学 位 論 文 の 要 旨

氏名　陶山　洋二

学　位　論　文　名　Effects of Six Functional SNPs on the Urinary 8-isoprostane Level in a General Japanese Population; Shimane COHRE Study.

発　表　雑　誌　名　Disease Markers
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著　　者　　名　Yoji Suyama, Chikashi Matsuda, Minoru Isomura, Tsuyoshi Hamano, Kenji Karino, Masayuki Yamasaki, Shuhei Yamaguchi, Kuninori Shiwaku, Junichi Masuda, Toru Nabika

論 文 内 容 の 要 旨

INTRODUCTION

Oxidative stress is one of important risk factors for various cardiovascular diseases. Many environmental and genetic factors are suggested to influence the oxidative stress, which, in turn, are inferred in the pathogenesis of atherosclerosis, coronary heart diseases and cerebrovascular diseases.

Functional single-nucleotide polymorphisms (SNPs) have been identified in the genes encoding enzymes regulating oxidative stress response. Although the biological significance of those SNPs was confirmed in functional assays evaluating the promoter and the enzyme activity as well as quantity of the mRNA and of the enzyme, relative lack of information on the effects of such SNPs on the level of oxidative stress in the human population is apparent.

In this study, we therefore performed a cross-sectional analysis on effects of SNPs on the urinary 8-isoprostane (IsoP) level, a marker for oxidative stress, to examine a hypothesis that some functional SNPs affect oxidative stress in the general population.

MATERIALS AND METHODS

Participants of the health examination in two neighboring counties (K and M county) were recruited in a mountainous region of Shimane prefecture (n=1092) through health examinations performed by the the Center for Community-based Health Research and Education (COHRE) of Shimane University. As a marker for the oxidative stress, the urinary 8-isoprostane (IsoP) was measured by ELISA. Six functional SNPs were evaluated in the study; they are T-107*C* and Q192R in the *paraoxonase 1* (*PON1*), T-786C in the *endothelial nitric oxide synthase* (*eNOS*), C677T in the *methylenetetrahydrofolate reductase* (*MTHFR*), G994T in the l*ipoprotein-associated phospholipase A2* (*Lp-PLA2*) and C242T in the *p22phox* gene, all of which were shown to regulate either the promoter activity (*eNOS* T-786C and *PON1* T-107C), the enzyme activity (*PON1* Q192R, *Lp-PLA2* G994T and *p22phox* C242T), or the stability of the enzyme (*MTHFR* C677T) in the previous studies. The six SNPs were genotyped using the Taqman method. The Student's t-test, the contingency table analysis, the simple regression analysis with Pearson's r and ANOVA were used in the univariate analyses when they were appropriate. Effects of interaction among the 6 SNPs were tested using the Generalized Multiple Dimensionality Reduction (GMDR). The linear regression analysis was performed on the potential factors influencing the IsoP levels.

RESULTS AND DISCUSSION

Age was significantly correlated with IsoP in a univariate analysis (r=0.082, p=0.03 and r=0.13, p=0.009 in K and M counties, respectively). High-density lipoprotein cholesterol, low-density lipoprotein cholesterol and estimated glomerular filtration rate showed modest but significant correlations with IsoP level in one of the two populations.

The genotype and allele frequencies were not significantly different between the two regions studied. Allele frequencies of the four SNPs in the *p22phox*, *eNOS*, *LpPLA2* and *PON1* genes in these populations were similar to those in the public database

(www.ncbi.nim.nih.gov/projects/SNP) and/or in previous reports. In contrast, the both populations had substantially greater frequency of the minor allele for *MTHFR* C677T, when compared with those in a previous report on Japanese.

None of the SNPs had significant effects on the IsoP level either in the two populations by ANOVA. However, the GMDR method identified that the combination of the two SNPs, *MTHFR* C677T and *eNOS* T-786C, showed a significant effect on the IsoP level in this population. The linear regression analysis confirmed that the high risk genotype identified in the GMDR was an independent factor influencing the IsoP even after adjustment of confounding factors (β=0.02±0.008, p=0.01). This result suggested that GMDR analysis might be useful to identify concealed effects of combined SNPs.

CONCLUSION

A combination of functional SNPs may have a synergistic effect on the oxidative stress in a general population. GMDR may be a useful method to dissect effects of gene-gene and gene-environmental interactions on complex traits.