Association of GWAS-Identified Lung Cancer Susceptibility Loci with Survival Length in Patients with Small-Cell Lung Cancer Treated with Platinum-Based Chemotherapy

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Abstract

Genetic variants have been shown to affect length of survival in cancer patients. This study explored the association between lung cancer susceptibility loci tagged by single-nucleotide polymorphisms (SNPs) identified in the genome-wide association studies and length of survival in small-cell lung cancer (SCLC). Eighteen SNPs were genotyped among 874 SCLC patients and Cox proportional hazards regression was used to examine the effects of genotype on survival length under an additive model with age, sex, smoking status and clinical stage as covariates. We identified 3 loci, 20q13.2 (rs4809957G>A), 22q12.2 (rs36600C>T) and 5p15.33 (rs401681C>T), significantly associated with the survival time of SCLC patients. The adjusted hazard ratio (HR) for patients with the rs4809957 GA or AA genotype was 0.80 (95% CI, 0.66–0.96; P=0.0187) and 0.73 (95% CI, 0.55–0.96; P=0.0263) compared with the GG genotype. Using the dominant model, the adjusted HR for patients carrying at least one T allele at rs36600 or rs401681 was 0.78 (95% CI, 0.63–0.96; P=0.0199) and 1.29 (95% CI, 1.08–1.55; P=0.0047), respectively, compared with the CC genotype. Stratification analyses showed that the significant associations of these 3 loci were only seen in smokers and male patients. The rs4809957 SNP was only significantly associated with length of...
survival of patients with extensive-stage but not limited-stage tumor. These results suggest that some of the lung cancer susceptibility loci might also affect the prognosis of SCLC.

Introduction

Lung cancer is the leading cause of cancer deaths all over the world, and categorized into non-small cell lung cancer and small-cell lung cancer (SCLC) [1]. SCLC, accounting for 15%–20% of total lung cancer, is a type of very aggressive neuroendocrine malignancies characterized by high growth rate, widespread metastases and poor prognosis [2, 3]. However, length of survival in patients with SCLC varies greatly and this has been known to be influenced by several clinical factors, such as patient's age, performance status and clinical stage. In recent years, evidence has been accumulated to show that genetic variants might also play a role in the prognosis and length of survival in patients [4, 5]. The identification of such loci might have valuable implication in precision treatment of cancer.

We have previously conducted a genome-wide association study (GWAS) on SCLC to identify genetic variants influencing length of survival in patients and found that the rs1820453T > G SNP, located in the promoter region of the YAP1 gene which creates a transcription factor binding site and results in down-regulation of YAP1 expression, is significantly associated [4]. However, this previous GWAS included only 245 samples in the discovery stage and 305 samples in the replication stage and the limited discovery power might obstruct to find most loci with small or moderate effect. Another GWAS on SNPs and survival in NSCLC identified two SNPs, rs7629386 and rs3850370, associated with survival in NSCLC patients derived from both Chinese and Caucasian populations [6]. Thus, other study strategies are warranted to uncover more genetic variants that are associated with length of survival in patients only with SCLC.

In recent years, several GWAS conducted in different ethnic populations to discover susceptibility variants for overall lung cancer have been reported. These published studies have identified at least 26 loci in 13 chromosomal regions that are significantly associated with risk for the development of lung cancer [7–15]. In these GWAS, most case subjects were non-small cell lung cancer patients with a proportion of them being patients with SCLC. It has been suggested in many studies that some cancer susceptibility variants may also contribute to disease progression and prognosis [16, 17]. Based on these observations, we sought to examine the hypothesis that the GWAS-identified lung cancer susceptibility loci may also be associated with outcome of SCLC.

Here, we report our study on the association between GWAS-identified lung cancer susceptibility loci and length of survival of SCLC, in which 18 susceptibility loci were analyzed in total of 874 patients. We found that three of these susceptibility loci, 20q13.2 (rs4809957), 22q12.2 (rs36600) and 5p15.33 (rs401681), are significantly associated with length of survival in SCLC patients.
Materials and Methods

Ethics statement
All participants provided written informed consent and the ethical committees of Cancer hospital of Chinese Academy of Medical Science and Nanjing Medical University approved this research project.

