Congenital diarrhea type 7 related to a novel mutation in the *DGAT1* gene: first report from India and review of published cases

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ABSTRACT

We report the first familial case of *DGAT1* gene related congenital diarrhea type 7 protein losing enteropathy (MIM615863), an autosomal recessive genetic disease from India. A couple had lost their previous child in the neonatal period. Next generation sequencing analysis for around 6500 clinically relevant genes was undertaken, which identified the couple to be carriers for a novel pathogenic mutation at the donor splice site junction of exon 6-intron 6 in the *DGAT1* gene (GRCh37: chr8: 145542123:C>T or NM_012079:exon6:c.574+1G>A). The couple chose prenatal diagnosis by fetal DNA mutation analysis for the *DGAT1* gene variant c.574+1G>A in their subsequent pregnancy, which showed the absence of this mutation in homozygous state. A healthy baby was delivered who is asymptomatic for diarrhea till four years of age.

KEYWORDS: *DGAT1* gene, novel, congenital diarrhea, genetic, autosomal recessive

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INTRODUCTION

Congenital diarrheas are a group of genetically heterogeneous enteropathies which present with vomiting, diarrhea, protein loss in the early infancy. The genetic etiologies vary from the impairment of intestinal enzymes, ion or nutrient transport channels, exocrine pancreatic insufficiency to lipid transport defect (Terrin G et al, 2012; Haas et al, 2012). Mutations in the following genes, *ADA, ADAM17, AICDA, AIRE, ANGPTL3, AP1S1,AP3B1, AP3D1, APOB, ARX, BCL10, BLOC1S3, BLOC1S6, BMPR1A, BTK, CARD11, CCBE1, CD3G, CD40LG, CD55, CFTR, CTLA4, CTRC, CYBA, CYBB, CYP27A1, DCLRE1C, DGAT1, DKC1, DOCK8, DTNBP1, DUOX2, EGFR, ELANE, EPCAM, FLNA, FOXP3, G6PC3, GUCY2C, HPS1, HPS3, HPS4, HPS5, HPS6, ICOS, IKBKG, IL10, IL10RA, IL10RB, IL21, IL2RA, IL2RG, ITGB2, KMT2D, LCT, LIG4, LIPA, LRBA, MALT1, MEFV, MGAM, MTTP, MVK, MYO5B, NCF2, NEUROG3, NFAT5, NFKB2, NLRC4, NOD2, PCSK1, PIK3CD, PLCG2, PLVAP, PNLIP, RAG1, RAG2, RFX6, RTEL1, SAMD9, SAR1B, SBDS, SI, SKIV2L, SLC10A2, SLC26A3, SLC2A2, SLC37A4, SLC39A4, SLC5A1, SLC7A7, SLC9A3, SLC9C1, SPINK1, STAT1, STAT3, SPINT2, STX3, STXBP2, TMPRSS15, TNFAIP3, TTC37, TTC7A, UBR1, WAS, WNT2B, XIAP, ZAP70, ZFP57*

(https://www.preventiongenetics.com/testInfo?sel=test&val=Congenital+Diarrhea+and+Enteropathies+Panel) account for the known congenital diarrheas. The mechanisms of diarrhea may vary from secretory, osmotic and inflammatory in nature. Secretory diarrhea as in microvillus inclusion disease due to mutations in the *MYO5B* gene is caused by increased secretion or impaired absorption of electrolytes and water by the enterocytes. Osmotic diarrhea is caused by the presence of non-assimilated nutrients in the gut driving water into the lumen as in sucrose-isomaltase deficiency (SI gene defect), unabsorbed disaccharide reaches colon causing diarrhea. Inflammatory diarrhea is caused by the damage or injury to the enterocytes as in immune dysregulation polyendocrinopathy enteropathy (*FOXP3* gene). Congenital diarrhea type 7, which is the subject of discussion, is caused by lipid transport defect in the enterocytes wherein an inflammatory diarrhea mechanism due to lipid toxicity is proposed. It is caused by biallelic mutations in the *DGAT1* gene on chromosome 8q24.1. *DGAT1* gene encodes Acyl-CoA:diacylglycerol acyltransferase, a microsomal enzyme that plays a central role in the metabolism of cellular diacylglycerol lipids and catalyzes the terminal and only committed step in triacylglycerol synthesis by using diacylglycerol (DAG) and fatty acyl CoA as substrates. DGAT had been considered necessary for adipose tissue formation and essential for survival (Gluchowski et al, 2017; van Rijn et al, 2018; Gupta et al, 2019). We report the first familial case of *DGAT1* gene-related congenital diarrhea type 7, protein-losing enteropathy (MIM615863) an autosomal recessive genetic disease from India.

