

Table S14. Biomarkers whose fold change (FC) expression was ≥ 50 and average TPM of control samples ≤ 10 .

#	Control			Tumor			Cnx ⁵	GC3	Isochore	References
	GS ¹	AV ²	SD ³	AV	SD	FC ⁴				
1	<u>AKR1B10</u> ⁶	2.5	5.9	747.8	1127.5	297.2	3	62.5	H1, H2	(Huang et al., 2016)
2	CA9	1.4	4.2	94.8	231.4	66.9	5	63.9	H2	(Suzuki et al., 2024)
3	CLCA2	3.7	8.9	240.9	268.3	64.9	1	37.9	L	(Shinmura et al., 2014)
4	COL7A1	1.6	1.3	102.8	110.7	64.3	8	57.0	H1, H2	(Koca et al., 2023)
5	COL17A1	2.4	2.9	169.9	257.4	72.0	7	60.7	H1, H2	(Koca et al., 2023)
6	CTAG2	0.3	1.0	21.1	62.3	82.2	9	64.9	H2	(Djureinovic et al., 2016)
7	CYP4F11	1.8	1.6	103.6	178.1	58.4	1	71.0	H2	(Jia et al., 2024)
8	DSC3	2.2	5.3	158.3	136.3	71.8	3	35.8	L	(Savci-Heijink et al., 2009)
9	GJB2	4.4	4.3	362.3	601.5	81.9	23	74.9	H2, H3	(Zhang et al., 2021; Liu et al., 2024)
10	GJB5	1.6	1.5	85.1	64.0	52.1	5	73.7	H2, H3	(Aasen et al., 2019)
11	GPX2	5.6	7.2	720.6	839.6	127.5	3	70.2	H2	(Peng et al., 2023)
12	KRT6B	2.0	3.1	563.8	836.1	274.5	28	73.3	H2, H3	(Song et al., 2022)
13	KRT13	3.5	4.4	653.4	1340.6	187.1	29	69.9	H2	(Yin et al., 2022)
14	KRT14	4.3	5.2	1627.7	3303.8	381.8	46	80.1	H3	(Koca et al., 2023)
15	KRT15	6.8	8.3	535.1	742.4	78.9	147	70.0	H2	(Wang and Zhu, 2023)
16	KRT16	4.0	9.2	1011.9	1645.7	254.7	69	78.5	H3	(Wang and Zhu, 2023)
17	LYPD3	3.6	2.2	219.6	272.5	61.3	15	70.3	H2	(Hu et al., 2020, 2022)
18	MMP1	6.6	8.9	358.8	797.1	54.3	2	43.1	L	(Zhang et al., 2022)
19	MMP12	3.6	5.3	184.3	237.4	51.2	1	43.1	L	(Li et al., 2024)
20	NTS	9.7	21.7	831.3	2095.5	86.0	3	31.3	L	(Moody et al., 2022)
21	PKP1	6.9	6.3	527.5	444.0	76.9	21	80.9	H3	(Ischenko et al., 2007)
22	PTHLH	1.1	1.0	146.9	233.6	137.0	1	65.2	H2	(Fang et al., 2022)
23	S100A7	1.8	3.3	638.4	2708.9	351.9	20	65.7	H2	(Wang et al., 2017)
24	SBSN	0.8	2.4	71.5	170.9	85.3	2	63.8	H2	(Houri et al., 2023)
25	SERPINB5	1.4	1.8	191.3	153.8	138.2	12	47.3	L, H1	(Huang et al., 2023)
26	SOST	0.7	1.7	43.2	110.4	59.3	3	88.3	H3	(Sebastian and Loots, 2018)
27	SPRR1A	6.3	21.2	899.3	1761.3	143.2	3	68.9	H2	(Zhang et al., 2021)
28	SPRR1B	4.5	10.5	950.8	1520.4	210.6	7	70.0	H2	(Zhang et al., 2021)
29	SPRR2A	3.3	10.9	603.2	1152.0	184.9	12	58.9	H1, H2	(Xu et al., 2020)
30	SPRR2D	1.9	4.7	261.1	511.0	133.7	4	58.9	H1, H2	(Kong et al., 2021)
31	SPRR2E	2.0	6.5	212.8	564.2	107.0	5	57.5	H1, H2	(Cabral et al., 2001)
32	SPRR3	1.9	5.7	366.3	757.3	194.9	1	53.5	H1	(Liao et al., 2024)
33	TMPRSS4	1.8	1.7	90.2	82.1	50.1	5	70.5	H2	(Villalba et al., 2019)
34	TP63	4.3	2.5	251.8	229.0	57.9	87	60.9	H1, H2	(Lim et al., 2003; Lin et al., 2024; Jiang et al., 2024)

