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Computational Analysis of Single Nucleotide polymorphisms (SNPs) in Human T-Cell Acute Lymphocytic Leukemia Protein 1 (*TAL1*) Gene/ Comprehensive Study

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Abstract

Background: *TAL1 is a proto-oncogene whose distorted modifications in committed T-cell Precursors is related with the development of T-ALL, it also found to be related to many other human hematological diseases such as lymphoblastic lymphoma, immunodeficiency 18, acute myeloid leukemia and diamond-blackfan Anemia.* ***Objectives:*** *This study aims to predict the effect of nsSNPs on TAL1 protein structure function* ***Methods:*** *Retrieved nSNPs in the coding and 3'UTR regions were analyzed using different in silico tools. Interactions of TAL1 with functionally similar genes were investigated using Genemania. Post-translational modifications in several sites of the protein were also investigated.* ***Results:*** *Out of ninety nsSNPs identified, only eight were found damaging to protein function of which one is located in the basis helix-loop-helix domain (bHLH). Two SNPs were anticipated by PolymiRTs to prompt disturbance or creation of miR binding sites.* ***Conclusion:*** *The present study is the first ever computational analysis of TAL1's nsSNPs hence this effort might be of help in the near future for inventing early diagnostic and therapeutic measures for T-ALL*

Keywords: *Acute lymphoblastic leukemia, TAL1, Computational analysis, Basic helix-loop-helix; Domain*

Introduction

Acute lymphoblastic leukemia (ALL) is a malignant disease of the bone marrow in which hematopoietic stem cells (HSC), which are called lymphoid cells in this case, are arrested and transformed in an early stage [1,2]. ALL accounts for 26% of childhood malignancy, making it the most common cancer in that age group [3]. There are two subtypes of the disease T-cell ALL (T-ALL) and B-cell precursor ALL (BCP-ALL), T-ALL involves thymocytes and responsible for about 15% of childhood and 25% of adult ALL [4]. *TAL1* was also found to be related to many human hematological diseases such as lymphoblastic lymphoma, immunodeficiency 18, acute myeloid leukemia and diamond-black fan Anemia [5-9].

Although the local alterations or chromosome translocation in committed T-cell precursors is associated with the development of T-ALL [10-12], literature review revealed that there are no previous studies on the effect of such alterations on *TAL1* structure and function. Therefore the aim of the present work was to conduct a full in silico analysis of *TAL1*'s SNPs using bioinformatics prediction tools to study the possible effect of the genetic variations on the protein structure and function.

Studies showed that tumor-specific activation of *TAL1* is found in 40-60% of T-ALL patients, resulting from interstitial chromosome mutations (25-30%), chromosomal translocation (4-5%) or by undefined mechanisms (60%) [13-16]. These mutations are expected to be because of single nucleotide polymorphisms (SNPs), which are the most well known kind of genetic variation among individuals, consisting about 90% of genetic polymorphisms [17]. One type of SNPs is the non-synonymous SNPs (nsSNPs), also known as missense SNPs, which are very important because they are responsible for changes in human proteins' functions by substituting amino acid residues [18].

Therefore, early prediction and better understanding of the *TAL1* gene functions could help in improving the prognosis of the disease. As this analysis is the first precise and broad computational study of functional SNPs in the *TAL1* gene, it might be of great help in the near

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future for inventing early diagnostic and therapeutic measures for T-ALL.

Materials and Methods

SNPs Retrieval

Polymorphisms in *TAL1* gene were retrieved from the national center of biotechnology information database; dbSNP/NCBI database NCBI [19]. The retrieved SNPs were then filtered for investigation.

Insilico analysis of non-synonymous single nucleotide polymorphisms (nSNPs)

Different soft-wares were utilized to study the impact of SNPs mutations on *TAL1* protein structure and function. Deleterious effect of nSNPs was investigated by SIFT and Polyphen-2 softwares. Stability changes was explored by I mutant-3. The association of nsSNPs with disease was done by PhD-SNP programming. The auxiliary changes in 3D structure were dissected utilizing Chimera programming. SNPs at the 3'UTR were likewise broke down to identify the impact on microRNA restricting destinations utilizing PolymiRTs programming. *TAL1* gene interactions were investigated using GENEMANIA. In this study, nsSNPs and those at the *3'UTR* regions were selected for analysis.

