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EC PROTEOMICS AND BIOINFORMATICS
Research Article

Homology Modeling of P30481: A Novel Drug Target for Psoriasis

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Received: July 28, 2017; **Published:** September 05, 2017

Abstract

In the modern era of Proteomics, Psoriasis was characterized by the expression of additional proteins apart from the human leucocyte antigens (HLAs) to explore the objective of novel drug target for Psoriasis. Since there is a lack of more proteomic profiles for Psosriasis, the computational approach of graph theory and homology modeling were executed to address the research problem.

Keywords: *Homology Modeling; P30481; Psoriasis*

Introduction

Psoriasis is a chronic skin disease in adults. The prevalence of Psoriasis is 2 to 3% across the globe [1,2]. Majorly, there are five types (erythrodermic psoriasis, plaque psoriasis, guttate or eruptive psoriasis, inverse psoriasis and pustular psoriasis) [3-5]. Since Psoriasis is a multi-factorial disease, there are more drug targets with a lack of rationality. Since the mechanism of action is not understood completely [6], current research on genetic and protein regulation by a cascade of pathway interference crates an impact to identify a drug target in Psoriasis [7]. Proteins of leucocytes play a vital role in the process of transcription and translation of disease pathology. Previous researches in leucocytes indicate the fact that gene regulation of autoimmunity can lead to malignant diseases [8]. Transcriptional factors are involved in the cellular process of autoimmune diseases to create diversity in development [9,10]. In case of disorders in inflammatory responses, immune cells of the innate/adaptive immune system are activated and recruited to the inflammation site [11]. The process of attraction and activation of immune cells is regulated by a variety of cytokines and chemokines to illustrate the effect of transcription factors in autoimmune diseases like psoriasis [11]. A characteristic profile of gene-protein interaction in psoriasis can suggest certain putative functions in the perturbed production of cytokine signaling during a chronic inflammatory condition in psoriasis [11].

Methodology

Genes associated with psoriasis were extracted from pubmed, DisGeNET and OMIM. After extraction the similar genes were subject to Uniprot for reviewed proteins (Target Proteins of expressed genes-validated by experiments). Then, identification of a specific set of reviewed proteins-gene pair was carried out. Further, the pair was subjected to network construction and analysis in cytoscape. Finally the protein with maximum connection with the gene set was subject to homology modeling and binding analysis.

Results and Discussion

Data mining of Psoriasis associated gene search in pubmed, DisGeNET and OMIM resulted in 104 genes and 141 proteins contain a connection (Table 1).

In the uniprot search for reviewed proteins, P30841 was obtained only for HLA-B and not for HLA-C. The inference is not only from the interaction alone, the complete network of gene-protein interaction pair was analyzed by various Statistical methods in Cytoscape software. From the analysis, it was observed that P30841 was closely related to the associated genes than other proteins (Figure 1).

Since, the structure of P30481 was not resolved by XRD or NMR, homology modeling technique was used to predict the 3D structure of protein (Figure 2). Homology Modeling was performed by IntFold [12] refined by Galaxy [13] and validated by Rampage. Finally, binding analysis was executed by Funfold2 [14].

Genes (Litrature/DisGeNET/OMIM)	Proteins (Uniprot-Reviewed)
HPSE	Q9Y251
TGM1	P22735
CCL20	P78556
IFIH1	Q9BYX4
STAT2	P52630
CCL2	P13500
EIF4E	P06730
FABP5	Q01469
PPARD	Q03181
ISG20	Q96AZ6
TAP2	Q03519
CYLD	Q9NQC7
IGF1	P05019
BCL2	P10415
AREG	P15514
VNN3	Q9NY84
MMP9	P14780
HBEGF	Q99075
TGFA	P01135
LHFP	Q9Y693
EGFR	P00533
SGCG	Q13326
SDC4	P31431
IGF1R	P08069
LEP	P41159
KLK13	Q9UKR3
HMOX1	P09601
KLK1	P06870
IFI6	P09912
SFXN1	Q9H9B4
PSORS7	NIL
IL23R	Q5VWK5
PTPN22	Q9Y2R2
PSORS4	NIL
FLG	P20930
LCE3C	Q5T5A8
LCE3B	NIL
LOR	P23490

