

Supplementary Information for

Clinical Implications and Prognostic Value of Leucine-Rich G Protein-Coupled Receptor 5 Expression as A Cancer Stem Cell Marker in Malignancies: A Systematic Review and Meta-Analysis

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Table S1: Quality assessment of studies using a Newcastle-Ottawa scale for assessing studies

Studies	Selection			Comparability		Exposure		Total quality score
Author (reference)	Is the case definition adequate	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate
Yoshizawa et al. (20)	*	*		*	*		*	*
AbdelMageed et al. (27)	*	*		*	*	*	*	
Lee et al. (28)	*	*	*	*	*		*	*
Xu et al. (14)	*	*	*	*	*	*	*	*
Kawasaki et al. (29)	*	*		*	*		*	*
Abdelrahman et al. (30)	*	*	*	*	*	*	*	
Ehara et al. (16)	*	*		*	*		*	*
Hagerling et al. (31)	*			*	*	*	*	*
Ogasawara et al. (19)	*	*		*	*		*	*
Kang et al. (32)	*	*	*	*	*		*	*
Zhang et al. (33)	*	*		*	*	*	*	*
Nagashima et al. (34)	*	*	*	*	*	*	*	
Ihemelandu et al. (35)	*	*	*	*	*	*	*	*
Shen et al. (36)	*	*		*	*	*	*	*
Shekarriz et al. (24)	*	*	*	*	*		*	*

Received: 30/August/2023, Revised: 08/November/2023, Accepted: 18/November/2023

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Table S1: Continued

Studies	Selection		Comparability		Exposure		Non-response rate		Total quality score
Author (reference)	Is the case definition adequate	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Liu et al. (13)	*	*		*	*	*	*	*	7
Freiin Grote et al. (37)	*		*	*	*	*	*		6
Ko et al. (38)	*	*		*	*	*	*	*	7
Ma et al. (39)	*	*	*	*	*		*	*	7
Rot et al. (40)	*	*		*	*	*	*	*	7
Yu et al. (15)	*	*	*	*	*		*	*	7
Kuraishi et al. (18)	*	*	*	*	*		*	*	7
Hou et al. (41)	*	*		*	*		*	*	6
Jang et al. (42)	*	*	*	*	*		*	*	7
Kim et al. (43)	*	*	*	*	*		*	*	7
Chen et al. (12)	*	*	*	*	*		*	*	7
Harada et al. (44)	*	*		*	*	*	*		6
Lv et al. (45)	*	*		*	*		*	*	6
Liu et al. (46)	*	*	*	*	*	*	*	*	8
Wu et al. (47)	*	*	*	*	*		*	*	7
Wu et al. (48)	*	*	*	*	*	*	*	*	8
Jang et al. (49)	*	*		*	*		*	*	6
Sun et al. (50)	*	*		*	*	*	*	*	7
Yang et al. (51)	*	*	*	*	*		*	*	7
Gao et al. (52)	*	*		*	*	*	*	*	7
Sun et al. (53)	*	*	*	*	*		*	*	7
Wang et al. (54)	*	*	*	*	*		*		6
Gao et al. (55)	*		*	*	*		*	*	6
Liu et al. (56)	*	*	*	*	*		*	*	7
He et al. (57)	*	*		*	*	*	*	*	7
Chen et al. (58)	*	*		*	*	*	*	*	7
Xi et al. (59)	*	*	*	*	*		*	*	7
Hsu et al. (60)	*	*		*	*	*	*	*	7
Jang et al. (61)	*	*	*	*	*		*		6
Zheng et al. (62)	*	*		*	*		*	*	6
Ryuge et al. (63)	*	*		*	*	*	*	*	7
Bu et al. (64)	*	*	*	*	*		*	*	7
Wu et al. (65)	*	*	*	*	*		*	*	7
Ziskin et al. (66)	*	*	*	*	*		*	*	7
Takahashi et al. (67)	*	*		*	*	*	*		6
Takeda et al. (68)	*	*		*	*		*	*	6
Becker et al. (69)	*	*		*	*	*	*		6
Fan et al. (70)	*	*	*	*	*		*	*	7

