Common and distinct features of potentially predictive biomarkers in small cell lung carcinoma and large cell neuroendocrine carcinoma of the lung by systematic and integrated analysis

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Abstract

Background: Large-cell neuroendocrine carcinoma of the lung (LCNEC) and small-cell lung carcinoma (SCLC) are neuroendocrine neoplasms. However, the underlying mechanisms of common and distinct genetic characteristics between LCNEC and SCLC are currently unclear. Herein, protein expression profiles and possible interactions with miRNAs were provided by integrated bioinformatics analysis, in order to explore core genes associated with tumorigenesis and prognosis in SCLC and LCNEC.

Methods: GSE1037 gene expression profiles were obtained from the Gene Expression Omnibus (GEO) database. Differentially expressed genes (DEGs) in LCNEC and SCLC, as compared with normal lung tissues, were selected using the GEO2R online analyzer and Venn diagram software. Gene ontology (GO) analysis was performed using Database for Annotation, Visualization and Integrated Discovery. The biological pathway analysis was performed using the FunRich database. Subsequently, a protein–protein interaction (PPI) network of DEGs was generated using Search Tool for the Retrieval of Interacting Genes and displayed via Cytoscape software. The PPI network was analyzed by the Molecular Complex Detection app from Cytoscape, and 16 upregulated hub genes were selected. The Oncomine database was used to detect expression patterns of hub genes for validation. Furthermore, the biological pathways of these 16 hub genes were re-analyzed, and potential interactions between these genes and miRNAs were explored via FunRich.

Results: A total of 384 DEGs were identified. A Venn diagram determined 88 common DEGs. The PPI network was constructed with 48 nodes and 221 protein pairs. Among them, 16 hub genes were extracted, 14 of which were upregulated in SCLC samples, as compared with normal lung specimens, and 10 were correlated with the cell cycle pathway. Furthermore, 57 target miRNAs for 8 hub genes were identified, among which 31 miRNAs were correlated with the progression of carcinoma, drug-resistance, radio-sensitivity, or autophagy in lung cancer.

Shenghua Dong and Jun Liang contributed equally to this work.
1 | INTRODUCTION

High-grade pulmonary neuroendocrine neoplasms (NENs), small-cell lung cancer (SCLC), and large-cell neuroendocrine carcinoma of the lung (LCNEC) are among the malignancies with the highest mortality rates. Since the revised 2015 World Health Organization classification of lung tumors classified LCNEC as a NEN (Travis, Brambilla, Burke, Marx, & Nicholson, 2015), debates and investigations of the new classification were ceaseless. LCNEC was grouped with NENs due to its similarities with SCLC in terms of morphology, DNA methylation, protein levels, mutational aspects, and transcriptional levels (Aly et al., 2019; Karlsson et al., 2015, 2014; Miyoshi et al., 2017; Rossi et al., 2005; Simbolo et al., 2017), in spite of a certain extent of heterogeneity (Clinical Lung Cancer Genome Project (CLCGP); Network Genomic Medicine (NGM), 2013; Rossi et al., 2005; Simbolo et al., 2017). In addition, despite the differences in histopathological characteristics between SCLC and LCNEC, their clinical characteristics are similar, including a generally poor outcome, greater incidence in men than in women, and advanced stage diagnosis (Asamura et al., 2006; Cerilli, Ritter, Mills, & Wick, 2001; Xu et al., 2019). With regard to treatment, individuals with SCLC and LCNEC may manifest different sensitivities to different types of treatment, owing to gene alterations between SCLC-like LCNEC and NSCLC-like LCNEC (Rekhtman et al., 2016).

Genome-based medicine, which has been used in oncology for >10 years, can rapidly detect differentially expressed genes and provide greater chances of reducing malignancy-related morbidity and mortality (Vogelstein et al., 2013). Therefore, a number of valuable clues obtained from the SCLC regulation and LCNEC development could be investigated from different perspectives using gene chips. However, the understanding of the genetic expression of these two types of NEN is limited. Genetic analysis was therefore conducted to clarify the genomic characteristics of NENs and determine the similarities between SCLC and LCNEC, consequently identifying more potential genetic candidates for treatment.

In this study, GSE1037 expression microarray data were downloaded from the Gene Expression Omnibus (GEO) database. DEGs were analyzed and their interaction patterns in this dataset were revealed through a protein–protein interaction (PPI) network. In addition, possible DEG functions were explored by gene and biological pathway enrichment analysis. The functions of the significant genes involved in major function terms were discussed, and a number of them might be novel candidates for SCLC and LCNEC treatment. The workflow of the present study is depicted in Figure 1 (free images were obtained from Servier Medical Art).

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

This article does not contain any studies with human participants or animals performed by any of the authors, and therefore no ethical compliance is required.

2.2 | Gene expression profile data

Gene expression profiles (GSE1037) were obtained from the GEO database, based on the GPL962 CHUGAI 41K platform. Data including 18 primary normal lung tissues, 8 primary LCNEC tissues, 15 primary small-cell lung carcinoma tissues, and 9 small-cell lung carcinoma cell lines were downloaded. The profiles of differentially expressed genes in SCLC and LCNEC are presented in a volcano plot online http://www.ehbio.com/ImageGP/.

2.3 | Data processing of DEGs

The mRNA expression raw data were analyzed by GEO2R online tools (Davis & Meltzer, 2007). To identify DEGs in SCLC and LCNEC, as compared with normal lung specimens, |logFC| > 2 and adjusted p < .05 were used as the threshold. A Venn diagram was drawn to visualize shared genes in SCLC and LCNEC specimens.

