Correlation of FLT3 Gene Mutations and mRNA Expression with FLT3 Receptor Protein (CD135) Expression in Acute Myeloid Leukemia

Thesis

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ارتباط ظهور طفرات جين ال FLT3 و الmRNA بظهور مستقبل ال FLT3 (CD135) في سرطان الدم الميلودى الحاد

رسالة

توطئة للحصول على درجة الدكتوراه فى الباثولوجيا الإكلينيكية والكيميائية

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Mariam Karam Youssef

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List of Abbreviations

Abb.	Full term
-	*Monosomy*
- PV	*Negative Predictive Value*
+	*Trisomy*
+ PV	*Positive Predictive Value*
ABL1	*Abelson Murine Leukemia Viral Oncogene Homolog 1*
Akt	*Protein Kinase B*
ALL	*Acute Lymphoblastic Leukemia*
AML	*Acute Myeloid Leukemia*
ANAE	*Alpha Naphthyl Acetate Esterase*
APL	*Acute Promyelocytic Leukemia*
AUC	*Area under the Curve*
BAALC	*Brain and Acute Leukemia, Cytoplasmic*
BAD	*BCL2 Associated Agonist of Cell Death*
BCL2	*B-Cell Lymphoma 2*
BCR	*Breakpoint Cluster Region*
BM	*Bone Marrow*
Bp	*Base Pair*
CBC	*Complete Blood Count*
CD	*Cluster of Differentiation*
cDNA	*Complementary DNA*
CEBPA	*CAAT/Enhancer-Binding Protein- Alpha*
CLL	*Chronic Lymphocytic Leukemia*
CML	*Chronic Myeloid Leukemia*
CN-AML	*The Cytogenetically Normal AML*
CNS	*Central Nervous System*
CR	*Complete Remission*
CREB1	*CAMP Responsive Element Binding Protein 1*
Ct	*Cycle Threshold*
CXCR4	*C-X-C Chemokine Receptor Type 4*
DCs	*Dendritic Cells*
Del	*Deletion*
DFS	*Disease-Free Survival*

List of Abbreviations (Cont...)

Abb.	Full term
dHPLC	*Denaturating High Performance Liquid Chromatography*
DIC	*Disseminated Intravascular Coagulopathy*
DNA	*Deoxyribonuleic Acid*
dNTP	*Deoxyribonucleotide Triphosphates*
Eff	*Efficacy*
EFS	*Event-Free Survival*
ELK1	*ETS Domain-Containing Protein*
EM	*Electron Microscopy*
ER	*Endoplasmic Reticulum*
ERG ETS	*(Erythroblast Transformation-Specific) Transcription Factor*
ERK	*Extracellular Signal-Regulated Kinase*
EtBr	*Ethidium Bromide*
FAB	*French-American-British*
FISH	*Fluorescence in-Situ Hybridization*
FITC	*Fluorescein Isothiocyanate*
FLK-2	*Fetal Liver Kinase-2*
FLT3	*FMS-Like Tyrosine Kinase-3*
FLT3L	*FLT3 Ligand*
FN	*False Negative*
FP	*False Positive*
gDNA	*Genomic DNA*
Hb	*Hemoglobin*
HLA	*Human Leucocyte Antigen*
HS	*Highly Significant*
HSM	*Hepatosplenomegaly*
HSPCs	*Hematopoietic Stem / Progenitor Cells*
IL	*Interleukin*
Inv	*Inversion*
IPT	*Immunophenotyping*
IQR	*Interquartile Range*
ITD	*Internal Tandem Duplication*

List of Abbreviations (Cont...)

