The microfibrillar protein fibrillin-1 is an important component of the vascular wall. Defects in fibrillin-1 predispose to vascular damage in Marfan syndrome but the role of fibrillin-1 in microvascular disease is unknown. We hypothesized that fibrillin-1 is involved in hypertensive glomerular disease.

Deoxycorticosterone (DOCA)-salt hypertension led to a significant increase in glomerular fibrillin-1 mRNA expression and protein deposition in rats (35.0 ± 4.0% of glomerular area positive for fibrillin-1 versus 16.7 ± 3.3% in controls) and mice. To test the functional role of fibrillin-1, DOCA-salt hypertension was induced in mice with a homozygous 5fold underexpression of fibrillin-1 (R/R), as well as in heterozygous (R/+ ) and wild type (+/+ ) littermates (n=6 to 9 male mice per genotype). Blood pressure was measured by a tail cuff method, and by direct intraarterial recordings in conscious mice. Animals were followed for 6 weeks. Untreated male R/R mice are known to die from aortic dissection during the first 6 months of life. After induction of DOCA-salt hypertension, all R/R mice died within the next two weeks from internal hemorrhage. DOCA-treated R/+ and +/+ displayed similar blood pressure levels but albuminuria was significantly lower in R/+ than in +/+ (33.2 ± 10.6 versus 170.4 ± 65.3 μg/24h) after DOCA treatment. Glomerular deposition of collagen IV was also significantly ameliorated in R/+ , compared with +/+ (22.1 ± 1.9 % of glomerular area in R/+ versus 10.9 ± 2.0 % in +/+ ) Blood pressure, albuminuria and glomerular collagen IV did not differ between normotensive R/R, R/+ and +/+ , respectively.

Thus, underexpression of fibrillin-1 predisposes to lethal aortic dissection in the presence of hypertension. On the other hand, microvascular damage in hypertension was ameliorated by fibrillin-1 underexpression. We conclude that the increased expression of fibrillin-1 may contribute to glomerular damage in hypertensive nephrosclerosis.

Key Words: Aortic Aneurysm, Fibrillin-1, Nephrosclerosis

P-211 GENETIC RISK FACTORS FOR ARTERIAL STIFFNESS
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Arterial stiffness plays a pivotal role in the pathogenesis of systolic hypertension. Aging and hypertension are potent predisposing factors for the development of arterial stiffness. In clinical practice, two parameters are used as indices of arterial stiffness, i.e. pulse wave velocity (PWV) and augmentation index (AI). Although PWV is the main factor affecting the AI, two parameters are regulated differently. The underlying pathophysiological alterations have also been shown to be different between PWV and AI. PWV is more relevant to arterial stiffness, while AI reflects the central arterial pressure and left ventricular loading. These findings may indicate the genetic factors for arterial stiffness could be different when analyzed using PWV and AI. In the present study, we evaluated the susceptible genetic factors for the elevation of PWV and AI in a Japanese general population.

315 community residents participated in the present study. Carotid arterial waveform was recorded non-invasively with tonometry method simultaneously with measuring PWV between right brachial artery and right ankle. Thirty known polymorphisms of genes encoding the components of the renin-angiotensin system, sympathetic nervous system, vasoactive peptides were genotyped in each subject. Of thirty gene polymorphisms examined, ACE insertion/deletion polymorphism was significantly associated with carotid AI (F=4.02, p=0.021), while MTHFR gene polymorphism was significantly related with PWV (F=4.79, p=0.0001). The associations remain significant even after correction with age, sex, body height, blood pressure, heart rate, and use of antihypertensive drugs. These findings indicate that underlying pathophysiological factors for the elevation of PWV and AI could be influenced by distinct genes.

Key Words: Augmentation Index, Arterial Stiffness, Pulse Wave Velocity

P-212 MATRIX METALLOPEPTIDASE GENE POLYMORPHISMS AND SILENT CEREBRAL INFARCT IN A LARGE JAPANESE GENERAL POPULATION
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Silent cerebral infarct (SCI) has been shown to be a potent risk factor for future symptomatic stroke and has been considered as a surrogate marker of stroke. Aging is the most potent risk factor of SCI in addition to hypertension. Since extracellular matrix composition determines elastic properties of the arterial wall, matrix metalloproteinases (MMP) could play important roles in the pathogenesis of age-related arterial sclerosis. In the present study, we investigated the possible association between genes encoding MMP family and MRI proven SCI in a large Japanese general population.

2203 subjects recruited in NILS-LSA study (National Institute for Longevity Sciences Longitudinal Study of Aging) aged 40-79 years old, 1104 men and 1099 women, participated in the study. Known SNPs in the promoter regions of MMP family, MMP-1 (1G/2G -1607), MMP-3 (5A/6A -1612), MMP-9 (C-1562T), and MMP-12 (A-82G) were genotyped in each subject. SCI and periventricular hyperintensity (PVH) were evaluated by MRI.

The prevalence of SCI was increased with age. 219 subjects (134 men and 85 women) had SCI and 193 of them (121 male and 72 women) had lacuna infarct. There were no significant difference in the prevalence of SCI among all genotypes examined in a total population and in men. However, in women, prevalence of SCI was significantly different between MMP-1 1G carriers (33/581) and 2G2G genotypes (52/518, χ²=7.29, p=0.0069).

These findings indicate that MMP-1 could be a susceptible gene for SCI in a Japanese female population. Sex-specific genetic mechanisms need to be further investigation.

Key Words: Cerebral Infarct, Matrix Metalloproteinase, Polymorphism

P-213 SYSTEMIC MULTIPLE CANDIDATE GENES APPROACH FOR IDENTIFICATION OF SUSCEPTIBLE GENES FOR HYPERTENSION IN A JAPANESE POPULATION
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A vigorous effort has been paid to identify genes for hypertension, however no consistent results have been reported. The candidate gene