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Clinical Significance and Potential Signal Pathway of Upregulated Pituitary Tumor-Transforming Gene 1 in Metastatic Prostate Cancer Based on Bioinformatic Methods

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KEYWORDS

PTTG1,
Prostate Cancer (PCa),
Metastatic Prostate Cancer (MPCa),
Differentially Co-Expressed Genes (DCEGs),
Biomarker Discrimination

ABSTRACT

This study examined the expression and clinical significance of pituitary tumor-transforming gene 1 (PTTG1) in prostate cancer (PCa) and metastatic prostate cancer (MPCa). Analysis of 19 PCa and 10 MPCa public datasets showed that PTTG1 expression was significantly upregulated in PCa (SMD=0.55, 95% CI: 0.29, 0.83) and MPCa (SMD=2.28, 95% CI: 1.38, 3.19). PTTG1 also demonstrated moderate discriminatory ability for PCa (AUC=0.75, 95% CI: 0.71, 0.79) and high discriminatory potential for MPCa from localized PCa (AUC=0.97, 95% CI: 0.95, 0.98). Differential co-expressed gene (DCEG) analysis identified 314 PTTG1-related genes, with CCNA2, CCNB1, and CDK1 emerging as key hub genes positively correlated with PTTG1. While most clinical parameters showed no correlation with PTTG1 expression, data from The Cancer Genome Atlas (TCGA) revealed an association between PTTG1 and both M-stage and recurrence. Enrichment analyses indicated that PTTG1 DCEGs were involved in cell division, nucleoplasm, protein binding, and the cell cycle pathway. These findings suggest that PTTG1 may serve as a marker for distinguishing MPCa from localized PCa and provide insights into its potential role in prostate cancer progression.

1. Introduction

Prostate cancer (PCa) brings a serious threat to health of patients in males, which is one of the most prevalent malignant tumor among males. In terms of incidence rate, PCa was identified as the most common cancer in males, and ranks the second most common mortality among cancers in males [1]. According to prediction of *Cancer Statistics, 2024*, about 34130 patients in United States will die caused by PCa [2]. To date, surgery and radiotherapy were considered as the main treatments for PCa in early stage, the 5-year-survival rate of patients after surgery or radiotherapy is able to reach 99% [3, 4]. Though localized PCa has a considerable prognosis, with the development of disease, the 5-year-survival

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rate of patients is less than 30% once tumor cells metastasize [5]. Previous studies had shown that the metastasis rate of PCa is increasing each year [6]. Unfortunately, early prediction for metastatic prostate cancer (MPCa) is immature, the molecular mechanisms of MPCa also had never been clarified yet. Therefore, it is vital to discover a molecular markers and explore the molecular mechanisms in MPCa.

Pituitary tumor-transforming gene 1 (PTTG1, also known as securin), located on 5q33.3, which is one of the major regulatory factors in separation of sister chromatids, transcription of mRNA and development of organs. Generally accepted function of PTTG1 is ensuring the stability of chromosome structure in mitotic stage [7, 8]. Recently, limited studies indicated that the expressed level of PTTG1 was upregulated in PCa, and might promote the development of PCa by regulating apoptosis of LNCaP cells [9]. Lin and colleagues reported that overexpressed PTTG1 could promote the occurrence of prostate cancer by activing MMP13 [10]. In vitro experiments, Huang et al. reported that the expression of PTTG1 was upregulated in PCa, and promote prostate cancer cell proliferation by regulating SMAD3 [11]. However, though PTTG1 expressed higher in PCa was also observed, Castilla et al. thought the downregulation of PTTG1 was able to promote the multiplication of prostate cancer cells through in vitro experiments [12]. Existed studies about the expression level of PTTG1 in PCa was consistent, but the functions of PTTG1 in PCa remains controversial. In addition, more stress was put on investigating the expression level of PTTG1 in localized PCa in previous studies, the expression level and molecular mechanism of PTTG1 in MPCa was still unclear.

Therefore, the present study is aiming to prove the expression level and effect of PTTG1 in PCa, meanwhile to investigate the expression and molecular mechanism of PTTG1 in MPCa, and the clinical value of PTTG1 differential expression in MPCa was identified. In addition, the co-expressed genes (CEGs) of PTTG1 were used to investigate the potential molecular mechanism in MPCa. PPI network analysis was conducted to determine the potential target genes of PTTG1 in MPCa. The molecular pathway of metastasis of PCa regulated by differential expressed PTTG1 was assessed through enrichment analysis.

2. Materials and Methods

2.1. Obtaining of the Expression Data of PTTG1 in PCa and MPCa

The microarray and RNA-seq data of PCa and MPCa were obtained from Gene Expression Omnibus (GEO), Sequence Read Archive (SRA), ArrayExpress, Oncomine and The Cancer Genome Atlas (TCGA) database. The following words were applied to retrieval datasets we need: (parastata OR prostatic gland OR prostate gland OR prostat*) AND (cancer OR carcinoma OR tumor OR neoplas* OR malignan* OR adenocarcinoma) AND (miR OR miRNA OR microRNA). The process of data screening was performed on Supplementary material 1 The microarray and RNA-seq data including PCa and non-PCa was showed on Figure 1, the microarray and RNA-seq data including MPCa and LPCa was showed on Figure 2. We downloaded the mRNA expression matrix data of mentioned series, and extracted mRNA expression data of PTTG1. Then, transferring PTTG1 expression data according to log2(x+1) conversion, the groups with cancer, normal, MPCa and LPCa patients were divided. RNA-seq data and clinical parameters of the TCGA and GTEx database were downloaded from UCSC Xena. The included datasets were showed in Table 1.

2.2. The Screening of PTTG1 Potential Target Genes in MPCa

2.2.1. The Screening of PTTG1 CEGs in MPCa

To gain the CEGs of PTTG1 in MPCa, we estimated Pearson's r-values of chips, and chose the gene for next step if p values < 0.05 and $r > 0.3$. The gene would be identified as CEG of PTTG1 when it appeared more than 5 times in 10 series.

