BRIEF REPORT

Apoptotic enteropathy, gluten-intolerance and IBD-like inflammation associated with lipotoxicity in DGAT1-deficiency-related diarrhea. A case report of a 17-year-old patient and literature review.

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Short title: Apoptotic enteropathy in *DGAT1*-related diarrhea.

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Abstract

We present a long-term follow-up in a 17-year-old girl with *DGAT1*-related diarrhea, an autosomal recessive disorder characterized by impaired triglyceride absorption. Neonatal presentation included severe congenital diarrhea, protein-losing enteropathy and failure to thrive requiring total parenteral nutrition. Duodenal biopsies revealed apoptotic enteropathy and acute inflammation with the presence of macrophages and Touton giant cells, related to the intake of fat. She was able to switch to enteral nutrition on a fat-free diet. However, at age 10 she developed gluten-induced enteropathy and then IBD-like inflammation five years later. Immunohistochemistry was able to confirm the diagnosis, while *DGAT1* sequencing remained inconclusive. This highlights the role of histopathology and immunohistochemistry, despite the increasing importance of genetic analysis in the diagnostic work-up. This report also illustrates that parenteral nutrition weaning is possible in *DGAT1*-related diarrhea, but gut barrier dysfunction might increase the risk of autoimmune intestinal disease.

Key words

DGAT-1 mutation, congenital diarrhea, protein losing enteropathy, apoptotic enteropathy, Touton giant cell, autoimmune intestinal disease

Introduction

Congenital diarrheal disorders (CDDs) include defects in digestion and absorption, enterocyte structure, neuroendocrine differentiation and intestinal immune homeostasis [8]. Deficiencies in digestion and absorption of carbohydrates, proteins or fat account for the majority of CDDs [3, 8]. *DGAT1*-related diarrhea, an autosomal recessive disorder first described in 2012, impairs triglyceride absorption [6, 8]. DGATs (acyl CoA:diacylglycerol acyltransferases) convert diacylglycerides to triglycerides by adding an acyl-CoA moiety, a crucial and final step in triacylglycerol synthesis. DGAT1 and DGAT2 accommodate for nearly all triglyceride synthesis [1, 2, 5]. DGATs are integral membrane proteins of the endoplasmic reticulum [1]. DGAT1 is highly expressed in the gut and plays an important role in the absorption of triglycerides in the small intestine [2]. Diarrhea may result from gut barrier dysfunction due to cytotoxicity caused by the dysregulated fatty acid metabolism with accumulation of free fatty acids in the cytoplasm of the enterocytes. DGAT2 is not expressed in the human gut, but is important in the liver where it produces triglycerides from fatty acids synthesized de novo or absorbed from the bloodstream [2]. Disease severity relates to the residual function of DGAT1 [4, 5, 7, 9-11, 13-15]. However, clinical variability within the same family has been reported.

We describe the disease evolution and histopathology of a 17-year-old patient with DGAT1-deficiency and provide an overview of reported histological findings.

Timeline

A 6-week-old girl was referred for severe congenital diarrhea, protein-losing enteropathy and failure to thrive, refractory to semi-elemental and elemental formula diet. Diarrhea subsided when enteral feeding was discontinued. Duodenal biopsies at 3 months and 2 years, and ileum and rectal biopsies at 5 months, while receiving TPN only, showed no significant histopathological changes.

At about 2.5 years, hemophagocytic syndrome was suspected. No bone marrow biopsy was performed. Liver biopsy failed to confirm hemophagocytosis, but showed clusters of macrophages with a vacuolated cytoplasm indicating intracytoplasmic lipid droplets. Some lipid droplets were located extracellularly. Though the significance of this finding was not clear at the time, intravenous lipids were limited. Immunodeficiency could not be confirmed as the cause of her CDD.

As it was noted that accidentally drinking soda and fruit juice did not cause diarrhea, enteral feeding was partially reintroduced at the age of 3. She developed vomiting and watery, non-bloody diarrhea, found to be related to fat intake through the gastrostomy tube and it became clear that she tolerated carbohydrates and proteins, but that her gastrointestinal complaints were related to the intake of both saturated and unsaturated fats. When symptomatic, a duodenal biopsy showed focal villous blunting

with erosions adjacent to a regenerative surface epithelium, and a pseudomembrane with apoptotic cells attached to the surface. The crypts showed also numerous apoptotic cells (Fig. 1A and Fig.1B). There was no increase in intraepithelial lymphocytes and only a mild increase in inflammatory cells in the lamina propria (Fig. 1A). Immunohistochemistry for CMV was negative. PAS diastase staining and CD10 immunohistochemistry revealed a brush border interrupted only at erosions and rare CD10-positive intracytoplasmic dots. EpCAM immunohistochemistry showed preserved epithelial membranous staining.