Clinical Report

A third-degree consanguineous couple came for pre-conception genetic counseling. Their first baby was admitted at 40 days of life with severe failure to thrive, vomiting, watery diarrhea and dehydration. The baby's heart rate on admission was 130/min, respiratory rate was 46/min, and pulse oximetry showed spO_2 reading of 97%. The baby was hyponatremic (106 eq/L), and hypokalemic (2.9 meq/L) and total leukocyte count was 17000/cmm. The baby was treated with intravenous fluids, antibiotics, dopamine, but diarrhea worsened and the baby succumbed after two days of circulatory collapse. No sample from the baby was available for DNA testing. After counseling, next-generation sequencing analysis for around 6500 clinically relevant genes was done for mother. The Exome (6500 genes) was captured using custom-designed (Agilent Sureselect) target specific probes and these targeted regions were sequenced using Illumina sequencing system at a mean coverage of more than 80-100X and read quality of more than Q20. The target region includes the exon and 10bp of flanking intronic

sequences. We followed the GATK best practices framework for the identification of variants in the sample using Sentieon (v201808.01). The sequences obtained were aligned to the human reference genome (GRCh37/hg19) using Sentieon aligner and analyzed using Sentieon for removing duplicates, recalibration and re-alignment of indels (Freed et al, 2017; Li et al, 2010). Sentieon haplotypecaller has been used to identify variants relevant to the clinical indication. Gene annotation of the variants was performed using VEP program against the Ensemble release 91 human gene model (McLaren et al, 2010; Zerbino et al, 2018). In addition to single nucleotide variants SNVs and small Indels, copy number variants (CNVs) were detected from targeted sequence data using the ExomeDepth (v1.1.10) method. This algorithm detects rare CNVs based on the comparison of read-depths of the test data with the matched aggregate reference dataset. (Plagnol et al, 2012). Bioinformatic analysis from the VCF file and interpretation of sequence variants was done. The bioinformatics pipeline used for analysing/annotation of VCF files were Annovar based (http://wannovar.wglab.org/). Variants were considered pathogenic if they were previously reported in OMIM indexed disorders or if they are pathogenic as per ACMG criteria (https://www.medschool.umaryland.edu/Genetic_Variant_Interpretation_Tool1.html/). Variants were also considered pathogenic if previously reported in ClinVar database and thought to have important clinical implications. Low somatic mosaic novel variants for dominant diseases with variable penetrance were not considered significant. Low quality and low coverage data were filtered out. Also, the type of mutation identified should have a known biological mechanism linked to the disease as per scientific publications or guidelines. Also, the variant should not have been reported in homozygous state in ExAC databases. In silico analysis for novel variants was done using software Sorting Tolerant from Intolerant (SIFT) (http://provean.jcvi.org/index.php), Polyphen2 (http://genetics.bwh.harvard.edu/pph2/), MutationTaster (http://www.mutationtaster.org/). The annotated vcf file was screened for variants in genes mentioned in the 46 gene congenital diarrhea gene panel (except *MGAM*, *SLC9C1*, *WNT2B* which were absent in the panel). The vcf file contained 172846 variants. After filtering for variants with a frequency more than 0.01 in ExAC, gnomAD, 1000Genomes, benign variants in Clinvar database, 29235 variants were remaining. Of these, 1016 variants were in the exonic regions or at splicing sites. There were 10 splice site variants, of which 2 had less than 5X depth. The remaining 8 variants were in the following genes: *ATP11C*, *CACNA2D1*, *DGAT1*, *DNAH7*, *PRUNE2*, *RNF207*, *TMEM2*. Of these, the most important gene was *DGAT1* gene known to be associated with congenital diarrhea type 7. The mother was thus identified to be a carrier for a novel pathogenic mutation at the donor splice site junction of exon 6-intron 6 in the *DGAT1* gene (GRCh37: chr8: 145542123:C>T or NM_012079:exon6:c.574+1G>A, depth 52x wild type allele depth 31x, mutant allele depth 21x). The mutation has not been described in the following databases Gnomad, 1000Genomes, ExAC database, Human Gene Mutation Database, UK (public version). This mutation was likely pathogenic as per the American College of Medical Genetics guidelines [criteria: PVS1 (null variant) + PM2 (absent from controls or at extremely low frequency if recessive in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium), PP3 (multiple lines of computational evidence support a deleterious effect on the gene or gene product conservation, evolutionary, splicing impact, etc.)] , The mutation was confirmed to be heterozygous in her and her husband by Sanger sequencing (see figure 1). The couple chose prenatal diagnosis by fetal DNA mutation analysis for the *DGAT1* gene mutation c.574+1G>A in their subsequent pregnancy, which showed the absence of this mutation in the homozygous state, followed by the delivery of a healthy baby who is asymptomatic for severe intractable diarrhea till 4 years of age.