Abb.	Full term
JM	*Juxtamembrane*
JMD	*Juxtamembrane Domain*
JMML	*Juvenile Myelomonocytic Leukemia*
K2-EDTA	*Ethylene Diamine Tetra-Acetic Acid Dipotassium Salt*
LDH	*Lactate Dehydrogenase*
LM	*Length Mutation*
LN	*Lymphadenopathy*
M3v	*M3 Variant*
MAPK	*mitogen-Activated Protein Kinase*
MDS	*Myelodysplastic Syndrome*
MECOM	*MDS1 and EVI1 Complex Locus*
MLL	*Mixed-Lineage Leukemia*
MM	*Multiple Myeloma*
MN1	*Meningioma 1*
MoAb	*Monoclonal Antibodies*
MPD	*Myeloproliferative Disorder*
MPO	*Myeloperoxidase*
MRC	*Myelodysplasia-Related Changes*
mRNA	*Messenger RNA*
mTOR	*Mammalian Target of Rapamycin*
NHL	*Non-Hodgkin's Lymphoma*
NK	*Natural Killer*
NOS	*Not Otherwise Specified*
NPM1	*Nucleophosmin 1*
NS	*Non-Significant*
NSE	*Non Specific Esterase*
OS	*Overall Survival*
PAS	*Periodic Acid Schiff*
PB	*Peripheral Blood*
PBS	*Phosphate Buffered Saline*
PC5	*Phycoerythrin-Cyanine 5*
PCR	*Polymerase Chain Reaction*

List of Abbreviations (Cont...)

Abb.	Full term
PE	*Phycoerythrin*
PI3K	*Phosphatidylinositol 3-Kinase*
PML/RARA	*Promyelocytic Leukemia/Retinoic Acid Receptor Alpha*
r	*Pearson Correlation*
RAEB-T	*Refractory Anemia with Excess Blasts in Transformation*
RFLP	*Restriction Fragment Length Polymorphism*
RNA	*Ribonucleic Acid*
ROC	*Receiver Operating Characteristic*
Rpm	*Revolution per Minute*
rs	*Spearman Correlation*
RSK	*Ribosomal S6 Kinase*
RTK	*Receptor Tyrosine Kinase*
RT-PCR	*Reverse Transcription PCR*
RUNX1	*Runt-Related Transcription Factor 1*
S	*Significant*
SBB	*Suddan Black B*
SD	*Standard Deviation*
Sig.	*Significance*
Sn	*Sensitivity*
Sp	*Specificity*
STAT	*Signal Transducer and Activator of Transcription*
STK-1	*Stem Cell Kinase-1*
t	*Translocation*
TBE	*Tris Borate EDTA*
TE	*Tris EDTA*
TdT	*Terminal Deoxynucleotidyl Transferase*
TK	*Tyrosine Kinase*
TKD	*Tyrosine Kinase Domain*
TLC	*Total Leucocytic Count*
TM	*Transmembrane*

List of Abbreviations (Cont...)

Abb.	Full term

TN..... *True Negative*
TP..... *True Positive*
UV..... *Ultraviolet*
VAF..... *Variant Allele Frequency*
WBC..... *White Blood Cell*
WHO ..... *World Health Organization*
WT1..... *Wilms Tumor Protein-1*

INTRODUCTION

Acute myeloid leukemia (AML) is a clonal hematopoietic stem cell disorder characterized by uncontrolled proliferation within the bone marrow (BM) of myeloid progenitors at the expense of normal hematopoietic elements ***(Estey, 2012).***

More recently, gene expression profiling has been shown to improve the molecular classification and prognosis of AML patients. Moreover, molecular testing has become mandatory among patients with normal cytogenetics, to further classify these patients into prognostic groups. This includes assessment for the nucleophosmin gene (NPM1), the CCAAT/enhancer-binding protein-Alpha (CEBPA) and the FMS-like tyrosine kinase-3 (FLT3) ***(Seegmiller et al., 2016).***

FLT3 (CD135) is a cytokine receptor protein belonging to the subclass III of receptor tyrosine kinases ***(Rosnet and Birnbaum, 1993),*** it is expressed mainly on early hematopoietic progenitors ***(Gilliland and Griffin, 2002; Verstraete et al., 2011).***

The FLT3 receptor protein is usually over expressed in leukemic blast cells of AML patients, while some cases possessed mutant FLT3 gene ***(Gilliland and Griffin, 2002).*** FLT3 gene mutation and over expression result in constitutive ligand independent activation of the receptor's tyrosine kinase

activity stimulating proliferation and inhibiting apoptosis of leukemic blasts ***(Mehta et al., 2012).*** Various studies found that FLT3 is an important prognostic biomarker and a potential therapeutic target in AML patients ***(Mrozek et al., 2007; Mehta et al., 2012; Elyamany et al., 2014).***