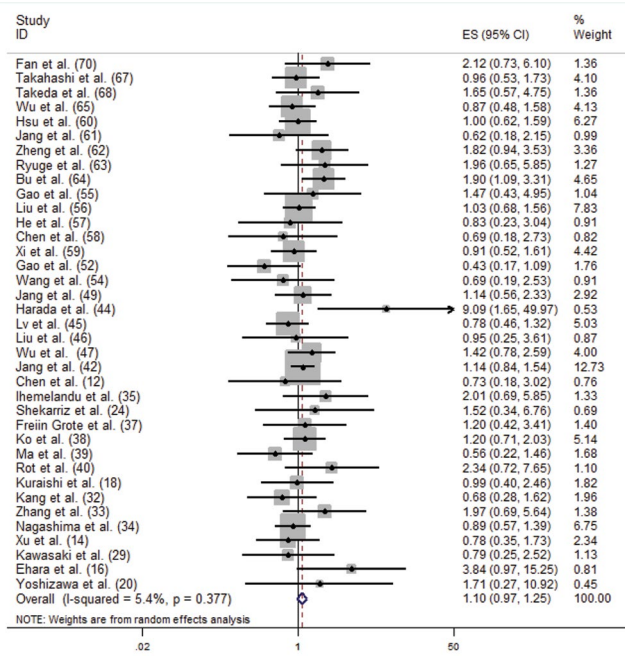


Fig.S1: Forest plot for the association between *LGR5* expression and gender (male vs. female).

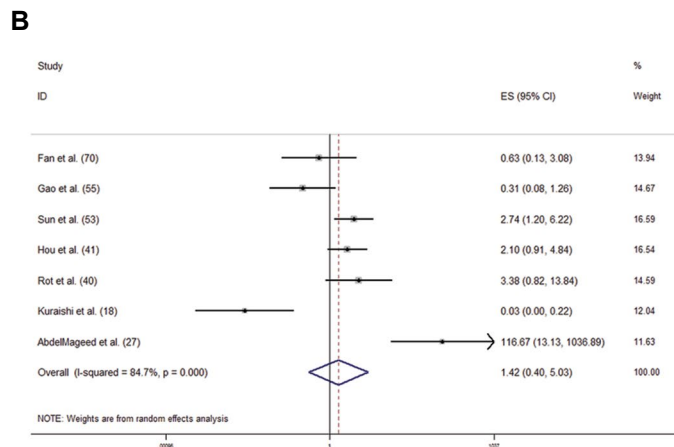
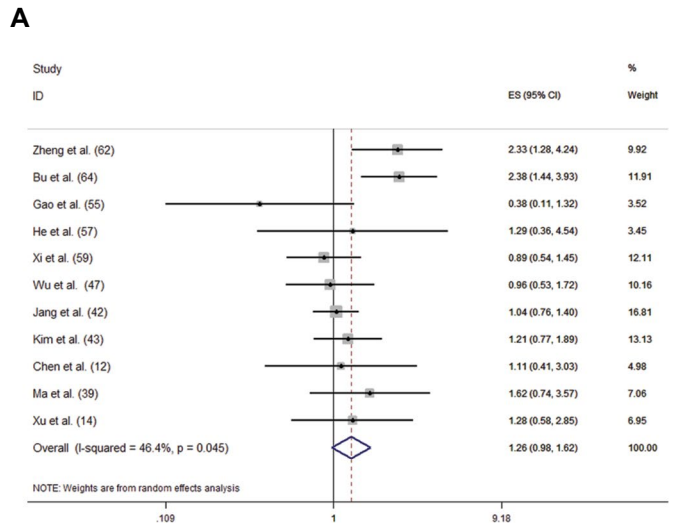


Fig.S2: Forrest plot of HR. **A.** Forest plot for the association between *LGR5* expression and age (old vs. young). **B.** Forest plot the association between *LGR5* expression tumor grade (high vs. low).

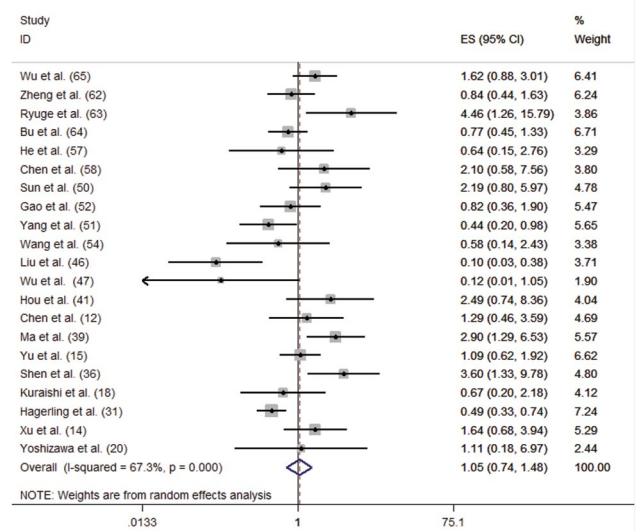


Fig.S3: Forest plot for the association between *LGR5* expression and tumor size (large vs. small).