Investigation of *TAL1* Gene's Interactions and Appearance in Networks in GENEMANIA Database

The online database GENEMANIA studies the gene function and interrelation with other genes using functional association data including protein and genetic interactions, pathways, co-expression, co-localization and protein domain similarity. It can also be used to find new members of a pathway or complex, find additional genes that may have been missed in screening or find new genes with a specific function, such as protein kinases [20]. Available at: http://www.genemania.org/.

nsSNPs' Structural impact

Functional effects of nsSNPs were analyzed using SIFT (http://sift.bii.a-star.edu.sg/) in which SNPs are characterized into tolerated and deleterious. The input SNPs' rs-IDs were submitted to the server for analysis, prediction was given as a tolerance index (TI) score going from 0.0 to 1.0. SNPs with TI score under 0.05 were anticipated to be deleterious; those more prominent than or equal to 0.05 were anticipated to be tolerated (http://blocks.fhcrc.org/sift/SIFT.html) [21].

Prediction of Deleterious nsSNPs

Polyphen software (Polymorphism Phenotyping v2; http://genetics.bwh.harvard.edu/ pph2) calculates position-specific independent count (PSIC) scores of which 1.0 is considered to be damaging. The SNPs are appraised quantitatively as benign, possibly damaging and probably damaging [22]. Positions of interest and new residue in protein FASTA sequence were submitted to Polyphen to investigate the functional effect of mutations.

Damaging SNPs in the above software were further analyzed by I mutant and PhD servers to estimate their effects on protein stability and disease associated variations, respectively.

nsSNPs' Impact on Protein Stability

I-Mutant3.0 server

I-Mutant is a web server for the automatic prediction of protein stability changes upon single-site mutations starting from the protein structure or sequence. It calculates the free energy change value (DDG) and predicts the indication of the free energy change value (DDG) (increase or decrease), along with a reliability index for the results (RI: 0–10, where 0 is the minimum reliability and 10 is the maximum reliability). A DDG < 0 corresponds to a decline in protein stability, whereas a DDG > 0 corresponds to an increase in protein stability [23]. The residues changes and protein sequence in FASTA format were submitted to I-mutant server to process DDG value (kcal/mol) and the RI value. Conditions for all enteries were set at temperature 25°C and pH 7.0. Available at http://gpcr2.biocomp.unibo.it/cgi/predictors/I-Mutant3.0/IMutant3.0.cgi.

Prediction of Disease Associated Variations

PhD-SNP is Support Vector Machine based classifier that predicts the disease associated variations upon single point mutation [24-26]. The residues changes and protein sequence in FASTA format were submitted to PhD-SNP server for the analysis. Available at: http://snps.biofold.org/phd-snp/phd-snp.html.

Prediction of the Impact of SNPs at the 3Un Translated Region (*3'UTR*) by PolymiRTS Database

PolymiRTS (v3.0) database is designed specifically for the analysis of non-coding SNPs at *3'UTR* and identification of nSNPS that affect miRNA (micro RNA) targets in human and mouse [27]. *3'UTR* SNPs in *TAL1* gene were analyzed in order to investigate the alteration of miRNA binding on target sites which may result in diverse functional consequences. Available at: http://compbio.uthsc.edu/miRSNP.

Project hope

HOPE is an online service, developed at the Centre for Molecular and Biomolecular Informatics CMBI at Radboud

University in Nijmegen. It gathers structural information from different sources, including calculations on the 3D protein structure, succession comments in UniProt and expectation from the Reprof software. HOPE consolidates this data to analyze the impact of specific mutation on the protein structure [28].

