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Functional Insights into The Role of LncRNA HOXA11-AS in Pancreatic Adenocarcinoma

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ABSTRACT

Background: Pancreatic adenocarcinoma is one of the most lethal cancer charachterized by extremely poor prognosis and diagnosis. lncRNAs, which are transcripts exceeding 200 nucleotides, have recently emerged as new drivers of tumorigenesis.

Objective: This study aimed to demonstrate the relation of the long non-coding RNA (lncRNA)—HOXA11-AS,—with the risk, pathological characteristics and survival rate of pancreatic adenocarcinoma.

Subjects and Methods: A total of 150 people included in this study: 75 pancreatic adenocarcinoma patients and 75 healthy individuals. Carcinoembryonic antigen (CEA) and CA19-9 were assayed using ELISA, while real-time PCR has been used for determination of the level of LncRNA *HOXA11-AS* (Homeobox (HOX) A11 antisense).

Results: Compared to controls, pancreatic adenocarcinoma patients had statistically significant higher levels of *HOXA11-As* expression. Nearly half of cases were still alive at the end of the research, which proves that the disease has high death rate. Patients with low *HOXA11-AS* expression survived longer (18.0 months) on average compared to those with high expression (13.04 months).

Conclusion: lncRNA *HOXA11-AS* may be utilized as diagnostic biomarker for pancreatic adenocarcinoma. Pancreatic adenocarcinoma has poor survival . CEA and CA19-9 are also significantly elevated in pancreatic adenocarcinoma.

Keywords: Carbohydrate antigen19-9; Carcinoembryonic antigen; Pancreatic cancer; pancreatic adenocarcinoma; Long non coding RNA.

INTRODUCTION

Pancreatic cancer (PC) is among the most lethal cancer types, with rising death and frequency rates. The frequency of pancreatic cancer has risen by one percent annually, while the mortality rate has elevated by 0.2 percent annually since 2000. PC is the 3rd leading etiology of mortality in 2024 and is predicted to become the 2nd most prevalent etiology of cancer-related mortality by 2040 in the United States. Moreover, about fifty percent of pancreatic cancer cases are identified at an advanced stage [1]. In Egypt, it represents the eleventh most common cancer representing 2.2 % of all cancers and the eighth most common cause of death [2].

Pancreatic ductal adenocarcinoma (PDAC) is an extremely deadly type of PC, which represents above ninety percent of pancreatic cancer. When the exocrine duct cells, which line the pancreas become malignant, the cancer is referred to as PDAC. PDAC accounts for 2% of all tumor cases [3].

Numerous risk factors for pancreatic ductal adenocarcinoma were recognized, like demographic features (e.g., black race, advancing age and male gender), environmental and lifestyle factors (e.g., history of tobacco use and obesity), genetic factors (e.g., hereditary pancreatic cancer genes and certain genetic cancer syndromes), and comorbidities (e.g., chronic pancreatitis, diabetes mellitus, and Helicobacter pylori infection) [4]. Consequently, it is essential to exclude the molecular events included in the development and initiation of PC. Long non coding RNA are a large and greatly diverse class of non coding RNAs exceeding 200 nucleotides in length, and hve been shown to ply a role in different malignancies, involving pancreatic cancer [5].

Non-coding RNAs are functional RNA molecules that do not undergo translation into proteins. Despite non-coding RNAs lacking the possiblility to encode proteins, they can influence the expression of numerous molecular targets and drive particular cellular biological responses and destinies. Long non-coding RNAs can regulate chromatin kinetics, control the operation and assembly of non-membrane-bound nucleosomes, alter the stability and translation efficacy of cytoplasmic mRNA, and interfere with signal transduction pathways [6].

In addition to regulating transcription and chromatin/histone remodeling, long non coding RNA function as microRNA (miRNA) sponges and protein scaffolds, alter the stability of mRNA and protein, and significantly influence cancer metabolism. Additionally, long non coding RNA may be packaged within exosomes and released into the tumor microenvironment to affect the biological behavior of adjacent cells. The primary function of long non coding RNA that has been extensively researched is the sponging of microRNA, which indirectly controls the expression of miRNA-targeted genes [7].

The recognition of unregulated long non coding RNA raises the potential for their application as diagnostic indicators and therapeutic targets. Long non coding RNA provide benefits as biomarkers due to their easy detection in biological fluids. The application of

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individual long non coding RNA in clinical medicine has begun [8].

