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Pediatric Gastrointestinal Histopathology in Patients with Tetratricopeptide Repeat Domain 7A (TTC7A) Germline Mutations: A Rare Condition Leading to Multiple Intestinal Atresias, Severe Combined Immunodeficiency and Congenital Enteropathy

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Abstract

Mutations in the tetratricopeptide repeat domain 7A (*TTC7A*) gene are a rare cause of congenital enteropathy that can result in significant morbidity. TTC7A deficiency leads to disruption of the intestinal epithelium. The histopathology of this condition has been partly described in case reports and clinical studies. This manuscript describes an in-depth investigation of the pediatric gastrointestinal pathology of the largest histologically examined cohort with confirmed *TTC7A* mutations reported to date and, for the first time, compared the findings to age- and sex-matched control patients with intestinal atresia not thought to be associated with *TTC7A* mutations. Hematoxylin and eosin-stained slides of endoscopically obtained mucosal biopsies and surgical resection specimens from seven patients with known *TTC7A* mutations were examined retrospectively. The microscopic findings were found to be on a spectrum from atresia-predominant to those with predominantly epithelial abnormalities. Several unique histopathologic characteristics were observed when compared to controls. These included neutrophilic colitis and prominent lamina propria eosinophilia throughout the gastrointestinal tract. Striking architectural

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abnormalities of the epithelium were observed in four of the seven patients. The five patients with intestinal atresia demonstrated hypertrophy and disorganization of the colonic muscularis mucosae accompanied by bland spindle cell nodules within the intestinal wall. The components of the latter were further elucidated using immunohistochemistry, and we subsequently hypothesize that they represent obliterated mucosa with remnants of the muscularis mucosae. Finally, atrophic gastritis was noted in four patients. In conclusion, the unique histopathologic characteristics of *TTC7A* mutation-associated enteropathy described herein more fully describe this novel disease entity in infants who present with congenital enteropathy or enterocolitis.

Keywords

Tetratricopeptide repeat domain 7A (*TTC7A*); congenital enteropathy; multiple intestinal atresias; severe combined immunodeficiency; very early onset idiopathic inflammatory bowel disease

INTRODUCTION

Tetratricopeptide repeat domain 7A (*TTC7A*) is a protein involved in the regulation of epithelial polarity and survival through poorly understood mechanisms that include interaction and complex formation with the phosphoinositide generating enzyme phosphatidylinositol 4-kinase IIIα (PI4KIIIα) (1–4). Defects in its function lead to loss of apicobasal polarity, derangement of cell adhesion, and increased apoptosis. These effects are particularly present in the gastrointestinal epithelium(1–4). Pathogenic germline mutations of the gene result in disruption of intestinal epithelium and impaired immune cell homeostasis, particularly in peripheral T lymphocytes, the consequence of which is a syndrome of combined immunodeficiency (CID), multiple intestinal atresia (MIA), and/or early onset enterocolitis (i.e. very early onset inflammatory bowel disease (VEOIBD))(1–13).

Mutations of *TTC7A* were first reported in humans in 2012 in a French-Canadian cohort with hereditary MIA, that was often fatal(3, 8, 12). The involved gene was identified by whole exome sequencing, and since then, more than 50 patients have been identified with more than 20 different *TTC7A* mutations(4, 7–9). It has been suggested that truncating mutations and mutations within the scaffolding domain of the protein result in more severe disease compared to non-truncating mutations (hypomorphic variants) although there are no definitive genotype-phenotype studies to date (2, 4, 11–14). Patients with *TTC7A* germline mutation have high rates of morbidity and the disease is often fatal, with a median survival age of approximately 12 months(4).

In addition to MIA, TTC7A patients very often have concurrent combined immunodeficiency (CID) resulting in increased risk of mortality due to infection and increased susceptibility to graft-versus-host disease(7). The latter is implicated in several different clinical settings including non-irradiated blood transfusion, small bowel transplantation after extensive surgical resection for atresia, liver transplantation for parenteral nutrition (PN)-associated liver disease, and bone marrow transplantation for CID(7). T cell lymphopenia and hypogammaglobulinemia, as well as milder NK and B cell lymphopenia have been reported(4, 7). Postmortem examination has shown significant

thymic hypoplasia compared to age-matched controls(4). There are two mouse models with mutations of *TTC7A,* both of which illustrate this CID phenotype: the *fsn* ("flaky skin") mutation results in anemia, psoriasis, gastric hyperplasia, and cortical thymic hypoplasia, while the *hea* mutation leads to early thymic atrophy and fatal anemia(8, 15).

Gastrointestinal pathology in patients with *TTC7A* mutation has been partially described in case reports(11, 13, 16–18) and clinical studies(1, 2, 8–10, 14), predominantly through examination of intestinal resection specimens from one to two patients with confirmed *TTC7A* mutations. The studies with larger numbers of patients either do not comprehensively describe the histopathologic findings of the gastrointestinal tract, or they do not have molecular confirmation of *TTC7A* mutation in all patients(1, 8, 10). Their observations most frequently consist of intestinal fibrosis at the sites of atresia, as well as apoptotic enterocolitis with regenerative changes, crypt drop-out, architectural disarray, villous atrophy of the small intestine, increased lamina propria eosinophils and neutrophils, and decreased numbers of plasma cells; one report describes disordered epithelial apicobasal polarity(13). Each study describes a different combination of these findings, and there is limited data available regarding the variability of these changes among different patients and various anatomic sites.

