

GENETIC VARIANTS OF APOLIPOPROTEIN C3 AS DETERMINANTS OF TRIGLYCERIDE-RICH LIPOPROTEIN METABOLISM AND RESIDUAL CARDIOVASCULAR RISK

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Apolipoprotein C3 (APOC3) is one of the key regulators of the metabolism of triglyceride-rich lipoproteins (TRLs) and their remnant particles, the accumulation of which is considered one of the mechanisms underlying residual cardiovascular (CV) risk. Genetic studies suggest that rare loss-of-function (LOF) variants and common APOC3 polymorphisms may exert distinct effects on lipid parameters and CV risk. Thus, investigating the genetic determinants of APOC3 may contribute to more accurate risk stratification and the development of personalized strategies for preventing CV events.

Analyze current data on APOC3 genetic variants and their association with TRL metabolism, remnant cholesterol and residual CV risk.

A total of 10 original studies and 5 systematic reviews and 2 meta-analyzed within the last 5 years were analyzed in the PubMed database using the following keywords: APOC3, APOC3 genetic variants, TRLs, residual cardiovascular risk.

Genetic studies of APOC3 have demonstrated that rare LOF variants, including the splice-site IVS2+1G>A (rs138326449), may be associated with lower plasma triglyceride (TG) concentrations and a reduced risk of coronary heart disease (CHD). However, the effects of APOC3 variants are heterogeneous: common variants such as rs5128 and rs734104 are associated with higher TG concentrations, whereas most rare LOF variants have not demonstrated a consistent association with CHD. In a large meta-analysis involving more than 130 thousand individuals, carriers of APOC3 LOF variants had 43% lower remnant cholesterol concentrations and 36% lower risk of CHD, highlighting the potential role of APOC3-mediated TRL metabolism in residual CV risk. Recent Mendelian randomization analyses provide further evidence that genetically mediated reductions in APOC3 are associated with lower risk of coronary artery disease, with remnant cholesterol emerging as an important mediator of this effect. Additionally, genetic inhibition of APOC3 was associated with an additional reduction in CHD when combined with genetically lower PCSK9 or HMGSR, supporting the potential role of APOC3 inhibition in reducing residual CV risk despite low-density lipoprotein cholesterol lowering.

Studying the functional significance and population prevalence of APOC3 genetic variants may help clarify their role in the metabolism of TRLs and the development of residual CV risk, improve genetic risk stratification, and advance personalized approaches to preventing CV complications.