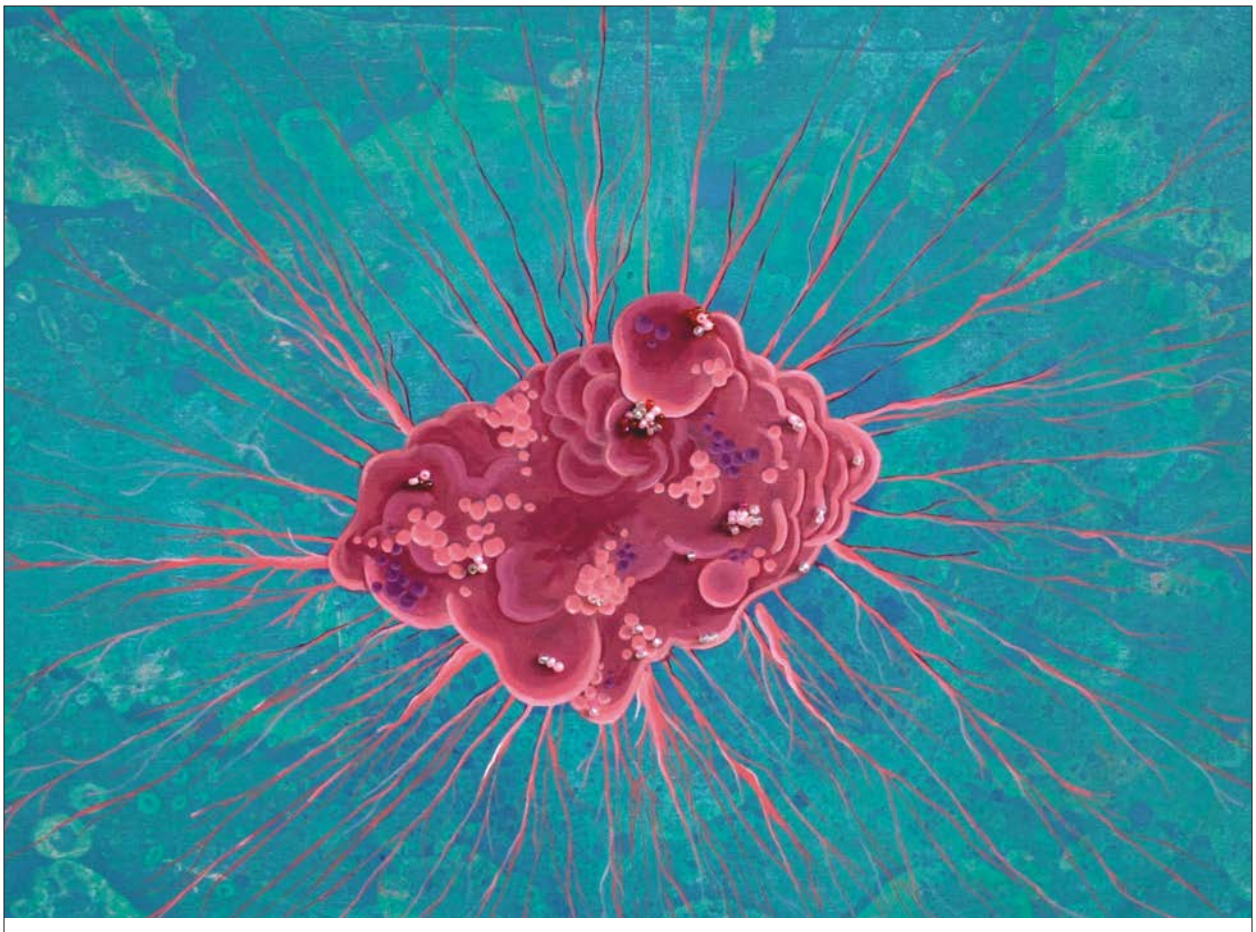

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Research Article
High Level Amplifications of *AKT3*, *SDCCAG8* and *SLC35F3* Genes at Chromosomal 1q42.2-44 Region in Non-small Cell Lung Cancer: Early and Prognostic Implications

