

Homology Modeling of P30481: A Novel Drug Target for Psoriasis

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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	KLK13 Q9UKR3	
HMOX1	HMOX1 P09601	
KLK1	P06870	
IFI6	P09912	
SFXN1	Q9H9B4	
PSORS7	NIL	
IL23R	Q5VWK5	
PTPN22	Q9Y2R2	
PSORS4	NIL	
FLG	P20930	
LCE3C	Q5T5A8	
LCE3B	NIL	
LOR	P23490	

S100A8P05109S100A7P31151IL10P22301IL20Q9NY1IL20Q9NY1IL21Q13007ADAM17P78536IL36RNQ9UBH0IL1RNP14778CTLA4P16410SGPP2Q8IWX5CX3CR1P49238CX3CR1P49238CX3CR1P49913PSORS5NILCSTAP01040RARRE51P49788PSORS3NILIL21Q9HBE4PSORS9NILIL21Q9HE4PSORS1NILIL28P29460CDKAL1Q5V42CDSNQ15517CCHCR1Q8TD31P10321P10321P10321P30508P30504Q29963Q29963P30510Q29960Q95604P30501Q97NN7P30505Q23960Q23960Q23960Q23960P30501Q23965P30505	S100A9	P06702	
S100A7 P31151 IL10 P22301 IL20 Q9NY1 IL24 Q13007 ADAM17 P78536 IL36RN Q9UBH0 IL1RN P14778 CTLA4 P16410 SGPP2 Q8IWX5 CX3CR1 P49238 CX3CR1 P49238 CX3CR1 P49913 CX3CR1 P49913 CX3CR1 P49788 CX3CR1 P49788 CX3CR1 P49788 PSORS5 NIL CSTA P01040 RARRES1 P49788 PSORS9 NIL IL21 Q9HBE4 PSORS9 NIL IRF2 P14316 PSORS1 NIL IL12B P29460 CDKAL1 Q5V42 CDSN Q1517 CCHCR1 Q8TD31 P10321 P10321 P10321 P30508 P30504 P30504 Q29963 P30510 Q29960 P30501 Q30505 Q95064 P30501 Q30505 Q299604 P30501 Q30505 Q239650	S100A8	P05109	
IL10P22301IL20Q9NYY1IL24Q13007ADAM17P78536IL36RNQ9UBH0IL1RNP14778CTLA4P16410SGPP2Q8IWX5CX3CR1P49238CX3CR1P49238CMPP49913PSORS5NILCSTAP01040RARRES1P49788PSORS3NILIL21Q9HBE4PSORS9NILIL4P29400CDSNQ15517CCHCR1Q8TD31CCHCR1Q8TD31P10321P30508P30504Q29963Q29963P30510Q29963P30511P30501Q29865	S100A7	P31151	
IL20Q9NY1IL24Q13007ADAM17P78536IL36RNQ9UBH0IL1RNP14778CTLA4P16410SGPP2Q8IWX5CX3CR1P49238CX3CR1P49913PSORS5NILCSTAP01040RARRE51P49788PSORS3NILIL21Q9HBE4PSORS9NILIRF2P14316PSORS11NILIL4P05112IL12BP29460CDKAL1Q5VV42CDSNQ15517CCHCR1Q8TD31P10321P30508P30506P30510HLA-CQ29963Q29963Q29963Q29960Q29960Q29960Q15517Q29963P30551P30550P30551Q29963P30550Q29963P30550Q29963Q29963Q29963Q29963Q29963Q29963Q29963Q29963Q29964P30551Q29965Q29965Q29865Q29865	IL10	P22301	
IL24Q13007ADAM17P78536IL36RNQ9UBH0IL1RNP14778CTLA4P16410SGPP2Q8IWX5CX3CR1P49238CX3CR1P49913PSORS5NILCSTAP01040RARRES1P49788PSORS3NILIL21Q9HBE4PSORS9NILIL21P14316PSORS11NILIL4P05112IL4Q5V42CDSNQ15517CCHCR1Q8TD31PG0508P10321PG0508P30508P30504P30504Q29963P30510Q29963Q29604Q95604Q95604P30505Q29865	IL20	Q9NYY1	
ADAM17P78536IL36RNQ9UBH0IL1RNP14778CTLA4P16410SGPP2Q8WX5CX3CR1P49238CAMPP49913CAMPP49913CSTAP01040RARRES1P49788PSORS3NILIL21Q9HBE4PSORS9NILIRF2P14316PSORS11NILIL12BP29460CDKAL1Q5VV42CDKAL1Q5VV42CDKAL1Q8TD31P30508P30499P49238P30508P30504P30504Q29963Q95604Q97NN7Q97NN7P30505Q29865	IL24	Q13007	