The long non-coding RNA Homeobox A11 antisense (HOXA11-AS) is a new lncRNA, which acts as an oncogene in many tumor types. Examples include hepatocellular carcinoma (HCC), glioma, non-small cell lung cancer (NSCLC), breast cancer, gastric cancer, laryngeal squamous cell carcinoma (LSCC), uveal melanoma (UM), renal cancer (RC), cervical cancer (CC), and osteosarcoma [9]. It is situated inside the HOXA gene cluster and was documented to influence the prevalence of various human illnesses and their progression [10]. *HOXA11-AS* is situated on chromosome 7p15.2. The *HOXA11-AS* gene measures 3,885 base pairs, while the *HOXA11-AS* transcript is 1,628 base pairs long [11].

The purpose of this research is to superior understand the pancreatic cancer development. Discovering novel pancreatic cancer-related long non coding RNA is urgently required. *HOXA11-AS* is a recently recognized long non coding RNA, which stimulates the progression of cancer. Nevertheless, the biological role of *HOXA11-AS* and it's mechanisms underlying cancer development remain inadequately documented in pancreatic cancer.

SUBJECTS AND METHODS

Subjects:

This research has been performed in cooperation with the departments of Pathology, and Medical Biochemistry and Molecular Biology at Menoufia University, Faculty of Medicine. There were 150 participants in all: 75 cases and 75 healthy people who were matched by age and sex. The cases were selected from Menoufia University's Department of Clinical Oncology and Nuclear Medicine outpatient clinics between February 2023 and August 2024. PC patients were diagnosed using computed tomography, elevated CA 19-9, and US, and the diagnosis was confirmed with a tissue sample [12].

Inclusion criteria: Newly diagnosed pancreatic adenocarcinoma of any stage, pathologically proven, both sexes, Eastern Cooperative Oncology Cohort performance status 0 or 1, and no history of chemotherapy or radiation therapy. The exclusion criteria, on the other hand, were: patients with uncontrolled systemic diseases like diabetes, hypertension, decompensated liver disease, or autoimmune illness; those who had started chemotherapy or radiation therapy; and those whose Eastern Cooperative Oncology Cohort performance status was ≥2.

Methodology:

Participants:

Every participant received a comprehensive clinical examination, had their anthropometric measurements recorded (e.g., height in meters without shoes, weight in kilograms while wearing light clothing), and their history was taken in detail, including age, gender, family history, smoking history, and occupation. Body weight (Kg) divided by height in square meters (m^2) to yield the body mass index (BMI) [13].

Metastatic workups for PC cases was done which included contrast studies, PET/CT scans, chest X-rays, bone scans, pelvi-abdominal ultrasounds, or CT scans of the pelvis, chest, and abdomen.The pathological staging was established using the AJCC TNM staging approach [14]. The Tumour Node Metastasis (TNM) classification for PC and the Anatomic stage/prognostic cohorts were used for clinical staging [15]. The staging workup and performance status were evaluated while adhering to the ECOG Performance Status [16]. Survivals was calculated after 18 months of follow- up.

Sample collection:

6 milliliters of venous blood have been withdrawn from each individual. The samples were divided into three fractions: 3 ml of blood were transferred into two EDTA tubes as an anticoagulant; 1 ml for measurement of blood hemoglobin and 2 ml was centrifuged for ten minutes at 3000 r.p.m, the plasma attained has been stored at -80 degrees Celisus for long non coding RNA extraction and detection expression levels of lnc RNA *HOXA11-AS* using real time PCR. 3 ml of blood were transferred into a plain tube, left at room temperature for thirty min to clot, susequently centrifuged for ten minutes at 3000 r.p.m. The serum attained has been kept frozen at -20ºC until assay of total bilirubin, CEA and CA 19-9.

Blood hemoglobin level and total bilirubin were measured in laboratory studies using an autoanalyzer based on suitable chemical principles.

Serum tumor marker measurement: Using a commercially available kit (DL Sci & Tech Development Co., LTD, China), serum CA 19-9 levels were measured by ELISA. The catalog number is DL-CA19-9-Hu [17]. The Human CEA PicoKineTM Fast ELISA Kit from Boster Biological Technology in the US was utilized to assess serum CEA [18].

HOXA11-AS lncRNA expression levels have been evaluated utilizing real-time PCR (RT-PCR). RNA has been extracted from plasma utilizing the miRNeasy Mini kit (Qiagen, Germany, Cat. No. / ID: 217004). The extraction was performed based on the kit's instructions. The isolated RNA was stored at -80°C.

