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Review

Genetic Polymorphisms Underlying Lung Cancer Susceptibility and Therapeutic Response

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Recent advances in genome analysis technologies have provided a detailed genome-wide view of cancerous and non-cancerous cells. Lung cancer is largely caused by tobacco smoking, but several studies have implicated inherited genetic factors in disease etiology. Genome-wide association studies (GWASs) using DNA chips have identified loci/genes with polymorphisms that underlie inter-individual differences in cancer susceptibility, including single nucleotide polymorphisms (SNPs). *CHRNA* (cholinergic receptor, nicotinic, alpha), *TERT* (telomerase reverse transcriptase) and *TP63* (tumor protein p63) loci have been linked to lung cancer susceptibility by GWASs. SNPs in *TERT* and *TP63* are preferentially associated with the risk of adenocarcinoma, the commonest histological type of lung cancer affecting both smokers and non-smokers, whereas those in *CHRNA* are associated with lung cancer risk irrespective of histological type. An association of functional polymorphisms in DNA repair/metabolic genes with the risk of squamous cell carcinoma, a major histological type developed in smokers, has been suggested, but it remains inconclusive. It was also suggested that an SNP in the *TP53* tumor suppressor gene influences the response to platinum-doublet chemotherapy in lung cancer patients. However, analyses have shown that only a subset of SNPs is involved in lung carcinogenesis/therapy. Further GWASs are needed to translate the information on genetic variations into cancer prevention and clinical practice by focusing on specific subtypes of lung cancers or therapeutic responses.

Key words: lung cancer, genome-wide association studies (GWASs), single nucleotide polymorphisms (SNPs), cancer susceptibility, DNA repair genes, metabolic genes

Introduction

Lung cancer is the leading cause of cancer mortality worldwide, with more than one million deaths each year. The different histological forms of lung cancer are typically divided into small cell lung cancer (SCLC, 20% in Japan) and non-small cell lung cancer (NSCLC, 80%), mainly adenocarcinoma (ADC, 40%) and squamous cell carcinoma (SQC, 30%) (1). Although lung cancer is largely caused by tobacco smoking, inherited genetic factors (i.e., genetic polymorphisms) may increase its risk according to recent genome-wide association studies (GWASs) using DNA chips, which allow the determination of genotypes for hundred thousands to millions of single nucleotide polymorphisms (SNPs) (2–7). Risk variants may result in different magnitudes of increased lung cancer risk depending on populations, smoking behavior, and histological types. Further studies of genetic factors will help to clarify the disease etiology and to identify high risk individuals for targeted screening and/or prevention. A recent study has also indicated that genetic polymorphisms also underlie inter-individual differences in response to cancer chemotherapy (8). Genetic polymorphisms provide a valuable tool for understanding the nature of human carcinogenesis and the outcomes of cancer therapy.

GWAS

Genetic polymorphisms responsible for cancer susceptibility have been investigated in case-control (association) studies where polymorphisms with different distributions between cancer cases and non-cancer controls have been identified (9) (Fig. 1A). Genetic factors involved in cancer susceptibility were previously studied in the polymorphisms of genes encoding proteins with the ability to metabolize carcinogens or suppress mutations induced by carcinogens. However, recent advances in molecular technology and knowledge of the distribution of genetic polymorphisms in the human genome have made it possible to identify genetic factors responsible for the development of common diseases using GWASs, including lung cancer (http://gwas.lifesciencedb.jp/cgi-bin/gwasdb/gwas_top.cgi) (10). Several cancer susceptibility genes/loci have been identified by GWASs. For example, gene polymorphisms in the *ABO* blood group gene (11) and the *ALDH2* (aldehyde dehydrogenase 2) gene (12) were associated with susceptibility to pancreat-