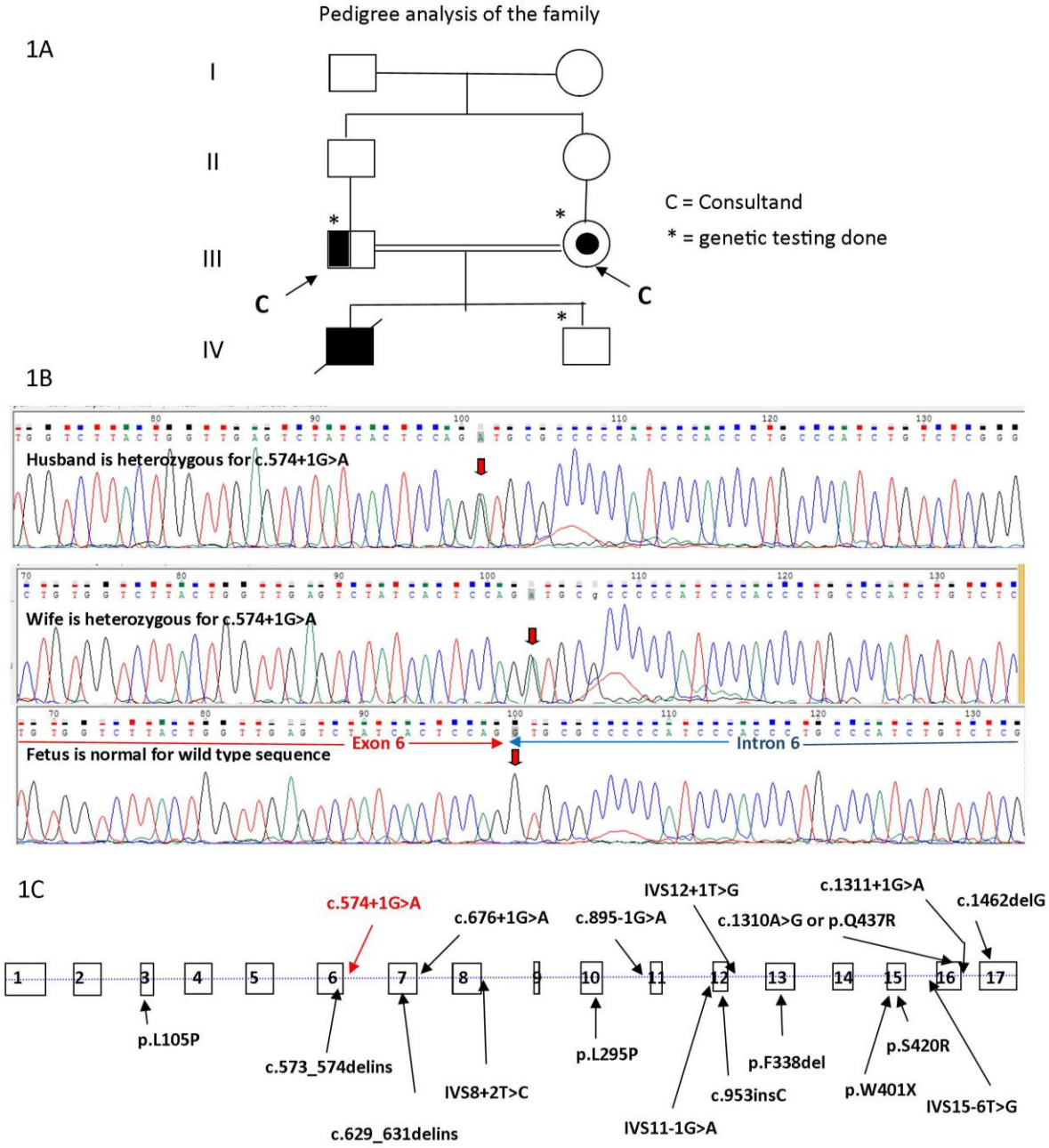

Figure 1a: Pedigree analysis of the family. 1b: Sequence chromatograms of the husband and wife showing heterozygosity for the c.574+1G>A splice site mutation and the fetus showing absence of the mutation (presence of wild type), 1c: Schematic representation of distribution of the published/known mutations in the *DGAT1* gene, the mutation highlighted in red is the mutation identified in this study.

Table 1: Summary of cases of *DGAT1* gene related protein losing enteropathy published in medical literature and details of our case

Paper/	Race	AaO	SID	Vx	Additional Features	Stool aAT	Bx	Mut.	Rx	Outcome
Haas *et al*, 2012/ Sib 1	Ash. Jews	Day3	Yes	Yes	FTT, e.TG, low Na, e.chol, low Ig, low.alb, rec. sepsis	Elev	DM	c.751+2T>C (intron 8)	AAF, MCT	Died 17m
Haas *et al*, 2012/ Sib2		Day3	Yes	Nil	FTT, low Ig, low Na	Elev	DM	c.751+2T>C (Intron 8)	AAF, MCT, CTM	Alive and well 46m
Joshi *et al*, 2016/ Family 1 Sib 1	AM	2 months	Yes	Nil	FTT, Clubbing, low.alb, low Na, e.TG, Low IgG, IgM, IgA, Low Hb, Low Fe	Elev	NA	c.T884C or p.L295P (exon 10)	IvIG, AAF, Iv.alb	Alive and well at 11m
Joshi *et al*, 2016/ Family 1 Sib 2		4 months	Yes	Nil	FTT, Edema, low.alb, Skin abscesses	NA	NA		NA	Died 16m
Joshi *et al*, 2016/ Family 2 Sib 1	Ash Jews	Day 8	Yes	Nil	FTT, Low.alb, normal lipid profile	Elev	NA	c.751+2T>C (intron 8)	TPN, AAF	Alive at 4.5 yrs
Joshi *et al*, 2016/ Family 2		Day 17	Yes	Nil	FTT, Meckel diverticulitis, crossed fused renal ectopia, e.TG, elevated VLDL	Elev	NA		TPN, AAF	Alive