¹ GS, Gene symbol. ² AV, Average. ³ SD, Standard deviation. ⁴ FC, Fold change. ⁵ Cnx, Connections score. ⁶ Biomarkers with FC > 100 are underlined.

Contextualization of Table S14 information

To make Table S14 more informative, we compiled and briefly summarized the quotations from its publication references as presented below.

Aldo-keto reductase family 1, member B10 (AKR1B10) is known to be significantly induced in the cells of various cancers and its overexpression promotes breast cancer cell migration and invasion via activation of ERK signaling (Li et al., 2017). Carbonic anhydrase 9 (CA9) is considered a marker of hypoxia and it has reported that CA9 is associated with tumor invasion and metastasis. It was found that CA9-positive patients presented significantly poorer survival rate for OS than that of the CA9-negative patients (Suzuki et al., 2024). The Chloride Channel Accessory 2 (CLCA2) is involved in chloride conductance and has been proposed as a biomarker to distinguish between LUSC and LUAD (Shinmura et al., 2014). Collagen Type VII Alpha 1 Chain (COL7A1) was identified as a hypoxia-related key gene in LUAD progression (Li et al., 2020). Its increased expression is correlated with tumor progression and aggressive forms of clear cell renal cell carcinoma (Koca et al., 2023). On the other hand, Collagen Type XVII Alpha 1 Chain (COL17A1) was confirmed to promote cell proliferation, migration, and invasion in vitro mediated by the epithelial-mesenchymal transition pathway. Thus, COL17A1 could be used as a prognostic marker in PC (Yang et al., 2022). Cancer testis antigens (CTAs) are of clinical interest as biomarkers and present valuable targets for immunotherapy (Djureinovic et al., 2016). Cytochrome P450 Family 4 Subfamily F Member 11 (CYP4F11) is significantly overexpressed in LUSC patients and promotes cell proliferation and migration in cancer (Jia et al., 2024). Desmocollin 3 (DSC3), a member of the Cadherin superfamily and a cell adhesion marker, is one of the markers to predict the risk of tumor progression based on the epithelial-mesenchymal transition. DSG3 can be a useful ancillary marker to identify subtypes of lung cancer (Savci-Heijink et al., 2009). Gap-junctional intercellular communication is crucial for epidermal cellular homeostasis. Gap junction protein beta-2 (GJB2) promotes hepatocellular carcinoma progression by activating glycolysis through cytoplasmic translocation and generating a suppressive tumor microenvironment. GJB2 is related to glycolysis, promoting NF- κ B pathway via inducing the ubiquitination degradation of I κ B α , and activating HIF-1 α /GLUT-1/PD-L1 pathway (Liu et al., 2024). In lung cancer, GJB5 connexin expression is unfavourable for patient outcome (Aasen et al., 2019). Glutathione peroxidase 2 (GPX2), an antioxidant enzyme, is involved in tumor progression and metastasis. Its elevated expression in NSCLC tissues is correlated with poor prognosis (Peng et al., 2023). Keratins 6B (Song et al., 2022), 13 (Yin et al., 2022), 14 (Gogoi et al., 2024), 15 (Wang and Zhu, 2023), and 16 (Wang et al., 2023) regulate the invasion as well as the stemness and is associated with tumor size and metastasis of several cancers. LY6/PLAUR Domain Containing 3 (LYPD3) is highly expressed in LUAD tumor (Hu et al., 2020). LYPD3 participates in tumorigenesis through p53 or/and the PI3K/AKT signaling pathway (Hu et al., 2022). Matrix Metalloproteinase 1 (MMP1) overexpression promotes cancer progression and is associated with poor patient outcome in head and neck carcinoma (Zhang et al., 2022), while MMP12 is a potential predictive and prognostic biomarker of various cancers including lung adenocarcinoma (Li et al., 2024). Neurotensin (NTS) receptor 1 regulates the growth non-small cell lung cancer cells. NTS binds with high affinity to NTSR1, leading to increased tyrosine phosphorylation of the EGFR and HER2, which lead to increased proliferation (Moody et al., 2022). Although desmosomes have generally been associated with

