Comprehensive genomic and prognostic analysis of the IL-17 family genes in lung cancer

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Abstract. The six members of the interleukin (IL)-17 gene family (IL-17A-F) have been identified in various types of cancer. Although lung cancer is the leading cause of cancer-related death worldwide and IL-17A was found to play a critical role in lung cancer, there is little knowledge concerning the association between the other five members of the IL-17 family and lung cancer. The genetic mutations and expression of IL-17 family members were investigated using the Catalogue of Somatic Mutations in Cancer (COSMIC), Oncomine, and cBio Cancer Genomics Portal (cBioPortal) databases. Prognostic values and interaction networks of the members were assessed by the Kaplan-Meier plotter, Search Tool for the Retrieval of Interacting Genes (STRING) database and FunRich software. The results found that, across 5,238 lung cancer patients in the cBioPortal, the results of IL-17 family gene alteration frequencies and types showed that IL-17A, IL-25 and IL-17F exhibited higher alteration frequencies (2, 2.1 and 1.9%, respectively), and gene amplification accounted for the majority of changes. IL-17B, IL-17C and IL-17D exhibited lower alteration frequencies (0.8, 1.1 and 1.1%, respectively), and deep deletion accounted for the majority of changes. The rates of point mutations in IL-17A through IL-17F family genes in lung cancer were 0.66, 0.18, 0.13, 0.09, 0.27 and 0.44% in the COSMIC database. Within the Oncomine database, five datasets showed that IL-17D was significantly decreased in lung cancer, while no dataset showed a significant difference in the expression of IL-17A, IL-17B, IL-17C, IL-25 or IL17-F between lung cancer and normal controls. The frequencies of IL-17A, IL-17B and IL-17C mRNA upregulation in lung squamous cell carcinoma were lower than those in lung adenocarcinoma (2.7, 1.9 and 2.1%, respectively), whereas the frequencies of IL-17D, IL-25 and IL-17F mRNA upregulation were higher in lung squamous cell carcinoma than those in lung adenocarcinoma (3, 6 and 6%, respectively). IL-17A and IL-17B were unrelated to overall survival (p=0.11; P=0.17), whereas IL-17C, IL-17D, IL-25 and IL-17F influenced prognosis (P=0.0023, P=0.0059, P=0.039 and P=0.0017, respectively) according to the Kaplan-Meier plotter. Moreover, the expression level of IL-17C was the highest in lung tissues, and IL-17 family genes mainly participate in the 'IFN-γ pathway' according to the STRING database and Funrich software. In conclusion, we performed the first comprehensive investigation of the IL-17 gene family in lung cancer, including gene mutation, mRNA expression levels, prognostic values and network pathways. Our results revealed that IL-17 family gene mutation rates were in general low and that amplification and deep deletion were the main mutation type. The expression and function of IL-17A and IL-17B in lung cancer are still not fully elucidated and warrant research with larger sample sizes. IL-17D was significantly decreased in lung cancer and was correlated with better OS. Studies of IL-17C-F in lung cancer are limited. Further experimental studies on the association between IL-17D and lung cancer progression are needed to identify more effective therapeutic targets for lung cancer.

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide. Despite improvements in treatment, the overall 5-year survival of lung cancer remains less than 18% in the United States (1,2), and the age-standardised 5-year net survival is in the range of 10-20% in most countries (2). Therefore, optimal therapies for lung cancer are urgently needed, the development of which requires extensive knowledge of the aetiology of lung cancer.

Interleukin (IL)-17 has been implicated in various cancers and is regarded as a double-edged sword in lung cancer (3). The greatest homogeneity is between IL-17A and IL-17F,

which, together with their producing cells, have been implicated in multiple types of cancer. IL-17 is generally referred to as IL-17A in the literature. Moreover, most studies have reported that the expression of IL-17A is positively correlated with tumour growth (4-7), while various investigations have shown the opposite result (8). For example, IL-17A produced by tumour-infiltrating immune cells was found to promote cancer cell growth through an IL-6/signal transducer and activator of transcription 3 (STAT3) pathway (7), and transfection with IL-17A was found to promote hepatocellular carcinoma (HCC) tumour growth via protein kinase B (AKT)-dependent activation of IL-6/Janus kinase 2 (JAK2)/STAT3 signalling (9). However, a low level of intratumoural IL-17A expression was found to be indicative of a poor prognosis (10).

However, other members of the IL-17 family have not been well investigated for their potential roles in cancer development. The IL-17 family includes IL-17A through IL-17F and their cognate receptors, IL-17RA to IL-17RE. IL-17A was first cloned and initially named cytotoxic T lymphocyte-associated antigen 8 (CTLA-8) in 1993. A decade later, IL-17A was found to be a distinctive feature of Th17 cells, as it was not found in Th1 and Th2 cells. The other five family members were discovered in quick succession and designated as IL-17B, IL-17C, IL-17D, IL-25 (IL-17E) and IL-17F.

IL-17B/IL-17RB signalling has been demonstrated to be implicated in tumour malignancies, such as breast cancer (11), pancreatic cancer (12) and gastric cancer (13). IL-17C is involved in the innate immune response of human bronchial epithelial cells (14) and mediates the recruitment of tumour-associated neutrophils with enhanced tumour growth (15). IL-17C has also been found to be upregulated in intestinal cancers and is critical for the microbiota-mediated contribution to tumour development (16). The function of IL-17D in cancer has not been well described. Some studies have shown that IL-17D is poorly expressed in cancer cells and induces tumour rejection through the recruitment of NK cells (17). IL-17E (also known as IL-25) is the most divergent member in the IL-17 family. The influence of IL-25 derived from tumour-associated fibroblasts (18), macrophages and T cells (19) on tumour progression has been explored in recent years. Studies have shown that IL-25/IL-17RB (IL-25R) signalling participates in inhibiting tumour metastasis and growth (18-20). Moreover, IL-25 has been demonstrated to bind IL-17RB through nuclear factor-κB (NF-κB) and JAK/STAT3 pathways to promote proliferation and nourish cancer stem cells in hepatocellular carcinoma (21). IL-17F, together with IL-17A, IL-25, and their receptors, has been described to be elevated in benign prostatic hyperplasia and prostate cancer (22). As mentioned above, IL-17F is the most homologous with IL-17A but lacks the same contributions to biological and physiological processes. Unlike the double-edged sword role of IL-17A in cancer (3), there is little clinical evidence illustrating the role of IL-17F in cancer, except that it has been shown to be a negative modulator that suppressed tumour angiogenesis in hepatocellular carcinoma in an animal model (23) and is a potential diagnostic biomarker when combined with vascular endothelial growth factor (VEGF) in oral squamous cell carcinoma (24).