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Abstract

Background: Genomic alterations in the early stage of Non-Small Cell Lung Cancer (NSCLC) have a tight relationship with tumor initiation and potentially activate downstream pathways that are implicated in tumor progression. **Methodology:** In this study, the most salient and consistent finding was frequentcopy number gains (log_2 ratio >0.25) at the long of chromosome 1, which occurred in 78.3% (18/23) of stage I/II NSCLC cases and the delineated minimal common region was 1q21.1-q44. More importantly, three distinct regions of amplifications in the 1q21.1-q44 region were detected in 17.4% (4/23) of the cases. **Results:** Among these amplified loci, the 1q44 locus comprises *AKT3* are presentative oncogene. In addition, *SDCCAG8* (1q44) and *SLC35F3* (1q42.2) genes were identified as probable genetic targets within the amplicon (12.5%), which have not been previously considered to play a pathogenic role in NSCLCs. These findings suggested that genetic alterations on chromosome 1q are the first step in the initiation of the genomic instability contributing to early NSCLC development. **Conclusion:** The newly identified genes at the 1q42.2-q44 amplified chromosomal region might be of interest for further studies of the pathophysiology of the early stages of NSCLC and are indicated as potential therapeutic targets.

Key words: Non-small cell lung cancer, array-CGH, copy number gain, high-level amplifications

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Non-Small Cell Lung Cancer (NSCLC) is a major global health burden and develops through the accumulation of genetic and epigenetic changes[1]. Genetic alterations in the early stages of cancer have a tight relationship with tumor initiation and potentially activate downstream pathways implicated in tumor progression, but the method of initiation in sporadic neoplasias is largely unknown[2]. With this in mind, initiation of appropriate treatment is perhaps more important for patients with early-stage disease than for those who present with advanced NSCLC, as the potential for a lost curative opportunity is greatest at earlier stages[3]. Clearly, early detection can save lives, but accurate screening tests for high-risk individuals are still lacking[4]. To improve the prognosis of NSCLC patients, it is necessary to identify suitable markers to select patients with poor prognosis who can benefit from adjuvant therapy after surgery. Additionally, new techniques such as molecular diagnosis and tumor profiling are promising to improve diagnostics of the early stages of NSCLC.

Lung tumorigenesis is a heterogeneous process that arises after a series of clonal molecular genetic alterations, including genomic gains and losses with deletion of tumor-suppressor genes and amplification of oncogenes playing significant roles. Thus, identification of these specific genomic aberrations may help to determine tumor-specific signatures involved in the initiation and progression of NSCLC and thus help to establish genomic biomarkers for the early detection of lung tumors[5]. Although, many studies have been performed to evaluate the genetic events associated with the development and progression of NSCLC, its molecular mechanism still remains to be understood. Furthermore, the genomic markers that predict aggressive clinical behavior of NSCLC still remain to be identified. Therefore, further investigations are needed to gain additional insight into the clinical significance of recurrent chromosomal alterations for early stages of NSCLCs.

In this study, we conducted whole-genome Comparative Genomic Hybridization (CGH) to identify early genetic alterations and new candidate genes that might be indicative and specific for the early stages of NSCLCs. These findings may replenish the pre-existing knowledge about the association between genetic alterations and early stages of NSCLS and have the potential to develop new therapies for this disease.

MATERIALS AND METHODS

Tumor samples: Twenty three NSCLC patients undergoing surgery as a primary treatment, without previous radiation or chemotherapy were analyzed. All cases were reviewed by pathologists to verify the original histopathological diagnosis, depth of tumor, invasion, tumor differentiation and lymph node metastasis. The written informed consent was obtained from each patient according to institutional regulations. This study has been reviewed and approved by the Institutional Review Board of the Chungnam National University Hospital. All of the patients were classified according to the WHO histologic typing of lung carcinomas and the UICC TNM (tumor-node-metastasis) staging system.

Array-CGH experiment: The DNA isolation was performed following the manufacturer's instructions (Promega, Madison, WI, USA) with some modifications as described before[5,6]. Array-CGH was performed the MacArray™ Karyo 4000 chips (Macrogen, Inc., Seoul)[7-10] according to the manufacturer's instructions and as described in previous studies[5,11]. Briefly, 500 ng of normal male DNA (reference) and digested tumor DNA (test) were labeled with Cy5-dCTP and Cy3-dCTP, respectively by random primed labeling (Array-CGH Genomic Labeling System; Invitrogen, CA, USA). The labeled probe and human Cot-I DNA were mixed and dissolved in hybridization solution. Hybridizations were performed in a sealed chamber for 48 h at 37°C. After hybridization, array slides were scanned on a GenePix 4200A two-color fluorescent scanner (Axon Instruments, Union City, CA, USA) quantification was performed using GenePix software (Axon instruments).