Homology modeling

The 3D models for protein wild type and mutated were produced utilizing two homology modeling portals; Phyre2 and Raptorx [29, 30]. The obtained structures were then visualized by Chimera 1.10.2

UCSF Chimera

It is an extensible program for interactive representation and investigation of molecular structures and related information, including density maps, supramolecular gathering, sequence arrangement, docking results and conformational ensembles [31]. Chimera [32] can give the 3D structure of the protein and then changing between wild and mutant amino acids with the candidate to show the resulted effect. Chimera accepts the input in the form of pdb ID or pdb file. (https://www.cgl.ucsf.edu/chimera/).

Predicting post translational modification (PTM) sites

The phosphorylation sites of *TAL 1* at serine, threonine and tyrosine residues were predicted by NetPhos server [33]. The ubiquitylation sites at lysine residue were investigated by UbPred and BDM-PUB tools [34].

Results

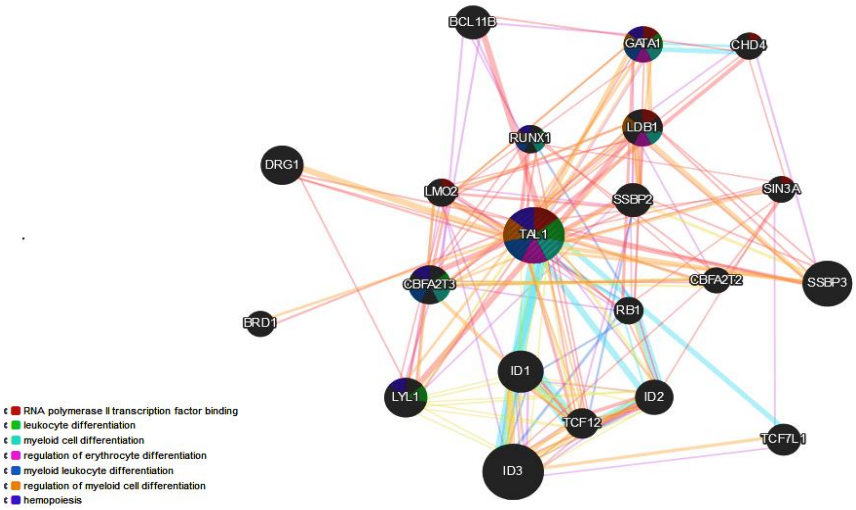


Figure 1: Functional interaction between *TAL1* and its related genes

Table1. Genes co-expressed, physical interaction and share a domain with *TAL1*

Gene symbol	Description	Co-expression	Physical interaction	Shared domain
ID3	inhibitor of DNA binding 3, HLH protein	NO	NO	YES
SSBP3	single stranded DNA binding protein 3	NO	YES	NO
ID1	inhibitor of DNA binding 1, HLH protein	NO	NO	YES
LYL1	lymphoblastic leukemia associated hematopoiesis regulator 1	NO	YES	YES
DRG1	developmentally regulated GTP binding protein 1	NO	YES	NO
CBFA2T3	CBFA2/RUNX1 translocation partner 3	NO	YES	NO
LDB1	LIM domain binding 1	NO	YES	NO
GATA1	GATA binding protein 1	YES	YES	NO
ID2	inhibitor of DNA binding 2, HLH protein	YES	NO	YES
SSBP2	single stranded DNA binding protein 2	NO	YES	NO
BCL11B	B-cell CLL/lymphoma 11B	NO	YES	NO
TCF7L1	transcription factor 7 like 1	NO	NO	NO
TCF12	transcription factor 12	NO	YES	YES
RUNX1	runt related transcription factor 1	NO	YES	NO
LMO2	LIM domain only 2	YES	YES	NO
RB1	RB transcriptional corepressor 1	NO	YES	NO
CHD4	chromodomain helicase DNA binding protein 4	NO	YES	NO
SIN3A	SIN3 transcription regulator family member A	YES	YES	NO
BRD1	bromodomain containing 1	NO	Yes	NO
CBFA2T2	CBFA2/RUNX1 translocation partner 2	NO	Yes	NO

