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ASSOCIATION OF THE MISSENSE GLU298ASP VARIANT OF ENOS GENE WITH LEFT VENTRICULAR HYPERTROPHY AND CAROTID ATHEROSCLEROSIS IN PATIENTS WITH ESSENTIAL HYPERTENSION

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Backgroud: Nitric oxide (NO) plays an important role in the regulation of blood pressure and regional blood flow. The missense Glu298Asp variant in exon7 of the endothelial nitric oxide synthase (eNOS) gene has been reported to be a risk factor for hypertension and coronary artery disease. We investigated the potential association of the missense Glu298Asp variant of eNOS gene with left ventricular hypertrophy and carotid atherosclerosis in patients with essential hypertension.

Methods: This study included 280 hypertensive patients (138 men and 142 women, mean;63 years). Left ventricular hypertrophy was evaluated by the left ventricular mass index (LVMI), assessed by M-mode echocardiography. Carotid atherosclerosis was evaluated by the carotid artery vascular mass (VM). The VM was calculated as : $VM=\rho L\pi\{(CAD/2+IMT)^2 - (CAD/2)^2\}$ (ρ:arterial wall density(=1.06), L:length of the arterial segment). Intima-media thickness (IMT) and the vessel diameter of the common carotid artery (CAD) were measured by B-mode ultrasonography. The eNOS genotypes were determined by polymerase chain reaction and restriction with the enzyme BanII.

Results: The eNOS / GG, GT, and TT genotypes were present in 193 (69%), 76 (27%), and 11 (4%) of 280 patients with essential hypertension, respectively. The LVMI of the patients with eNOS allele T (GT+TT) was significantly higher than those with GG genotype (GT+TT 140±21 g/m^2, GG 126±18, p=0.003). The VM of the patients with eNOS allele T (GT+TT) was significantly higher than those with GG genotype (GT+TT 23.1±8.7 mg/cm, GG 17.9±6.6, p=0.002). No significant difference was present between genotypes and age, sex, blood pressure, history of smoking, body mass index, T-cho, HDL-cho, and Lp(a). Multiple regression analysis showed the missense Glu298Asp variant to be an independent predictor of LVMI(p=0.001) and VM (p=0.002), respectively.

Conclusions: These findings suggest that the missense Glu298Asp variant of eNOS gene may be an independent risk factor for the left ventricular hypertrophy and carotid atherosclerosis in patients with essential hypertension.

Key Words: eNOS gene ,left ventricular hypertrophy, carotid atherosclerosis

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THE INFLUENCE OF GENE-GENE INTERACTIONS ON LEFT VENTRICULAR MASS

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Left ventricular hypertrophy (LVH) is associated with an increased risk for cardiovascular morbidity and mortality. Epidemiological studies suggest that LVH may be influenced by genetic factors. The evidence associating individual genes with left ventricular mass (LVM) is inconsistent and contradictory, suggesting that gene-gene interactions may be involved in this relationship.

We investigated the associations and interactions between angiotensin converting enzyme insertion(I)/deletion(D) (ACE), angiotensinogen M235T (AGT) and α-adducin G460W polymorphisms with LVM index (LVMI) in 162 men with mild, never treated hypertension who were recruited for the HARVEST study. The effect of each single, each pair and triplet of polymorphisms on LVMI was tested in one-, two-, and three-way ANCOVA using LVMI as the dependent variable after adjusting for covariates.

The α-adducin polymorphism was the only individual polymorphism independently associated with LVMI (F=7.78, p=0.006). Albeit rare, 50% of mutated homozygotes of that polymorphism had LVH (odds ratio 15.6, 95% CI 3.04-82.07). ACE (F=13.62, p<0.001) and AGT (F=5.72 p=0.018) polymorphisms were independently associated with LVMI but only when α-adducin polymorphism was considered. Moreover, effects of ACE - a-adducin (F=12.73, p<0.001) and AGT - α-adducin (F=3.83, p=0.05) polymorphism interactions on LVMI were found. In the absence of homozygosity for the α-adducin mutation, LVMI was virtually the same, regardless of ACE and AGT polymorphism. However, even within mutated homozygotes of α-adducin, LVMI was not always elevated. The presence of II or DD homozygotes of ACE polymorphism was associated with higher LVMI in mutated homozygotes of α-adducin polymorphism, regardless of underlying AGT polymorphism (p<0.03).

Our results underline the importance of studying several genes as well as gene-gene interactions, when evaluating the association between gene polymorphisms and complex traits, such as cardiac mass regulation.

Key Words: gene interactions, left ventricular mass, renin-angiotensin system

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INSULIN RESISTANCE AS DETERMINANT OF CARDIAC HYPERTROPHY IN NEVER TREATED HYPERTENSIVE PATIENTS WITH D/D ALLELE OF ACE-GENE POLYMORPHISM

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Epidemiologic data suggest that hypertensive cardiac hypertrophy and insulin resistance are important predictors of cardiovascular morbidity and mortality. To investigate the possible relationship among ACE-gene polymorphism, insulin resistance and cardiac mass in a group of never treated hypertensive patients. Two hundred and thirty (133M, 97F; age=45.4+5.4 years) hypertensive never treated outpatients were enrolled. We evaluated clinic and ambulatory blood pressure, echocardiographic left ventricular mass indexed by body surface area and height2.7, fasting glucose and insulin levels. Insulin resistance was calculated using the homeostasis model assessment (HOMA). ACE genotypes were detected by double PCR, and ACE activity by colorimetric kit. No significant differences were observed in age, body mass index, blood pressure and glucose among the three ACE genotypes (DD, ID, II). Instead, fasting insulin (μU/mL) and HOMA were significantly (p<0.0001) higher in DD genotype (16.4+4.1; 3.7+1.0) than ID (9.6+3.7; 2.1+0.8) and II (8.0+3.0; 1.8+0.7) groups. Similarly, the cardiac mass was significantly (p<0.0001) increased in DD patients (143.1+31.1 g/m2, and 65.9+31.1 g/m2.7) when compared with ID (126.8+25.8 g/m2, and 58.3+12.5 g/m2.7) and II (115.7+22.8 g/m2, and 52.0+11.1 g/m2.7) groups. However, the polymorphism of the ACE-gene affects cardiac mass only in males, suggesting a gender effect. Moreover, we detected a significant linear relationship (p<0.0001) between ACE activity and HOMA (r=0.678), and HOMA and cardiac mass (r=0.620). The final model for cardiac mass included only HOMA (38.4%) and blood pressure (5.1%). In conclusion, our data suggest that insulin resistance is a powerful independent determinant of left ventricular mass in hypertensive DD patients.

Key Words: insulin resistance, cardiac hypertrophy, ACE-gene polymorphism