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Common polymorphisms in the 5-lipoxygenase pathway confer risk of myocardial infarction - A Danish case-cohort study

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Background: The 5-lipoxygenase pathway is an inflammatory pathway that has been implicated in the development and manifestation of cardiovascular disease. Studies have suggested, that genetic polymorphisms related to key enzymes in this pathway may confer risk of myocardial infarction (MI).

Purpose: This study investigated the association of pre-selected genetic polymorphisms related to four key enzymes in the 5-lipoxygenase pathway (arachidonate 5-lipoxygenase and an activating protein (ALOX-5 and ALOX-5 AP), leukotriene A4 hydroxylase (LTA4-H) and leukotriene C4 synthase (LTC4-S)) with incident MI.

Methods: In a Danish cohort study 57,053 participants, aged 50–64 at enrolment, were recruited from 1993–97. We conducted a case-cohort study including cases with incident MI and a randomly selected sub cohort of 3,000 participants. Cases were identified from national registries through July 2013. Based on a literature review, a total of 22 SNP's were selected and genotypes were assessed using the commercially available KASP™ genotyping assay. A tandem-repeat polymorphism, located at the promoter region of the ALOX-5 gene, was genotyped by multi-titre plate sequencing. Associations were evaluated using a weighted Cox proportional hazards model adjusting for potential confounders. An additive model of inheritance was assumed unless otherwise stated.

Results: During a median follow-up of 17.0 years we identified 3,089 cases of incident MI. Two SNP's in the gene encoding ALOX-5 AP were associated with incident MI (rs9551963 & rs17222842), suggesting a negative association when comparing homozygotes for the major allele with one or two (rs9551963) and two (rs17222842) copies of the minor allele, respectively. One SNP (rs2247570), located at the genomic region of LTA4-H, was associated with higher risk of MI (HR=1.28, 95% CI: 1.03–1.59) in subjects with two copies of the minor allele compared to homozygotes for the major allele. Furthermore, the promoter polymorphism of ALOX-5 was associated with risk of MI, when assuming a recessive model. For carriers of two variant alleles a HR of 1.43 was observed (95% CI: 1.01–2.02) when compared to carriers of one or two wildtype alleles.

Conclusions: Common polymorphisms in candidate genes of the 5-lipoxygenase pathway was associated with incident MI, suggesting a potential role for this pathway in the development of cardiovascular disease.