Sib 2										
Gluchowski *et al*, 2017 Twin 1	SA	Sab	Yes	Yes	FTT, Low fe, zinc, copper, low.alb e.TG	Elev	NA	c.C314T or p.L105P	BT, TPN, IvIG, FRD	Alive at 31m
Gluchowski *et al*, 2017 Twin 2		Sab	Yes	Yes	FTT	Elev	Na		TPN, AAF, FRD	
Schlegel *et al*, 2018	His	Day 49	Yes	Yes	FTT, Low Na, potassium, phosphorus	Elev	DM, GM, AET	c.751+2T>C (intron 8)	TPN, AAF, FRD	Alive at 2 years
Ratchford *et al*, 2018	Cauca sian	Day30	Yes	Yes	FTT, Pneumatosis intestinalis, ELA, met.acid, low phosphorus, osteopenia, rib fractures, rickets, low fat soluble vitamins, e.TG	Elev	Norm al	c.1013_1015del TCT or p.F338del in exon 13/ c.C1260G or p.S420R in exon 15	FRD, Ivlg	Alive at 17m
Van Rijn *et al*, 2018 Patient 1	Turk	Sab	Yes	Yes	Recurrent infections, otitis media, low Na and potassium, bulky greasy stools with positive Sudan black staining at six months age, low.alb, low HDL, low fat soluble vitamins, low Ig	NA	Norm al	c.G1202A or p.W401X in exon 15	Lactose free formula, AAF, casein hydrolysate, Iv.Alb, Basic-F, MCT	Alive at 4.5 yrs
Van Rijn *et al*, 2018 Patient 2 (Sib of patient		Sab	Yes	Yes	Recurrent infections, low HDL, low Ig	NA	NA		IvAlb	Died at 6m

1)										
Van Rijn *et al*, 2018 Patient 3	Turk	Day21	Yes	Yes	At 11 months, kidney stones, corneal cystine crystals, hypocalcemia, secondary hyperparathyroidism seen, e.TG, low HDL	Normal	DVA, LD	c.573_574delAGinsCCCATCCCACCCTGCCCATCT in exon 6	TPN till 13 mths, Iv.alb, MCT	Alive at 2yrs
Van Rijn *et al*, 2018 Patient 4	Turk	2m	Yes	Yes	Low alb, e.chol, low Ig	NA	Normal	c.937-1G>A	CTM	Alive at 8 yrs
Van Rijn *et al*, 2018 Patient 5	Turk	Day40	Yes	Yes	Dysentery, low alb, low Ig, At one year had hepatomegaly and jaundice, elevated SGPT, SGOT and GGT, direct hyperbilirubinemia. Liver biopsy showed hepato-canalicular and ductular cholestasis, hepatic steatosis, bile duct paucity, portal fibrosis of 3/6,	NA	Nonspecific results at 5m	c.953insC in exon 12 or p.I319Hfs*31	Creon pancreatic enyxyme and, Hydrolysed formula	Alive at 2yrs
Van Rijn *et al*, 2018 Patient 6 (sib of pt5)		2.5m	Yes	Yes	Recurrent infection, elevated VLDL, low HDL	NA	FV, DVA		Creon pancreatic enyxyme and, Hydrolysed formula	Alive at 6yrs
Van Rijn *et al*, 2018 Patient 7	Dutch	1m	No	Yes	Gilles de la Tourette syndrome, low HDL	NA	Normal	c.629_631delCCT in exon 7 or	Intralipid, Omegaven, FRD	Alive at 14yrs

