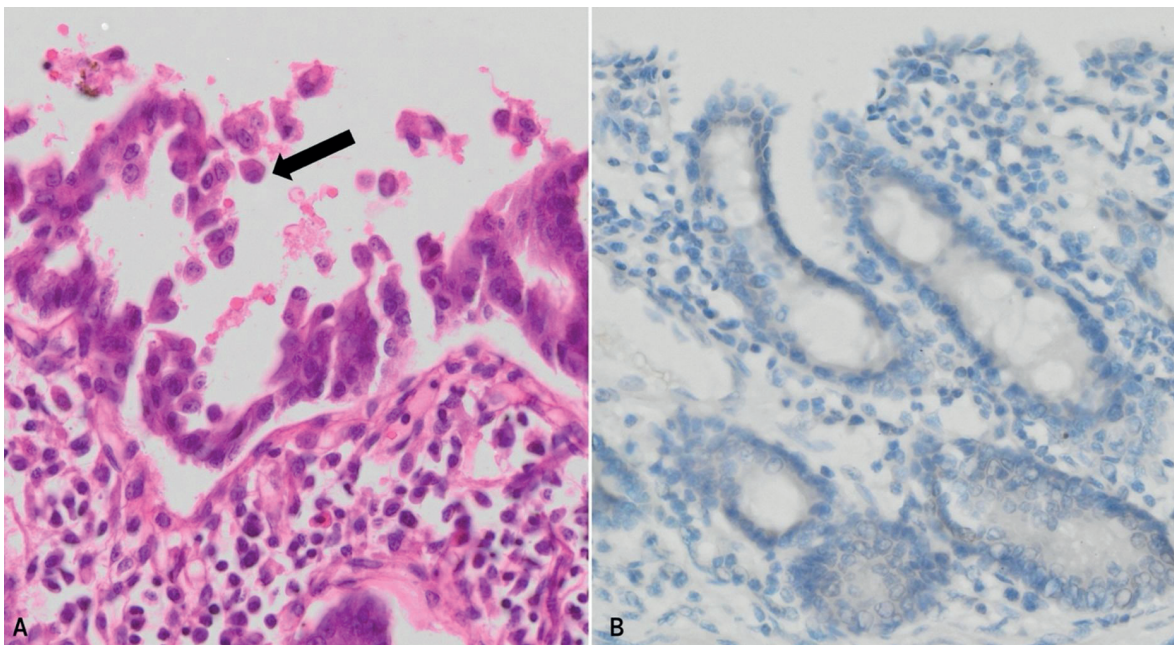
The third case is a 10-month-old male infant who had vomiting and diarrhea that commenced 2 days following birth. The parents were first-degree relatives who were healthy. The patient was initially examined for metabolic diseases due to the presence of reducing substances in urine. However, tandem mass spectrometry was normal. Sweat test for cystic fibrosis was also negative. The endoscopic

biopsy from the duodenum was diagnostic as it revealed clustering of epithelial cells forming characteristic teardrop cells (Fig. 3A). The brush border was examined with periodic acid-Schiff (PAS) staining and was preserved. There was also partial villous atrophy, a minimal increase in lymphocytes in the lamina propria and crypt hyperplasia. The EpCAM immunohistochemistry was negative (Fig. 3B). Genetic testing could not be performed for this patient and no follow-up information was available.

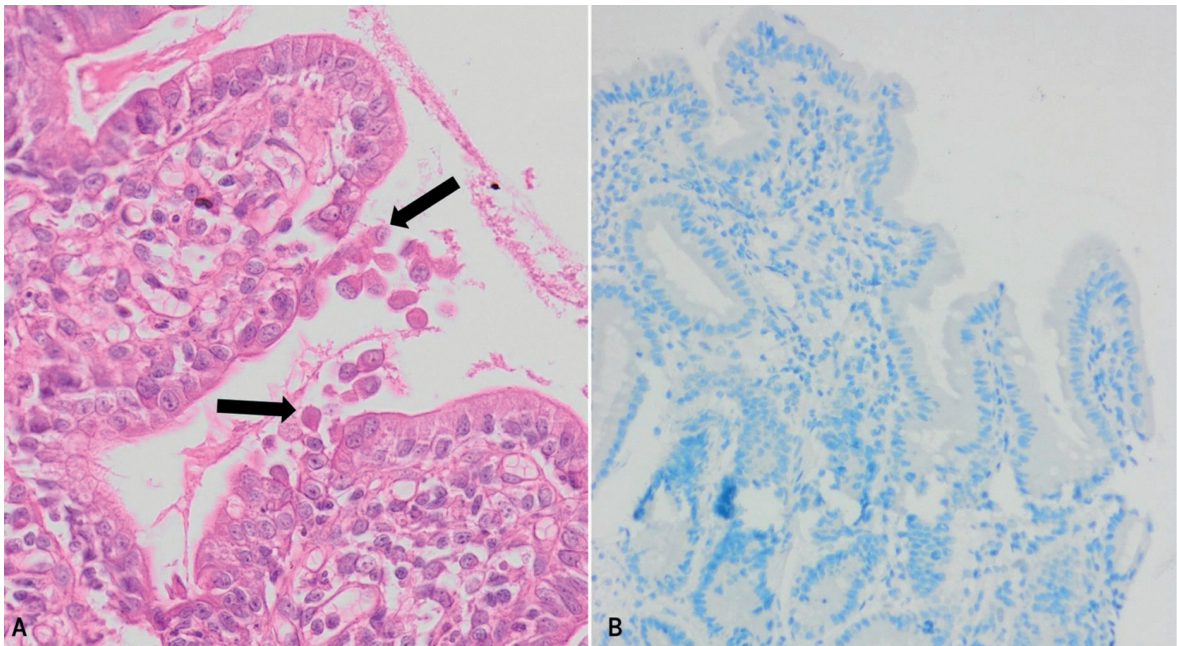
Informed consent could not be obtained from the families because one case dated back more than 10 years and the other two families could not be reached. Therefore, permission from the ethics committee was obtained (number: 2024/17-03).