tumor suppressor functions, it has been found that Plakophilin 1 (PKP1) is recurrently overexpressed in LUSC to exert an oncogenic role by enhancing the translation of MYC (Boyer et al., 2022). Cachexia is the most common risk factor for increased mortality rates among patients with advanced lung cancer. The parathyroid hormone-like hormone (PTHrH) is reported to be involved in the pathogenesis of cancer cachexia (Fang et al., 2022). PTHrH expression leads to increasing tumor growth and is a poor prognosis marker in head and neck squamous cell carcinoma (HNSCC) patients (Chang et al., 2017). The calcium-modulated S100A7 protein promotes lung adenocarcinoma to squamous carcinoma transdifferentiation, and the Hippo-YAP pathway in lung cancer cells differentially regulates its expression (Wang et al., 2017). Suprabasin (SBSN) is a secreted protein that induces various cellular processes such as proliferation, invasion, metastasis, migration, angiogenesis, apoptosis, therapy and immune resistance. It is involved in the maintenance of survival and proliferation, invasion and angiogenesis of LUSC cells under hypoxia (Houry et al., 2023). Serine protease inhibitor B5 (SERPINB5) is a prognostic biomarker and promotes proliferation, metastasis and epithelial-mesenchymal transition in LUAD (He et al., 2023). Sclerostin (SOST) is an endogenous inhibitor of bone formation. Up-regulated SOST expression was associated with breast cancer bone metastases and worse patient survival, which prompted Sun et al. (2022) to propose SOST as a new class of potential therapeutics for treatment of bone metastasis in breast cancer. The expressions of Small Proline Rich Protein 1B (SPRR1B) and SPRR2D in multiple tumor data sets were higher in tumor tissues than in normal tissues including in lung cancer. Thus, SPRR1B and SPRR2D could serve as a biomarker (Zhang et al., 2021). The fact that Serum Small Proline-Rich Protein 2A (SPRR2A) levels in gastric cancer patients were associated with lymph node metastasis and the tumor-node-metastasis suggest that it can be used as an effective marker for this disease (Xu et al., 2020). SPRR2E and SPRR3 are also all highly expressed in the H1299 cell line (Xiong et al., 2017). SPRR3 has been proposed as a promising diagnostic and prognostic biomarker for a diverse array of cancers and including LUAD (Liao et al., 2024). Transmembrane protease serine 4 (TMPRSS4) is a member of the type II transmembrane serine protease. When highly upregulated, it plays a role in facilitating the growth and metastatic spread of cancer cells. TMPRSS4 protein expression can be used to stratify patients at high risk of relapse/death in very early stages NSCLC patients (Villalba et al., 2019). Tumor Protein P63 (TP63) is a DNA-binding protein member of the p53 family, which regulates the differentiation and proliferation of epithelial progenitor cells. It is likely to be involved in the development of LUSC (Lim et al., 2003). Its variation is a risk factor for the development of lung adenocarcinoma in the UK population. Furthermore, they provide additional insight into the subtype-specificity of the 3q28 lung cancer association (Wang et al., 2011). Patients with elevated TP63 expression had poorer overall survival and lower 3-year recurrence-free survival (Lin et al., 2024).