2.4 | Functional enrichment analysis of DEGs

Annotation, Visualization and Integrated Discovery (DAVID) (Huang da, Sherman, & Lempicki, 2009a, 2009b),
DONG et al. provide a bioinformatics online tool that provides functional annotations and gene analysis. Purpose genes were integrated using Gene ontology (GO) analysis in DAVID, to identify their biological properties. Biological pathway analysis of DEGs and hub genes was performed using FunRich software (Pathan et al., 2017), a self-contained software tool used for function enrichment and interaction network evaluation of sets of genes and proteins.
2.5 PPI network construction and module analysis

Search Tool for the Retrieval of Interacting Genes (STRING) (Szklarczyk et al., 2015)) is a database of known and potential PPIs. DEGs were evaluated by STRING and a combined score of ≥0.4 was set as the cut-off value. The network was visualized by Cytoscape (Shannon et al., 2003) and the Cytoscape app Molecular Complex Detection (MCODE) was then used to examine marked modules of the PPI network, with the advanced option set to a max. depth of 100, degree cut-off of 2, k-core of 2, and node score cut-off of 0.2.

2.6 Oncomine analysis

To validate the hub genes, the Oncomine website (www.oncomine.org) was used to obtain mRNA expression data to compare SCLC and normal lung tissues from Bhattacharjee et al. (2001) and Garber et al. (2001).

2.7 Prediction of target miRNAs for DEGs

To detect predicted miRNAs corresponding to core genes selected from MCODE, miRNA enrichment in FunRich software was performed and miRNAs found to interact with hub genes were defined. The results were input into and visualized by Cytoscape.

2.8 Statistical analysis

In this study, a student’s t-test was carried out using GraphPad Prism 5 to generate a p-value for the comparison of cancerous specimens and normal control samples. p < .05 was considered to indicate a statistically significant difference.

3 RESULTS

3.1 Identification of DEGs

DEGs in the SCLC and LCNEC samples, as compared with normal ones, were determined using GEO2R online analyzer (|logFC| > 2 and adjusted p < .05) (Davis & Meltzer, 2007). A total of 270 and 114 DEGs were extracted from SCLC and LCNEC samples, respectively. A “volcano plot” between p-values and fold changes was established to plot the differentially expressed genes (Figure 2). A Venn diagram was then drawn to confirm the shared DEGs in the two subtypes (Figure 3). Finally, 88 common DEGs were confirmed.
including 56 downregulated and 32 upregulated genes in the SCLC and LCNEC samples (Table 1).

### 3.2 Enrichment analysis

All 88 DEGs were analyzed using DAVID and FunRich software. The GO analysis results were as follows: (a) For biological processes (BP), the significantly enriched terms of upregulated DEGs were cell division, regulation of transcription, DNA repair, homologous chromosome segregation, positive regulation of exit from mitosis, mitotic nuclear division, glucose import, chromosome organization, protein K11-linked ubiquitination, mitotic spindle organization and mitotic spindle assembly, and the significant terms of downregulated DEGs were caveola assembly, cell adhesion, receptor-mediated endocytosis of virus by host cell, dopamine catabolic process, neurotransmitter catabolic process, multicellular organismal water homeostasis, angiogenesis, bleb assembly, ethanol oxidation, glycerol transport, and cellular water homeostasis; (b) for molecular function (MF), the notably enriched terms of upregulated DEGs were ubiquitin protein ligase binding, DNA binding, adenosine triphosphate (ATP) binding, peptidase inhibitor activity and ubiquitin conjugating enzyme activity, and those for downregulated DEGs were oxidoreductase, transporter, alcohol dehydrogenase (zinc-dependent), water transmembrane transporter, primary amine oxidase, glycerol channel and water channel activities; (c) for GO cell component (CC), the upregulated DEGs were particularly enriched in cytoplasm, nucleus, axon hillock, chromosome passenger complex, nucleoplasm, pronucleus and spindle midzone, and downregulated DEGs in extracellular exosome, plasma membrane,

### Table 1 Commonly DEGs in the SCLC and LCNEC samples

| DEGs                  | Genes name                                                                 |
|-----------------------|-----------------------------------------------------------------------------|
| Upregulated           | ZNF829 BCCIP PTTG1 CENPA FAM123A SESN2 CSE1L LOC256676///CDCA5 PBK UBE2TC5orf13 ZNF587 UNQ353///CSNK1G1///KIAA0101 HMGB3 SOX4 FARPI C1orf215///STMN1 MLF1IP AURKA MYBL2 ZWINTAS///ZWINT UBE2C EZH2 RFC4 CDCA8 SLC2A1 LOC253012 TPX2 TTKCDA7 TOP2A NUF2 |
| Downregulated         | ADH1B CAV1 WIFI SFPTC FMO2 TSHZ2///ADAMTS8 USP42 MFAP4 SCGB1A1 IGSF10 TIMP3 CLDN18 OGN CAV2 MAOA FABP4 ZNF521 SVEPI EPS11P TPSB2///TPSB1 FHL1 FAT4 CAB39L ADH1C PI4KAP1 C2orf34 AGER LOC144571///RFP///A2M AQP4 FAM75A1 SFTPH AQPI CAMP HBE1 EMCN HRNPH1 SLC39A8 SUSD2 FLJ44379 LIMCHI SLPI CYBRD1 HOPX C13orf15 LOC100131277///TACC1 LYVE1 GPR116 MAOB SELENBP1 PGM5 EMP2 PMP22 S1PR1 ABCA8 ANGPTL1 RGS2 |

Abbreviations: DEGs, differentially expressed genes; LCNEC, large cell neuroendocrine carcinoma; SCLC, small cell lung carcinoma.
caveola, extracellular region, membrane raft, apical part of cell, integral component of membrane, extracellular matrix, extracellular space, and acrosomal membrane (Table 2). These results are displayed in bar graphs produced on GraghPad Prism 5 (Figure 4).