Table2. Illustrates the *TAL1* functions and its appearance in network and genome

Function	*FDR	Genes in network	Genes in genome
RNA polymerase II transcription factor binding	2.40746E-06	6	**74**
granulocyte differentiation	1.72765E-05	4	**16**
regulatory region DNA binding	4.0226E-05	7	**268**
regulatory region nucleic acid binding	4.0226E-05	7	**268**
transcription factor complex	4.30288E-05	6	**155**
transcription regulatory region DNA binding	0.000906689	6	**267**
myeloid cell differentiation	0.002041367	5	**165**
regulation of erythrocyte differentiation	0.003955733	3	**22**
myeloid leukocyte differentiation	0.006093148	4	**94**
regulation of myeloid cell differentiation	0.00610707	4	**97**
leukocyte differentiation	0.00610707	5	**226**
Hemopoiesis	0.00636298	5	**232**
negative regulation of sequence-specific DNA binding transcription factor activity	0.007074313	4	**107**
RNA polymerase II activating transcription factor binding	0.007230266	3	**32**
hematopoietic or lymphoid organ development	0.007328562	5	**250**
immune system development	0.009460283	5	**267**
histone deacetylase complex	0.01368668	3	**42**
histone H3 acetylation	0.01489199	3	**44**
erythrocyte differentiation	0.015105508	3	**45**
positive regulation of myeloid cell differentiation	0.016375495	3	**47**
activating transcription factor binding	0.016623954	3	**48**
response to thyroid hormone	0.043653839	2	**10**
Chromatin	0.059999159	4	**213**
positive regulation of erythrocyte differentiation	0.08071214	2	**14**
regulation of chromosome organization	0.092141062	3	**90**
regulation of transcription regulatory region DNA binding	0.098119367	2	**16**

*False discovery rate is greater than or equal to the probability that this is a false positive

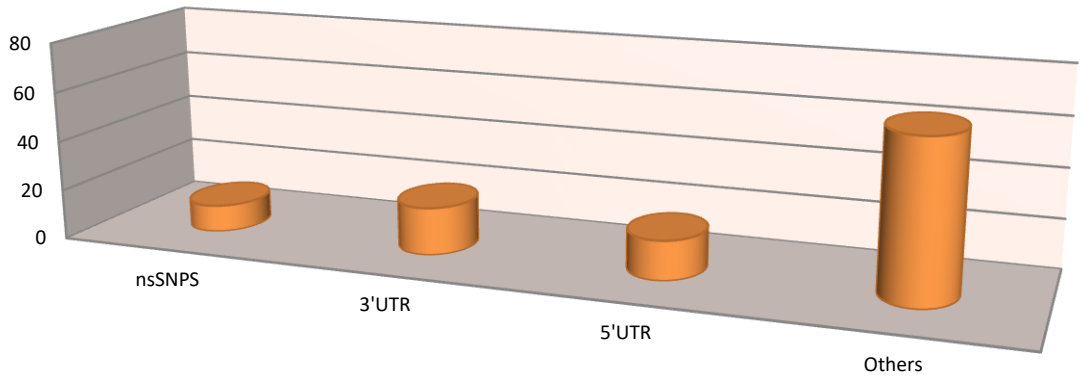
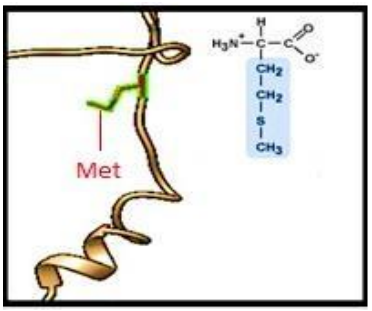
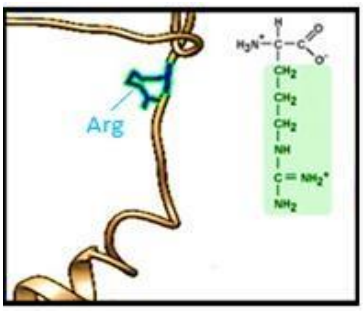