Van Rijn *et al*, 2018 Patient 8 (Sib of pt7)		1m	No	Yes	Gilles de la Tourette syndrome, low HDL	NA	Normal	p.S210_Y211delinsY		Alive at 17yrs
Van Rijn *et al*, 2018 Patient 9	Dutch	Sab	Yes	Yes	Recurrent infections, low HDL, low alb, low Ig	Elev	MVID	c.629_631delCCT in exon 7 or p.S210_Y211delinsY	TPN, small bowel transplant	Alive at 10 yrs, tolerates enteral feeding, stunted
Van Rijn *et al*, 2018 Patient 10 (twin of pt9)		Sab	Yes	yes	Recurrent infections, low alb, low Ig	Elev			TPN, FRD	Alive at 10 yrs, tolerates enteral feeding, stunted
Gupta *et al*, 2019 Patient 1	Mennonite	Day14	Yes	Yes	FTT, Hypotonia, respiratory failure, 2 vessel cord, prolonged prothombin time, ELA, met.acid, low.alb	NA	DVA	c.629_631delCCT or p.S210_Y211delinsY in exon 7	Low fat elemental formula (100 percent free amino acid with 2 percent fat)	Alive at 15m
Gupta *et al*, 2019 Patient 2	NA	Day21	No	Yes	IUGR, FTT, Microarray normal, Russell Silver workup normal, low serum magnesium	NA	NA	c.1310A > G or p.Q437R in exon 16 / c.981+1T>G in intron 12	TPN, vitamin D skin patches	Alive at 27m
Gupta *et al*, 2019	Mexican	Day 11	Yes	Yes	FTT, Rectal bleeding, vitamin D deficiency, delayed bone	NA	NA	c.676+1G>A in intron 7	TPN, Neocate,	Alive at 2yr, given

Patient 3					maturation, osteopenia, fractures, low serum calcium, phosphorus				Elacare, Vivonex	speech therapy
Gupta *et al*, 2019 Patient 4	NA	Day7	No	Yes	FTT, facial features of DiGeorge syndrome prominent nasal bridge, short palpebral fissures, protuberant ears with simplified helices, long tapered fingers, microcephaly at 3m age, low Ig	Elev	St, RScEso	c.1311+1G>A or IVS16+1G>A in intron 16 /c.1462delG or p.A448Pfs*26 in exon 17	TPN first 6 months, latern Enfaport diet, IvIg	Alive at 12m
Ye *et al*, 2019 Case 24	Chinese	Sab	Yes	Yes	FTT, ASD, Ct scan- SII, low.alb,	NA	IL	c.895-1G>A	TPN, Iv.alb, IvIg	Died
Ye *et al*, 2019 Case 27		30m	No	No	FTT, Low.alb	NA	NA	c.1249-6T >G	TPN, Iv.alb, peptjunior	Died
Our study	MH	Day 40	Yes	Yes	Leucocytosis, Low Na,	NA	NA	Parents are heterozygous for c.574+1G>A or IVS6+1G>A in intron 6	Intravenous fluids, antibiotics, inotropic support	Died at 42days

Abbreviations: Ash. Jews: Ashkenazi Jews, AM: Arab Muslim, SA: South Asian, His: Hispanic, MH: Maharashtrian Indian, AaO: age at onset, Sab: soon after birth, SID: presentation as severe, intractable diarrhea, Vx: vomiting, FTT: failure to thrive, e.TG: elevated triglycerides, e.chol: elevated cholesterol, LowIg: low serum immunoglobulin G, low.alb: Low serum albumin, rec.sepsis: recurrent sepsis, VLDLL very low density lipoprotein, NA: not available, low Na: low serum sodium, Low Fe: low serum iron, ASD: atrial septal defect, SII: small intestine intensified, met.acid: metabolic acidosis, ELA: elevated liver transaminases, IUGR: intrauterine growth retardation, aAT: alpha antitrypsin, elev:elevated, Bx: biopsy: dystrophic microvilli in duodenum, GM: gastric metaplasia, AET: apical enterocyte transport defect reversed by fat restricted diet, IL: intestinal lymphangiectasia, DVA: duodenal villous atrophy, St RScEso: Eosinophilia of the stomach and rectosigmoid colon with lymphohistiocytic inflammatory component giving a diagnosis of food protein induced enterocolitis syndrome, LD: lipid droplets in apical enterocytes, FV: focal vacuolation, MVID: Misdiagnosis of microvillus inclusion disease on CD10 positive globules and laterally located microvilli on Electron microscope, Mut:mutation, Rx:Treatment, AAF: enteral amino acid formula, MCT: medium chain triglycerides, CTM: cholestyramine, IvIG: intravenous immunoglobulin, TPN: total parenteral nutrition, Iv.alb:intravenous albumin, FRD: fat restricted oral diet such as chicken soup, rice water, m:months, d: days.