Assuring RNA quantity and purity

The quantity of RNA was determined by measuring its absorbance at 260 nm (A260). Absorbance readings should be greater than 0.15 to ensure significance. The ratio between the absorbance value at 260 and 280 nm (A260 /A280) gives an estimate of RNA purity. (A260 / A280) ratio greater than 1.6 was accepted.

Two stages have been utilized to determine the expression levels of *HOXA11-AS*

cDNA Synthesis (RT-Step) was the first step (QuantiTect Reverse Transcription Kit, Qiagen, Applied

Biosystems, USA, 2012). All RNA transcript areas were guaranteed to synthesize cDNA by RT Primer Mix. High cDNA template yielded for real-time PCR analysis were made possible by this. For real-time PCR, the reverse-transcription products were kept at -20°C.
The second step was PCR, which uses SYBR Green II cDNA amplification with low ROX to identify the expression levels of the lncRNA under research (QuantiTect SYBR Green PCR Kit, Applied Biosystems, USA).

Primers used:
Forward and reverse primers of HOXA11-AS:

- forward, 5′-GCCAAGTTGTACTTACTACGTC-3`; reverse: 5`-GTTGGAGGAGTAGGAGTATGTC-3`

Forward and reverse primers of glyceraldehyde-3-phosphate dehydrogenase GAPDH (endogenous healthy individual):

- forward, 5`-CCACTCCTCCACCTTTGAC-3`; reverse, 5'-ACCCTGTTGCTGTAGCCA-3’

The following conditions were present when the PCR procedure was carried out: ten microliters of 2x QuantiTect SYBR Green PCR Master Mix, three microliters of Template CDNA, one microliter each of forward and reverse primers, and five microliters of RNase-free water were used for each reaction, which had a final volume of twenty microliters. The mixture has been heated to ninety-five degrees Celisus for 15 minutes during 45 cycles of 210 minutes each, followed by denaturation for 15 seconds, annealing for 30 seconds, and extension for 34 seconds.

Version 2.0.1 of the Applied Biosystems 7500 software has been utilized to examine the information. The ΔΔCt approach used the comparative Ct methodology to conduct relative measurement of gene expression. HOXA11-AS level were compared to those of GAPDH, the housekeeping gene, using a normalization technique. A melting curve analysis has been performed to confirm that the amplification was selective and that primer dimers were not present **(Figure 1)**.

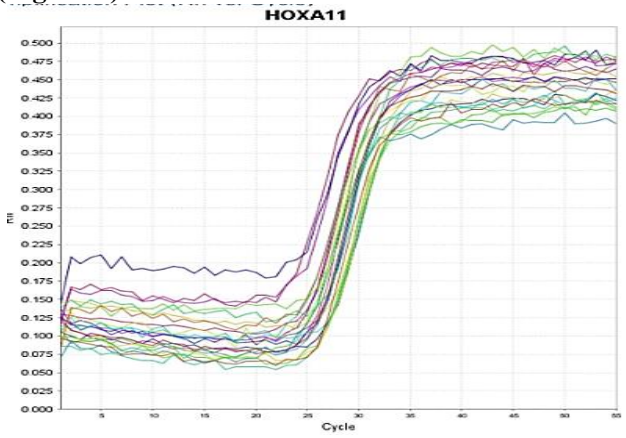

Figure 1. Amplification plot of HOXA11-AS: The qPCR amplification plot for HOXA11 shows normal sigmoidal curves with Ct values between cycles 28 and 33. This means that HOXA11 is moderately expressed in all of the samples. The consistent and steep exponential phase shows that the amplification is efficient and specific, which is good for reliable quantification.

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median. Significance of the obtained results was judged at the 5% level. The used tests were: Chi-square test For categorical variables, to compare between different groups. Mann Whitney test For abnormally distributed quantitative variables, to compare between two studied groups

Ethical Approval:

The research has been approved by the Menoufia University Faculty of Medicine's Ethical Committee of Medical Research (code 4/ 2023BIO 36), and each participant gave written, informed consent. The Helsinki Declaration was followed throughout the study's conduct.