In summary, every member of the IL-17 family has been identified to play critical roles in cancer, with the main focus on IL-17A and the interstitial cells that produce IL-17A in the tumour microenvironment. In this study, the expression and genetic alterations in IL-17 family members were investigated through the Catalogue of Somatic Mutations in Cancer (COSMIC), Oncomine and cBioPortal databases. The prognostic value and interaction network were then analysed by the Kaplan-Meier plotter and FunRich software.

Materials and methods

COSMIC analysis. The COSMIC database (https://cancer.sanger.ac.uk/cosmic) (25), an online resource providing gene mutation information, is the world's largest and most comprehensive resource for exploring the impact of somatic mutations in human cancer. Primary access to COSMIC is via the search box in the left side panel, which accepts multiple parameters including gene names, disease descriptions, mutation syntax and stable COSMIC IDs. Full mutation distribution across all tissues and cancer diseases for the IL-17 family were acquired by typing a gene name in the search bar. After clicking on 'lung cancer', we obtained mutation information for the IL17 family in lung cancer.

ONCOMINE analysis. ONCOMINE gene expression array datasets (www.oncomine.org) (26) is a cancer microarray database and web-based data-mining platform aimed at facilitating discovery from genome-wide expression analyses and comparing the transcriptome data in various types of cancer with respective normal tissues. 'IL-17A-IL-17F' were used as keywords in the Oncomine search, 'Cancer vs. Normal Analysis' was used as the primary filter, and 'Lung Cancer' was chosen as the cancer type. In this study, we selected 2.0-fold change, P-value=0.05 and top 10% gene rank as the threshold.

Kaplan-Meier plotter. Kaplan-Meier plotter (http://kmplot.com/analysis) (27,28) can assess the effect of 54,675 genes on survival using 10,461 cancer samples. These samples include 5,143 breast, 1,816 ovarian, 2,437 lung and 1,065 gastric cancer patients. IL-17 family members were entered into the database to obtain Kaplan-Meier survival plots. A total of 1,926 lung cancer samples with available clinical data were split into two groups according to median expression (high vs. low expression). The two patient groups were compared by a Kaplan-Meier survival plot for overall survival (OS) using the hazard ratio (HR), 95% confidence intervals (CIs) and log-rank P-values. $P<0.05$ was considered statistically significant.

cBioPortal. The cBio Cancer Genomics Portal (http://cbioportal.org) (29) is an open-access resource for interactive exploration of multidimensional cancer genomics datasets. The IL-17 family gene mutation and expression information in cancers were obtained according to the cBioPortal's online instructions. A mutation analysis was performed in 169 cancer studies, including mutation, amplification and deletion. Additionally, two mRNA analyses for lung cancer, namely, 'Lung Adenocarcinoma TCGA, PanCancer Atlas' and 'lung squamous cell carcinoma TCGA, PanCancer Atlas', were made available on cBioPortal, with 510 and 487 samples, respectively.

STRING database. STRING database (Search Tool for the Retrieval of Interacting Genes; available at *http://string-db.org/*) (30) provides uniquely comprehensive coverage and easy access to protein-protein interaction information. The common gene networks of the IL-17 family were constructed independently by importing gene symbols. We selected the interactions pertaining to *Homo sapiens* and showed minimum interactions with a confidence score >0.9. Only the interactions with a combined score >0.4 were considered significant.

Functional analysis. Functional enrichment analysis of the interaction proteins was performed using FunRich (http://www.funrich.org), which is an open access, standalone functional enrichment and network analysis tool (31). The functional analysis of related genes that interact with IL-17 family genes was conducted with FunRich software. The STRING interaction proteins were imported into FunRich, and significantly enriched pathways and site of expression were analysed.

Statistical analysis. Student's t-test (two-tailed) was used to compare the means between two groups. mRNA expression data are presented as fold change, and P-values <0.05 were considered statistically significant. Overall survival (OS) data are displayed as Kaplan-Meier plots, with P-values calculated using the log-rank test. P-values <0.05 were considered statistically significant

Results

IL-17 family gene mutations in lung cancer. The IL-17 family gene mutations in lung cancers were assessed using cBioPortal (29). IL-17 family genes were examined in 169 cancer studies of genetic mutations. As shown in Fig. 1A, IL-17 genetic mutations in lung adenocarcinoma (TCGA; https://tcga-data.nci.nih.gov) (32) were not the highest compared with those in neuroendocrine prostate cancer (NEPC) (Trento/Cornell/Broad 2016) (33) and breast cancer (BCCRC Xenograft) (34) but were present in 10% of the 230 cases. The IL-17 family gene mutation frequencies and types in 5,238 samples from 12 lung cancer studies are shown in Fig. 1B. IL-17A, IL-25 and IL-17F exhibited higher mutation frequencies (2, 2.1 and 1.9%, respectively), and gene amplification accounted for the majority of changes. IL17B, IL17C and IL17D exhibited lower alteration frequencies (0.8, 1.1 and 1.1%, respectively), and deep deletions accounted for the majority of changes. We also investigated the mutation frequencies of IL-17 family genes (including point mutations and copy number variation (CNV)) using the COSMIC database (COSMIC v83 released 07-Nov-17), a comprehensive resource for exploring somatic mutations in human cancer (25). The genetic point mutations of IL-17A to IL-17F family genes in lung cancer were 0.66, 0.18, 0.13, 0.09, 0.27% and 0.44%, respectively. Notably, IL-25, rather than IL-17A or IL-17F, exhibited the highest CNV (1.51%) (Table I), which was positively related to mRNA expression (Fig. 1C).

