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Short communication

# TTC7A mutation must be considered in patients with repeated intestinal atresia associated with early inflammatory bowel disease: Two new case reports and a literature review

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ABSTRACT

TTC7A mutations cause multiple neonatal intestinal atresias with early inflammatory bowel disease and severe combined immunodeficiency. There are no treatment protocols for this rare disease. Two new cases are described for which radical early treatment measures – total enterectomy, home parenteral nutrition, immunoglobulin therapy and intravenous antibiotic prophylaxis – have allowed both patients to develop optimally.



## 1. Introduction

Intestinal atresias are rare but not exceptional. Their cause is usually not found. The *TTC7A* gene has recently been implicated in cases of multiple intestinal atresias associated with early inflammatory bowel disease and severe combined immunodeficiency [1–5]. The TTC7A protein is involved in the polarization and differentiation of intestinal and likely thymic epithelial cells; TTC7A mutations dysregulate the distribution of α-integrin and actin in the epithelial surface, leading to tissue architecture disorganization and thus to dysfunctions from the fetal stage onwards [1]. To facilitate early diagnosis and improve knowledge of the treatment options, we report two cases with three new mutations, and summarize the recent literature on this subject.

## 2. Material and methods

A systematic search was conducted to identify studies reporting cases of patients with the TTC7A mutation. The literature search and evaluation were performed in two databases MEDLINE (Pubmed) and CENTRAL (Cochrane Central Register of Controlled Trials) between January 2000 and December 2017. The following

*Abbreviations:* D, day; GVHD, graft-versus-host disease; IBD, inflammatory bowel disease; PN, parenteral nutrition; SCID, severe combined immunodeficiency; TTC7A, tetratricopeptide repeat domain 7A.

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key words in English were used: Tetratricopeptide Repeat Domain 7A (TTC7A), multiple intestinal atresia (MIA), combined immune deficiency (CID), and very early onset inflammatory bowel disease (VEOIBD). The title, abstract and full-length text were screened for all suitable articles. We excluded duplicate articles or the same data published in journals, and animal studies.

### 2.1. Patient 1 (P1)

This patient (female) was delivered by cesarean section at a gestational age of 33 weeks following the detection of ascites and hyperechogenic bowel. The patient's parents are of North African origin and are first cousins. The fetal karyotype was normal.

Emergency surgery was performed on day 1 of life (D1) for bowel occlusion due to multiple level intestinal atresias requiring proximal duodenectomy. Microscopic examination of duodenal and appendix specimens revealed similar pathological features: the intestinal mucosa was either ulcerated or abnormal with dystrophic enterocytes, loss of nuclear polarity, numerous apoptotic bodies, and a tendency toward desquamation inside the lumen. The crypts were rarefied and also contained numerous apoptotic bodies. The duodenal mucosa was flat with total or subtotal villous atrophy without increased intraepithelial lymphocytes. Lymphoid follicles were rare and small inside the wall. Parenteral nutrition (PN) was then initiated.

A second surgical operation was performed on D64 following persistent vomiting. Further multiple small bowel atresias were discovered. Three anastomosis resections were performed, leaving 85 cm of small bowel and a jejunostomy was formed. On pathological examination, all resection specimens were characterized by multiple areas of stenosis, sometimes devoid of lumen, and replacement fibrosis of the different layers of the intestinal wall. The fibrosis was calcified in places. The nonstenotic areas exhibited features similar to those described as above with epithelial desquamation, numerous apoptotic bodies, and villous atrophy. The lymphoid follicles were small, rare, and devoid of germinal centers.

On D148, persistent rectal bleeding and the observation on ultrasonography of small-bowel wall thickening (4 mm) suggested chronic enterocolitis. The third surgery revealed multiple stenoses of the small bowel and the ileocecal valve. Enterolysis was performed with multiple intestinal resections/anastomoses, leaving 24 cm of small bowel. Pathological features similar to those described above were observed.

On D288, a subtotal enterectomy was performed along with a duodenostomy and an antireflux procedure following persistent rectal bleeding and wall thickening.