### Discussion

Our three cases illustrate the diagnostic challenges of CTE. Although the disease is genetically defined, the histological findings



**Fig. 2.** Histopathological findings of Case 2. **A.** Diffuse tear-drop formation forming tufts (arrow) on the surface epithelium of duodenal sections obtained during autopsy (H&E, original magnification 200x). **B.** Complete lack of staining in BerEP4 immunohistochemistry (original magnification 200x).



**Fig. 3.** Histopathological findings of Case 3. **A.** Endoscopic biopsy of duodenal tissue shows shed tear-drop epithelial cells (arrows) (H&E, original magnification 200x). **B.** BerEP4 immunohistochemistry was negative (original magnification 100x).

can also aid in the diagnosis. In this section, we highlight the variability of the clinical course and emphasize the complementary value of histopathology and genetics in diagnosis.

While most patients depend on total parenteral nutrition (PN), there are reported cases where weaning from PN was achieved.<sup>11,19</sup> One of these case reports describing two siblings with tufting enteropathy showed complete loss of EpCAM in immunohistochemistry and a homozygous variant in the *EPCAM* gene. Certain patients may have a better prognosis due to unknown factors.<sup>19</sup> The only accepted treatment to date is small bowel transplantation, which has many complications such as liver failure, infections and rejection.<sup>3</sup>

Although the diagnosis of tufting enteropathy usually depends on genetic analysis, the histopathological examination can also be diagnostic if the pathologist is aware of CTE in the differential diagnosis. However, the histological findings of CTE can be overlooked and interpreted as nonspecific, which was the major challenge in 2 of our cases. Only

after genetic confirmation did retrospective review reveal the subtle epithelial tufts and teardrop formations. This highlights the risk of underdiagnosis if CTE is not specifically considered. When provided with a history of intractable diarrhea in an infant, the gastrointestinal biopsies should be carefully examined for epithelial tufts and villous atrophy, and BerEP4 immunohistochemistry can be performed on cases showing villous atrophy without inflammation or when the histological findings are equivocal. Genetic testing remains essential for definitive diagnosis, prognosis, and family counseling, but increased histopathological awareness can reduce diagnostic delay and guide appropriate workup.<sup>14</sup>

In conclusion, our experience shows that while subtle, the histological features of CTE are characteristic when interpreted in the correct clinical context. Greater awareness of these findings, combined with timely EpCAM immunohistochemistry and genetic analysis, can improve recognition of this rare but important cause of intractable infantile diarrhea.

## Ethical approval

The study was approved by Hacettepe University Ethics Committee (date: October 08, 2024, number: 2024/17-03).

## Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: DO, literature review: AN, draft manuscript preparation: AN, EG, HHG, HD, DO. All authors reviewed the results and approved the final version of the manuscript.

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The authors declare the study received no funding.

## Conflict of interest

The authors declare that there is no conflict of interest.