2.2.2. The Screening of PTTG1 Differential Upregulated Genes in MPCa

We analyzed mRNA-seq series with limma-voom package and analyzed chip-seq with limma package, then we got DEGs in resepective series (p values $<$ 0.05, |log2FC| $>$ 1). The differential upregulated genes of PTTG1 in MPCa would be identified when it appeared more than 5 times in 10 series. Genes meeting from CEGs and differential upregulated genes were interacted and considered as PTTG1 potential target genes.

2.3. Functional Enrichment Analysis of Potential PTTG1 Targets

The potential target genes of PTTG1 were entered into the Database for Annotation, Visualization, and

Table 1 | The included databases with PTTG1 expression in PCa and non-PCa.

ID	Country	Platform	year	Number of samples	
				PCa	Non-PCa
GSE26910	Italy	GPL570	2011	6	6
GSE32448	USA	GPL570	2011	40	40
GSE32982	Finland	GPL570	2011	6	3
GSE38043	USA	GPL570	2012	3	3
GSE46602	Denmark	GPL570	2013	34	14
GSE69223	Germany	GPL570	2015	15	15
GSE104749	China	GPL570	2017	4	4
GSE27616	USA	GPL4133	2011	9	4
GSE12378	UK	GPL5175	2008	36	3
GSE72220	USA	GPL5175	2015	57	90
GSE94767	UK	GPL5175	2017	185	33
GSE28204	China	GPL6480	2011	4	4
GSE35988	USA	GPL6480	2012	76	12
GSE32571	Germany	GPL6947	2011	59	39
GSE134073	Germany	GPL11154	2020	56	8
GSE60329	Italy	GPL14550	2014	108	28
GSE73397	China	GPL20952	2015	3	3
GSE88808	USA	GPL22571	2016	49	49
GSE134051	Germany	GPL26898	2020	216	39
TCGA+GTEx	NA	NA	NA	499	152

NOX4, NADPH oxidase 4; PCa: prostate cancer; TCGA: The Cancer Genome Atlas; GTEx: The Genotype-Tissue Expression.

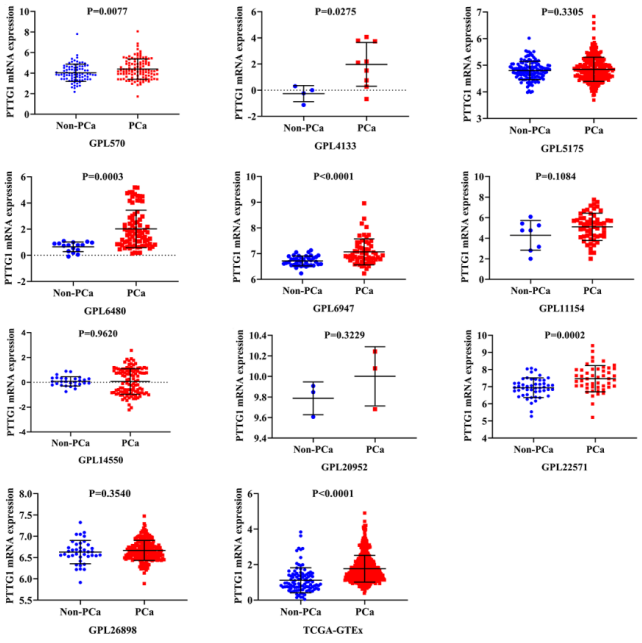

Figure 1 | The expression levels of PTTG1 in Non-PCa and PCa.

PTTG1, Pituitary tumor-transforming gene 1; PCa, prostate cancer.

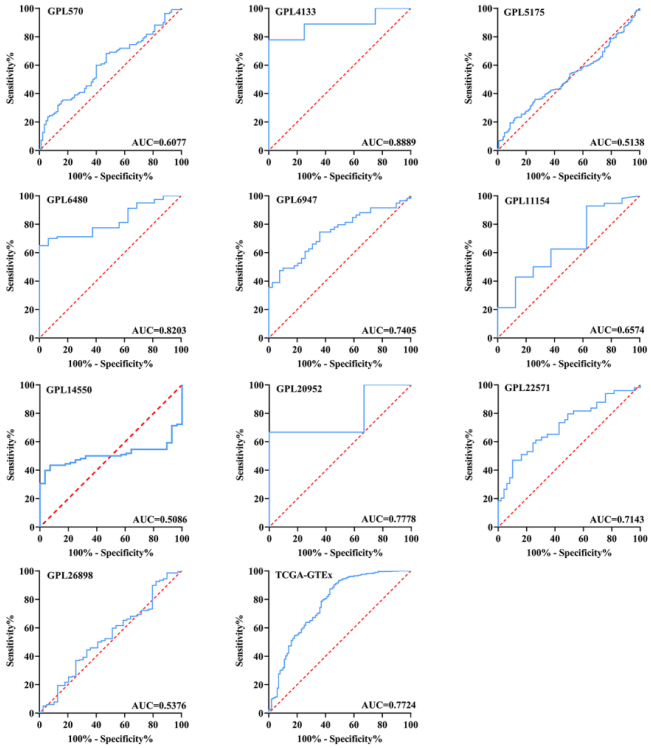

Figure 2 | ROC curves of PTTG1 in PCa.

PTTG1, Pituitary tumor-transforming gene 1; ROC, receiver operating characteristic; AUC, area under the curve;PCa, prostate cancer.

Table 2 | The means and standard deviations of PTTG1 expression values for PCa and non-PCa based on 11 studies.

Study	Sample type	PCa			Non-PCa		
		N	M	SD	N	M	SD
GPL570	Tissue	110	4.393	0.987	85	4.034	0.838
GPL4133	Tissue	9	1.971	1.676	4	-0.265	0.613
GPL5175	Tissue	278	4.847	0.455	126	4.802	0.345
GPL6480	Tissue	80	2.017	1.436	16	0.647	0.370
GPL6947	Tissue	59	7.068	0.504	39	6.717	0.192
GPL11154	Tissue	56	5.105	1.325	8	4.281	1.443
GPL14550	Tissue	108	0.072	1.029	28	0.081	0.379
GPL20952	Tissue	3	10.001	0.288	3	9.787	0.159
GPL22571	Tissue	49	7.466	0.767	49	6.939	0.575
GPL26898	Tissue	216	6.667	0.234	39	6.628	0.274
TCGA+GTEx	Tissue	499	1.767	0.754	152	1.120	0.708

NOX4, NADPH oxidase 4; PCa: prostate cancer; N: number; M: mean; SD: standard deviation; TCGA: The Cancer Genome Atlas; GTEx: The Genotype-Tissue Expression.

