APOC3 A43T Variant Promotes ApoC-III Catabolism and Accelerates TG-rich Lipoprotein Clearance in Mice and Humans

Sumeet A. Khetarpal, John S Millar, Amritha Varshini, Cecilia Vitali, Univ of Pennsylvania, Philadelphia, PA; Xuemei Zeng, Univ of Pittsburgh, Pittsburgh, PA; Paolo Zanoni, Univ of Pennsylvania, Philadelphia, PA; Zhiyuan Sun, Univ of Pittsburgh, Pittsburgh, PA; David Nguyen, James T McParland, Mary G McCoy, Univ of Pennsylvania, Philadelphia, PA; Pradeep Natarajan, Massachusetts General Hosp, Boston, MA; Marina Cuchel, Leland Mayne, S. Walter Englander, Sissel Lund-Katz, Michael C. Phillips, Univ of Pennsylvania, Philadelphia, PA; Nathan A Yates, Univ of Pittsburgh, Pittsburgh, PA; Sekar Kathiresan, Massachusetts General Hosp, Boston, MA; Daniel J Rader, Univ of Pennsylvania, Philadelphia, PA

Humans with loss-of-function (LoF) variants in *APOC3*, the gene encoding apolipoprotein C-III (apoC-III), have significantly reduced plasma triglycerides (TG) and protection from coronary disease. These findings suggest that apoC-III may be a viable therapeutic target for decreasing vascular risk through TG reduction, and that elucidation of the protective mechanism of *APOC3* LoF variants would inform such strategies. We report here the protective mechanism of the *APOC3* A43T missense variant, one of four recently identified CAD-protective variants. By genotyping >8,000 human participants with low TG, we identified 17 *APOC3* A43T carriers and phenotyped 6 carriers and 54 matched controls. A43T heterozygotes demonstrate a significant reduction in apoC-III levels relative to non-carriers (50% reduction, $P<0.05$), resulting in decreased plasma TG (50% reduction, $P<0.05$). We generated viral vectors expressing WT or A43T apoC-III and expressed these in humanized mouse models to further explore the mechanism of reduced apoC-III levels due to the A43T variant. Mice expressing human CETP and the apoC-III A43T variant exhibit reduced plasma apoC-III (50% reduction, $P<0.0001$) despite equal hepatic expression and secretion relative to controls expressing WT human apoC-III. These mice also exhibit reduced plasma TG and VLDL-C, and increased HDL-C relative to WT-expressing mice, fully recapitulating the protective lipoprotein profile of the human A43T carriers. Radioisotope-labeled apoC-III turnover studies showed that the A43T mutation causes a >3-fold higher apoC-III clearance rate *in vivo* ($P<0.0001$) due to defective integration into lipoprotein particles and accelerated renal catabolism (40% increase, $P<0.01$). This results in increased lipoprotein lipase (LPL) activity (27% increase, $P<0.01$) and faster chylomicron-TG clearance (97% increase, $P<0.01$) *in vivo*. We are currently performing analogous studies of WT vs. A43T apoC-III turnover and VLDL clearance in human *APOC3* A43T carriers. Collectively, our results support the rationale for therapeutic efforts to target circulating apoC-III through disruption of its binding to lipoproteins, mirroring the genetics-driven approaches for targeting *PCSK9* that have recently yielded novel therapies.

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