Patients and clinical characteristics
A total of 874 patients with SCLC were included in this study. Among them, 569 were recruited at Cancer hospital, Chinese Academy of Medical Science (Beijing) between July 2000 and October 2011 and 305 were recruited at Cancer Hospital of Jiangsu Province, the First Affiliated Hospital of Nanjing Medical University and Nanjing Thoracic Hospital (Nanjing), and four tertiary referral hospitals at Wuhan city, Hubei Province between March 2002 and March 2008. All of them were self-reported ethnic Han Chinese. To be included in this study, all patients had to have cytologically confirmed SCLC and received the first-line carboplatin (AUC 5–6, day 1) or cisplatin (60–80 mg/M², day 1) plus etoposide (100 mg/M², days 1–3) chemotherapy for at least two cycles. Participants did not receive other therapeutics. According to the Veterans’ Administration Lung Study Group, patients were classified as having limited disease or extensive disease on the basis of the results of a physical examination; computed tomography scan of the chest, liver, and adrenal glands; a magnetic resonance imaging scan or computed tomography scan of the head; and a bone scan. Characteristics and clinical information including age, sex, smoking status and clinical stage, were obtained from patients’ medical records and are shown in Table 1. Length of survival of patients was measured from the date of treatment to the date of last follow-up or death. Whether and when a patient had died were obtained from inpatient and outpatient records, patients’ families, or local Public Security Census Register Office through follow-up telephone calls. The last date of follow-up was December 20th, 2012. Patients alive on the last follow-up date were considered censored. Written informed consents were from all patients and this study was approved by the Institutional Review Board of Cancer hospital, China Academy of Medical Science. Most patients have been reported in our previous study [4].

SNP selection, genotyping and quality control
Genomic DNA from each patient was extracted from blood samples using commercial Flexi Gene DNA extraction kit (Qiagen, Hilden, Germany). Twenty-six SNPs at 13 chromosomal regions were reported to be associated with risk of lung cancer in the previous GWAS [7–15]. We did quality control of these SNPs using the genotyping information from Version 3 of 1000 Genomes Project data. Among these SNPs, six SNPs with minor allele frequency (MAF) <0.05 were excluded. We then computed the correlation coefficient (r) of each pair of adjacent SNPs at the same chromosome to assess the LD status. SNPs with r²>0.8 were considered to be in one LD block, and we thus selected one SNP in the block.
for further analyses. With these criteria, we finally selected 18 tagSNPs for genotyping in this study. The information of these loci was shown in Table 2. Among these loci, only 15 can be readily genotyped by using the MassARRAY system (Sequenom, San Diego, CA). Two loci, rs17728461 and rs2736100, were genotyped by TaqMan assays using ABI 7900HT system (Applied Biosystems, Foster City, CA). Due to the failure of genotyping using both Sequenom or TaqMan assay, the remaining rs2395185 SNP was replaced with rs28366298 SNP as a surrogate, a locus in perfect linkage disequilibrium (LD) with rs2395185 (r^2 = 1.00) in the same LD block at 6p21.32 and this SNP was also genotyped by TaqMan assay. The primers and probes for genotyping, which were commercially designed by ABI Company (Applied Biosystems), are available upon request.

Several quality-control measures were implemented in genotyping analysis, including (i) duplicated samples were mixed in the plates; (ii) persons performing the genotyping assays were not aware of the status of the duplicated samples; (iii) both positive and negative (no DNA) control samples were included on every 384-well assay plate and (iv) 20% masked random samples were genotyped twice by different investigators and all the results were completely concordant, with the concordance being 100%.

