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01.5

Endothelium-dependent arterial dilatation is determined by genetic endothelial constitututive nitric oxide synthase Glu298Asp variant

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Endothelial dysfunction plays an important role in atherosclerotic cardiovascular disease. As the origin of endothelial dysfunction is largely unclear we studied the relation between genetic endothelial constitutive nitric oxide synthase (ecNOS) Glu298Asp ($G^{894}T$) polymorphism and endothelium dependent dilatation in 100 healthy, nonhypertensive and nonobese postmenopausal women.

One hundred women aged 52-67 years, participating in a research project on the role of endogenous and exogenous hormones in risk of cardiovascular disease, were included in the study. None of the women used hormone replacement therapy. Endothelial function was assessed noninvasively by measuring percent lumen diameter change in the brachial artery during reactive hyperemia (endothelium-dependent) and nitroglycerine sublingual spray (endothelium-independent).

In all subjects the median flow mediated dilatation (FMD) was 4,4% and the nitroglycerine mediated dilatation (NMD) 7,2%. FMD in TT (median 0,4%) was reduced compared with GG (median 6,1%) (p=0,05). Subjects with GT genotype did not differ statistically in FMD compared to GG or TT. The difference in FMD between the homozygote wild type and variant groups could not be explained by differences in age, body mass index, blood pressure or smoking.

Our findings suggest that endothelium dependent dilatation is reduced in subjects with the TT genotype of the ecNOS Glu298Asp polymorphism. This supports the view that a genetic basis for atherosclerosis may be found in part through endothelial dysfunction.

01.6

Effects of genetic polymorphisms on the response of serum cholesterol to dietary fat in man

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Dietary treatment of hypercholesterolemia is not effective for everyone. Early identification of individuals who respond to diet could make cholesterol-lowering treatment more effective.

We therefore studied the relationship between polymorphisms in genes involved in lipid metabolism with the response of serum total cholesterol, as measured in 9 dietary trials performed between 1963 and 1974 in four monasteries. In 1996, 56 monks and nuns who had participated in one to seven (on average 3.3) of these dietary trials took mouth swabs from which we isolated DNA.

In contrast with other studies, responses of 10 subjects (28 observations) with the Apoprotein (Apo-)E ε e4 allele did not differ significantly from those of subjects with the E3E3 genotype. The cholesterol response was larger in 6 subjects (28 observations) with the ApoB EcoRI E-E- genotype (0.84 ± 0.09 mmol/l) than in 30 subjects (97 observations) with the E+E+ genotype (0.56 ± 0.05 mmol/l; 95% CI 0.02 to 0.55 mmol/l) or in 20 subjects (61 observations) with the E+E- genotype (0.42 ± 0.07 mmol/l; 95% CI 0.13 to 0.70 mmol/l). Some other studies show a similar effect of the ApoB EcoRI polymorphism. The cholesterol response was smaller in 11 subjects (32 observations) with the ApoA-I 83 MspI M+M- genotype (0.36 ± 0.09 mmol/l) than in 45 subjects (154 observations) with the M+M+ genotype (0.60 ± 0.04mmol/l; 95% CI 0.05 to 0.44 mmol/l). Other polymorphisms in genes encoding for ApoA-I and ApoA-IV, cholesteryl ester transfer protein, microsomal triglyceride transfer protein, and intestinal fatty acids binding protein were not significantly related to the cholesterol response. Additional adjustments for sex, body mass index, age, year of trial, diet, and apoE genotype did not affect the results.

In conclusion, the cholesterol response to dietary fat may be affected by polymorphisms of the ApoE, ApoB, and ApoA-I genes.

01.7

Homozygosity for the 870 CT polymorphism in platelet glycoprotein alpha2-beta1 is associated with an increased risk of cardiovascular mortality in female smokers.

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Platelet adhesion to collagen is the initial step in hemostasis and thrombosis. Platelet-collagen adhesion is mediated by α2β1, an integrin on the surface of platelet membranes. Recently, a 807 C to T single nucleotide exchange polymorphism in the gene coding for the α2-sub-unit of α2β1 has been identified. The 807 T allele is associated with increased α2β1 density on the platelet membrane and is associated with platelet adhesion to collagen in vitro.

We studied the relation of α2β1 807 CT genotype to cardiovascular mortality in a prospective cohort study of 12,239 women living in the city of Utrecht, who were initially aged between 52 and 67 years. Women were followed on vital status between 1976 and 1995 (168,513 years). The α2β1 807 CT

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