Figure 2: Percentages of the SNPs in *TAL1* gene. (nsSNPs: 10.8%; *3'UTR* SNPs: 19%; *5'UTR* SNPs: 15.7%; Other SNPs: 63%)

SNPs ID	3 D structure		Position
	wild residue	mutant residue	
rs147015002			M160R M162R

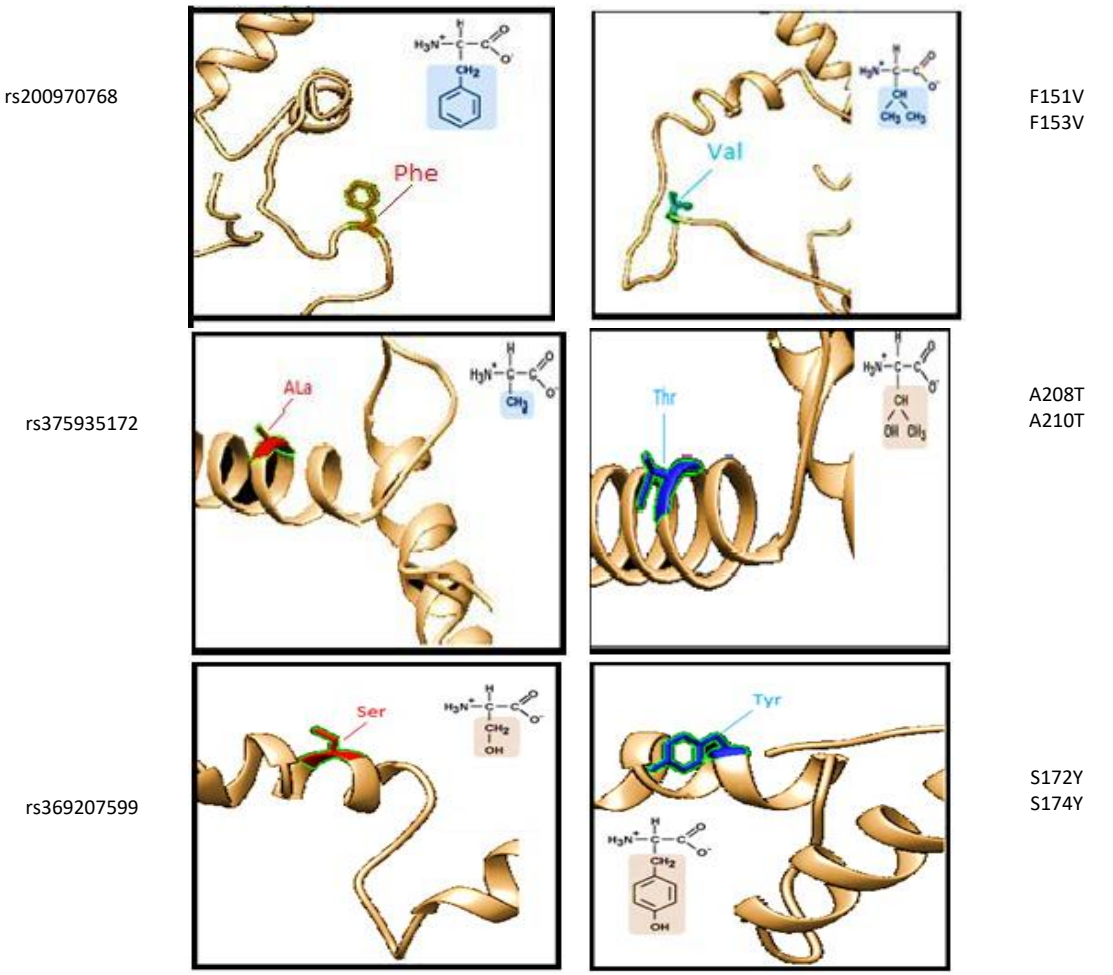


Figure 3. 3D model of *TAL1* protein (visualized by Chimera 1.10.2)

