Common genetic variation in zinc finger protein 202, HDL cholesterol and risk of severe atherosclerosis and ischemic heart disease

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ABSTRACT

This PhD dissertation is based on studies performed at Department of Clinical Biochemistry, Rigshospitalet, University of Copenhagen, Denmark. The results are presented in the form of three papers, two published and one submitted.

ZNF202 is a transcriptional repressor located in a susceptibility locus for familial hypoalphalipoproteinemia. *ZNF202* binds promoter elements found in genes involved in blood vessel maintenance and lipid metabolism, especially HDL metabolism. This suggests that *ZNF202* might be important for the development of atherosclerosis dependent or independent of lipid levels, and thus a potential candidate gene for ischemic heart disease (IHD).

The objective of this study was to identify functional genetic variants in *ZNF202* which were associated with variation in HDL cholesterol levels in the general population and predicted risk of severe atherosclerosis and IHD.

We re-sequenced the promoter and protein coding region of *ZNF202* in individuals with the 1% highest (N=95) and 1% lowest (N=95) HDL cholesterol levels among 9259 Danish adults from the Copenhagen City Heart Study, and determined the association of the protein coding single nucleotide polymorphisms (SNPs; minor allele frequency >1%) identified with variation in HDL cholesterol in the general population. SNPs in the coding region of *ZNF202* did not make a major contribution to plasma levels of HDL cholesterol. However, we found that a common nonsynonymous SNP (p.A154V) was associated with an increased risk of IHD and myocardial infarction (MI) in the general population independent of lipid and lipoprotein levels. Because p.A154V was not conserved between species (human, mouse, rat) and substituted similar nonpolar amino acids, the effect on risk of IHD and MI was most likely due to linkage disequilibrium with a functional SNP in the promoter region. We therefore tested whether p.A154V was in linkage disequilibrium with a SNP in the *ZNF202* promoter, and found almost complete linkage disequilibrium between p.A154V and the promoter SNP, g.-660A>G. In in vitro studies, we showed that g.-660G was consistently associated with a more than 60% reduction in transcriptional activity compared to g.-660A, confirming that this was a functional SNP. In a cross sectional study with 5467 individuals, g.-660A>G was associated with an increased odds ratio for severe atherosclerosis as determined by an ankle brachial index ≤0.7 versus >0.7, and predicted an increased hazard ratio for IHD in a prospective study with 10,522 individuals with 28-years follow-up and 1526 incident IHD events. Finally, the results for risk of IHD were confirmed in two independent case-control studies including 2492 cases with IHD and 8996 controls.

These results suggest that *ZNF202* is a new candidate gene for atherosclerosis and ischemic IHD.