This study further elucidates the gastrointestinal histopathology in a cohort of patients with documented *TTC7A* germline mutations; we compare these findings to a control group of patients with intestinal atresia and clinicopathologic findings incompatible with *TTC7A* mutation. It was also possible to examine findings in the gallbladder, liver, pancreas, and spleen of one patient who underwent multivisceral transplant. The goal was to identify microscopic characteristics that will allow pathologists to diagnose this rare but very severe pediatric disease. We also attempted to correlate the pathologic phenotype with the specific molecular alteration, when possible.

MATERIALS and METHODS

Cases and Controls

A retrospective chart review of seven patients with molecularly confirmed *TTC7A* mutations and available pathology material from endoscopically obtained mucosal biopsies and/or gastrointestinal resection specimens was conducted over a period of 20 years (2001–2021). Cases were obtained by search of the pathology database in combination with a congenital diarrhea and enteropathy clinical database maintained by one of the authors (JT). Comparison was made to thirteen age- and sex-matched controls (two per TTC7A patient except patient #4, where only one age/sex matched control was available) that were presumed to have wild-type *TTC7A* based on the clinical impression. All controls had intestinal atresia (10 small intestine and 3 colon). Ten controls had single intestinal atresia and 3 had multiple atresias. The patients with multiple atresias either had a negative genetic workup that revealed wild-type *TTC7A* (1 patient) or had multiple atresias due to previous episodes of necrotizing enterocolitis (two patients).

All cases were reviewed by 2 pathologists (KD and JDG). The evaluated histopathologic parameters, which were determined after comparison to controls, included intestinal atresia,

cytologic and architectural abnormalities of the epithelium, atrophic gastritis, lamina propria eosinophilia, neutrophilic colitis, hypertrophy and/or disorganization of the muscularis mucosae, and the presence of spindle cell nodules within the intestinal wall (further described below).

Immunohistochemistry

Immunohistochemical staining was performed on 4 μm sections of selected cases in the standard fashion on Bond automated immunohistochemistry instruments (Leica Biosystems, Buffalo Grove, IL) using the following antibodies: smooth muscle actin (clone AlphaSM-1; prediluted; Leica Biosystems), desmin (clone DE-R-11; prediluted; Leica Biosystems), e-cadherin (clone 36; prediluted; Ventana/Roche Tissue Diagnostics, Oro Valley, AZ), CD10 (clone 56C6; prediluted; Leica Biosystems), S-100 (polyclonal; Leica Biosystems), gastrin (clone 256A-18; prediluted, Cell Marque, Rocklin, CA), chromogranin (clone LK2H10; prediluted, Cell Marque), cytomegalovirus (clone 213M18; prediluted, Cell Marque), adenovirus (clone MAB8052; dilution 1:100, MiliporeSigma, Burlington MA), and MOC-31 (clone MOC-31; prediluted, Biocare Medical, Pacheco, CA).

RESULTS

The TTC7A cohort, all of whom had molecularly confirmed *TTC7A* mutations, included six male and one female patient. Four patients were diagnosed with intestinal obstruction prenatally, one was found to have obstruction shortly after birth, two patients had severe enterocolitis, and one patient suffered from severe infantile-onset diarrhea with feeding intolerance. Four of the seven patients demonstrated a phenotype of severe combined immunodeficiency (SCID) and one was found to have chronically low white blood cell counts. (Table 1)

H&E slides of resection specimens were available from four patients including small bowel from all, colon from three patients, and one patient with a multivisceral explant (gallbladder, liver, spleen, stomach, small intestine, and pancreas). Four patients each had at least one upper and lower endoscopy with biopsies. Two patients had multiple endoscopies with biopsies available for review. The mean age of first tissue procurement was 3 months (range 2d – 1 year). (Table 1)

Macroscopically, the resection specimens showed multiple atresias of the small intestine and colon; the atretic segments ranged from 0.4 – 11 cm in length (mean 3.2 cm). The endoscopic appearance of the mucosa showed various non-specific findings including pale esophageal mucosa, gastric erythema and mild friability of the terminal ileum and colon. Characteristic endoscopic findings were not identified.

Three patients' histologies were characterized predominantly by intestinal atresia, two showed primarily microscopic epithelial changes, and two showed combined features (Table 1).

Epithelial abnormalities included cribriform growth and patchy crypt degeneration characterized by markedly attenuated epithelium with dilated crypt lumina. Varying degrees

of cytologic atypia were seen, from “regenerative-like” changes to those mimicking high-grade dysplasia, with loss of nuclear polarity and anisonucleosis. This was accompanied by pronounced epithelial apoptosis with occasional apoptotic debris filling and distending crypt lumina (Figure 1). The epithelial changes were most pronounced in the colon. CD10, E-cadherin, and MOC-31 immunohistochemistry highlighted normal brush border, basolateral, and membranous staining, respectively.

Five patients had intestinal atresia. Microscopic examination of areas adjacent to the atretic segments revealed hypertrophy and disorganization of the muscularis mucosae in all of cases often accompanied by lamina propria fibrosis. Cytologically bland spindle cell nodules in the vicinity of the deep mucosa / superficial submucosa were noted, which contained admixed small vessels, nerves, and clusters of ganglion cells (Figure 2).

Immunohistochemistry was performed to further elucidate the nature of these nodules. Smooth muscle actin (SMA) and desmin stains highlighted vessel walls and a ring of smooth muscle at the periphery of most of these lesions (Figure 3, left panel), while the nerves and ganglion cells were highlighted by S100 staining (Figure 3, right panel).