Expression of IL-17 family members in lung cancer. The expression levels of the six IL-17 family members in cancers were investigated using Oncomine (26) and cBioPortal (29). We first measured the expression levels of six IL-17 family members in 20 types of cancers and compared the expression levels to those in normal individuals. Four datasets showed significantly increased expression of IL-17A in cancers such as brain cancer, leukaemia and sarcoma, and nine datasets showed decreased expression of IL-17A in cancers such as oesophageal carcinoma, cervical cancer and pancreatic cancer. However, no dataset showed a significant difference in IL-17A expression between lung cancer and controls. Likewise, two datasets showed that IL-17B was highly expressed in brain cancer, and four datasets showed decreased IL-17B expression in breast cancer. Two datasets showed that IL-17C was overexpressed in other cancers, and five datasets showed that IL-17E was decreased in four types of cancer. Notably, five datasets showed that IL-17D was significantly decreased in lung cancer. Data on IL-17F in cancer are rare, and no results showed changes in its expression in cancer Fig. 2). Therefore, we assessed the mRNA expression of IL-17 family members in different lung cancer datasets. Table II shows that IL-17A, IL-17B, IL-17C and IL-25 mRNA overexpression was not significant in the Hou *et al* (35), Beer *et al* (36), Garber *et al* (37), Selamat *et al* (38) and Landi *et al* (39) lung datasets. According to the Garber *et al* (37), Okayama *et al* (40) and Hou lung datasets, IL-17D downregulation was observed in lung adenocarcinoma and squamous cell lung carcinoma compared with normal lung tissue, with a fold change >2.0. We also evaluated whether alterations in IL-17 family gene mRNA are associated with a specific histological type of non-small cell lung cancer (NSCLC) using cBioPortal (Fig. 3). In the TCGA PanCancer Atlas (https://gdc.cancer.gov/about-data/publications/pancanatlas) (41), 510 samples of lung adenocarcinoma and 484 samples of lung squamous cell carcinoma with mRNA data (RNA Seq V2) were investigated. An mRNA expression z-score ±2.0 was set as the threshold. The result showed that the IL-17A-F mRNA upregulation frequencies in lung adenocarcinoma were 4, 4, 4, 2.4, 5 and 2.5%, respectively. The IL-17A, IL-17B and IL-17C mRNA upregulation frequencies in lung squamous cell carcinoma were lower than those in lung adenocarcinoma (2.7, 1.9 and 2.1%, respectively), whereas the IL-17D, IL-25 and IL-17F mRNA upregulation rates were higher in lung squamous cell carcinoma (3, 6 and 6%, respectively).

Prognostic analysis of IL-17 family genes in lung cancer. The prognostic information of IL-17 family genes in lung cancer is freely available at http://kmplot.com/analysis (27). However, there were no significant associations of IL-17A and IL-17B expression levels with the OS of lung cancer patients (Fig. 4A and B). High IL-17C (HR 1.29 (1.09-1.52); P=0.0023) and IL-25 (HR 1.14 (1.01-1.3); P=0.039) mRNA expression levels were associated with poor OS in lung cancer patients. Conversely, higher mRNA levels of IL-17D (HR 0.79 (0.67–0.94); P=0.0059) and IL-17F (HR 0.77 (0.65–0.91); P=0.0017) were associated with better long-term OS (Fig. 4C-F).

Network pathway regulation analysis of the IL-17 family. To explore the interactions of the IL-17 family and regulation in biological processes, we constructed protein-protein interaction (PPI) networks by submitting an IL-17 family gene list to the STRING data and analysed the networks using FunRich software (31). Each constructed common gene network had

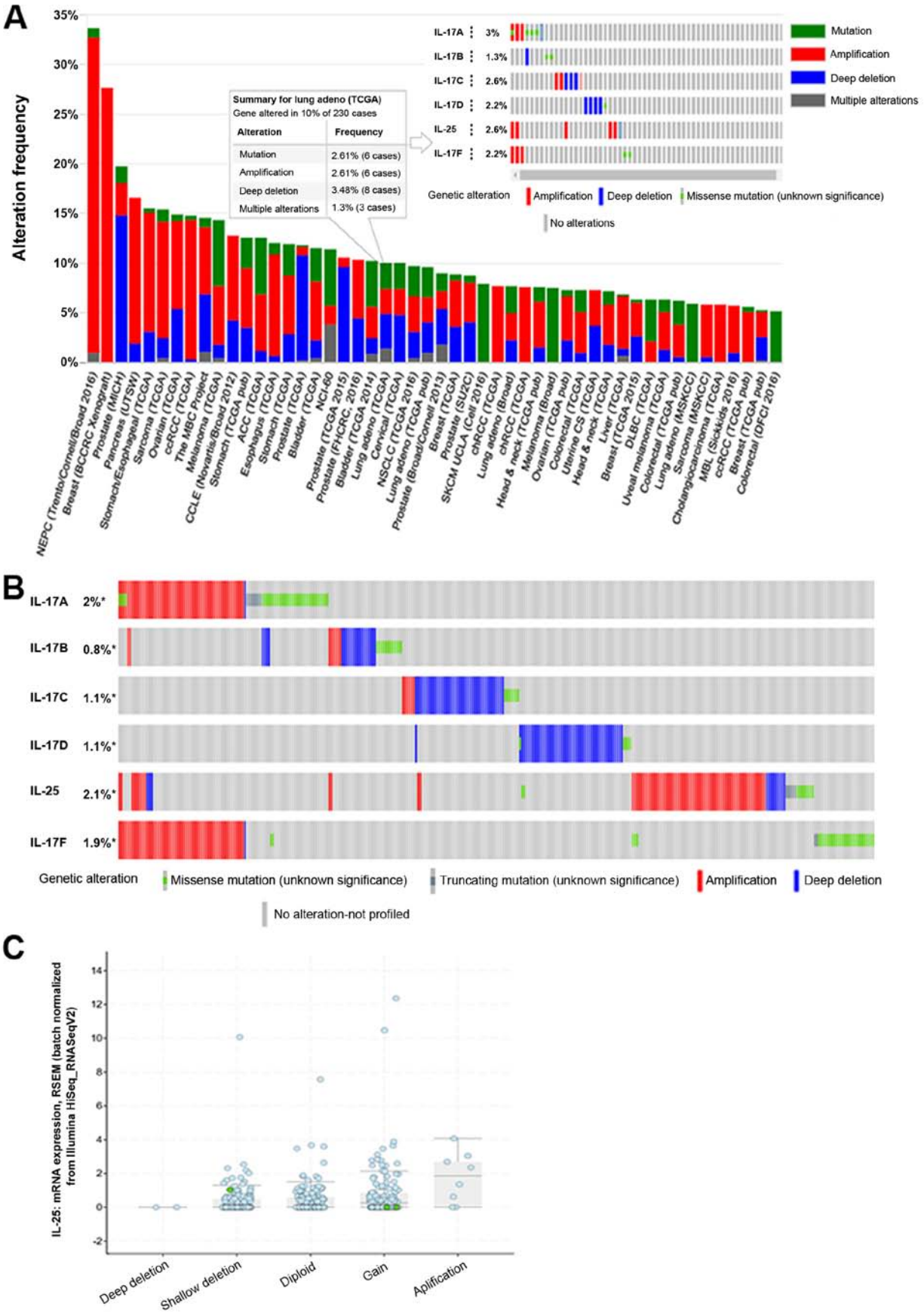

Figure 1. Analysis of IL-17 family gene mutations using the Oncomine database. (A) Gene mutation frequencies of IL-17 family members in various carcinoma types. The red bars indicate gene amplifications, blue bars are homozygous deletions, green bars are non-synonymous mutations, gray bars indicate multiple alterations. (B) IL-17 family gene mutation frequencies and types in 5,238 lung cancer samples. The red bars indicate gene amplifications, blue bars are deep deletions, green bars are missense mutations, gray bars indicate truncating mutations. (C) The correlation between mRNA expression and copy number variations (CNVs) of IL-25. IL-25 mRNA was increased in the lung cancer tissues in which IL-25 was amplified. Deep deletion, homozygously deleted; Shallow deletion, heterozygously deleted; Diploid, two alleles present; Gain, low-level gene amplification event; Amplification, high-level gene amplification event.