Integrated Discovery (DAVID) 6.8. for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis to predict potential signal pathways. The terms with p values < 0.05 were screened out. The PPI network was constructed by Search Tool for the Retrieval of Interacting Genes (STRING) and Cytoscape software 3.8.2. CCNA2, CCNB1 and CDK1 had the highest degree of connectivity in the PPI network and were further discussed.

2.4. Correlation Analysis Between PTTG1 and CCNA2, CCNB1 and CDK1

The expression data and clinical parameters of PTTG1 and CCNA2, CCNB1 and CDK1 in MPCa was obtained from public database. And then the correlation between miRNA-221-3p and CELSR3 was analyzed.

2.5. Immune-Related Analysis

The correlation modules supported by Tumor Immune Estimation Resource (TIMER) 2.0 and Gene Expression Profiling Interactive Analysis (GEPIA) were used to assess the abundance of immune infiltrates in PCa tumor and paired paracancerous tissue. We verified significantly correlated immune genes of PTTG1 through GEPIA database.

2.6. Statists Analysis

All statistical analysis were computed using SPSS 23.0. Student's t-tests were used to assess differences between different groups, mean ± standard deviation was represent values. In addition, receiver operating characteristic (ROC) curves analysis was conducted to evaluate sensitivity and specificity of above datasets. We also used Stata 14.0 to estimate standard mean difference (SMD) and summary ROCs (sROCs). Study was considered to be heterogeneous when $P < 0.05$ or $I^2 > 50\%$, and a random-effects model would be adopted, or else a fixed-effects model was applied. To probe the source of heterogeneity, subgroup and sensitivity analysis was applied. Begg's test and Egger's test were applied to uncover publication bias. Supplementary material 2 depicts our study workflow.

3. Result

3.1. Expression and Discrimination Potential of PTTG1 in PCa

First, a total of 19 qualified GEO chips and some TCGA+GTEx sequencing data were collected, including 1,467 prostate cancer samples and 549 normal samples, from which we extract the expression data of PTTG1. The expression of PTTG1 in each mRNA chip or section of TCGA+GTEx sequencing data was clarified through independent t-tests. According to collected data, PTTG1's mRNA was found to be upregulated in prostate cancer tissues compared to normal tissues (Table.2 and Fig.1), the ROC curves of all data was drawn (Fig. 2). The meta-analysis results indicated that PTTG1 was significantly upregu-

Table 3 | The means and standard deviations of PTTG1 expression values in LPCa and MPCa based on 10 studies

Study	Country	Year	Sample type	MPCa			LPCa		
				N	M	SD	N	M	SD
GSE3325	USA	2005	tissue	4	11.805	1.797	5	8.945	0.177
GSE32269	USA	2011	tissue	29	6.613	1.247	22	4.879	1.257
GSE77930	USA	2016	tissue	149	3.446	0.848	22	0.791	1.079
GSE6919	USA	2007	tissue	25	8.010	0.557	66	6.511	0.548
GSE116918	UK	2018	tissue	22	0.172	0.306	225	0.148	0.121
GSE68882	USA	2015	tissue	9	7.848	0.263	23	7.579	0.265
GSE55935	Norway	2014	tissue	8	9.371	1.339	38	6.281	0.902
GSE27616	USA	2011	tissue	4	13.937	1.367	5	-3.681	0.543
GSE35988	USA	2012	tissue	32	14.108	1.411	59	13.309	1.353
TCGA	NA	NA	tissue	21	2.506	0.890	478	1.733	0.722

CELSR3: cadherin EGF LAG seven-pass G-type receptor 3; LPCa: localized prostate cancer; MPCa: metastatic prostate cancer; N: number; M: mean; SD: standard deviation; TCGA: The Cancer Genome Atlas.

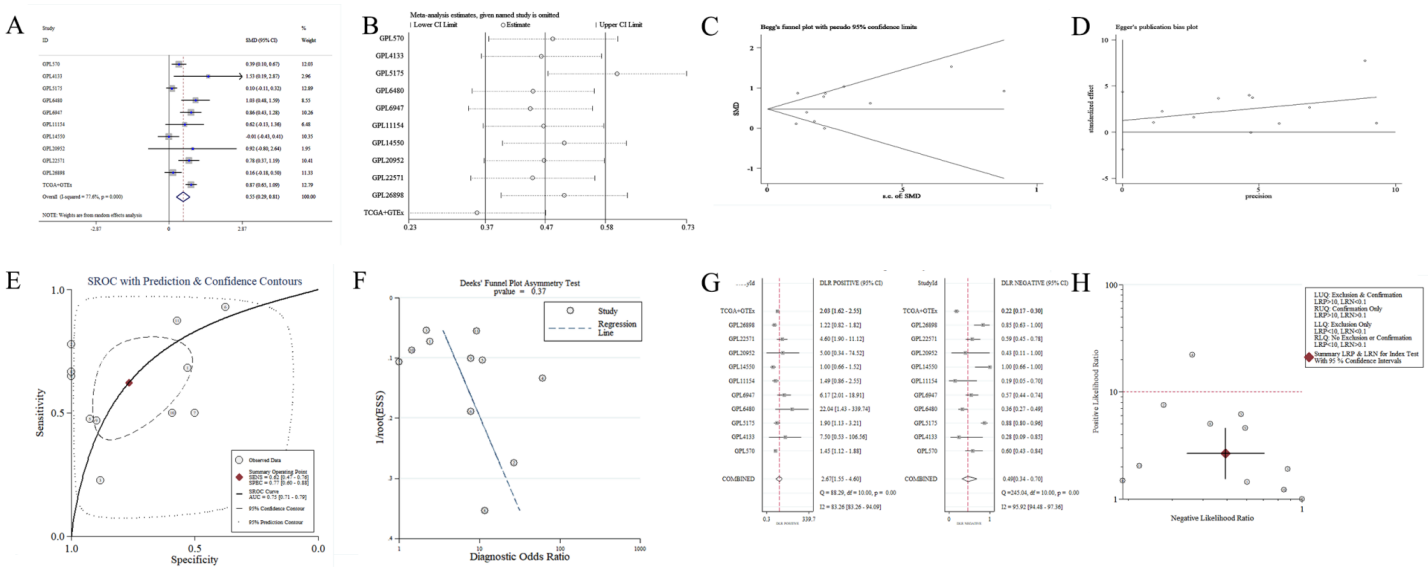

Figure 3 | The expression level and discrimination potential of PTTG1 in PCa.

