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## Genetics of metabolic syndrome and related traits

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## Estrogen induced hypertriglyceridemia in an apolipoprotein AV deficient patient

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## INTRODUCTION

Occasionally severe hypertriglyceridemia (HTG) may develop or exacerbate in females during pregnancy or use of exogenous estrogens<sup>1-3</sup>. Estrogens might increase production of triglyceride-rich very low density lipoproteins (VLDL) by the liver impair lipolysis of triglycerides through reduction of the concentration of lipoprotein lipase and hepatic lipase<sup>4,5</sup>. These effects might be induced as a result of a decrease of insulin sensitivity by estrogens<sup>6,7</sup>.

Recently, a new apolipoprotein designated AV (apoAV) was discovered which is associated with VLDL-production in the liver and might stimulate lipoprotein lipase (LPL) in hydrolyzing triglycerides in fatty acids<sup>8</sup>. APOA5 is closely linked to a well-studied apolipoprotein cluster located on chromosome 11q23, which involves the genes APOA4, APOC3 and APOA1. ApocIII plays an important role as inhibitor of lipoprotein lipase (LPL) in hydrolyzing triglycerides in fatty acids<sup>8</sup>. Several reports have shown that deficiency for apolipoprotein AV (apoAV) in humans is associated with HTG<sup>9,10</sup>.

## METHODS AND RESULTS

Here, we report a patient deficient for apoAV, yet having a variable TG phenotype. The study was approved by the medical ethical committee of our institution. A healthy 31-year old woman was referred to our Lipid clinic for HTG, detected by routine medical examination. She had no physical complaints, rarely consumed alcohol and used an oral contraceptive, ethinylestradiol/desogestrel, for more than four years. No abnormalities were detected by physical examination. Her body mass index (BMI) was 23 kg/m<sup>2</sup>.

Laboratory examination showed HTG: plasma-TG 19.4 mmol/L, elevated VLDL-cholesterol and VLDL-TG and low HDL-cholesterol (data not shown). Her apoE phenotype was E3E2. The apoAV, determined by ELISA<sup>11,12</sup>, was not detectable. She was advised to adhere to a diet low in fat (National

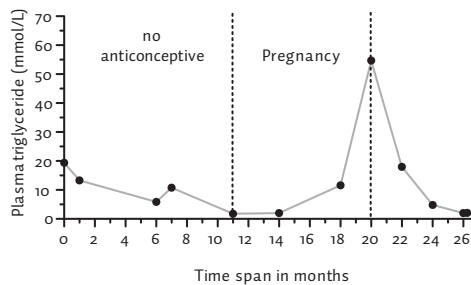


Fig.1. The variable plasma triglyceride phenotype of the apoAV deficient patient over a time span of 26 months; stop intake oral contraceptive at 0 months, start pregnancy at 11 months, delivery at 20 months.

Cholesterol Education Program 2). During the diet, her plasma TG did not normalize (6.0 – 13.3 mmol/L). However, after she stopped with the oral contraceptive medication her plasma TG normalized 1.8 mmol/L. During her pregnancy, plasma TG increased to 54.0 mmol/L and normalized after delivery (Figure 1). Since then, plasma TG have remained normal (data not shown). The plasma apocIII levels determined by ELISA<sup>11,12</sup> decreased from 37.5 mg/dl in the presence of HTG to 9.3 mg/dl in the normo-triglyceridemic state (Table 1).

Sequence analysis revealed that the patient was homozygous for a novel mutation in the APOA5 gene: c.161 + 5G (guanine) > C (cytosine). Computational splice site analysis<sup>13</sup> indicated that the c. 161 + 5G > C variant severely decreased its binding capacity as donor splice site in intron 3 (sc35 weight matrix; fold change = -3.2), which suggests a splicing defect. Both parents of the apoAV-null patient were heterozygous for the same variant. Her parents did not show any alterations in plasma lipid levels nor plasma apoAV and apocIII levels (Table 1), except for a mild combined hyperlipidemia (T-cholesterol

Table 1: Single nucleotide polymorphism (SNP) data of proband and parents

SNP	Mother	Father	Proband
APOA5 c.161 + 5G>C	1/2	1/2	2/2
APOA5 S19W	1/1	1/1	1/1
APOA5 SNP3	1/2	1/2	2/2
APOC3 Sst-1	1/2	1/2	2/2

1: common allele, 2: rare allele.

6.7 mmol/L and TG 3.9 mmol/L) of the obese (BMI 30.2 kg/m<sup>2</sup>) mother of the proband.

The following additional SNPs in the APOA5-APOC3 locus were analyzed in proband and parents: APOA5 S19W (rs3135506), APOA5 SNP3 (rs662799) and APOC3 Sst-1(rs5128), using PCR followed by restriction enzyme analysis<sup>14</sup>. Interestingly, the c.161 + 5G>C variant is linked to the rare alleles of the APOA5 SNP3 and APOC3 Sst-1 variants and

the patient is thus homozygous for both rare variants (Table 1). These data indicate that apoAV-deficiency alone was not sufficient for the induction of HTG in this patient. Exogenous estrogens and hyperestrogenemia of pregnancy may be the additional factor causing HTG in the presence of genetic susceptibility.

## DISCUSSION

Whether the genetic susceptibility in the patient is defined by the APOA5 splice mutation (and associated apoAV-deficiency) or the presence of the linked variants APOA5 SNP3 and/or APOC3 Sst-1 cannot be concluded from these analyses. However, it is intriguing to note that many of the patients with null-mutations in APOA5 described to date, are carriers of TG-raising alleles in the APOA5-APOC3 gene locus (reviewed by Talmud<sup>15</sup>).

Thus, the patient described here confirms the notion that expression of HTG in apoAV-deficiency requires the presence of additional genetic and/or environmental factors.

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