References

- Aasen T, Leithe E, Graham SV, Kameritsch P, Mayán M.D, Mesnil M, Pogoda K, Tabernero A. 2019. Connexins in Cancer: Bridging the Gap to the Clinic. *Oncogene* **38**, 4429. (doi:10.1038/S41388-019-0741-6)
- Boyero L, Martin-Padron J, Fárez-Vidal ME, Rodriguez MI, Andrades Á, Peinado P, Arenas AM, Ritoré-Salazar F, Alvarez-Perez JC, Cuadros M, et al. 2022. PKP1 and MYC Create a Feedforward Loop Linking Transcription and Translation in Squamous Cell Lung Cancer. *Cell. Oncol.* **45**, 323–332. (doi:10.1007/S13402-022-00660-1)
- Chang WM, Lin YF, Su CY, Peng HY, Chang YC, Hsiao JR, Chen CL, Chang JY, Shieh YS, Hsiao M, et al. 2017. Parathyroid Hormone-Like Hormone Is a Poor Prognosis Marker of Head and Neck Cancer and Promotes Cell Growth via RUNX2 Regulation. *Sci. Rep.* **7**, 41131. (doi:10.1038/SREP41131)
- Djureinovic D, Hallström BM, Horie M, Margareta Mattsson JS, La Fleur L, Fagerberg L, Brunnström H, Lindskog C, Madjar K, Rahnenführer J, et al. (2016). Profiling Cancer Testis Antigens in Non–Small-Cell Lung Cancer. *JCI Insight* **1**, e86837. (doi:10.1172/JCI.INSIGHT.86837)
- Fang XQ, Kim YS, Lee YM, Lee M, Lim WJ, Yim WJ, Han MW, Lim J.H. 2022. Polygonum Cuspidatum Extract (Pc-Ex) Containing Emodin Suppresses Lung Cancer-Induced Cachexia by Suppressing TCF4/TWIST1 Complex-Induced PTHrP Expression. *Nutrients* **14**, 1508. (doi:10.3390/NU14071508)
- Gogoi B, Lalrinpuia B, Lalhmingliana Kumar NS. 2024. KRT14 as a Potential Prognostic Marker for Metastasis in Metaplastic Breast Carcinoma. *Hum. Gene* **42**, 201341. (doi:10.1016/J.HUMGEN.2024.201341)
- He X, Ma Y, Huang Z, Wang G, Wang W, Zhang R, Guo G, Zhang X, Wen Y, Zhang L. 2023. SERPINB5 Is a Prognostic Biomarker and Promotes Proliferation, Metastasis and Epithelial-Mesenchymal Transition (EMT) in Lung Adenocarcinoma. *Thorac. cancer* **14**, 2275–2287. (doi:10.1111/1759-7714.15013)
- Houri A, Mukudai Y, Abe Y, Watanabe M, Nara M, Miyamoto S, Kurihara M, Shimane T, Shirota T. 2023. Suprabasin Enhances the Invasion, Migration, and Angiogenic Ability of Oral Squamous Cell Carcinoma Cells under Hypoxic Conditions. *Oncol. Rep.* **49**. (doi:10.3892/OR.2023.8520)
- Hu P, Huang Y, Gao Y, Yan H, Li X, Zhang J, Wang Y, Zhao Y. 2020. Elevated Expression of LYPD3 Is Associated with Lung Adenocarcinoma Carcinogenesis and Poor Prognosis. *DNA Cell Biol.* **39**, 522–532. (doi:10.1089/DNA.2019.5116)
- Hu T, Zhang Y, Yang T, He Q, Zhao M. 2022. LYPD3, a New Biomarker and Therapeutic Target for Acute Myelogenous Leukemia. *Front. Genet.* **13**, 795820. (doi:10.3389/FGENE.2022.795820)
- Huang WC, Jang TH, Tung SL, Yen TC, Chan SH, Wang LH. 2019. A Novel MiR-365-3p/EHF/Keratin 16 Axis Promotes Oral Squamous Cell Carcinoma Metastasis, Cancer Stemness and Drug Resistance via Enhancing B5-Integrin/c-Met Signaling Pathway. *J. Exp. Clin. Cancer Res.* **38**, 89. (doi:10.1186/S13046-019-1091-5)