(A) Forest plot showing the combined SMD of 0.55 (0.29 to 0.81), indicating that the expression of PTTG1 in PCa is higher compared to that of non-PCa. (B) Sensitivity analysis showing the combined SMD is stable. (C) Begg's test showing no publication bias ($p > 0.05$). (D) Egger's test showing no publication bias ($p > 0.05$). (E) sROC curve assessing the discrimination potential of PTTG1 in PCa. (F) Funnel chart showed no publication bias ($p = 0.37$). (G)The expression of PTTG1 is able to distinguish PCa and non-PCa. (H) Likelyhood ratio of PTTG1 in PCa. PTTG1, Pituitary tumor-transforming gene 1; SMD, standard mean deviation; CI, confidence interval; sROC, summary receiver operating characteristic; AUC, area under the curve; PCa, prostate cancer.

lated in PCa tissues with the SMD of the random-effect model being 0.55 (95CI%: 0.29, 0.83), and there was no publication bias (Fig. 3). We also did not find significant data heterogeneity (Fig.3). In addition, the AUC of sROC was 0.75 (95%CI: 0.71, 0.79), with pooled sensitivity and specificity being 0.62 and 0.77 which showed PTTG1 has a medium discrimination potential to discriminate PCa from normal cells (Fig. 3).

3.2. Expression and Discrimination Potential of PTTG1 in MPCa Based on Chips, TCGA Data

Subsequently, 303 metastatic prostate cancer (MPCa) samples and 943 localized prostate

cancer(LPCa) samples were performed to the follow-up research (Fig.4 and Fig.5). We found the expression of PTTG1 was clearly high expressed in MPCa tissues with the SMD of the random-effect model being 2.28 (95CI%: 1.38, 3.19) (Table 3 and Fig.6), the result was no publication bias (Fig.6). Similarly, we did not find the source of heterogeneity (Fig.6). After producing the ROC curves and constructing the sROC curve, we thought PTTG1 has an extremely high potential to be identified as a target to discriminate MPCa from LPCa cells, for the AUC of sROC was 0.97 (95%CI: 0.95, 0.98) (Fig.5 and Fig.6).

3.3. Identification of PTTG1 DCEGs in MPCa

After interacting 1054 CEGs with 742 DEGs, 314 genes were identified as PTTG1 DCEGs in MPCa totally.

3.4. Enrichment Analysis of PTTG1 DCEGs

Through GO analysis, PTTG1 DCEGs were significantly enriched in cellular response to cell division, nucleoplasm and protein. Moreover, KEGG analysis demonstrated PTTG1 DCEGs was significantly enriched in cell cycle (Fig.7). The Fig.8 presents PPI network of PTTG1 DCEGs. CCNA2, CCNB1 and CDK1 were identified as PTTG1 hubgenes in MPCa (Fig.9).

3.5. Association of PTTG1 Expression With Hubgenes and Clinical Parameters

As mentioned, CCNA2, CCNB1 and CDK1 were identified as hubgenes of PTTG1 in MPCa, the correlation between PTTG1 and hubgenes was showed on Fig.10. Interestingly, there were significant differences in the expression of M-stage and recurrence in the larger TCGA samples (Fig.11). As for other factors such as T, N stages of PCa or ages, there is no significant relevance to be found.

4. Discussion

Herein we extracted the mRNA microarray and RNA-Seq data with 325 MPCa samples and 724 LPCa samples from GEO and TCGA databases, and determined the PTTG1 expression level by estimating SMD and sROCS. Our analysis was observed that the PTTG1 expression level in MPCa was higher than that in LPCa. In addition, PTTG1 is also highly expressed in PCa. Moreover, enrichment analysis were also used to explore the potential molecular mecha-

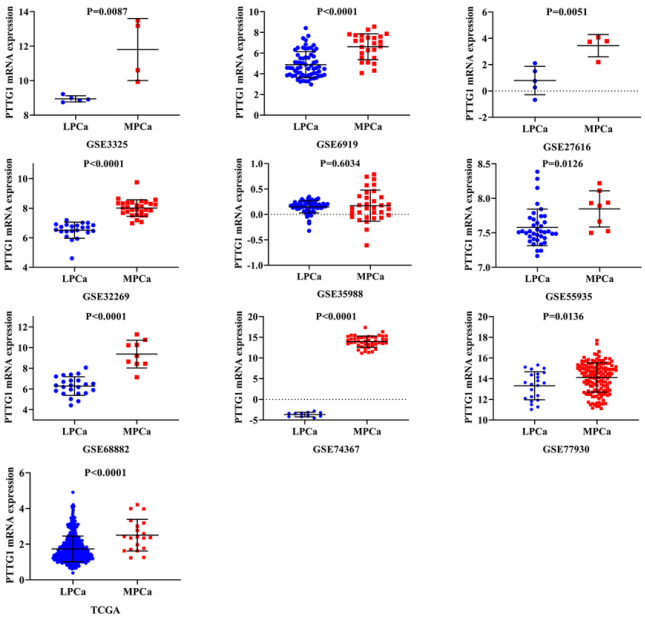

Figure 4 | The expression levels of PTTG1 in LPCa and MPCa

PTTG1, Pituitary tumor-transforming gene 1; MPCa, metastatic prostate cancer; LPCa, localized prostate cancer.

