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Homozygosity for a partial deletion of apoprotein A-V signal peptide results in intracellular missorting of the protein and chylomicronemia in a breast-fed infant

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ABSTRACT

Deficiency of apoprotein A-V (apoA-V) can cause hypertriglyceridemia. In an 11 months old boy presenting with a severe hypertriglyceridemia, a formerly unknown 24 nucleotide deletion in exon 2 of the *APOA5* gene was detected. The homozygous mutation results in an eight amino acid loss in the signal peptide sequence (c.16_39del; p.Ala6_Ala13del). Screening of control persons proved that this deletion is a rare mutation. Hypertriglyceridemia in the patient was only found at the time when he was breast fed, while after weaning, triglyceride levels were close to normal. Under both dietary conditions, apoA-V protein was undetectable in plasma while post-heparin plasma lipoprotein lipase activity was normal.

Expression analysis of normal and mutated protein by Western blot and immunofluorescence in apoA-V deficient primary hepatocytes revealed that, due to changes in the signal peptide, mutated apoA-V was intracellularly missorted to lipid droplets and not secreted. Wild type apoA-V, instead, was not targeted to lipid droplets but transported via endosomal compartments to the plasma membrane for secretion.

It is concluded that the c.16_39del mutation in the *APOA5* gene leads to hepatic missorting and impaired secretion, which consequently results in undetectable apoA-V plasma levels. The absence of apoA-V in plasma leads under conditions of fat-rich diets to severe chylomicronemia, suggestive for a modulatory role of apoA-V for lipoprotein lipase mediated intravascular triglyceride lipolysis.

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1. Introduction

Type 1 chylomicronemia is characterized by fasting plasma triglyceride (TG) concentrations above 850 mg/dl (10 mmol/l). The onset of this disorder is usually during childhood; the most common clinical presentation is recurrent acute pancreatitis. Typically, this condition is caused by mutations in the lipoprotein lipase gene (*LPL*) resulting in a deficient hydrolysis of TG from chylomicrons and VLDL. Less commonly, variants in the genes of apoprotein C-II (*APOC2*, an essential LPL cofactor), apoprotein A-V (*APOA5*, functions see below), GPI-anchored HDL-binding protein 1 (*GPIHBP1*, binding and transporting LPL to the endothelial surface) or the lipase maturation factor 1 (*LMF1*, a factor involved in maturation and translocation of lipases as LPL) can cause this phenotype. A recent study revealed the majority of severe hypertriglyceridemia type 1 cases being contributed to LPL defects (51%), about one third being without detectable rare variants or with common variants, and only about one sixth being caused by mutations in *APOC2*, *APOA5* or *GP1HBP1*. In type 5 hypertriglyceridemia, in most cases common (77%) or no genetic variants were found [1].

Identified in 2001, apoA-V is one of the key players in plasma TG metabolism. Since its discovery, different hypotheses explaining

Abbreviations: ApoA-V, apolipoprotein A-V; *APOA5*, human apoA-V gene; ΔSP-A5, c.16_39del_apoA-V; apoC-II, apolipoprotein C-II; *APOC2*, human apoC-II gene; LPL, lipoprotein lipase; TG, triglycerides; GPIHBP1, GPI-anchored HDL-binding protein 1; SNPs, single nucleotide polymorphisms; WT, wild type.

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the mode of action have been proposed: First, it can activate endothelial bound LPL and thereby decreases plasma TG concentration [2,3]. Interactions with GPIHBP1 may be involved in this process [4]. Second, apoA-V may act as a ligand to hepatocellular receptors or proteoglycans [5,6]. Third, based on its structure, a role of apoA-V in hepatocellular lipid secretion has been discussed [7]. Recent data suggested in addition, that apoA-V may guide TG towards lipid droplet formation thereby decreasing hepatic VLDL production [8].

With more than 40 single nucleotide polymorphisms (SNPs) and other variations being reported, the human *APOA5* gene is relatively polymorphic. However, for most sequence aberrations, there are no robust data regarding their functional relevance. Three widespread haplotypes have been described to result in significant differences in human plasma TG levels, with *APOA5*1* (most common variants at all positions); *APOA5*2* (rare alleles: −1131T>C, c.−3A>G, IVS3+476G>T, c.1259T>C) and *APOA5*3* (S19W; c.56C>G; signal peptide variant) [9]. In genome wide association studies (GWAS), *APOA5* was found repeatedly to be one of the most significant gene loci influencing TG levels [10]. Beyond TG levels, *APOA5* SNPs were associated with cardiovascular disease, metabolic syndrome as well as the response to a weight loosing diet and lipid medication [5,11].