Data analysis: We applied LOWESS normalization, a form of smoothing adjustment that removes intensity-dependent dye bias. The spot quality criteria were set as foreground-to-background greater than 3.0 and standard deviation of triplicates less than 0.2. The break point detection and status assignment of genomic regions is performed by the GLAD software was used[12]. A low-level copy number gain was definedas a $\log_2$ ratio >0.25 and a copy number loss was definedas a $\log_2$ ratio <-0.25. High-level amplifications of clones was defined as an intensity ratio of higher than 1 on the $\log_2$ scale. This threshold value was determined empirically as a value 3-fold that of the standard deviation calculated from 30 normal male to normal females in hybridization experiments. Macrogen's MAC viewer version 1.6.6, CGH-explorer 2.55 and avadis 3.3 prophetic were used for graphical illustration and image analysis of array-CGH data.

RESULTS

Genome-wide array analysis in early NSCLC cases: To identify DNA copy number alterations and new candidate genes associated with the early stages of NSCLCs, we performed a

Table 1: A detailed overview of clinicopathological data of the 23 early stages of non-small cell lung cancer

Gender	Age	TNM[a] classification	Tumor stage	Histology
M	61	T2N0M0	IB	SCC
F	50	T1N0M0	IA	AC
F	47	T2N0M0	IB	SCC
M	66	T1N0M0	IA	SCC
M	65	T1N1M0	IIA	SCC
F	61	T1N0M0	IA	AC
F	56	T2N1M0	IIB	AC
M	72	T1N0M0	IA	SCC
M	61	T1N0M0	IIB	SCC
F	70	T2N1M0	IIA	SCC
M	60	T2N0M0	IB	SCC
M	70	T2N1M0	IIA	SCC
M	75	T1N0M0	IA	AC
F	69	T1N0M0	IA	AC
M	72	T1N0M0	IA	SCC
M	70	T2N1M0	IIA	SCC
M	65	T2N1M0	IIA	SCC
F	56	T2N0M0	IB	SCC
M	59	T2N0M0	IB	SCC
M	71	T1N0M0	IA	AC
M	62	T2N0M0	IIA	AC
M	55	T1N0M0	IA	SCC
F	62	T1N0M0	IA	AC

[a]TNM: Tumor-node-melastasis

genome-wide array-CGH with 23 cases of stage I/IIN SCLCs. The majority of clones were frequently gained (log_2 ratio >0.25) or lost (log_2 ratio <-0.25), with 97.5% of the clones gained or lost in 62.7% of the cases. The most notable finding was the frequent and consistent copy number gains at the long arm of chromosome 1, which was identified in 78.3% (18/23) of the NSCLCs. More specifically, high-level gains (>0.5 log_2 ratio) and high-level amplifications (>1 log_2 ratio) on chromosome 1q were detected in 43.5% (10/23) and 17.4% (4/23) of the cases, respectively. A detailed overview of clinicopathological data of 23 NSCLCs is shown in Table 1.

Delineation of the 1q amplicon in early-stage NSCLCs: A more detailed analysis of chromosome 1q identified three distinct regions of alterations across the chromosome. The minimal common region identified by array-CGH was located between BAC53_O05 and BAC38_P06. The first locus is located at the 1q21.1-q25.3 region (101.1-102.9 Mb). According to the information archived in human genome databases (http://genome.ucsc.edu/), this locus is flanked by the BAC clones BAC53_O05 and BAC124_E11 and contains 51 possible target clones (1.1 Mb segment). Notably, ahigh frequency of copy number gains (>0.25 log_2 ratio) and high-level gains (>0.5 log_2 ratio) from this region were detected in 47.8% (11/23) and 26.1% (6/23) of the cases, respectively. More specifically, high-level amplification (>1 log_2 ratio) at the 1q21.1 region was noted in 4.3% (1/23) of the cases.