Table 1. Clinical characteristics of 874 patients with small-cell lung cancer.

| Characteristics       | N=874 | No. (%) | MST (month) | P^1 |
|-----------------------|-------|---------|-------------|-----|
| Dead                  | 521   | (59.6)  | 25          |     |
| Alive                 | 353   | (40.4)  |             |     |
| Sex                   |       |         |             | 0.0274 |
| Male                  | 666   | (76.2)  | 24          |     |
| Female                | 208   | (23.8)  | 29          |     |
| Age                   |       |         |             | 0.0018 |
| ≤50 years             | 231   | (26.4)  | 27          |     |
| 51–60 years           | 318   | (36.4)  | 27          |     |
| >60 years             | 325   | (37.2)  | 22          |     |
| Smoking status        |       |         |             | 0.0229 |
| Nonsmoker             | 249   | (28.5)  | 29          |     |
| Smoker                | 625   | (71.5)  | 24          |     |
| Clinical stage*       |       |         |             | <0.0001 |
| Limited               | 479   | (54.8)  | 32          |     |
| Extensive             | 395   | (45.2)  | 18          |     |

Abbreviation: No., number of patients; MST, median survival time.
^P values for log-rank test.
*Classified according to the Veterans’ Administration Lung Study Group.

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For the association between each SNP and length of survival of SCLC patients, we conducted a Cox proportional hazards regression under a log-additive genetic model and hazard ratio (HR) and their 95% confidence interval (CI) were adjusted for age (≤50, 51–60 or >60 years), sex (male or female), smoking status (nonsmoker or smoker) and clinical stage (limited stage or extensive stage). Kaplan-Meier survival estimates were assessed using the log-rank test. All statistical tests were carried out in a two-sided manner using the 'survival package' in R.

Table 2. Associations of 18 candidate SNPs and survival of patients with small-cell lung cancer.

| SNP ID   | Chromosome | Putative Gene | Minor Allele | MAF | HR (95% CI) | P* |
|----------|------------|---------------|--------------|-----|-------------|----|
| rs4809957 | 20q13.2    | CYP24A1       | A            | 0.38| 0.84 (0.74–0.96) | 0.0098 |
| rs36600   | 22q12.2    | MTMR3         | T            | 0.12| 0.82 (0.68–0.98) | 0.0261 |
| rs401681  | 5p15.33    | CLPTM1L       | T            | 0.29| 1.14 (1.01–1.28) | 0.0356 |
| rs17728461| 22q12.2    | HORMAD2       | G            | 0.22| 0.87 (0.75–1.01) | 0.0594 |
| rs1663689 | 10p14      | GATA3         | C            | 0.37| 0.89 (0.78–1.01) | 0.0634 |
| rs2853677 | 5p15.33    | TERT          | G            | 0.39| 0.92 (0.81–1.04) | 0.1841 |
| rs247008  | 5q31.1     | CSF2          | A            | 0.47| 0.92 (0.82–1.04) | 0.2063 |
| rs28366298| 6p21.32    | HLA-DRB1      | C            | 0.36| 1.08 (0.96–1.22) | 0.2153 |
| rs10937405| 5q32       | TP63          | T            | 0.32| 1.09 (0.95–1.25) | 0.2466 |
| rs2736100 | 5p15.33    | TERT          | C            | 0.42| 0.94 (0.83–1.07) | 0.3762 |
| rs753955  | 13q12.12   | MIPEP         | G            | 0.37| 0.95 (0.83–1.08) | 0.4002 |
| rs465498  | 5p15.33    | CLPTM1L       | G            | 0.18| 1.08 (0.90–1.28) | 0.4148 |
| rs2895680 | 5q32       | STK32A        | C            | 0.32| 0.96 (0.84–1.10) | 0.5410 |
| rs7216064 | 17q24.3    | BPTF          | G            | 0.36| 1.04 (0.92–1.18) | 0.5414 |
| rs7066803 | 10q25.2    | VTL1A         | A            | 0.26| 1.03 (0.89–1.19) | 0.6792 |
| rs4488809 | 3q28       | TP63          | C            | 0.49| 0.98 (0.87–1.11) | 0.7392 |
| rs9387478 | 6q22.2     | DCBLD1        | C            | 0.48| 0.98 (0.87–1.11) | 0.7726 |
| rs8042374 | 15q24      | CHRNA3        | A            | 0.27| 1.01 (0.88–1.15) | 0.9128 |

Abbreviation: MAF, minor allele frequency; HR, hazard ratio; CI, confidence interval. The results with P<0.05 were shown in bold.