IL36RNQ9UBH0IL1RNP14778CTLA4P16410SGPP2Q8IWX5CX3CR1P49238CAMPP49913CAMPP49913CSTAP1040CSTAP10140CSTAP10140RARES1Q9HBE4PSORS3NILIL21Q9HBE4PSORS9NILIRF2P14316PSORS11NILIL4P05112IL12BP29460CDKAL1Q5VV42CDSNQ15517CCHCR1Q8TD31PS0859P10321HLA-CP30508P30504Q29963Q29963Q3501Q5004Q3505Q97NN7Q29865	ADAM17	P78536	
ILIRNP14778CTLA4P16410SGPP2Q8IWX5CX3CR1P49238CAMPP49913CAMPP49913CSTAP01040CSTAP01040RARES1P49788PSORS3NILIL21Q9HBE4PSORS9NILIRF2P14316PSORS11NILIL12BP29460CDKAL1Q5VV42CDSNQ15517CCHCR1Q8TD31P30508P10321P450510P30508P30504P30504Q29963P30510Q29960Q95604Q30505Q29865	IL36RN	Q9UBH0	
CTLA4P16410SGPP2Q8IWX5CX3CR1P49238CAMPP49913CAMPP49913CSTAP01040CSTAP01040RARES1P49788PSORS3NILIL21Q9HBE4PSORS9NILIRF2P14316PSORS11NILIL4P05112IL12BP29460CDKAL1Q5VV42CDSNQ15517CCHCR1Q8TD31P10321P10321IL5P30508P30508Q29963Q29963Q3501Q3505Q95604Q3505Q29865	IL1RN	P14778	
SGPP2Q8IWX5CX3CR1P49238CAMPP49913PSORS5NILCSTAP01040RARRES1P49788PSORS3NILIL21Q9HBE4PSORS9NILIRF2P14316PSORS11NILIL4P05112IL12BP29460CDKAL1Q8TD31CDSNQ15517CCHCR1Q8TD31P10321P30508P30504Q29963Q195510Q29960Q195011Q1000Q195011Q1000Q195011Q1000Q195011Q1000Q195011Q1000Q195011Q1000Q195011Q1000Q195011Q1000Q1950510Q1000Q1950511Q1000Q1950511Q1000Q1950511Q1000Q1950511Q1000Q1950511Q1000 </td <td>CTLA4</td> <td colspan="2">P16410</td>	CTLA4	P16410	
CX3CR1P49238CAMPP49913PSORS5NILCSTAP01040RARRES1P49788PSORS3NILIL21Q9HBE4PSORS9NILIRF2P14316PSORS11NILIL4P05112IL12BP29460CDSNQ15517CDSNQ15517CCHCR1Q8TD31P10321P30508P30504Q29963Q195510Q29963Q195011Q195014Q195011Q195011P30501Q197NN7P30505Q29865	SGPP2	Q8IWX5	
CAMPP49913PSORS5NILCSTAP01040RARRES1P49788PSORS3NILIL21Q9HBE4PSORS9NILIRF2P14316PSORS11NILIL28P29460CDKAL1Q5VV42CDSNQ15517CCHCR1Q8TD31CCHCR1Q8TD31P30508P30508P30504Q29963Q29963Q29963Q95604Q95604Q97NN7Q29865	CX3CR1	P49238	
PSORS5NILCSTAP01040RARRES1P49788PSORS3NILIL21Q9HBE4PSORS9NILIRF2P14316PSORS11NILIL4P05112IL12BP29460CDKAL1Q5VV42CDSNQ15517CCHCR1Q8TD31P10321P10321P30508P30499P30504Q29963Q29963Q3510Q29960Q95604Q95604P30505Q29865P30505	CAMP	P49913	
CSTA P01040 RARRES1 P49788 PS0RS3 NIL IL21 Q9HBE4 PS0RS9 NIL IRF2 P14316 PS0RS11 NIL IL4 P05112 IL12B P29460 CDKAL1 Q5VV42 CDSN Q15517 CCHCR1 Q8TD31 P10321 P30508 P30499 P04222 P30504 Q29963 Q29963 P30510 Q29960 P30501 Q95604 P30501 Q97NN7 P30505 Q29865 P30505	PSORS5	NIL	
RARRES1P49788PSORS3NILLL21Q9HBE4PSORS9NILIRF2P14316PSORS11NILIL4P05112IL12BP29460CDKAL1Q5VV42CDSNQ15517CCHCR1Q8TD31P10321P30508P30508P30508P30504Q29963Q29963Q15517Q07000Q2960Q15510P30510P30510Q29963P30501Q2960Q95604P30505Q29865P30505	CSTA	P01040	
PSORS3NILIL21Q9HBE4PSORS9NILIRF2P14316PSORS11NILIL4P05112IL12BP29460CDKAL1Q5VV42CDSNQ15517CCHCR1Q8TD31P10321P30508P30508P30499P04222P30504Q29963P30510Q29960Q95604Q95604P30505Q29865P30505	RARRES1	P49788	