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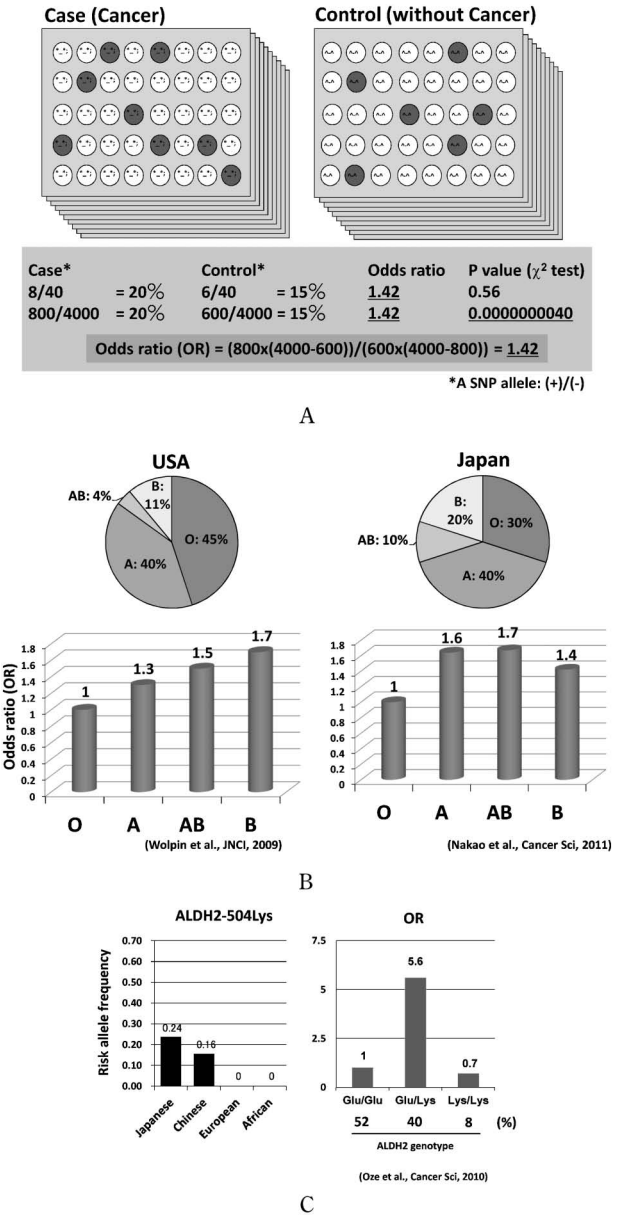

Fig. 1. GWAS. (A) Case-control study. The odds ratio (OR) is calculated as a measure of the effect size describing the strength of an association. OR is the ratio of the odds of an event occurring in one group (case) to the odds of it occurring in another group (control). Hundred thousands to millions of SNPs are examined in GWASs, which means that a very high number of case and control subjects must be tested to obtain statistically significant associations after correcting for the problem of multiple comparisons, e.g., using a Bonferroni correction. (B) ORs of individuals with each ABO blood type in the USA and Japan. Individuals in blood group O had a lower risk for pancreatic cancer than those in groups A, B or AB. The upper graphs show the ratio of ABO blood type in the USA and Japanese populations. (C) The left graph shows frequencies of chromosomes for risk allele in all chromosomes in each population. The frequencies were determined by the HapMap project. The right graph shows ORs of individuals with each *ALDH2* genotype in the Japanese population. Individuals with the *ALDH2 Glu/Lys* genotype had a higher risk for esophageal cancer than those with the *ALDH2 Glu/Glu* genotype.

ic and esophageal cancers, respectively. These results were consistent with earlier epidemiological evidence suggesting that blood group O subjects may have a lower risk of pancreatic cancer than groups A, B, or AB (13,14) (Fig. 1B), and that the *ALDH2 Glu/Lys* genotype confers a higher susceptibility to esophageal cancer than the *ALDH2 Glu/Glu* genotype due to the decreased elimination of acetaldehyde (15) (Fig. 1C).

GWASs of Lung Cancer Risk

Three chromosomal loci, 15q24-25.1, 5p15.33 and 6p21, were found to be associated with lung cancer risk in GWASs of European/American populations (2–4), while locus 3q28 was associated with lung ADC risk in a GWAS of Japanese/Korean populations (7). The chromosomal 15q24-25.1 region contains nicotinic acetylcholine receptor subunit genes, i.e., *CHRNA3* (cholinergic receptor, nicotinic, alpha 3) and *CHRNA5*, and their products are expressed in pulmonary epithelial cells and bind to nicotine, an addictive compound found in cigarette smoke, and nitrosamines, which are potential lung carcinogens in cigarette smoke and food (16,17). The associated lung cancer risk of intronic SNPs in 15q24-25.1 was replicated in Asian populations (18,19). However, the frequency of risk alleles was much lower than that in populations of European descent (Fig. 2A, left). Thus, the *CHRNA* risk alleles make a smaller subset of individuals more susceptible to lung cancer in Asians compared with European and American populations. Interestingly, the association with lung cancer risk was found irrespective of smoking and histological types in many studies, so *CHRNA* SNPs might contribute to the risk in a (active) smoking-independent manner (Fig. 2A, right). The involvement of other factors should be further investigated, such as food intake and passive smoking. On the other hand, the contribution of *CHRNA* SNPs to lung cancer risk via tobacco addiction has been also suggested (20). Thus, further studies need to investigate a cohort of subjects where detailed data are available on lung cancer development, food intake, active and passive smoking exposure, nicotine dependence, and the duration and intensity of smoking to elucidate how *CHRNA* SNPs contribute to lung cancer risk. The 5p15.33 region contains the *TERT* (telomerase reverse transcriptase) gene. TERT is known to function in telomere replication and maintenance, and it promotes epithelial cell proliferation (21). The risk allele frequency of the landmark SNP (rs2736100) is similar among ethnic populations (Fig. 2B, left), and associations have been detected in among Europeans, American and Asians (22,23) (Fig. 2B, right). Interestingly, this SNP is associated with the risk of ADC, but not SQC or SCLC (5,6,22–24), suggesting a preferential association of this locus with lung cancer risk in never-smokers (Fig. 2B, right). Risk associations of the