With fat-free formula, she was weaned from TPN. However, she had developed a marked food aversion, requiring a gastrostomy until age 6. Oral feeding with a strict low-fat diet supplemented with essential fatty acids was introduced slowly.

At age 10, she noticed diarrhea and abdominal pain unrelated to fat intake. Workup revealed markedly elevated anti-tissue transglutaminases (> x10). Bulbar duodenal biopsies showed blunted villi with an increase in intraepithelial lymphocytes. Distal duodenal biopsies were normal. Celiac disease was suspected and on a gluten-free diet her gastro-intestinal complaints decreased.

At age 17, the clinical picture was further complicated by anorexia nervosa. At about the same time, more pronounced abdominal cramps and diarrhea with intermittent bloody stools appeared, likely associated with ingestion of small amounts of fat. Faecal calprotectin was elevated. Gastric biopsies showed focally enhanced gastritis, and duodenal biopsies revealed crypt hyperplasia with partial villus atrophy with few intraepithelial lymphocytes and no apoptosis, but with infiltration of polymorphonuclear cells in the lamina propria, cryptitis and crypt abscesses. The lamina propria additionally showed aggregates of macrophages and multinucleated giant-cells, including Touton giant cells (Fig. 1C). Lower endoscopy showed colitis with ulceration. Ileal biopsies showed limited focal active ileitis and colon biopsies diffuse chronic colitis with crypt distortion, basal plasmacytosis, erosions, cryptitis and crypt abscesses. This combination of findings were suggestive of Crohn's disease, while the clinical picture was more consistent with ulcerative colitis. During treatment, she first developed azathioprine-related toxic hepatitis and then infliximab-induced autoimmune hepatitis-like syndrome. No lipid-laden macrophages were observed in the liver biopsy at that time.

Due to suspicion for *DGAT1*-related diarrhea, exome sequencing with a targeted analysis of a congenital diarrhea panel identified a paternally inherited likely pathogenic variant in *DGAT1* (NM_012079.4: c.629_631del, p(Ser210del), exon 7). This variant has been identified in 17/280928 alleles in GnomAD, is predicted pathogenic by multiple *in silico* prediction programs, and has been previously reported in patients with *DGAT1*-related diarrhea [5, 7, 13]. However, a second variant could not be identified on the other allele, despite complete coverage of all exons and exon-intron

boundaries, exome-depth analysis and copy number variation sequencing. Immunohistochemistry for DGAT1 (monoclonal antibody, clone A-5, sc-271934, Santa Cruz, CA, US, dilution 1/800) however showed total loss of DGAT1 expression in the gut and liver (Fig. 2).

Discussion

We report the clinical course of a girl with DGAT1-deficiency. Molecular analysis could reveal only one pathogenic variant [5, 7, 13]. Since obligate carriers are asymptomatic, a non-coding variant was probably missed. Immunohistochemistry confirmed complete loss of DGAT1-expression in the gut epithelial cells and in hepatocytes, consistent with biallelic *DGAT1* inactivation.

A wide range of histopathological findings has been reported in DGAT1-deficiency-related diarrhea, ranging from normal histology, mainly on a fat-free diet, to acute colitis with presence of macrophage aggregates (Table 1) [4, 5, 9, 10, 13, 14].

When on TPN alone, the biopsies in our patient were within normal limits. Enteral fat was associated with severe damage to the duodenal mucosa with villus blunting and erosions with neutrophilic infiltration into the lamina propria, and pronounced crypt epithelial cell apoptosis. This adds DGAT1-deficiency-related diarrhea to the apoptotic enteropathies [12]. Interruption of CD10 staining in areas of erosion, along with the presence of rare CD10-positive dots in enterocytes, may explain why this condition has been mistaken for microvillus inclusion disease [13]. At the time of symptom flare-up, associated with ingestion of small amounts of fat, duodenal biopsies revealed villus blunting without apoptosis or increase in intraepithelial lymphocytes, and with severe acute inflammation with presence of aggregates of macrophages and multinucleated giant-cells, including Touton giant cells, likely related to the inability to digest fat. We hypothesize that the type and amount of dietary fat may determine the variability of anomalies seen on biopsy. Pronounced apoptosis and mucosal sloughing can occur with high exposure to fat, while limited exposure allows uptake of diacylglycerol and free fatty acids, with subsequent release into the lamina propria from damaged enterocytes and accumulation in foamy macrophages and Touton giant cells. However, nutritional deficiency due to inability to absorb fat or anorexia nervosa, medication, and coincident IBD or celiac disease may have complicated the histopathological picture.

