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Titel des Beitrags:
Loss-of-function mutations in APOC3, triglycerides, and coronary disease.
Abstract:
Plasma triglyceride levels are heritable and are correlated with the risk of coronary heart disease. Sequencing of the protein-coding regions of the human genome (the exome) has the potential to identify rare mutations that have a large effect on phenotype. We sequenced the protein-coding regions of 18,666 genes in each of 3734 participants of European or African ancestry in the Exome Sequencing Project. We conducted tests to determine whether rare mutations in coding sequence, individually or in aggregate within a gene, were associated with plasma triglyceride levels. For mutations associated with triglyceride levels, we subsequently evaluated their association with the risk of coronary heart disease in 110,970 persons. An aggregate of rare mutations in the gene encoding apolipoprotein C3 (APOC3) was associated with lower plasma triglyceride levels. Among the four mutations that drove this result, three were loss-of-function mutations: a nonsense mutation (R19X) and two splice-site mutations (IVS2+1G->A and IVS3+1G->T). The fourth was a missense mutation (A43T). Approximately 1 in 150 persons in the study was a heterozygous carrier of at least one of these four mutations. Triglyceride levels in the carriers were 39% lower than levels in noncarriers (P=1×10(-20)), and circulating levels of APOC3 in carriers were 46% lower than levels in noncarriers (P=8×10(-10)). The risk of coronary heart disease among 498 carriers of any rare APOC3 mutation was 40% lower than the risk among 110,472 noncarriers (odds ratio, 0.60; 95% confidence interval, 0.47 to 0.75; P=4×10(-6)). Rare mutations that disrupt APOC3 function were associated with lower levels of plasma triglycerides and APOC3. Carriers of these mutations were found to have a reduced risk of coronary heart disease. (Funded by the National Heart, Lung, and Blood Institute and others.)