## REFERENCES

1. Reifen RM, Cutz E, Griffiths AM, Ngan BY, Sherman PM. Tufting enteropathy: a newly recognized clinicopathological entity associated with refractory diarrhea in infants. *J Pediatr Gastroenterol Nutr* 1994; 18: 379-385.
2. Goulet O, Salomon J, Ruemmele F, de Serres NPM, Brousse N. Intestinal epithelial dysplasia (tufting enteropathy). *Orphanet J Rare Dis* 2007; 2: 20. <https://doi.org/10.1186/1750-1172-2-20>
3. Das B, Sivagnanam M. Congenital tufting enteropathy: biology, pathogenesis and mechanisms. *J Clin Med* 2020; 10: 19. <https://doi.org/10.3390/jcm10010019>
4. Patey N, Scoazec JY, Cuenod-Jabri B, et al. Distribution of cell adhesion molecules in infants with intestinal epithelial dysplasia (tufting enteropathy). *Gastroenterology* 1997; 113: 833-843. [https://doi.org/10.1016/s0016-5085\(97\)70178-1](https://doi.org/10.1016/s0016-5085(97)70178-1)
5. Bird LM, Sivagnanam M, Taylor S, Newbury RO. A new syndrome of tufting enteropathy and choanal atresia, with ophthalmologic, hematologic and hair abnormalities. *Clin Dysmorphol* 2007; 16: 211-221. <https://doi.org/10.1097/MCD.0b013e328274264b>
6. Sivagnanam M, Janecke AR, Müller T, Heinz-Erian P, Taylor S, Bird LM. Case of syndromic tufting enteropathy harbors SPINT2 mutation seen in congenital sodium diarrhea. *Clin Dysmorphol* 2010; 19: 48. <https://doi.org/10.1097/MCD.0b013e328331de38>
7. Ranganathan S, Schmitt LA, Sindhi R. Tufting enteropathy revisited: the utility of MOC31 (EpCAM) immunohistochemistry in diagnosis. *Am J Surg Pathol* 2014; 38: 265-272. <https://doi.org/10.1097/PAS.000000000000106>
8. Holt-Danborg L, Vodopiutz J, Nonboe AW, et al. SPINT2 (HAI-2) missense variants identified in congenital sodium diarrhea/tufting enteropathy affect the ability of HAI-2 to inhibit prostasin but not matriptase. *Hum Mol Genet* 2019; 28: 828-841. <https://doi.org/10.1093/hmg/ddy394>
9. Ayyıldız Civan H, Leitner C, Östreicher I, et al. Three novel EPCAM variants causing tufting enteropathy in three families. *Children (Basel)* 2021; 8: 503. <https://doi.org/10.3390/children8060503>
10. Goulet OJ, Brousse N, Canioni D, Walker-Smith JA, Schmitz J, Phillips AD. Syndrome of intractable diarrhoea with persistent villous atrophy in early childhood: a clinicopathological survey of 47 cases. *J Pediatr Gastroenterol Nutr* 1998; 26: 151-161. <https://doi.org/10.1097/00005176-199802000-00006>
11. Sivagnanam M, Mueller JL, Lee H, et al. Identification of EpCAM as the gene for congenital tufting enteropathy. *Gastroenterology* 2008; 135: 429-437. <https://doi.org/10.1053/j.gastro.2008.05.036>
12. Pathak SJ, Mueller JL, Okamoto K, et al. EPCAM mutation update: variants associated with congenital tufting enteropathy and Lynch syndrome. *Hum Mutat* 2019; 40: 142-161. <https://doi.org/10.1002/humu.23688>
13. Cai C, Chen Y, Chen X, Ji F. Tufting enteropathy: a review of clinical and histological presentation, etiology, management, and outcome. *Gastroenterol Res Pract* 2020; 2020: 5608069. <https://doi.org/10.1155/2020/5608069>
14. Salomon J, Goulet O, Canioni D, et al. Genetic characterization of congenital tufting enteropathy: epcam associated phenotype and involvement of SPINT2 in the syndromic form. *Hum Genet* 2014; 133: 299-310. <https://doi.org/10.1007/s00439-013-1380-6>
15. Heinz-Erian P, Müller T, Krabichler B, et al. Mutations in SPINT2 cause a syndromic form of congenital sodium diarrhea. *Am J Hum Genet* 2009; 84: 188-196. <https://doi.org/10.1016/j.ajhg.2009.01.004>

16. Roche O, Putterman M, Salomon J, et al. Superficial punctate keratitis and conjunctival erosions associated with congenital tufting enteropathy. *Am J Ophthalmol* 2010; 150: 116-121.e1. <https://doi.org/10.1016/j.ajo.2010.01.034>
17. Güvenoğlu M, Şimşek-Kiper PÖ, Koşukcu C, et al. Homozygous missense epithelial cell adhesion molecule variant in a patient with congenital tufting enteropathy and literature review. *Pediatr Gastroenterol Hepatol Nutr* 2022; 25: 441-452. <https://doi.org/10.5223/pghn.2022.25.6.441>
18. Chen S, Goldsmith JD, Fawaz R, Al-Ibraheemi A, Perez-Atayde AR, Vargas SO. Liver pathology, including MOC31 immunohistochemistry, in congenital tufting enteropathy. *Am J Surg Pathol* 2021; 45: 1091-1097. <https://doi.org/10.1097/PAS.0000000000001710>
19. Ozler O, Brunner-Véber A, Fatih P, Müller T, Janecke AR, Arikan C. Long-term follow-up of tufting enteropathy caused by EPCAM mutation p.Asp253Asn and absent EPCAM expression. *JPGN Rep* 2020; 2: e029. <https://doi.org/10.1097/PJG9.0000000000000029>