RESULTS

In the current research, 150 participants were involved, 53.3% were males and 46.7% were females. Regarding age and gender, there were no statistically significant differences (p: 1.000, 0.130 respectively) between the cases with pancreatic adenocarcinoma and the healthy individuals. However, a statistically significant difference was observed in terms of BMI (p = 0.019), CA 19-9 (p-value below 0.001), CEA (p-value below 0.001), and total bilirubin (p-value below 0.001) were all considerably greater in the case cohort compared to healthy individual cohort**.**

Clinical presentations of pancreatic adenocarcinoma included abdominal pain in 41 out of 75 patients, jaundice in 22 patients, persistent vomiting in 3 patients, stomach pain and weight loss in 3 patients, epigastric edema and vomiting in 3 patients, and abdominal pain accompanied by jaundice in 3 patients. Regarding case clinicopathological data, 54 patients had pancreatic head tumors, 52 patients had grade II tumors, and 33 patients had stage IV tumors.
There was significant statistical increase of *HOXA11-As* level in patients` group in comparison with controls **(Table 1)**. So *HOXA11-AS* might have a role in cancer development or progression and may be used as a diagnostic biomarker for pancreatic adenocarcinoma.

Table (1): Comparison between the two studied groups according to HOXA11-AS.

	Patient (n = 75)	Control (n = 75)	p
HOXA11-AS			
Min – Max.	0.92 – 19.10	0.82 – 1.19	<0.001*
Median (IQR)	2.34 (1.52 – 9.92)	0.97 (0.88 – 1.05)	

IQR: Interquartile range, *: Statistically significant.

The ROC curve evaluated how well HOXA11-AS expression can differentiate between patients (n = 75) and healthy controls (n = 75). The curve demonstrates a robust upward trend toward the top-left corner of the graph, indicating great diagnostic accuracy. This suggests an area under the curve (AUC) likely over 0.90, which indicates excellent ability to separate the two groups. Overall, the figure supports the potential of HOXA11-AS as a reliable biomarker for distinguishing patients from controls **(Figure 2)**.

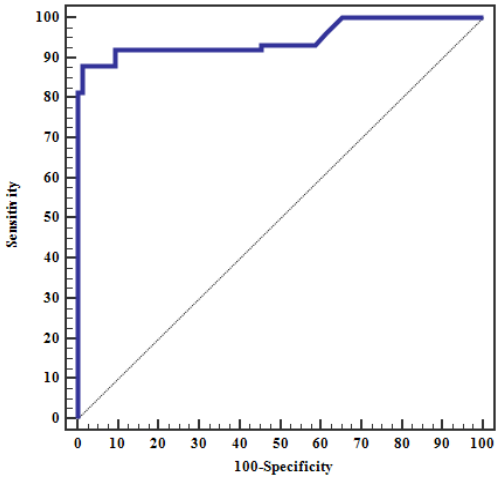

Figure (2): ROC curve for HOXA11-AS to discriminate patients (n = 75) from control (n = 75).

At the end of the research, following a monitor duration of 18 months, only 50.7% of patients wre alive indicating the high mortality rate of PC and very poor survival **(Table 2)**.

Table 2 . Kaplan–Meier survival curve for overall survival.

	Mean (months)	% End Study
Overall Survival	13.440	50.7%

There was a crucial association between the survival rate and the expression of HOXA11-AS with low expression survival was 100.0% and with high expression survival was 46.4% **(Table 3).**

Table (3): Kaplan-Meier survival curve for overall survival with HOXA11-AS

	Mean	% End of study	Log rank	
			χ^2	P
HOXA11-AS				
Low expression	18.0	100.0	4.661	0.031*
High expression	13.04	46.4		

DISCUSSION

Pancreatic ductal adenocarcinoma is a cancer with a poor prognosis, exhibiting an overall five-year survival rate of ten percent. The frequency of pancreatic ductal adenocarcinoma is constantly rising, with fifty to fifty-five percent of cases presenting with metastatic disease upon identification, rendering curative treatment unfeasible [19].

Pancreatic ductal adenocarcinoma carcinogenesis, similar to all solid cancers, is facilitated by the progressive accumulation of driver mutations, like the tumor suppressor gene TP53 and the oncogene KRAS (G12D mutation). Molecular modifications are associated with corresponding histological changes throughout various phases of pancreatic ductal adenocarcinoma progression [20].

PDAC is diagnosed clinically by tumor indicators as CA 19-9 and CEA but novel lncRNAs can be used as diagnostic biomarkers for PDAC .

