Common and low-frequency genetic variants in the PCSK9 locus influence circulating PCSK9 levels

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Background: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a circulating protein that influences plasma low-density lipoprotein (LDL) concentration and susceptibility to coronary heart disease (CHD). Circulating PCSK9 levels show considerable inter-individual differences, but the factors responsible for this variation are largely unknown.

Methods and Results: We analyzed circulating PCSK9 levels in four cohorts of healthy, middle-aged Swedes (n=5722) and found that PCSK9 levels varied over ~ 50-fold range, showed a positive relationship with plasma LDL-cholesterol concentration, and were associated with plasma triglyceride, fibrinogen, insulin and glucose concentrations. A genome-wide association study conducted in two cohorts (n=1215) failed to uncover common genetic variants robustly associated with variation in circulating PCSK9 level. As expected, the minor allele of the PCSK9 R46L variant was in all cohorts associated with reduced PCSK9 levels and decreased plasma LDL-cholesterol concentrations, but no relationship was observed with the plasma triglyceride concentration. Further mapping of the PCSK9 locus revealed a common polymorphism (rs2479415, minor allele frequency 43.9%), located ~6kb upstream from PCSK9, which is independently associated with increased circulating PCSK9 levels.

Conclusion: Common and low frequency genetic variants in the PCSK9 locus influence the pronounced inter-individual variation in circulating PCSK9 levels in healthy, middle-aged Caucasian (predominantly Swedish) subjects.

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