The liver contained aggregates of macrophages with a vacuolated cytoplasm suggesting intracytoplasmic lipid droplets. This may relate to compensatory increased triglyceride syntheses in the liver associated with intravenous administration of fatty acids taken up in the liver. Macrophages containing lipid droplets were not observed in a liver biopsy taken during enteral feeding, supporting this hypothesis.

The development of celiac disease and IBD-like inflammation may link to gut barrier dysfunction. Although yet unconfirmed in other patients described in the literature, with albeit much shorter follow-up, vigilance is warranted for an increased risk of autoimmune bowel disease in DGAT1-deficiency. It cannot be excluded that some patients with atypical presentation of celiac disease or IBD, are patients with DGAT1-deficiency with less severe disturbance of fat metabolism. Genetic testing is cumbersome and not widely available, but this condition can be easily ruled out by DGAT1 immunohistochemistry.

Conclusion

This report of DGAT1 deficiency highlights the role of histopathology and immunohistochemistry, despite the increasing importance of genetic analysis in the diagnostic work-up. Immunohistochemistry was able to confirm the diagnosis of DGAT1-related CDD, while *DGAT1* sequencing remained inconclusive. It demonstrates that it is worthwhile investigating in immunohistochemistry, even for rare diseases. Long-term follow-up in *DGAT1*-related CDD moreover illustrates that parenteral nutrition weaning is possible, but highlights a potential risk of autoimmune induced bowel disease. Early diagnosis is important as it may prevent food aversion later in life.

Compliance with Ethical Standards: This study was approved by the Medical Ethics Committee of Ghent University Hospital; written informed consent was obtained from the patient (EC/022-2020/sds).

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Author contributions: Ellen Deolet analysed and interpreted the biopsies, reviewed the literature and contributed to manuscript drafting. Bert Callewaert supervised and interpreted the molecular analysis and contributed to manuscript drafting. Stephanie Van Biervliet, Saskia Vande Velde and Myriam Van Winckel are involved in follow-up of the patient and contributed to collecting the data and conception of the study. Myriam Van Winckel contributed to manuscript drafting. Jeroen Geldof is involved in follow-up of the patient and contributed to collecting the data and manuscript drafting. Jo Van Dorpe contributed to conception of the study and interpretation of the molecular analysis. Anne Hoorens analysed and interpreted the biopsies, contributed to conception of the study, reviewed the literature and contributed to manuscript drafting. All authors participated in revision of the manuscript for important intellectual content and issued final approval for the version submitted.

Table 1: Gastro-intestinal histopathologic and electron microscopy findings associated with DGAT1 mutation in all until January 31, 2022 reported patients.