The inflammatory infiltrate was more pronounced in all patient samples compared to controls and manifested as prominent lamina propria eosinophilia (Figure 4, right panel) with a component of neutrophilic colitis (Figure 4, left panel). A lack of plasma cells was noted in all four patients with SCID-phenotype. Helicobacter pylori-negative gastritis with gastric oxyntic atrophy was seen in all three patients with available stomach biopsies (Figure 5), two of which also had associated squamoid metaplasia (Figure 5, inset); one showed enterochromaffin-like cell hyperplasia, as seen on chromogranin immunohistochemistry. Stains for cytomegalovirus and adenovirus were negative in all cases and the lack of G-cells on gastrin immunostains confirmed sampling of oxyntic mucosa

A summary of the findings in each TTC7A patient is shown in Table 2. None of these findings described above were seen in the age- and sex-matched controls apart from atresia. Calcification and variable villous atrophy (in small bowel resections) were frequently seen in areas of atresia in both *TTC7A*-mutated and control specimens.

Of note, H&E slides were available from a multivisceral transplant from patient #3, which was performed at five years of age. The explant included gallbladder, liver, spleen, stomach, small Intestine, and pancreas. No unique histopathologic characteristics were seen in the sections of gallbladder, liver, or pancreas that could be separated from changes secondary to long-term total parenteral nutrition which included chronic cholecystitis and cholesterolosis, micronodular cirrhosis with bile ductular proliferation and damage, cholestasis, portal/lobular neutrophilic inflammation, and marked chronic pancreatitis. The spleen showed reduced white pulp and prominent hemosiderin-laden macrophages, which were also considered nonspecific findings.

While all patients had confirmed *TTC7A* mutations, detailed mutation information was only available in 4 patients (Table 3). These patients harbored a variety of both frameshift and missense mutations. Patient 2 had one allele with the relatively common Glu71Lys variant that has been reported in a number of TTC7A patients(4). Interestingly patients 6 and 7

have one variant in common despite no known relationship or consanguinity between these patients. Initial protein stability analysis by homology modeling to the known structure of TTC7B indicated that many of the mutations are likely highly destabilizing to the protein. It is notable that patients 1 and 6, whose two destabilizing mutations predict complete loss of protein function, exhibited a combined atresia and epithelial abnormalities. In contrast, the other two patients (patients 2 and 7), who had an epithelial phenotype without MIA, had at least one mutation that was not predicted to be highly destabilizing.

DISCUSSION

Mutations in *TTC7A* have recently been shown to present early in life with severe symptoms that fall on a spectrum of MIA with CID and enterocolitis. The newly described TTC7A-deficiency falls into the category of congenital diarrheas and enteropathies (CODEs), rare diseases characterized by life-threatening chronic diarrhea of the neonate as well as the category of very early onset inflammatory bowel disease (VEO-IBD)(10, 19). It should be considered in the clinical differential diagnosis of congenital tufting enteropathy, microvillous inclusion disease, autoimmune enteropathy, abetalipoproteinemia, other causes of early onset enterocolitis/VEO-IBD and CODEs(4, 19).

As more is understood about the genetic etiologies for congenital diarrheal illnesses and enteropathies, it is important for pathologists to examine histopathologic correlates in order to assist with the diagnosis of these morbid diseases. This manuscript outlines a retrospective histologic review and immunohistochemical examination from the largest pathologically analyzed *TTC7A*-mutated cohort reported to date, including not only intestinal specimens, but biopsies and excisions from the upper GI tract. Additionally, the findings were compared to a control group of intestinal resection specimens in patients with clinical presentations incompatible with *TTC7A* mutation. Finally, the gallbladder, liver, pancreas, and spleen of one patient who underwent multivisceral explant were also reviewed.

Similar to what can be gleaned from the literature(1, 2, 8–11, 13, 14, 16–18), patients with *TTC7A* mutations exhibited variable histologic phenotypes: three were characterized predominantly by intestinal atresia, two showed primarily microscopic epithelial changes, and two had combined features.

The epithelial changes were histologically characterized by architectural distortion, crypt degeneration, and pronounced apoptosis, as have been described in the literature(1, 2, 8, 10, 11, 14). More specifically, we observed gland cribriforming, anisonucleosis, epithelial apoptosis and loss of nuclear polarity, the latter of which is also mentioned by Agarwal *et al*(13). A novel finding is that the epithelial changes were invariably more striking in the colon than those found in the stomach and small intestine. Lemione *et al.* does note relative sparing of the small intestine in one patient(2).

Immunohistochemical analysis of CD10, MOC31, and E-cadherin, which have not been previously reported in the context of *TTC7A*-mutation, demonstrated normal patterns of staining.

The four patients with intestinal atresia demonstrated hypertrophy and disorganization of the muscularis mucosae, often accompanied by lamina propria fibrosis, which was not seen in control cases. Conspicuous spindle cell nodules were also present, comprised of central fibrous tissue with a rim of smooth muscle and admixed small vessels, nerves, and clusters of ganglion cells. Based on the morphologic and immunohistochemical findings, we hypothesize that these lesions represent the remnants of obliterated mucosal lumens with remnants of the muscularis mucosae and submucosal (Meissner's) nerve plexus. Fibrosis obscuring the intestinal lumen has been reported multiple times in the literature, including Fernandez *et al*, Yang *et al*, Mandia *et al*, and Agarwal *et al,* however these spindle-cell nodules have not been previously described(8, 9, 13, 17).