IIL21 Q9HBE4 PSORS9 NIL IRF2 P14316 PSORS11 NIL IL4 P05112 IL12B P29460 CDKAL1 Q5VV42 CDSN Q15517 CCHCR1 Q8TD31 P10321 P30508 P30508 P30508 P30504 Q29963 Q29963 P30510 Q29960 Q29960 Q95604 P30501 Q97NN7 P30505 Q29865 Q29865	PSORS3	NIL	
PSORS9 NIL IRF2 P14316 PSORS11 NIL IL4 P05112 IL12B P29460 CDKAL1 Q5VV42 CDSN Q15517 CCHCR1 Q8TD31 P10321 P10321 P30508 P30508 P30504 P30504 Q29963 P30510 P30510 Q29960 Q95604 P30501 Q97NN7 P30505 Q29865 P30505	IL21	Q9HBE4	
IRF2 P14316 PSORS11 NIL IL4 P05112 IL12B P29460 CDKAL1 Q5VV42 CDSN Q15517 CCHCR1 Q8TD31 P10321 P30508 P30508 P30508 P30504 Q29963 Q29963 P30510 Q29960 Q95604 P30501 Q97NN7 Q07005 Q29865	PSORS9	NIL	
PSORS11 NIL IL4 P05112 IL12B P29460 CDKAL1 Q5VV42 CDSN Q15517 CCHCR1 Q8TD31 P10321 P30508 P30508 P30499 P04222 P30504 Q29963 P30510 HLA-C Q07000 Q95604 P30501 Q97NN7 Q97NN7 Q29865 Q29865	IRF2	P14316	
IL4 P05112 IL12B P29460 CDKAL1 Q5VV42 CDSN Q15517 CCHCR1 Q8TD31 P10321 P30508 P30499 P04222 P30504 Q29963 Q29963 Q29963 Q29960 Q29960 Q95604 P30501 Q97NN7 P30505 Q29865 P30505	PSORS11	NIL	
IL12B P29460 CDKAL1 Q5VV42 CDSN Q15517 CCHCR1 Q8TD31 P10321 P10321 P30508 P30499 P30504 Q29963 P30510 Q29963 Q07000 Q29960 Q95604 P30501 Q97NN7 P30505 Q29865 P30505	IL4	P05112	
CDKAL1 Q5VV42 CDSN Q15517 CCHCR1 Q8TD31 P10321 P10321 P30508 P30508 P30509 P04222 P30504 Q29963 P30510 Q29960 Q29960 Q95604 Q95604 Q97NN7 P30505 Q29865	IL12B	P29460	
CDSN Q15517 CCHCR1 Q8TD31 P10321 P30508 P30499 P30499 P04222 P30504 Q29963 P30510 P30510 Q29960 Q29960 Q95604 Q95604 P30501 Q97NN7 P30505 Q29865 P30505	CDKAL1	Q5VV42	
CCHCR1 Q8TD31 P10321 P30508 P30499 P30422 P04222 P30504 Q29963 P30510 HLA-C Q07000 Q29960 Q95604 Q95001 Q97NN7 P30505 Q29865	CDSN	Q15517	
P10321 P30508 P30499 P04222 P30504 Q29963 P30510 Q29960 Q29960 Q95604 P30501 Q97NN7 P30505 Q29865	CCHCR1	Q8TD31	
P30508 P30499 P04222 P30504 Q29963 P30510 Q07000 Q29960 Q95604 P30501 Q97NN7 P30505 Q29865		P10321	
P30499 P04222 P30504 Q29963 P30510 Q07000 Q29960 Q95604 P30501 Q9TNN7 P30505 Q29865		P30508	
P04222 P30504 Q29963 P30510 Q07000 Q29960 Q95604 P30501 Q97NN7 P30505 Q29865		P30499	
P30504 Q29963 P30510 Q07000 Q29960 Q95604 P30501 Q97NN7 P30505 Q29865	HLA-C	P04222	
Q29963 P30510 Q07000 Q29960 Q95604 P30501 Q97NN7 P30505 Q29865		P30504	
HLA-C P30510 Q07000 Q29960 Q95604 P30501 Q97NN7 P30505 Q29865		Q29963	
HLA-C Q07000 Q29960 Q95604 P30501 Q9TNN7 P30505 Q29865		P30510	
Q29960 Q95604 P30501 Q9TNN7 P30505 Q29865		Q07000	
Q95604 P30501 Q9TNN7 P30505 Q29865		Q29960	
P30501 Q9TNN7 P30505 Q29865		Q95604	
Q9TNN7 P30505 Q29865			
P30505 Q29865		P30501	
Q29865		Q9TNN7	
		Q9TNN7 P30505	