The biological pathway analysis results are shown in Figure 5, indicating that upregulated DEGs were notably enriched in cell cycle (mitotic), DNA replication, ataxia telangiectasia-mutated (ATM) pathway, mitotic M-M/G1 phases, signaling by Aurora kinases, M phase, mitotic prometaphase, while downregulated DEGs in lipid digestion, mobilization and transport, noradrenaline and adrenaline degradation, and serotonin degradation (Figure 5).

3.3 | PPI network and module analysis

Using STRING, a PPI network containing 48 nodes and 221 protein pairs was constructed, with a combined score of >0.4. As shown in Figure 6, most nodes in the PPI network were upregulated DEGs in SCLC and LCNEC specimens. Next, the MCODE app in Cytoscape was used for further analysis, which showed that 16 of 48 nodes were hub nodes (Figure 6). These core nodes were all upregulated genes: Enhancer of zeste homolog 2 (EZH2, OMIM:601573), cell division cycle-associated 1 (CDCA1/NUF2, OMIM:611772), PDZ binding kinase, CDCA8/OMIM:609977, CDCA7/OMIM:609937), aurora kinase A (AURKA, OMIM:603072), replication factor C4 (RFC4, OMIM:102577), ubiquitin conjugating enzyme E2 C (UBE2C, OMIM:605574), centromere protein A (CENPA, OMIM:117139), targeting protein for xklp2 (TPX2, OMIM:605917), TTK protein kinase (TTK, OMIM:604092), V-Myb avian myeloblastosis viral oncogene homolog-like 2 (MYBL2, OMIM:601415), pituitary tumor transforming gene 1 (PTTG1, OMIM:604147), DNA topoisomerase II α (TOP2A, OMIM:126430), centromere protein U (CENPU, OMIM:611511), and UBE2T (OMIM:610538).

3.4 | Analysis of core genes by the Oncomine database

The Oncomine database (www.oncomine.org) was used to determine the expression patterns of 16 hub genes between normal and cancerous lung tissues. Due to the rarity of LCNEC, the expression pattern was only obtained in SCLC samples and compared with normal lung samples. The results showed that, except for TTK (deficiency in expression data), 14 of 15 genes were highly expressed in SCLC specimens, as compared with normal ones, which was consistent with the GSE1037 data (Figure 7).

3.5 | Re-analysis of hub genes by biological pathway analysis

To better apprehend the pathway correlated with these 16 selected DEGs, biological pathway analysis was performed again by FunRich. The results showed that these 16 core genes were markedly enriched in the cell cycle pathway, mitotic prometaphase, DNA replication and M phase (Figure 8). Among them the cell cycle pathway was the most markedly enriched, containing 10 genes (CDCA1, CDCA8, AURKA, RFC4, UBE2C, CENPA, CENPU, MYBL2, PTTG1, and TOP2A) \((p = 2.30182e-11)\).

3.6 | Prediction of target miRNAs for hub genes

The target human miRNAs for hub genes were determined by FunRich software, and the mRNA-miRNA network was displayed by Cytoscape (Figure 9). The genes found to be connected with miRNAs were TTK, PTTG1, MYBL2, EZH2, CENPA, CDCA8, CDCA7, and AURKA. Hub genes and their corresponded target miRNAs are presented in Table 3. Finally, 31 miRNAs, whose functions were correlated with tumor progression (Chang et al., 2019; Chang et al., 2017; Chen et al., 2015; Gao et al., 2018; Gu et al., 2014; Han et al., 2019; He et al., 2019; Kucuksayan et al., 2019; Li, Ma, Zhang, Ji, & Jin, 2014; Li, Ran, et al., 2018; Li & He, 2014; Li, Fu, et al., 2019; Li, Cui, Li, Zhang, & Li, 2018; Liu et al., 2017; Liu, Liu, Deng, et al., 2019; Liu, Liu, & Lu, 2019; Liu, Liu, Zhang, Tong, & Gan, 2019; Liu, Miao, et al., 2016; Luo et al., 2018; Tang et al., 2018; Wang et al., 2017; Wang, Cao, Su, Li, & Yan, 2019; Wu et al., 2015; Wu, Mo, Wan, & Hu, 2019; Xia, Jing, Li, & Lv, 2018; Xu et al., 2018; Zeng et al., 2018; Zhang, Hao, et al., 2018; Zhang et al., 2014, 2017; Zhu et al., 2017), drug resistance (Bian et al., 2019; Gao et al., 2014; Lin, Xie, Lu, Hu, & Chang, 2018; Pan, Chen, Shen, & Tantai, 2019; Su et al., 2016; Xu et al., 2017; Zhou, Wang, & Feng, 2014), radiosensitivity (Liu, Li, & Gao, 2016), recurrence (Sim et al., 2018) or autophagy (Pan et al., 2019) in lung cancer, were identified (Table 4).