Finally, the inflammatory infiltrate was more pronounced in TTC7A patients compared to controls, characterized by prominent lamina propria eosinophilia and neutrophilic colitis. Lemione *et al*. and Lien *et al*. also report this as a distinct feature in some of their patients. Due to the altered immune homeostasis and T-cell dysfunction noted in patients with germline mutations of *TTC7A*, it is possible that the finding of increased lamina propria inflammatory inflammation is secondary to immune dysregulation / autoimmune enterocolitis(2, 14). Autoimmune enterocolitis might therefore be considered in the differential diagnosis of *TTC7A* mutation-associated enteropathy, but would not be characterized by atresia or the epithelial changes described above, with the exception of epithelial apoptosis. Additionally, we observed *Helicobacter pylori*-negative atrophic gastritis, confirmed by immunohistochemistry, which has not been previously described in TTC7A patients.

A more detailed comparison of the four patients with available mutational variant data indicated that an intestinal atresia clinical phenotype, and possibly a combined atresia and epithelial histopathologic phenotype, may correlate with the presence of either severe frameshift mutations (premature stop codon) or highly destabilizing missense mutations, in keeping with previous suggestions that this phenotype is associated with severe loss of function variants(4). Interestingly, structural homology modeling of TTC7A using the known structure of TTC7B suggested that the missense variants present in the two cases without atresia coalesce at different aspects of the putative complex interfaces with PI4IIIα or EFR3, suggesting that TTC7A- PI4IIIα -EFR interactions(20) may be a key factor in the etiology of the epithelial phenotype. Further studies probing these interactions are needed to understand the mechanisms of the profound polarity and structural changes observed in the epithelium.

The histopathology of *TTC7A* mutation shows distinct findings when compared to other histologically recognizable causes of congenital enteropathy, with characteristic features including epithelial dysmaturation, remnant muscularis mucosae seen in resection specimens, and congenital atrophic gastritis. These features can be used to distinguish this entity from other CODEs including microvillous inclusion disease, congenital tufting enteropathy, autoimmune enteropathy, enteroendocrine dysplasia, and other causes of early onset enterocolitis/VEOIBD.

This study is limited by the small sample size due to the rarity of disease and the fact that the authors were not blinded to the diagnosis during analysis. In addition, molecular analysis of the control group was not performed, so it is an unlikely possibility that some of the control group patients harbored *TTC7A* mutations that resulted in a subtle clinicopathologic phenotype.

Our findings suggest that there is a spectrum of distinct histopathologic findings associated with *TTC7A* mutations, with patients that are atresia-predominant, others with characteristic epithelial changes, and some with combined features. We believe that these histologic features can be used to prospectively diagnose patients with germline *TTC7A* mutations based on pathologic findings. As such, *TTC7A* germline mutation as a cause of congenital diarrhea and MIA should be added to the group of other histologically recognizable CODEs.

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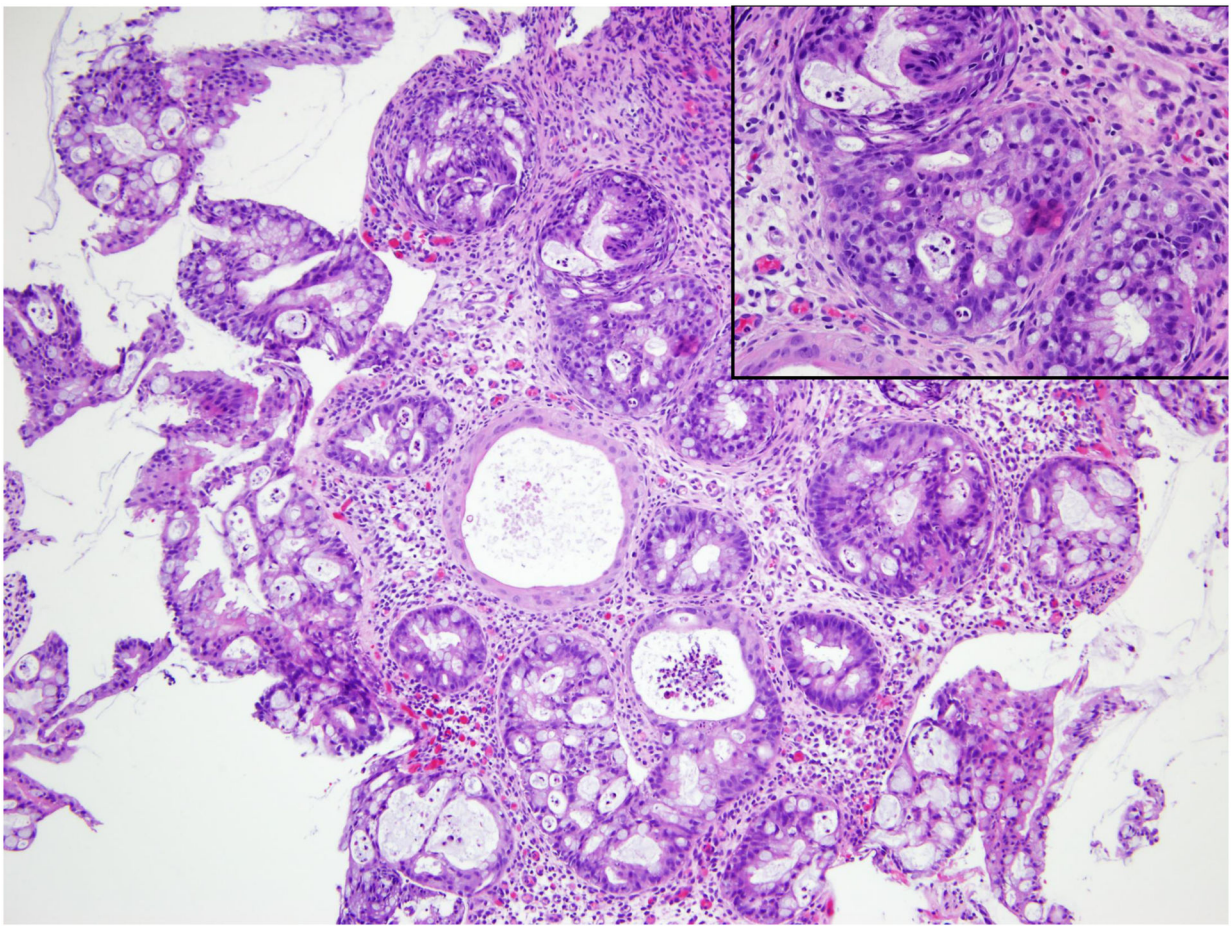

