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Dysregulation of PVT1 and NEAT1 lncRNAs in pituitary adenomas

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ABSTRACT

Pituitary adenomas are slow-growing tumors originated from the anterior part of pituitary gland. These tumors are associated with dysregulation of a number of long non-coding RNAs (lncRNAs). PVT1, TUG1, MALAT1, NEAT1 and GAS5 are among lncRNAs with important roles in the regulation of cell proliferation, cell apoptosis, cell differentiation and cell cycle transition. In the current study, we assessed expression levels of PVT1, TUG1, MALAT1, NEAT1 and GAS5 in the pituitary adenoma samples compared with adjacent non-cancerous samples to find their relevance with this type of tumors and their potential as diagnostic markers in these tumors. Expression of NEAT1 was significantly higher in total adenoma tissues (Expression ratio (95% CI)= 7.06 (2.31–21.4), P value= 0.02) and in non-functioning pituitary adenoma (NFPA) samples (Expression ratio (95% CI)= 8.5 (2.17–33.12), P value= 0.04) compared with corresponding controls. Although both lncRNAs had appropriate sensitivity values for discrimination of NFPAs from adjacent non-cancerous tissues (0.84 and 0.90 for PVT1 and NEAT1, respectively), the calculated AUC values were not adequate for either lncRNAs (0.63 ± 0.04 and 0.58 ± 0.04 for PVT1 and NEAT1, respectively). Therefore, NEAT1 and PVT1 lncRNAs are dysregulated in NFPA. The current study suggests the role of NEAT1 and PVT1 in the pathogenesis of NFPA.

1. Introduction

Pituitary adenomas are slow-growing tumors originated from the anterior part of pituitary gland [13]. They can be classified to their size to microadenoma (<10 mm), macroadenoma (>10 mm), and giant tumors (>40 mm) [13]. Alternatively, secreting pituitary adenomas are classified based on the cell of origin to somatotroph, corticotroph, lactotroph, and thyrotroph adenomas [12]. Another subgroup of adenomas include non-functioning pituitary adenomas (NFPA) which are frequently associated with mass effect problems, accounting for optic chiasm compression or deficiencies in hormone secretion due to compression of normal cells of anterior pituitary gland [1].

Recent genomic and transcriptomic analyses have identified significant alterations in pituitary adenoma samples. For instance, lactotroph adenomas have exhibited extensive genomic copy number amplifications [2]. Besides, high copy number variations in this type of adenomas have been associated with elevation in prolactin production, drug resistance and proliferative capacity [2]. Moreover, integration of DNA methylation and mRNA signature has resulted in identification of important genes which are involved in the pathoetiology of invasive NFPAs [3].

A group of transcripts which have recently attained attention of researchers are long non-coding RNAs (lncRNAs) [4]. A recent study has identified tens of differentially expressed lncRNAs in invasive versus paired noninvasive pituitary adenomas. Notably, the majority of these transcripts have been found to be involved in the posttranslational