S100A9	P06702
S100A8	P05109
S100A7	P31151
IL10	P22301
IL20	Q9NYY1
IL24	Q13007
ADAM17	P78536
IL36RN	Q9UBH0
IL1RN	P14778
CTLA4	P16410
SGPP2	Q8IWX5
CX3CR1	P49238
CAMP	P49913
PSORS5	NIL
CSTA	P01040
RARRES1	P49788
PSORS3	NIL
IL21	Q9HBE4
PSORS9	NIL
IRF2	P14316
PSORS11	NIL
IL4	P05112
IL12B	P29460
CDKAL1	Q5VV42
CDSN	Q15517
CCHCR1	Q8TD31
HLA-C	P10321
	P30508
	P30499
	P04222
	P30504
	Q29963
	P30510
	Q07000
	Q29960
	Q95604
	P30501
	Q9TNN7
	P30505
	Q29865

HLA-B	P01889
	P30464
	P03989
	P30685
	P30475
	Q04826
	P30481
	P18464
	P30460
	P30461
	P30466
	Q95365
	P30479
	P30491
	P30493
	P18465
	Q31612
	P30462
	P18463
	P30480
	P30483
	P30484
	P30485
	P30486
	P30487
	P30488
	P30490
	P30492
	P30495
	P10319
	Q29940
	Q29836
	P30498
	Q31610
	Q29718
HCP5	Q6MZN7
LTA	P01374
TNF	P01375
TNXB	P22105
TRAF3IP2	O43734

CCR6	P51684
IL6	P05231
DEFB4A	O15263
CRH	P06850
LYNX1	Q9BZG9
CCL27	Q9Y4X3
TNFSF8	P32971
RARRES3	Q9UL19
TNFRSF1A	P19438
VDR	P11473
IL23A	Q9NPF7
IL22	Q9GZX6
NTS	P30990
SELPLG	Q14242
ITGAL	P20701
PSORS8	NIL
NOD2	Q9HC29
IL17C	Q9P0M4
STAT3	P40763
SLC9A3R1	O14745
SOCS3	O14543
CARD14	Q9BXL6
RPTOR	Q8N122
ZNF750	Q32MQ0
PSORS10	NIL
PSORS6	NIL
BSG	P35613
C3	P01024
JUNB	P17275
TGFB1	P01137
PI3	P19957
RNF114	Q9Y508
ITGB2	P05107