Figure 1 (colon endoscopic biopsy, H&E):
The striking epithelial abnormalities were best seen in the colon and showed occasional crypt degeneration with epithelial attenuation (center). Most crypts showed marked epithelial dysmaturation with cribriform architecture, variable nuclear size, and prominent epithelial apoptosis including apoptotic debris within crypt lumina (inset).

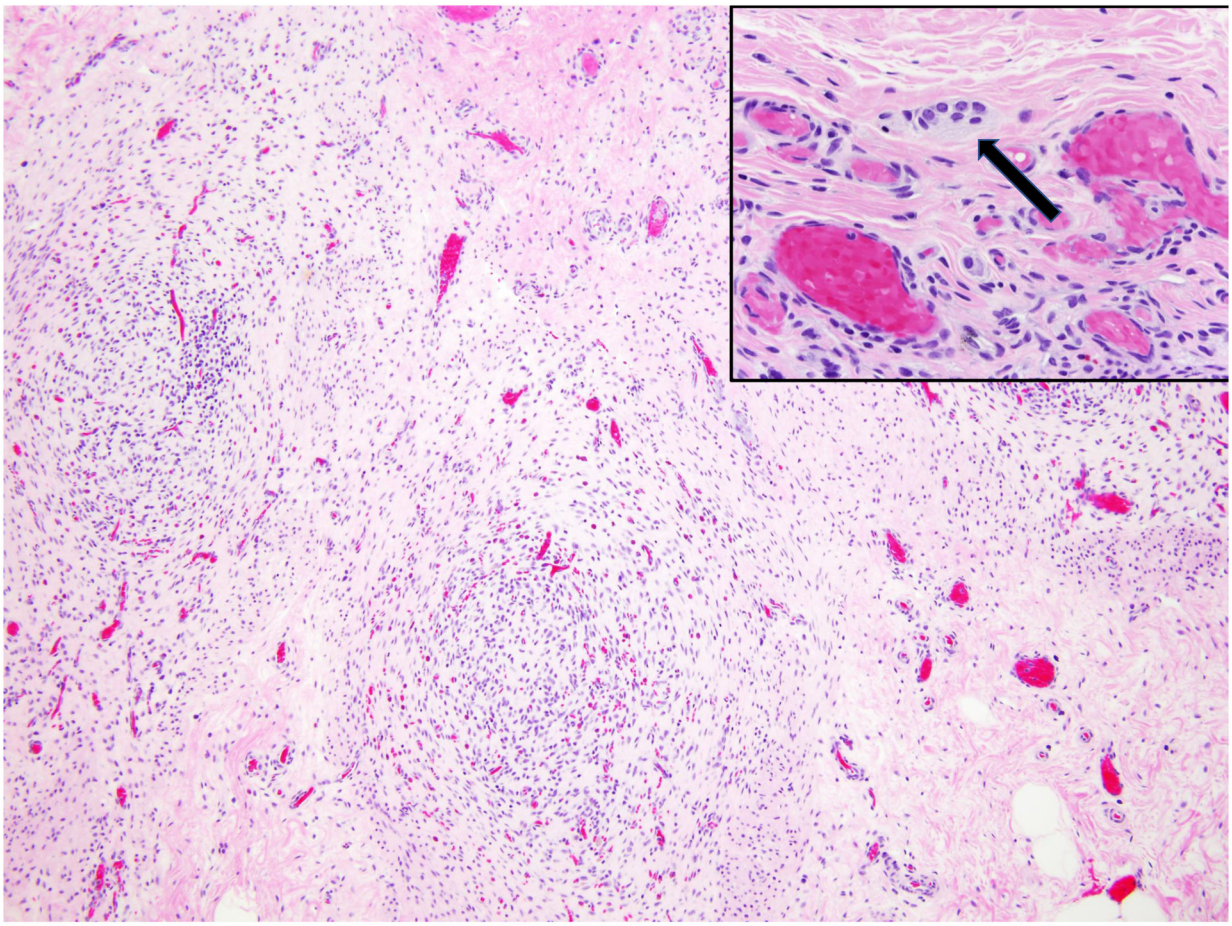

Figure 2 (small intestinal resection, H&E):
In resection specimens in the areas of atresia, bland spindle cell nodules were identified. Close examination revealed ganglion cells at the periphery of these nodules (inset, arrowhead).