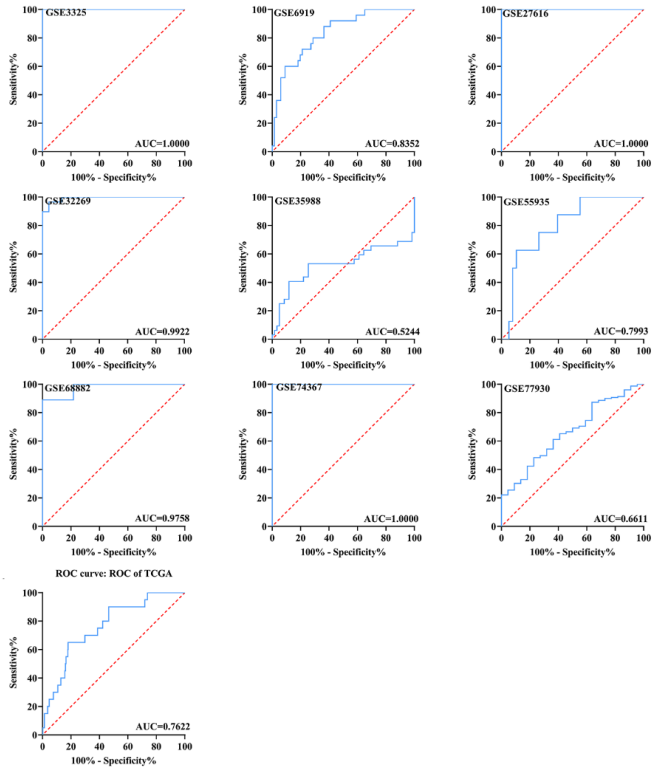

Figure 5 | ROC curves of PTTG1 in MPCa.

PTTG1, Pituitary tumor-transforming gene 1; ROC, receiver operating characteristic; AUC, area under the curve; MPCa, metastatic prostate cancer.

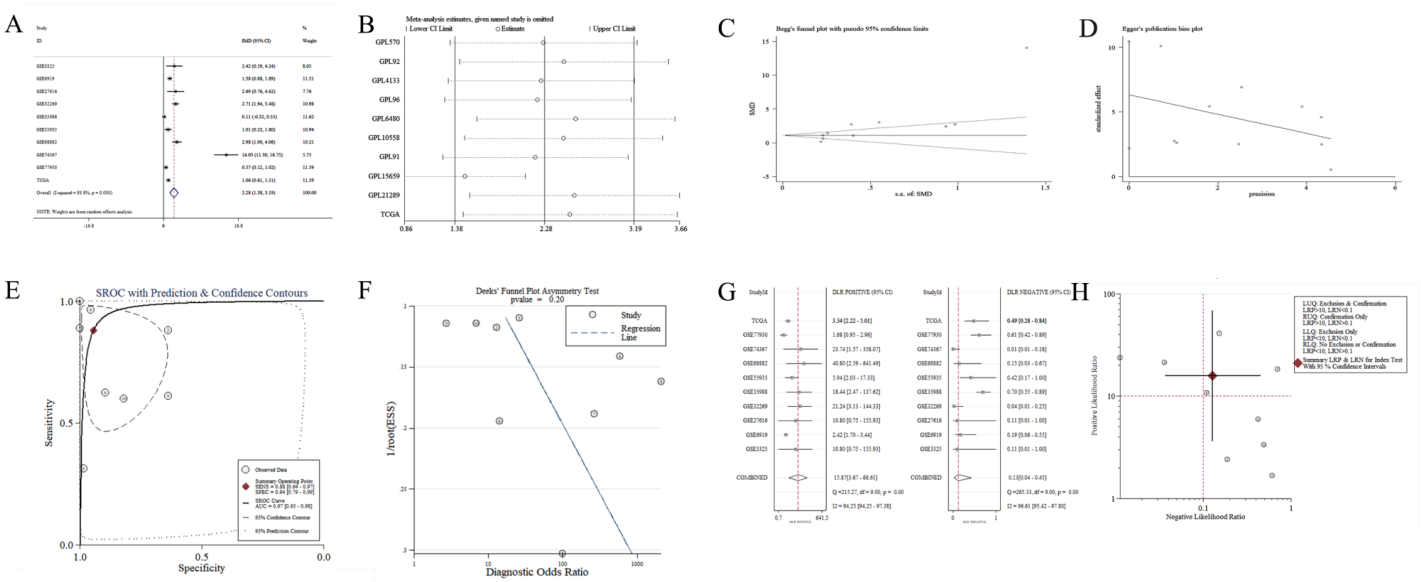

Figure 6 | The expression level and discrimination potential of PTTG1 in MPCa

(A) Forest plot showing the combined SMD of 2.28 (1.38 to 3.19), indicating that the expression of PTTG1 in MPCa is higher compared to that of LPCa. (B) Sensitivity analysis showing the combined SMD is stable. (C) Begg's test showing no publication bias ($p > 0.05$). (D) Egger's test showing no publication bias ($p > 0.05$). (E) sROC curve assessing the discrimination potential of PTTG1 in PCa. (F) Funnel chart showed no publication bias ($p = 0.20$). (G)The expression of PTTG1 is able to distinguish MPCa and LPCa. (H) Likelyhood ratio of PTTG1 in MPCa. PTTG1, Pituitary tumor-transforming gene 1; SMD, standard mean deviation; CI, confidence interval; sROC, summary receiver operating characteristic; AUC, area under the curve; PCa, prostate cancer.

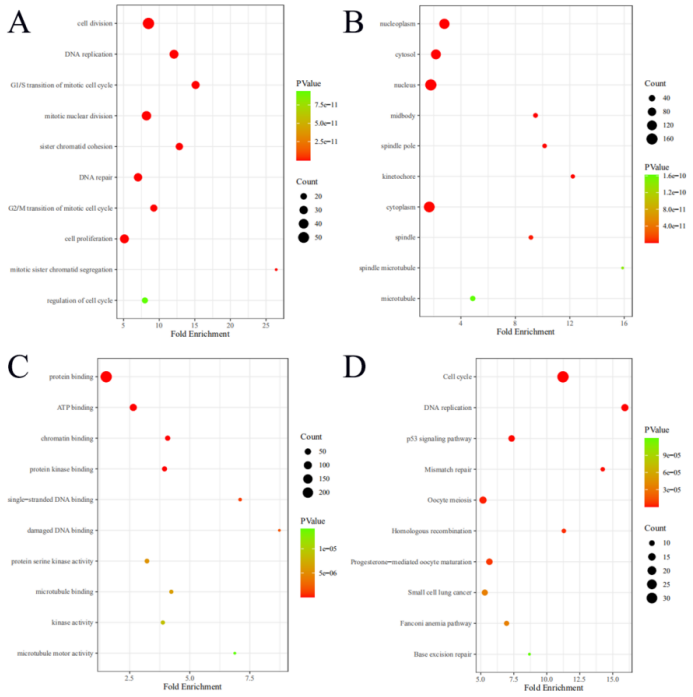

Figure 7 | GO and KEGG analysis based on PTTG1 related differentially expressed and co-expressed genes

(A) Biological process; (B) Cellular component; (C) Molecular function; (D) KEGG pathway. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; PTTG1, Pituitary tumor-transforming gene 1.