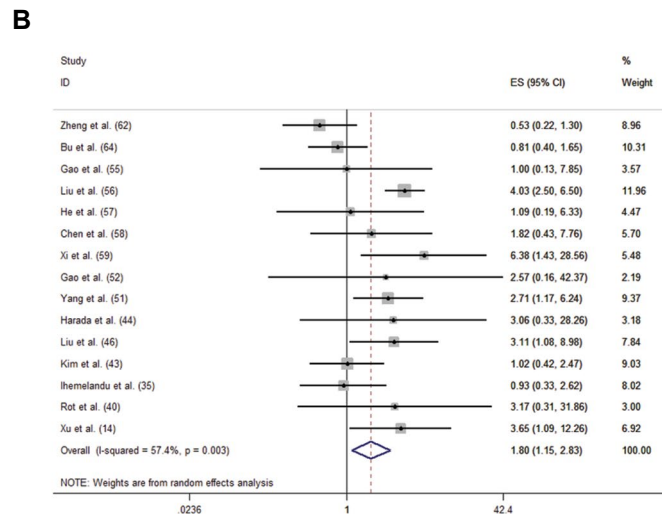
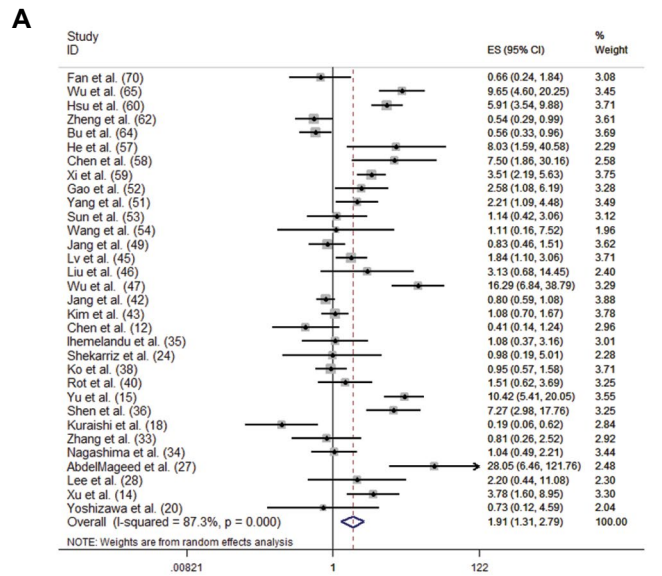


Fig.S4: Forrest plot of HR. **A.** Forest plot for the association between *LGR5* expression and tumor stage (high vs. low). **B.** Forest plot for the association between *LGR5* expression and distant metastasis (present vs. absent).

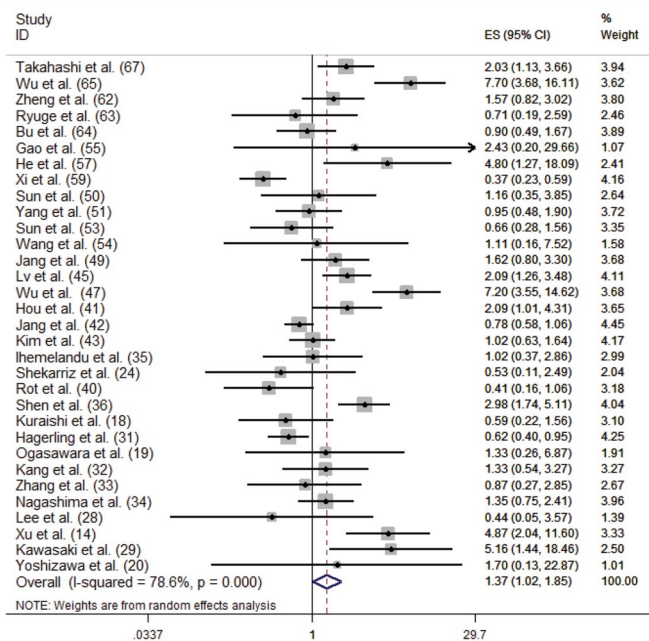


Fig.S5: Forest plot for the association between *LGR5* expression and lymph node metastasis (present vs. absent).

References

- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021; 71(3): 209-249.
- Li Y, Wang Z, Ajani JA, Song S. Drug resistance and cancer stem cells. *Cell Commun Signal.* 2021; 19(1): 19.
- Kelley RK, Wang G, Venook AP. Biomarker use in colorectal cancer therapy. *J Natl Compr Canc Netw.* 2011; 9(11): 1293-1302.
- Hung KF, Yang T, Kao SY. Cancer stem cell theory: are we moving past the mist? *J Chin Med Assoc.* 2019; 82(11): 814-818.
- Marzagalli M, Fontana F, Raimondi M, Limonta P. Cancer stem cells-key players in tumor relapse. *Cancers (Basel).* 2021; 13(3): 376.
- Lathia JD, Mack SC, Mulkearns-Hubert EE, Valentim CL, Rich JN. Cancer stem cells in glioblastoma. *Genes Dev.* 2015; 29(12): 1203-1217.
- Carnero A, Garcia-Maya Y, Mir C, Lorente J, Rubio IT, Lleonart ME. The cancer stem-cell signaling network and resistance to therapy. *Cancer Treat Rev.* 2016; 49: 25-36.
- Xu H, Li W, Song X, Zhang H, Wang H, Wang J, et al. Expression and prognostic value of Lgr5 in patients with recurrent nasopharyngeal carcinoma. *Int J Gen Med.* 2023; 16: 2023-2034.
- Walcher L, Kistenmacher AK, Suo H, Kite R, Dluczek S, Strauß A, et al. Cancer stem cells-origins and biomarkers: perspectives for targeted personalized therapies. *Front Immunol.* 2020; 11: 1280.
- Haegebarth A, Clevers H. Wnt signaling, Lgr5, and stem cells in the intestine and skin. *Am J Pathol.* 2009; 174(3): 715-721.
- de Lau W, Peng WC, Gros P, Clevers H. The R-spondin/Lgr5/Rnf43 module: regulator of Wnt signal strength. *Genes Dev.* 2014; 28(4): 305-316.
- Chen W, Fu Q, Fang F, Fang J, Zhang Q, Hong Y. Overexpression of leucine-rich repeat-containing G protein-coupled receptor 5 predicts poor prognosis in hepatocellular carcinoma. *Saudi J Biol Sci.* 2018; 25(5): 904-908.
- Liu XS, Lin XK, Mei Y, Ahmad S, Yan CX, Jin HL, et al. Regulatory T cells promote overexpression of Lgr5 on gastric cancer cells via TGF-beta1 and confer poor prognosis in gastric cancer. *Front Immunol.* 2019; 10: 1741.
- Xu N, Gao K, Luo H, Wu Y, Shen B, Liu K. Correlation of Lgr5 expression with clinicopathological features of colorectal cancer and its diagnostic and prognostic values. *J BUON.* 2021; 26(1): 87-92.
- Yu L, Mao X, Wu S, Zhou L, Song W, Gong X, et al. The correlation

of the expressions of WWOX, LGR5 and vasohibin-1 in epithelial ovarian cancer and their clinical significance. *Int J Clin Exp Pathol.* 2019; 12(1): 327-336.

- Ehara T, Uehara T, Nakajima T, Kinugawa Y, Kobayashi S, Iwaya M, et al. LGR5 expression is associated with prognosis in poorly differentiated gastric adenocarcinoma. *BMC Cancer.* 2021; 21(1): 228.
- Sato K, Uehara T, Nakajima T, Iwaya M, Miyagawa Y, Watanabe T, et al. Inverse correlation between PD-L1 expression and LGR5 expression in tumor budding of stage II/III colorectal cancer. *Ann Diagn Pathol.* 2021; 52: 151739.
- Kuraishi Y, Uehara T, Kobayashi Y, Nakajima T, Watanabe T, Shimizu A, et al. Correlation of clinicopathological features and leucine-rich repeat-containing G-protein-coupled receptor 5 expression in pancreatic ductal adenocarcinoma. *Pathol Res Pract.* 2019; 215(11): 152623.
- Ogasawara S, Uehara T, Nakajima T, Iwaya M, Maeno K, Tsuchiya S, et al. Correlation of clinicopathological features and LGR5 expression in triple-negative breast cancer. *Ann Diagn Pathol.* 2020; 46: 151491.
- Yoshizawa T, Uehara T, Iwaya M, Asaka S, Kobayashi S, Nakajima T, et al. Correlation of LGR5 expression and clinicopathological features in intrahepatic cholangiocarcinoma. *Pathol Res Pract.* 2022; 232: 153832.
- Nagata H, Ishihara S, Kishikawa J, Sonoda H, Muroto K, Emoto S, et al. CD133 expression predicts post-operative recurrence in patients with colon cancer with peritoneal metastasis. *Int J Oncol.* 2018; 52(3): 721-732.
- Cao W, Li M, Liu J, Zhang S, Noordam L, Verstegen MMA, et al. LGR5 marks targetable tumor-initiating cells in mouse liver cancer. *Nat Commun.* 2020; 11(1): 1961.
- Sato K, Uehara T, Iwaya M, Nakajima T, Miyagawa Y, Ota H, et al. Correlation of clinicopathological features and LGR5 expression in colon adenocarcinoma. *Ann Diagn Pathol.* 2020; 48: 151587.
- Shekarriz R, Montazer F, Alizadeh-Navaei R. Overexpression of cancer stem cell marker Lgr5 in colorectal cancer patients and association with clinicopathological findings. *Caspian J Intern Med.* 2019; 10(4): 412-416.
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.* 2009; 339: b2700.
- Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* 2010; 25(9): 603-605.
- AbdelMageed M, Ismail HTH, Olsson L, Lindmark G, Hammarström ML, Hammarström S, et al. Clinical significance of stem cell biomarkers EpCAM, LGR5 and LGR4 mRNA levels in lymph nodes of colon cancer patients. *Int J Mol Sci.* 2021; 23(1): 403.
- Lee HJ, Myung JK, Kim HS, Lee DH, Go HS, Choi JH, et al. Expression of LGR5 in mammary myoepithelial cells and in triple-negative breast cancers. *Sci Rep.* 2021; 11(1): 17750.
- Kawasaki K, Kuboki S, Furukawa K, Takayashiki T, Takano S, Ohtsuka M. LGR5 induces β -catenin activation and augments tumour progression by activating STAT3 in human intrahepatic cholangiocarcinoma. *Liver International.* 2021; 41(4): 865-881.
- Abdelrahman AE, El-Azany A, Elsebai E, Ibrahim HM. Prognostic impact of LGR5, Prox1, and Notch1 biomarkers in stage II to III colon cancer. *Appl Immunohistochem Mol Morphol.* 2022; 30(2): 126-135.
- Hagerling C, Owyong M, Sitarama V, Wang C-Y, Lin C, Van Den Bijgaart R J, et al. LGR5 in breast cancer and ductal carcinoma in situ: a diagnostic and prognostic biomarker and a therapeutic target. *BMC Cancer.* 2020; 20(1): 542.
- Kang XL, He LR, Chen YL, Wang SB. Role of doublecortin-like kinase 1 and leucine-rich repeat-containing G-protein-coupled receptor 5 in patients with stage II/III colorectal cancer: cancer progression and prognosis. *World J Gastroenterol.* 2020; 26(43): 6853-6866.
- Zhang X, Yuan A, Zhao X, Li Z, Cui G. Tumoral expression of CD166 in human esophageal squamous cell carcinoma: implications for cancer progression and prognosis. *Cancer Biother Radiopharm.* 2020; 35(3): 214-222.
- Nagashima T, Oshima T, Hiroshima Y, Yokose T, Woo T, Rino Y, et al. Clinical significance of tumour CD44v and MIST1 expression in patients with non-small-cell lung cancer. *Anticancer Res.* 2020; 40(11): 6407-6416.
- Ihemelando C, Naeem A, Parasido E, Berry D, Chaldekias K, Harris BT, et al. Clinicopathologic and prognostic significance of LGR5, a

- cancer stem cell marker in patients with colorectal cancer. *Colorectal Cancer*. 2019; 8(4): CRC11.
36. Shen R, Wu T, Huang P, Shao Q, Chen M. The clinicopathological significance of ubiquitin-conjugating enzyme E2C, leucine-rich repeated-containing G protein-coupled receptor, WW domain-containing oxidoreductase, and vasculogenic mimicry in invasive breast carcinoma. *Medicine (Baltimore)*. 2019; 98(16): e15232.
 37. Freiin Grote A, Halske C, Behrens HM, Krüger S, Wilhelm F, Egberts JH, et al. Expression of LGR5, FZD7, TROY, and MIST1 in perioperatively treated gastric carcinomas and correlation with therapy response. *Dis Markers*. 2019; 2019: 8154926.
 38. Ko CJ, Li CJ, Wu MY, Chu PY. Overexpression of LGR-5 as a predictor of poor outcome in patients with hepatocellular carcinoma. *Int J Environ Res Public Health*. 2019; 16(10): 1836.
 39. Ma Z, Guo D, Wang Q, Liu P, Xiao Y, Wu P, et al. Lgr5-mediated p53 repression through PDCD5 leads to doxorubicin resistance in hepatocellular carcinoma. *Theranostics*. 2019; 9(10): 2967-2983.
 40. Rot S, Kaune T, Taubert H, Greither T, Kotrba J, Güttler A, et al. Prognostic impact of mRNA levels of LGR5 transcript variants in OSCC patients. *BMC Cancer*. 2019; 19(1): 155.
 41. Hou MF, Chen PM, Chu PY. LGR5 overexpression confers poor relapse-free survival in breast cancer patients. *BMC Cancer*. 2018; 18(1): 219.
 42. Jang BG, Kim HS, Chang WY, Bae JM, Kim WH, Kang GH. Expression profile of LGR5 and its prognostic significance in colorectal cancer progression. *Am J Pathol*. 2018; 188(10): 2236-2250.
 43. Kim YJ, Kang DH, Song GJ, Ahn TS, Son MW, Lee MS, et al. Clinical relevance of Lgr5 expression in colorectal cancer patients. *Korean J Clin Oncol*. 2018; 14(2): 76-82.
 44. Harada Y, Kazama S, Morikawa T, Muroto K, Yasuda K, Otani K, et al. Leucine-rich repeat-containing G protein-coupled receptor 5 and CD133 expression is associated with tumor progression and resistance to preoperative chemoradiotherapy in low rectal cancer. *Oncol Lett*. 2017; 14(6): 7791-7798.
 45. Lv Z, Yu JJ, Zhang WJ, Xiong L, Wang F, Li LF, et al. Expression and functional regulation of stemness gene Lgr5 in esophageal squamous cell carcinoma. *Oncotarget*. 2017; 8(16): 26492-26504.
 46. Liu J, Yu GZ, Cheng XK, Li XD, Zeng XT, Ren XQ. LGR5 promotes hepatocellular carcinoma metastasis through inducing epithelial-mesenchymal transition. *Oncotarget*. 2017; 8(31): 50896-50903.
 47. Wu Z, Song W, Cheng Z, Yang D, Yu L. Expression of LGR5 in oral squamous cell carcinoma and its correlation to vasculogenic mimicry. *Int J Clin Exp Pathol*. 2017; 10(11): 11267-11275.
 48. Wu W, Cao J, Ji Z, Wang J, Jiang T, Ding H. Co-expression of Lgr5 and CXCR4 characterizes cancer stem-like cells of colorectal cancer. *Oncotarget*. 2016; 7(49): 81144-81155.
 49. Jang BG, Lee BL, Kim WH. Prognostic significance of leucine-rich-repeat-containing G-protein-coupled receptor 5, an intestinal stem cell marker, in gastric carcinomas. *Gastric Cancer*. 2016; 19(3): 767-777.
 50. Sun B, Ye X, Li Y, Zhang W. Lgr5 is a potential prognostic marker in patients with cervical carcinoma. *Int J Clin Exp Pathol*. 2015; 8(2): 1783-1789.
 51. Yang L, Tang H, Kong Y, Xie X, Chen J, Song C, et al. LGR5 promotes breast cancer progression and maintains stem-like cells through activation of Wnt/ β -catenin signaling. *Stem Cells*. 2015; 33(10): 2913-2924.
 52. Gao F, Zhou B, Xu JC, Gao X, Li SX, Zhu GC, et al. The role of LGR5 and ALDH1A1 in non-small cell lung cancer: Cancer progression and prognosis. *Biochem Biophys Res Commun*. 2015; 462(2): 91-98.
 53. Sun Y, Jia X, Wu X. High expressions of Lgr5 and ALDH1 in primary epithelial ovarian cancer correlate with advanced tumor stage and grade as well as poor prognosis of the patients. *Gynecol Obstet Invest*. 2015 (ahead of print)
 54. Wang Y, Jiang CQ, Fan LF. Correlation of Musashi-1, Lgr5, and pEGFR expressions in human small intestinal adenocarcinomas. *Tumour Biol*. 2015; 36(8): 6075-6082.
 55. Gao FJ, Chen JY, Wu HY, Shi J, Chen M, Fan XS, et al. Lgr5 overexpression is positively related to the tumor progression and HER2 expression in stage pTNM IV colorectal cancer. *Int J Clin Exp Pathol*. 2014; 7(4): 1572-1579.
 56. Liu Z, Dai W, Jiang L, Cheng Y. Over-expression of LGR5 correlates with poor survival of colon cancer in mice as well as in patients. *Neoplasma*. 2014; 61(2): 177-185.
 57. He S, Zhou H, Zhu X, Hu S, Fei M, Wan D, et al. Expression of Lgr5, a marker of intestinal stem cells, in colorectal cancer and its clinicopathological significance. *Biomed Pharmacother*. 2014; 68(5): 507-513.
 58. Chen WW, Wang F, Zhang DS, Luo HY, Wang ZQ, Wang FH, et al. Primary small cell carcinoma of the esophagus: clinicopathological study of 44 cases. *BMC Cancer*. 2014; 14: 222.
 59. Xi HQ, Cai AZ, Wu XS, Cui JX, Shen WS, Bian SB, et al. Leucine-rich repeat-containing G-protein-coupled receptor 5 is associated with invasion, metastasis, and could be a potential therapeutic target in human gastric cancer. *Br J Cancer*. 2014; 110(8): 2011-2020.
 60. Hsu HC, Liu YS, Tseng KC, Hsu CL, Liang Y, Yang TS, et al. Overexpression of Lgr5 correlates with resistance to 5-FU-based chemotherapy in colorectal cancer. *Int J Colorectal Dis*. 2013; 28(11): 1535-1546.
 61. Jang BG, Lee BL, Kim WH. Distribution of LGR5+ cells and associated implications during the early stage of gastric tumorigenesis. *PLoS One*. 2013; 8(12): e82390.
 62. Zheng ZX, Sun Y, Bu ZD, Zhang LH, Li ZY, Wu AW, et al. Intestinal stem cell marker LGR5 expression during gastric carcinogenesis. *World J Gastroenterol*. 2013; 19(46): 8714-8721.
 63. Ryuge S, Sato Y, Jiang SX, Wang G, Kobayashi M, Nagashio R, et al. The clinicopathological significance of Lgr5 expression in lung adenocarcinoma. *Lung Cancer*. 2013; 82(1): 143-148.
 64. Bu Z, Zheng Z, Zhang L, Li Z, Sun Y, Dong B, et al. LGR5 is a promising biomarker for patients with stage I and II gastric cancer. *Chin J Cancer Res*. 2013 Feb; 25(1): 79-89.
 65. Wu XS, Xi HQ, Chen L. Lgr5 is a potential marker of colorectal carcinoma stem cells that correlates with patient survival. *World J Surg Oncol*. 2012; 10: 244.
 66. Ziskin JL, Dunlap D, Yaylaoglu M, Fodor IK, Forrest WF, Patel R, et al. In situ validation of an intestinal stem cell signature in colorectal cancer. *Gut*. 2013; 62(7): 1012-1023.
 67. Takahashi H, Ishii H, Nishida N, Takemasa I, Mizushima T, Ikeda M, et al. Significance of Lgr5(+ve) cancer stem cells in the colon and rectum. *Ann Surg Oncol*. 2011; 18(4): 1166-1174.
 68. Takeda K, Kinoshita I, Shimizu Y, Matsuno Y, Shichinohe T, Dosaka-Akita H. Expression of LGR5, an intestinal stem cell marker, during each stage of colorectal tumorigenesis. *Anticancer Res*. 2011; 31(1): 263-270.
 69. Becker L, Huang Q, Mashimo H. Lgr5, an intestinal stem cell marker, is abnormally expressed in Barrett's esophagus and esophageal adenocarcinoma. *Dis Esophagus*. 2010; 23(2): 168-174.
 70. Fan XS, Wu HY, Yu HP, Zhou Q, Zhang YF, Huang Q. Expression of Lgr5 in human colorectal carcinogenesis and its potential correlation with beta-catenin. *Int J Colorectal Dis*. 2010; 25(5): 583-590.
 71. Hsu SY, Liang SG, Hsueh AJ. Characterization of two LGR genes homologous to gonadotropin and thyrotropin receptors with extracellular leucine-rich repeats and a G protein-coupled, seven-transmembrane region. *Mol Endocrinol*. 1998; 12(12): 1830-1845.
 72. Leng Z, Xia Q, Chen J, Li Y, Xu J, Zhao E, et al. Lgr5+CD44+EpCAM+ strictly defines cancer stem cells in human colorectal cancer. *Cell Physiol Biochem*. 2018; 46(2): 860-872.
 73. Wang X, Wang X, Liu Y, Dong Y, Wang Y, Kassab MA, et al. LGR5 regulates gastric adenocarcinoma cell proliferation and invasion via activating Wnt signaling pathway. *Oncogenesis*. 2018; 7(8): 57.
 74. Xu L, Lin W, Wen L, Li G. Lgr5 in cancer biology: functional identification of Lgr5 in cancer progression and potential opportunities for novel therapy. *Stem Cell Res Ther*. 2019; 10(1): 219.
 75. Vaquero J, Guedj N, Clapéron A, Nguyen Ho-Boulidoires TH, Paradis V, Fouassier L. Epithelial-mesenchymal transition in cholangiocarcinoma: From clinical evidence to regulatory networks. *J Hepatol*. 2017; 66(2): 424-441.
 76. Liu S, Gong Z, Chen M, Liu B, Bian D, Wu K. Lgr5-positive cells are cancer stem cells in skin squamous cell carcinoma. *Tumour Biol*. 2014; 35(11): 11605-11612.
 77. Trimboli AJ, Fukino K, de Bruin A, Wei G, Shen L, Tanner SM, et al. Direct evidence for epithelial-mesenchymal transitions in breast cancer. *Cancer Res*. 2008; 68(3): 937-945.
 78. Montazer F, Boozari B, Alizadeh-Navaei R. Evaluation of LGR5 cancer stem cell marker expression in breast cancer and its relationship with hormonal profile and clinical pathological features. *Asian Pac J Cancer Prev*. 2023; 24(2): 467-470.
 79. Kim H, Lee DH, Park E, Myung JK, Park JH, Kim DI, et al. Differential epithelial and stromal LGR5 expression in ovarian carcinogenesis. *Sci Rep*. 2022; 12(1): 11200.
 80. Bauer L, Langer R, Becker K, Hapfelmeier A, Ott K, Novotny A, et al. Expression profiling of stem cell-related genes in neoadjuvant-treated gastric cancer: a NOTCH2, GSK3B and β -catenin gene signature predicts survival. *PLoS One*. 2012; 7(9): e44566.
 81. Jia Y, Li Z, Cheng X, Wu X, Pang F, Shi J, et al. Depletion of death-associated protein-3 induces chemoresistance in gastric cancer

- cells through the β -catenin/LGR5/Bcl-2 axis. *J Invest Med*. 2019; 67(5): 856-861.
82. Clark-Corrigall J, Myssina S, Michaelis M, Cinatl J Jr, Ahmed S, Carr-Wilkinson J. Elevated expression of LGR5 and WNT signaling factors in neuroblastoma cells with acquired drug resistance. *Cancer Invest*. 2023; 41(2): 173-182.
 83. Nakata S, Phillips E, Goidts V. Emerging role for leucine-rich repeat-containing G-protein-coupled receptors LGR5 and LGR4 in cancer stem cells. *Cancer Manag Res*. 2014; 6: 171-180.
 84. Liu X, Mazanek P, Dam V, Wang Q, Zhao H, Guo R, et al. Deregulated Wnt/beta-catenin program in high-risk neuroblastomas without MYCN amplification. *Oncogene*. 2008; 27(10): 1478-1488.
 85. Vicari L, Colarossi C, Giuffrida D, De Maria R, Memeo L. Cancer stem cells as a potential therapeutic target in thyroid carcinoma. *Oncol Lett*. 2016; 12(4): 2254-2260.
 86. Michelotti G, Jiang X, Sosa JA, Diehl AM, Henderson BB. LGR5 is associated with tumor aggressiveness in papillary thyroid cancer. *Oncotarget*. 2015; 6(33): 34549-34560.
 87. Posey TA, Jacob J, Parkhurst A, Subramanian S, Francisco LE, Liang Z, et al. Loss of LGR5 through therapy-induced downregulation or gene ablation is associated with resistance and enhanced MET-STAT3 signaling in colorectal cancer cells. *Mol Cancer Ther*. 2023; 22(5): 667-678.
 88. Yang L, Lin Y, Liu Z, Li Y, Liu Y, Liang R. Impact of LGR5 in colorectal cancer on overall and progression-free survival: a systematic review and meta-analysis. *Int J Clin Exp Med*. 2016; 9(9): 10537-10543.
 89. Sigal M, Rothenberg ME, Logan CY, Lee JY, Honaker RW, Cooper RL, et al. *Helicobacter pylori* activates and expands Lgr5(+) stem cells through direct colonization of the gastric glands. *Gastroenterology*. 2015; 148(7): 1392-1404. e21.
 90. Kim HS, Song HJ, Kim HU, Jeong IH, Koh HM, Shin JH, et al. Expression profile of intestinal stem cell and cancer stem cell markers in gastric cancers with submucosal invasion. *Pathol Res Pract*. 2021; 218: 153336.
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