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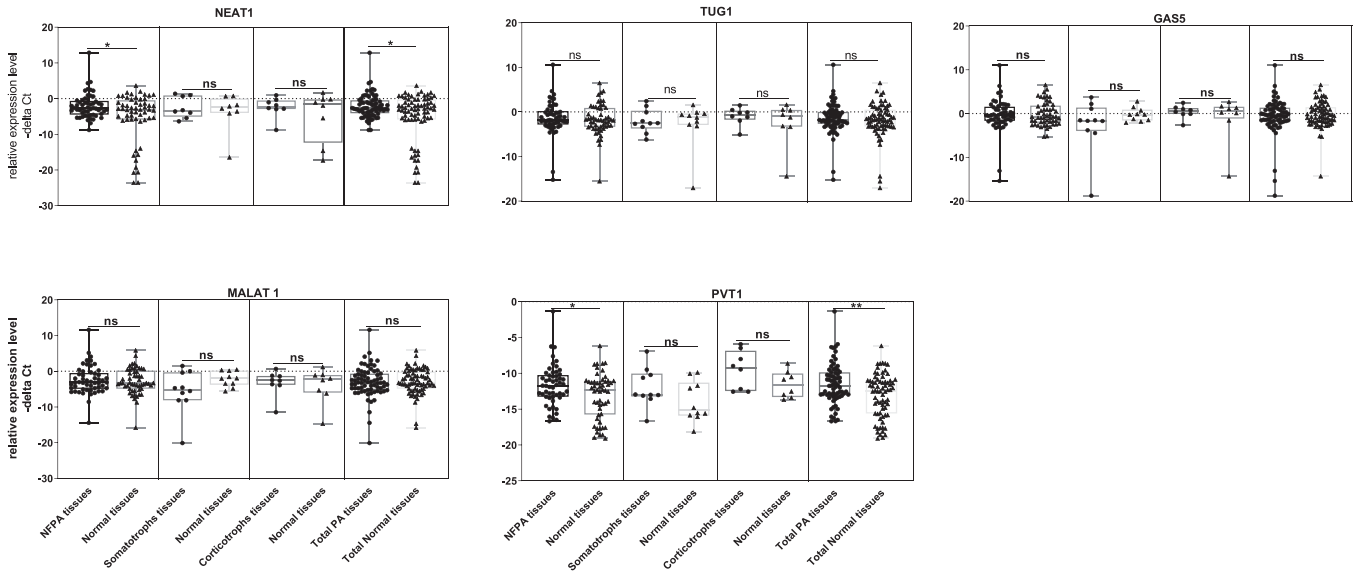

Fig. 1. Relative expression levels of lncRNAs s in three different pituitary adenoma tissue subtypes and total pituitary adenoma tissues relative to the adjacent normal tissues as described by –delta Ct values (Ct Housekeeping gene- Ct Target gene). – delta Ct Data were plotted as box and whisker plots. Data was analyzed using the Wilcoxon rank-sum test or paired t test, and $P < 0.05$ was considered as statistically significant. Asterisks indicate significant difference between two mentioned groups (*P value < 0.05, ns; non-significant).

Table 1
Results of expression study of five lncRNAs in three different pituitary adenoma tissue subtypes and total pituitary adenomas compared with the relevant adjacent normal tissues. The expression ratio of each gene is shown as mean and 95% confidence interval and SEM.

Studied genes	Tumor subtypes	Expression ratio (95% CI)	Number of pairs	SEM	P Value
NEAT1	NFPA	8.5 (2.17–33.12)	56	0.98	**0.04**
	Somatotrophs	2.36 (0.13–0.42)	8	1.77	0.94
	Corticotrophs	5.5 (0.18–171)	8	2.1	0.46
	Total PA	7.06 (2.31–21.4)	73	0.8	**0.02**
MALAT1	NFPA	1.23 (0.47–3.2)	53	0.69	0.88
	Somatotrophs	0.1 (0.006–1.5)	10	1.77	0.08
	Corticotrophs	1.6 (0.28–9.5)	8	1.08	0.54
	Total PA	0.9 (0.38–2.04)	71	0.6	0.69
TUG1	NFPA	1.26 (0.5–3.22)	53	0.67	0.49
	Somatotrophs	1.54 (0.21–11)	10	1.25	> 0.99
	Corticotrophs	2.98 (0.35–25)	8	1.3	0.25
	Total PA	1.43 (0.67–3)	71	0.54	0.34
PVT1	NFPA	2.78 (1.3–5.89)	53	0.54	**0.012**
	Somatotrophs	4 (0.38–42)	10	1.5	0.2
	Corticotrophs	4 (0.59–28)	8	1.18	0.12
	Total PA	3 (1.59–5.85)	71	0.47	**0.002**
GAS5	NFPA	0.89 (0.36–2.18)	53	0.64	0.8
	Somatotrophs	0.18 (0.01–2.9)	10	1.75	0.27
	Corticotrophs	2.8 (0.22–35)	8	1.54	0.74
	Total PA	0.81 (0.37–1.8)	71		0.96

modifications of proteins [14].