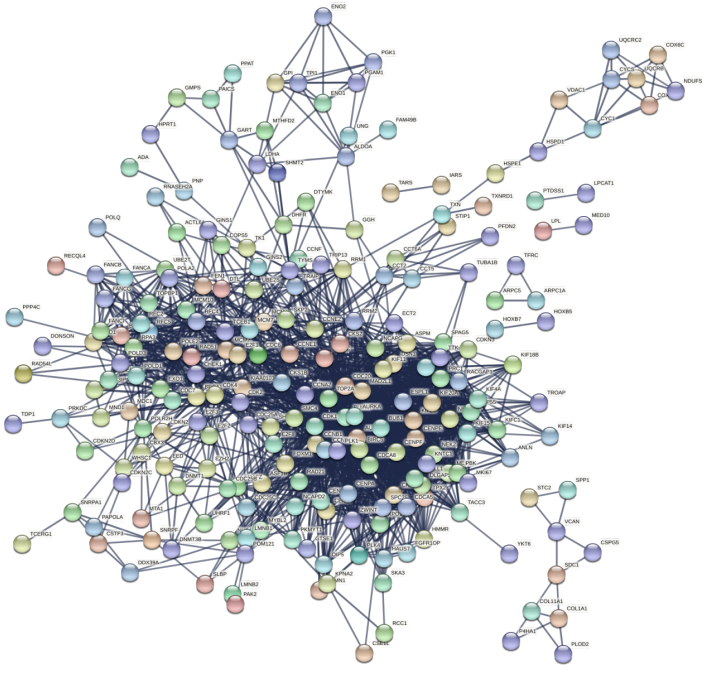

Figure 8 | PPI network analysis of PTTG1 target genes in MPCa

PPI, Protein-protein interaction; PTTG1, Pituitary tumor-transforming gene 1; MPCa, metastatic prostate cancer.

nisms and signal pathways of differential expressed PTTG1 in regulating of PCa metastasis.

As a multifunctional protein, PTTG1 plays an important role in cell transformation, repairing of DNA, and transcriptional regulation. Previous study have shown that overexpression of PTTG1 plays important roles in accelerating the division and differentiation of tumor cells and the formation of tumor cells [13]. Currently, many studies have shown that upregulated PTTG1 was associated with poor prognosis in many malignant tumors, including liver cancer, lung cancer, breast cancer and esophageal squamous cell carcinoma [14-18]. Through changing the transcriptional profile of siRNA-mediated LNCap-AI cells, Cao et al. found that downregulated PTTG1 could inhibit the invasions of PCa cells and promote their apoptosis [19]. After treating LNCap cells with paclitaxel, Castilla et al. believed that the overexpression of PTTG1 in PCa was a protective factor in tumor apoptosis [12]. Moreover, PTTG1 has also been shown to be associated with MPCa. Dai et al. predicted that PTTG1 was differential expressed in MPCa by bioinformatics method, which had been verified in small samples [20]. However, to our knowledge, no studies have proved the differences of PTTG1 expression levels between MPCa and LPCa. Fraune et al. concluded that the differential expression of PTTG1 in MPCa but the result was not statistically significant [21]. It is noteworthy that, for the first time, we reported the upregulation of PTTG1 expression is significantly associated with metastasis of PCa and have a high potential to discriminate MPCa from LPCa cells.

At present, the molecular mechanism of PTTG1 in MPCa transfer had never been reported. Lin et al. suggested that upregulated PTTG1 might upregulate the expression of MMP3 through the PI3K/Akt pathway, and then promoted PCa metastasis. A research managed by Zhang reported that androgen response elements on the PTTG1 promoter increased the affinity of androgen and the receptor, which promoted PCa metastasis [22]. Nevertheless, existed researches were not able to clarify the potential signal pathways that how PTTG1 influences the metastasis of PCa. Our enrichment results showed that the DCEGs of PTTG1 were significantly enriched in the cell cycle pathway. After searching the literature, we found some meaningful views. It has been reported that high PTTG1 expression probably promoted the proliferation of PCa cells by inhibiting TGFβ signaling mediated through activating the cell cycle inhibitor SMAD3, which was similar to our results [11]. Al-

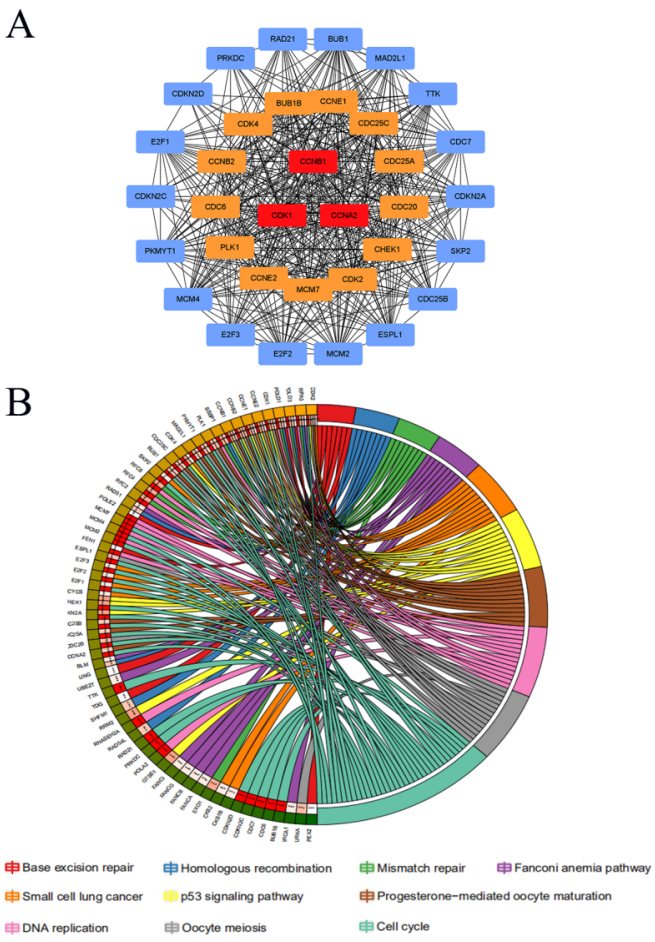

Figure 9 | PTTG1 related differentially expressed and co-expressed genes were significantly enriched in Cell cycle pathway; CCNA2, CCNB1 and CDK1 were identified as hubgenes in Cell cycle