- Jia H, Brixius B, Bocianoski C, Ray S, Koes DR, Brixius-Anderko S. 2024. Deciphering the Role of Fatty Acid-Metabolizing CYP4F11 in Lung Cancer and Its Potential As a Drug Target. *Drug Metab. Dispos.* **52**, 69–79. (doi:10.1124/DMD.123.001463)
- Jiang Y, Zheng Y, Zhang YW, Kong S, Dong J, Wang F, Ziman B, Gery S, Hao JJ, Zhou D, et al. 2024. Reciprocal Inhibition between TP63 and STAT1 Regulates Anti-Tumor Immune Response through Interferon- γ Signaling in Squamous Cancer. *Nat. Commun.* **15**, 2484. (doi:10.1038/S41467-024-46785-9).
- Koca D, Séraudie I, Jardiller R, Cochet C, Filhol O, Guyon L. 2023. COL7A1 Expression Improves Prognosis Prediction for Patients with Clear Cell Renal Cell Carcinoma atop of Stage. *Cancers* **15**, 2701. (doi:10.3390/cancers15102701)
- Li J, Guo Y, Duan L, Hu X, Zhang X, Hu J, Huang L, He R, Hu Z, Luo W, et al. 2017. AKR1B10 Promotes Breast Cancer Cell Migration and Invasion via Activation of ERK Signaling. *Oncotarget* **8**, 33694. (doi:10.18632/ONCOTARGET.16624)
- Li GS, Tang YX, Zhang W, Li J-D, Huang HQ, Liu J, Fu ZW, He RQ, Kong JL, Zhou HF, et al. 2024. MMP12 Is a Potential Predictive and Prognostic Biomarker of Various Cancers Including Lung Adenocarcinoma. *Cancer Control* **31**, 10732748241235468. (doi:10.1177/10732748241235468)
- Li H, Tong L, Tao H, Liu Z. 2020. Genome-Wide Analysis of the Hypoxia-Related DNA Methylation-Driven Genes in Lung Adenocarcinoma Progression. *Biosci. Rep.* **40**, BSR20194200. (doi:10.1042/BSR20194200)
- Liao S, Zhao W, Yin S, Xu J, Yang L, Yang Y, Yan H, Ou T, Zeng X. 2024. Predictive Role and Molecular Biological Function of Proline-Rich Small Repeat Protein SPRR3 in the Diagnosis of Lung Adenocarcinoma. *Int. J. Biol. Macromol.* **278**, 134674. (doi:10.1016/J.IJBIOMAC.2024.134674)
- Lim S, Kim JY, Park K. 2003. Expression of P63 in Lung Cancer. *J. Pathol. Transl. Med.* **37**, 100–107. (<https://www.jpatholm.org/upload/pdf/kjp-37-2-100.pdf>)
- Lin C-H, Cheng P-L, Chuang C-Y, Kang Y-T, Lee L-W, Hsiao T-H, Hsu C-P. 2024. The Expression of TP63 as a Biomarker of Early Recurrence in Resected Esophageal Squamous Cell Carcinoma after Neoadjuvant Chemoradiotherapy. *Biomedicines* **12**, 1101. (doi:10.3390/biomedicines12051101)
- Liu H, Li X, Zhang C, Hao X, Cao Y, Wang Y, Zhuang H, Yu N, Huang T, Liu C, Cao H, Lu Z, Song J, Liu L, Wang H, Li Z, Tang W. 2024. GJB2 Promotes HCC Progression by Activating Glycolysis Through Cytoplasmic Translocation and Generating a Suppressive Tumor Microenvironment Based on Single Cell RNA Sequencing. *Adv Sci.* **11**, e2402115. (doi:10.1002/advs.202402115)
- Moody TW, Ramos-Alvarez I, Jensen RT. 2022. Adding of Neurotensin to Non-Small Cell Lung Cancer Cells Increases Tyrosine Phosphorylation of HER3. *Peptides* **156**, 170858. (doi:10.1016/J.PEPTIDES.2022.170858)
- Peng F, Xu Q, Jing X, Chi X, Zhang Z, Meng X, Liu X, Yan J, Liu X, Shao S. 2023. GPX2 Promotes EMT and Metastasis in Non-Small Cell Lung Cancer by Activating PI3K/AKT/MTOR/Snail Signaling Axis. *FASEB bioAdvances* **5**, 233–250. (doi:10.1096/FBA.2022-00045)