PVT1, TUG1, MALAT1, NEAT1 and GAS5 are among lncRNAs with important roles in the regulation of cell proliferation, cell apoptosis, cell differentiation and cell cycle transition [5–8,18]. Based on these important functions in the regulation of cell hemostasis, they might be involved in the pathogenesis of pituitary adenomas as a manifestation of abnormal cell proliferation/apoptosis. However, the role of these lncRNAs in pituitary adenomas has not been vastly investigated. In the current study, we assessed expression levels of PVT1, TUG1, MALAT1, NEAT1 and GAS5 in the pituitary adenoma samples compared with adjacent non-cancerous samples to find their relevance with this type of tumors and their potential as diagnostic markers in these tumors.

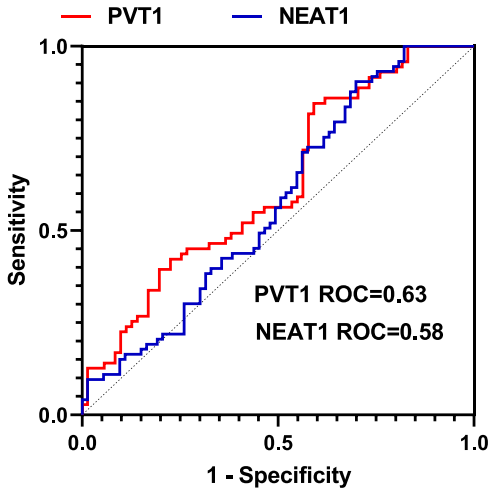

Fig. 2. ROC curve of PVT1 and NEAT1 lncRNAs for discrimination of NFPA tumors from adjacent normal tissues. AUC indicates area under the ROC curve.

2. Materials and methods

2.1. Patients

Expression assays were conducted on pituitary adenoma samples and paired normal samples. Tissue samples were excised during surgery from patients admitted to hospital affiliated to Shahid Beheshti University of Medical Sciences during 2021–2022. None of them had received any chemo/radiotherapy before tumor excision. The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences. Informed consent forms were obtained from all participants.

2.2. Expression assays

Total RNA was extracted using RNJia extraction kit (RN983006, Roje

Table 2
Results of ROC curve analysis for PVT1 and NEAT1 lncRNAs for discrimination of NFPA tumors genes from adjacent normal tissues.

PVT1				NEAT1			
AUC±SD	Sensitivity	Specificity	P Value	AUC±SD	Sensitivity	Specificity	P Value
0.63 ± 0.04	0.84	0.41	0.01	0.58 ± 0.04	0.90	0.30	0.11

Table 3
Spearman's correlations between lncRNAs among the total pituitary adenoma tumor tissues and adjacent normal tissues.

	MALAT1		TUG1		PVT1		GAS5	
	adjacent	Tumor	adjacent	Tumor	adjacent	Tumor	adjacent	Tumor
NEAT1	0.78**	0.9**	0.73**	0.8**	0.25*	0.39**	0.68**	0.95**
MALAT1			0.89**	0.87**	0.07	0.3*	0.85**	0.87**
TUG1					0.21	0.33*	0.83**	0.8**
PVT1							0.15	0.37*

* $p < 0.05$

Technologies Company, Iran). cDNA was produced using AddScript cDNA Synthesis Kit (Cat. No. 22701, ADDBIO Company, South Korea). RT-qPCR was conducted using RealQ Plus 2x Master Mix Green with high ROX purchased (AMPLIQON, Denmark), and primers provided by the METABION Company (Germany). Table S1 shows detailed features of primers.