4 | DISCUSSION

To determine more possible targets for the exploration of SCLC and LCNEC biomarkers and molecular mechanisms, integrated bioinformatics methods based on the GSE1037 profile dataset were performed in the present study. Eighteen primary normal lung tissues, 8 primary LCNEC tissues, 15 primary SCLC tissues, and 9 SCLC cell lines were enrolled and analyzed. Using GEO2R and
| Category       | Term                                                      | Count | %      | p-Value  | FDR       |
|---------------|-----------------------------------------------------------|-------|--------|----------|-----------|
| **Upregulated** |                                                           |       |        |          |           |
|               | GOTERM_BP_DIRECT GO:0051301–cell division                  | 6     | 0.142993327 | 4.04E-06 | 0.004971483 |
|               | GOTERM_BP_DIRECT GO:0006355–regulation of transcription   | 7     | 0.166825548 | 3.53E-04 | 0.432578524 |
|               | DNA-templated                                             |       |        |          |           |
|               | GOTERM_BP_DIRECT GO:0006281–DNA repair                     | 4     | 0.095328885 | 8.15E-04 | 0.997007591 |
|               | GOTERM_BP_DIRECT GO:0045143–homologous chromosome         | 2     | 0.047664442 | 0.006639221 | 7.86341138 |
|               | segregation                                               |       |        |          |           |
|               | GOTERM_BP_DIRECT GO:0031536–positive regulation of exit    | 2     | 0.047664442 | 0.008292426 | 9.731016783 |
|               | from mitosis                                              |       |        |          |           |
|               | GOTERM_BP_DIRECT GO:0007067–mitotic nuclear division       | 3     | 0.071496663 | 0.013030094 | 14.89218414 |
|               | GOTERM_BP_DIRECT GO:0046323–glucose import                 | 2     | 0.047664442 | 0.018156528 | 20.17047326 |
|               | GOTERM_BP_DIRECT GO:0051276–chromosome organization        | 2     | 0.047664442 | 0.023053317 | 24.9298377 |
|               | GOTERM_BP_DIRECT GO:0070979–protein K11-linked             | 2     | 0.047664442 | 0.037603917 | 37.57710332 |
|               | ubiquitination                                             |       |        |          |           |
|               | GOTERM_BP_DIRECT GO:0007052–mitotic spindle                | 2     | 0.047664442 | 0.037603917 | 37.57710332 |
|               | organization                                              |       |        |          |           |
|               | GOTERM_CC_DIRECT GO:0005737–cytoplasm                      | 15    | 0.357483317 | 2.21E-05 | 0.022280174 |
|               | GOTERM_CC_DIRECT GO:0005634–nucleus                       | 14    | 0.333651096 | 5.40E-05 | 0.054460588 |
|               | GOTERM_CC_DIRECT GO:0032030–axon hillock                   | 2     | 0.047664442 | 0.00741693 | 7.237425098 |
|               | GOTERM_CC_DIRECT GO:0032133–chromosome passenger           | 2     | 0.047664442 | 0.00741693 | 7.237425098 |
|               | complex                                                   |       |        |          |           |
|               | GOTERM_CC_DIRECT GO:0005654–nucleoplasm                    | 7     | 0.166825548 | 0.010502317 | 10.10650713 |
|               | GOTERM_CC_DIRECT GO:0045120–pronucleus                    | 2     | 0.047664442 | 0.031312558 | 12.64989615 |
|               | GOTERM_CC_DIRECT GO:0051233–spindle midzone                | 2     | 0.047664442 | 0.022093237 | 20.18460143 |
|               | GOTERM_MF_DIRECT GO:0031625–ubiquitin protein ligase        | 3     | 0.076628352 | 0.011662791 | 10.93819391 |
|               | binding                                                   |       |        |          |           |
|               | GOTERM_MF_DIRECT GO:0008301–DNA binding bending             | 2     | 0.051085568 | 0.015851015 | 14.59560577 |
|               | GOTERM_MF_DIRECT GO:0005524–ATP binding                    | 6     | 0.153256705 | 0.027091606 | 23.75384229 |
|               | GOTERM_MF_DIRECT GO:0030414–peptidase inhibitor activity   | 2     | 0.051085568 | 0.03054212  | 26.01571812 |
|               | GOTERM_MF_DIRECT GO:0061631–ubiquitin conjugating          | 2     | 0.051085568 | 0.038482685 | 32.12464677 |
|               | enzyme activity                                            |       |        |          |           |
| **Downregulated** |                                                           |       |        |          |           |
|               | GOTERM_BP_DIRECT GO:0070836–caveola assembly               | 3     | 0.046260601 | 6.99E-05  | 0.098559412 |
|               | GOTERM_BP_DIRECT GO:0007155–cell adhesion                  | 6     | 0.092521203 | 0.007419687 | 9.97732032 |
|               | GOTERM_BP_DIRECT GO:0019065–receptor-mediated              | 2     | 0.030840401 | 0.008018493 | 10.74080337 |
|               | endocytosis of virus by host cell                          |       |        |          |           |
|               | GOTERM_BP_DIRECT GO:0042420–dopamine catabolic process     | 2     | 0.030840401 | 0.013329193 | 17.25342044 |
|               | GOTERM_BP_DIRECT GO:0042135–neurotransmitter               | 2     | 0.030840401 | 0.021243157 | 26.14357095 |
|               | catabolic process                                          |       |        |          |           |
|               | GOTERM_BP_DIRECT GO:0050891–multicellular organismal        | 2     | 0.030840401 | 0.021243157 | 26.14357095 |
|               | water homeostasis                                          |       |        |          |           |
|               | GOTERM_BP_DIRECT GO:0001525–angiogenesis                   | 4     | 0.061680802 | 0.021777665 | 26.71078904 |
|               | GOTERM_BP_DIRECT GO:0032060–bleb assembly                  | 2     | 0.030840401 | 0.026484616 | 31.53309357 |
|               | GOTERM_BP_DIRECT GO:0006069–ethanol oxidation              | 2     | 0.030840401 | 0.031698626 | 36.53140253 |
|               | GOTERM_BP_DIRECT GO:0015793–glycerol transport             | 2     | 0.030840401 | 0.034295382 | 38.8915575 |

(Continues)
Venn tools, 88 common DEGs were detected (|logFC| > 2, adjusted \( p < 0.05 \)) in SCLC and LCNEC, including 32 up-(|logFC < 0) and 56 downregulated DEGs (|logFC < 0).