*Calculated with multivariate Cox regression under an additive genetic model adjusted for age, sex, smoking status and clinical stage.

**P** values were obtained from the comparisons of the minor allele with the major allele.

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Statistical analysis

For the association between each SNP and length of survival of SCLC patients, we conducted a Cox proportional hazards regression under a log-additive genetic model and hazard ratio (HR) and their 95% confidence interval (CI) were adjusted for age (≤50, 51–60 or >60 years), sex (male or female), smoking status (nonsmoker or smoker) and clinical stage (limited stage or extensive stage). Kaplan-Meier survival estimates were assessed using the log-rank test. All statistical tests were carried out in a two-sided manner using the 'survival package' in R.

Results

Patient characteristics

The clinical characteristics of 874 SCLC patients are shown in Table 1. Up to the last follow-up date, 521 (59.6%) patients had died of SCLC, with a median survival time (MST) of 25 months; 353 (40.4%) patients are still alive. The median follow-up time was 40 months. Among these patients, 479 (54.8%) had limited disease and 395 (45.2%) had extensive disease. The MST for limited disease was 32
months and for extensive disease was 18 months, indicating that clinical stage is a parameter strongly associated with length of survival in SCLC patients ($P<0.0001$). In addition, patient's age was also strongly associated with length of survival, with older patients ($>60$ years) having shorter survival time than younger patients ($\leqslant60$ years) ($P=0.0018$).

### Association of genetic susceptibility loci with length of patients’ survival

We found that, among the 18 loci analyzed, three SNPs, i.e., rs4809957 in CYP24A1 at 20q13.2, rs36600 in MTMR3 at 22q12.2 and rs401681 in CLPTM1L at 5p15.33, were significantly (all $P<0.05$) associated with length of survival in SCLC patients (Table 2).

The rs4809957G > A locus was the most significant one, with the adjusted HR for death of patients being 0.84 (95% CI, 0.74–0.96; $P=0.0098$) under the additive model (Table 2). The MST for the rs4809957 GG, GA or AA genotypes was 22, 27 or 28 months, respectively. The adjusted HR for death of patients with the rs4809957 GA or AA genotype was 0.80 (95% CI, 0.66–0.96; $P=0.0187$) and 0.73 (95% CI, 0.55–0.96; $P=0.0263$) compared with the GG genotype (Table 3). In a dominant model, patients with the rs4809957 GA or AA genotype had significantly longer MST (27 months) than those with the GG genotype, with the adjusted HR being 0.78 (95% CI, 0.65–0.93; $P=0.0067$) (Table 3 and Fig. 1).

The rs36600C > T SNP was also significantly associated with length of survival in SCLC patients, with the adjusted HR being 0.82 (95% CI, 0.68–0.98; $P=0.0261$; Table 2). Compared with patients with the CC genotype (MST, 24 months), patients carrying at least one T allele had longer length of survival (MST, 29 months), with the adjusted HR being 0.78 (95% CI, 0.63–0.96; $P=0.0199$) (Table 3 and Fig. 1).

In contrast with the above two loci showing favorable effects of minor alleles on patient’s survival, the rs401681C > T change showed a poor effect on length of survival, with the adjusted HR for death of patients being 1.14 (95% CI, 1.01–1.28; $P=0.0356$) under the additive model (Table 2). Compared with patients carrying the rs401681 CC genotype (MST, 28 months), patients carrying the CT or TT genotype had significantly shorter survival time (MST, 23 or 24 months) with the adjusted HR being 1.35 (95% CI, 1.11–1.63; $P=0.0022$) or 1.20 (95% CI, 0.92–1.57; $P=0.1819$), respectively (Table 3). Under a dominant model, patients with at least one T allele had significantly shorter survival time (MST, 23 months; adjusted HR, 1.29, 95% CI, 1.08–1.55; $P=0.0047$) compared with those with the CC genotype (Table 3 and Fig. 1).