2.3. Statistical methods

Analyses were performed using SPSS v.22.0 (SPSS Inc., Chicago, IL). Graphics were created using GraphPad Prism v.9.0 (GraphPad Software, La Jolla California USA). Expression levels of five lncRNAs, namely NEAT1, MALAT1, PVT1, TUG1 and GAS5 were compared between pituitary adenoma tissues and adjacent normal tissues. Expression levels in each sample were calculated using the Efficiency adjusted Ct of normalizer gene (B2M) - Efficiency adjusted Ct of target gene method (comparative –delta Ct method). The normal/gaussian distribution of the values was assessed by the Shapiro-wilk test. Wilcoxon matched-pairs signed rank test or paired t test was used to identify differentially expressed genes between the adenoma tissues and adjacent normal tissues.

The correlation of expression of studied genes was measured using Spearman correlation coefficient. Mann-Whitney test and Kruskal–Wallis one-way ANOVA were used for comparing gene expression levels between different groups of patients. Chi-square test was used to find out the association between expression of lncRNAs and clinicopathological factors.

The receiver operating characteristic (ROC) curve was illustrated by the GraphPad Prism v.9 software. The p value < 0.05 was considered as significant.

3. Results

3.1. General data of study participants

Totally, 55 patients with NFPA, 10 patients with somatotroph adenoma, 8 patients with corticotroph adenoma and one patient with lactotroph adenoma were included in this study [15]. Table S2 shows the general data of study participants.

3.2. Expression assays

Fig. 1 shows relative expressions of mentioned lncRNAs in total adenoma tissues and three subtypes (NFPA, somatotroph and corticotroph) tumors compared with adjacent tissues.

Expression of NEAT1 was significantly higher in total adenoma tissues (Expression ratio (95% CI)= 7.06 (2.31–21.4), P value= 0.02) and in NFPA samples (Expression ratio (95% CI)= 8.5 (2.17–33.12), P value= 0.04) compared with corresponding controls. Similarly, PVT1 was shown to be over-expressed in both total adenoma tissues (Expression ratio (95% CI)= 3 (1.59–5.85), P value= 0.002) and in NFPA samples (Expression ratio (95% CI)= 2.78 (1.3–5.89), P value= 0.012) compared with paired controls. Expressions of other lncRNAs were not different between adenoma and adjacent tissues (Table 1).

Then, we assessed the diagnostic power of PVT1 and NEAT1 in separation of NFPA samples from adjacent tissues (Fig. 2 and Table 2).

Although both lncRNAs had appropriate sensitivity values for discrimination of NFPAs from adjacent non-cancerous tissues (0.84 and 0.90 for PVT1 and NEAT1, respectively), the calculated AUC values were not adequate for either lncRNAs (0.63 ± 0.04 and 0.58 ± 0.04 for PVT1 and NEAT1, respectively).

We also determined the correlations between expression levels of lncRNAs in adenoma tissues as well as adjacent non-cancerous tissues (Table 3). The highest correlation coefficient was between NEAT1 and PVT1 (correlation coefficient=0.95) and between PVT1 and MALAT1 (correlation coefficient=0.95) in adenoma tissues.

** $p < 0.001$.

There was a significant positive association between age of NFPA patients and drug administration history ($\chi2 = 6.25$, p value= 0.012) and invasiveness of NFPA ($\chi2 = 4$, p value= 0.047). Moreover, a significant positive association was detected between disease duration and CSF leak ($\chi2 = 16.1$, p value=0.003). Finally, there was a significant positive association between tumor size and Knosp classification ($\chi2 = 15.57$, p value= 0.004) and invasiveness of NFPA ($\chi2 = 7.6$, p value= 0.02). However, expression of none of lncRNAs was different between different groups of NFPA patients (Table 4).

