A Functional Variant, rs967591G>A, in the 19q13.3 and Survival of Early-Stage Lung Cancer

1Lung Cancer Center, Kyungpook National University Medical Center, Daegu, Departments of 2Internal Medicine and Thoracic Surgery, School of Medicine, Kyungpook National University, Daegu, 3Department of Thoracic and Cardiovascular Surgery, Seoul National University School of Medicine, Seoul, Korea

박재용1,2, Hyo-Sung Jeon1, Seung Soo Yoo1,1, Shin Yup Lee1,2, Jaehee Lee2, Seung-Ick Cha2, Chang Ho Kim2, Eung Bae Lee1,3, Young Tae Kim4, Sanghoon Jheon4

Purpose: This study was conducted to investigate the associations between single nucleotide polymorphisms (SNPs) in 19q13.3 and survival of early-stage non-small cell lung cancer (NSCLC) patients, and to define the causative functional SNP of the association.

Methods: A two-stage study design was used to evaluate five SNPs in relation to survival outcomes in 328 patients and then to validate the results in an independent patient population (n=565). Luciferase assay and real-time PCR was performed to examine functional relevance of a potentially functional SNP.

Results: Of the five SNPs, three SNPs (rs105165C>T, rs967591G>A and rs735482A>C) were significantly associated with survival outcomes in a stage 1 study. The rs967591A allele had significantly higher promoter activity of CD3EAP compared with the rs967591G allele (P=0.002), but the SNP did not have an effect on the promoter activity of PPP1R13L. The rs967591G>A was associated with the level of CD3EAP mRNA expression in lung tissues (P=0.01). The rs967591G>A exhibited consistent associations in a stage 2 study. In combined analysis, the rs967591 AA genotype exhibited a worse overall survival (adjusted hazard ratio=1.69, 95% confidence interval=1.29-2.20, P=0.0001).

Conclusion: The rs967591G>A affects CD3EAP expression and thus influences survival in early-stage NSCLC. The analysis of the rs967591G>A polymorphism can help identify patients at high risk of a poor disease outcome.

Association between Common Genetic Polymorphisms in 1,994 Cancer-related Genes and Survival of Early-stage Non-small Cell Lung Cancer

1Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, 2Lung Cancer Center, Kyungpook National University Medical Center, Daegu, 3Department of Thoracic Surgery, School of Medicine, Kyungpook National University, Daegu, 4Department of Thoracic and Cardiovascular Surgery, Seoul National University School of Medicine, Seoul, Korea

유승수1,2, Yi-Young Choi2, Hyo-Sung Jeon2, Shin Yup Lee1,2, YangKi Seok2,3, Jae-Hee Lee1, Seung Ick Cha1, Chang Ho Kim1, Eung Bae Lee2,3, Young Tae Kim4, Sanghoon Jheon4, Jae Yong Park1,2

Purpose: This study was conducted to identify genetic polymorphisms associated with the prognosis of patients with early-stage non-small cell lung cancer (NSCLC).

Materials and Methods: We genotyped 2,228 potentially functional single nucleotide polymorphisms (SNPs) of 1,994 genes using the Affymetrix custom-made GeneChip, which were related to the development and progression of cancer, in 166 NSCLC patients who underwent curative surgical resection. A replication study was performed on an independent cohort of 626 patients. The functional effect of GNB2L1 SNPs was evaluated by promoter assay and electrophoretic mobility shift assay (EMSA).

Results: Among 2,228 SNPs, 13 SNPs which were associated with overall survival (OS) and/or disease-free survival (DFS) with log-rank P values lower than 0.10 in a discovery set were selected for validation. Among the 13 validation SNPs, 5 SNPs (C3 rs2287845, GNB2L1 rs1279736 and rs3756585, FANCD2 rs7647987, and SCGB1D2 rs2232950) were found to be associated with survival outcomes in the same direction as the discovery set. In combined analysis, the rs1279736 and rs3756585 were most significantly associated with OS and DFS in multivariate analysis (p for OS<0.0001, both; and P for DFS=0.003, both; under a codominant model). The promoter assay and EMSA revealed that the rs3795685 lead to change of promoter activity and binding of transcription factors.

Conclusions: We identified five SNPs as markers for prognosis of patients with surgically resected NSCLC.