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Titel des Beitrags: Functional characterization of promoter variants of the adiponectin gene complemented by epidemiological data.

Abstract: OBJECTIVE: Adiponectin (APM1, ACDC) is an adipocyte-derived protein with downregulated expression in obesity and insulin-resistant states. Several potentially regulatory single nucleotide polymorphisms (SNPs) within the APM1 gene promoter region have been associated with circulating adiponectin levels. None of them have been functionally characterized in adiponectin-expressing cells. Hence, we investigated three SNPs (rs16861194, rs17300539, and rs266729) for their influence on adiponectin promoter activity and their association with circulating adiponectin levels. RESEARCH DESIGN AND METHODS: Basal and rosiglitazone-induced promoter activity of different SNP combinations (haplotypes) was analyzed in 3T3-L1 adipocytes using luciferase reporter gene assays and DNA binding studies comparing all possible APM1 haplotypes. This functional approach was complemented with analysis of epidemiological population-based data of 1,692 participants of the MONICA/KORA S123 cohort and 696 participants from the KORA S4 cohort for SNP and haplotype association with circulating adiponectin levels. RESULTS: Major to minor allele replacements of the three SNPs revealed significant effects on promoter activity in luciferase assays. Particularly, a minor variant in
rs16861194 resulted in reduced basal and rosiglitazone-induced promoter activity and hypoadiponectinemia in the epidemiological datasets. The haplotype with the minor allele in all three SNPs showed a complete loss of promoter activity, and no subject carried this haplotype in either of the epidemiological samples (combined P value for statistically significant difference from a random sample was 0.006). CONCLUSIONS: Our results clearly demonstrate that promoter variants associated with hypoadiponectinemia in humans substantially affect adiponectin promoter activity in adipocytes. Our combination of functional experiments with epidemiological data overcomes the drawback of each approach alone.