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An Overview of Genetic Polymorphism and Lung Cancer Risk

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risk for lung cancer for prevention. Both environmental and genetic factors are related to the development of lung cancer. For example, cigarette smoking, passive (secondhand) smoking, asbestos exposure, and air pollution are associated with lung cancer. Genetic polymorphisms, including Single Nucleotide Polymorphisms (SNPs), underlie inter-individual differences in cancer susceptibility, and genetic loci for lung cancer risk have been identified by Genome-Wide Association Studies (GWAS) in both European/American and Asian populations. Recent GWAS of lung cancer have identified genetic susceptibility variants on Chromosome 15q25 (CHRNA), 5p15 (TERT), 3q28 (TP63), 6q22 (DCBLD1), 6p21 (BAT3-MSH2 and BTNL2), 10q25 (VTI1A), and 17q.24 (BPTF); however, loci significantly associated with lung cancer risk differ among ethnicities. Here, we review previous GWAS and discuss genetic factors that may be useful for the early detection or prevention of lung cancer .

Keywords: Lung cancer; Genome-wide association study; Single nucleotide polymorphism; Cancer susceptibility

Introduction

Lung cancer is a leading cause of cancer-related mortality in developed and developing countries, and its incidence is increasing. Advanced cancer genome technologies can be used to detect alterations in oncogenes, such as EGFR, KRAS, BRAF, HER2/ERBB2, ALK, RET, and ROS1 [1,2]. Despite the development of molecular-targeted drugs for oncogenic mutations, there are few e f cient therapies for the advanced stage of lung cancer. Owing to acquired resistance to therapy, recurrence rates are still high. In fact, the 5-year survival rate for stage IV lung cancer is less than 20%, in contrast to the 71.4% 5-year survival rate for stage IA [3]. T ese results suggest that earlier detection and treatment of lung cancer would signi f cantly improve outcomes and reduce mortality. Cigarette smoke is a major cause of lung cancer. Cigarette smoke, including secondhand smoke, is associated with a substantially elevated risk of mortality [4]. Lung cancer types are typically histologically classi f ed as Small Cell Lung Cancer (SCC) and non-small cell lung cancer, which includes Adenocarcinoma (ADC) and Squamous Cell Carcinoma (SQC) [5]. Smoking is more weakly associated with the development of ADC than with the development of SCC and SQC [6], indicating that the mechanism

e results of previous GWAS are summarized in the Table 1.

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everal studies report that three chromosomal loci, 15q24-25.1, 5p15.33, and 6p21, are associated with lung cancer risk in European and American populations [7-14], while four, 3q28, 5p15.33, 6p21, and 17q24.2, are associated with ADC risk in Japanese and/or Korean populations [10,11]. In addition, loci at 5q32, 10p14, 13q12.12, 20q13.2, and 22q12.2 are associated with lung cancer risk in the Chinese population [12,15] and loci at 10q25 and 6p21 are associated with susceptibility to lung cancer in females who have never smoked in the Asian population [16]. Loci at 12p13.33 and 12q23.1 are associated with SQC risk in individuals of European ancestry [17] and in the Chinese population [18]. However, the associations for some susceptibility loci were not validated in independent samples, and further veri f cation is needed.

T e chromosomal 15q24–25.1 region contains nicotinic acetylcholine receptor subunit genes, i.e., CHRNA3 (cholinergic receptor, nicotinic, alpha 3) and CHRNA5. T ese subunits are expressed in pulmonary epithelial cells and bind to nicotine and nitrosamines, including potential lung carcinogens in cigarette smoke and food [19,20]. T e binding induces proliferation of cancer cells [20]. In Asia, associations between SNPs in these genes and lung cancer risk have been reported [21,22], but studies have yielded con f icting results [23]. Because the frequency of risk alleles in the Asian population is much lower than that in European populations, the con f icting results probably re f ect the lower statistical power in these studies. At minimum, the contribution of the CHRNA risk alleles to lung cancer risk di f ers between Asian and European populations. T us, it is necessary to investigate a cohort of subjects or large sample sets in Asian populations.

Therefore, genetic modifers and/or environmental factors might contribute to diferences among histological types. The rs2736100 SNP is associated with susceptibility to other cancer types, including cancers of the brain, bladder, prostate, uterine cervix, and skin, as well as testicular cancer and chronic lymphocytic leukemia [28,29]. There are conficting results regarding the association between the TERT SNPs and telomere length in leukocytes [28,30]. However, variants in the TERT promoter region (rs2853669 and rs2735940) and intron 4 (rs10069690) are likely to afect telomere length in leucocytes or non-cancerous tissues [31,32]. The rs2853669 SNP is associated with ADC risk (rs2853669, odds ratio (OR) = 1.38); however, neither rs2853669 nor rs10069690 is statistically associated with ADC risk in the Japanese population (OR=1.06 and 1.07, respectively) [11]. To elucidate the efects of TERT SNPs, additional studies are needed to determine the relationships among TERT SNPs, ADC risk, and telomere length in non-cancerous or normal lung tissues.

CLPTM1L is located near TERT. This gene was identifed by screening and ovarian cancer cell line for Cisplatin (CDDP) resistance-related genes. A recent meta-analysis suggested that the association between rs31489 located in CLPTM1L and lung cancer risk was stronger in a population of European ancestry than in Asians [29]. CLPTM1L is required for lung tumorigenesis in a conditional K-RasG12D transgenic mouse model [33]. The frequency of KRAS-mutated ADC is diferent among Caucasians and Asians. KRAS protein is activated by a single amino acid substitution (at codons 12 or 13) in 20–30% of ADC cases in the American population and in 8–10% of ADC cases in the East Asian population [26]. CLPTM1L SNPs

oncogene mutations, such as EGFR and KRAS mutations. Understanding the underlying genetic factors will help greatly in clarifying the disease etiology and in identifying high-risk individuals for targeted screening and/or prevention based on a combination of genetic and environmental factors.

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