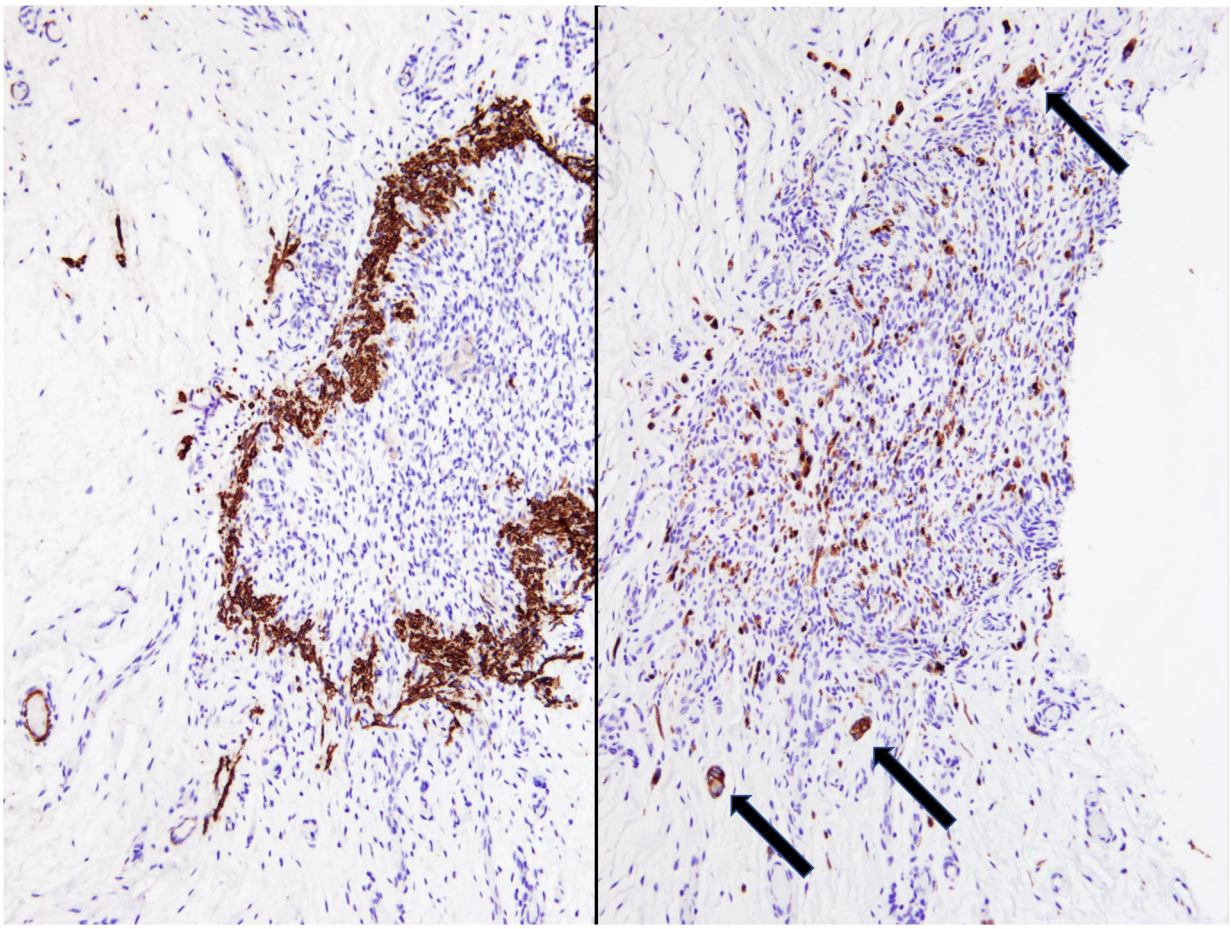

Figure 3 (small intestinal resection):
Desmin immunohistochemistry of the spindle cell nodules (left) showed a well-organized band of smooth muscle. S-100 immunostains confirmed the H&E impression of ganglion cells (right, arrowheads). This led us to the conclusion that these nodules represented remnant muscularis mucosae.