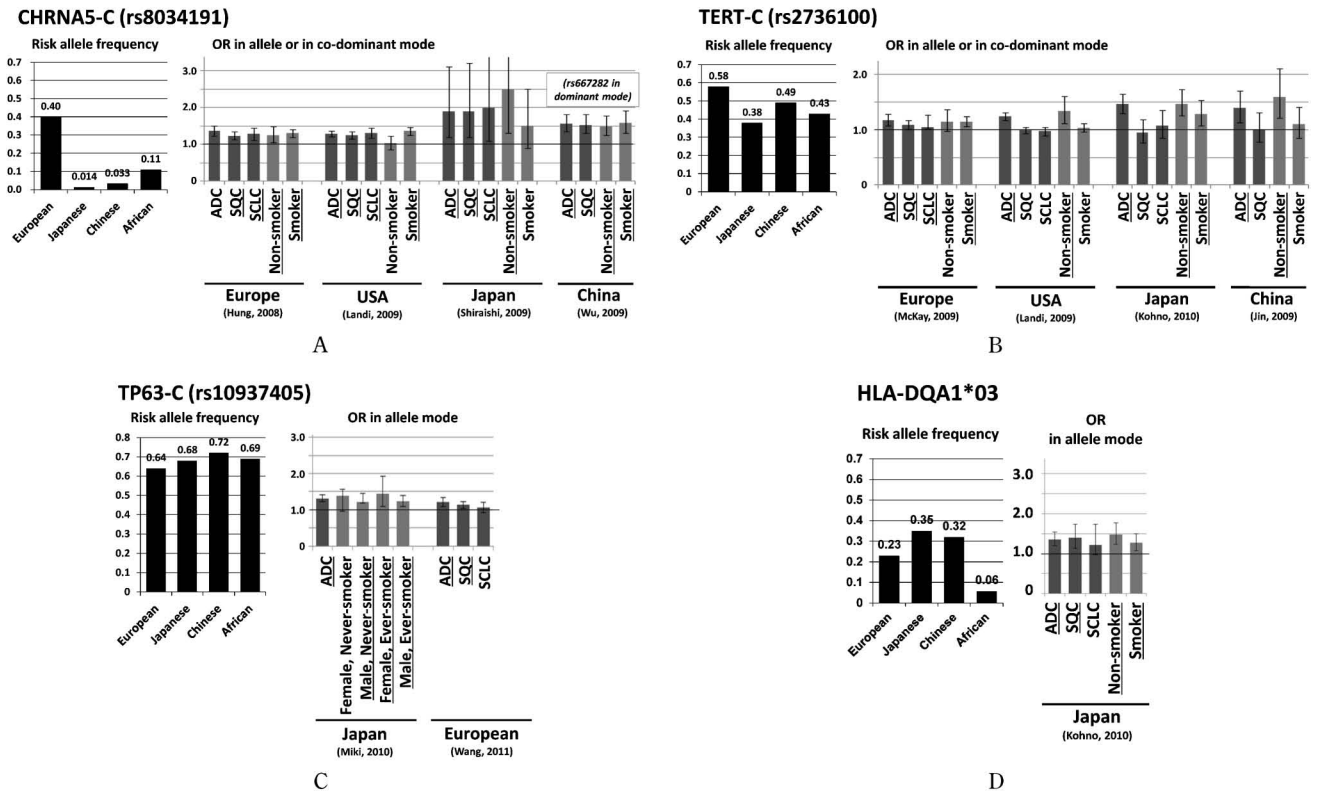

Fig. 2. Increased lung cancer risk with SNPs identified by GWASs according to populations, smoking behavior, and histological types. Categories where statistically significant association was observed are underlined. (A) rs8034191 (*CHRNA5*) at 15q24–25.1. (B) rs2736100 (*TERT*) at 5p15.33. (C) rs10937405 (*TP63*) at 3q28. (D) HLA-DQA1*03 (*HLA-DQA1*) at 6p21. The left graphs show frequencies of chromosomes for risk allele in all chromosomes in each population. Frequencies were determined by the HapMap project or the International Histocompatibility Working Group are shown on the left.