DISCUSSION

The *DGAT1* gene, present on locus 8q24.3, encodes a multipass transmembrane protein that functions as a diacyl CoA: diacylglycerol acyl transferase, which converts diacylglycerides to triglycerides. Patients with bi-allelic *DGAT1* gene mutations present with chronic diarrhea, vomiting sometimes soon after birth to early months of life leading to protein-losing enteropathy and failure to thrive (Table 1). Till date, about 26 patients (18 families) have been reported with the disorder in the medical literature (Gupta et al, 2019). They have been reported in Ashkenazi Jews, Turkish, Dutch, Hispanic, South Asian and Caucasian ethnicities (Gluchowski et al, 2017; van Rijn et al, 2018; Gupta et al, 2019). Biochemical abnormalities of this protein-losing enteropathy include dehydration, low serum sodium, potassium, calcium, phosphorus, iron, zinc and copper; metabolic acidosis, low serum albumin, fibrinogen and immunoglobulins, elevated serum transaminases, triglycerides and VLDL, low HDL. Stool frequently contains fat globules and elevated stool alpha-1-antitrypsin (normally less than 3 mg/gm of stool). Biopsies may show gastric eosinophilia, gastric metaplasia, abnormal duodenal microvilli and mild focal changes of chronic inflammation in esophagus, stomach and colon. There is no lymphangiectasia (which is present in other PLE) and neuroendocrine cells are normally present (Ratchford et al, 2018, Gupta et al, 2019). In one patient, abnormal brain morphology was seen on magnetic resonance imaging (Gupta et al, 2019).

Regarding the mutations known in the *DGAT1* gene-related published cases, the details of each case have been highlighted here in this study. Briefly, there are 17 unique mutations; the first described mutation was reported in Ashkenazi Jews, c.751+2T>C (IVS8+2T>C) at the intron 8 donor splice site (founder mutation) in three unrelated families (Haas et al., 2012; Joshi et al., 2016). The c.629_631delins is also found in three unrelated families, two Caucasian families from the Netherlands and one Mennonite family (van Rijn et al., 2018; Gupta et al., 2019). Rest of the mutations are documented in one family each. There are four missense mutations namely c.314C>T (p.L105P), c.884T>C (p.L295P), c.1260C>G (p.S420R) and c.1310A>G (p.Q437R). The in-silico analysis of these mutations was performed by HOPE software (https://www3.cmbi.umcn.nl/hope/input). The L105P and L295P substitutions: The wild-type residue L105 and L295 are located in the α-helical regions. Proline disrupts α-helix when not located at one of the first 3' positions of that helix. The S420R substitution: serine is smaller than arginine; serine is neutral while arginine is positively charged. S420 forms a hydrogen bond with E416 which is likely disturbed by the mutation. The Q437R substitution: arginine is bigger than glutamine, arginine is positively charged while glutamine is neutral in nature, Q437 forms a hydrogen bond with W374, which is likely disturbed by the mutation and Q437 residue is 100% conserved. There are four mutations affecting the splice junctions, namely c.676+1G>A (IVS7+1G>A), c.751+2T>C (IVS8+2T>C), c.895-1G>A (IVS10-1G>A), c.937-1G>A (IVS11-1G>A), c.981+1T>G (IVS12+1T>G), c.1249-6T>G (IVS15-6T>G), c.1311+1G>A (IVS16+1G>A). There are three indels namely c.1013_1015delTCT (p.F338del), c.629_631delCCT (p.S210_Y211delinsY) and c.573_574delAGins CCCATCCCACCCTGCCCATC (p,V192Pins193_198SHPAHL). There are three truncating variants, namely c.953insC (p.I319Hfs*31), c.G1202A (p.W401X), c.1462delG (p.A448Pfs*26) (van Rijn et al, 2019)