Subsequently, functional enrichment and GO analysis were performed by DAVID, which showed the following: (a) For BP, the significantly enriched terms of up-regulated DEGs

| Category Term                                                                 | Count | %   | p-Value | FDR          |
|-------------------------------------------------------------------------------|-------|-----|---------|--------------|
| GOTERM_BP_DIRECT GO:0009992–cellular water homeostasis                          | 2     | 0.030840401 | 0.34295382 | 38.89185575 |
| GOTERM_CC_DIRECT GO:0070062–extracellular exosome                             | 16    | 0.246723207 | 0.01317986 | 1.408901211 |
| GOTERM_CC_DIRECT GO:0005886–plasma membrane                                   | 19    | 0.292983809 | 0.003743762 | 3.95504143 |
| GOTERM_CC_DIRECT GO:0005901–caveola                                           | 3     | 0.046260601 | 0.010295194 | 10.53630766 |
| GOTERM_CC_DIRECT GO:0005576–extracellular region                              | 10    | 0.154202005 | 0.01150877 | 11.70950819 |
| GOTERM_CC_DIRECT GO:0045121–membrane raft                                     | 4     | 0.061680802 | 0.012603718 | 12.75603307 |
| GOTERM_CC_DIRECT GO:0045177–apical part of cell                               | 3     | 0.046260601 | 0.013532583 | 13.63498448 |
| GOTERM_CC_DIRECT GO:0016021–integral component of membrane                   | 20    | 0.308404009 | 0.018955008 | 18.60768595 |
| GOTERM_CC_DIRECT GO:0031012–extracellular matrix                             | 4     | 0.061680802 | 0.32469722 | 29.89178143 |
| GOTERM_CC_DIRECT GO:0005615–extracellular space                               | 8     | 0.123361604 | 0.036771948 | 33.17391345 |
| GOTERM_CC_DIRECT GO:0002080–acrosomal membrane                                | 2     | 0.030840401 | 0.043912815 | 38.31524409 |
| GOTERM_MF_DIRECT GO:0016491–oxidoreductase activity                          | 4     | 0.061680802 | 0.014279333 | 14.99791487 |
| GOTERM_MF_DIRECT GO:0005215–transporter activity                             | 4     | 0.061680802 | 0.014662761 | 15.37073704 |
| GOTERM_MF_DIRECT GO:0004024–alcohol dehydrogenase activity zinc-dependent     | 2     | 0.030840401 | 0.015188693 | 15.87969632 |
| GOTERM_MF_DIRECT GO:0005732–water transmembrane transporter activity          | 2     | 0.030840401 | 0.015188693 | 15.87969632 |
| GOTERM_MF_DIRECT GO:0008131–primary amine oxidase activity                   | 2     | 0.030840401 | 0.015188693 | 15.87969632 |
| GOTERM_MF_DIRECT GO:0015254–glycerol channel activity                        | 2     | 0.030840401 | 0.030151975 | 29.24210187 |
| GOTERM_MF_DIRECT GO:0015250–water channel activity                           | 2     | 0.030840401 | 0.040003884 | 36.95130237 |

Abbreviations: DEGs, differentially expressed genes; Go, Gene ontology.

**FIGURE 4** GO terms of overlapped differentially expressed genes. (a) Up-regulated genes. (b) Down-regulated genes. Green bars, biological process; blue bars, cellular component; red bars, molecular function. GO, Gene ontology.
were cell division, regulation of transcription, DNA repair, homologous chromosome segregation, positive regulation of exit from mitosis, mitotic nuclear division, glucose import, chromosome organization, protein K11-linked ubiquitination, mitotic spindle organization and mitotic spindle assembly, and the significantly enriched terms of downregulated DEGs were caveola assembly, cell adhesion, receptor-mediated endocytosis of virus by host cell, dopamine catabolic process, neurotransmitter catabolic process, multicellular organismal water homeostasis, angiogenesis, bleb assembly, ethanol oxidation, glycerol transport, and cellular water homeostasis; (b) for MF, the notably enriched terms of upregulated DEGs were ubiquitin protein ligase binding, DNA binding, ATP binding, peptidase inhibitor activity and ubiquitin conjugating enzyme activity, and those of downregulated DEGs were oxidoreductase, transporter, alcohol dehydrogenase (zinc-dependent), water transmembrane transporter, primary amine oxidase, glycerol channel and water channel activities; (c) for CC, upregulated DEGs were particularly enriched in the cytoplasm, nucleus, axon hillock, chromosome passenger complex, nucleoplasm, pronucleus and spindle midzone, and down-regulated DEGs in extracellular exosome, plasma membrane, caveola, extracellular region, membrane raft, apical part of cell, integral component of membrane, extracellular matrix, extracellular space and acrosomal membrane. To further explore the role of DEGs in biological pathways, the FunRich database was used. It was revealed that upregulated DEGs were notably enriched in the cell cycle pathway (mitotic), DNA replication, ATM pathway, mitotic M-M/G1 phases, signaling by Aurora kinases, M phase, and mitotic prometaphase, while downregulated DEGs in lipid digestion, mobilization transport, noradrenaline and adrenaline degradation, and serotonin degradation.