5p15.33 genotype have been detected in lung cancer and other types of cancers, including cancers of the brain, bladder, prostate, uterine cervix, and skin (25). The rs2736100 SNP is located in intron 2 of *TERT*, which is a putative regulatory region. It was previously suggested that risk alleles in the *TERT* gene are associated with shorter telomeres (25). Therefore, these variants may lead to an increase in the gradual shortening of telomeres over time, leading to genomic instability driving carcinogenesis in many organs. Thus, functional analyses of *TERT* SNPs are warranted. The 3q28 region contains the *TP63* gene that encodes a member of the tumor suppressor *TP53* (also known as p53) gene family, which is involved in development, differentiation, and the cellular stress response (26). The risk allele frequency of the landmark SNP (rs10937405) was similar among ethnic populations (Fig. 2C, left) and associations with lung ADC risk were detected in both Asians and Europeans (7,27) (Fig. 2C, right). However, the association appears to be stronger in Asians than Europeans (27). In Europeans, there is a weaker association with lung SQC risk, while the association with SQC risk is unknown in Asians. SNPs associated with lung cancer risk are located in intron 1 of *TP63* and it has been suggested that they have a functional role in the regulation of *TP63* gene expression. *TP63* is induced after the exposure of cells to DNA damage. Therefore, inter-individual differences in the accumulation of DNA damage and the response to genotoxic stress might contribute to lung cancer susceptibility. Associations of SNPs in the 6p21 region were found in a GWAS of Europeans (4). This region contains the *BAT3* (HLA-B associated transcript 3) and *MSH5* (mutS homolog 5) genes. The BAT3 protein complexes with a histone acetyltransferase, p300, which acetylates p53 protein in response to DNA damage, while MSH5 is involved in DNA mismatch repair. However, a recent pooled analysis by the International Lung Cancer Consortium failed to replicate the association of these SNPs with lung cancer risk (24). Our GWAS on Japanese lung ADC indicated that the HLA-DQA1 locus encoding a HLA (human leukocyte antigen)-class II protein (1 Mb proximal to the BAT3-MSH5 locus) is a significant region in 6p21. The *DQA1*03* allele of the *HLA-DQA1* gene was associated with an increased risk of the development of all major histological types of lung cancer (23) (Fig. 2D). It is possible that the *HLA-DQA1* polymorphism confers lung cancer susceptibility due to inter-individual

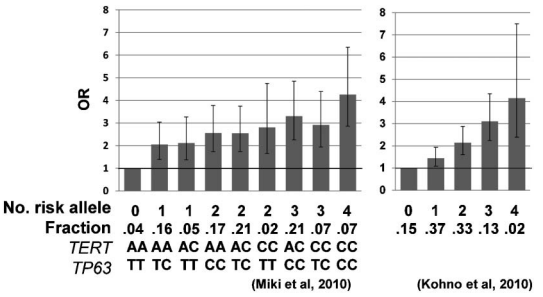

Fig. 3. Lung ADC risk of combined genotypes. Left: ORs of combined *TERT* (rs2736100) and *TP63* (rs10937405) genotypes. Right: ORs of combined *TERT* (rs2736100), *CHRNA3* (rs105173), and *HLA-DQA1* (*03) genotypes.

differences in the immune response against tumor cells. However, 6p21 is a highly polymorphic region containing major histocompatibility complex genes, therefore, the observed associations might have simply reflect differences in the population substructure (6). Further investigation of this region is warranted.

Lung ADC risk based on combined genotypes: Miki *et al.* and we estimated the risk of lung ADC caused by combined genotypes with multiple lung ADC susceptibility loci (7,23) (Fig. 3). These loci were suggested to independently confer risk, and carriers of all risk alleles, i.e., $<10\%$ of the population, had an odds ratio (OR) of >4.0 compared with those having no risk alleles. The results are significant when we consider that the OR of smoking for lung ADC risk is <2.0 in the Japanese population (28). The relative risk of carrying these variants should now be assessed in a cohort study to the relative ratios of these combined genotypes and to identify high risk individuals in near future.

Functional polymorphisms in DNA repair and metabolic genes: Studies of DNA adducts/damage, including that produced by tobacco carcinogens and their repair processes, have led to the identification of various metabolic and DNA repair genes with functional polymorphisms, which might possibly produce inter-individual differences in the rate of somatic mutation and the susceptibility to tobacco-related cancers (29). Representative SNPs in *TP53*, *OGG1*, and *CYP1A1* have been indicated to be associated with lung cancer risk for a long time (30–34) and the risk allele frequencies of those SNPs are shown to be different among ethnic populations. (Fig. 4A). The risk (72Pro) allele of the *TP53-Arg72Pro* SNP in the TP53 gene encodes a protein with a weaker apoptotic activity that better allows the survival of DNA-damaged cells compared with the 72Arg allele (35), while the risk (326Cys) allele of the Ser326Cys SNP in the *OGG1* gene encodes a DNA glycosylase with a weaker activity in repairing an oxidatively damaged promutagenic base produced by tobacco carcinogens, 8-hydroxyguanine, compared with the