4. Discussion

Expression levels of lncRNAs has been assessed in pituitary adenomas in previous studies leading to identification of association between lncRNA profile and progression of this type of tumors [16]. Moreover, a number of lncRNAs have been shown to be associated with the recurrence of NFPAs [9]. In the current study, we assessed expression of five lncRNAs in pituitary adenoma tissues and adjacent non-tumoral samples and reported up-regulation of NEAT1 and PVT1 in both total adenoma tissues and in NFPA samples compared with paired controls. Expressions of other lncRNAs were not different between adenoma and adjacent tissues. A previous study has reported over-expression of PVT1 pituitary adenoma tissues and cancer cell lines [17]. This lncRNA has been shown to exert an oncogenic role in these cells, since its silencing has led to suppression of cell migration and proliferation. Mechanistically, the oncogenic role of PVT1 is mediated through regulation of Wnt/β-catenin signaling [17]. Thus, the observed

Table 4
Expression levels of lncRNAs in NFPA patients based on clinicopathologic factors. Mann-Whitney test and Kruskal–Wallis one-way ANOVA were used for comparing gene expression levels between different groups of patients.

Parameters	Subclasses	Number of patients (%)	Relative expression level of NEAT1 (mean±SD)	P-value	Relative expression level of MALAT1 (mean ±SD)	P-value	Relative expression level of TUG1 (mean ±SD)	P-value	Relative expression level of PVT1 (mean ±SD)	P-value	Relative expression level of GAS5 (mean ±SD)	P-value
Tumor subtypes	NFPA	41	-2 ± 0.48	0.96	-2.3 ± 0.5	0.96	-1.2 ± 0.5	0.72	-11.7 ± 0.45	0.3	0.23 ± 0.35	0.77
	NFPA +CD+AP	13	-0.96 ± 1.5		-1.2 ± 1.48		0.15 ± 1.24		-11 ± 0.76		1.16 ± 1.15	
Age	22–48	30	-1.4 ± 0.73	0.44	-1.71 ± 0.72	0.43	-0.39 ± 0.58	0.31	-11.6 ± 0.51	0.85	0.48 ± 0.55	0.95
	49–77	25	-2.15 ± 0.72		-2.46 ± 0.76		-1.5 ± 0.8		-11.4 ± 0.61		0.44 ± 0.54	
Gender	Female	13	-2.7 ± 0.78	0.33	-3.2 ± 0.81	0.32	-2.64 ± 1.17	0.16	-11.9 ± 0.58	0.67	-0.31 ± 0.55	0.42
	Male	42	-1.44 ± 0.62		-1.6 ± 0.63		-0.35 ± 0.5		-11.4 ± 0.48		0.71 ± 0.47	
Disease duration	< 1 y	28	-2.1 ± 0.72	0.5	-2.36 ± 0.77	0.56	-1.4 ± 0.76	0.58	-11.7 ± 0.6	0.15	0.27 ± 0.54	0.69
	1 y	13	-0.75 ± 1.3		-1.26 ± 1.2		0.02 ± 1.08		-10.5 ± 0.82		1.17 ± 0.98	
	> =2 y	14	-2 ± 0.66		-2.18 ± 0.6		-0.79 ± 0.54		-12.2 ± 0.47		0.14 ± 0.52	
Tumor Size (cm)	< 500 mm^2	17	-2.24 ± 0.91	0.5	-2.57 ± 0.97	0.47	-1 ± 0.75	0.61	-11.2 ± 0.86	0.88	0.31 ± 0.71	0.75
	500–800 mm^2	19	-1.9 ± 0.8		-2.16 ± 0.82		-0.56 ± 0.61		-11.8 ± 0.58		0.39 ± 0.6	
	> 800 mm^2	19	-1.17 ± 0.98		-1.47 ± 0.95		-1.2 ± 1.12		-11.63 ± 0.63		0.66 ± 0.73	
CSF leak	No	29	-1.7 ± 0.77	0.84	-2 ± 0.78	0.85	-0.66 ± 0.61	0.95	-10.9 ± 0.62	0.21	0.53 ± 0.59	0.72
	Low flow	11	-1.8 ± 1.2		-1.9 ± 1.3		-0.61 ± 1		-12.2 ± 0.61		0.33 ± 0.91	
	High flow	15	-1.5 ± 0.82		-1.9 ± 0.79		-1.5 ± 1/2		-12.1 ± 0.67		0.7 ± 0.58	
Knosp classification	1	13	-2.78 ± 0.56	0.2	-3.18 ± 0.58	0.14	-1.34 ± 0.48	0.63	-12.2 ± 0.61	0.4	0.15 ± 0.43	0.3
	2	21	-2.35 ± 0.78		-2.67 ± 0.83		-0.98 ± 0.63		-11.1 ± 0.46		-0.1 ± 0.59	
	3	21	-0.53 ± 0.99		-0.71 ± 0.96		-0.58 ± 1.1		-11.5 ± 0.84		1.24 ± 0.76	
Invasiveness	invasive	9	-1.7 ± 0.58	0.98	-2 ± 0.59	0.93	-0.54 ± 0.46	0.39	-11.1 ± 0.42	**0.01**	0.48 ± 0.44	0.72
	non invasive	46	-2 ± 1.1		-2.19 ± 1.1		-2.7 ± 1.7		-13.6 ± 0.7		0.34 ± 0.72	
Drug history	Yes	11	-2.15 ± 0.59	0.06	-2.43 ± 0.59	0.062	-0.88 ± 0.47	0.28	-11.8 ± 0.38	0.13	0.19 ± 0.43	0.09
	No	44	-0.27 ± 0.96		-0.57 ± 1		-1.05 ± 1.57		-10.22 ± 1.12		1.5 ± 0.8	