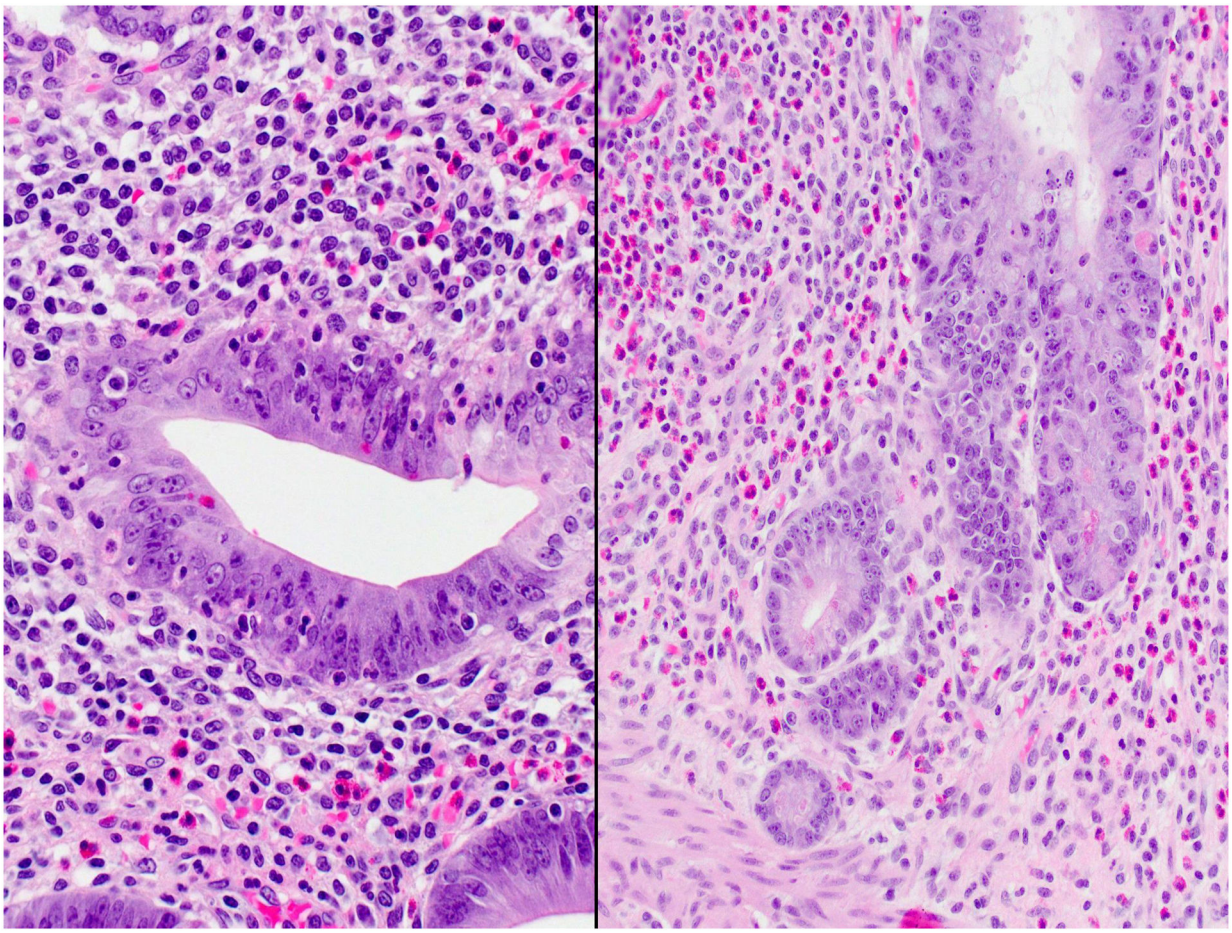

Figure 4 (colon, resection, H&E):
The inflammatory changes were characterized by neutrophilic inflammation and epithelial regenerative changes (left). A patchy increase in lamina propria eosinophils was also noted (right).

