Identification and Validation of Survival-Associated Core Genes in the VAV1 Gene Network in Acute Myeloid Leukemia

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Background

Acute Myeloid Leukemia (AML) is a bone marrow malignancy and is caracterized by the proliferation of immature bone marrow cells. There are many gene mutations and genes with varying expression rates that cause AML disease. In addition, activated signaling pathways also cause the poor course of the disease. PI3K/AKT signaling pathway is one of these pathways. It is known that this pathway is effective in processes such as growth, proliferation, transcription, and regulation of metabolic events. In addition, PI3K/AKT signaling pathway is active in AML, as many types of cancer. Due to the importance of the pathway in the disease, in a previous study that we conducted the effect of the signaling pathway on survival in AML disease and the expression levels of the genes in the pathway in the disease state were investigated. As a result of research, there is a negative effect of guanine nucleotide factor (VAV1) and related genes on survival and this gene has become an important focus with the increase in gene expression in AML. VAV1 gene is a signal transducer gene and literature research has shown that it has high expression in many types of malignancies.

Objective

In our study, we aimed to propose novel drugs for inhibition of VAV1 gene and related hub genes to create new treatment options for AML patient by using drug repurposing approaches.

Methods

- AML patients' gene intensity values were used from M-NCBI Geo database (GSE37642 dataset with GPL570 platform)
- Differentially expressed genes (DEGs) were identified by using R 4.3.2 program and "limma" package.
- Gene enrichment analysis were conducted with DEGs.
- Survival analysis of identified DEGs were achieved by using R 4.3.2 "survival" package.
- Hub genes were identified by using Cytoscape program and CytoHubba plugin.

A

Ranking Method: Degree

Rank	Node
1	PCNA
2	RUVBL2
3	MAPK1
4	RAD51
5	CHAF1A
6	CDC20
7	DNMT1
8	KPNB1
9	VAV1
10	CUL4A

B

Ranking Method: Closeness

Rank	Node
1	PCNA
2	RUVBL2
3	MAPK1
4	KPNB1
5	MYC
6	TP53
7	UBC
8	CUL4A
9	CDT1
10	CHEK1

Figure 2 : Top 10 hub genes of survival releted DEGs which were calculated with respect to A) Degree B) Closeness methods.

Results

Table 1 : The first 10 DEGs which were sorted with respect to logFC values.

GEN ADI	LOGFC VALUE
MAFF	7.249927
ANXA1	7.089476
MSRB3	6.500354
CA2	6.473616
MBNL1	6.292171
GSK3B	2.526908
TSC2	2.463193
PIK3CA	2.177388
LAMTOR1	2.074624
VAV1	1.813881

Table 2 : The first 10 survival related genes and their hazard ratio values.

GENE SYMBOL	P VALUE	HAZARD RATIO
CFL1	0.01373488	3.840731
COA6	9.30E-05	3.411125
UQCRH	0.005215637	2.585768
PSMA7	0.000899459	2.548686
HADHB	0.006434213	2.484177
LONP1	0.000528493	2.428868
SNRPG	0.02515713	2.411584
PSMA6	0.01647193	2.317957
CYB5R3	0.007614735	2.211765
YARS1	0.001355127	2.186904

