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.

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.