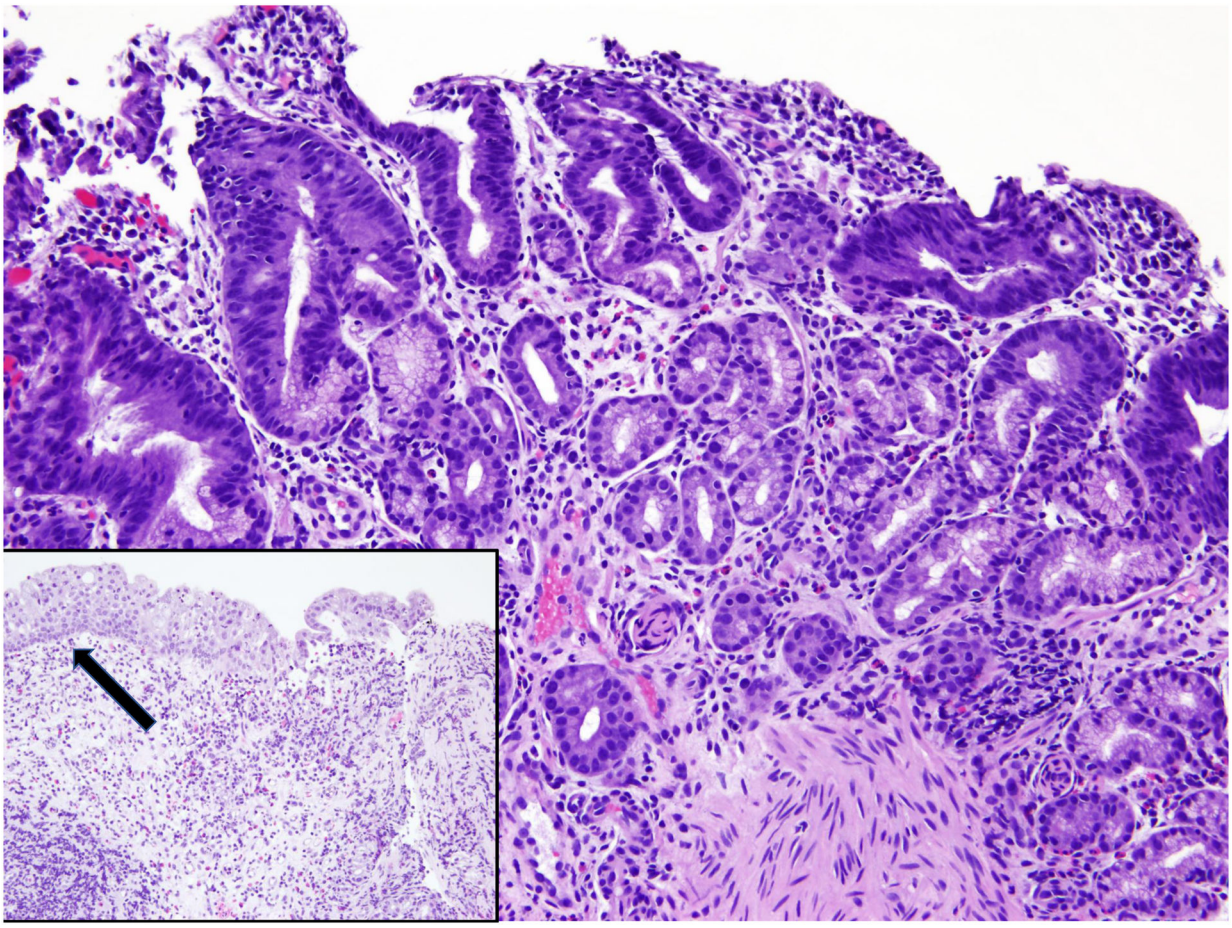

Figure 5 (stomach, endoscopic biopsy, H&E):
Four cases showed atrophic gastritis in oxyntic mucosa with full thickness inflammation and complete oxyntic atrophy. Intestinal metaplasia was not identified; however, two cases showed squamoid metaplasia (inset, arrowhead).

Table 1.

Summary of *TTC7A* Patients

Patient	Sex	Age at Procedure	Clinical Presentation	Procedure	Specimen(s)	Dominant Pathology
1	M	4 mos	Multiple intestinal atresias; SCID-phenotype	Resection	Small bowel, Colon	Epithelial abnormalities and atresias
2	F	3 mos	Congenital diarrhea with TPN dependence; SCID-phenotype	Upper and Lower Endoscopy	Duodenum, Stomach, Esophagus, Colon	Epithelial abnormalities
		6 mos		Upper and Lower Endoscopy	Duodenum, Stomach, Esophagus, Colon	
		7 mos		Upper and Lower Endoscopy	Duodenum, Colon, Rectum	
3	M	11 mos	Multiple intestinal atresias; SCID-phenotype	Resection	Small bowel, Colon	Atresia-predominant
		13 mo		Upper and Lower Endoscopy	Duodenum, Stomach, Esophagus, Rectum	
		15 mo		Resection	Small bowel, Colon	
		23 mo		Upper and Lower Endoscopy	Duodenum, Stomach, Esophagus, Ileum	
		3 yrs		Upper and Lower Endoscopy	Stomach, Esophagus, Ileum, Rectum	
		5 yrs		Multivisceral Transplant	Gallbladder, Liver, Spleen, Stomach, Small Intestine, Pancreas	
4	M	1 yr	Multiple intestinal atresias; Chronically low white blood cell counts	Resection	Small bowel	Atresia-predominant
5	M	2 days	Multiple intestinal atresias; SCID-phenotype	Resection	Small bowel, Colon	Atresia-predominant
6	M	1 mo	Multiple intestinal atresias; Enterocolitis/VEO IBD Phenotype	Upper and Lower Endoscopy	Duodenum, stomach, esophagus, rectosigmoid colon	Epithelial abnormalities and atresias
7	M	2 mo	Enterocolitis/VEO IBD Phenotype	Upper and Lower Endoscopy	Duodenum, stomach, esophagus, colon	Epithelial abnormalities

SCID: Severe combined immune deficiency; TPN: Total parenteral nutrition; VEO IBD: Very early onset idiopathic inflammatory bowel disease

Table 2.

Histologic Findings in TTC7A

Patient	Atrophic Gastritis	Prominent Lamina Propria Eosinophilia and Neutrophilic Colitis	Epithelial Abnormalities	Atresia	Hypertrophy/ Disorganization of the Muscularis Mucosae	Spindle Cell Nodules
1	*	+	+	+	+	+
2	+	+	+			
3	+	+		+	+	+
4	*	+		+	+	+
5	+	+		+	+	+
6	+	+	+	+		
7	*	+	+			
Controls				+		

+ Finding present

* Slides not available for review.

Table 3:

Clinicopathologic / Molecular Correlation

Patient	Variant 1	Variant 2	Mutation Types	Predicted protein destabilizing	Clinical Phenotype	Histopathologic Phenotype
1	c.674delA (p.H225fs)	c.674delA (p.H225fs)	Homozygous frameshift	Yes (Var 1+2)	MIA SCID	Combined
2	c.211G>A (p.Glu71Lys)	c.911delT (p.Leu304Argfs)	Compound heterozygote: Missense/ frameshift	Yes (Var2)	Chronic Diarrhea SCID Enterocolitis	E
3	NA	NA	NA	NA	MIA SCID	A
4	NA	NA	NA	NA	MIA	A
5	NA	NA	NA	NA	MIA SCID	A
6	c.1288–1G>T (p.Leu324Arg)	c.1433T>C (p.Leu478Pro)	Compound heterozygote: Missense	Yes (Var 1+2)	MIA Enterocolitis	Combined
7	c.1433T>C (p.Leu478Pro)	c.2495C>T (p.Ala832Val)	Compound heterozygote: Missense	Yes (Var1)	Enterocolitis	E

NA: Not available; MIA = Multiple intestinal atresia; SCID = Severe Combined Immunodeficiency; E = Epithelial abnormalities; A = Atresia.