- Savci-Heijink CD, Kosari F, Aubry MC, Caron BL, Sun Z, Yang P, Vasmatazis G. 2009. The Role of Desmoglein-3 in the Diagnosis of Squamous Cell Carcinoma of the Lung. *Am. J. Pathol.* **174**, 1629. (doi:10.2353/AJPATH.2009.080778)
- Shinmura K, Igarashi H, Kato H, Kawanishi Y, Inoue Y, Nakamura S, Ogawa H, Yamashita T, Kawase A, Funai K, et al. 2014. CLCA2 as a Novel Immunohistochemical Marker for Differential Diagnosis of Squamous Cell Carcinoma from Adenocarcinoma of the Lung. *Dis. Markers* **2014**, 619273. (doi:10.1155/2014/619273)
- Song Q, Yu H, Cheng Y, Han J, Li K, Zhuang J, Lv Q, Yang X, Yang H. 2022. Bladder Cancer-Derived Exosomal KRT6B Promotes Invasion and Metastasis by Inducing EMT and Regulating the Immune Microenvironment. *J. Transl. Med.* **20**, 308. (doi:10.1186/S12967-022-03508-2)
- Sun Y, Cheng Z, Liu S. 2022. MCM2 in Human Cancer: Functions, Mechanisms, and Clinical Significance. *Mol. Med.* **28**, 1–15. (doi:10.1186/S10020-022-00555-9)
- Villalba M, Exposito F, Pajares MJ, Sainz C, Redrado M, Remirez A, Wistuba I, Behrens C, Jantus-Lewintre E, Camps C, et al. 2019. Tmprss4: A Novel Tumor Prognostic Indicator for the Stratification of Stage IA Tumors and a Liquid Biopsy Biomarker for NSCLC Patients. *J. Clin. Med.* **8**, 2134. (doi:10.3390/JCM8122134)
- Wang Y, Broderick P, Matakidou A, Vijayakrishnan J, Eisen T, Houlston RS. 2011. Variation in TP63 Is Associated with Lung Adenocarcinoma in the UK Population. *Cancer Epidemiol. Biomarkers Prev.* **20**, 1453–1462. (doi:10.1158/1055-9965.EPI-11-0042)
- Wang R, Li Y, Hu E, Kong F, Wang J, Liu J, Shao Q, Hao Y, He D, Xiao X. 2017. S100A7 Promotes Lung Adenocarcinoma to Squamous Carcinoma Transdifferentiation, and Its Expression Is Differentially Regulated by the Hippo-YAP Pathway in Lung Cancer Cells. *Oncotarget* **8**, 24804. (doi:10.18632/ONCOTARGET.15063)
- Wang J, Zhu G. 2023. Silencing of Keratin 15 Impairs Viability and Mobility While Facilitating the Doxorubicin Chemosensitivity by Inactivating the B-catenin Pathway in Liver Cancer. *Oncol. Lett.* **26**, 447. (doi:10.3892/OL.2023.14034)
- Xiong Y, Li MZ, Zhang PP, Zhang LY, Yang Y. 2017. Study on Genotype in Lung Squamous Carcinoma by High-Throughput of Transcriptome Sequence. *Chinese J. Lung Cancer* **20**, 727–731. (doi:10.3779/J.ISSN.1009-3419.2017.11.01)
- Xu X, Wei S, Chen Y, Yu D, Wang X, Dong X. 2020. Serum Small Proline-Rich Protein 2A (SPRR2A) Is a Noninvasive Biomarker in Gastric Cancer. *Dis. Markers* **2020**, 8493796. (doi:10.1155/2020/8493796)
- Yang J, Li Y, Sun Z, Fan Z, Shi M, Liu S, Meng Y, Zhou B, Jiang Y, Zhan H. 2022. COL17A1 Facilitates Tumor Growth and Predicts Poor Prognosis in Pancreatic Cancer. *Biochem. Biophys. Res. Commun.* **632**, 1–9. (doi:10.1016/J.BBRC.2022.09.049)

Yin L, Li Q, Mrdenovic S, et al. 2022. KRT13 promotes stemness and drives metastasis in breast cancer through a plakoglobin/c-Myc signaling pathway. *Breast Cancer Res.* **24**, 7. (doi: 10.1186/s13058-022-01502-6)

Zhang W, Huang X, Huang R, Zhu H, Ye P, Lin X, Zhang S, Wu M, Jiang F. 2022. MMP1 Overexpression Promotes Cancer Progression and Associates with Poor Outcome in Head and Neck Carcinoma. *Comput Math Methods Med.* **2022**, 3058342. (doi: 10.1155/2022/3058342)

Zhang JY, Shi K.Z, Liao XY, Li S.J, Bao D, Qian Y, Li DJ. 2021. The Silence of PSMC6 Inhibits Cell Growth and Metastasis in Lung Adenocarcinoma. *Biomed Res. Int.* **2021**, 9922185. (doi:10.1155/2021/9922185)