Genetic predisposition to vascular complications of diabetes.

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The aim of the study is to investigate whether there is an association between common genetic polymorphisms and the risk of myocardial infarction (Ml) or retinopathy (by retinal photography, Wisconsin score) in non-insulin-dependent diabetes mellitus (NIDDM). Patients are selected from the United Kingdom Prospective Diabetes Study. Approximately 200 cases with each complication and 200 matched controls were genotyped for four polymorphisms. Cases and controls were matched prospectively for gender, age, duration of disease, fasting plasma glucose, blood pressure, with MI patients matched additionally for smoking, and LDL and HDL cholesterol. Polymorphisms studied, all of which have been found to be associated either with MI itself or atherosclerosis, include the plasminogen activator inhibitor-l (PAI-1) promoter 4G/5G, the tissue plasminogen activator (tPA) alu insertion/deletion, factor XIIA P/L564 and stromelysin (Sly) promoter 5A/6A. The PAI-l and Sly polymorphisms were genotyped by PCR with fluorescently labelled primers and resolution of the allelic PCR products each differing by one basepair, on the AB1377. The factor XIIA P/L564 polymorphism was genotyped by PCR using a mutagenized primer and PstI digestion. The tPA alu ins/del polymorphism was genotyped by PCR using primers spanning the insertion followed by size separation. Paired data were analyzed by McNemar's test and retinopathy score using analysis of variance. Data analysis is currently underway for PAI-1, IPA and Sly. In 542 subjects, the factor XIIIA L564 allele was associated with retinopathy (p=0.0l9, RR1 .6) with a co-dominant effect: median Wisconsin retinopathy scores were 10 10 for the PP564 homozygotes, 20 10 for heterozygotes and 31 <31 for the LL564 homozygotes, with a significant test for trend. This polymorphism was not associated with MI. Thus, common genetic polymorphisms may predispose certain individuals to more severe vascular complications of NIDDM.