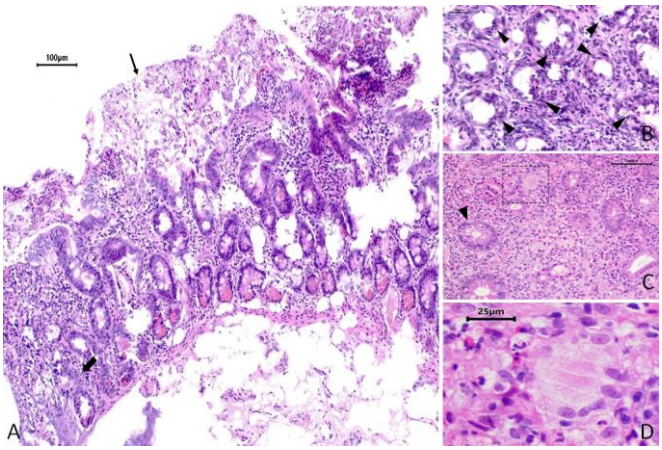
Patient	Diet at biopsy	Endoscopy	Light microscopy	Electron Microscopy	Reference
1	NR	NR	Duodenum: focal villus atrophy, no increased inflammation in lamina propria, no increase in intraepithelial lymphocytes	Duodenum: focal distorted/separated microvilli, slight dilatation ER, increase in lysosomes	[6]
2	Breast milk/soy formula	NR	Duodenum: focal villus atrophy, no increased inflammation in lamina propria, no increase in intraepithelial lymphocytes	Duodenum: focal distorted/separated microvilli, slight dilatation ER, increase in lysosomes	[6]
3	NR	Upper GI: NL	NR	NR	[11]
4	NR	NR	NR	NR	[11]
5	NR	NL	NL	NR	[11]
6	NR	NL	NL	NR	[11]
7	NR	NL	NL	NR	[4]
8	NR	NL	NL	NR	[4]
9	1st biopsy: NR	NL	Esophagus : mild chronic inflammation Stomach: mild chronic inflammation Duodenum: focal foveolar metaplasia Colon: focal acute colitis with cryptitis	NR	[9]
	2nd biopsy: TPN + AA formula	NL	NL	NL	
10	NL diet	NL	Duodenum: villus blunting, patchy foveolar metaplasia Loss of immunostaining for DGAT1 and loss of CD10 at villus tips Redistribution of junctional markers	Clustered microvilli interspersed with areas of NL brush border. Unusual granules with heterogeneous contents below apical membranes	[10]
11	Lactose-free/ AA formula	Upper + lower GI: NL	NL Duodenum, ileum, colon: loss of immunostaining for DGAT1	NL	[13]
12	NL diet	Upper GI: NL	NL Duodenum, ileum, colon: loss of immunostaining for DGAT1	NR	[13]
13	NL diet	Upper + lower GI: NL	Duodenum: marked villus flattening	Lipid accumulation in enterocytes, lack of microvilli	[13]
14	NL diet	Upper + lower GI: NL	NL	NR	[13]
15	AA formula	Upper GI: NL	NL	NR	[13]
16	AA formula	Upper + lower GI: NL	Duodenum: focal vacuolization, partially blunted villi Colon: NL	NR	[13]
17	Fat-free diet	Upper + lower GI: NL	NL	NR	[13]
18	Fat-free diet	Upper + lower GI: NL	NL	NL	[13]
19	TPN	Upper + lower GI: NL	Duodenum: cytosolic CD10 positive globules	Laterally located microvilli	[13]
20	TPN	Upper + lower GI: NL	Idem patient 19	Idem patient 19	[13]
21	NR	NR	NR	NR	[15]
22	NR	NR	NR	NR	[15]
23	Elemental formula	NR	Duodenum: villous atrophy	NL	[5]
24	NR	NR	NR	NR	[5]
25	NR	NR	NR	NR	[5]
26	NL diet	NR	Stomach: eosinophilia and lymphohistiocytic inflammation Colon:: idem	NR	[5]
27	1st biopsy: soy formula	NR	Duodenum: villous blunting and non-specific chronic inactive duodenitis	NR	[7]

	2nd biopsy: TPN	NR	Duodenum: partial villous blunting, crypt hyperplasia, enterocyte vacuolization	NL	
28	AA formula or eH formula	Upper GI: Slightly flat villi in descending duodenum	Antrum: slight inflammation Duodenum (descending part): chronic mucosa inflammation	NR	[14]
29	1st biopsy TPN	NL	NL	Slightly separated microvilli	Present case
	2nd biopsy TPN + NL diet	NL	Duodenum: focal villous blunting, erosions, pseudomembrane, crypt apoptosis	ND	
	3rd biopsy Fat-free diet with TPN supplementation	Villus atrophy	Stomach: NL Duodenum bulbus: villous blunting, increase in intra-epithelial lymphocytes and in inflammatory cells in the lamina propria[a] Distal duodenum: NL	ND	
	4rd biopsy Gluten-free/fat-free diet, no TPN	Upper GI: NL Terminal ileum: NL Colon: colitis, edema, ulceration	Esophagus: NL Stomach: focally enhanced gastritis[b] Duodenum: partial villus atrophy, crypt hyperplasia, few intra-epithelial lymphocytes, cryptitis and crypt abscesses, aggregates of macrophages and multinucleated giant-cells, including Touton-like giant cells in lamina propria Terminal ileum: limited focal active[b] Colon: diffuse active chronic colitis[b]	Separated microvilli, dilatation of endoplasmic reticulum	
	5th biopsy Gluten-free/fat-free diet, no TPN	Lower GI: NL	Colon: NL	ND	