Table 3. Prediction results of SIFT, Polyphen, I mutant and PhD-SNP

						I mutant			PhD-SNP	
SNP	Amino Acid Change	Sift Score	Sift Prediction	Polyphen score	Polyphen prediction	SVM2	DDG	RI	Effect	RI
rs147015002	M160R	0.009	Deleterious	0.835	Possibly damaging	Decrease	-1.08	2	Neutral	1
rs147015002	M162R	0.01	Deleterious	0.835	Possibly damaging	Decrease	-1.08	2	Neutral	1
rs200970768	F151V	0.013	Deleterious	0.615	Possibly damaging	Decrease	-0.99	6	Neutral	5
rs200970768	F153V	0.035	Deleterious	0.745	Possibly damaging	Decrease	-1.07	6	Neutral	5
rs369207599	S172Y	0.004	Deleterious	0.981	Probably damaging	Increase	-0.29	2	Disease	1
rs369207599	S174Y	0.006	Deleterious	0.939	Probably damaging	Increase	-0.29	2	Disease	1
rs375935172	A210T	0.006	Deleterious	0.97	Probably damaging	Decrease	-0.79	8	Disease	5
rs375935172	A208T	0.006	Deleterious	0.97	Probably damaging	Decrease	-0.79	8	Disease	4

*DDG: free energy change value; SVM2: support vector machine; RI: reliability index

Table 4. SNPs and INDELs in miRNA target sites

Location	dbSNP ID	Wobble base pair	Ancestral Allele	Allele	miR ID	Conser-vation	miRSite	Function Class	Exp Support	context+ score change
47682966	rs181722922	N	C	C	hsa-miR-6134	2	tcctctCACCTCA	D	N	0.004
				T	hsa-let-7a-5p	2	tcctctTACCTCA	C	N	0.004
					hsa-let-7b-5p	2	tcctctTACCTCA	C	N	0.004
					hsa-let-7c-5p	2	tcctctTACCTCA	C	N	0.004
					hsa-let-7d-5p	2	tcctctTACCTCA	C	N	-0.003
					hsa-let-7e-5p	2	tcctctTACCTCA	C	N	0.004
					hsa-let-7f-5p	2	tcctctTACCTCA	C	N	-0.003
					hsa-let-7g-5p	2	tcctctTACCTCA	C	N	0.004
					hsa-let-7i-5p	2	tcctctTACCTCA	C	N	0.004
					hsa-miR-202-3p	2	tcctctTACCTCA	C	N	0.003
					hsa-miR-4458	2	tcctctTACCTCA	C	N	0.004
					hsa-miR-4500	2	tcctctTACCTCA	C	N	0.008
					hsa-miR-98-5p	2	tcctctTACCTCA	C	N	0.004
47683869	rs145888818	N	C	C	hsa-miR-4419a	2	agccctCTCCCTC	D	N	0.009
					hsa-miR-4510	2	agccctCTCCCTC	D	N	0.018
					hsa-miR-4721	3	AGCCCTCtccctc	D	N	-0.074
					hsa-miR-6127	2	agccctCTCCCTC	D	N	-0.01
					hsa-miR-6129	2	agccctCTCCCTC	D	N	-0.001
					hsa-miR-6130	2	agccctCTCCCTC	D	N	0.018
					hsa-miR-6133	2	agccctCTCCCTC	D	N	-0.01
				A	hsa-miR-6731-5p	2	agccCTCTCCCtc	D	N	0.038
					hsa-miR-6760-5p	2	agcccTCTCCCTc	D	N	0.085
					hsa-miR-8085	2	agccCTCTCCCtc	D	N	0.038
					hsa-miR-3158-3p	3	AGCCCTAtccctc	C	N	-0.005
					hsa-miR-4446-3p	3	AGCCCTAtccctc	C	N	0.001
					hsa-miR-5088-5p	3	AGCCCTAtccctc	C	N	-0.002
					hsa-miR-5191	2	agcCCTATCCctc	C	N	0.017

* Function Class:
D: The derived allele disrupts a conserved miRNA site (ancestral allele with support ≥2).
N: The derived allele disrupts a nonconserved miRNA site (ancestral allele with support < 2).
C: The derived allele creates a new miRNA site.
O: The ancestral allele cannot be determined.