**FIGURE 5** Biological pathway analysis for DEGs. (a) Biological pathways for upregulated DEGs. (b) Biological pathways for downregulated DEGs. DEGs, differentially expressed genes.
A PPI network complex of 48 nodes with 221 edges was then generated using STRING and Cytoscape. Next, 16 key upregulated genes were selected by MCODE analysis. Furthermore, following a re-analysis of biological pathways by FunRich, 10 genes (CDCA1, CDCA8, AURKA, RFC4, UBE2C, CENPA, CENPU, MYBL2, PTTG1, and TOP2A) enriched in the cell cycle pathway were screened. In the meantime, target miRNAs associated with hub genes were predicted, and 8 genes (TTK, PTTG1, MYBL2, EZH2, CENPA, CDCA8, CDCA7, and AURKA) and 51 miRNAs.
FIGURE 7  Significantly expressed 14 genes in SCLC tissues, as compared with normal tissues. SCLC, small cell lung carcinoma

FIGURE 8  Re-analysis of 16 hub genes by biological pathway enrichment. X axis represents significant biological pathway terms; Y axis represents percentage of genes or –log10 (p-value)
FIGURE 9  Target gene-miRNA networks of hub genes. Blue node stands for 8 hub genes, pink node stands for miRNA. The network was visualized by Cytoscape.
Table 3: Hub genes and corresponded target miRNAs

| Gene    | miRNA                                                                 |
|---------|------------------------------------------------------------------------|
| TTK     | hsa-miR-101-3p hsa-miR-212-3p hsa-miR-132-3p hsa-miR-140-5p hsa-miR-455-3p hsa-miR-582-5p |
| PTTG1   | hsa-miR-655-3p hsa-miR-374c-5p                                          |
| MYBL2   | hsa-miR-29a-3p hsa-miR-29b-3p hsa-miR-30c-5p hsa-miR-30a-5p hsa-miR-30b-5p hsa-miR-30d-5p hsa-miR-29c-3p hsa-miR-30e-5p hsa-miR-423-5p hsa-miR-3184-5p |
| EZH2    | hsa-miR-101-3p hsa-miR-124-3p hsa-miR-137 hsa-miR-138-5p                |
| CENPA   | hsa-miR-873-5p                                                          |
| CDCA8   | hsa-miR-30a-5p hsa-miR-30b-5p hsa-miR-30c-5p hsa-miR-30d-5p hsa-miR-302a-3p hsa-miR-302b-3p hsa-miR-302c-3p hsa-miR-302d-3p hsa-miR-302e-3p |
| AURKA   | hsa-miR-25-3p hsa-miR-92a-3p hsa-miR-363-3p hsa-miR-367-3p hsa-miR-490-3p hsa-miR-92b-3p hsa-miR-421 hsa-miR-32-5p |

Table 4: Functions of miRNAs in lung cancer

| Gene    | miRNA                                                                 |
|---------|------------------------------------------------------------------------|
| TTK     | hsa-miR-101-3p hsa-miR-212-3p hsa-miR-132-3p hsa-miR-140-5p hsa-miR-455-3p hsa-miR-582-5p |
| PTTG1   | hsa-miR-655-3p hsa-miR-374c-5p                                          |
| MYBL2   | hsa-miR-29a-3p hsa-miR-29b-3p hsa-miR-30c-5p hsa-miR-30a-5p hsa-miR-30b-5p hsa-miR-30d-5p hsa-miR-29c-3p hsa-miR-30e-5p hsa-miR-423-5p hsa-miR-3184-5p |
| EZH2    | hsa-miR-101-3p hsa-miR-124-3p hsa-miR-137 hsa-miR-138-5p                |
| CENPA   | hsa-miR-873-5p                                                          |
| CDCA8   | hsa-miR-30a-5p hsa-miR-30b-5p hsa-miR-30c-5p hsa-miR-30d-5p hsa-miR-302a-3p hsa-miR-302b-3p hsa-miR-302c-3p hsa-miR-302d-3p hsa-miR-302e-3p |
| AURKA   | hsa-miR-25-3p hsa-miR-92a-3p hsa-miR-363-3p hsa-miR-367-3p hsa-miR-490-3p hsa-miR-92b-3p hsa-miR-421 hsa-miR-32-5p |

Involved in the mRNA-miRNA regulatory network of SCLC and LCNEC were identified.

CDCA1, a centromeric protein (Nabetani, Koujin, Tsutsumi, Haraguchi, & Hiraoka, 2001), also known as NUF2. The gene has been reported to be co-expressed with cell cycle-related genes, including CDC2, cyclin, TOP2A, and others (Walker, 2001), which was in line with the present results. It has been identified that the co-activation of KNTC2 and CDCA1 and their co-activated interactions had an impact on pulmonary carcinogenesis, and that the inhibition of the KNTC2-CDCA1 complex would provide a novel strategy for therapy of lung cancer treatment. CDCA1 was also regarded as a potential interacting protein for ZW10, a prognostic marker for lung cancer (Hayama et al., 2006; Yuan et al., 2018). In addition, CDCA1 is projected to be a candidate of tumor-associated antigens (TAA) in SCLC. CDCA1, with increasing levels in SCLC, could act as a TAA in inducing cytotoxic T lymphocytes (CTLs) which killed tumor cell lines, and therefore made differences in immunotherapy.(Harao et al., 2008).

CDCA8, a member of the chromosomal passenger complex, is indispensable for the transmission of the genome in the process of cell division (Hindriksen, Meppelink, & Lens, 2015). Bidkhori et al constructed a co-expression network and identified CDCA8 as a crucial gene in lung adenocarcinoma (Bidkhori et al., 2013). Another study implied that the CDCA8-AURKB pathway participated in the process of lung carcinogenesis (Hayama et al., 2007). However, we failed to obtain studies of the impact of CDCA8 neither in SCLC nor in LCNEC.