up-regulation of PVT1 in pituitary adenoma samples in the current study is in line with the reported oncogenic role for this lncRNA in this type of tumors.

NEAT1 has been shown to act as an miR-148b-3p sponge to affect expression of ROCK1 [11]. Notably, miR-148b is among miRNAs that regulate proliferation and invasion of pituitary adenomas cells [10]. Therefore, the sponging effect of NEAT1 on miR-148b might be a possible mechanism for involvement of NEAT1 in the pathogenesis of pituitary adenomas.

Although both NEAT1 and PVT1 had appropriate sensitivity values for discrimination of NFPAs from adjacent non-cancerous tissues, the calculated AUC values were not adequate for either lncRNAs. Thus, these lncRNAs cannot be suggested as putative markers for this type of tumor. Therefore, future studies should find appropriate lncRNAs for this purpose.

We also determined the correlations between expression levels of lncRNAs in adenoma tissues as well as adjacent non-cancerous tissues. The highest correlation coefficient was between NEAT1 and PVT1 and between PVT1 and MALAT1 in adenoma tissues. The intensified level of correlation between these lncRNAs in tumoral tissues compared with normal tissues suggests the importance of interactions between these lncRNAs in the pathogenesis of pituitary tumors.

Although expression of none of lncRNAs was different between different groups of NFPA patients, there was a significant positive association between age of NFPA patients and drug administration history as well as invasiveness of NFPA. Moreover, a significant positive association was detected between disease duration and CSF leak. Finally, there was a significant positive association between tumor size and Knosp classification as well as invasiveness of NFPA. Taken together, the current study suggests the role of NEAT1 and PVT1 in the pathogenesis of NFPA. We suggest accomplishment of functional studies to evaluate the role of these lncRNAs in pituitary adenoma.

Ethics approval and consent to Participant

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent forms were obtained from all study participants. Informed consent forms were obtained from all study participants. The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences. All methods were performed in accordance with the relevant guidelines and regulations.

Consent of publication

Not applicable.

Funding

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CRediT authorship contribution statement

SGF wrote the draft and revised it. MT and GS designed and supervised the study. SE analyzed the data. FA, BMH, NAD and AN performed the experiment and data collection. All the authors read and approved the submitted version.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

Data Availability

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prp.2023.154573.

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