Table 5: Phosphorylation sites predicted by NetPhos 3.1

Serine		Threonine		Tyrosine	
Position	**Score**	**Position**	**Score**	**Position**	**Score**
49	0.739	73	0.973	23	0.518
70	0.870	112	0.937	375	0.969
78	0.986	161	0.559		
83	0.804	255	0.552		
193	0.898	263	0.693		
217	0.728	322	0.946		
243	0.998	327	0.979		
265	0.984				
295	0.978				
357	0.807				
360	0.531				
364	0.822				
371	0.785				
374	0.996				
387	0.621				

Table 6: Ubiquitylation sites predicted by Ub-Pred and BDM-PUB

Ub-Pred		BD-PUB	
Position	**Score**	**Position**	**Score**
39	0.80	75	2.84
75	0.84	221	2.60
255	0.84	222	1.49
258	0.79	225	2.70
311	0.92	255	0.93
		258	1.60
		311	1.02

Discussion

Genetic polymorphism in *TAL1* gene was found sharing protein domain (bHLH domain) with five genes and associated in many diseases such as lymphoblastic leukemia, craniosynostosis, anemia and fibrodysplasia ossificans progressive.

Our present study detected eight SNPs in *TAL1* coding region to be highly damaging. The interesting finding was that the clinical significance for the four disease-related SNPs was unknown in the dbSNP/NCBI database. Insilico analysis of single nucleotide polymorphisms (SNPs) has become a valuable and essential tool for prediction of variants most likely associated with disease. This approach has been done for many disorders especially for cancer related genes [35-38]. Our methods in bioinformatics analysis were in conjunction with previous papers analyzing disease-related genes such as *VCAM-1*, *MSH6*, *GRM4*, *MYC* and *TAGAP* genes [39-42].

TAL1 has similar expression to four genes which are mainly either inhibitors of protein binding or regulating transcription binding factors (Figure 1, Table 1).

It has many molecular functions; it enables RNA polymerase II transcription factor activity and colocalizes with histone deacetylase complex (Table2). HSCs undergo differentiation when TAL1 activates transcription by recruiting a core complex DNA consisting of *E2A*/*HEB*, *GATA1/2/3*, *LMO1/2*, *LDB1*, and an additional complex comprising *ETO2*, *RUNX1*, *ERG* or *FLI1* [43]. The *TAL1*'s regulatory functions (lineage priming, activation, and repression of gene expression programs) give knowledge into principal developmental and transcriptional components and features mechanistic parallels between typical and oncogenic processes [44]. Also, Bae et al found that one intronic SNP of *TAL1* gene (rs2250380) was significantly associated with Schizophrenia [45].

Four thousand two hundred and twelve SNPs in *TAL1* gene were retrieved from dbSNP/NCBI in May 2018. There were nsSNPs, *3'UTR*, *5'UTR* and others (Figure 2). All nsSNPs in the coding region were subjected to different tools to test their effect on protein function and stability. Ninety nsSNPs were determined by SIFT to be tolerated or deleterious. According to Polyphen2, they were found to be benign, possibly or probably damaging. SNPs which scored ≤ 0.05 in SIFT and ~1 in Polyphen-2 were then selected so that only the deleterious and damaging ones would be analyzed.

The eight shortlisted damaging SNPs were further analyzed by I-Mutant to predict the effect of the mutant amino acids on the protein stability. The obtained results reflected that the stability with related free energy will be different due to mutation. Six SNPs (M →R, F→ V, A→ T in different positions) had decrease effect on stability with DDG values ranged between -0.79 − -1.08, while the two SNPs (S → Y; rs369207599) increase the stability of protein and also analyzed to be disease related using PHD- SNPs software (Table 3).