The second candidate locus spanned 82.6-94.5 Mb and mapping at the 1q31.1-q32.3 region determined ahigh frequency of copy number gains in 9 of 23 (39.1%) cases. The most frequently gained clone was BAC43_H23 at the 1q32.1 region (26.1%, 6/23), which comprises the genes *IL24*, *FAIM3*, *PIGR* and *FCAMR*. Notably, high-level gains (>0.5 log_2 ratio) from this region were also detected in 8.7% (2/23) of the cases.

The third region (93.2-109.6 Mb) showed copy number gains in 14 of 23 NSCLCs (60.9%). It was flanked by BAC170_F20 and BAC38_P06,and mapped to the 1q41-q44 region. The NSCLC cases with 1q41-q44 gains displayed varying degrees of copy number increases, predominantly from 1q44 (47.8%, 11/23), 1q42.13 (30.4%, 7/23) and 1q41 (26.1%, 6/23). Notably, high-level gains (>0.5 log_2 ratio) from these regions were detected in 13.0% (4/23) of the cases. More specifically, two independently amplified (>1 log_2 ratio) loci at these regions were detected in NSCLCs: One spanning an 86.6 Mb region on 1q42.2 (4.3%, 1/23) and the other spanning an approximately 101.6 Mb region on 1q44 (8.7%, 2/23). The amplified locus on 1q42.2 comprised one candidate target gene, solute carrier family 35, member F3 (*SLC35F3*). Furthermore, two possible candidate target genes, serologically defined colon cancer antigen 8 (*SDCCAG8*) and RAC-gamma serine/threonine-protein kinase (*AKT3*) were also identified at the 1q44 region in 8.7% (2/23) of the cases. The median span of the copy number amplifications was 15.0 Mb (range: 86.6-101.6 Mb) and all copy number amplifications were located between BAC168_C19 and BAC160_M11. An example of an individual profile of NSCLC cases are presented in Fig. 1. High-level gains at 1q44 region (Fig. 1a) are shown in the upper portion and high-level amplifications at the 1q21.1 region (Fig. 1b) are presented in below. A representative weighted frequency (%) diagram with high-level amplifications in the 1q21.1-q44 region for all of the 23 NSCLC cases is shown in Fig. 2.

DISCUSSION

Lung cancer is the leading cause of cancer-related death over the world[13]. The annual mortality rate for lung cancer exceeds the annual rate for breast, prostate and colon cancer combined, all of which have successful clinical screening tools for the detection of early-stage disease[14]. For this reason, the search for diagnostic strategies for early lung cancer detection has intensified[15].