NR = Not reported or not clear from the information provided in the paper
ND = Not done
NL = Normal
AA formula = Amino acid formula
eH formula = Extensively hydrolyzed formula
[a] Clinical findings and biopsy findings compatible with celiac disease
[b] Clinical findings and biopsy findings compatible with ulcerative colitis

Legend to the figures

Fig. 1



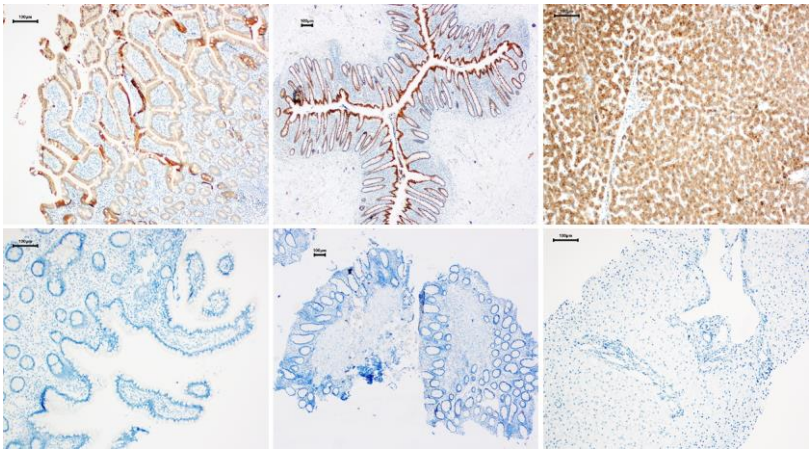
A. Duodenal biopsy demonstrating focal blunting of microvilli with erosions next to a multilayered regenerative surface epithelium. An inflammatory pseudomembrane with numerous apoptotic cells is attached to the surface (fine arrow). There is no increase in intra-epithelial lymphocytes and only a mild increase in inflammatory cells in the lamina propria. Basally in the crypts a prominent increase in apoptotic epithelial cells is observed (thick arrow).

B. Basal crypts with numerous apoptotic cells (arrowheads).

C. Duodenal biopsy with Increase in inflammatory cells in the lamina propria with a prominent component of polymorphonuclear cells and cryptitis (arrowhead). The lamina propria shows aggregates of macrophages and multinucleated giant-cells, including Touton giant cells (rectangle).

D. Higher magnification of a Touton giant cell in E. marked with a rectangle, demonstrating the foamy cytoplasm.

Fig. 2



DGAT1 immunohistochemistry: ileum (left), colon (middle), and liver (right); patient (bottom) compared to control tissue (top); DGAT1 expression is completely lost in the patient

