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METHYLATION OF P15INK4B AND EXPRESSION OF ANRIL ON CHROMOSOME 9P21 ARE ASSOCIATED WITH CORONARY ARTERY DISEASE

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[1]Jianhui Zhuang, [1]Wenhui Peng, [1]Hailing Li, [2]Wei Wang, [1]Yidong Wei, [1]Weiming Li, [1]Yawei Xu. *[1]Shanghai Tenth People's Hospital, Tongji University School of Medicine; [2]Laboratory of Blood and Vascular Biology, The Rockefeller University*

Objectives Genome-wide association studies have identified that multiple SNPs on Chr9p21 are tightly associated with CAD. However, the mechanism linking this risk locus to CAD remains unclear.

Methods The methylation status of six candidate genes (BAX, BCL-2, TIMP3, p14ARF, p15INK4b and p16INK4a) in 205 patients and controls who underwent coronary angiography were analysed by quantitative MethyLight assay. Rs10757274 was genotyped and expression of INK4/ARF and antisense non-coding RNA in the INK4 locus (ANRIL) was determined by real-time RT-PCR. Serum levels of TGF-β1 were measured by ELISA.

Results Compared with controls, DNA methylation levels at p15INK4b promoter significantly increased in CAD patients (p=0.006). The rs10757274 genotype was significantly associated with CAD (p=0.003) and GG genotype carriers had a higher level of ANRIL exon 1–5 expression compared among three genotypes (p=0.009). There was a stepwise increase in p15INK4b and p16INK4a methylation as ANRIL exon 1–5 expression elevated (r=0.23, p=0.001 and r=0.24, p=0.001, respectively), although neither of two loci methylation was directly linked to rs10757274 genotype.

Conclusions p15INK4b methylation is associated with CAD and ANRIL expression. The epigenetic changes in p15INK4b methylation and ANRIL expression may involve in the mechanisms of Chr9p21 on CAD development.