Table I. Genetic alterations from COSMIC database.

	IL-17A		IL-17B		IL-17C		IL-17D		IL-25		IL-17F	
Genetic alteration	Mutated (%)	Tested	Mutated (%)	Tested	Mutated (%)	Tested	Mutated (%)	Tested	Mutated (%)	Tested	Mutated (%)	Tested
Point Mutations	0.66	2,256	0.18	2,256	0.13	2,256	0.09	2,256	0.27	2256	0.44	2,256
Copy Number gain	1.18	1,186	0.17	1,186	0	1,186	0.08	1,186	1.26	1186	1.18	1,186
Copy number loss	0.17	1,186	0.25	1,186	0.17	1,186	0.42	1,186	0.25	1186	0.17	1,186

COSMIC v82, released 03-Aug-17. The genetic point mutations of IL-17A to IL-17F family genes were accessed in 2,256 lung cancer patients. The CNV of IL-17A to IL-17F family genes were accessed in 1,186 lung cancer patients. IL-17A exhibited the highest point mutation rate (0.66%), whereas IL-25 showed the highest copy number variation (1.51%).

31 nodes, which were considered the most highly connected protein interactions (Fig. 5). Many of the interacting proteins were also connected with molecules in other networks, probably indicating that IL-17 family members share functional associations with each other. The potential targeted genes were used for the biological pathway and site expression analysis with FunRich software. The results showed that IL-17A was significantly enriched in proteins involved in the 'IFN-γ pathway' (83.87%) and 'α9β1 integrin signalling events' (80.65%). IL-17B was significantly enriched in 'IFN-γ' (83.87%) and 'IL-23-mediated signalling events' (83.87%). IL-17C was enriched in 'TNF receptor signalling pathway' (38.71%) and 'IFN-γ' (45.16%). IL-17D was enriched in 'α9β1 integrin signalling events' (51.61%) and 'IFN-γ' (48.39%). IL-25 was enriched in 'IL-23-mediated signalling events' (40%) and 'IFN-γ' (43.33%), and IL-17F was mainly enriched in 'transcription' (61.29%) (Fig. 6A). Moreover, the analysis based on the term 'site of expression' showed that IL-17C expression levels were higher in the lung than in other family members in other sites (Fig. 6B).

Discussion

The IL-17 family, a subset of cytokines consisting of IL-17A-F, plays crucial roles in inflammation, autoimmune diseases and cancer. IL-17A and IL-17F are primarily secreted by immune cells, whereas IL-17B, IL-17C, IL-17D, and IL-25 are derived from a wide range of cells (42). Among all members, the expression and biological function of IL-17A have been widely studied in lung cancer (Table III). Initial studies have shown that increased expression of IL-17A in cancer tissue and serum were associated with poor survival of patients with lung cancer (43-47). Overexpression or exogeneous IL-17A can promote tumour growth (48), angiogenesis (49,50) and metastasis (51). Other studies have observed that high levels of intratumoral IL-17A expression may indicate good prognosis in gastric adenocarcinoma (10), and similar results have been obtained in oesophageal squamous cell carcinoma (52) and cervical adenocarcinoma (53). These previous studies with small cohorts had limited statistical and clinical power. Furthermore, very little is known about the expression of other IL-17 cytokines in lung cancer. Large databases such as Oncomine and TCGA provide large samples and datasets. Through the integration and analysis of massive bioinformatic data, we can avoid errors associated with small sample experimental research and increase the credibility of the research results. In the present study, the gene mutations, mRNA expression levels, prognostic values and network pathways of different IL-17 family members were investigated, aiming to find directions for further studies and potential therapeutic targets in lung cancer.

A number of studies have reported that IL-17 genetic family polymorphisms are associated with increased risk of cancer. It was demonstrated that IL-17A and IL-17F gene polymorphisms were associated with an increased risk of lung cancer (54-56), gastric cancer (57), acute myeloid leukaemia (58), and colorectal cancer (59). Furthermore, IL-17A polymorphisms may upregulate IL-17A expression (60) and are associated with clinicopathological features and tobacco smoking history in lung cancer patients (54). The relationships between the