The patient was discharged from hospital at 12 months of age with home PN. She suffered bouts of acute pancreatitis (lipase 625 IU/L) at 22 months of age for which no cause was discovered despite infectious screening, genetic analysis, and several ultrasound explorations and a bili-RMI, which did not identify any stenosis or dilation of the Wirsung channel. These bouts recurred roughly once a month, requiring morphine treatment at home, before disappearing spontaneously at 35 months of age. The patient showed cytolysis (AST/ALT, 156/115 IU/L) and cholestasis (GGT, 176 IU/L) from age 12 months, for 2 years (Table 1). Laboratory tests performed for chronic cytolysis were normal including negative autoimmune hepatitis antibodies. The liver biopsy revealed only mild steatosis and fibrosis consistent with PN. Immune function tests were performed at 2 years of age following six bouts of acute otitis media in 4 months. A severe T-lymphocyte deficiency with hypogammaglobulinemia was discovered (Table 1). The lymphopenia was initially attributed to exudative enteropathy secondary to the chronic enterocolitis. Then prophylaxis was initiated by intravenous immunoglobulin (Privigen®) every 3 weeks and injections of trimethoprim-sulfamethoxazole (Bactrim®) three times weekly. The growth curve shows regular growth on average since birth. At the last follow-up (4 years and 6 months), the child weighed 18 kg and measured107 cm (75th percentile).

This association of multiple intestinal atresias and early inflammatory intestinal disease with immunodeficiency led to a molecular investigation of the *TTC7A* gene (sequence number NM_020458.2), which revealed a homozygous mutation: c.1709A>G leading to p.His570Arg.

Patient 1 had a severe form including VEOIBD with multiple and early recurrent stenosis leading to a total enterectomy and a duodenostomy, a severe combined immune deficiency, a hepatic steatosis and fibrosis but with long-term PN.

### 2.2. Patient 2 (P2)

This patient (female) was born by vaginal delivery without complications at a gestational age of 37 weeks. Her parents are not related and their medical history is unremarkable. The obstetrical ultrasound scan had shown ascites, a hyperechogenic bowel and a dilated jejunum, suggestive of jejunal atresia. The infant presented symptoms of bowel occlusion at birth, with bilious vomiting. Surgery revealed a duodenal diaphragm, multiple small-bowel stenoses, meconium peritonitis due to perforation of the first ileal loop, and a Meckel diverticulum. Total intestinal enterolysis was performed with pyloroplasty and jejunostomy of the dilated jejunal loop. Microscopic examination of the jejunum specimen showed lumen stenosis with extensive areas of calcified fibrosis of the wall. The mucosa exhibited total or subtotal villous atrophy, desquamation of the epithelium, crypt rarefaction, loss of nuclear polarity of the enterocytes, and numerous apoptotic bodies inside the superficial epithelium and the crypts. PN was initiated.

On D46 and D86, surgical procedures were performed due to persistent intestinal occlusion. Recurrent stenosis led to resection-plasty and a distal ileostomy was performed leaving 80 cm of small intestine. The resection specimen presented similar microscopic features to those described above. The lymphoid follicles were again small, rare, and devoid of germinal centers.

On D120, in light of chronic intestinal bleeding and diffuse parietal thickening associated with mesenteric fat infiltration, a subtotal enterectomy was performed with a duodenostomy, a colectomy leaving only the sigmoid colon, and a gastrostomy to pass a calibration tube up to the duodenostomy.

Immune function tests performed immediately after the initial diagnosis of multiple atresias (D1) showed lymphopenia (mostly CD4 and CD8) and severe hypogammaglobulinemia (Table 1). On early investigation, TTC7A (sequence number NM_020458.2) was found to carry a composite heterozygous mutation: c.189C>G producing p.Asp63Glu, and c.412C>T producing a stop codon, p.Arg138*. Therapy was initiated with intravenous immunoglobulin substitution (Privigen®) and antibiotic prophylaxis using trimethoprim-sulfamethoxazole (Bactrim®).

As summarized in the Table 1, this patient's progression was favorable; she has remained in excellent general condition with a median growth rate. She suffered just one bout of septicemia and moderate hepatopathy, stable at 1 year of age. The growth curve shows regular growth on average since birth. At the last follow-up (2 years and 7 months), the child weighed 12.5 kg and measured 85.5 cm (50th percentile).

Patient 2 also had VEOIBD with multiple and early recurrent stenosis leading to a total enterectomy and a duodenostomy, severe combined immune deficiency, but without hepatopathy despite long-term PN. The stoma flow of patient 2 is about 2 L per 24 h. She received 1.5 L of total parenteral nutrition (TPN) and drinks around 2 L of water per day. The flow is very stable and does

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