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Review

# Rare *APOA5* mutations—Clinical consequences, metabolic and functional effects An ENID review

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**Abstract**

In 2001, a gene encoding a novel apolipoprotein (apo), *APOA5*, was identified by comparative human/mouse sequencing. The encoded protein, apoAV, had been missed in routine apolipoprotein identification because it occurs at very low plasma concentrations and only DNA analysis led to its identification. Knockout and transgenic mouse models of apoAV showed an inverse relationship with plasma triglyceride levels. In human studies, common *APOA5* variants have shown near consistent association with elevated plasma TG levels, confirming apoAV as playing a role in human triglyceride metabolism. Based on mouse knockout models it was predicted that individuals with rare mutations in *APOA5* would present with severe hypertriglyceridaemia and apoAV deficiency. However, considering the small number of mutation carriers identified to date, the mode of inheritance is variable and in the recessive form TG levels are within the normal range, and apoAV deficiency only occurs in the homozygous state. Furthermore, penetrance of the mutations is low and appears to require co-inheritance of a common *APOA5* TG-raising allele as well as environmental factors for expression of the hypertriglyceridaemia. In this review the clinical and metabolic consequences and phenotype of the three *APOA5* mutations reported to date, which lead to premature truncations of apoAV are described. The insight these truncated protein give to the structure–function relationship of apoAV is explored and the relative importance of plasma and liver apoAV discussed.


*Keywords:* Apolipoprotein AV; Chylomicronaemia; Rare mutations

## Contents



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## 1. Background

The use of comparative sequencing of human and mouse DNA to discover new genes, became possible in this 'post-genomic age', and led to the identification of a novel apolipoprotein (apo) gene, *APOA5*, closely linked to the well-studied apolipoprotein locus *APOA4/APOC3/APOA1* on chromosome 11q23 [1], increasing the apolipoprotein locus size to 60 kb [2]. What intrigued those working in the field of lipid metabolism was that this apolipoprotein, apoAV, had not been detected before on routine protein gels. The reason for this became apparent when it was found that the concentration of the protein in human plasma was in the order of 170–250 ng/ml, or roughly 300-fold less than apoC-III [3]. At the same time as the initial sequence identification of apoAV [2], van der Vliet et al. identified apoAV as a gene upregulated in the regeneration of liver after partial rat hepatectomy [4]. ApoAV is expressed primarily in the liver but its potential hepatic function has not been fully examined and therefore its role in liver regeneration remains unclear. In the circulation apoAV is associated with HDL particles and in the post-prandial state with TG-rich particles [5].

Initial insight into the functional role of apoAV came from mouse models of over expression of human *APOA5* and knockout of *Apoa5* identifying apoAV as playing a major role in triglyceride (TG) metabolism, with an inverse relationship between apoAV and plasma TG levels [2]. Manipulating both *APOA5* and *APOC3* in mouse models showed that their effects on plasma triglycerides were independent and opposing [6]. This role in TG metabolism has been confirmed in many human studies where there is a strong association of common variants of *APOA5* with elevated plasma TG levels, an effect that is remarkably consistent across ethnic groups (reviewed in Refs. [7,8]). Two haplotypes, *APOA5*2* and *APOA5*3*, show association with raised plasma TG levels [9] and can be 'tagged', respectively, by the rare allele of −1131T > C, and the coding single nucleotide polymorphism (SNP) S19W (56C > G) [10].

Thus it seems clear that, as in the mouse, human apoAV plays a significant role in TG metabolism. Although, adenoviral-mediated transfer of *apoA5* into mice did appear to reduce liver VLDL-TG production [11], on the whole, mouse models seem to suggest that apoAV has less influence on the production of TG-rich lipoproteins, and more on the lipolysis and thus catabolism of TG rich lipoproteins [11,12]. In support of this, in humans apoAV does not seem to influence VLDL production in the liver [13]. However, the exact function and the relative importance of plasma and liver apoAV remain unclear. It was hoped that rare mutations of *APOA5* might aid in providing answers to these questions.

Extrapolating from the *apoA5* knock-out mouse model, rare mutation of *APOA5* would be expected to be associated with severe hypertriglyceridaemia (hyperTG), with a predicted lipoprotein phenotype of either Type I (generally accepted to be a recessive disorder of deficiency of LPL or its activator apoCII; OMIM *238600*) or Type V (OMIIM *144650*, likely to be polygenic) hyperlipoproteinaemia. To date, three rare *APOA5* mutations, all causing premature truncation of the protein, have been identified ([14–16] and reviewed in Ref. [17] (OMIM *606368*). However, the effects of these mutations, in the heterozygous (HTZ) and homozygous (HMZ) states on apoAV and TG levels, and their mode of inheritance and clinical consequences have not been as clear-cut as anticipated.

## 2. *APOA5* Q148X

The first reported case of a mutation in *APOA5* associated with severe hyperTG was reported by Oliva et al. [14]. The proband was a 9-year old boy from a consanguineous marriage. His phenotype was described as Type I hyperlipoproteinaemia, yet *LPL* and *APOC2* mutations had been excluded. Sequencing of his *APOA5* gene revealed homozygosity for Q148X which resulted in premature truncation of the protein predicting a protein 40% of the full-length apoAV. The mutation was originally designated Q145X [14] since a second ATG, three codons downstream of the translation initiation site, was taken as the start codon. Details of the boys clinical and lipid profile are given in Table 1. No

Table 1
Comparison of the baseline and lipid characteristics of *APOA5* mutation probands

| Trait | 148XX/19WW homozygote 9-year old boy | Q139X/S19W heterozygote 63-year old man | c161 + 3g > c/-1131C heterozygote 51-year old man |
|---|---|---|---|
| Age of onset of HyperTG (years) | 5 | 38 | NA |
| ApoAV (ng/ml) | Not detectable | 172.6 | 269 |
| TG mmol/l | 50 | 41.3 | 15.9 |
| Cholesterol (mmol/l) | 7.8 | 16.7 | 6.1 |
| HDL mmol/l | 0.61 | NA | 0.57 |
| ApoCIII (mg/dl) | 27.4 | Elevated | 15.3 |
| Post-heparin plasma LPL (μmolFFA/ml/h) | 5.08 | 1.9 | 4.5 |
| BMI (kg/m$^2$) | 14 | 26 | 24 |
| Pancreatitis | No but had abdominal pain | No | No |
| Responsiveness to fibrates | No | No | NA |
| Other features | Planar and eruptive cutaneous xanthomas | Mild type 2 diabetes | No |