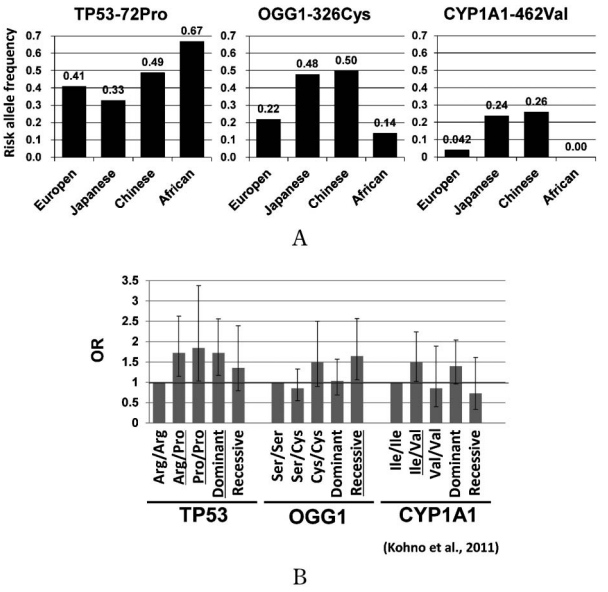

Fig. 4. Increased lung SQC risk with functional SNPs in the *TP53* (rs1042522), *OGG1* (rs1052133), and *CYP1A1* (rs1048943) genes. (A) Frequencies of risk alleles in each population determined by the HapMap project. (B) ORs of *TP53*, *OGG1*, and *CYP1A1* genotypes. *TP53-72Pro*, *OGG1-326Cys* and *CYP1A1-462Val* alleles were shown to be statistically significantly associated with lung SQC risk. Genotypes showing statistically significant association are underlined.

326Ser allele (36,37). The risk (462Val) allele of the Ile462Val SNP in the *CYP1A1* gene encodes a metabolic protein with a higher activity in bio-activating the major tobacco procarcinogens, polycyclic aromatic hydrocarbons (PAHs), than the 462Ile allele (38). However, the associations of these functional polymorphisms were not investigated in previous GWASs due to the lack of probes for discriminating these polymorphisms in the platforms used by GWASs (http://www.ncbi.nlm.nih.gov/snp), so they remain unconfirmed. We previously demonstrated the association of these functional SNPs with lung SQC risk in a population where polymorphisms of the GWAS genes show associations (39). Genotypes for two DNA repair genes, *TP53* and *OGG1*, and a metabolic gene, *CYP1A1*, showed significant associations with SQC risk along with those for CHRNA3 and HLA-DQA1 (Fig. 4B). Based on these results, there is a need to analyze various functional polymorphisms together with millions of GWAS marker SNPs. This will provide a powerful method for analyzing these polymorphisms in populations that were tested in recent GWASs.

SNPs in DNA repair genes and therapeutic responses: Genetic polymorphisms underlie inter-individual differences in terms of susceptibility to disease and also the therapeutic response, although published association studies in this area lack sufficient case numbers (40). Agents that damage DNA or that disrupt