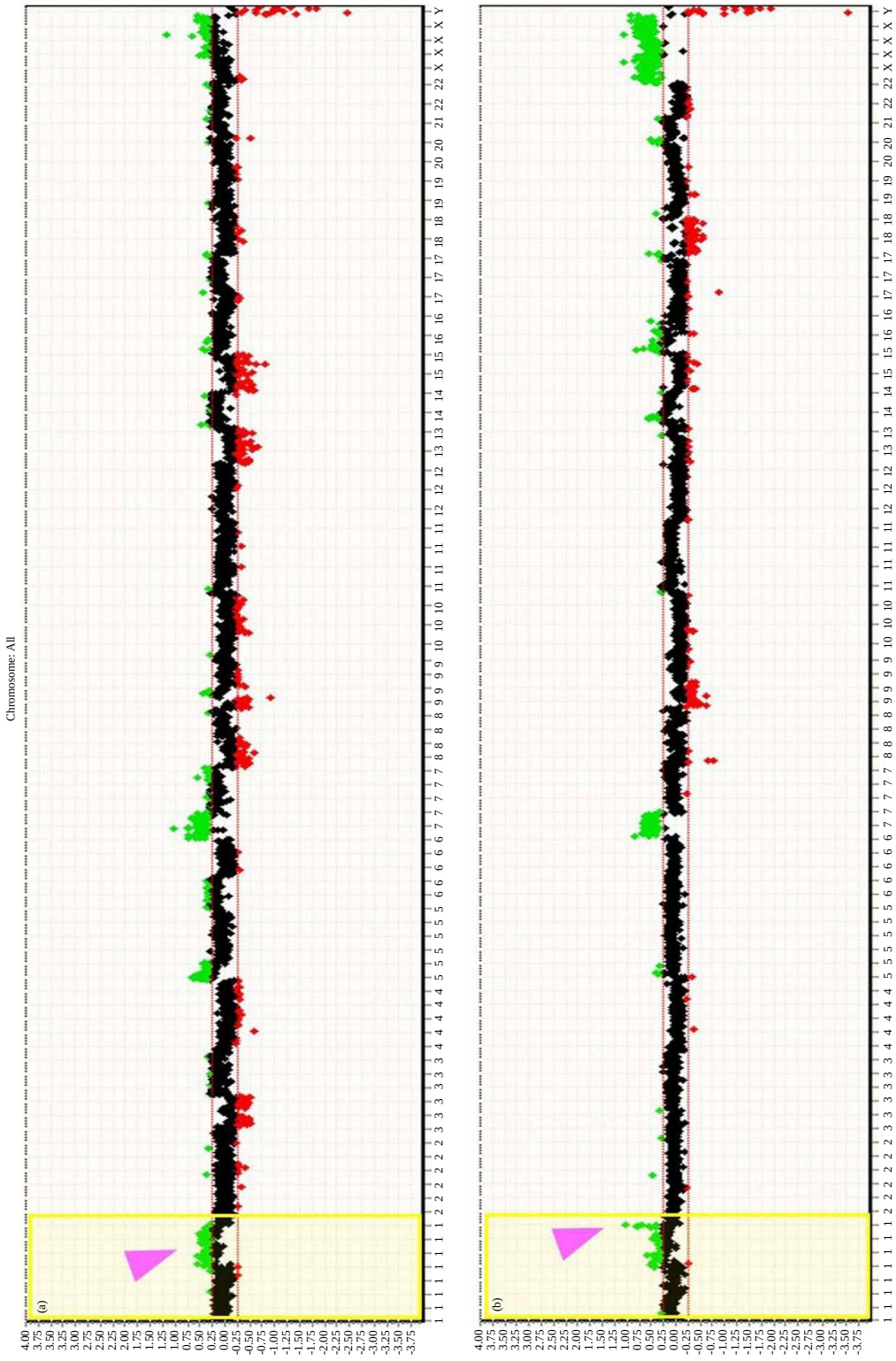

Fig. 1(a-b): Examples of microarray-CGH results from patients (a) 12 and (b) 17. A $\log_2$ ratio over 0.25 represents a genomic copy number gain and a $\log_2$ ratio below -0.25 represents a genomic copy number loss. Clones are ordered from chromosome 1p-22q. For the profiles, the x-axis represents the mapped position of the corresponding clone and the intensity ratios are assigned to the y-axis, (a) High-level gains at 1q44 (>0.5 $\log_2$ ratio) and (b) High-level amplifications (>1 $\log_2$ ratio) at the 1q21.1 region are highlighted in yellow