AURKA, a serine-threonine protein kinase, was found to be involved in several crucial mitotic events and was regarded as an oncogene in multiple types of cancer (Vader & Lens, 2008). In SCLC cell lines, a decreased level of AURKA inhibited cell proliferation and promoted apoptosis, and the inhibition of AURKA may be involved in the G2/M phase arrest of the cell cycle (Lu et al., 2014). Apart from that way, AURKA was involved in immunotherapy in SCLC by being regarded as a TAA to induce CTLs.(Babiak et al., 2014) Recently, more and more studies are concentrating on Aurora Kinase Inhibitors, PF-03814735 and AZD1152, which establishes that the inhibition of the KNTC2-CDCA1 complex would provide a novel strategy for therapy of lung cancer treatment. CDCA1 was also regarded as a potential interacting protein for ZW10, a prognostic marker for lung cancer (Hayama et al., 2006; Yuan et al., 2018). In addition, CDCA1 is projected to be a candidate of tumor-associated antigens (TAA) in SCLC. CDCA1, with increasing levels in SCLC, could act as a TAA in inducing cytotoxic T lymphocytes (CTLs) which killed tumor cell lines, and therefore made differences in immunotherapy.(Harao et al., 2008).

RFC4 is a member of the RFC family and has been found to be involved in DNA replication (Arai et al., 2009). In colorectal cancer, the forced expression of RFC4 was associated
with tumor progression, poor prognosis (Xiang et al., 2014), and radioresistance (X. C. Wang, Yue, et al., 2019). RFC4 knockdown in liver cancer cells could suppress proliferation and induce apoptosis (Arai et al., 2009). In lung adenocarcinoma, RFC4 was regulated by an oncogene, protein kinases C (PKC)- iota, and correlated with the PKC- iota expression in several more tumor types (Erdogan, Klee, Thompson, & Fields, 2009).

UBE2C, a ubiquitin-conjugating enzyme, works with the ubiquitin-activating enzyme E1 and ubiquitin protein ligase E3 to degrade key regulatory molecules in cell cycle progression (Mayer, 2000). In addition, UBE2C intervened in the cell cycle, apoptosis and transcription processes and controlled tumorigenesis. Previous studies have implied that UBE2C promotes cell growth (Jin et al., 2019; van Ree, Jeganathan, Malureau, & van Deursen, 2010; Sivakumar et al., 2017) in NSCLC and is correlated with poor prognosis (Chen et al., 2011; Guo et al., 2017; Psyrri et al., 2012). In addition, UBE2C participated in the miR 495-UBE2C-ABCG2/ERCC1 axis regulating cisplatin resistance and mediating autophagy in NSCLC (Guo, Jin, et al., 2018; Guo, Wu, et al., 2018). UBE2C were in similarly high level in small-cell prostate carcinoma (SCPC) and LCNEC of the prostate with xenografts, and the expression of UBE2C in SCLC and LCNEC of the lung might bear a strong resemblance to that of SCPC and LCNEC of the prostate (Tzelepi et al., 2012).

CENPA, a centromere-specific 17-kDa protein, is a crucial histone H3 variant that acts as a vital epigenetic mark for the identity and propagation of the centromere (Allshire & Karpen, 2008). CENPA played an essential role in cell cycle regulation and tumor cell survival (Takada et al., 2017). Recent studies have identified the impacts of CENPA in lung cancer. Liu et al. (2018) used integrated microarray analysis and confirmed CENPA, cyclin-dependent kinase 1, and cell-division cycle protein 20 as a cluster of prognostic biomarkers for patients with lung adenocarcinoma. It has also been revealed that CENPA intensifies the aggressive phenotype of lung adenocarcinoma and is associated with patient prognosis (Cheng et al., 2019; Wu et al., 2014, 2012).

CENPU, also known as PBPIP1/KLIP1/CENP-50/MLF1IP, is indispensable for kinetochore-microtubule attachment, chromosome segregation, and recovery from spindle damage (Kagawa et al., 2014; Walter et al., 2015). Mounting evidence (Li, Zhang, Zhang, & Wang, 2018; Wang et al., 2017; Zhang et al., 2015) has indicated that CENPU influences several types of cancer, such as bladder and ovarian cancer, and prostate carcinoma. Furthermore, CENPU predicted poor survival in patients with lung carcinoma and affected lung tumor growth (Li, Wang, Pang, Zhang, & Wang, 2019; Wang et al., 2018; Zhang, Li, Zhang, & Shi, 2018).

MYBL2 participated in cell cycle regulation, cell survival, and EMT-associated processes in carcinoma (Musa, Ayna, Mirabeau, Delattre, & Grunewald, 2017). Accumulating evidence has indicated that MYBL2 regulated tumorigenesis and cancer progression in multiple types of cancer. The high expression of MYBL2 disrupted the DREAM complex and then hindered the cell cycle process in breast and ovarian cancer (Iness et al., 2019). In liver cancer cells, YAP supported cell proliferation in an MYBL2- dependent manner (Wei et al., 2019). In addition, Fan et al. (2018) and Jin et al. (2017) stressed the oncogenic impacts of MYBL2 and its capacity to serve as a therapeutic target in NSCLC. Moreover the overexpression of MYBL2 was found to be related to that of the ubiquitin carboxyterminal hydrolase UCHL1 (an enzyme expressed in neurons and neuroendocrine cells in the lung) in murine, because of the reciprocal action of the UCHL1 enzyme and MYBL2 (Long, Long, Tsirigotis, & Gray, 2003).

PTTG1 is a novel proto-oncogene that is overexpressed in different types of human cancers, including endocrine- and nonendocrine-related types (Vlotides, Eigler, & Melmed, 2007). Wu, Zhang, et al. (2019) revealed the importance of PTTG1 as a potential biomarker in NSCLC. Accordingly, Wang, Liu, and Chen (2016) emphasized the prognostic value of PTTG1 in lung cancer, showing the level of PGGT1 as an optimal parameter to predict malignant status and prognosis in NSCLC patients.