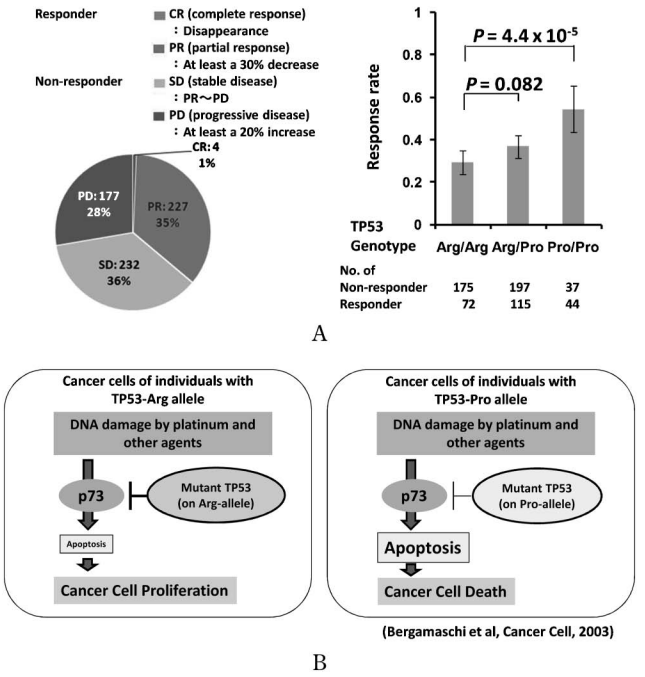

Fig. 5. Association of a *TP53* functional SNP (rs1042522) with the response to platinum-doublet therapy in 640 NSCLC patients. (A) Association result. The therapeutic response evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) was used as the primary end point of outcome to search for predictive factors. Patients were divided into two categories: responders were those with complete response and partial response, and non-responders were those with stable disease and progressive disease. ORs for the response (i.e., responder vs nonresponder) according to genotypes were calculated as a measure of difference in the response rate against therapy using an unconditional logistic regression analysis. The, the *TP53* SNP was defined as the one significantly associated with response. Left: Character of 640 NSCLC patients according to their response. Right: Difference in the response rate (i.e., fraction of responders) according to their *TP53* genotype. (B) Possible mechanism for the differential response. p73 is a p53-related protein that plays a role in apoptosis of cancer cells carrying *TP53* mutations via anticancer agents, although its function is abrogated by mutant p53 proteins. p53 mutants with a proline residue in codon 72 only weakly inhibit the function of p73 protein in NSCLC cells, so they efficiently induce the apoptosis of NSCLC cells treated with platinum and other anticancer agents.

chromosomal integrity are used in chemotherapy, so any variation in activities that repair DNA/chromosome damage might possibly influence the outcome for patients after chemotherapy (41). Thus, 640 patients with non-small-cell lung cancer (NSCLC) who received platinum-based doublet chemotherapy and whose responses were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) were evaluated in an association study to test for any link between their responses and the genotypes of 30 non-synonymous SNPs in 27 DNA repair genes (8). Homozygotes for the *TP53-72Pro* allele had a better response rate (54%) than those for the major allele *TP53-72Arg* (29%), irrespective of therapeutic regimens (Fig. 5A). The p53-72Arg protein has a greater activity in inducing apoptosis than the p53-72Pro protein, as described above (35), however, the opposite relationship was reported for mutant p53 proteins. p73 is a p53-related protein that plays a role in the apoptosis of cancer cells carrying *TP53* mutations via anticancer agents, and its function is abrogated by mutant p53 proteins. This abrogating activity is greater in mutant p53 proteins with an Arg residue at codon 72 compared with those with a Pro residue (42) and, therefore, the *TP53-72Pro* allele may lead to a better response to platinum-based doublet chemotherapy in NSCLC patients (Fig. 5B). This study indicates the potential utility of SNP as predictive markers for responses to chemotherapy.

Future Directions

Genetic factors affecting lung cancer risk have been identified by GWASs and other association studies. The results indicate that risk variants confer different magnitudes of increased risk in different populations for a variety of reasons, including differences in allele frequency and the genetic and environmental backgrounds that interact with the variants. Given the statistical power applied to the detection of associations in GWASs to date, there are unlikely to be many additional SNPs (tagged by commercially available DNA chips) with similar effects on alleles with high frequencies (>0.2) in populations of European ancestry (5,6). Thus, several different GWAS approaches are required to identify additional genetic factors underlying lung cancer risk. This should include GWASs of Asian populations. The fraction of lung ADC patients who are never-smokers and female is considerably higher in Asians than Europeans/Americans (43,44), suggesting that the former experience a greater or more distinct effect of genetic factors than the latter. Therefore, GWASs of Asians would be highly useful. In addition, GWASs focusing on specific lung cancer types would be worthwhile, because some genetic factors might be specifically associated with the risk of a specific type of lung cancer, such as SCLC, lung cancers in female never-smokers, or lung cancers with defined gene mutations. Lung ADC is known to develop via several carcinogenic pathways defined by oncogenic driver mutations in *EGFR*, *KRAS*, *HER2*, *ALK*, and *RET* genes, and the etiological factors are suggested to be different among those pathways (1,45,46). Finally, low frequency variants and common SNPs that have not been tagged by the DNA chips used in previous studies might also be involved in lung cancer risk (47,48). Thus, efforts to expand the scale of GWASs in terms of both sample size and SNP coverage, and to increase the number of SNPs taken forward to large-scale replication, may also lead to the identification of additional variants for lung cancer. Understanding the remaining genetic factors will help greatly in clarifying the disease etiology

and also in identifying high risk individuals for targeted screening and/or prevention. SNPs in DNA repair genes are associated with the response to platinum-doublet therapy. SNPs can be examined using blood cells and they may provide useful biomarkers in the clinical decision-making process for patients with advanced NSCLC who do not received surgery, which makes the molecular analysis of cancer cells difficult. No large-scale GWASs have been performed to investigate links with the response to lung cancer therapy or drug toxicities to the best of our knowledge, and these will also be useful for identifying biomarkers with clinical applications.

