**GENETIC VARIANTS REDUCING MTR GENE EXPRESSION INCREASE RISK OF CONGENITAL HEART DISEASE IN HAN CHINESE POPULATION**

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Background: Homocysteine elevation is known to be a risk factor of CHD, but its mechanism remains unknown. During early embryonic development, the homocysteine removal is dictated exclusively by the embryonic MTR activity. To examine that role of MTR in CHD risk, we identified genetic variants in MTR and investigated the mechanisms that affect the expression level of MTR, and that increase the risk of CHDs in Chinese populations.

Methods: The association between regulatory variants of the MTR gene and CHD was examined in three independent case-control studies in a total of 2,340 CHD patients and 2,270 controls. Functional consequences of these variants were demonstrated using dual-luciferase assay, real-time PCR, EMSA, SPR, CHIP and bisulfate sequencing as well as by a group of predicted microRNAs using gene reporter system.

Results: Two regulatory variants -186T>G and +905G>A of the MTR gene were associated with an increased risk of CHD in both the separate and combined case-control studies (-186GG P=1.32X10E9; +905AA P=6.35X10E14). The -186G allele had significantly lower promoter activity, decreased hnRNA and mRNA levels, reduced transcription factor binding affinity and a more highly methylated promoter, compared with the major T allele. The +905A allele had statistically stronger binding with the functional microRNAs, which down-regulate MTR expression at the translational level. Both minor alleles were correlated with elevated plasma homocysteine concentrations, and hyperhomocysteine could be attributed genetically.

Conclusions: The regulatory variants of the MTR gene increase CHD risk by reducing MTR expression and inducing the homocysteine accumulation and elevation.