Analyses stratified by patients’ age, sex, smoking status and clinical stage were further performed and the results are shown in Table 4. The association with length of survival of patients for the rs4809957, rs36600 and rs401681 SNPs were only seen in smokers and males. After stratified by clinical stage of the disease, we found that rs4809957 but not rs36600 and rs401681 was specifically significantly associated with length of survival in patients with extensive disease (adjusted HR,
0.80, 95% CI, 0.67–0.96; \(P = 0.0181\). The 3 SNPs did not display significantly different association with length of patient survival in terms of patients’ age.

**Discussion**

Based on the GWAS-identified lung cancer susceptibility loci, this study explored whether they are also associated with length of survival in SCLC patients. We found that, of the 18 investigated lung cancer susceptibility SNPs, 3 are also associated with survival of Chinese SCLC patients. To the best of our knowledge, this is the first report connecting the lung cancer susceptibility loci to the prognosis of SCLC. Our results are in line with the findings that some cancer susceptibility variants may also contribute to disease progression and prognosis\,[16, 17]. Our results denoted that male patients were more susceptibility to cancer aggression, as compared with female patients, evidenced by less survival rate. This observation is congruent with recent publications, supporting that there is a disparity between genders, where the male’s origin cells also exhibited more susceptibility\,[18, 19].

The rs4809957 SNP is located in the 3′-untranslated region (3′-UTR) of CYP24A1 at 20q13.2. It has been well known that SNPs located at 3′-UTR of genes might modulate gene expression by affecting certain microRNA’s binding to their transcript. As a result, such a SNP in the 3′-UTR of CYP24A1 might act through

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**Table 3. HR and MST of patients with small-cell lung cancer for the 3 significant SNPs.**

| Genotype | No. | Dead/Alive | MST (months) | HR (95% CI) | \(P^*\) |
|----------|-----|------------|--------------|-------------|---------|
| rs4809957 |     |            |              |             |         |
| GG       | 299 | 194/105    | 22           | 1.00 (Reference) |
| GA       | 433 | 250/183    | 27           | 0.80 (0.66–0.96) | 0.0187 |
| AA       | 127 | 67/60      | 28           | 0.73 (0.55–0.96) | 0.0263 |
| GA+AA    | 560 | 317/243    | 27           | 0.78 (0.65–0.93) | 0.0067 |
| rs36600  |     |            |              |             |         |
| CC       | 640 | 396/244    | 24           | 1.00 (Reference) |
| CT       | 197 | 102/95     | 30           | 0.78 (0.63–0.98) | 0.0296 |
| TT       | 23  | 14/9       | 24           | 0.77 (0.45–1.31) | 0.3336 |
| CT+TT    | 220 | 116/104    | 29           | 0.78 (0.63–0.96) | 0.0199 |
| rs401681 |     |            |              |             |         |
| CC       | 379 | 209/170    | 28           | 1.00 (Reference) |
| CT       | 360 | 224/136    | 23           | 1.35 (1.11–1.63) | 0.0022 |
| TT       | 115 | 74/41      | 24           | 1.20 (0.92–1.57) | 0.1819 |
| CT+TT    | 475 | 298/177    | 23           | 1.29 (1.08–1.55) | 0.0047 |

Abbreviation: No., number of patients; MST, median survival time; HR, hazard ratio; CI, confidence interval. Because of genotyping failure of some DNA samples, the number of subjects may not add up to the total number.

*Calculated with multivariate Cox regression models adjusted for age, sex, smoking status and clinical stage. *

\(P\) values were obtained from the comparison with the major genotype.

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impacting the gene expression level to consequently influence patients’ survival.

CYP24A1 plays an important role in vitamin D homeostasis in tissues by catabolizing the active form of vitamin D (1,25-D3), which has anti-proliferative effect in cancer, to inactive calcitroic acid. Previous studies have shown that CYP24A1 is overexpressed in many types of human cancer including lung cancer.

