Genre Wide Association Study Of Osteonecrosis Of Femoral Head In The Korean

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Introduction: Osteonecrosis of femoral head (ONFH) frequently leads to progressive collapse of the femoral head followed by a degenerative arthritis of the hip joint. Diverse conditions have been implicated in the development of ONFH. There are some well accepted common associations; corticosteroids use, alcohol abuse, systemic lupus erythematosus, Legg-Calve-Perthes disease, sickle cell anemia, radiation, cytotoxic agents, Gaucher’s disease, dysbarism, HIV, hyperlipidemia, pancreatitis, and gout. Idiopathic ONFH refers when there are no identifiable factors. ONFH is believed to be multifactorial and associated in some cases with both a genetic predisposition and exposure to certain risk factors. The incidence or prevalence of idiopathic ONFH reflect ethnic differences. Particularly, idiopathic ONFH in twins and a clustering of cases in families imply that genetic factors are involved. Therefore, We conducted a genomewide association study to search for genetic variants with a large effect size that increase the risk for idiopathic ONFH.

Methods: Subjects: The GWAS was performed on DNA samples (n=217) from idiopathic ONFH patients enrolled between 2001-2007 at the Kyungpook National University Hospital (Daegu, Korea). The replication study was performed in idiopathic patients (n=96) enrolled between 2001-2006 at Kyunghee University Hospital (Seoul, Korea). Normal samples and their records were obtained from National Biobank of Korea (Osong, Korea) with approved by Institutional Review Board. All individuals gave informed consent for study participation and the study was approved by the Institutional Review Board.

Genotyping: Axiom (Affymetrix) were genotyped for initial GWA of 434 Korean (Patients 217, Control 217). After quality control, 509,886 SNPs were included in the association analysis. For the replication stage, 48 of the selected SNPs were genotyped with the Fludigm Array. Three SNPs (rs12376144, rs6708239, rs11820502) were genotyped using SNaPshot (Applied Biosystems®).

Results: To identify the genetic loci associated with ONFH susceptibility, we performed Chi-square or Cochran-Armitage trend tests for allelic comparison and for genotypic comparison under additive, dominant, recessive, and co-dominant models. Sexual chromosomes were excluded for analysis. Quantile-quantile plots of test statistics comparing allele frequencies confirmed the genetic homogeneity of the Korean subjects recruited for this study. The genome-wide test results are shown in Figure 1. A total of 79 SNPs (4 in X chromosome) passed our arbitrary threshold for replication (P < 1 x 10⁻⁴). Of these, the rs3881953 (G>A; Arg40Lys), CDS-nonsynonymous polymorphism, located in PPP1R2B gene was most significantly associated with ONFH (P=1.68×10⁻¹⁹) after Bonferroni correction. For replication, among the 79 significant SNPs, we selected 52 SNPs depending selection priority. The selected top 10 SNPs within the intra- or intergenic regions with the lowest P-values are listed in Table 1. Statistical analysis of replication study set is in progress.
**Discussion:** The majority association studies of ONFH have concentrated on gene polymorphisms affecting the coagulation and fibrinolytic systems. However, the association between genetic predisposition and thrombotic tendency may differ between ethnic groups. In our genome-wide study of a Korean ONFH population, we identified several SNPs associated with idiopathic ONFH. Although a larger number of study subjects and further functional evaluations are needed, to our knowledge, the current report is the first GWAS association study with idiopathic ONFH. Our preliminary findings from this study could provide new insight into the genetic factors associated with risk of ONFH.

**Significance:** The current report is the first GWAS association study with idiopathic ONFH.