The rs375935172 caused amino acid substitution A208T and A210T. The mutant residue is bigger and more hydrophilic than the wild-type residue, which may cause loss of interactions with other molecules on the surface of the protein. This mutation is the most important as it is situated in the bHLH domain. The change presents an amino acid with various properties, which can disturb this domain and abrogate its function. The mutated residue is situated in a domain that is essential for binding of other molecules. It is possible that the mutation affects these contacts and might influence the interaction disturb signal transfer from binding domain to the activity domain.

The rs147015002 results in the substitution of amino acid M to R at positions 160 and 162. The original wild-type residue and newly introduced mutant residue differ in their specific size, charge, and hydrophobicity-value. The mutant residue is bigger than the wild-type residue which might lead to bumps. The wild-type residue charge was neutral; the mutant residue charge is positive which can cause repulsion of ligands or other residues with the same charge. The wild-type residue is more hydrophobic than the mutant residue. Hydrophobic interactions, either in the core of the protein or on the surface, will be lost.
The rs200970768 caused conversion of amino acid F to smaller amino acid V at position 151 or 153, while the rs369207599 result in replacement of S into Y at position 172 or 174 which differ in size. The mutant residue is bigger and this might lead to bumps. The mutant residue prefers to be in another secondary structure; therefore, the local conformation will be slightly destabilized (Figure 3).

Functional SNPs in three translated region in *TAL1* gene was analyzed using PolymiRTS software. Among 227 SNPs in *3'UTR* there were only 48 functional SNPs predicted (S1 Table). rs181722922 SNP contain (C) allele has 12 miRNA Sites as Target binding site can create a new microRNA site. rs145888818 SNP contain (D) allele has 10 miRNA Sites which they are derived allele that disrupts a conserved miRNA site (Table 4).

PTMs are imperative in directing structures and functions of proteins hence are engaged in numerous biological events, for example, protein-protein interactions and cell signaling etc [46, 47]. Phosphorylation of proteins is an essential regulatory mechanism as it changes the structural conformation of a protein, resulting in making it to become activated, deactivated, or altering its function [48]. Target amino acid is usually serine, threonine or tyrosine residues. Net Phos predicted 15 Serine, 7 Threonine and 2 Tyrosine residues which have high potentiality to be phosphorylated (Table 5).

Ubiquitination (or ubiquitylation) is an enzymatic post-translational modification in which an ubiquitin protein is linked to a substrate protein. It changes cellular process by regulating the decomposition of proteins (via the proteasome and lysosome), arranging the cellular localization of proteins, activating and inactivating proteins, and modulating protein-protein

interactions [49-51]. UbPred and BDM-PUB tools predicted five and seven Lysine residues, respectively which undergo ubiquitylation (Table 6). Although PTMs are not coincided in position with the nsSNPs in *TAL1* gene, results by similarity revealed that phosphorylation of Ser-122 in *TAL1*gene is strongly stimulated by hypoxia and subsequently ubiquitination targets the protein for rapid degradation via the ubiquitin system (Table 6). This process may be characteristic for microvascular endothelial cells, since it could not be observed in large vessel endothelial cells.

Conclusion

This study predicted that the stability and function of *TAL1* protein is affected by eight high risk nsSNP. One of these mutationS (rs375935172) is located at the highly conserved bHLH domain region; hence it is of high concern as this is the only functional region of the protein. In addition to these findings, the study identifies several *TAL1* sites that undergo post transitional modification. Therefore, further investigations and wet lab experimentation are required to determine the effects of these polymorphisms on the protein function which can be a hit for discovering new drugs.

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Conflict of interest

Authors declare no conflict of interest.

Data availability

The authors confirm that all data underlying the findings described in the manuscript are fully available without restriction.

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