Functional analyses of the *DGAT1* gene mutations have previously shown that they affect lipid droplet formation in cells thereby affecting its transport (van Rijn et al, 2018). Accumulation of lipid intermediates can be postulated to have a toxic effect on the enterocytes (Joshi et al, 2016). This hypothesis has been reinforced by the study showing that Dgat1-/- knockout mice have abnormal lipid droplet accumulation in enterocytes, in part due to interference with lysosomal acidification (Hung et al, 2019). Previous

reports have also shown that exclusive breastfeeding or soy-based formulas are not tolerated (Joshi et al, 206; Gluchowski et al, 2017; Gupta et al, 2019). A combination of the formula containing low fat or fat-free enteral diet (FFF), such as Basic- F, Nutricia, Portugal (content per 100 gm: protein 14 gm, lipids less than 0.5, carbohydrates 79 gm, fiber 0 gm, kcal 374) formulae with hydrolysed proteins with medium-chain triglycerides (MCT) shows the immediate and long-lasting response in terms of resolution of diarrhea, hypoalbuminemia, intestinal pathology and normalization in the rate of growth (van Rijn et al, 2018). In one study, a hospital designed diet of chicken soup formula, rice water and oral rehydration solution was shown to stop diarrhea and improve serum albumin (Joshi et al, 2016). Dairy products are to be avoided. Total fat content in oral intake is restricted, with ranges of 2 to 10 percent of total calorie intake and in small amounts throughout the day rather than large boluses (Joshi et al, 206; Gluchowski et al, 2017; Gupta et al, 2019). Omega-3 fatty acids have been used to treat elevated triglycerides. Fat soluble vitamins A, D, E, and K are to be given in the maintenance doses. Total parenteral nutrition (TPN), intravenous albumin, or amino acid mix, lipids, immunoglobulin and antibiotics have temporary benefit, but may be needed as per the symptoms. Cholestyramine has also been used in cases of cholestasis documented by jaundice or elevated liver transaminases. As the child grows up, low-fat-age-appropriate solid food diet, with FFF and MCT supplementation is required. The mortality and morbidity is highest in infancy, but several patients have survived beyond to live till 17 years of age. One patient also received intestine transplant (van Rijn et al,2018). The long-term effect includes stunted growth, but a proper diet can avoid this. The complications of treatment included recurrent sepsis through the TPN central catheter (Haas et al, 2012; Joshi et al, 2016; Gupta et al, 2019).

This report also shows the efficacy of exome sequencing in screening consanguineous couples for pathogenic mutations even in case of lack of DNA diagnosis in previous affected children. Since the disease had high mortality and morbidity, prenatal diagnosis was opted by the family in our study. Of the 27 cases that have so far been reported (inclusive of our patient), six (22.22 %) children have died and 21 (77.78 %) are living. However, improved understanding shows that early diagnosis and dietary interventions can reduce mortality and morbidity.

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Conflict of interest statement

The authors have declared to have no conflict of interest.

Authors' contributions

PMT, VPT, MK performed clinical evaluation of patient, PMT, VPT, SM, DM, LV performed genetic testing, PMT, VPT wrote the first draft, all authors contributed to final draft and approval of the manuscript.

Declaration of originality

The authors declare that they have not copied text, figures or data from a particular source without appropriate permissions or citation.

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