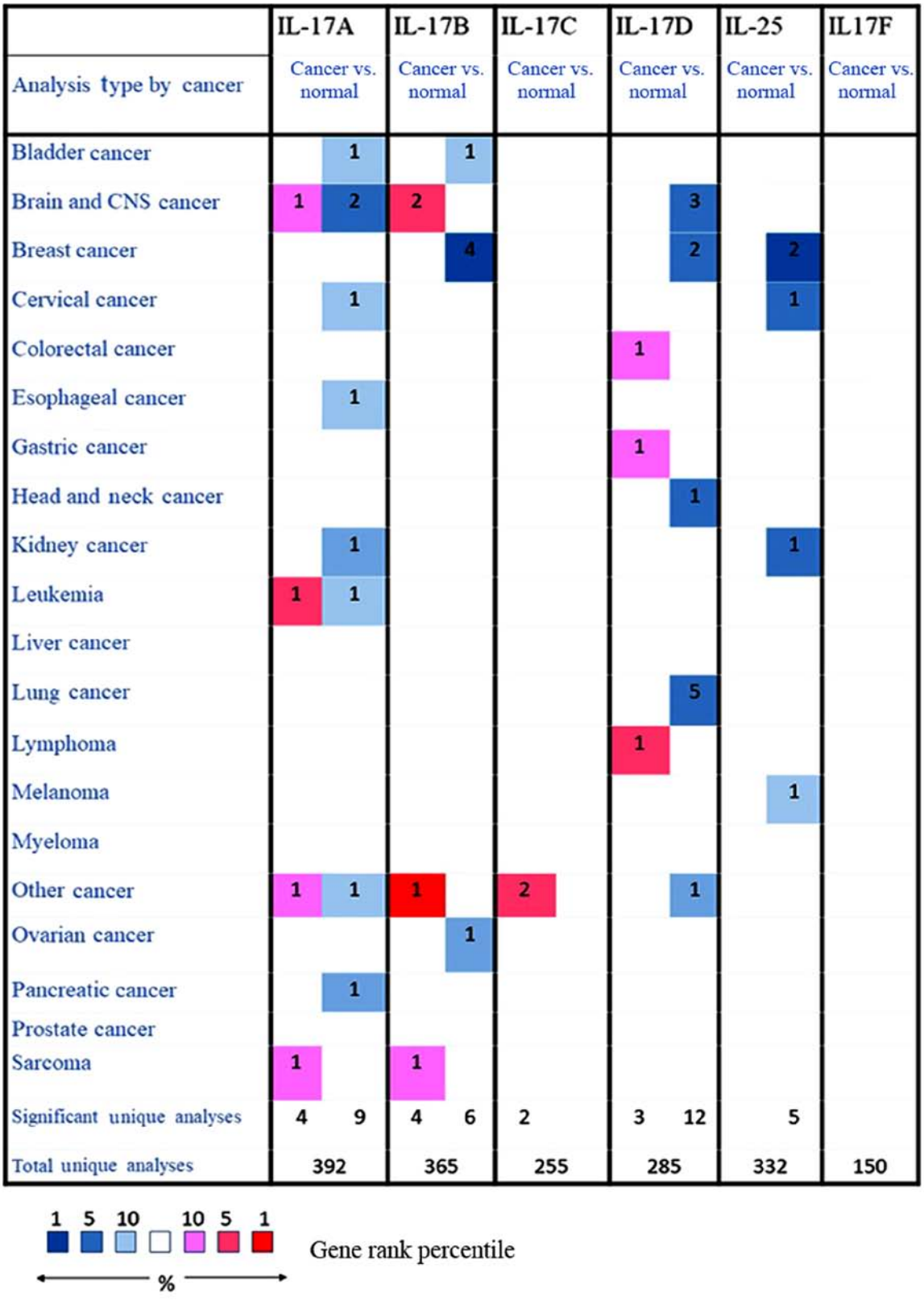

Figure 2. IL-17 family member expression status in different types of cancers with the threshold of P≤0.05, fold change ≥2, and gene rank ≥top 10%, according to the Oncomine database. The numbers in the cells represent the number of datasets that met the threshold settings. The colour indicates the gene expression trend: red represents significant overexpression and blue represents reduced expression. The depth of the colour indicates the degree of overexpression or underexpression.

genetic polymorphisms of other IL-17 family members and lung cancer susceptibility are not fully understood. In our study, the frequencies and types of alterations of IL-17 family genes were analysed through the COSMIC and cBioPortal databases. The present results revealed that IL-17 family gene mutation rates were in general low, and amplification and

Table II. Expression status of IL-17 family at the transcriptional levels in different lung cancer datasets (Oncomine database).

Gene	Types of lung cancer	Fold change	P-value	Sample	t-test	(Refs.)
IL-17A	Lung adenocarcinoma	1.143	0.035	96	1.848	(36)
	Large cell lung carcinoma	1.067	0.023	156	2.096	(35)
IL-17B	Large cell lung carcinoma	1.517	0.008	73	3.045	(37)
	Squamous cell lung carcinoma	1.148	0.002	156	3.114	(35)
IL-17C	Squamous cell lung carcinoma	1.227	1.77E-5	156	4.630	(35)
	Lung adenocarcinoma	1.156	1.47E-4	156	3.788	(35)
	Large cell lung carcinoma	1.132	0.009	156	2.502	(35)
	Lung adenocarcinoma	1.071	0.031	116	1.905	(38)
IL-17D	Lung adenocarcinoma	-2.408	6.34E-5	73	-5.947	(37)
	Lung adenocarcinoma	-2.321	1.01E-11	246	-10.346	(40)
	Lung adenocarcinoma	-2.313	3.85E-17	156	-9.994	(35)
	Squamous cell lung carcinoma	-2.298	7.56E-11	156	-7.993	(35)
IL-25	Lung adenocarcinoma	1.062	0.018	156	2.131	(35)
	Large Cell Lung Carcinoma	1.049	0.104	156	1.292	(35)
	Squamous cell lung carcinoma	1.092	0.002	156	3.073	(35)
	Lung adenocarcinoma	1.033	0.082	107	1.405	(39)
IL-17F	Lung adenocarcinoma	-1.002	0.558	116	-0.146	(38)