TOP2A is a type of isozyme type II topoisomerases (Li & Liu, 2001). A dysregulated TOP2A has been observed in multiple types of cancer and been used in the treatment of several carcinomas (Lan et al., 2014; Li et al., 2015; Wesierska-Gadek & Skladanowski, 2012). TOP2A has been shown to be involved not only in NSCLC (Chien et al., 2019; Olaussen & Postel-Vinay, 2016), but also in SCLC (Chiappori et al., 2010). Chiappori et al. (2010) recommended TOP2A as a biomarker of chemotherapeutic efficacy in SCLC. Chang et al. (2017)) and Gray et al. (2017) considered TOP2A as a target of anti-small cell lung cancer agents. Furthermore, in silico analyses showed TOP2A as target gene of miR-27a-5p and miR-34b-3p, both of whom were tumor suppressors in SCLC (Mizuno et al., 2017). A current research showed that compared with lung adenocarcinoma, TOP2A was a potential drug target of the therapy in LCNEC due to its overexpression examined by immunohistochemistry (Makino et al., 2016). Although TOP2A was highly expressed in NEs, no evident difference in expression levels was found between SCLC and LCNEC (Neubauer et al., 2016).

The results of re-analysis of biological pathway revealed that most key genes were enriched in cell cycle (mitotic), mitotic prometaphase, DNA replication, and M phase. Accordingly, because of the high genome instability as a result of high level replication stress in SCLC, the inhibition
of DNA-replication stress-response, especially in combination with cisplatin, was one of the vulnerabilities of SCLC, which provided a novel therapy for this type of cancer (Bian & Lin, 2019; Nagel et al., 2019). Prometaphase arrest caused by mitotic spindle formation defects that resulting from the depletion of Aurora A, was also involved with the inhibition of cell growth in SCLC (Du et al., 2019). Additionally, the inhibition of a pivotal mitotic regulator led to the increase in the population of cells in the G2/M phase (Wang et al., 2018), while treatment with etoposide in TP53 gene abnormalities ones resulted in the lack of G1/S arrest (Souses, Wiltshire, & Smith, 2001), all of which were associated with pathways of mitotic cell cycle or M phase in SCLC cell lines.

To sum up, CDCA1 and AURK4 might be characteristic especially to SCLC, while MYBL2 is the biomarker of LCNEC. The biological pathway of DNA replication, mitotic cell cycle, mitotic prometaphase, and M phase might be characteristic to SCLC. In contrast, no evidence has shown that any pathway enrichment is related to LCNEC, and the genes of CDCA8, RFC4, UBE2C, CENPA, CENPU, PTTG1, and TOP2A are not predicted to participate particularly in SCLC or LCNEC. Although further researches should be performed focusing on more functions of these key genes and pathways, our discoveries provide potential candidates useful for the diagnosis and discrimination between SCLC and LCNEC.

miRNAs play essential roles in the genesis, development, and progression of carcinoma (Rupaimoole & Slack, 2017). Aberrant miRNA expression profiles have been identified in multiple subtypes of lung cancer (Lai et al., 2019; Mao et al., 2019; Wang et al., 2018). In addition to DEGs and their functions, miRNAs can influence multiple processes of lung cancer, including drug resistance, tumor progression and recurrence, autophagy and radio-sensitivity. The role of miRNAs in tumor growth is shown in Table 4. Recent studies have also revealed the impacts of miRNAs, including miR-363-3p, miR-30a-5p, miR-133b, miR-98-5p, miR-138-5p, miR-137, and miR-138-5p, on drug resistance in NSCLC, showing that miRNAs participated in the mechanisms of traditional chemotherapeutic drugs [gemcitabine (Bian et al., 2019), paclitaxel (Xu et al., 2017), and cisplatin (Lin et al., 2018; Pan et al., 2019; Su et al., 2016; Zhou et al., 2014)] as well as targeted drugs [gefitinib (Gao et al., 2014)]. In addition, Sim et al demonstrated that let-7g-5p was associated with recurrence in stage I lung adenocarcinoma (Sim et al., 2018). Other studies also elucidated the roles of miRNAs in autophagy and radio-sensitivity (Liu, Miao, et al., 2016; Pan et al., 2019).

However, the present study had several limitations. First, due to the rarity of LCNEC and SCLC, we failed to provide meaningful prognosis information from public databases. Second, the present data were obtained from the GEO database, so the reliability and quality of the statistics cannot be evaluated. Third, this study lacks more convincing evidence, such as qPCR and immunohistochemistry results.

5 CONCLUSIONS

In conclusion, common DEGs of SCLC and LCNEC were identified by integrated bioinformatics methods and 16 hub genes were selected from PPI network, among which 10 genes were shown to be related to the most significantly enriched pathway, cell cycle pathway. The roles of these genes and pathways in lung cancer were further discussed and the application of these genes in treatment of SCLC and LCNEC is worthy of further study. In addition, the functions in lung cancer of miRNAs corresponding to 16 core genes were discussed. Several studies have tried to explore novel strategies (Christopoulos et al., 2017; Kujtan et al., 2018; Saunders et al., 2015) for the treatment of SCLC and LCNEC. Attempts at identifying the values of molecular targets, such as spread through air spaces, and immune therapy, such as the expression of PD-L1 and mutation burden, are ongoing (Aly et al., 2019; Kim et al., 2018). To determine the various roles of emerging molecules in the process of tumorigenesis and progression of SCLC and LCNEC, further research should be conducted.

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CONFLICT OF INTEREST

None declared.

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