Interleukin 18 is an important mediator of inflammation and has been associated with the development and aggravation of cardiovascular diseases. We report that common variation in the interleukin 18 gene is related to acute myocardial infarction, a frequent clinical manifestation of atherosclerosis and thrombosis in coronary arteries. In a population of European, mainly (90%) German, ancestry (2136 cases with acute myocardial infarction and 1211 controls), the association was based on specific alleles and haplotypes derived from a set of six tagging single nucleotide polymorphisms. The rs1946519-G (located in the 5' upstream region), rs360717-C (exon 1), rs5744241-G (intron 1), rs1834481-C (intron 3), and rs3882891-A (intron 5) alleles (P=0.22). These observations suggest that the interleukin 18 gene is a susceptibility locus for acute myocardial infarction, a finding of potential interest in the clinical practice.