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References

1 Herbst RS, Heymach JV, Lippman SM. Lung cancer. N Engl J Med. 2008; 359: 1367–80.
2 Hung RJ, McKay JD, Gaborieau V, Boffetta P, Hashibe M, et al. A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. Nature, 2008; 452: 633–7.
3 McKay JD, Hung RJ, Gaborieau V, Boffetta P, Chabrier A, et al. Lung cancer susceptibility locus at 5p15.33. Nat Genet. 2008; 40: 1404–6.
4 Wang Y, Broderick P, Webb E, Wu X, Vijayakrishnan J, et al. Common 5p15.33 and 6p21.33 variants influence lung cancer risk. Nat Genet. 2008; 40: 1407–9.
5 Broderick P, Wang Y, Vijayakrishnan J, Matakidou A, Spitz MR, et al. Deciphering the impact of common genetic variation on lung cancer risk: a genome-wide association study. Cancer Res. 2009; 69: 6633–41.
6 Landi MT, Chatterjee N, Yu K, Goldin LR, Goldstein AM, Rotunno M, et al. A genome-wide association study of lung cancer identifies a region of chromosome 5p15 associated with risk for adenocarcinoma. Am J Hum Genet. 2009; 85: 679–91.
7 Miki D, Kubo M, Takahashi A, Yoon KA, Kim J, et al. Variation in TP63 is associated with lung adenocarcinoma susceptibility in Japanese and Korean populations. Nat Genet. 2010; 42: 893–6.
8 Shiraishi K, Kohno T, Tanai C, Goto Y, Kuchiba A, et al. Association of DNA repair gene polymorphisms with response to platinum-based doublet chemotherapy in patients with non-small-cell lung cancer. J Clin Oncol. 2010; 28: 4945–52.
9 Breslow NE, Day NE. Statistical methods in cancer research. Volume I—The analysis of case-control studies. IARC Sci Publ. 1980: 5–338.
10 Easton DF, Eeles RA. Genome-wide association studies in cancer. Hum Mol Genet. 2008; 17(R2): R109–15.
11 Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, Fuchs CS, Petersen GM, et al. Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. Nat Genet. 2009; 41: 986–90.
12 Cui R, Kamatani Y, Takahashi A, Usami M, Hosono N, et al. Functional variants in ADH1B and ALDH2 coupled with alcohol and smoking synergistically enhance esophageal cancer risk. Gastroenterology. 2009; 137: 1768–75.
13 Wolpin BM, Chan AT, Hartge P, Chanock SJ, Kraft P, et al. ABO blood group and the risk of pancreatic cancer. J Natl Cancer Inst. 2009; 101: 424–31.
14 Nakao M, Matsuo K, Hosono S, Ogata S, Ito H, et al. ABO blood group alleles and the risk of pancreatic cancer in a Japanese population. Cancer Sci. 2011; 102: 1076–80.
15 Oze I, Matsuo K, Hosono S, Ito H, Kawase T, et al. Comparison between self-reported facial flushing after alcohol consumption and ALDH2 Glu504Lys polymorphism for risk of upper aerodigestive tract cancer in a Japanese population. Cancer Sci. 2010; 101: 1875–80.
16 Minna JD. Nicotine exposure and bronchial epithelial cell nicotinic acetylcholine receptor expression in the pathogenesis of lung cancer. J Clin Invest. 2003; 111: 31–3.
17 Schuller HM. Nitrosamines as nicotinic receptor ligands. Life Sci. 2007; 80 (24–25): 2274–80.
18 Shiraishi K, Kohno T, Kunitoh H, Watanabe SI, Goto K, et al. Contribution of nicotine acetylcholine receptor polymorphisms to lung cancer risk in a smoking-independent manner in the Japanese. Carcinogenesis. 2009; 30: 65–70.
19 Wu C, Hu Z, Yu D, Huang L, Jin G, et al. Genetic variants on chromosome 15q25 associated with lung cancer risk in Chinese populations. Cancer Res. 2009; 69: 5065–72.
20 Thorgeirsson TE, Geller F, Sulem P, Rafnar T, Wiste A, et al. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. Nature. 2008; 452: 638–42.
21 Baird DM. Variation at the TERT locus and predisposition for cancer. Expert Rev Mol Med. 2010; 12: e16.
22. Jin G, Xu L, Shu Y, Tian T, Liang J, et al. Common genetic variants on 5p15.33 contribute to risk of lung adenocarcinoma in a Chinese population. Carcinogenesis. 2009; 30: 987–90.
23 Kohno T, Kunitoh H, Shimada Y, Shiraishi K, Ishii Y, et al. Individuals susceptible to lung adenocarcinoma defined by combined HLA-DQA1 and TERT genotypes. Carcinogenesis. 2010; 31: 834–41.
24 Truong T, Hung RJ, Amos CI, Wu X, Bickeboller H, et al. Replication of lung cancer susceptibility loci at chromosomes 15q25, 5p15, and 6p21: a pooled analysis from the International Lung Cancer Consortium. J Natl Cancer Inst. 2010; 102: 959–71.
25 Rafnar T, Sulem P, Stacey SN, Geller F, Gudmundsson