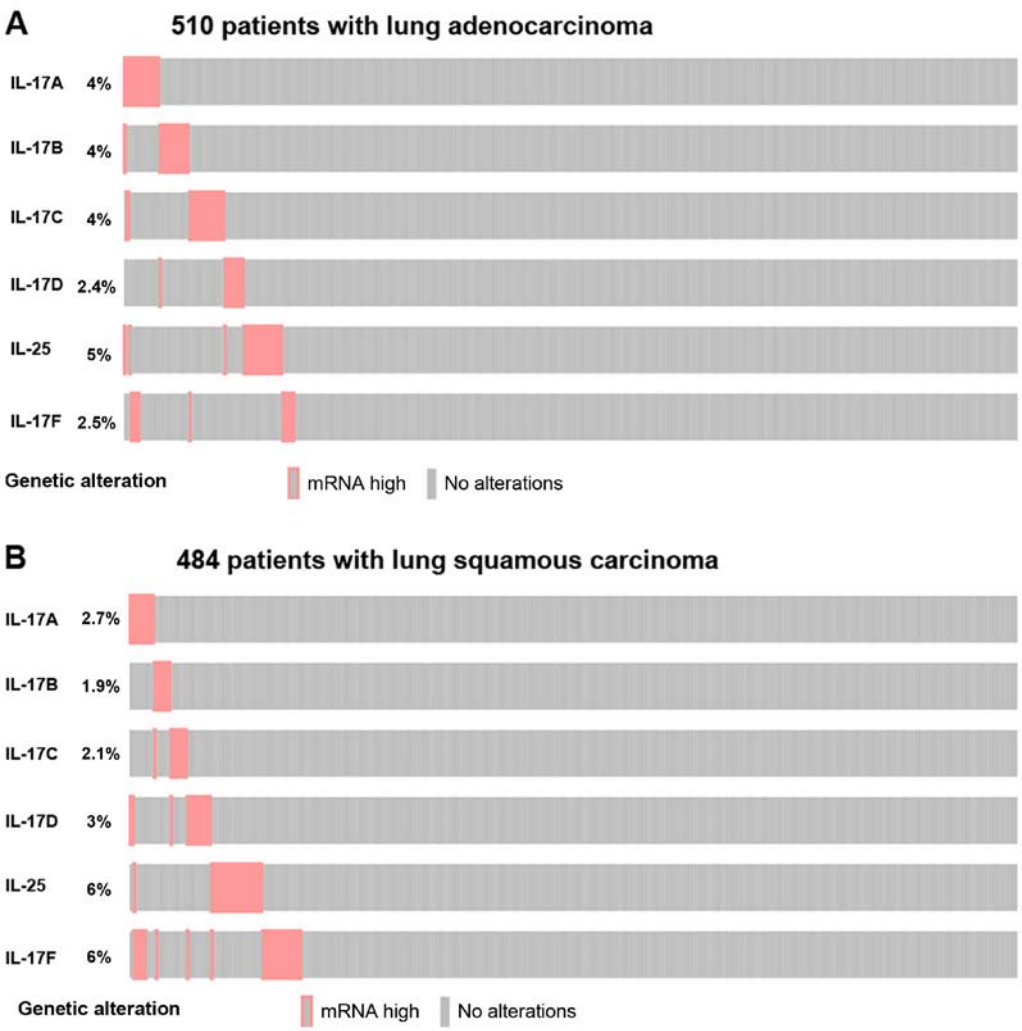

Figure 3. IL-17 family gene mRNA alterations in lung adenocarcinoma and lung squamous cell carcinoma. (A) Dysregulation of IL-17 family mRNA levels in 510 patients with lung adenocarcinoma. (B) Dysregulation of IL-17 family mRNA levels in 484 patients with lung squamous cell carcinoma. Red bars indicate mRNA upregulation, gray bars indicate no alterations.

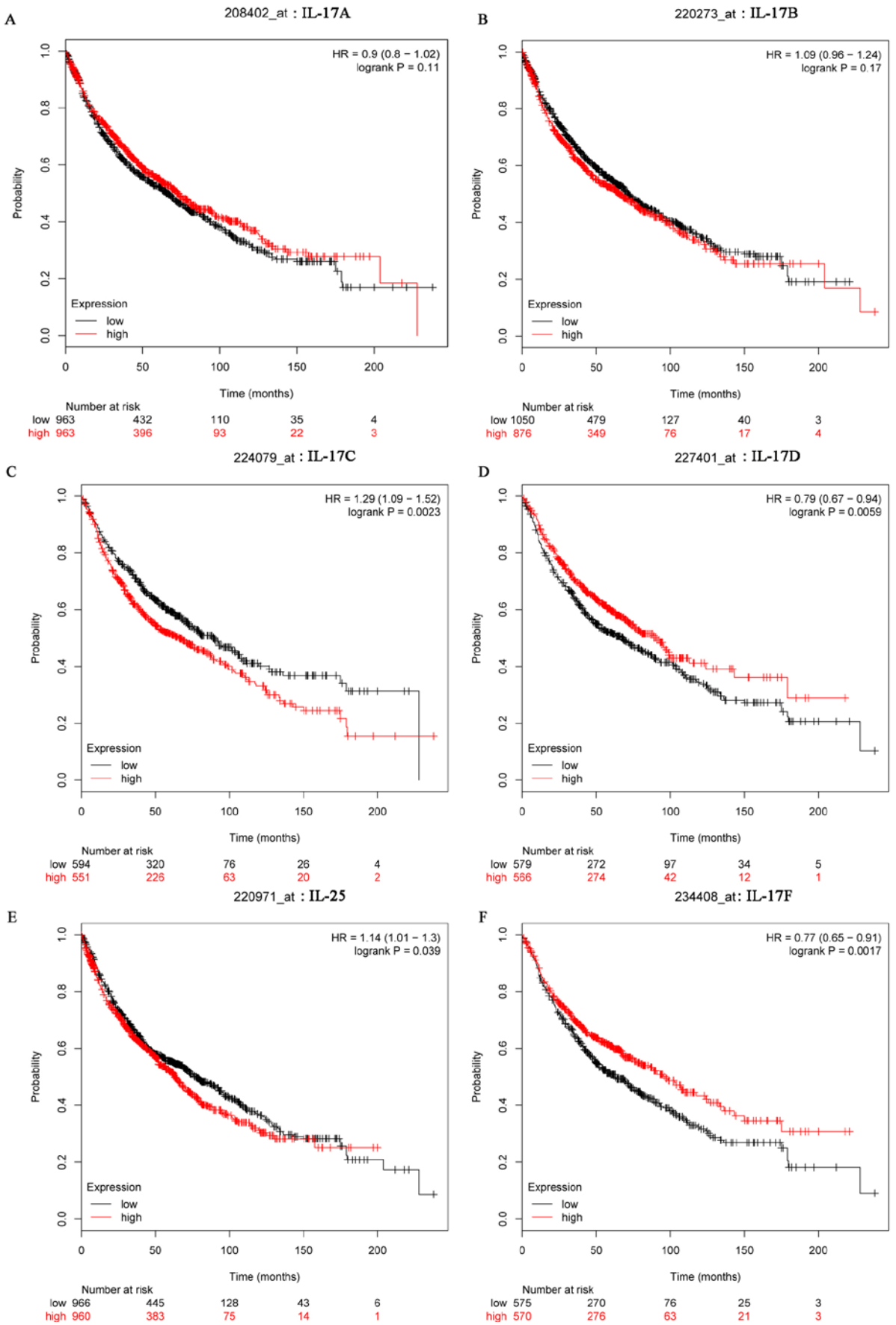

Figure 4. The prognostic value of mRNA levels of IL-17 family members in lung cancer patients (OS in Kaplan-Meier plotter). (A) Prognostic value of IL-17A expression. Affymetrix ID for IL-17A:208402_at. (B) Prognostic value of IL-17B expression. Affymetrix ID for IL-17B:220273_at. (C) Prognostic value of IL-17C expression. Affymetrix ID for IL-17C:224079_at. (D) Prognostic value of IL-17D expression. Affymetrix ID for IL-17D:227401_at. (E) Prognostic value of IL-25 expression. Affymetrix ID for IL-17E:220971_at. (F) Prognostic value of IL-17F expression. Affymetrix ID for IL-17F:234408_at. OS, overall survival.