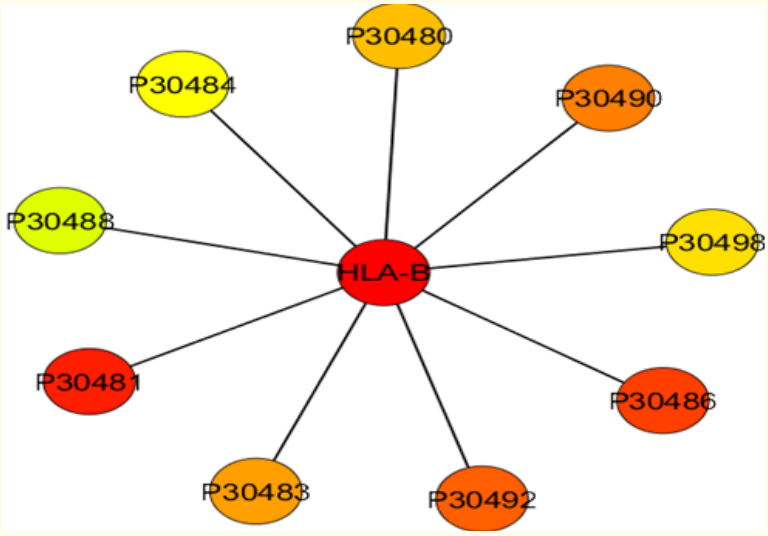

Figure 1: *Interaction of P30481 and allied proteins of HLA-B.*

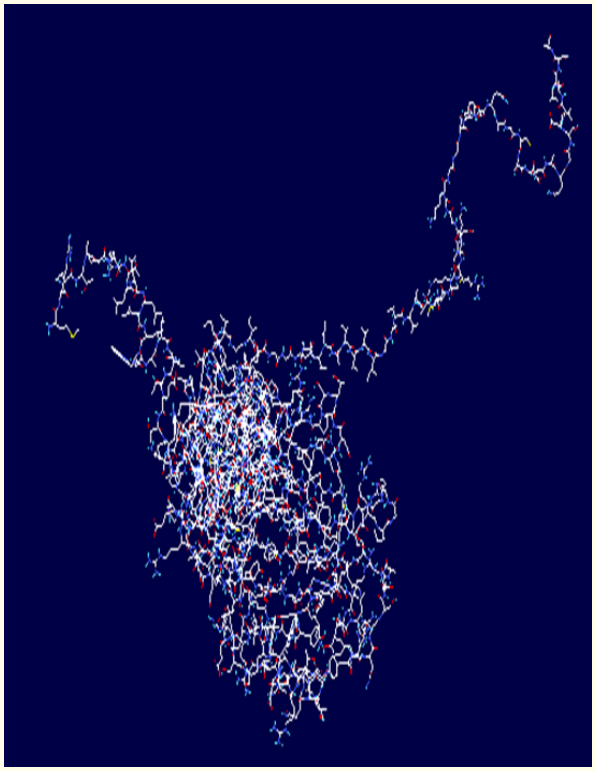

Figure 2: *Predicted Structure of P30481 by homology modeling.*

Implication of homology model was calculated by Ramachandran Plot (Figure 3, Figure 4). In our modeled structure 98.3% residues are present in the favored region (Figure 5).

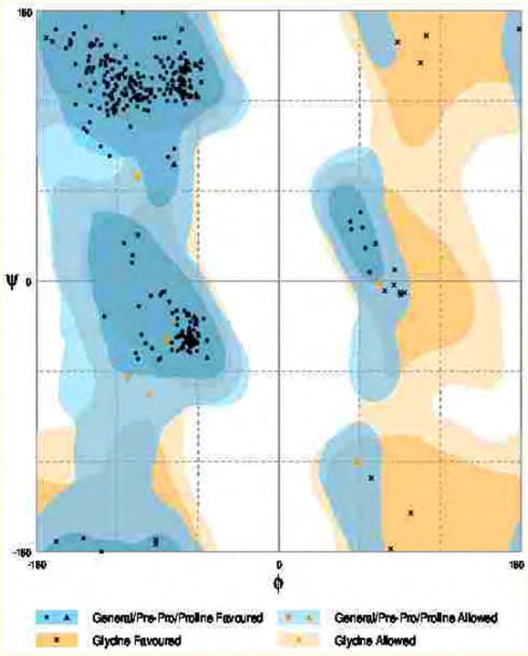

Figure 3: *R Plot evaluation of residues in the predicted structure (Rampage Analysis).*

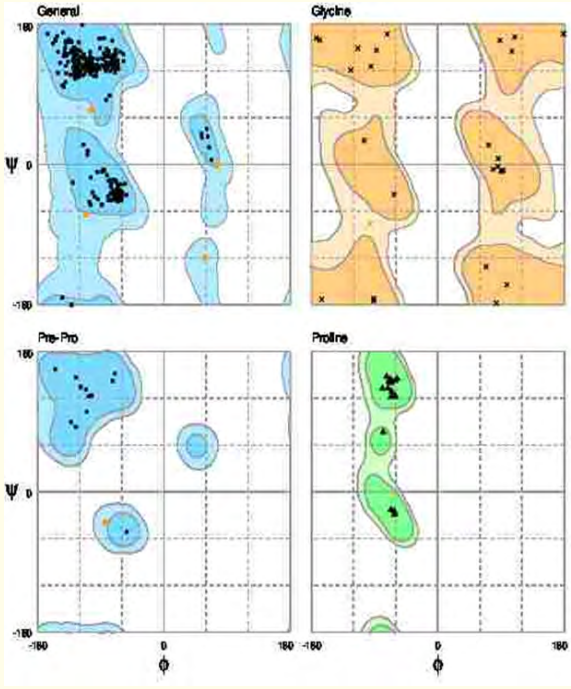

Figure 4: *Extended R Plot evaluation of residues in the predicted structure (Rampage Analysis).*

