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CHROMOSOME 9P21 LOCUS AND CORONARY ARTERY DISEASE – COLLABORATIVE META-ANALYSIS ON ANGIOGRAPHIC BURDEN AND MOLECULAR FUNCTION ANALYSIS

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Background Chromosome 9p21 variants showed the strongest association with coronary heart disease in genome-wide association studies. But questions remain on the mechanism underlying the risk rendered by this locus, and clinically whether the locus contributes to coronary atheroma burden or plaque instability. We investigated the relationship of 9p21 locus with (1) angiographic coronary artery disease (CAD) burden and progression to myocardial infarction (MI); and (2) biological function of vascular smooth muscle cell (VSMC).

Methods and results We established a collaboration of 21 studies consisting of 33,673 patients with information on both CAD (clinical or angiographic) and MI status along with 9p21 genotype. We first confirmed an association between 9p21 and CAD using angiographically defined cases and controls (pooled odds ratio (OR)=1.31 (95% CI 1.20–1.43)). Among subjects with angiographic CAD (n=20,987), random-effects model identified an association with multi-vessel CAD, compared to those with single-vessel disease (OR=1.10 (95% CI 1.04–1.17) per copy of risk allele). However, there was no significant association between 9p21 and prevalent MI when both cases (n=17,791) and controls (n=15,882) had underlying CAD (OR=0.99 (95% CI 0.95-1.03) per risk allele). Immunohistochemical staining of human atherosclerotic plaque showed co-localization of VSMC with the cell-cycle regulator proteins $p16^{INK4a}$, $p14^{ARF}$ and $p15^{INK4b}$, which are encoded by the genes *CDKN2A* and *CDKN2B* genomically located nearby the 9p21 locus. The 9p21 risk genotype confers reduced $p15^{INK4b}$ levels ($p=3.7x10^{-2}$) and higher VSMC content ($p=5.6x10^{-4}$) in the plaques. We further examined the influence of 9p21 genotype on primary cultures of VSMC isolated from human umbilical cord. The risk genotype was associated with reduced expression of $p16^{INK4a}$, $p15^{INK4b}$ ($p=1.2x10^{-5}$, $1.4x10^{-2}$), and increased VSMC proliferation ($p=1.6x10^{-2}$).

Conclusions The 9p21 locus shows convincing association with greater burden of CAD, but not with MI in the presence of underlying CAD, indicating that the 9p21 locus primarily mediates an atherosclerotic phenotype. This is supported by the observations from atherosclerotic plaques and primary cell cultures indicating its influence on VSMC proliferation, a process featured in atherosclerotic pathogenesis.