Novel Missense Single Nucleotide Polymorphisms of Human CD38 Gene Allied to Chronic Lymphocytic Leukemia: A Bioinformatics Approach

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Background

B-cell chronic lymphocytic leukemia (CLL) is a hematological malignancy that develops from abnormal lymphoid stem cells in the bone marrow and secondary lymphoid tissue (B-lymphocytes).(1,2) One of the significant contributors to the pathogenesis of CLL is a mutation of CD38 protein. CD38 is a multifunctional ectoenzyme expressed in B-lymphocytes, with a poorly understood in the pathogenesis of CLL.(3)

Objective

Here we aimed to bioinformatically appraise CD38 missense single nucleotide polymorphisms allied to CLL and to predict their effect on the structure and function of CD38 protein.

Methods & Results

A literature review identified two SNPs in the CD38 gene that had been discovered by PCR of patients with CLL. Functional analysis by SIFT, Polyphen2, and PROVEAN revealed nine deleterious SNPs in the CD38 coding region. These SNPs were further analyzed by SNAP2, SNP@GO. PMut, STRING(Figure 1), and other software packages which confirmed nine of those SNPs to be truly pathogenic. Stability analysis performed using I-Mutant identified seven SNPs that were predicted to decrease the stability of CD38 and two SNPs predicted to increase it; while MUpro identified eight SNPs that were predicted to decrease. the stability of the protein and one SNP that was predicted to increase it. Physiochemical analysis was done using Project HOPE to visualize the most significant SNPs using the Chimera software(Figure 2). Finally, the following SNPs (S193C, D147G, and P98L) were predicted as deleterious in relation to the structure and function of CD38 protein by most of the software used in this study (Table 1).

Table 1: Prediction of the nsSNPs on the stability of CD38 protein using I-Mutant and MUpro Servers. Data shown are qualitative and quantitative scoring effects.

Residue	I-Mutant Prediction Effect	Score	MUpro Prediction Effect (Stability)	Score
R140W	Decrease	0.13	Decrease	-0.743
T148M	Increase	-0.07	Decrease	-0.471
K234N	Decrease	-0.23	Decrease	-0.666
S193C	Decrease	-0.60	Decrease	-0.168
D147G	Decrease	-0.92	Decrease	-1.514
F284C	Decrease	-1.90	Decrease	-1.285
D179G	Decrease	-1.39	Decrease	-1.131
T144N	Increase	-0.52	Decrease	-0.770
P98L	Decrease	-0.30	Increase	0.217

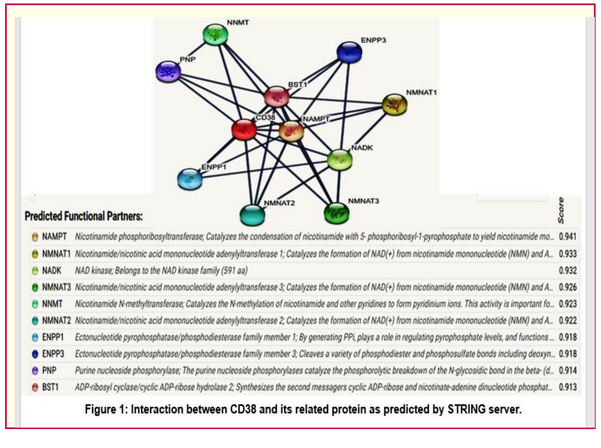


Figure 1: Interaction between CD38 and its related protein as predicted by STRING server.

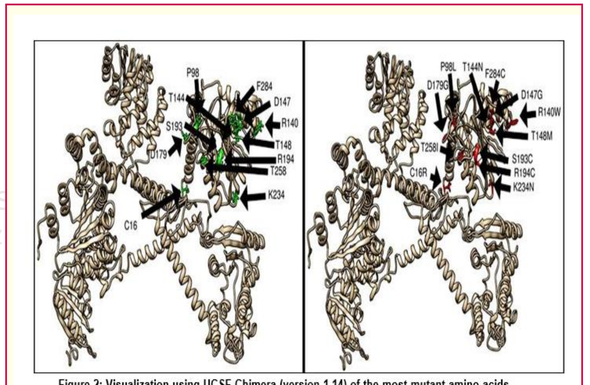


Figure 2: Visualization using UCSF Chimera (version 1.14) of the most mutant amino acids (redon the right) in the CD38 protein and their wild type counterparts (green on the left).

Discussion

In a previous study performed by Fadl et al(4), a significant correlation between CD38 SNP and the age and sex of patients was found in her work, with a higher frequency of the rs1800561-CT genotype among younger patients (age ≤60) years and in males.Following that a comprehensive bioinformatics analysis has been conducted to predict the effect of nsSNPs on the structure and function of CD38, which is a key mediator in the pathogenesis of CLL. Three novel nsSNPs (S193C, D147G, and P98L) were predicted, by most of the software packages used in the study, to cause the most damaging mutations for CD38.They were predicted to lead to loss or disturbance of the protein's internal and external interactions. This ultimately causes loss of the protein's function that could impact many pathways implicated in the disease development. Therefore novel nsSNPs and the predicted alteration in CD38 structure/function relationship are expected to modulate the risk of the disease. Lastly, those nsSNPs may influence CD38 role as a prognostic marker by increasing its enzymatic activity and then aggressiveness of CLL.

Conclusions

We reported three novel driver SNPs in the CD38 gene that could result in deleterious effects on protein structure. This genetic variation might eventually alter the molecular functions of CD38 protein implicated in the development of CLL.

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