(A) Ten signaling pathways were analyzed based on KEGG enrichment; (B) The 34 genes enriched in Cell cycle pathway of KEGG were further explored. PTTG1, Pituitary tumor-transforming gene 1;KEGG, Kyoto Encyclopedia of Genes and Genomes.

though there is no direct evidence that overexpressed PTTG1 promotes PCa metastasis by participating in the cell cycle pathway, many studies have reported that the occurrence and development of MPCa was correlated with the cell cycle pathway. Huang et al. found that Ganoderma tsugae ethanol extract was able to inhibit the cell cycle by inhibiting the expression of cyclin, and blocking the PI3K/Akt and MAPK/ERK signaling pathways, and then inhibiting the proliferation and metastasis of PCa cells [23]. Marques et al. indicated that Radium-223 had the ability to activate cell cycle checkpoints, which causing MPCa cell cycle arrest and promoting cell death [24]. Besides, existed studies also suggested that the cell cycle pathway was involved in the metastasis of a vari-

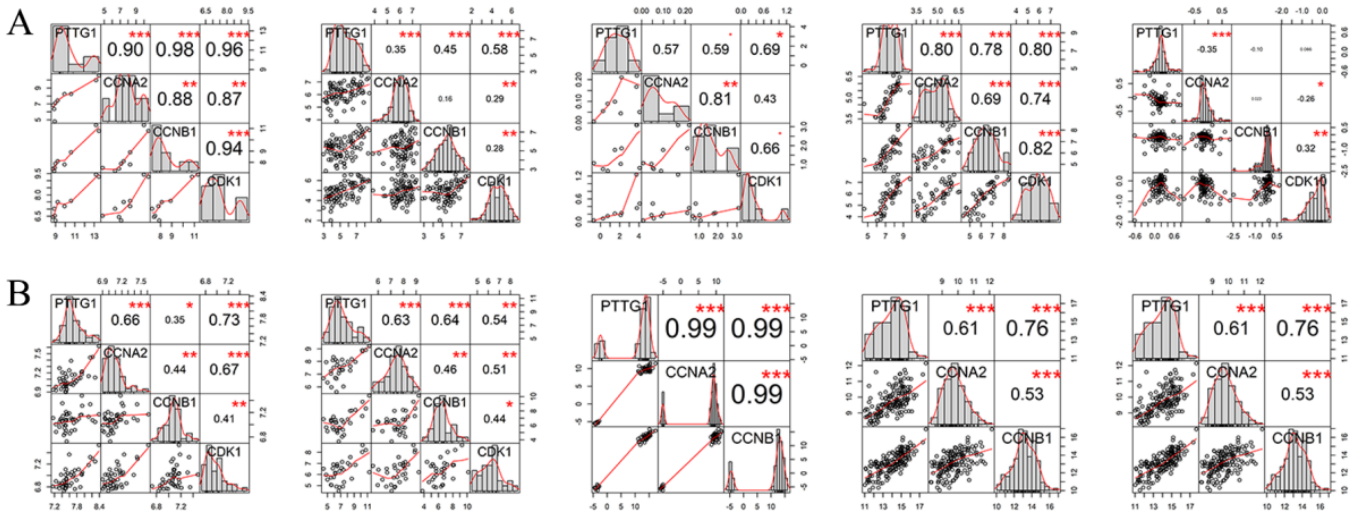

Figure 10 | The expression of PTTG1 is positively correlated with the expression of CCNA2, CCNB1 and CDK1

The number in bold represents Pearson correlation coefficient, and one or more " * " represent significant difference. A: GSE3325, GSE6919, GSE27616, GSE32269, GSE35988; B: GSE55935, GSE68882, GSE74367, GSE77930, TCGA.

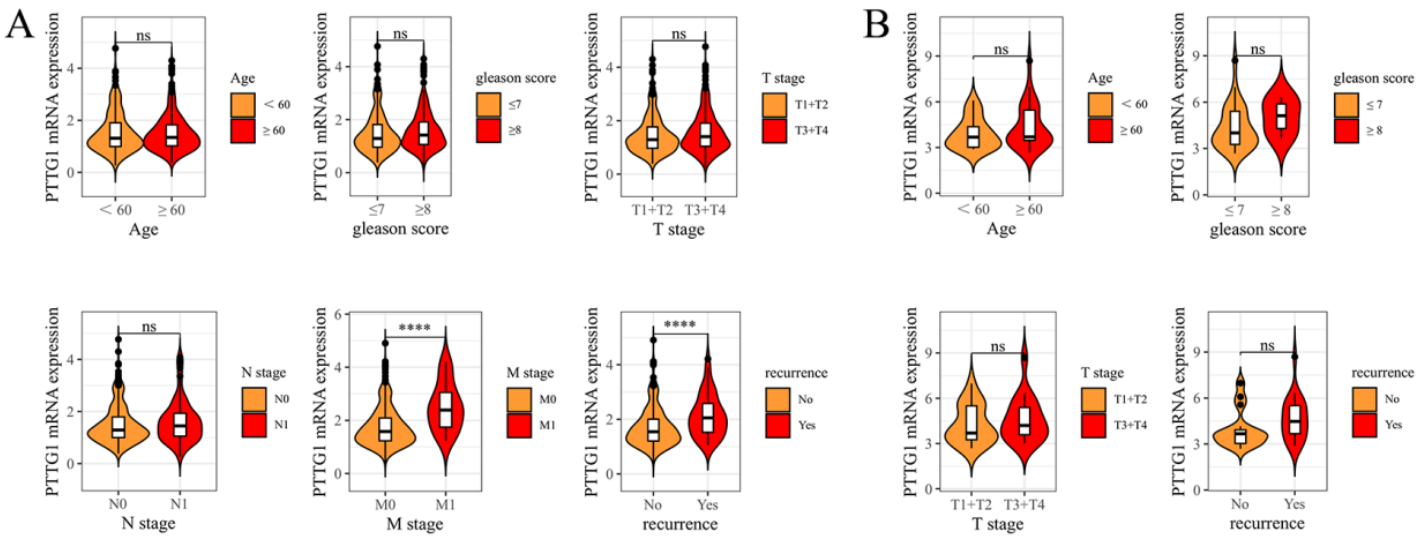

Figure 11 | Correlation analysis of clinical parameters

One or more " * " represent significant difference. (A) TCGA data set; (B) GSE46602 data set.