J, Sigurdsson A, et al. Sequence variants at the TERT-CLPTM1L locus associate with many cancer types. Nat Genet. 2009; 41: 221–7.
26 Petitjean A, Hainaut P, Caron de Fromentel C. TP63 gene in stress response and carcinogenesis: a broader role than expected. Bull Cancer. 2006; 93: E126–35.
27 Wang Y, Broderick P, Matakidou A, Vijayakrishnan J, Eisen T, Houlston RS. Variation in TP63 is associated with lung adenocarcinoma in the UK population. Cancer Epidemiol Biomarkers Prev. 2011; 20: 1453–62.
28 Marugame T, Sobue T, Nakayama T, Suzuki T, Kuniyoshi H, et al. Filter cigarette smoking and lung cancer risk; a hospital-based case—control study in Japan. Br J Cancer. 2004; 90: 646–51.
29 Dong LM, Potter JD, White E, Ulrich CM, Cardon LR, Peters U. Genetic susceptibility to cancer: the role of polymorphisms in candidate genes. Jama. 2008; 299: 2423–36.
30 Sugimura H, Wakai K, Genka K, Nagura K, Igarashi H, et al. Association of Ile462Val (Exon 7) polymorphism of cytochrome P450 IA1 with lung cancer in the Asian population: further evidence from a case-control study in Okinawa. Cancer Epidemiol Biomarkers Prev. 1998; 7: 413–7.
31 Sugimura H, Kohno T, Wakai K, Nagura K, Genka K, et al. hOGG1 Ser326Cys polymorphism and lung cancer susceptibility. Cancer Epidemiol Biomarkers Prev. 1999; 8: 669–74.
32 Fan R, Wu MT, Miller D, Wain JC, Kelsey KT, et al. The p53 codon 72 polymorphism and lung cancer risk. Cancer Epidemiol Biomarkers Prev. 2000; 9: 1037–42.
33 Houlston RS. CYP1A1 polymorphisms and lung cancer risk: a meta-analysis. Pharmacogenetics. 2000; 10: 105–14.
34 Li H, Hao X, Zhang W, Wei Q, Chen K. The hOGG1 Ser326Cys polymorphism and lung cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2008; 17: 1739–45.
35 Dumont P, Leu JI, Della Pietra AC, 3rd, George DL, Murphy M. The codon 72 polymorphic variants of p53 have markedly different apoptotic potential. Nat Genet. 2003; 33: 357–65.
36 Kohno T, Shinmura K, Tosaka M, Tani M, Kim SR, et al. Genetic polymorphisms and alternative splicing of the hOGG1 gene, that is involved in the repair of 8-hydroxyguanine in damaged DNA. Oncogene. 1998; 16: 3219–25.
37 Yamane A, Kohno T, Ito K, Sunaga N, Aoki K, et al. Differential ability of polymorphic OGG1 proteins to suppress mutagenesis induced by 8-hydroxyguanine in human cell *in vivo*. Carcinogenesis 2004; 25: 1689–94.
38 Bartsch H, haugen A, Risch A, Shields P, Vineis P. Genetic susceptibility. In: Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC, editors. World health organization classification of tumors: Pathology and genetics, tumours of lung, pleura, thymus and heart. Lyon: IARC Press; 2004. p. 24–25.
39 Kohno T, Kunitoh H, Mimaki S, Shiraishi K, Kuchiba A, Yamamoto S, et al. Contribution of the TP53, OGG1, CHRNA3, and HLA-DQA1 genes to the risk for lung squamous cell carcinoma. J Thorac Oncol. 2011; 6: 813–7.
40 Camps C, Sirera R, Iranzo V, Taron M, Rosell R. Gene expression and polymorphisms of DNA repair enzymes: cancer susceptibility and response to chemotherapy. Clin Lung Cancer. 2007; 8: 369–75.
41 Olaussen KA, Dunant A, Fouret P, Brambilla E, Andre F, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med. 2006; 355: 983–91.
42 Bergamaschi D, Gasco M, Hiller L, Sullivan A, Syed N, et al. p53 polymorphism influences response in cancer chemotherapy via modulation of p73-dependent apoptosis. Cancer Cell. 2003; 3: 387–402.
43 Subramanian J, Govindan R. Lung cancer in never smokers: a review. J Clin Oncol. 2007; 25: 561–70.
44 Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers--a different disease. Nat Rev Cancer. 2007; 7: 778–90.
45 Lovly CM, Carbone DP. Lung cancer in 2010: One size does not fit all. Nat Rev Clin Oncol. 2011; 8: 68–70.
46 Kohno T, Ichikawa H, Totoki Y, Yasuda K, Hiramoto M, Nammo T, et al. KIF5B-RET fusions in lung adenocarcinoma. Nat Med. 2012; 18: 375–7.
47 Bodmer W, Bonilla C. Common and rare variants in multifactorial susceptibility to common diseases. Nat Genet. 2008; 40: 695–701.
48 Cirulli ET, Goldstein DB. Uncovering the roles of rare variants in common disease through whole-genome sequencing. Nat Rev Genet. 2010; 11: 415–25.