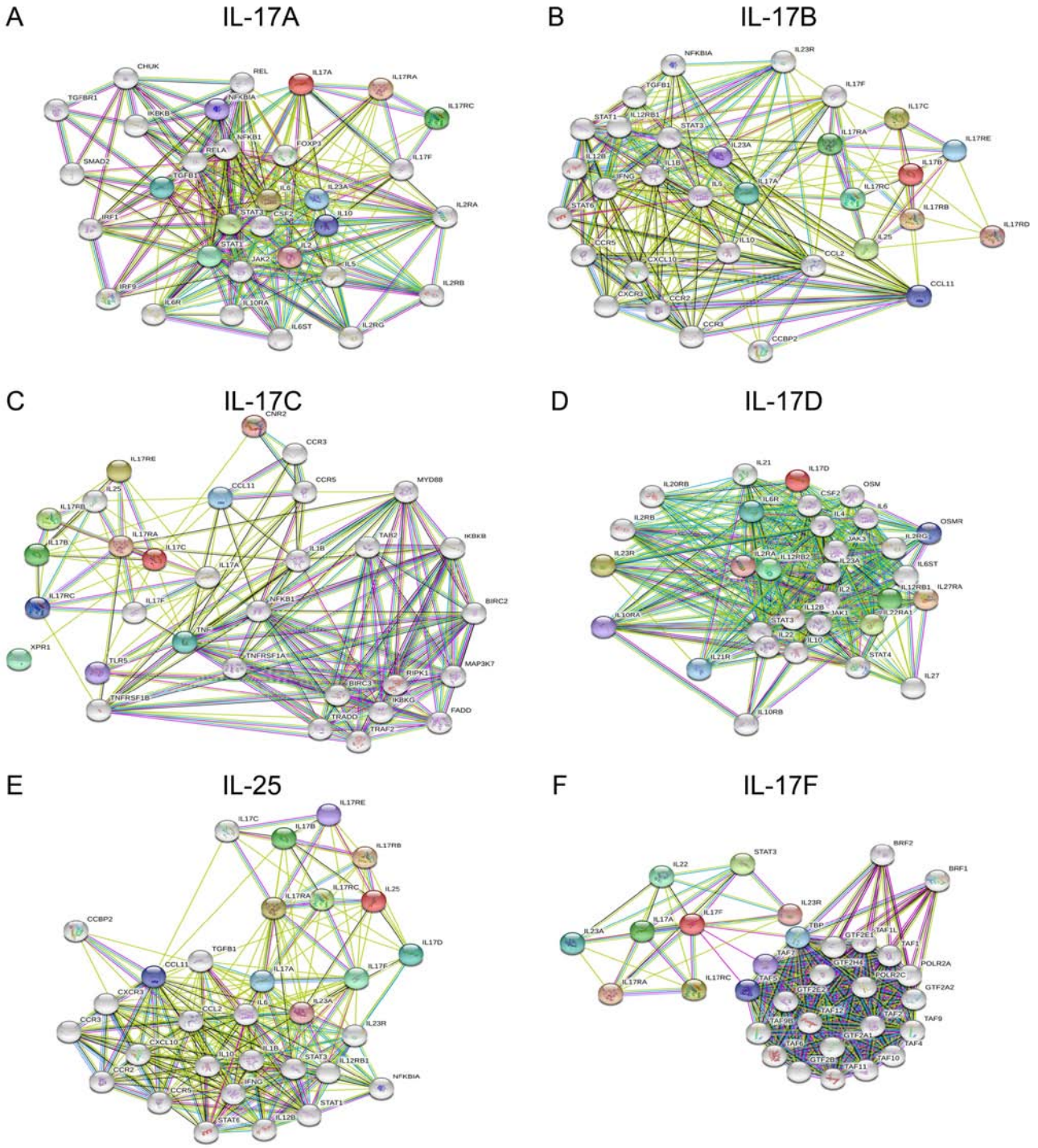

Figure 5. IL-17 family protein-protein interaction network derived from STRING database. In a biological network, a node is any biological molecule and an edge indicates the interaction between two nodes. (A) Interaction network of IL-17A. (B) Interaction network of IL17-B (C) Interaction network of IL-17C. (D) Interaction network of IL-17D. (E) Interaction network of IL-25. (F) Interaction network of IL-17F.

deep deletion were the main mutation type. The incidence of CNV was found to be higher than that of point mutations, and IL-17E exhibited the highest CNV, which was positively related to mRNA expression in lung cancer. IL-17E, which had the highest CNV in lung cancer, represents a promising potential oncogene in lung cancer that warrants further clinical and experimental investigation in the future.

Among the IL-17 family, IL-17A, IL-17B, IL17C and IL-17F were reported to have promoting effects on lung cancer development. In the Oncomine database, our results revealed that five datasets showed significantly decreased IL-17D expression in lung cancer, and no dataset showed a significant difference in the expression of IL-17A, IL-17B, IL-17C, IL-25 or IL17-F between lung cancer and controls. In other lung cancer datasets, IL-17A, IL-17B, IL-17C and IL-25 mRNA levels were upregulated, but the increase was small. IL-17D mRNA levels were downregulated with a fold change >2.0 in NSCLC. Analysis of the cBioPortal database revealed that IL-17 family mRNA alteration frequencies may be associated with specific histological types of NSCLC. IL-17A, IL-17B

Table III. Studies of the IL-17 family genes in lung cancer.

Gene	Alteration	Effects	Mechanism	(Refs.)
IL-17A	Gene polymorphisms	+	Tumourigenesis	(54-56,60)
IL-17A	High expression	+	Poor survival	(43-47,62)
IL-17A	High expression	+	Tumourigenesis	(63,64)
IL-17A	High expression	--	Proliferation	(64,65)
IL-17A	High expression	+	Proliferation	(66)
IL-17A	High expression	+	Apoptosis	(66)
IL-17A	High expression	+	Angiogenesis	(48-50,64,65)
IL-17A	High expression	+	Lymphangiogenesis	(67)
IL-17A	High expression	+	Metastasis	(48,51,63,68-70)
IL-17A	High expression	+	Recruit MDSCs	(71)
IL-17A	High expression	+	Recruit TAN	(5)
IL-17A	High expression	+	Recruit macrophages	(72)
IL-17B	High expression	+	Metastasis	(73)
IL-17C	High expression	+	Recruit TAN	(15)
IL-17F	Gene polymorphisms	+	Tumourigenesis	(54)
IL-17F	High expression	+	Tumourigenesis	(74)

'+' means pro-tumor; '--'means on effects; MDSCs, myeloid-derived suppressor cells; TAN, tumor-associated neutrophils.