ety of cancers, such as hepatocellular carcinoma and breast cancer [25, 26]. However, whether the upregulated PTTG1 promotes the occurrence and development of MPCa through the cell cycle pathway still requires further in vitro and in vivo experiments.

By analyzing PTTG1 expression levels in PCa patients with different clinical parameters, the authors found that PTTG1 expression levels did not differ among patients with different ages, stages, relapses, and Gleason scores in datasets with a small sample. However, in larger sample sizes (data from TCGA), we found that PTTG1 is upregulated in patients with tumor metastatic and recurrence, which is very interesting. In the processes of literature retrieval, we did not find any studies that reported the relationship between the expression level of PTTG1 and patients with different clinical parameters. Our results provides a new research idea and need to be verified with more samples in the future.

This study also has some limitations: (1) a significant heterogeneity was observed in this study. Due to insufficient sample size and sample information, we

were unable to find the source of heterogeneity, a random-effects model was applied. Further validation of our findings is required in a larger clinical cohort. (2) all the samples of MPCa herein were collected from tissues, thus the expression of PTTG1 in the body fluids of MPCa should be estimated to verify their diagnostic value. (3) the functions of PTTG1 and three identified hubgenes in MPCa need to be further validated in vivo and in vitro.

In conclusion, by analyzing samples from public databases, we proposed for the first time that PTTG1 is upregulated in MPCa and plays an important role in the occurrence and development of MPCa.

Reference

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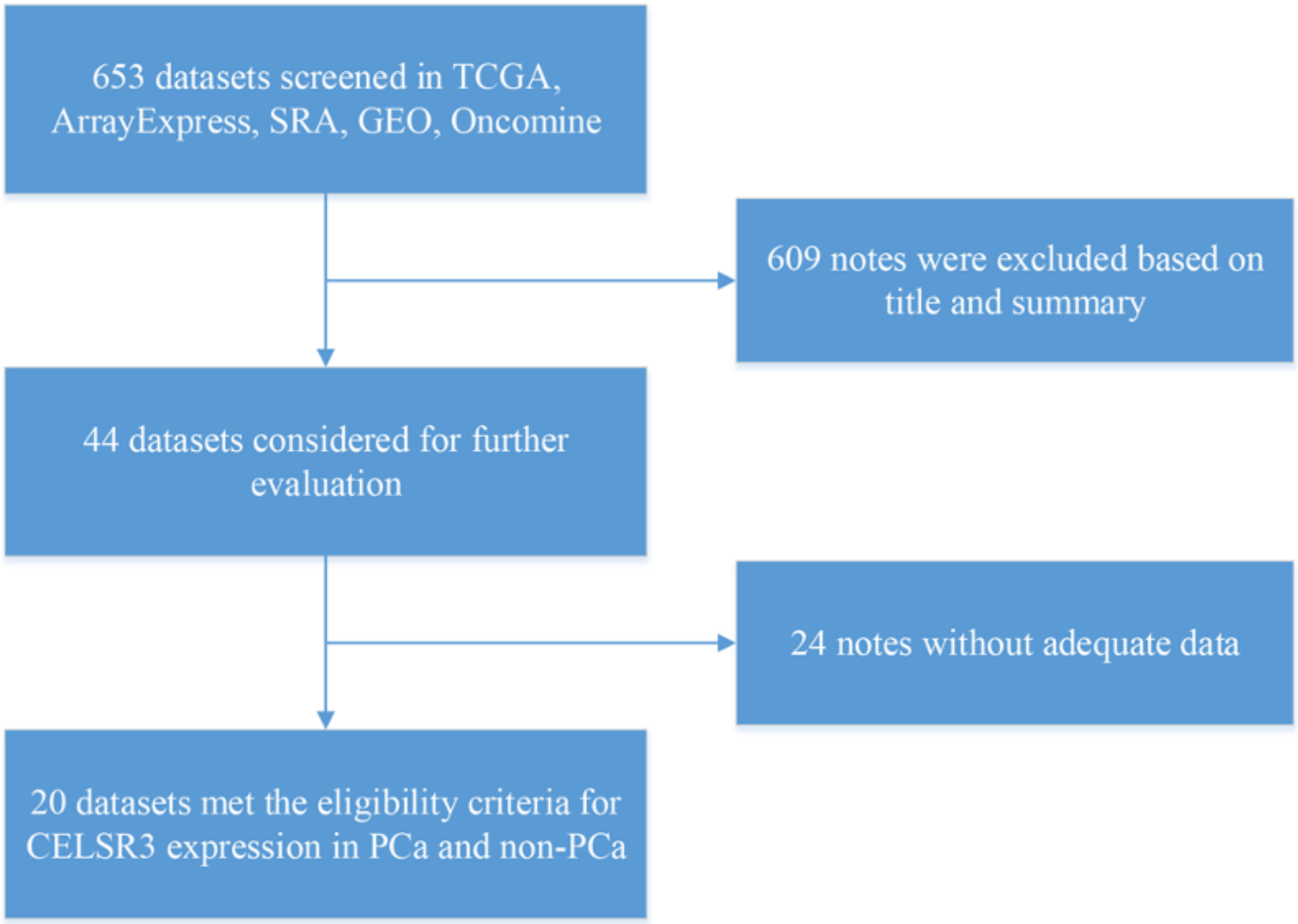
Supplementary material 1 | The process of data screening



Supplementary material 2 | The study workflow