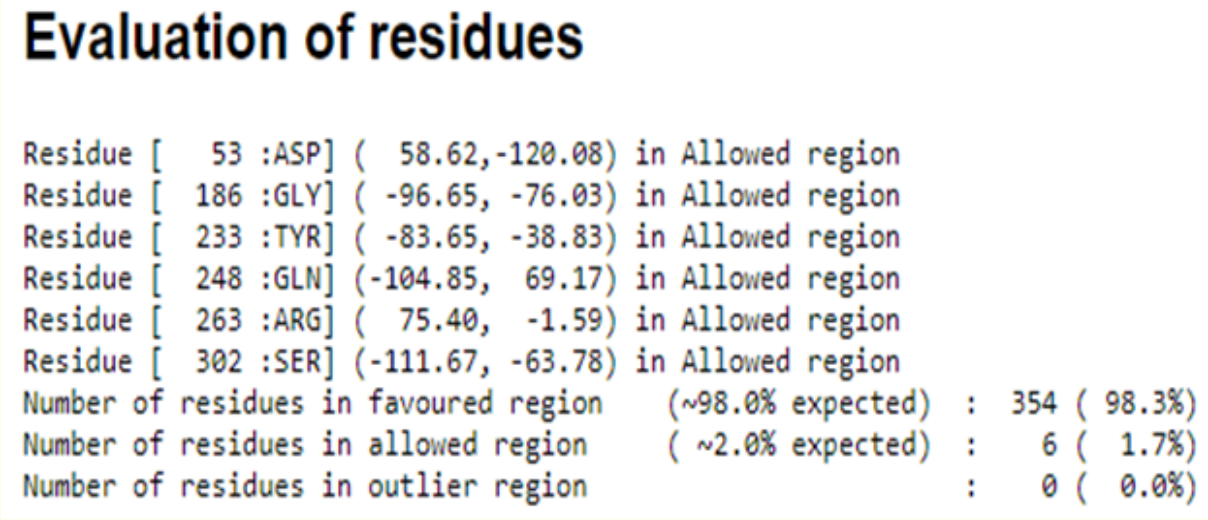

Figure 5: *Evaluation of residues in the predicted structure (Rampage Analysis).*

Binding Analysis was done by fun fold program by calculating the clustered topologies of the active centers without the hindrance of steric to predict the residues involved in the binding site of the protein (Figure 6).

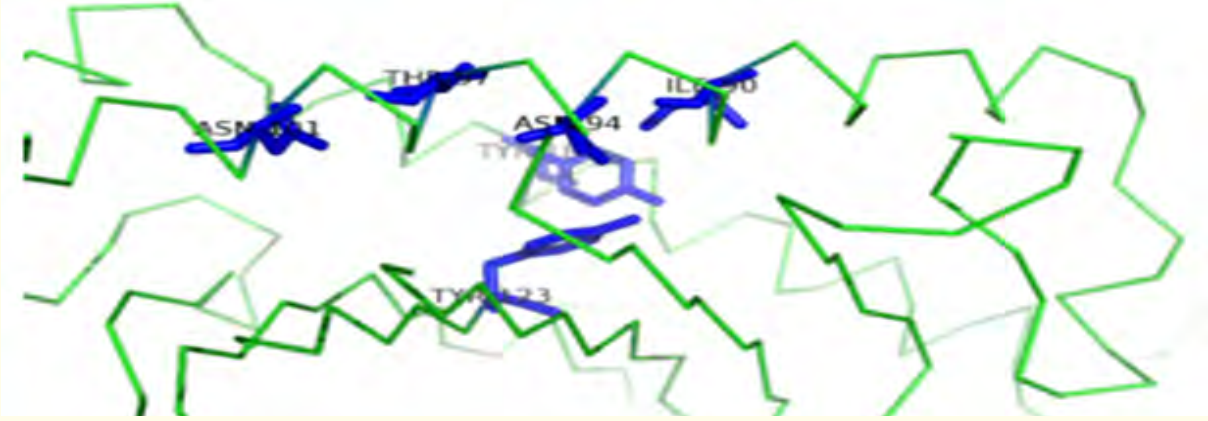

Figure 6: *Binding Analysis of predicted structure (Funfold Analysis- Binding site- 90, 94, 97, 101, 123).*

Conclusion

Psoriasis is a chronic inflammatory disease of complex nature in skin with a multiple expression of proteins and till date there is no specific target protein to treat Psoriasis, current drug targets can only reduce the lesions. Gene protein interaction is the basic criteria for "Rational based drug design and identifying a therapeutic target". In the analysis part only the Psoriasis associated genes from pubmed, DisGeNET, and OMIM were extracted and that has no connection with the transcriptome. From the analysis, it was observed that P30841 was closely related to the associated genes than other proteins. Homology modeling technique was used to predict the 3D structure of P30841, due to lack of resolved structures in PDB (Protein Data Bank). Implication of homology model was calculated by Ramachandran Plot. In this manuscript, an overview of gene-protein interaction and their impact in psoriasis was analyzed. Though, the exact mechanism

of gene-protein interaction in psoriasis was not understood completely, a novel drug target of Psoriasis was mediated by analyzing the gene-protein interaction to reveal the initiation of rational drug design in psoriasis.

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Volume 1 Issue 1 September 2017