To date, only few alterations in the *APOA5* gene have been found that cause type 1 or type 5 hypertriglyceridemia (Fig. 1). Three nonsense mutations, p.Gln97X (c.289C>T) [12], p.Gln139X (c.415C>T) [13], and p.Gln148X (c.442C>T) [14] result in a protein truncation, and another three, c.49+1G>A [15], c.161+3G>C [16], and c.161+5G>C [17] cause aberrant splicing. Moreover, sequencing of the *APOA5* gene in severely hypertriglyceridemic patients has revealed additional, so far unclassified missense variants, p.Glu255Gly (c.764A>G), p.Gly271Cys (c.821G>T), p.His321Leu (c.962A>T) [18], p.Gly185Cys (c.553G>T) [19] and p.Thr133Arg (c.398C>G) [1]. However, additional genetic or environmental conditions are usually necessary to express the full hypertriglyceridemic phenotype [20].

Here, we report a deletion of eight amino acids in the apoA-V signal peptide which results in an intracellular protein missorting and a hepatic apoA-V secretion defect. Clinically, the mutation caused severe hypertriglyceridemia in an 11 months old boy at a time when he was exclusively breast-fed. Remarkably, after weaning on a normal diet the boy had almost normal plasma TG concentrations.

2. Case report

A Turkish boy 11 months of age presented in an outlying children's hospital with intermittent abdominal pain. He was fully breast fed without any restriction regarding frequency and time of meals. Episodes of abdominal discomfort were not related to the feeding status, they were explained by a mild pancreatitis with repeatedly elevated plasma lipase activity up to 231 U/l (normal <60 U/l) in the past. During blood drawing, a lipemic serum was found. No medication had been taken recently.

Table 1
Plasma lipid and apoA-V concentrations in the patient, in his parents, an apoC-II deficient subject and in age-matched healthy controls.

	Triglycerides [mg/dl]	Cholesterol [mg/dl]	HDL cholesterol [mg/dl]	apoA-V [ng/ml]
Patient, breast-fed	2230	223	26	n.d.
Patient, after weaning	201	118	29	n.d.
Father	325	178	39	397
Mother	103	195	62	300
ApoC-II deficient control	2252	219	32	2534
Healthy controls[a]	151 ± 100	169 ± 50	38 ± 20	1113 ± 537

n.d., not detectable.
[a] Means of 10 healthy children between 0 and 3 years.

2.1. Past medical history

The pregnancy was uncomplicated. The boy was born at term by Caesarean section, with a normal length and weight of 52 cm and 3.4 kg, respectively. Besides recurrent bronchitis and a norovirus infection, his medical history was unremarkable.

2.2. Family history

The parents were first degree cousins, with their mothers being siblings. The paternal grandfather had a cardiac infarction at age 45; his plasma TG concentration was found to be slightly elevated (284 mg/dl; 3.35 mmol/l). The maternal grandfather suffered from an early cardiac infarction at age 51; his plasma TG concentration was 481 mg/dl (5.7 mmol/l) (Table 1). Except for the parents, none of the family members was available for further analyses since they are living in a rural area in Turkey.

2.3. Physical examination

On presentation, the patient's length was 80 cm (90th percentile) and his weight was 11.1 kg (75th percentile). Physical examination of lungs and heart was normal. The liver was palpable 1.5 cm below costal margin; the spleen was not palpable. No lipoid corneal arc, xanthomata, or xanthelasma were found. Psychomotor skills were appropriate for age. An abdominal ultrasound revealed a slightly enhanced echo texture of liver and spleen. At that time, the pancreas did not show any abnormal findings.

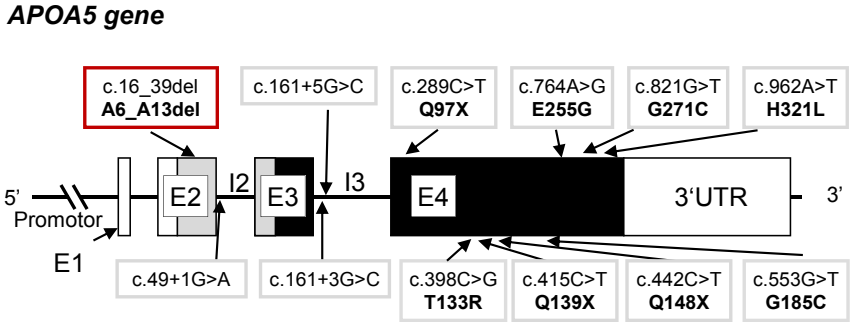

Fig. 1. Structural mutations of the APOA5 gene. The newly discovered mutation is marked with a red box. White boxes, untranslated regions (UTR); gray boxes, signal peptide; black boxes, mature protein; I1–I3; introns, E1-E4: exons. See text for references.

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