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The genetics of coronary heart disease, including atherosclerosis, is poorly understood outside of traditional risk factors like blood cholesterol levels, hypertension and smoking. Although human genome-wide association studies have met with recent success in identifying candidate regions of the genome harboring disease susceptibility genes, determining genotype-phenotype relations in humans is difficult due to genetic complexity. Animal models offer an alternative approach for the genetic analysis of complex diseases. The B6-Ldlr-/- mouse strain is a widely-established model of atherosclerosis. Crossing a small region of chromosome 4 (Athsq1, Atherosclerosis susceptibility QTL1) from the wild-derived MOLF strain onto the B6-Ldlr-/- background results in ~4.5-fold increased atherosclerotic lesion area, and increased lesional accumulation of a presumably pro-atherogenic extracellular matrix component (versican), compared to B6-Ldlr-/- controls. The location of the causative gene within the MOLF-derived interval has been narrowed to a region that includes ~130 genes. Interestingly, this region contains the mouse homology with a widely-replicated human locus for CHD and aneurysm. The major goals of this proposal are: I) identify the gene(s) underlying the murine Athsq1 locus; 2) to determine the relevance of Athsq1 to the human chr 9p21 CHD locus; and 3) to determine the mechanism by which the underlying gene may influence versican accumulation in lesions and accelerated atherogenesis. A standard mouse genetics approach will be utilized to narrow the location of the underlying gene. In addition, differential gene expression in relevant tissues will be determined to predict candidate genes within the interval. Mechanistic studies in primary cells derived from Athsq1 and B6-Ldlr-/- controls will be performed to assess the role of candidate genes in versican accumulation and potential pro-atherogenic pathways, in vitro. These studies will include gene-specific knockdowns. Proof of causality will be addressed with atherosclerosis studies, in vivo, using transgenic, gene knockout or gene knock-in mice. Finally, atherosclerotic vessels from individuals carrying risk or non-risk alleles at the 9p21 CHD locus will be assessed for relative accumulation of versican. The long range goals of this proposal are to identify a novel gene(s) underlying susceptibility to atherosclerosis, potentially suggesting new diagnostic and/or therapeutic strategies for CHD.