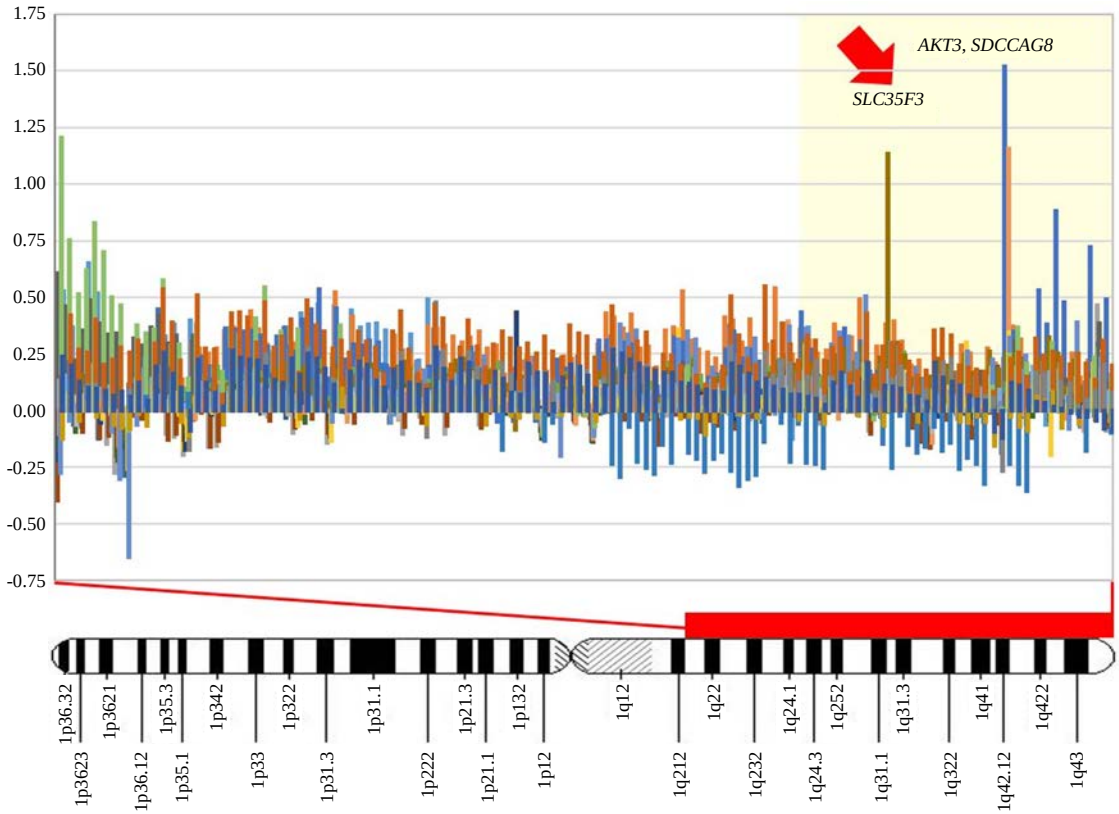

Fig. 2: A diagram showing weighted frequencies (%) of NSCLC cases on the long arm of chromosome 1. In the profiles, the y-axis represents the mapped position of the corresponding clone and the intensity ratios are assigned to the x-axis. Cytobands are shown in the bottom of the ideogram. Log_2 ratio was >1 in this BAC clone, suggesting that high-level amplification soccurred at the *AKT3*, *SDCCAG8* and *SLC35F3* genes loci. The high-level amplifications at 1q21.1-q44 regions are highlighted in yellow

In this study, we performed a whole-genome microarray-CGH to identify early genetic alterations that can be used as prognostic markers for patients with the early stages of NSCLC. On array based profiles, copy number changes on chromosomal arms with gains on 1q, 3q, 5p, 8q, 9q, 12q and 20q (log_2 ratio >0.25) and losses on 7p, 8q, 9p, 14q and 18q (log_2 ratio <-0.25) (>30% of patients) were investigated as potential targets for NSCLCs. These results support the previous findings that NSCLC has a complex pattern of chromosomal alterations that can be due to general chromosomal instability related to the advanced stages of squamous cell of lung cancer[5,9,15].

This present study, the most prominent findingwas the high frequency of copy number alterations atthe long arm of chromosome 1, which occurred in 78.3% (18/23) of the stage I/II NSCLCs. Chromosomal band 1q has long been implicated as one of the most frequently amplified regions and its rearrangements are regarded to be independent prognostic factors for lung cancer[16-18]. Forus *et al.*[16] reported high frequency of copy number gains and high-level amplifications at 1q in squamous cell carcinoma of the lung and high-level amplifications at 1q in primary lung adenocarcinomas were also described[17]. Furthermore, Wong *et al.*[18] demonstrated that the high-level amplifications of 1q were significantly associated with tumor recurrence in patients with NSCLC ($p<0.05$)and array-CGH identified the commonest aberrations consisting of DNA gains in chromosome 1q[19]. Taken together, these results and the findings of our study suggest the likelihood that the long arm of chromosome 1 harbors oncogenes that are important in the pathogenesis of NSCLC and/or genomic features fragile during lung carcinogenesis.