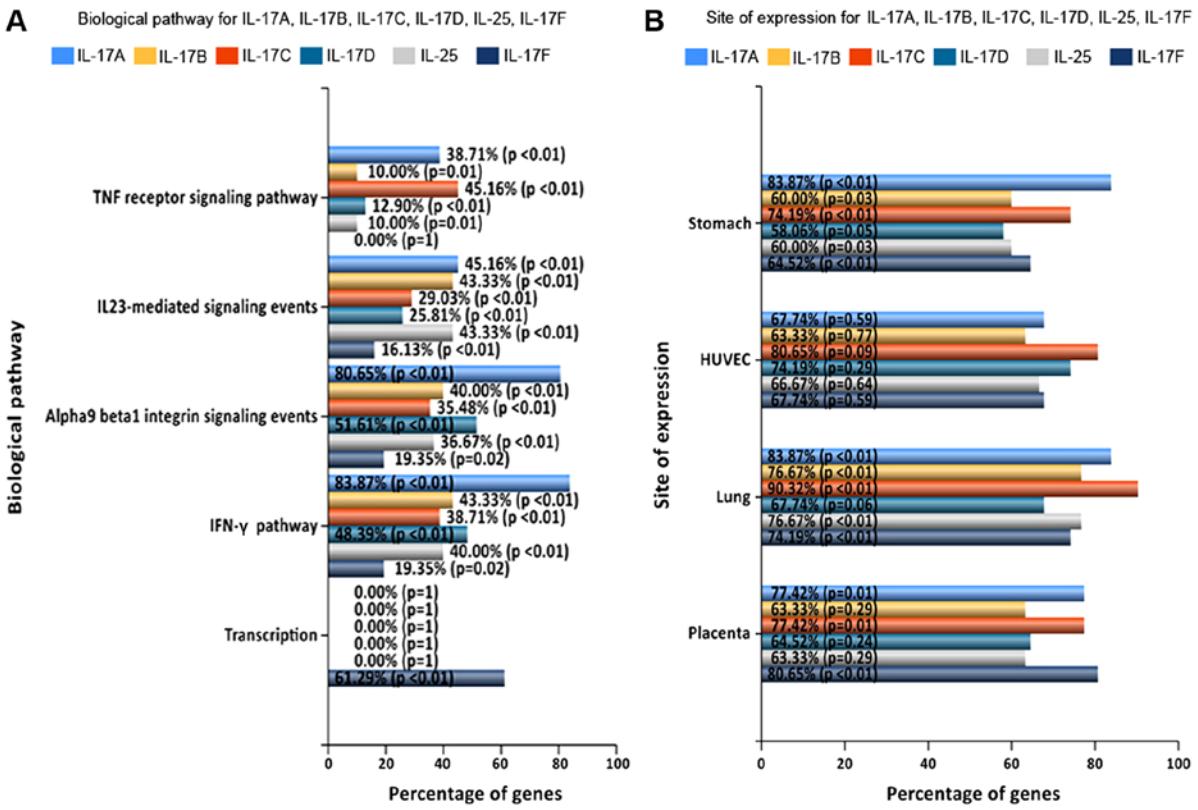

Figure 6. FunRich analysis. (A) The possible biological pathways and (B) site of expression of IL-17 family genes as determined by FunRich. FunRich is a Functional Enrichment tool. (A) IL-17 family genes were significantly enriched in proteins involved in the 'IFN-γ pathway' (83.87%, P<0.01), 'Alpha9beta1 (α9β1) integrin signalling events' (80.65%, P<0.01), 'Transcription' (61.29%, P<0.01), 'TNF receptor signalling pathway' (45.16%, P<0.01), and 'IL-23-mediated signalling events' (45.16%, P<0.01). (B) IL-17A-F expression levels in the lung were 83.87, 76.67, 90.32, 67.74, 76.67 and 74.19%, respectively.

and IL-17C mRNA upregulation frequencies were lower in lung squamous cell carcinoma than in lung adenocarcinoma. IL-17D, IL-25 and IL-17F mRNA upregulation rates were higher in lung squamous cell carcinoma than in lung adenocarcinoma. However, the prognostic information indicated that IL-17A and IL-17B showed no effect on the OS of patients

with lung cancer. High mRNA expression levels of IL-17C and IL-25 were associated with poor OS in lung cancer patients; conversely, high mRNA levels of IL-17D and IL-17F were correlated with better OS.

Analysis of the interaction network and regulation of IL-17 family genes revealed that the biological pathways of IL-17D and IL-17A overlapped. Moreover, all IL-17 family genes, except IL-17F, mainly participated in the 'IFN-γ pathway'. Th1-associated cytokines (IFN-γ) have been suggested to augment anti-tumour responses by positively modulating cancer-directed immune effectors, such as dendritic cells (DCs), T cells and NK cells (61). This information suggests that the relationship between IL-17 family genes and the lung cancer immune microenvironment should be studied in-depth. Based on our results, we can conclude that IL-17 family gene mutation rates were in general low and that amplification and deep deletion were the main mutation type. The expression and function of IL-17A and IL-17B in lung cancer are still not fully elucidated and require studies with larger sample sizes. The survival results revealed that IL-17C, IL-25 and IL-17F have prognostic roles in lung cancer. IL-17D was significantly decreased in lung cancer and was correlated with better OS. The interaction network and biological pathway analyses of the IL-17 family indicated that IL-17 family genes share functional associations with each other. These findings can provide a reference for further experimental studies to identify the molecular mechanism of IL-17D in lung cancer progression.

Nevertheless, some limitations exist in the present study. First, the correlation between the IL-17 gene family and OS within each subclass of clinical parameters, namely, pathologic N stage, pathologic T stage, and pathologic M stage, was not analysed due to data limitations. Second, the mutations and expression levels of IL-17 genes in lung cancer cells need to be validated in a future experimental study. In addition, future functional investigations are required to explore the underlying mechanisms of the IL-17 gene family in lung cancer development. In conclusion, in the present study, we performed the first comprehensive investigation of the IL-17 gene family in lung cancer, including gene mutations, mRNA expression levels, prognostic values and network pathway analysis. Although gene mutations and mRNA expression levels were abnormal in lung cancer patients, IL-17 family gene mutation rates were low in general, and only IL-17D was significantly decreased in lung cancer and was correlated with better OS. The expression and function of IL-17A and IL-17B in lung cancer are still not fully elucidated and require studies with larger sample sizes. Studies of IL-17C-F in lung cancer are limited. Therefore, more research attention should be given to the association between IL-17D and lung cancer progression to identify more effective therapeutic targets for lung cancer.

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Availability of data and materials

The datasets generated and analyzed during the current study are available in The COSMIC database (http://cancer.sanger.ac.uk/cosmic), ONCOMINE gene expression array datasets (https://www.oncomine.org/), Kaplan-Meier plotter (http://www.kmplot.com/analysis/index), The cbio cancer genomics portal (http://www.cbioportal.org/), STRING database (http://string-db.org/) and Funrich (http://www.funrich.org).

Authors' contributions

YJ and TTL conceived and designed the experiments. TTL, JSF and ZLL prepared the figures and tables, and drafted and revised the manuscript. JJX, FW, GHY, QH, GRH, MFG, MZ, LMD and SFW prepared the figures and interpreted the data. All authors read and approved the manuscript and agreed to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors state that they have no competing interests

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