Figure 1. Kaplan–Meier estimates of overall survival of patients with small-cell lung cancer according to rs480957G > A (a), rs36600C > T (b) or rs401681C > T (c) genotypes.

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and overexpression of this enzyme is an independent prognostic maker of survival in patients with lung adenocarcinoma [22]. In our previous lung cancer GWAS, it seems that the rs4809957A allele was the risk allele compared with the G allele [9]. However, in the current study, the A allele was found to be the favorable allele for survival of SCLC patients. This disparity effect of the CYP24A1 variant in lung cancer susceptibility and SCLC survival is currently unknown. To address this, it would be interesting to analyze the allele-specific expression of CYP24A1 in normal lung tissues and lung cancer tissues.

The rs36600 SNP is located in the intronic region of the MTMR3 gene at 22q12.2 and the T allele was associated with better survival in SCLC patients. This association direction is different from that for lung cancer susceptibility, as the previous GWAS reported that the rs36600T allele was associated with increased risk of lung cancer [9]. MTMR3 encodes myotubularin-related protein-3, which belongs to myotubularin phosphatase gene family [23]. It has been shown that MTMR3 is involved in cancer cell proliferation, migration and invasion [24]. MTMR3 is also involved in autophagic activity [25], an important mechanism in the inhibition of tumor growth. The rs36600 SNP is located in the intron of MTMR3, which might influence the gene splicing or expression [26]. Therefore, it is plausible that genetic variation in MTMR3 is associated with SCLC survival, although the function of the rs36600 SNP remains elusive.

Located in the TERT-CLPTM1L region at 5p15.33 harboring multiple variants that are associated with susceptibility to many types of human cancer, the variant...
rs401681T allele is associated with increased risk for death of SCLC in this study. Previous GWAS showed that the rs401681T allele is associated with decreased risk of lung, prostate, bladder, cervical and basal cell cancers, but increased risk of pancreatic cancer, melanoma and chronic lymphocytic leukemia [27–30].

CLPTM1L, also known as cisplatin resistance related gene 9 (CRR9), has been found to be overexpressed in human ovarian cancer cells that are resistant to cisplatin-induced apoptosis [31]. Recent study also showed that CLPTM1L is overexpressed in lung cancer tissues compared with matched normal lung tissues and its overexpression seems to protect from apoptosis induced by cisplatin [32,33]. Taken together, these findings suggest that the rs401681 SNP may affect the efficacy of platinum-based chemotherapy, the first-line regime for SCLC, which is consequently associated with poor survival in patients.

The present study has several strengths. First, the sample size was relative larger. We recruited 874 patients with SCLC for analysis, which had suitable statistical power to identify the true association with length of survival. Second, main and simple treatment with platinum-based chemotherapy and relatively shorter survival time of SCLC might minimize the bias of our results by unknown confounding factors and enhanced our ability to find genetic factors associated with survival. Therefore, our results are convincing. However, this study also has some limitations. Although patients with SCLC were recruited from several different hospitals, this study should be considered as a single-center study. Thus, confirmation studies with larger sample size from different ethnic populations are needed. In addition, it would be interesting to elucidate the functional relevance of the variants to get insight into the mechanism underlying the association.

In summary, our studies found that three GWAS identified lung cancer susceptibility loci are also associated with length of survival in SCLC patients treated with platinum-based chemotherapy. It seems that, however, these lung cancer susceptibility loci display different direction in the association with survival of patients, suggesting that the acting mechanism of these variant loci may be different between lung cancer susceptibility and prognosis. Our findings might be valuable in precision treatment of patients with SCLC.

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**Author Contributions**

Conceived and designed the experiments: D. Lin D. Li CW WT. Performed the experiments: LXW ZLD. Analyzed the data: JC DKY. Contributed reagents/materials/analysis tools: PY BHX HBS TCW. Wrote the paper: D. Li D. Lin.
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