The dysregulation of lncRNAs has been implicated in numerous human illnesses, involving tumor. Long non coding RNA exhibit either oncogenic or tumor-suppressive functions in different malignancies, involving pancreatic ductal adenocarcinoma. There is a high interest in identifying long non coding RNA that can serve as cancer biomarkers. Long non coding RNA have greatly tissue and disease specificity, rendering them attractive candidates for the progression as illness biomarkers [21].

In our study *HOXA11-AS* was significantly elevated in patients, which was in agreement with **Zhan *et al*.** study that reported an *HOXA11-AS* overexpression that promote hepatocellular carcinoma proliferation and invasion and stimulated the Epithelial-Mesenchymal Transition (EMT) [22]. By acting as “sponges” for miRNAs, lncRNAs were shown to have an essential roles in controlling diseases and cancer[23]. Overexpression of *HOXA11-AS* suppress the miR-214-3p expression. So *HOXA11-AS*/miR-214-3p axis was responsible for progression of hepatocellular carcinoma[22].

Zhan *et al*. demonstrated that the miR-214-3p expression has been down-regulated in hepatocellular carcinoma tissues and that its expression exhibited a negative association with the HOXA11-AS expression. The findings indicated that lncRNAs HOXA11-AS acts as an oncogene in hepatocellular carcinoma through

functioning as a competing endogenous RNA for miR-214-3p[22].

Liu *et al.* indicated that the changed expression of miR−214-3p has a role in tumorigenesis. miR−214-3p expression was recognized to suppress cancer proliferation and migration through the regulation of epithelial-mesenchymal transition. Upregulation of miR−214-3p might suppress the development of pancreatic cancer. The data demonstrate that the downregulation of miR−214-3p reversed the inhibitory influences of si-circ−0014784 on epithelial-mesenchymal transition, proliferation, migration, and angiogenesis in pancreatic cancer cells [24].

There was a strong association between the survival rate and the expression of HOXA11-AS with p value 0.031 with low expression 100.0% and high expression 46.4%. This was matched with pervious studies as **Sun *et al.*** who documented that Homeobox A11 antisense is significantly upregulated in gastric cancer tissues. Great expression of Homeobox A11 antisense is closely related to poor differentiation, lymph node metastasis, larger size of cancer and advanced pathological phase in gastric cancer [25].

Investigators observed that progression-free survival (PFS) and overall survival rates exceeding three years were reduced in the group exhibiting elevated expression levels of *HOXA11-AS* compared to the group with reduced expression levels of Homeobox A11 antisense. Overexpression of Homeobox A11 antisense results in elevated rates of cell growth, migration, invasion, and suppression of apoptosis in gastric cancer [26].

Liu *et al*. observed that elevated Homeobox A11 antisense expression are significantly related to cirrhosis, vascular invasion, Edmondson grade and tumor size. The overall survival (OS) rate of cases with elevated levels of Homeobox A11 antisense expression is markedly shorter in comparison with those with reduced levels of Homeobox A11 antisense expression. *HOXA11-AS* overexpression stimulates cell cycle development, proliferation, invasion, and epithelial-mesenchymal transition, in addition to repressing apoptosis in hepatocellular carcinoma cells [27].

At the end of the research, following a monitor duration of 1.5 years, only half of the patients were alive indicating the high mortality rate of PC as reported in previous studies.

Pancreatic cancer consistently ranks last among all malignancies for case prognosis results and is expected to become the 2nd leading etiology of cancer death in certain areas. Pancreatic cancer exhibits a poor five-year survival rate, varying between two percent and nine percent, with little variance among high-income and low- to middle-income countries.

The five-year survival rate of pancreatic cancer differs worldwide in various areas and countries, however it does not exceed ten percent. Cases with nonoperative pancreatic cancer are expected to have a reduced five-year survival rate [28].

CONCLUSION

In all, our data revealed that *HOXA11-AS* can be a candidate prognostic biomarker and a target for novel therapies in PC cases as there was a strong association between the survival rate and the expression of *HOXA11-AS*. CA19-9 and CEA are signifintly elevated in pancreatic cancer. Pancreatic ductal adenocarcinoma has poor survival.

Limitations of the research

A small sample size and a lack of longitudinal data to evaluate biomarker changes over time are two of the study's shortcomings. To improve practical application, future research should examine the impact of treatment on biomarker expression, longitudinal changes in lncRNA level, and larger, multicenter populations.

DECLARATIONS

- **Consent for publication:** I certify that each author has granted permission for the work to be submitted.
- **Funding:** No fund
- **Availability of data and material:** Available
- **Conflicts of interest:** None
- **Competing interests:** None

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