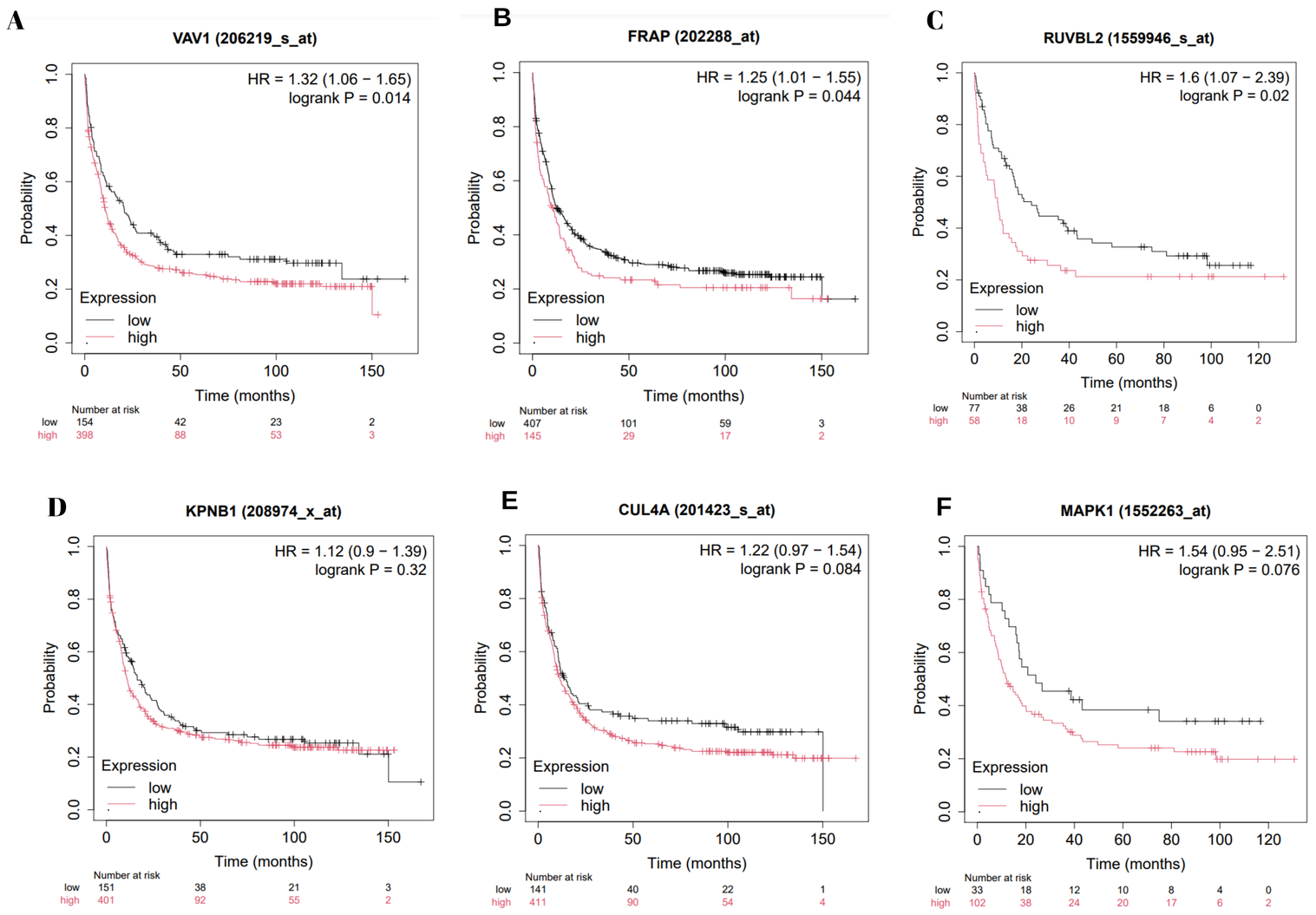

Figure 1 : Kaplan Meier Plots of survival related hub genes. A) VAV1, B) FRAP (MTOR), C) RUVBL2, D) KPNB1, E) CUL4A, F) MAPK1, G) PCNA genes were shown.

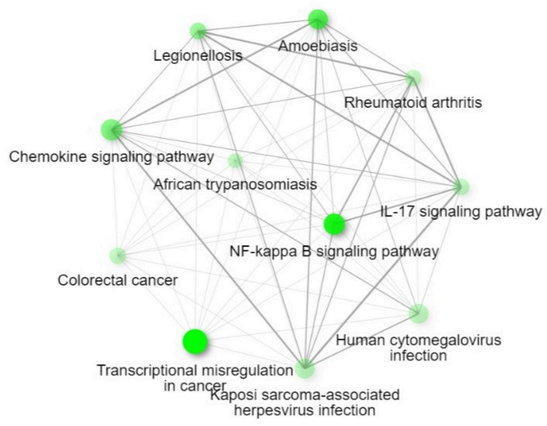

Figure 3 : The results of enrichment analysis 7877 DEGs.

Table 3 : Enrichment table of 7877 DEGs.

Enrichment FDR	nGenes	Pathway Genes	Fold Enrichment	Pathway	Genes
0.000347933	7	104	11.15990803	NF-kappa B signaling pathway	TNFSF13B CXCL2 CXCL3 CXCL8 PTGS2 BCL2A1 BCL10
6.00E-05	10	193	8.590898851	Transcriptional misregulation in cancer	H3-3B HHEX CXCL8 LMO2 MPO REL BCL2A1 BCL6 NFKBIZ RUNX
0.047515749	4	93	7.131369799	IL-17 signaling pathway	CXCL2 CXCL3 CXCL8 PTGS2
0.008733579	7	191	6.076599135	Chemokine signaling pathway	RASGRP2 GNAQ CXCL2 CXCL3 CXCL8 PIK3R1 GNB4

Conclusion and Future Perspective

In our study, drug docking analysis will be performed by using these genes and candidate drugs and appropriate inhibitor drugs will be identified. It is plann,ng to use novel drug administration approaches targeting VAV1 and related hub genes. In this context, it is primarily aimed to identify drugs that have not been widely used in AML and have been tested in non-cancer diseases using drug repurposing methods.