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Functional Analysis of a Novel Genome-Wide Association Study Signal in SMAD3 That Confers Protection From Coronary Artery Disease - DTU Orbit (09/11/2017)

Functional Analysis of a Novel Genome-Wide Association Study Signal in *SMAD3* That Confers Protection From Coronary Artery Disease

OBJECTIVE—: A recent genome-wide association study meta-analysis identified an intronic single nucleotide polymorphism in *SMAD3*, rs56062135C>T, the minor allele (T) which associates with protection from coronary artery disease. Relevant to atherosclerosis, *SMAD3* is a key contributor to transforming growth factor-β pathway signaling. Here, we seek to identify ≥1 causal coronary artery disease–associated single nucleotide polymorphisms at the SMAD3 locus and characterize mechanisms whereby the risk allele(s) contribute to coronary artery disease risk. APPROACH AND RESULTS—: By genetic and epigenetic fine mapping, we identified a candidate causal single nucleotide polymorphism rs17293632C>T (D′, 0.97; r, 0.94 with rs56062135) in intron 1 of *SMAD3* with predicted functional effects. We show that the sequence encompassing rs17293632 acts as a strong enhancer in human arterial smooth muscle cells. The common allele (C) preserves an activator protein (AP)-1 site and enhancer function, whereas the protective (T) allele disrupts the AP-1 site and significantly reduces enhancer activity (PT single nucleotide polymorphism represents a novel functional cis-acting element at the *SMAD3* locus. The protective (T) allele of rs17293632 disrupts a consensus AP-1 binding site in a *SMAD3* intron 1 enhancer, reduces enhancer activity and *SMAD3* expression, altering human arterial smooth muscle cells proliferation.

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