References

1. Cases S, Smith SJ, Zheng YW, Myers HM, Lear SR, Sande E, Novak S, Collins C, Welch CB, Lusis AJ, Erickson SK, Farese RV, Jr. (1998) Identification of a gene encoding an acyl CoA:diacylglycerol acyltransferase, a key enzyme in triacylglycerol synthesis Proceedings of the National Academy of Sciences of the United States of America 95:13018-13023. doi: 10.1073/pnas.95.22.13018
2. Cases S, Stone SJ, Zhou P, Yen E, Tow B, Lardizabal KD, Voelker T, Farese RV, Jr. (2001) Cloning of DGAT2, a second mammalian diacylglycerol acyltransferase, and related family members The Journal of biological chemistry 276:38870-38876. doi: 10.1074/jbc.M106219200
3. Ensari A, Kelsen J, Russo P (2018) Newcomers in paediatric GI pathology: childhood enteropathies including very early onset monogenic IBD Virchows Archiv : an international journal of pathology 472:111-123. doi: 10.1007/s00428-017-2197-9
4. Gluchowski NL, Chitraju C, Picoraro JA, Mejhert N, Pinto S, Xin W, Kamin DS, Winter HS, Chung WK, Walther TC, Farese RV, Jr. (2017) Identification and characterization of a novel DGAT1 missense mutation associated with congenital diarrhea Journal of lipid research 58:1230-1237. doi: 10.1194/jlr.P075119
5. Gupta A, Dsouza NR, Zarate YA, Lombardo R, Hopkin R, Linehan AR, Simpson J, McCarrier J, Agre KE, Gavrilova RH, Stephens MC, Grothe RM, Monaghan KG, Xie Y, Basel D, Urrutia RA, Cole CR, Klee EW, Zimmermann MT (2020) Genetic variants in DGAT1 cause diverse clinical presentations of malnutrition through a specific molecular mechanism European journal of medical genetics 63:103817. doi: 10.1016/j.ejmg.2019.103817
6. Haas JT, Winter HS, Lim E, Kirby A, Blumenstiel B, DeFelice M, Gabriel S, Jalas C, Branski D, Grueter CA, Toporovski MS, Walther TC, Daly MJ, Farese RV, Jr. (2012) DGAT1 mutation is linked to a congenital diarrheal disorder The Journal of clinical investigation 122:4680-4684. doi: 10.1172/jci64873
7. Little R, Gonska T (2020) A110 DGAT1 MUTATION OF LIPID TRAFFICKING ASSOCIATED WITH A RARE CASE OF CONGENITAL DIARRHEA Journal of the Canadian Association of Gastroenterology 3:127-129. doi: 10.1093/jcag/gwz047.109
8. Pezzella V, Grimaldi G, Russo M, Mazza S, Mariniello DF, Paparo L, Elce A, Castaldo G, Canani RB (2017) New insights and perspectives in congenital diarrheal disorders Current Pediatrics Reports 5:156-166
9. Ratchford TL, Kirby AJ, Pinz H, Patel DR (2018) Congenital Diarrhea From DGAT1 Mutation Leading to Electrolyte Derangements, Protein-losing Enteropathy, and Rickets Journal of pediatric gastroenterology and nutrition 66:e82-e83. doi: 10.1097/mpg.0000000000001750
10. Schlegel C, Lapierre LA, Weis VG, Williams JA, Kaji I, Pinzon-Guzman C, Prasad N, Boone B, Jones A, Correa H, Levy SE, Han X, Wang M, Thomsen K, Acra S, Goldenring JR (2018) Reversible deficits in apical transporter trafficking associated with deficiency in diacylglycerol acyltransferase Traffic (Copenhagen, Denmark) 19:879-892. doi: 10.1111/tra.12608
11. Stephen J, Vilboux T, Haberman Y, Pri-Chen H, Pode-Shakked B, Mazaheri S, Marek-Yagel D, Barel O, Di Segni A, Eyal E, Hout-Siloni G, Lahad A, Shalem T, Rechavi G, Malicdan MC, Weiss B, Gahl WA, Anikster Y (2016) Congenital protein losing enteropathy: an inborn error of lipid metabolism due to DGAT1 mutations European journal of human genetics : EJHG 24:1268-1273. doi: 10.1038/ejhg.2016.5
12. Umetsu SE, Brown I, Langner C, Lauwers GY (2018) Autoimmune enteropathies Virchows Archiv : an international journal of pathology 472:55-66. doi: 10.1007/s00428-017-2243-7
13. van Rijn JM, Ardy RC, Kuloğlu Z, Härter B, van Haaften-Visser DY, van der Doef HPJ, van Hoesel M, Kansu A, van Vugt AHM, Thian M, Kokke FTM, Krolo A, Başaran MK, Kaya NG, Aksu A, Dalgıç B, Ozcay F, Baris Z, Kain R, Stigter ECA, Lichtenbelt KD, Massink MPG, Duran KJ, Verheij J, Lugtenberg D, Nikkels PGJ, Brouwer HGF, Verkade HJ, Scheenstra R, Spee B, Nieuwenhuis EES, Coffer PJ, Janecke AR, van Haaften G, Houwen RHJ, Müller T, Middendorp S, Boztug K (2018)

Intestinal Failure and Aberrant Lipid Metabolism in Patients With DGAT1 Deficiency Gastroenterology 155:130-143.e115. doi: 10.1053/j.gastro.2018.03.040
14. Xu L, Gu W, Luo Y, Lou J, Chen J (2020) DGAT1 mutations leading to delayed chronic diarrhoea: a case report BMC medical genetics 21:239. doi: 10.1186/s12881-020-01164-1
15. Ye Z, Huang Y, Wang Y, Lu J, Wu J, Yu Z (2019) Phenotype and Genotype of a Cohort of Chinese Children with Early-Onset Protein-Losing Enteropathy The Journal of pediatrics 208:38-42.e33. doi: 10.1016/j.jpeds.2018.12.003