Dokumenttyp: journal article

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Titel des Beitrags: Genetic variation at chromosome 1p13.3 affects sortilin mRNA expression, cellular LDL-uptake and serum LDL levels which translates to the risk of coronary artery disease.

Abstract: BACKGROUND: A single nucleotide polymorphism (SNP) rs599839 located at chromosome 1p13.3 has previously been associated with risk of coronary artery disease (CAD) and with serum levels of low-density lipoprotein cholesterol (LDL-C). A functional link explaining the association of SNP rs599839 with LDL-C levels and CAD risk has not yet been elucidated. METHODS: We analyzed the association of rs599839 with LDL-C in 6605 individuals across a wide age spectrum and with CAD in four case-control studies comprising 4287 cases and 7572 controls. Genome-wide expression array data was used to assess the association of SNP rs599839 with gene expression at chromosome 1p13. Finally, we overexpressed sortilin in transfected cells to study LDL-uptake in vitro. RESULTS: Each copy of the G-allele of rs599839 associated with a decrease of serum LDL-C by 0.14 mmol/L (90% confidence interval (CI) 0.09-0.17 mmol/L, p=2.6 x 10(-11)). Moreover, each copy of the G-allele associated with a 9% decrease of CAD risk (90% CI 4-14%) in the presently studied four case-control
samples and with a 13% decrease (90% CI 10-17%, p=2.18 x 10(-9)) in a pooled meta-analysis including recent genome-wide association studies on CAD. The same allele was associated with higher mRNA-expression levels of the multiligand receptor sortilin (log transformed mRNA AA vs. GG=8.31 vs. 8.55; p=0.01). Overexpression of SORT1 cDNA resulted in a significant increase in LDL-particle uptake (+23%, p=0.01). CONCLUSIONS: Rs599839 associates with decreased LDL-C and a lower risk of CAD. Effects appear to be mediated by increased sortilin expression and subsequently enhanced LDL-uptake into cells.

Zeitschriftentitel / Abkürzung:
Atherosclerosis

Jahr:
2010

Band:
208

Heft / Issue:
1

Seiten:
183-9

Sprache:
eng

Pubmed:

Print-ISSN:
0021-9150

TUM Einrichtung:
r Humangenetik

Occurences:
- Einrichtungen > Fakultäten > Fakultät für Medizin > Kliniken und Institute > Institut für Humangenetik > 2010

entries: