(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 113584163 A
(43)申请公布日 2021.11.02

(21)申请号 202110699497.0

(22)申请日 2021.06.23

(71)申请人 江南大学附属医院
地址 214000 江苏省无锡市惠河路200号

(72)发明人 王北 陈丹丹 袁凤来

(74)专利代理机构 苏州市中南伟业知识产权代理事务所(普通合伙) 32257
代理人 夏苏娟

(51)Int.Cl.
C12Q 1/6886(2018.01)
C12N 15/11(2006.01)
A61K 45/00(2006.01)
A61P 35/00(2006.01)

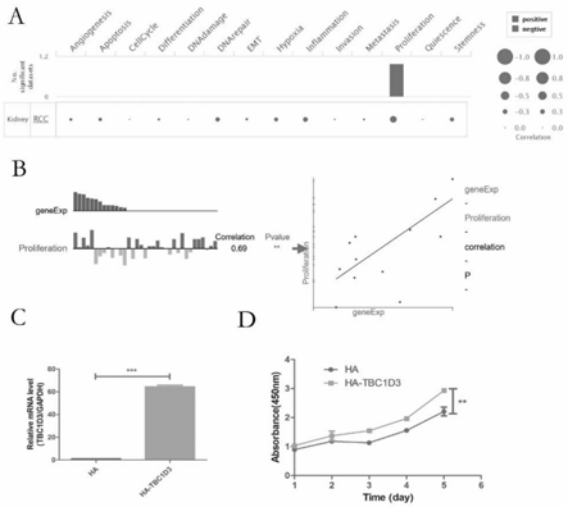
权利要求书1页 说明书6页
序列表9页 附图19页

(54)发明名称

TBC1D3及其家族在制备肿瘤诊断药物与预后判断药物中的应用

(57)摘要

本发明提供了TBC1D3及其家族在制备肿瘤诊断药物与预后判断药物中的应用,属于生物医药技术领域。本发明发现肾透明细胞癌组织中TBC1D3及其家族基因的表达显著高于癌旁正常组织;肾透明细胞癌中TBC1D3及其家族蛋白的表达水平与患者的预后密切相关。本发明提出TBC1D3可作为肾透明细胞癌诊断和预后判断的分子标记及治疗药物的靶标。TBC1D3家族成员可以作为肾透明细胞癌的免疫治疗靶点。



CN 113584163 A

1.TBC1D3、TBC1D3B、TBC1D3C、TBC1D3D、TBC1D3E、TBC1D3F、TBC1D3G或TBC1D3H作为肿瘤诊断及预后标记物的应用。

2.根据权利要求1中所述的应用，其特征在于，所述TBC1D3、TBC1D3B、TBC1D3C、TBC1D3D、TBC1D3E、TBC1D3F、TBC1D3G和TBC1D3H的核苷酸序列分别如SEQ ID NO.1-SEQ ID NO.8所示。

3.根据权利要求1所述的应用，其特征在于，所述肿瘤为肾透明细胞癌、肾乳头状细胞癌、肝癌、肺腺癌、肺鳞状细胞癌或甲状腺癌。

4.TBC1D3、TBC1D3B、TBC1D3C、TBC1D3F、TBC1D3G和TBC1D3H的RNA干扰靶点序列分别如SEQ ID NO.9-SEQ ID NO.14所示。

5.如权利要求4所述的TBC1D3、TBC1D3B、TBC1D3C、TBC1D3F、TBC1D3G或TBC1D3H的RNA干扰靶点序列在制备治疗肿瘤药物中的应用。

6.根据权利要求5所述的应用，其特征在于，所述的肿瘤为肾透明细胞癌、肾乳头状细胞癌、肝癌、肺腺癌、肺鳞状细胞癌或甲状腺癌。

7.一种抗肿瘤的药物，其特征在于，所述药物中含有权利要求4中所述TBC1D3、TBC1D3B、TBC1D3C、TBC1D3F、TBC1D3G或TBC1D3H的RNA干扰靶点序列。

8.根据权利要求7中所述的药物，其特征在于，所述药物还包括CD4+T细胞或T细胞耗竭的抑制剂。

9.根据权利要求7所述的药物，其特征在于，所述的肿瘤为肾透明细胞癌、肾乳头状细胞癌、肝癌、肺腺癌、肺鳞状细胞癌或甲状腺癌。

TBC1D3及其家族在制备肿瘤诊断药物与预后判断药物中的应用

技术领域

[0001] 本发明属于生物医药技术领域,尤其是指TBC1D3及其家族在制备肿瘤诊断药物与预后判断药物中的应用。

背景技术

[0002] 肾透明细胞癌是肾癌中最常见的恶性肿瘤,占原发性肾脏恶性肿瘤的75-82%。在各 种临床和基因组研究中,肾透明细胞癌被证明是一种高度免疫浸润的肿瘤,是最早的免疫治疗肿瘤之一。由于肾透明细胞癌对常规放疗和化疗不敏感,其治疗主要依赖于靶向 治疗和免疫治疗。靶向治疗包括酪氨酸激酶抑制剂,如舒尼替尼和索拉非尼。然而,肿 瘤异质性、动态变化和对治疗的适应细胞死亡相关信号通路的改变显著限制了靶向药物 在肾透明细胞癌治疗中的应用。

发明内容

[0003] 本发明通过在线数据库发现肾透明细胞癌组织中TBC1D3及其家族基因的表达显著 高于癌旁正常组织;肾透明细胞癌中TBC1D3及其家族蛋白的表达水平与患者的预后密切相关,肾透明细胞癌组织中TBC1D3及其家族蛋白表达水平高的患者总的生存率低于 表达低的患者。同时我们构建TBC1D3质粒,转染肾透明细胞癌细胞,发现可以促进其 细胞增殖。同时发现TBC1D3家族成员与免疫浸润相关。

[0004] RNA干扰(RNA interference,RNAi)是指内源性或外源性双链RNA介导的细胞内mRNA发生特异性降解,导致靶基因的表达沉默,产生相应的功能表型缺失。它可高效、特异地阻断体内特定基因的表达,导致其降解,从而引起生物体内特异基因的沉默,使 细胞表现出某种基因表型的缺失,是近年来新兴的一种常用的研究基因功能、寻找疾病 治疗方法的实验室技术。目前,RNAi特异性的抑制基因表达,已应用于基因病、病毒 感染性疾病、癌症的基因治疗等方面。

[0005] TBC1D3、TBC1D3B、TBC1D3C、TBC1D3D、TBC1D3E、TBC1D3F、TBC1D3G 或TBC1D3H作为肿瘤诊断及预后标记物的应用。

[0006] 在本发明的一个实施例中,所述TBC1D3、TBC1D3B、TBC1D3C、TBC1D3D、 TBC1D3E、TBC1D3F、TBC1D3G或TBC1D3H的核苷酸序列分别如SEQ ID NO.1-SEQ ID NO.8所示。

[0007] 在本发明的一个实施例中,所述肿瘤为肾透明细胞癌、肾乳头状细胞癌、肝癌、肺腺癌、肺鳞状细胞癌和甲状腺癌。

[0008] TBC1D3、TBC1D3B、TBC1D3C、TBC1D3D、TBC1D3E、TBC1D3F、TBC1D3G 或TBC1D3H的RNA干扰靶点序列分别如SEQ ID NO.9-SEQ ID NO.14所示。

[0009] 所述的TBC1D3、TBC1D3B、TBC1D3C、TBC1D3F、TBC1D3G或TBC1D3H的 RNA干扰靶点序列在制备治疗肿瘤药物中的应用。

[0010] 在本发明的一个实施例中,所述肿瘤为肾透明细胞癌、肾乳头状细胞癌、肝癌、肺

腺癌、肺鳞状细胞癌或甲状腺癌。

[0011] 一种抗肿瘤的药物，所述药物中含有所述TBC1D3、TBC1D3B、TBC1D3C、TBC1D3F、TBC1D3G或TBC1D3H的RNA干扰靶点序列。

[0012] 在本发明的一个实施例中，所述药物还包括抑制CD4+T细胞或T细胞耗竭的抑制剂。

[0013] 在本发明的一个实施例中，所述肿瘤为肾透明细胞癌、肾乳头状细胞癌、肝癌、肺腺癌、肺鳞状细胞癌或甲状腺癌。

[0014] 在本发明的一个实施例中，所述TBC1D3、TBC1D3B、TBC1D3C、TBC1D3F、TBC1D3G或TBC1D3H的RNA干扰靶点序列分别如SEQ ID NO.9-SEQ ID NO.14所示。

[0015] 本发明的上述技术方案相比现有技术具有以下优点：

[0016] 本发明首次证实TBC1D3及其家族是一个肾透明细胞癌预后标记物，首次发现TBC1D3可作为肾透明细胞癌诊断和预后判断的分子标记及治疗药物的靶标。TBC1D3 家族成员可以作为肾透明细胞癌的免疫治疗靶点。

附图说明

[0017] 为了使本发明的内容更容易被清楚的理解，下面根据本发明的具体实施例并结合附 图，对本发明作进一步详细的说明，其中

[0018] 图1-1与图1-2是本发明TBC1D3泛癌表达分析，TBC1D3家族在TCGA数据库中 的表达。

[0019] 图2是本发明中TBC1D3家族成员的基因组改变以及TBC1D3家族基因的基因-基 因和蛋白质-蛋白质相互作用网络。

[0020] 图3-1、图3-2与图3-3是本发明中TBC1D3家族成员在肾透明细胞癌中预后表达。

[0021] 图4是本发明中TBC1D3家族成员在肾透明细胞癌中的功能。

[0022] 图5-1、图5-2、图5-3与图5-4是本发明中TBC1D3家族蛋白与免疫抑制剂的相关性。

[0023] 图6-1、图6-2、图6-3、图6-4与图6-5是本发明中TBC1D3家族成员蛋白与肾透 明细胞癌免疫浸润相关性。

[0024] 图7-1、图7-2与图7-3是本发明中肾透明细胞癌免疫浸润水平与TBC1D3家族成员不同体细胞拷贝数改变的相关性。

具体实施方式

[0025] 下面结合附图和具体实施例对本发明作进一步说明，以使本领域的技术人员可以更 好地理解本发明并能予以实施，但所举实施例不作为对本发明的限定。

[0026] 实施例1 TBC1D3及其家族在肾功能透明细胞癌中的表达

[0027] 通过GSCA数据库分析，TBC1D3在肾透明细胞癌中的表达。发现TBC1D3表达在 肾透明细胞癌、肾乳头状细胞癌、肝癌、肺腺癌、肺鳞状细胞癌和甲状腺癌中高表达，在 头颈部鳞状细胞癌中低表达。我们同时通过UALCAN数据库和下载肾透明细胞癌TCGA 数据，通过R语言分析数据，发现TBC1D3家族(TBC1D3，TBC1D3B，TBC1D3C， TBC1D3D，TBC1D3E，TBC1D3F，TBC1D3G，TBC1D3H)在肾透明细胞癌中相比于癌 旁组织都高表达。

[0028] 实施例2 TBC1D3及其家族的基因和蛋白网络的基因改变

[0029] 我们使用cBioportal数据库来确定TCGA KIRC样本中TBC1D3家族改变的类型和频率。结果显示TBC1D3家族成员很少发生突变(少于5个频率),这是高度保守的(结 果见图2-A)。然后,我们使用cBioportal的"相关分析"对TBC1D3家族的五个成员进行 分析,结果表明,TBC1D3家族成员之间的关联呈正相关,但TBC1D3C与TBC1D3G 呈负相关(结果见图2-D)。利用GeneMANIA和STRING生成的基因-基因和蛋白质-蛋 白质相互作用网络显示,20个潜在靶基因和11个潜在靶蛋白与TBC1D3家族相互作用 (结果见图2-B与图2-C)。

[0030] 实施例3 TBC1D3家族成员在肾透明细胞癌中预后表达

[0031] 使用GSCA、TISIDB、LinkedOmics和Kaplan-Meier绘图仪评估TBC1D3家族表达 对生存率的影响。GSCA分析显示,TBC1D3在KIRC多发性肿瘤中的表达与OS和PFS 呈正相关。此外,高表达的TBC1D3存活时间短(结果见图3-1)。TISIDB和LinkedOmics 的总生存率分析表明,TBC1D3家族成员高表达的患者总生存期较短(结果见图3-2与 图3-3)。为了进一步探讨TBC1D3在KIRC临床特征中的作用,我们使用Kaplan-Meier 绘图仪研究了TBC1D3表达与KIRC临床病理特征之间的关系。如表1所示,TBC1D3 和TBC1D3B的高表达与I期、II期、III期、IV期、3级和4级患者的OS恶化相关。为了探讨TBC1D3表达是否是KIRC患者总生存率的独立预测因素,我们进行了单变量 和多变量Cox回归分析。单因素Cox回归分析显示,年龄、分级、分期、TNM分级均 为OS的独立危险因素(p=0.012、3.61E-08、1.26E-10、2.69E-08、2.76E-10和0.001); 在多变量Cox回归分析中,年龄、年级和TBC1D3表达是OS的独立危险因素(分别 p=0.0003、0.014和0.013)(结果见表2)。

[0032] 表1

[0033]

临床参数	总存活(530)					
	TBC1D3			TBC1D3B		
	N	Hazard ratio	p-value	N	Hazard ratio	p-value
分期						
女	186	2.18(1.32-3.6)	**0.0019**	186	1.79(1.07-2.01)	**0.024**
男	344	1.92(1.31-2.83)	**0.00075**	344	1.85(1.25-2.74)	**0.0018**
分期						
1	67	3.88(1.1-13.74)	**0.024**	265	1.94(1.07-3.52)	**0.025**
2	57	6.57(1.73-25.01)	**0.0018**	57	7.72(2.33-25.58)	**9.6E-05**
3	123	2.18(1.23-3.86)	**0.0061**	123	1.8(1-3.26)	**0.048**
4	82	2.01(1.21-3.36)	**0.0064**	82	1.43(0.84-2.42)	0.19

[0034]

分级						
1		\			\	
2	227	1.35(0.75-2.45)	0.32	227	2.32(1.2-4.51)	**0.01**
3	206	2.37(1.47-3.81)	**0.00027**	206	1.72(1.07-2.75)	**0.023**
4	75	1.85(1.04-3.29)	**0.033**	75	1.93(1.06-3.53)	**0.03**

[0035] 注:粗体字表示p<0.05。

[0036] 表2

[0037]

	单变量分析		多变量分析	
因素	HR (95%CI)	P value	HR (95%CI)	P value
年龄	1.023(1.004-1.041)	**0.012**	1.037(1.017-1.059)	**0.0003**
性别	1.013(0.666-1.541)	0.95	1.272(0.813-1.992)	0.292
分期	2.242(1.682-2.988)	**3.61E-08**	1.508(1.086-2.095)	**0.014**
分级	1.862(1.541-2.251)	**1.26E-10**	1.416(0.839-2.389)	0.192
T 分期	1.943(1.538-2.456)	**2.69E-08**	0.992(0.604-1.628)	0.974
M 分期	4.073(2.634-6.301)	**2.76E-10**	1.877(0.832-4.238)	0.129
N 分期	2.932(1.516-5.668)	**0.001**	1.67(0.804-3.47)	0.169
TBC1D3	379.35(0.01-1.17E8)	0.26	23299.765(7.84-6.92E8)	**0.013**

[0038] 注:粗体字表示p＜0.05。

[0039] 表3

[0040]

	Gene markers	KIRC			
		None		Purity	
		Cor	P	Cor	P
CD8 + T cell	CD8A	0.077	ns	0.062	ns
	CD8B	0.061	ns	0.053	ns
T cell(general)	CD3D	0.072	ns	0.054	ns
	CD3E	0.101	*	0.085	ns
	CD2	0.111	*	0.093	*
B cell	CD19	0.133	*	0.117	*
	CD79A	-0.022	ns	-0.014	ns
Monocyte	CD86	0.051	ns	0.072	ns
	CD115（CSF1R）	0.099	ns	0.112	*
TAM	CCL2	-0.008	ns	-0.028	ns
	CD68	0.006	ns	0.031	ns
	IL10	0.068	ns	0.18	ns
M1 Macrophage	INOS(NOS2)	-0.003	ns	-0.002	ns
	IRF5	0.365	***	0.358	***
	COX2(PTGS2)	-0.001	ns	-0.044	ns

[0041]

M2 Macrophage	CD163	0.034	ns	0.067	ns
	VSIG4	0.054	ns	0.079	ns
	MS4A4A	0.031	ns	0.049	ns
Neutrophils	CD66b(CEACAM8)	0.169	***	0.166	***
	CD11B(ITGAM)	0.151	***	0.168	***
	CCR7	0.088	ns	0.09	ns
Natural killer cell	KIR2DL1	0.022	ns	0.018	ns
	KIR2DL3	0.049	ns	0.07	ns
	KIR2DL4	0.061	ns	0.067	ns
	KIR3DL1	-0.02	ns	-0.017	ns
	KIR3DL2	0.004	ns	-0.009	ns
	KIR3DL3	-0.002	ns	-0.016	ns
	KIR2DS4	-0.027	ns	-0.029	ns
Dendritic cell	HLA-DPB1	0.011	ns	0.025	ns
	HLA-DQB1	0.056	ns	0.065	ns
	HLA-DRA	0	ns	0.02	ns
	HLA-DPA1	0.023	ns	0.032	ns
	BDCA-1(CD1C)	0.043	ns	0.057	ns
	BDCA-4(NRP1)	0.041	ns	0.065	ns
	CD11c(ITGAX)	0.424	***	0.436	ns
Th1	T-bet (TBX21)	0.241	***	0.24	***
	STAT4	0.366	***	0.363	***
	STAT1	0.079	ns	0.082	ns
	IFN-γ(IFNG)	0.176	***	0.172	***
	TNF-α(TNF)	0.249	***	0.245	***
Th2	GATA3	0.062	ns	0.065	ns
	STAT6	0.357	***	0.383	***
	STAT5A	0.163	***	0.177	***
	IL13	0.36	***	0.327	***
T fh	BCL6	0.347	***	0.332	***
	IL21	0.069	ns	0.071	ns
Th17	STAT3	0.093	ns	0.012	**
	IL17A	0.002	ns	-0.023	ns
Treg	FOXP3	0.2	***	0.187	***
	CCR8	0.187	***	0.199	***
	STAT5B	0.163	***	0.177	***
	TGFβ(TGFB1)	0.017	ns	0.011	ns
T cell exhaustion	PD-1(PDCD1)	0.171	**	0.15	**
	CTLA4	0.33	***	0.314	***
	TIM-3(HAVCR2)	-0.024	ns	-0.015	ns
	GZMB	0.046	ns	0.05	ns
	LAG3	0.167	***	0.141	***
	PDL1(CD274)	0.106	**	0.099	*

[0042] 注:TAM,肿瘤相关巨噬细胞;Th,T辅助细胞;Tfh,卵泡辅助性T细胞;Treg,调节性T细胞;*P<0.01;**P<0.001;***P<0.0001。

[0043] 实施例4 TBC1D3在肾透明细胞癌中的功能

[0044] 为了研究TBC1D3家族在KIRC中的功能,我们使用CancerSEA进行了单细胞分析。结果表明,TBC1D3D正调控KIRC细胞的增殖,负调控炎症(图4A-B)。我们构建了 TBC1D3质粒并转染Caki-1细胞,结果显示TBC1D3能促进肾透明细胞癌细胞的增殖(结 果见图4-C)。TBC1D3的生物学过程通过过表达富集分析(ORA)进行鉴定,结果表明 TBC1D3的表达与免疫应答密切相关(结果见图4-D)。

[0045] 实施例5 TBC1D3家族表达与免疫抑制剂在肾透明细胞癌中的相关性

[0046] 选择TISIDB数据库研究TBC1D3家族表达与免疫抑制效应之间的关系。因此,TBC1D3、TBC1D3B、TBC1D3C和TBC1D3G是TBC1D3家族的四个成员,分别与CD160、 CTLA4、CD244、KDR、LAG3、PDCD1、PDCD1LG2和TIGIT相关。此外,TGFBR1 和HAVCR2与TBC1D3、TBC1D3B和TBC1D3G相关。CD274与TBC1D3B、TBC1D3C 和TBC1D3G相关。此外,TBC1D3与LGALS9相关。TBC1D3B与CD274相关。TBC1D3C 与CD96和LGALS9相关。TBC1D3G与IL10RB和PVRL2相关(结果见图5-1,图5-2, 图5-3,图5-4)。

[0047] 实施例6 TBC1D3家族表达与免疫浸润在肾透明细胞癌中的相关性

[0048] 采用TIMER数据库探讨TBC1D3家族表达与肾透明细胞癌浸润淋巴细胞的关系。TBC1D3家族表达与CD4+T细胞浸润水平呈正相关。此外,巨噬细胞浸润水平仅与 TBC1D3表达显著相关,树突状细胞浸润水平与TBC1D3B表达呈负相关。中性粒细胞 浸润水平与TBC1D3和TBC1D3H表达呈正相关(结果见图6-1,图6-2,图6-3,图6-4, 图6-5)。为了进一步证实TBC1D3在KIRC中的表达与免疫细胞浸润水平之间的关系, 我们使用TIMER数据库来探讨TBC1D3表达与各种免疫浸润相关标记物之间的关系。我们的结果显示,TBC1D3的表达与大多数中性粒细胞、Th1、Th2、Treg和T细胞衰竭 的标志物之间存在显著相关性(结果见表3)。特别是T细胞衰竭,结果与DISTIB分析 一致。体细胞拷贝数改变(SCNA)模块显示TBC1D3家族成员的臂水平缺失与肾透明 细胞癌中的免疫细胞浸润水平显著相关(结果见图7-1,图7-2,图7-3)。

[0049] 显然,上述实施例仅仅是为清楚地说明所作的举例,并非对实施方式的限定。对于所属领域的普通技术人员来说,在上述说明的基础上还可以做出其它不同形式变化或变动。这里无需也无法对所有的实施方式予以穷举。而由此所引申出的显而易见的变化或 变动仍处于本发明创造的保护范围之中。

SEQUENCE LISTING

<110> 江南大学附属医院

<120> TBC1D3及其家族在制备肿瘤诊断药物与预后判断药物中的应用

<130> 14

<160> 14

<170> PatentIn version 3.3

<210> 1

<211> 2077

<212> RNA

<213> (人工合成)

<400> 1

aguggucuac agcaguuaca cacaggcagu gguaucugug agcagcucug uggacucaaa 60
gguuuucucc cugagaggca ugacccaggc cagcugauuc aucagaauca ggauggacgu 120
gguagagguc gcgggcaguu ggugggcaca agagcgagag gacaucauua ugaaauacga 180
aaagggacac cgagcugggc ugccagagga caaggggccu aagccuuuuc gaagcuacaa 240
caacaacguc gaucauuugg ggauuguaca ugagacggag cugccuccuc ugacugcgcg 300
ggaggcgaag caaauucggc gggagaucag ccgaaagagc aagugggugg auaugcuggg 360
agacugggag aaauacaaaa gcagcagaaa gcucauagau cgagcguaca agggaaugcc 420
caugaacauc cggggcccga uguggucagu ccuccugaac acugaggaaa ugaaguugaa 480
aaaccccgga agauaccaga ucaugaagga gaagggcaag aggucaucug agcacaucca 540
gcgcaucgac cgggacguaa gcgggacauu aaggaagcau auauucuuca gggaucgaua 600
cggaaccaag cagcgggaac uacuccacau ccuccuggca uaugaggagu acaacccgga 660
ggugggcuac ugcagggacc ugagccacau cgccgccuug uuccuccucu aucuuccuga 720
ggaggaugca uucugggcac uggugcagcu gcuggccagu gagaggcacu cccugcaggg 780
auuucacagc ccaaauggcg ggaccgucca ggggcuccaa gaccaacagg agcauguggu 840
agccacguca caacccaaga ccauggggca ucaggacaag aaagaucuau gugggcagug 900
uucccccguua ggcugccuca uccggauauu gauugacggg aucucucucg ggcucacccu 960
gcgccugugg gacguguauc ugguagaagg cgaacaggcg uugaugccga uaacaagaau 1020
cgccuuuaag guucagcaga agcgccucac gaagacgucc aggugugccc cgugggcacg 1080
uuuuugcaac cgguucguug auaccugggc cagggaugag gacacugugc ucaagcaucu 1140
uagggccucu augaagaaac uaacaagaaa gaagggggac cugccacccc cagccaaacc 1200
cgagcaaggg ucgucggcau ccaggccugu gccggcuuca cguggcggga agacccucug 1260
caagggggac aggcaggccc cuccaggccc accagcccgg uucccgcggc ccauuugguc 1320
agcuucccccg ccacgggcac cucguucuuc cacacccugu ccuggugggg cuguccggga 1380
agacaccuac ccugugggca cucagggugu gcccagcccg gcccuggcuc agggaggacc 1440
ucaggguucc uggagauucc ugcaguggaa cuccaugccc cgccucccaa cggaccugga 1500
cguagagggc ccuugguucc gccauuauga uuucaggcag agcugcuggg uccgugccau 1560
aucccaggag gaccagcugg ccccccugcug gcaggcugaa cacccugcgg agcgggugag 1620

aucggcuuuc gcugcaccca gcacugauuc cgaccagggc acccccuuca gagcuaggga 1680
cgaacagcag ugugcuccca ccucagggcc uugccucugc ggccuccacu uggaaaguuc 1740
ucaguucccu ccaggcuucu agaagcaucu gggccagggc ucauggcugg auaauuuccc 1800
uaggcuuaac aacccaagca agcuucgcau ccucguuuua uuuuugguua aacuuaugaa 1860
aauguauuaa gaaagagugc agcucgagag agauucagag auggaacaca ccagacccca 1920
gaucacaaag ccaaccaugc ccagccccuc ccagcacccc cagccccacg accaucguuc 1980
ugaauucuga cgacaccgug agccugccuu uguacuucaa acucauggaa ggauaaccac 2040
cuucauguuu ugaaauaaau guuuccuguu gaaauga 2077

<210> 2

<211> 1620

<212> RNA

<213> (人工合成)

<400> 2

agaaugucac uggugcuuag caccuaucug cucucuggcc ugccucagug gucuacagca 60
guuacacaca ggcaguggua ucugugagca gcucugugga cucaaagguu uucucccuga 120
gaggcaugac ccaggccagc ugauucauca gaaucaggau ggacguggua gaggucgcgg 180
guaguuggug ggcacaagag cgagaggaca ucauuaugaa auacgaaaag ggacaccgag 240
cugggcugcc agaggacaag gggccuaagc cuuuucgaag cuacaacaac aacgucgauc 300
auuuggggau uguacaugag acggagcugc cuccucugac ugcgcgggag gcgaagcaaa 360
uucggcggga gaucagccga aagagcaagu ggguggauau gcugggagac ugggagaaau 420
acaaaagcag cagaaagcuc auagaucgag cguacaaggg aaugcccaug aacauccggg 480
gcccgaugug gucaguccuc cugaacauug aggaaaugaa guugaaaaac cccggaagau 540
accagaucau gaaggagaag ggcaagaggu caucugagca cauccagcgc aucgaccggg 600
acauaagcgg gacauuaagg aagcauaugu ucuucaggga ucgauacgga accaagcagc 660
gggaacuacu ccacauccuc cuggcauaug aggaguauaa cccggaggug ggcuacugca 720
gggaccugag ccacaucgcc gccuuguucc uccucuaucu uccugaggag gaugcauucu 780
gggcacuggu gcagcugcug gccagugaga ggcacucccu gcagggauuu cacagcccaa 840
auggcgggac cguccagggg cuccaagacc aacaggagca ugugguagcc acgucacaau 900
ccaagaccau ggggcaucag gacaagaaag aucuaugugg gcaguguucc ccguuaggcu 960
gccucauccg gauauugauu gacgggaucu cucucgggcu cacccugcgc cugugggacg 1020
uguaucuggu agaaggcgaa caggcguuga ugccgauaac aagaaucgcc uuuaagguuc 1080
agcagaagcg ccucacgaag acguccaggu guggcccgug ggcacguuuu ugcaaccggu 1140
ucguugauac cugggccagg gaugaggaca cugugcucaa gcaucuuagg gccucuauga 1200
agaaacuaac aagaaagcag ggggaccugc cacccccagc caaacccgag caagggucgu 1260
cggcauccag gccugugccg gcuucacgug gcaggaagac ccucugcaag ggggacaggc 1320
aggccccucc aggcccacca gcccgguucc cgcggcccau uuggucagcu uccccgccac 1380
gggcaccucg uucuuccaca cccuguccug gugggggcugu ccgggaagac accuacccug 1440
ugggcacuca gggugugccc agcccggccc uggcucaggg aggaccucag gguuccugga 1500
gauuccugca guggaacucc augccccgcc ucccaacgga ccuggacgua gaggggccuu 1560

gguuccgcca uuaugauuuc agacagagcu gcuggguccg ugccauaucc caggaggacc 1620

<210> 3

<211> 1620

<212> RNA

<213> (人工合成)

<400> 3

agcaccuauc ugcucucugg ucugccucag uggucuacag caguuacaca caggcagugg 60
uaucugugag cagcucugug gacucaaagg uuuucucccu gagaggcacg acccaggcca 120
gcugauucau cagaaucagg auggacgugg uagaggucgc gggcaguugg ugggcacaag 180
agcgagagga caucauuaug aaauacgaaa agggacaccg agcugggcug ccagaggaca 240
aggggccuaa gccuuuucga agcuacaaca acaacgucga ucauuugggg auuguacaug 300
agacggagcu gccuccucug acugcgcggg aggcgaagca aauucggcgg gagaucagcc 360
gaaagagcaa guggguggau augcugggag acugggagaa auacaaaagc agcagaaagc 420
ucauagaucg agcguacaag ggaaugccca ugaacauccg gggcccgaug uggucagucc 480
uccugaacac ugaggaaaug aaguugaaaa accccggaag auaccagauc augaaggaga 540
agggcaagag gucaucugag cacauccagc gcaucgaccg ggacguaagc gggacauuaa 600
ggaagcauau auucuucagg gaucgauacg gaaccaagca gcgggaacua cuccacaucc 660
uccuggcaua ugaggaguac aacccggagg ugggcuacug cagggaccug agccacaucg 720
ccgccuuguu ccuccucuau cuuccugagg aggaugcauu cugggcacug gugcagcugc 780
uggccaguga gaggcacucc cugcagggau uucacagccc aaauggcggg accguccagg 840
ggcuccaaga ccaacaggag caugugguag ccacgucaca acccaagacc auggggcauc 900
aggacaagaa agaucuaugu gggcaguguu ccccguuagg cugccucauc cggauauuga 960
uugacgggau cucucucggg cucacccugc gccuguggga cguguaucug guagaaggcg 1020
aacaggcguu gaugccgaua acaagaaucg ccuuuaaggu ucagcagaag cgccucacga 1080
agacguccag guguggcccg ugggcacguu uuugcaaccg guucguugau accugggcca 1140
gggaugagga cacugugcuc aagcaucuua gggccucuau gaagaaacua acaagaaaga 1200
agggggaccu gccacccccа gccaaacccg agcaaggguc gucggcaucc aggccugugc 1260
cggcuucacg uggcgggaag acccucugca agggggacag gcaggccccu ccaggcccac 1320
cagcccgguu cccgcggccc auuuggucag cuuccccgcc acgggcaccu cguucuucca 1380
cacccugucc ugguggggcu guccgggaag acaccuaccc ugugggcacu cagggugugc 1440
ccagcccggc ccuggcucag ggaggaccuc aggguuccug gagauuccug caguggaacu 1500
ccaugccccg ccucccaacg gaccuggacg uagagggccc uugguuccgc cauuaugauu 1560
ucagacagag cugcuggguc cgugccauau cccaggagga ccagcuggcc cccugcuggc 1620

<210> 4

<211> 2065

<212> RNA

<213> (人工合成)

<400> 4

caguuacaca caggcagugg uaucugugag cagcucugug gacucaaagg uuuucucccu 60

gagaggcacg acccaggcca gcugauucau cagaaucagg auggacgugg uagaggucgc 120
gggcaguugg ugggcacaag agcgagagga caucauuaug aaauacgaaa agggacaccg 180
agcugggcug ccagaggaca aggggccuaa gccuuuucga agcuacaaca acaacgucga 240
ucauuugggg auuguacaug agacggagcu gccuccucug acugcgcggg aggcgaagca 300
aauucggcgg gagaucagcc gaaagagcaa guggguggau augcugggag acugggagaa 360
auacaaaagc agcagaaagc ucauagaucg agcguacaag ggaaugccca ugaacauccg 420
gggcccgaug uggucagucc uccugaacac ugaggaaaug aaguugaaaa accccggaag 480
auaccagauc augaaggaga agggcaagag gucaucugag cacauccagc gcaucgaccg 540
ggacguaagc gggacauuaa ggaagcauau auucuucagg gaucgauacg gaaccaagca 600
gcgggaacua cuccacaucc uccuggcaua ugaggaguau aacccggagg ugggcuacug 660
cagggaccug agccacaucg ccgccuuguu ccuccucuau cuuccugagg aggaugcauu 720
cugggcacug gugcagcugc uggccaguga gaggcacucc cugcagggau uucacagccc 780
aaauggcggg accguccagg ggcuccaaga ccaacaggag caugugguag ccacgucaca 840
acccaagacc auggggcauc aggacaagaa agaucuaugu gggcaguguu ccccguuagg 900
cugccucauc cggauauuga uugacgggau cucucucggg cucacccugc gccugуggga 960
cguguaucug guagaaggcg aacaggcguu gaugccgaua acaagaaucg ccuuuaaggu 1020
ucagcagaag cgccucacga agacguccag guguggcccg ugggcacguu uuugcaaccg 1080
guucguugau accugggcca gggaugagga cacugugcuc aagcaucuua gggccucuau 1140
gaagaaacua acaagaaagc agggggaccu gccaccccca gccaaacccg agcaaggguc 1200
gucggcaucc aggccugugc cggcuucacg uggcgggaag acccucugca agggggacag 1260
gcaggccccu ccaggcccac cagcccgguu cccgcggccc auuuggucag cuuccccgcc 1320
acgggcaccu cguucuucca cacccugucc ugguggggcu guccgggaag acaccuaccc 1380
ugugggcacu cagggugugc ccagcccggc ccuggcucag ggaggaccuc aggguuccug 1440
gagauuccug caguggaacu ccaugccccg ccucccaacg gaccuggacg uagagggccc 1500
uugguuccgc cauuaugauu ucagacagag cugcuggguc cgugccauau cccaggagga 1560
ccagcuggcc cccugcuggc aggcugaaca cccugcggag cgggugagau cggcuuucgc 1620
ugcacccagc acugauuccg accagggcac ccccuucaga gcuagggacg aacagcagug 1680
ugcucccacc ucagggccuu gccucugcgg ccuccacuug gaaaguucuc aguucccucc 1740
aggcuucuag aagcaucugg gccagggcuc auggcuggau aauuucccua ggcuuaacaa 1800
cccaagcaag cuucgcaucc ucguuuuauu uuugguuaaa cuuaugaaaa uguauuaaga 1860
aagagugcag cucgagagag auucagagau ggaacacacc agaccccaga ucacaaagcc 1920
aaccaugccc ggccccuccc agcaccccca gccccacgac caucguucug aauucugacg 1980
acaccgugag ccugccuuug uacuucaaac ucauggaagg auaaccaccu ucauguuuug 2040
aaauaaaaugu uuccuguuga aauga 2065

<210> 5
<211> 2082
<212> RNA
<213> (人工合成)
<400> 5

gccucagugg ucuacagcag uuacacacag gcagugguau cugugagcag cucuguggac 60
ucaaagguuu ucucccugag aggcaugacc caggccagcu gauucaucag aaucaggaug 120
gacgugguag aggucgcggg caguuggugg gcacaagagc gagaggacau cauuaugaaa 180
uacgaaaagg gacaccgagc ugggcugcca gaggacaagg ggccuaagcc uuuucgaagc 240
uacaacaaca acgucgauca uuuggggauu guacaugaga cggagcugcc uccucugacu 300
gcgcgggagg cgaagcaaau ucggcgggag aucagccgaa agagcaagug gguggauaug 360
cugggagacu gggagaaaua caaaagcagc agaaagcuca uagaucaagc guacaaggga 420
augcccauga acauccgggg cccgaugugg ucaguccucc ugaacacuga ggaaaugaag 480
uugaaaaacc ccggaagaua ccagaucaug aaggagaagg gcaagaaguc aucugagcac 540
auccagcgca ucgaccggga cguaagcggg acauuaagga agcauauauu cuucagggau 600
cgauacggaa ccaagcagcg ggaacuacuc cacauccucc uggcauauga ggaguacaac 660
ccggaggugg gcuacugcag ggaccugagc cacaucgccg ccuuguuccu ccucuaucuu 720
ccugaggagg augcauucug ggcacuggug cagcugcugg ccagugagag gcacucccug 780
cagggauuuc acagcccaaa uggcgggacc guccaggggc uccaagacca acaggagcau 840
gugguagcca cgucacaacc caagaccaug gggcaucagg acaagaaaga ucuauguggg 900
caguguuccc cguuaggcug ccucauccgg auauugauug acgggaucuc ucucgggcuc 960
acccugcgcc ugugggacgu guaucuggua gaaggcgaac aggcgcugau gccgauaaca 1020
agaaucgccu uuaagguuca gcagaagcgc cucacgaaga cguccaggug uggcccgugg 1080
gcacguuuuu gcaaccgguu cguugauacc ugggccaggg augaggacac ugugcucaag 1140
caucuuaggg ccucuaugaa gaaacuaaca agaaagaagg gggaccugcc acccccagcc 1200
aaacccgagc aagggucguc ggcauccagg ccugugccgg cuucacgugg cgggaagacc 1260
cucugcaagg gggacaggca ggccccucca ggcccaccag cccgguuccc gcggcccauu 1320
uggucagcuu ccccgccacg ggcaccucgu ucuuccacac ccuguccugg uggggcuguc 1380
cgggaagaca ccuacccugu gggcacucag ggugugccca gcccggcccu ggcucaggga 1440
ggaccucagg guuccuggag auuccugcag uggaacucca ugccccgccu cccaacggac 1500
cuggacguag agggcccuug guuccgccau uaugauuuca gacagagcug cuggguccgu 1560
gccauauccc aggaggacca gcuggccccc ugcuggcagg cugaacaccc ugcggagcgg 1620
gugagaucgg cuuucgcugc acccagcacu gauuccgacc agggcacccc cuucagagcu 1680
agggacgaac agcagugugc ucccaccuca gggccuugcc ucugcggccu ccacuuggaa 1740
aguucucagu ucccuccagg cuucuagaag caucugggcc agggcucaug gcuggauaau 1800
uucccuaggc uuaacaaccc aagcaagcuu cgcauccucg uuuuauuuuu gguuaaacuu 1860
augaaaaugu auuaagaaag agugcagcuc gagagagauu cagagaugga acacaccaga 1920
ccccagauca caaagccaac caugcccagc cccucccagc acccccagcc ccacgaccau 1980
cguucugaau ucugacgaca ccgugagccu gccuuuguac uucaaacuca uggaaggaua 2040
accaccuuca uguuuugaaa uaaauguuuc cuguugaaau ga 2082

<210> 6
<211> 2077
<212> RNA
<213> (人工合成)

<400> 6

aguggucuac agcaguuaca cacaggcagu gguaucugug agcagcucug uggacucaaa 60
gguuuucucc cugagaggca ugacccaggc cagcugauuc aucagaauca ggauggacgu 120
gguagagguc gcggguaguu ggugggcaca agagcgagag gacaucauua ugaaauacga 180
aaagggacac cgagcugggc ugccagagga caaggggccu aagccuuuuc gaagcuacaa 240
caacaacguc gaucauuugg ggauuguaca ugagacggag cugccuccuc ugacugcgcg 300
ggaggcgaag caaauucggc gggagaucag ccgaaagagc aagugggugg auaugcuggg 360
agacugggag aaauacaaaa gcagcagaaa gcucauagau cgagcguaca agggaaugcc 420
caugaacauc cggggcccga uguggucagu ccuccugaac auugaggaaa ugaaguugaa 480
aaaccccgga agauaccaga ucaugaagga gaagggcaag aggucaucug agcacaucca 540
gcgcaucgac cgggacguaa gcgggacauu aaggaagcau auauucuuca gggaucgaua 600
cggaaccaag cagcgggaac uacuccacau ccuccuggca uaugaggagu acaacccgga 660
ggugggcuac ugcagggacc ugagccacau cgccgccuug uuccuccucu aucuuccuga 720
ggaggaugca uucugggcac uggugcagcu gcuggccagu gagaggcacu cccugcaggg 780
auuucacagc ccaaauggcg ggaccgucca ggggcuccaa gaccaacagg agcauguggu 840
agccacguca caacccaaga ccaugggga ucaggacaag aaagaucuau gugggcagug 900
uucccguua ggcugccuca uccggauauu gauugacggg aucucucucg ggcucacccu 960
gcgccugugg gacguguauc ugguagaagg cgaacaggcg uugaugccga uaacaagaau 1020
cgccuuuaag guucagcaga agcgccucac gaagacgucc aggugguggcc cgugggcacg 1080
uuuuugcaac cgguucguug auaccugggc cagggaugag gacacugugc ucaagcaucu 1140
uagggccucu augaagaaac uaacaagaaa gaaggggac gugccacccc cagccaaacc 1200
cgagcaaggg ucgucggcau ccaggccugu gccggcuuca cguggcggga agacccucug 1260
caaggggac agacaggccc cuccaggccc accagcccgg uucccgcggc ccauuugguc 1320
agcuucccg ccacgggcac cucguucuuc cacacccugu ccuggugggg cuguccggga 1380
agacaccuac ccuguggca cucagggugu gcccagcccg gcccuggcuc agggaggacc 1440
ucaggguucc uggagauucc ugcaguggaa cuccaugccc cgccucccaa ccgaccugga 1500
cguagagggc ccuugguucc gccauuauga uuucagacag agcugcuggg uccgugccau 1560
aucccaggag gaccagcugg ccccccugcug gcaggcugaa cacccugcgg agcgggugag 1620
aucggcuuuc gcugcaccca gcacugauuc cgaccagggc acccccuuca gagcuaggga 1680
cgaacagcag ugugcuccca ccucagggcc uugccucugc ggccuccacu uggaaaguuc 1740
ucaguucccu ccaggcuucu agaagcaucu gggccagggc ucauggcugg auaauuuccc 1800
uaggcuuaac aacccaagca agcuucgcau ccucguuuua uuuuugguua aacuuaugaa 1860
aauguauuaa gaaagagugc agcucgagag agauucagag auggaacaca ccagacccca 1920
gaucacaaag ccaaccaugc ccagccccuc ccagcacccc cagccccacg accaucguuc 1980
ugaauucuga cgacaccgug agccugccuu uguacuucaa acucauggaa ggauaaccac 2040
cuucauguuu ugaaauaaau guuuccuguu gaaauga 2077

<210> 7

<211> 2065

<212> RNA

<213>（人工合成）

<400> 7

caguuacaca caggcagugg uaucugugag cagcucugug gacucaaagg uuuucucccu 60
gagaggcaug acccaggcca gcugauucau cagaaucagg auggacgugg uagaggucgc 120
gggcaguugg ugggcacaag agcgagagga caucauuaug aaauacgaaa agggacaccg 180
agcugggcug ccagaggaca aggggccuaa gccuuuucga agcuacaaca acaacgucga 240
ucauuugggg auuguacaug agacggagcu gccuccucug acugcgcggg aggcgaagca 300
aauucggcgg gagaucagcc gaaagagcaa guggguggau augcugggag acugggagaa 360
auacaaaagc agcagaaagc ucauagaucg agcguacaag ggaaugccca ugaacauccg 420
gggcccgaug uggucagucc uccugaacau ugaggaaaug aaguugaaaa accccggaag 480
auaccagauc augaaggaga agggcaagag gucaucugag cacauccagc gcaucgaccg 540
ggacauaagc gggacauuaa ggaagcauau guucuucagg gaucgauacg gaaccaagca 600
gcgggaacua cuccacaucc uccuggcaua ugaggaguau aacccggagg ugggcuacug 660
cagggaccug agccacaucg ccgccuuguu ccuccucuau cuuccugagg aggaugcauu 720
cugggcacug gugcagcugc uggccaguga gaggcacucc cugcagggau uucacagccc 780
aaauggcggg accguccagg ggcuccaaga ccaacaggag caugugguag ccacgucaca 840
acccaagacc auggggcauc aggacaagaa agaucuaugu gggcaguguu ccccguuagg 900
cugccucauc cggauauuga uugacgggau cucucucggg cucacccugc gccuguggga 960
cguguaucug guagaaggcg aacaggcguu gaugccgaua acaagaaucg ccuuuaaggu 1020
ucagcagaag cgccucacga agacguccag guguggcccg ugggcacguu uuugcaaccg 1080
guucguugau accugggcca gggaugagga cacugugcuc aagcaucuua gggccucuau 1140
gaagaaacua acaagaaagc agggggaccu gccaccccca gccaaacccg agcaaggguc 1200
gucggcaucc aggccugugc cggcuucacg uggcgggaag acccucugca agggggacag 1260
gcaggccccu ccaggcccac cagcccgguu cccgcggccc auuuggucag cuuccccgcc 1320
acgggcaccu cguucuucca cacccugucc ugguggggcu guccgggaag acaccuaccc 1380
ugugggcacu cagggugugc ccagcccggc ccuggcucag ggaggaccuc aggguuccug 1440
gagauuccug caguggaacu ccaugccccg ccucccaacg gaccuggacg uagagggccc 1500
uugguuccgc cauuaugauu ucagacagag cugcuggguc cgugccauau cccaggagga 1560
ccagcuggcc cccugcuggc aggcugaaca cccugcggag cgggugagau cggcuuucgc 1620
ugcacccagc acugauuccg accagggcac ccccuucaga gcuagggacg aacagcagug 1680
ugcucccacc ucagggccuu gccucugcgg ccuccacuug gaaaguucuc aguucccucc 1740
aggcuucuag aagcaucugg gccagggcuc auggcuggau aauuucccua ggcuuaacaa 1800
cccaagcaag cuucgcaucc ucguuuuauu uuugguuaaa cuuaugaaaa uguauuaaga 1860
aagagugcag cucgagagag auucagagau ggaacacacc agaccccaga ucacaaagcc 1920
aaccaugccc agccccuccc agcaccccca gccccacgac caucguucug aauucugacg 1980
acaccgugag ccugccuuug uacuucaaac ucauggaagg auaaccaccu ucauguuuug 2040
aaauaaaaugu uuccuguuga aauga 2065

<210> 8

<211> 2077

<212> RNA

<213> (人工合成)

<400> 8

aguggucuac agcaguuaca cacaggcagu gguaucugug agcagcucug uggacucaaa 60
gguuuucucc cugagaggca ugacccaggc cagcugauuc aucagaauca ggauggacgu 120
gguagagguc gcgggcaguu ggugggcaca agagcgagag gacaucauua ugaaauacga 180
aaagggacac cgagcugggc ugccagagga caaggggccu aagccuuuuc gaagcuacaa 240
caacaacguc gaucauuugg ggauuguaca ugagacggag cugccuccuc ugacugcgcg 300
ggaggcgaag caaauucggc gggagaucag ccgaaagagc aagugggugg auaugcuggg 360
agacugggag aaauacaaaa gcagcagaaa gcucauagau cgagcguaca agggaaugcc 420
caugaacauc cggggcccga uguggucagu ccuccugaac acugaggaaa ugaaguugaa 480
aaaccccgga agauaccaga ucaugaagga gaagggcaag aggucaucug agcacaucca 540
gcgcaucgac cgggacauaa gcgggacauu aaggaagcau auguucuuca gggaucgaua 600
cggaaccaag cagcgggaac uacuccacau ccuccuggca uaugaggagu auaacccgga 660
ggugggcuac ugcagggacc ugagccacau cgccgccuug uuccuccucu aucuuccuga 720
ggaggaugca uucugggcac uggugcagcu gcuggccagu gagaggcacu cccugcaggg 780
auuucacagc ccaaauggcg ggaccgucca ggggcuccaa gaccaacagg agcauguggu 840
agccacguca caacccaaga ccaugggga ucaggacaag aaagaucuau gugggcagug 900
uuccccguua ggcugccuca uccggauauu gauugacggg aucucucucg ggcucacccu 960
gcgccugugg gacguguauc ugguagaagg cgaacaggcg uugaugccga uaacaagaau 1020
cgccuuuaag guucagcaga agcgccucac gaagacgucc agguguggcc cgugggcacg 1080
uuuuugcaac cgguucguug auaccugggc cagggaugag gacacugugc ucaagcaucu 1140
uagggccucu augaagaaac uaacaagaaa gcagggggac cugccacccc cagccaaacc 1200
cgagcaaggg ucgucggcau ccaggccugu gccggcuuca cguggcggga agacccucug 1260
caagggggac aggcaggccc cuccaggccc accagcccgg uucccgcggc ccauuugguc 1320
agcuuccccg ccacgggcac cucguucuuc cacacccugu ccuggugggg cuguccggga 1380
agacaccuac ccugugggca cucagggugu gcccagcccg gcccuggcuc agggaggacc 1440
ucaggguucc uggagauucc ugcaguggaa cuccaugccc cgccucccaa cggaccugga 1500
cguagagggc ccuugguucc gccauuauga uuucagacag agcugcuggg uccgugccau 1560
aucccaggag gaccagcugg ccccccugcug gcaggcugaa cacccugcgg agcgggugag 1620
aucggcuuuc gcugcaccca gcacugauuc cgaccagggc acccccuuca gagcuaggga 1680
cgaacagcag ugugcuccca ccucagggcc uugccucugc ggccuccacu uggaaaguuc 1740
ucaguucccu ccaggcuucu agaagcaucu gggccagggc ucauggcugg auaauuuccc 1800
uaggcuuaac aacccaagca agcuucgcau ccucguuuua uuuuugguua aacuuaugaa 1860
aauguauuaa gaaagagugc agcucgagag agauucagag auggaacaca ccagacccca 1920
gaucacaaag ccaaccaugc ccagccccuc ccagcacccc cagccccacg accaucguuc 1980
ugaauucuga cgacaccgug agccugccuu uguacuucaa acucauggaa ggauaaccac 2040
cuucauguuu ugaaauaaau guuuccuguu gaaauga 2077

<210> 9

<211> 21
<212> RNA
<213> (人工合成)
<400> 9
uaggcugccu cauccggaua u 21
<210> 10
<211> 21
<212> RNA
<213> (人工合成)
<400> 10
gcuugagaga cauucagaga u 21
<210> 11
<211> 21
<212> RNA
<213> (人工合成)
<400> 11
cgauaacaag aaucgccuuu a 21
<210> 12
<211> 21
<212> RNA
<213> (人工合成)
<400> 12
ccagaucaca aagccaacca u 21
<210> 13
<211> 21
<212> RNA
<213> (人工合成)
<400> 13
auaacaagaa ucgccuuuaa g 21
<210> 14
<211> 21
<212> RNA
<213> (人工合成)
<400> 14
aggcguugau gccgauaaca a 21

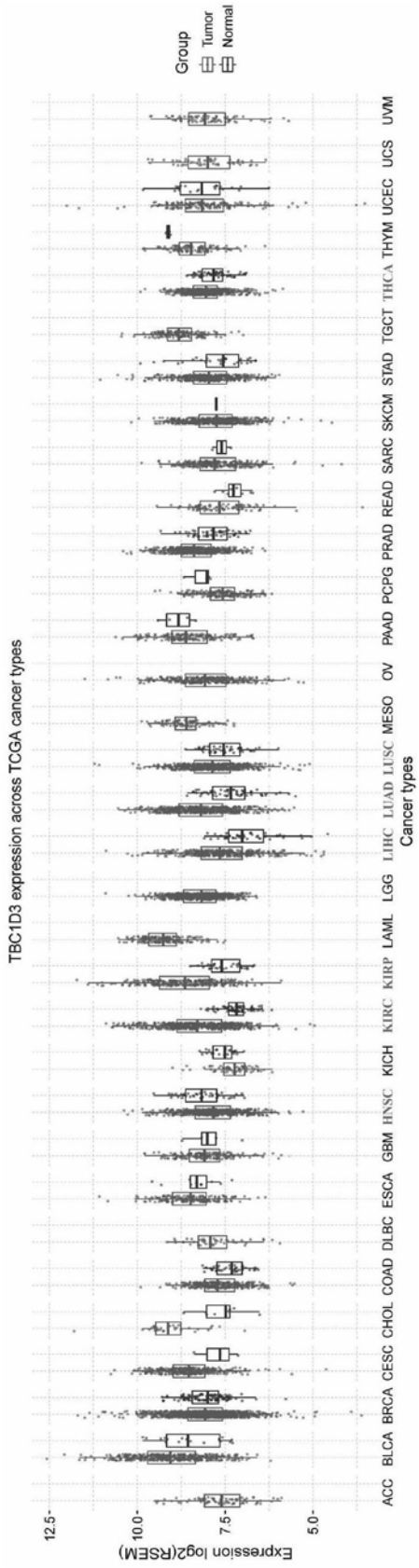

Group
Tumor
Normal
TBC1D3 expression across TCGA cancer types
Expression log2(RSEM)
12.5
10.0
7.5
5.0
Cancer types
ACC BLCA BRCA CESC CHOL COAD DLBC ESCA GBM HNSC KICH KIRC KIRP LAML LGG LIHC LUAD LUSC MESO OV PAAD PCPG PRAD READ SARC SKCM STAD TGCT THCA THYM UCEC UCS UVM

图1-1

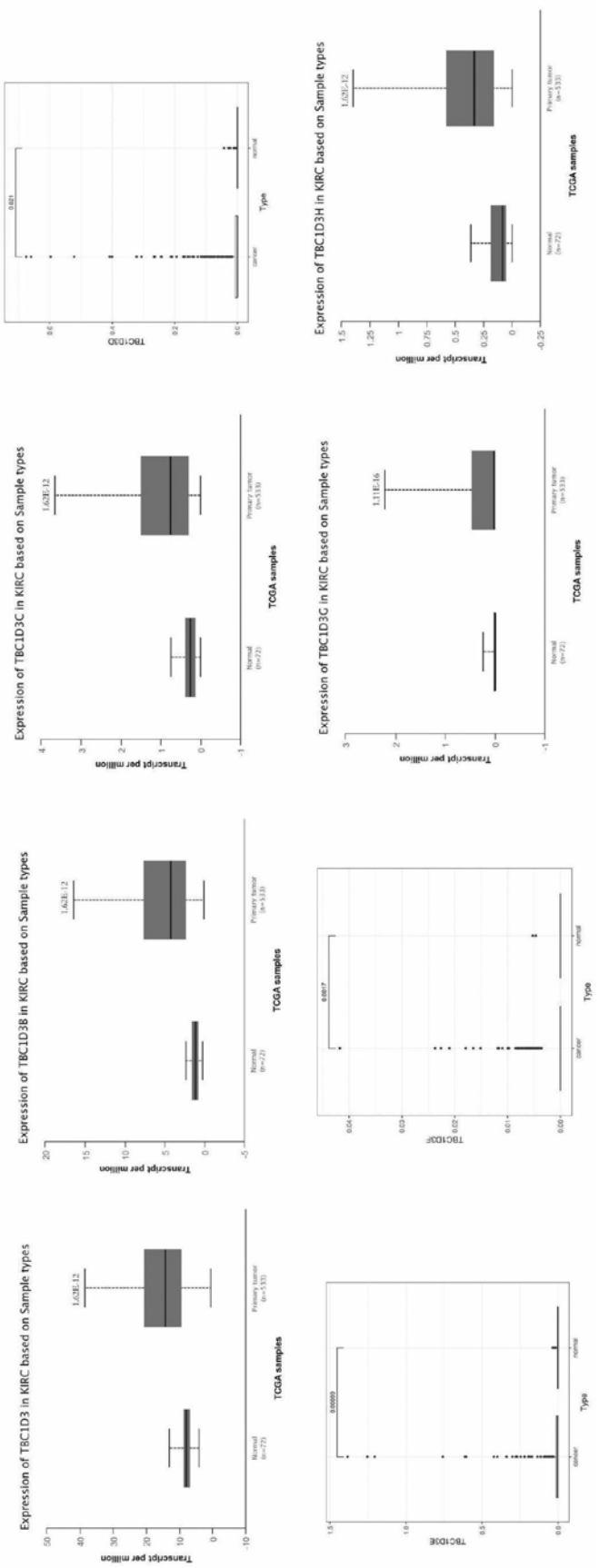

Expression of TBC1D3 in KIRC based on Sample types
Expression of TBC1D3B in KIRC based on Sample types
Expression of TBC1D3C in KIRC based on Sample types
Expression of TBC1D3G in KIRC based on Sample types
Expression of TBC1D3H in KIRC based on Sample types
Transcript per million
TCGA samples
Normal (n=72)
Primary tumor (n=533)
Type
normal
tumor
TBC1D3
TBC1D3B
TBC1D3C
TBC1D3E
TBC1D3G
TBC1D3H

图1-2

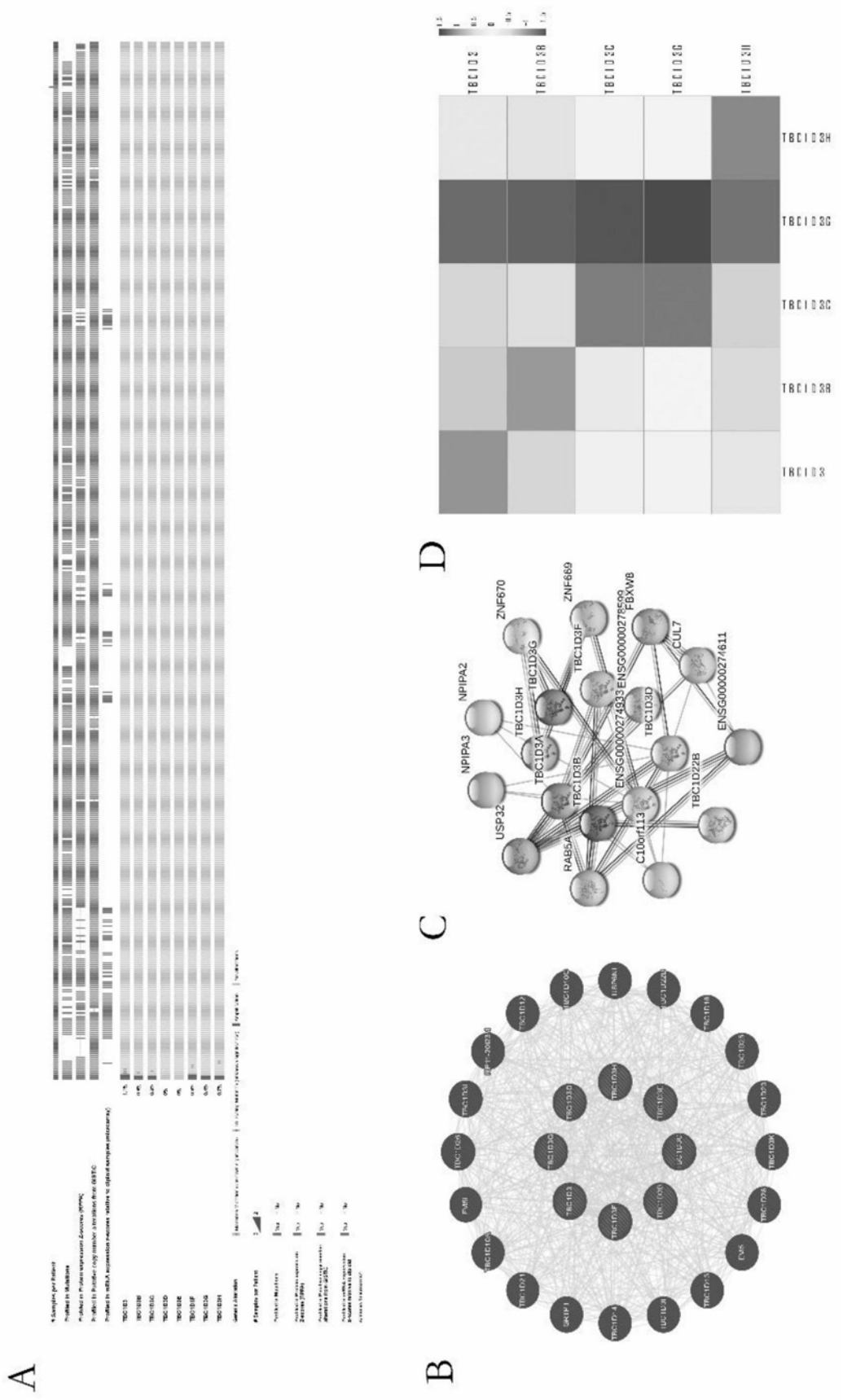

A
B
C
D
TBC1D3H
TBC1D3G
TBC1D3C
TBC1D3B
TBC1D3
ZNF670
ZNF669
NPIPA2
NPIPA3
TBC1D3H
TBC1D3G
TBC1D3F
TBC1D3A
TBC1D3B
TBC1D3D
FBXW8
CUL7
ENSG00000274611
TBC1D22B
USP32
RAB5A
C10orf113

图2

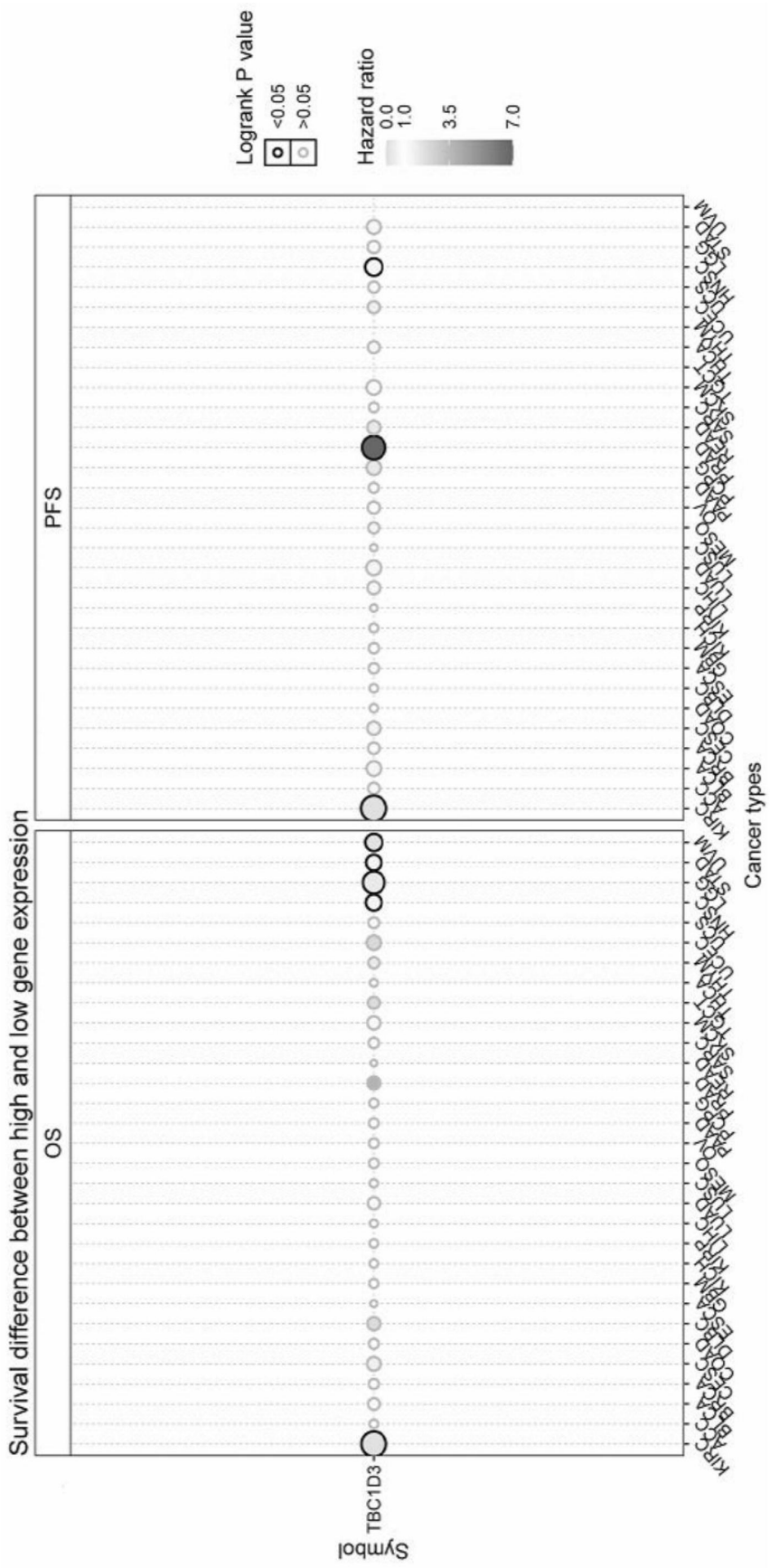

Logrank P value
<0.05
>0.05
Hazard ratio
0.0
1.0
3.5
7.0
PFS
OS
Survival difference between high and low gene expression
Cancer types
Symbol
TBC1D3

图3-1

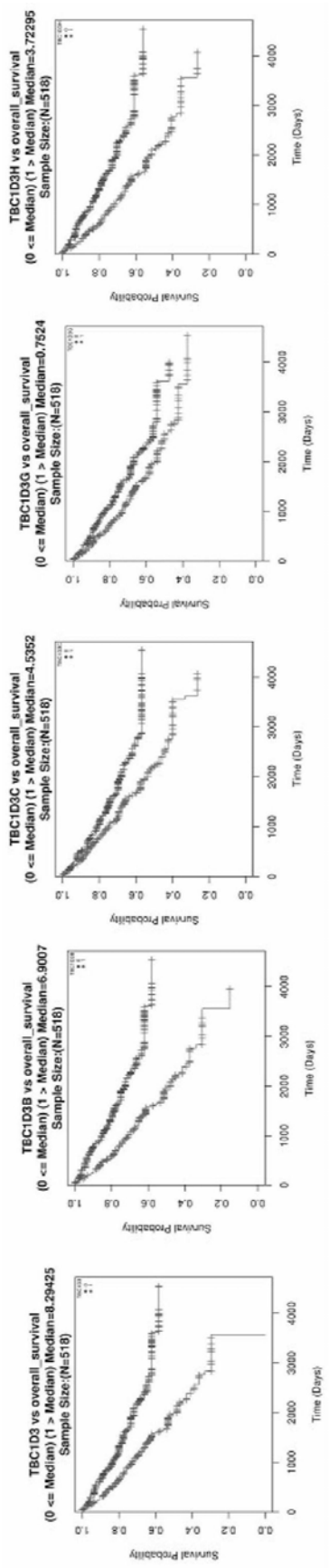

TBC1D3H vs overall_survival
(0 <= Median) (1 > Median) Median=3.72295
Sample Size:(N=518)
TBC1D3G vs overall_survival
(0 <= Median) (1 > Median) Median=0.7524
Sample Size:(N=518)
TBC1D3C vs overall_survival
(0 <= Median) (1 > Median) Median=4.5352
Sample Size:(N=518)
TBC1D3B vs overall_survival
(0 <= Median) (1 > Median) Median=6.9007
Sample Size:(N=518)
TBC1D3 vs overall_survival
(0 <= Median) (1 > Median) Median=8.29425
Sample Size:(N=518)
Survival Probability
Time (Days)

图3-2

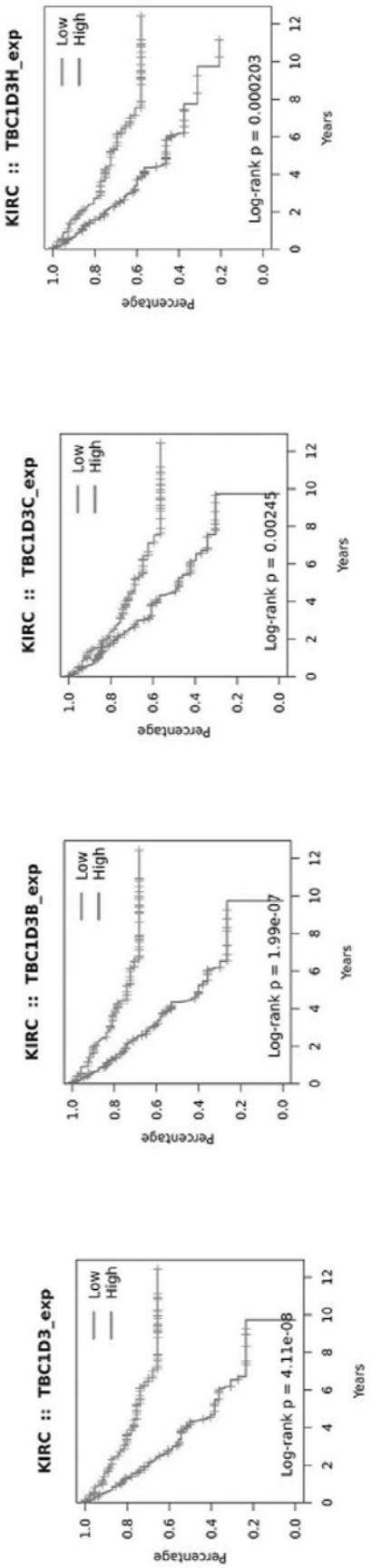

KIRC :: TBC1D3H_exp
Low
High
Log-rank p = 0.000203
Percentage
Years
KIRC :: TBC1D3C_exp
Low
High
Log-rank p = 0.00245
Percentage
Years
KIRC :: TBC1D3B_exp
Low
High
Log-rank p = 1.99e-07
Percentage
Years
KIRC :: TBC1D3_exp
Low
High
Log-rank p = 4.11e-08
Percentage
Years

图3-3

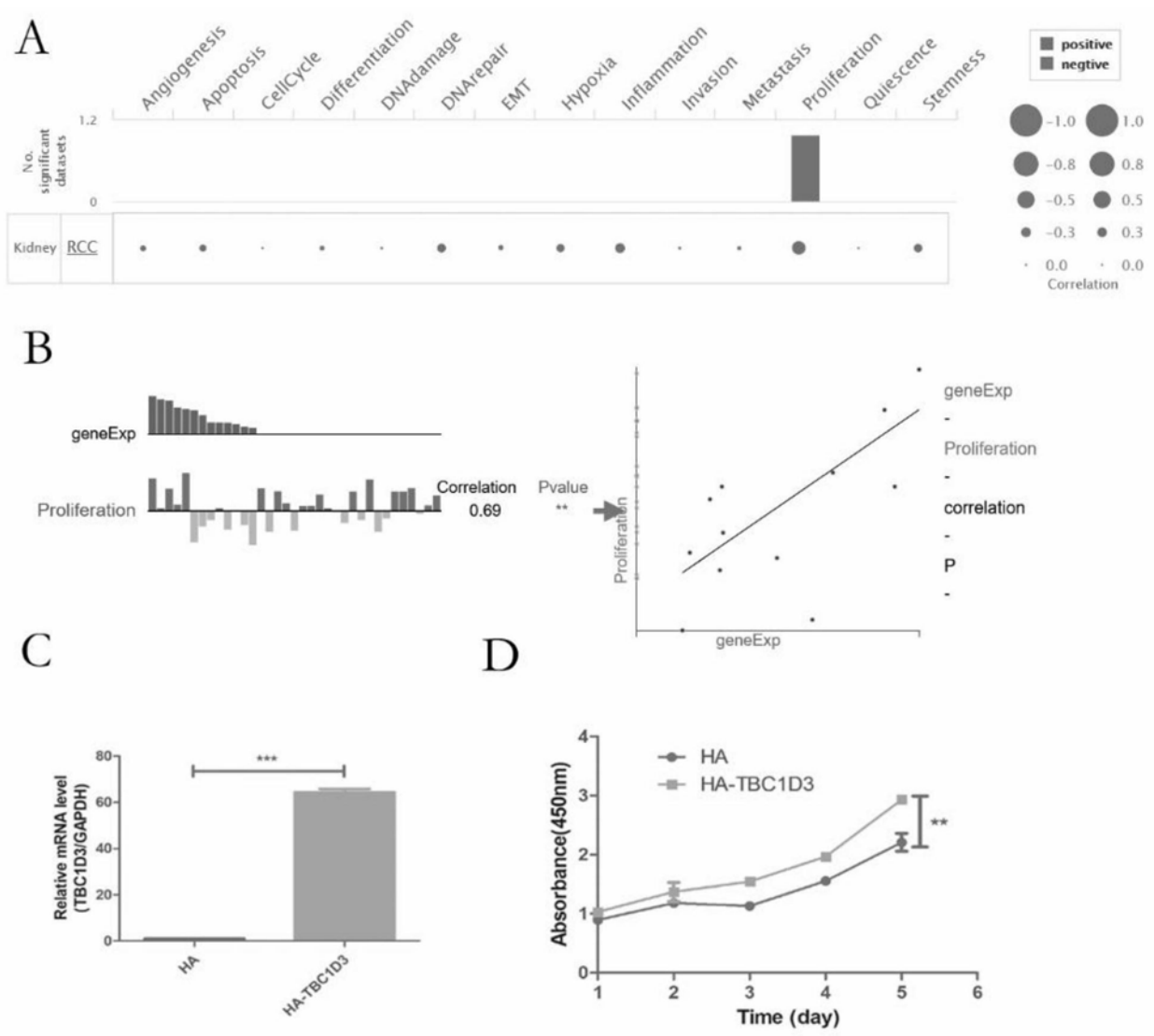

A
Angiogenesis
Apoptosis
CellCycle
Differentiation
DNAdamage
DNArepair
EMT
Hypoxia
Inflammation
Invasion
Metastasis
Proliferation
Quiescence
Stemness
positive
negtive
No. significant datasets
1.2
0
Kidney
RCC
1.0
0.8
0.5
0.3
0.0
Correlation
B
geneExp
Proliferation
Correlation
0.69
Pvalue
**
geneExp
Proliferation
correlation
P
C
Relative mRNA level (TBC1D3/GAPDH)
***
HA
HA-TBC1D3
D
HA
HA-TBC1D3
Absorbance(450nm)
**
Time (day)

图4

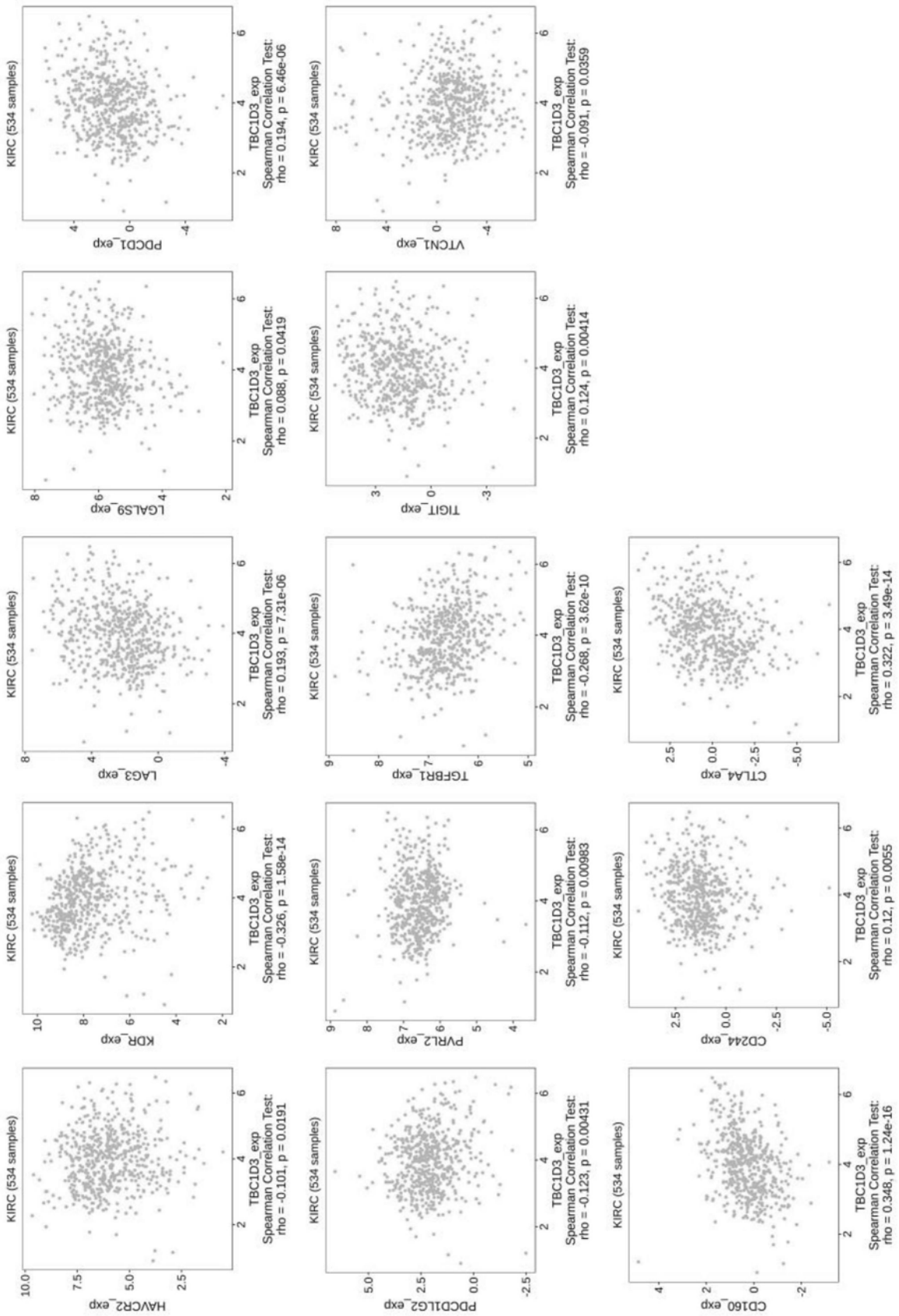

KIRC (534 samples)
TBC1D3_exp
Spearman Correlation Test:
rho = 0.194, p = 6.46e-06
PDCD1_exp
rho = -0.091, p = 0.0359
VTCN1_exp
rho = 0.088, p = 0.0419
LGALS9_exp
rho = 0.124, p = 0.00414
TIGIT_exp
rho = 0.193, p = 7.31e-06
LAG3_exp
rho = -0.268, p = 3.62e-10
TGFBR1_exp
rho = 0.322, p = 3.49e-14
CTLA4_exp
rho = -0.326, p = 1.58e-14
KDR_exp
rho = -0.112, p = 0.00983
PVRL2_exp
rho = 0.12, p = 0.0055
CD244_exp
rho = -0.101, p = 0.0191
HAVCR2_exp
rho = -0.123, p = 0.00431
PDCD1LG2_exp
rho = 0.348, p = 1.24e-16
CD160_exp

图5-1

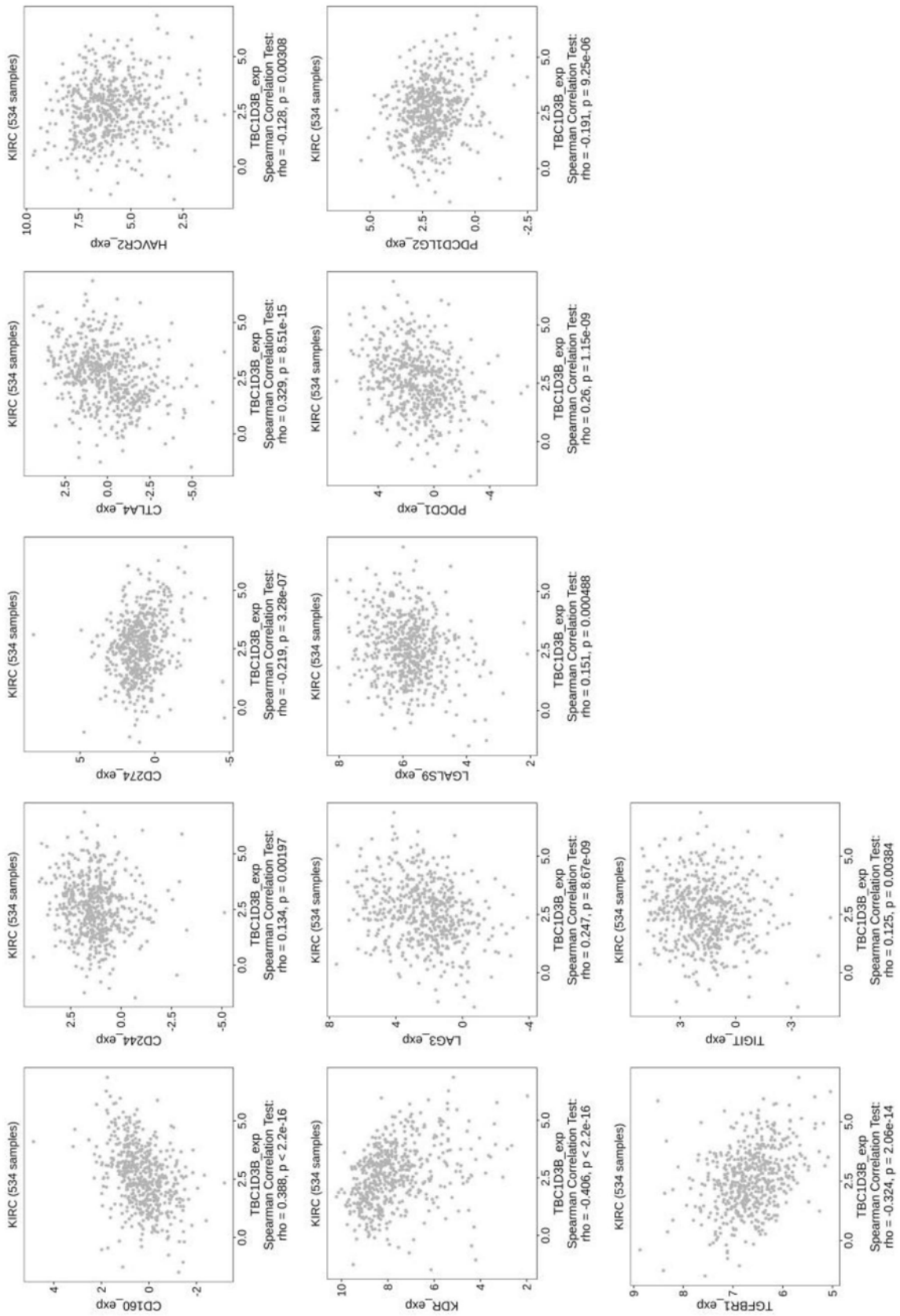

KIRC (534 samples)
TBC1D3B_exp
Spearman Correlation Test:
rho = -0.128, p = 0.00308
HAVCR2_exp
rho = -0.191, p = 9.25e-06
PDCD1LG2_exp
rho = 0.329, p = 8.51e-15
CTLA4_exp
rho = 0.26, p = 1.15e-09
PDCD1_exp
rho = -0.219, p = 3.28e-07
CD274_exp
rho = 0.151, p = 0.000488
LGALS9_exp
rho = 0.134, p = 0.00197
CD244_exp
rho = 0.247, p = 8.67e-09
LAG3_exp
rho = 0.125, p = 0.00384
TIGIT_exp
rho = 0.388, p < 2.2e-16
CD160_exp
rho = -0.406, p < 2.2e-16
KDR_exp
rho = -0.324, p = 2.06e-14
TGFBR1_exp

图5-2

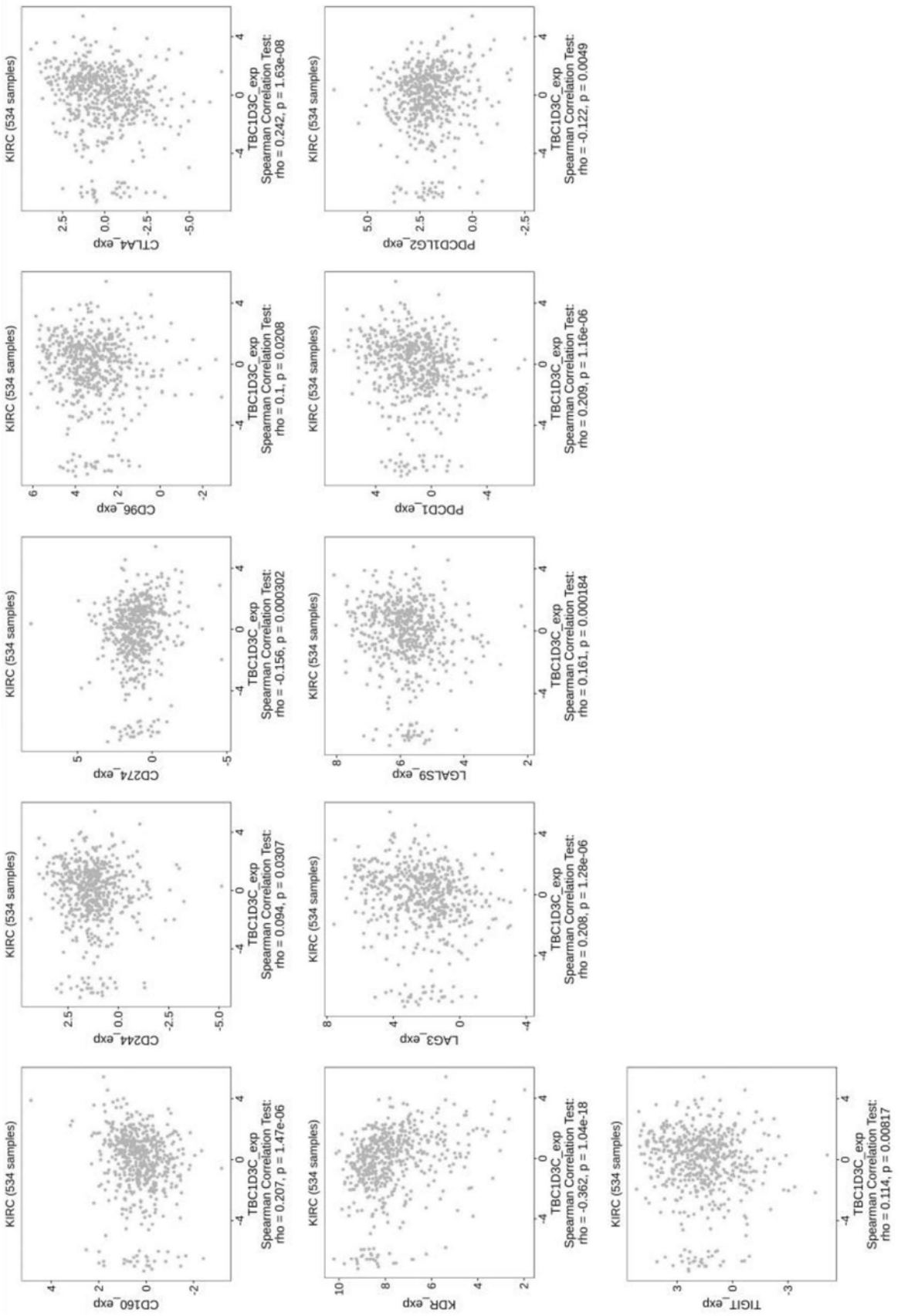

KIRC (534 samples)
TBC1D3C_exp
Spearman Correlation Test:
rho = 0.242, p = 1.63e-08
CTLA4_exp
rho = -0.122, p = 0.0049
PDCD1LG2_exp
rho = 0.1, p = 0.0208
CD96_exp
rho = 0.209, p = 1.16e-06
PDCD1_exp
rho = -0.156, p = 0.000302
CD274_exp
rho = 0.161, p = 0.000184
LGALS9_exp
rho = 0.094, p = 0.0307
CD244_exp
rho = 0.208, p = 1.28e-06
LAG3_exp
rho = 0.207, p = 1.47e-06
CD160_exp
rho = -0.362, p = 1.04e-18
KDR_exp
rho = 0.114, p = 0.00817
TIGIT_exp

图5-3

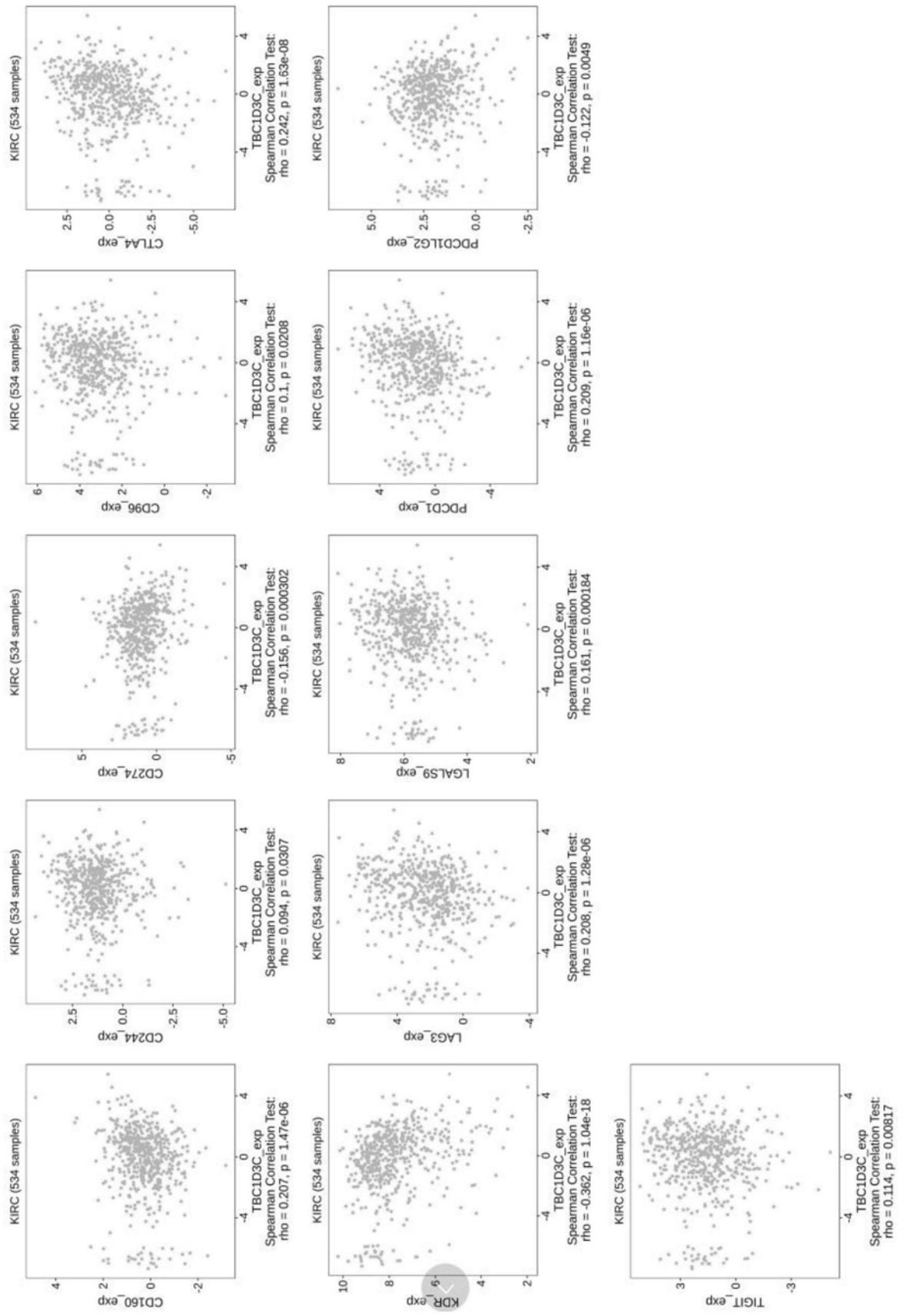

KIRC (534 samples)
TBC1D3C_exp
Spearman Correlation Test:
rho = 0.242, p = 1.63e-08
CTLA4_exp
rho = -0.122, p = 0.0049
PDCD1LG2_exp
rho = 0.1, p = 0.0208
CD96_exp
rho = 0.209, p = 1.16e-06
PDCD1_exp
rho = -0.156, p = 0.000302
CD274_exp
rho = 0.161, p = 0.000184
LGALS9_exp
rho = 0.094, p = 0.0307
CD244_exp
rho = 0.208, p = 1.28e-06
LAG3_exp
rho = 0.207, p = 1.47e-06
CD160_exp
rho = -0.362, p = 1.04e-18
KDR_exp
rho = 0.114, p = 0.00817
TIGIT_exp

图5-4

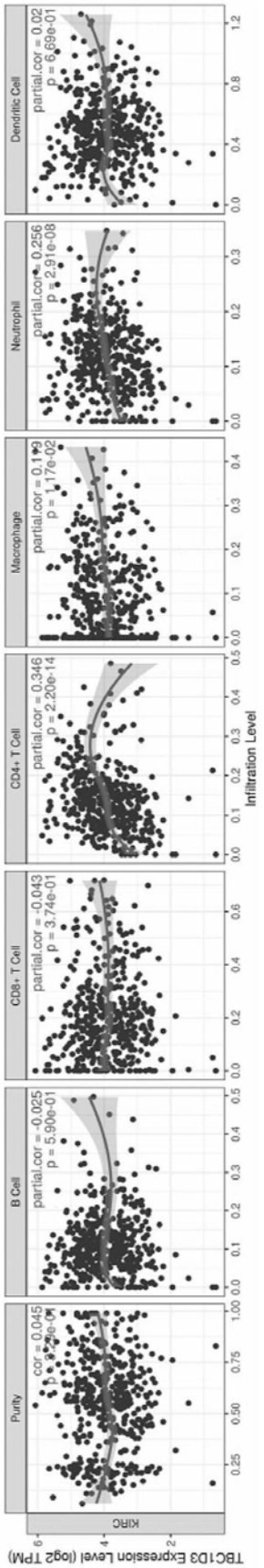

Purity
B Cell
CD8+ T Cell
CD4+ T Cell
Macrophage
Neutrophil
Dendritic Cell
KIRC
TBC1D3 Expression Level (log2 TPM)
Infiltration Level

图6-1

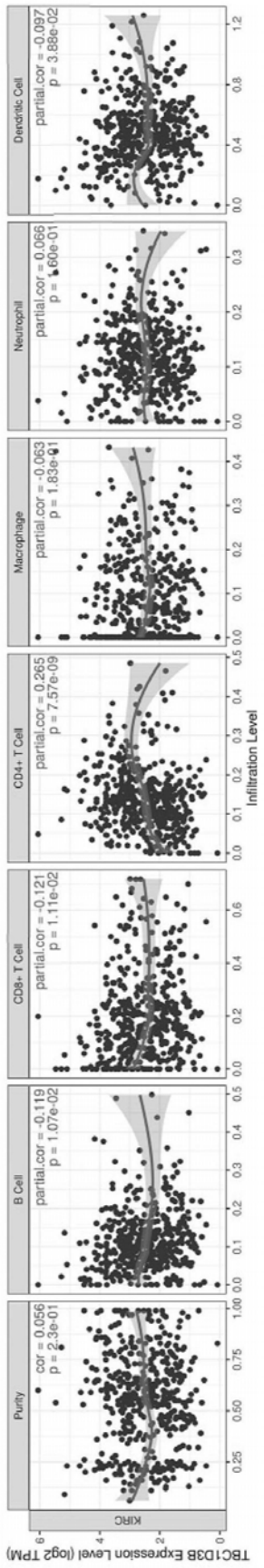

Purity
B Cell
CD8+ T Cell
CD4+ T Cell
Macrophage
Neutrophil
Dendritic Cell
KIRC
cor = 0.056
p = 2.3e-01
partial.cor = -0.119
p = 1.07e-02
partial.cor = -0.121
p = 1.11e-02
partial.cor = 0.265
p = 7.57e-09
partial.cor = -0.063
p = 1.83e-01
partial.cor = 0.066
p = 1.60e-01
partial.cor = -0.097
p = 3.88e-02
TBC1D3B Expression Level (log2 TPM)
Infiltration Level

图6-2

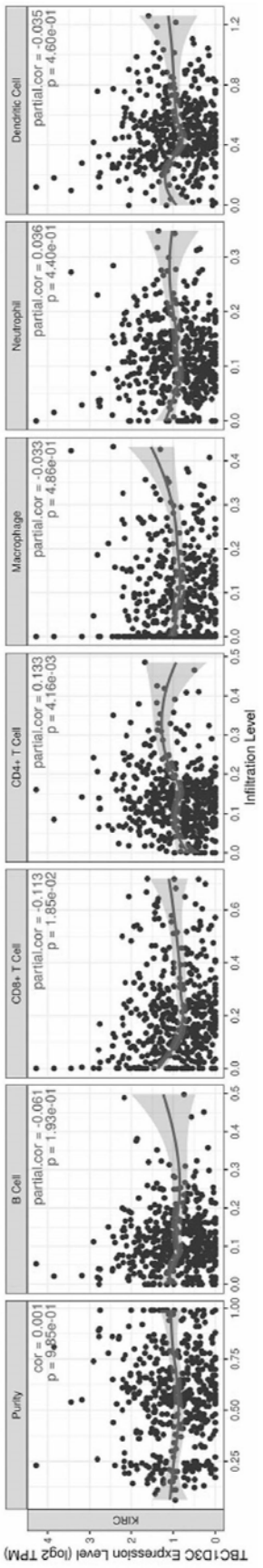

Purity
B Cell
CD8+ T Cell
CD4+ T Cell
Macrophage
Neutrophil
Dendritic Cell
KIRC
cor = 0.001
p = 9.85e-01
partial.cor = -0.061
p = 1.93e-01
partial.cor = -0.113
p = 1.85e-02
partial.cor = 0.133
p = 4.16e-03
partial.cor = -0.033
p = 4.86e-01
partial.cor = 0.036
p = 4.40e-01
partial.cor = -0.035
p = 4.60e-01
TBC1D3C Expression Level (log2 TPM)
Infiltration Level

图6-3

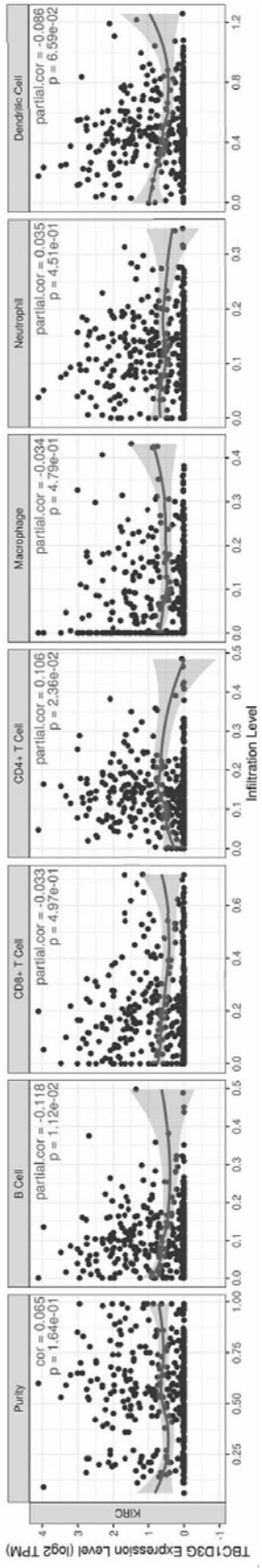

KIRC
Purity
cor = 0.065
p = 1.64e-01
B Cell
partial.cor = -0.118
p = 1.12e-02
CD8+ T Cell
partial.cor = -0.033
p = 4.97e-01
CD4+ T Cell
partial.cor = 0.106
p = 2.36e-02
Macrophage
partial.cor = -0.034
p = 4.79e-01
Neutrophil
partial.cor = 0.035
p = 4.51e-01
Dendritic Cell
partial.cor = -0.086
p = 6.59e-02
Infiltration Level
TBC1D3G Expression Level (log2 TPM)

图6-4

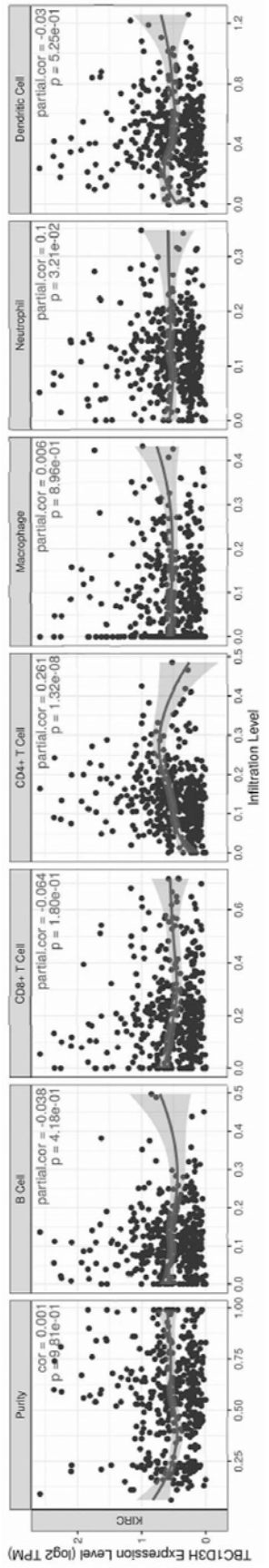

Purity
B Cell
CD8+ T Cell
CD4+ T Cell
Macrophage
Neutrophil
Dendritic Cell
KIRC
cor = 0.001
p = 9.81e-01
partial.cor = -0.038
p = 4.18e-01
partial.cor = -0.064
p = 1.80e-01
partial.cor = 0.261
p = 1.32e-08
partial.cor = 0.006
p = 8.96e-01
partial.cor = 0.1
p = 3.21e-02
partial.cor = -0.03
p = 5.25e-01
TBC1D3H Expression Level (log2 TPM)
Infiltration Level

图6-5

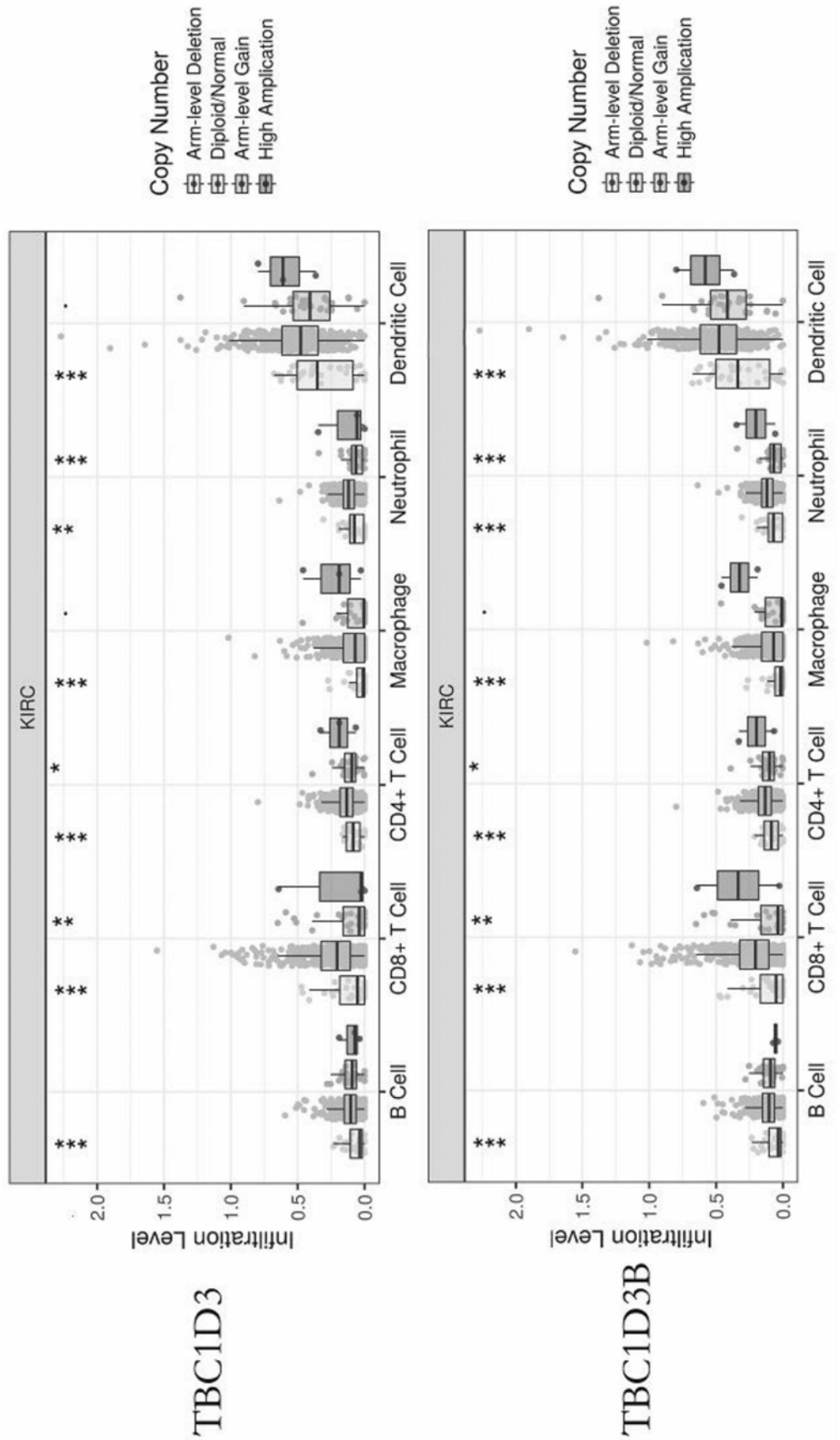

Copy Number
Arm-level Deletion
Diploid/Normal
Arm-level Gain
High Amplication
KIRC
Infiltration Level
B Cell
CD8+ T Cell
CD4+ T Cell
Macrophage
Neutrophil
Dendritic Cell
TBC1D3
TBC1D3B

图7-1

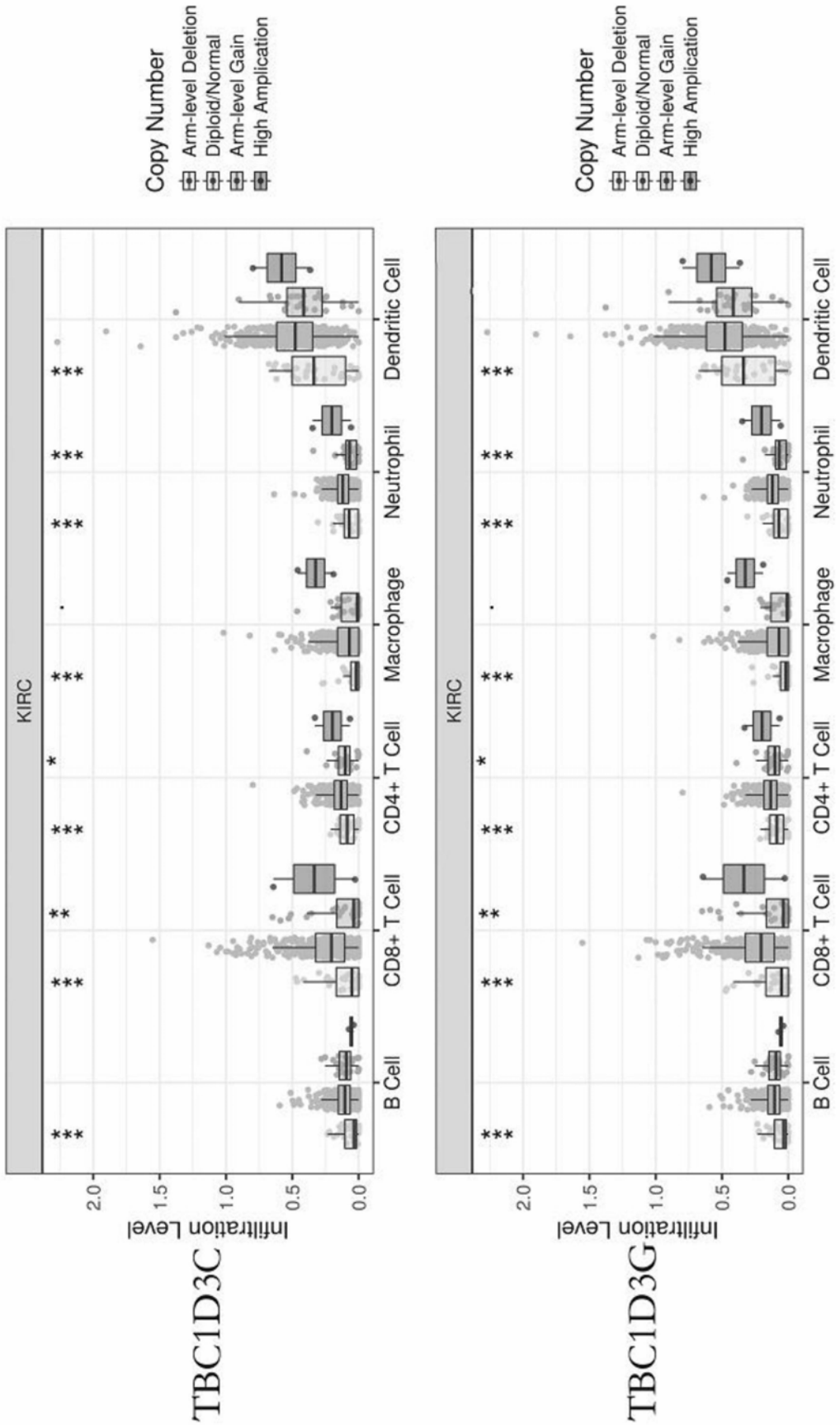

Copy Number
Arm-level Deletion
Diploid/Normal
Arm-level Gain
High Amplication
KIRC
Infiltration Level
0.0
0.5
1.0
1.5
2.0
B Cell
CD8+ T Cell
CD4+ T Cell
Macrophage
Neutrophil
Dendritic Cell
TBC1D3C
TBC1D3G

图7-2

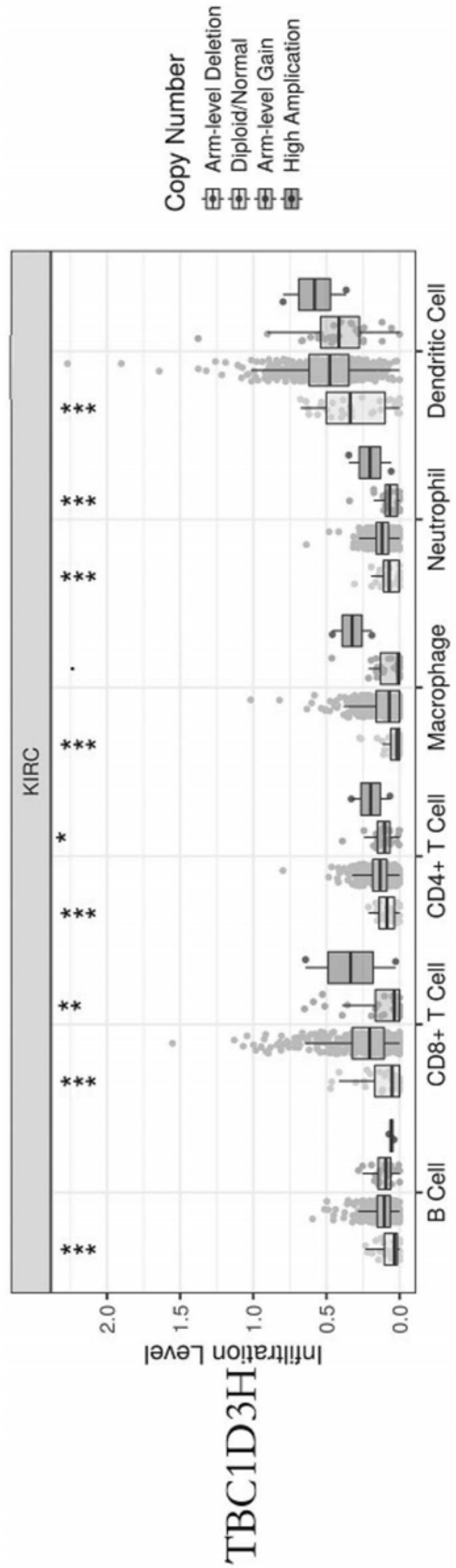

TBC1D3H
Infiltration Level
2.0
1.5
1.0
0.5
0.0
KIRC
***
***
**
***
*
***
***
***
B Cell
CD8+ T Cell
CD4+ T Cell
Macrophage
Neutrophil
Dendritic Cell
Copy Number
Arm-level Deletion
Diploid/Normal
Arm-level Gain
High Amplication

图7-3