شبكة المعلومات الجامعية

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بسم الله الرحمن الرحيم

HANAA ALY

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جامعة عين شمس

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HOTAIR Expression and Prognostic Impact in Acute Myeloid Leukemia Patients

Thesis

Submitted for Partial Fulfillment of M.D degree in Clinical and Chemical Pathology

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بسم الله الرحمن الرحيم

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

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Abstract

Background: Acute myeloid leukemia (AML) is a disorder characterized by a rapid onset of symptoms attributable to bone marrow failure due to clonal proliferation of primitive hematopoietic stem cells or progenitor cells. Epigenetic abnormalities play an important role in the development and progression of acute leukemia. Long non-coding ribonucleic acid (lncRNA) plays an important role in epigenetic regulation. Homeobox (Hox) transcript antisense intergenic RNA (HOTAIR) is a lncRNA which has been determined to be a negative prognostic indicator in various solid-tumor patients. However; its role in hematopoietic tumors as AML is to be assessed. This study aimed at measuring lncRNA HOTAIR in newly diagnosed AML patients and correlating its expression with different clinicopathological prognostic variables. This provides a new prospective for novel marker involved in development and progression of AML which can be used as diagnostic marker and target of therapy. The current study included 65 subjects divided into 35 newly diagnosed AML adult patients (before initiation of therapy) and 30 non-leukemic adult patients as controls. HOTAIR expression was measured by quantitative reverse transcription polymerase chain reaction (qRT-PCR).

Results: HOTAIR expression was found to be significantly upregulated in AML patients ($p = 0.000$) and showed to have a diagnostic ability of AML as confirmed by significant difference between cases and controls using receiver operating characteristic curve (ROC) analysis. However; it was not significantly correlated with event free survival (EFS) or clinicopathological prognostic variables.

Conclusion: This study showed that the expression of HOTAIR is upregulated in de novo AML patients and can be used as a diagnostic marker. However; highly expressed HOTAIR is not associated with poor prognosis.

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List of Abbreviations

Abb.	Full term
AL	*Acute leukemia*
AML	*Acute myeloid leukemia*
ASXL1	*additional sex combs like 1*
AUC	*Area under the curve*
BM	*Bone marrow*
CASC15	*Cancer susceptibility 15*
CBC	*Complete bood picture*
CBF	*Core binding factor*
CCAAT	*cytidine-cytidine-adenosine-adenosine-thymidine*
CD	*Cluster of differentiation*
cDNA	*Complementary deoxyribonucleic acid*
CEBPA	*CCAAT/enhancer-binding protein alpha*
CML	*Chronic myelogenous leukemia*
CpG	*Cytosine next to guanine*
CT	*Computed tomography*
Ct	*Cycle threshold*
DIC	*Disseminated intravascular coagulation*
DLBCL	*Diffuse large B cell lymphoma*
DNA	*Deoxyribonucleic acid*
DNMT3A	*DNA methyltransferase 3A*
EFS	*Event free survival*
ELN	*European Leukemia Net*
ETV6	*Translocation-Ets- leukemia virus variant gene 6 protein*
EZH2	*enhancer of zeste homolog 2*
FAB	*French-American-British*
FISH	*fluorescence in situ hybridization*
FLT3-ITD	*Fetal liver tyrosine kinase- internal tandem duplication*

List of Abbreviations (Cont...)

Abb.	Full term
g	*Gram*
g/dL	*Gram/dL*
GATA	*Trans-acting T cell specific transcription factor*
H1	*Histone 1*
H2A	*Histone 2A*
H2B	*Histone 2B*
H3B	*histone 3*
H4	*Histone 4*
HB	*Hemoglobin*
HCT	*Hematopoietic cell transplantation*
HLA	*Human leucocyte antigen*
HOTAIR	*Homeobox transcript antisense intergenic ribonucleic acid*
HOX	*Homeobox*
HS	*Highly significant*
HSM	*Hepatosplenimegaly*
IDH2R172	*isocitrate dehydrogenase 2 R172*
Inv	*Inversion*
IPI	*international prognostic index*
IPT	*Immunophenotyping*
IQR	*Interquartile range*
K2-EDTA	*K2-ethylene diamine tetraacetic acid*
KIT	*Tyrosine protein kinase*
KMT2A	*lysine specific methyltransferase 2A*
K-RAS	*Kirsten rat sarcoma viral oncogene*
LncRNA	*Long non-coding ribonucleic acid*
LP	*Lumber puncture*
LSD1	*Lysine specific histone demethylase 1A*
MBD	*Methyl-CpG binding domain*

List of Abbreviations (Cont...)

Abb.	Full term
MBP	*Methyl-CpG binding proteins*
MDS	*Myelodysplastic syndrome*
mL	*Mililiter*
MRI	*Magnetic resonance imaging*
MS	*Myelosarcoma*
ncRNA	*Non-coding ribonucleic acid*
NPM1	*Nucleophosmin 1*
NS	*Non-significant*
PB	*Peripheral blood*
PET	*Positron emission tomography*
pg	*Picogram*
PLT	*Platelets*
PRC2	*Polycomb Repressive Complex 2*
PV	*Predictive value*
p-value	*Probability value*
qRT-PCR	*Quantitative reverse transcription polymerase chain reaction*
r	*Correlation*
RBCs	*Red blood cells*
Rn –	*Emission Intensity of Reporter PCR without template*
Rn +	*Emission Intensity of Reporter PCR with template Emission Intensity of Passive Reference*
ROC	*Receiver operating characteristic*
RUNX1	*Runt-related transcription factor 1*
S	*Significant*
SFRSF2	*splicing factor arginine/serine-rich 2*
SOX4	*SRY-box transcription factor 4*

List of Abbreviations (Cont...)

Abb.	Full term
SPSS	*statistical package for social science*
t	*Independent t-test*
t	*Translocation*
t-AML	*Therapy related AML*
TERT	*Telomerase reverse transcriptase*
TET2	*ten-eleven translocation-2*
Th2	*T-helper 2*
TLC	*Total leucocytic count*
TP53	*Tumor protein p53*
TRDMT1	*Transfer RNA cytosine 5 methyltransferase 1*
uL	*Microliter*
WBCs	*White blood cells*
WHO	*World Health Organization*
X^2	*Chi-square test*

INTRODUCTION

Acute myeloid leukemia (AML) is a disorder characterized by a clonal proliferation derived from primitive hematopoietic stem cells or progenitor cells. It occurs at all ages, but predominantly in older people (>60 years of age). AML typically presents with a rapid onset of symptoms attributable to bone marrow failure **(O'Donnell et al., 2012).**

Progress in therapeutic approaches such as chemotherapy, radiotherapy, biological regulations and hematopoietic stem cell transplantation resulted in significant advancements; however, leukemia continues to be a significant health burden. An effective molecular marker for early diagnosis, prognosis and treatment guidance, is therefore, required **(Lin et al., 2018).**

Numerous studies have shown that epigenetic abnormalities play an important role in the development and progression of acute leukemia. Non-coding ribonucleic acid (ncRNA) showed to play an important role in epigenetic regulation **(Muto et al., 2015).**

The sequencing technologies and genome-wide analysis have indicated that the majority of the genome is the so-called dark matter that is transcribed into noncoding ncRNA **(Nagano and Fraser, 2011).**