More strikingly, three distinct high-level amplifications at the 1q21.1-q44 region were detected in 17.4% (4/23) of the cases: one spanning a 101.1 Mb region on 1q21.1, another spanning an 86.6 Mb region on 1q42.2 and the third spanning a 101.6 Mb region on 1q44. These regions contain several interesting oncogenes. One of the most relevant genes at the 1q44 region is *AKT3*, which is considered to be a prime target

on chromosome 1q. In this study, high-level amplifications of the *AKT3* gene were detected in 8.7% (2/23) of the cases, showing the highest level of amplifications among the cases. Over expression or high-level amplifications of the *AKT3* gene have already been described in connection with various types of tumors. Kagawa *et al.*[20] described high-level amplification of the *AKT3* gene in both medulloblastoma and primitive neuroectodermal tumors. Additionally, frequent copy number gains of the *AKT3* gene in both early and advanced stages of hepatocellular carcinomas have also been documented[21]. Furthermore, Soengas and Lowe[22] suggested that *AKT3* is the predominant isoform in melanomas, playing a critical role in invasion, metastasis and therapeutic resistance. More importantly, Dobashi *et al.*[23] reported that overexpression of *AKT3* was frequently observed in small cell carcinoma of the lung and an increase in the *AKT3* protein expression levels was noted in 40.0% of the cases due to polysomy of chromosome 1. These previous results as well as those of the present study suggest that *AKT3* may play a critical role in the development or progression of several cancers and may represent a new target for amplifications in the initiation of NSCLCs[24].

In addition, serologically defined colon cancer antigen 8 (*SDCCAG8*) was identified in 8.7% (2/23) of the cases, representing another candidate oncogene target within the 1q44 amplicon. Although, involvement of *SDCCAG8* in the pathogenesis of NSCLChas not been previously described, genetic mutations of the gene are consistently reported in different kinds of disorders[25-28]. According to Liu *et al.*[26] *SDCCAG8* is necessary for the presentation of TNF-receptor 1 on the cell surface and the gene was uniquely expressed in a MASPIN-expressing lung cell line. Insolera *et al.*[27] suggested that expression of *SDCCAG8* carrying a human mutation causes neuronal migration defects. Moreover, Divers *et al.*[28] reported an interaction between *SDCCAG8* variants and *APOL1* to modulate the risk for non-diabetic end-stage kidney disease. These findings suggest that genetic mutations of *SDCCAG8* may be a probable target within the 1q44 amplicon related to the development of NSCLCs. Further investigations are needed to validate and clarify the vital functions of *SDCCAG8* as a novel target for NSCLCs in larger studies using multiple samples.

In the present genomic profiles, we also identified *SLC35F3* (1q42.2) as a possible target gene, which has not been previously assumed to play a pathogenic role in NSCLC. Although, involvement of *SLC35F3* in the pathogenesis of NSCLChas not been previously described, the expression levels of *SLC35F5* have been implicated in various stages of the development of human diseases. For example, transcripts of *SLC35A2* specifically were found to be more abundant in colon cancer cells than in non-malignant tissues obtained from the same patients[29]. Moreover, Zang *et al.*[30] suggested that *SLC35F3* may be associated with the regulation of hypertension and kidney function. Furthermore, Matsuyama *et al.*[31] have reported that *SLC35F5* has significantly different expression profiles in 5-fluorouracil-nonresponding and responding tumors. These results suggest that genetic mutation of *SLC35F5* gene may play a crucial role in development or progression of several different types of disorders and may serve as a novel prognostic indicator for lung cancer. Moreover, genetic mutations of these developmental gene may contribute to lung tumorigenesis at an early stage and highlight the value of examining the genomes of pre-invasive stages of cancer attiling resolution[32]. Further investigation is needed to validate and clarify the vital functions of these genes as novel targets for early NSCLCs, in larger studies using multiple samples.

In summary, the results of the present study significantly extend previous findings and firmly establish critical regions on the 1q chromosome that are implicated in early NSCLC. The present findings warrant future studies to identify the putative oncogenes at 1q to gain a better understanding of the molecular pathogenesis of early stages of NSCLCs. Although, this result supports previous findings that 1q gain is one of the major drivers of initiation of NSCLC, it also suggests the concept of a genomic stage and others routes of progression of NSCLCs. Furthermore, disease stage or degree of histological differentiation could be estimated by an analysis of the genomic alterations on certain chromosomal regions prior to the initiation of treatment[33].

CONCLUSION

In addition, we described here for the first time high-level amplifications of the *SDCCAG8* (1q44) and *SLC35F3* (1q42.2) genes as potential targets for the underlying amplification in NSCLCs. The identified aberrations and candidate genes at 1q42.2-q44 chromosomal sites could be used as starting points for more specific investigations for pathogenesis in early stages of NSCLCs and should provide important clues with regards to the genetic mechanisms underlying the initiation and progression of this disease.

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