	P01889
	P30464
	P03989
	P30685
	P30475
	Q04826
	P30481
	P18464
HLA-B	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
НСР5	Q6MZN7
LTA	P01374
TNF	P01375
TNXB	P22105
TRAF3IP2	043734

CCR6	P51684	
IL6	IL6 P05231	
DEFB4A	015263	
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	014745	
SOCS3	014543	
CARD14	CARD14 Q9BXL6	
RPTOR	RPTOR Q8N122	
ZNF750	Q32MQ0	
PSORS10	NIL	
PSORS6	NIL	
BSG	P35613	
С3	P01024	
JUNB	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).

Evaluation of residues		
Residue [53 :ASP] (58.62,-120.08) in Allowed region Residue [186 :GLY] (-96.65, -76.03) in Allowed region Residue [233 :TYR] (-83.65, -38.83) in Allowed region Residue [248 :GLN] (-104.85, 69.17) in Allowed region Residue [263 :ARG] (75.40, -1.59) in Allowed region Residue [302 :SER] (-111.67, -63.78) in Allowed region Number of residues in favoured region (~98.0% expected)	:	354 (98.3%)
Number of residues in allowed region (~2.0% expected) Number of residues in outlier region	:	6 (1.7%) 0 (0.0%)

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.

Bibliography

- 1. Zhao YK., *et al.* "Developing Shingles-Induced Koebner Phenomenon in a Patient With Psoriasis: A Case Report". *Medicine* 94.26 (2015): e1009.
- 2. Sonkoly E., et al. "MicroRNAs: novel regulators involved in the pathogenesis of psoriasis?" PLoS One 2.7 (2007): e610.
- 3. Boehncke WH and Schön MP. "Psoriasis". Lancet 386.9997 (2015): 983-994.
- 4. Chandra A., et al. "Genetic and epigenetic basis of psoriasis pathogenesis". Molecular Immunology 64.2 (2015): 313-323.
- 5. Trowbridge RM and Pittelkow MR. "Epigenetics in the pathogenesis and pathophysiology of psoriasis vulgaris". *Journal of Drugs in Dermatology* 13.2 (2014): 111-118.
- 6. Jinnin M. "[microRNA in autoimmune disorders]". Nihon Rinsho Meneki Gakkai Kaishi 34.6 (2011): 439-446.
- Deng X., *et al.* "The role of microRNAs in autoimmune diseases with skin involvement". *Scandinavian Journal of Immunology* 81.3 (2015): 153-165.
- 8. Ivey KN and Srivastava D. "microRNAs as developmental regulators". Cold Spring Harbor Perspectives in Biology 7.7 (2015): a008144.
- 9. Singh RP, et al. "The role of miRNA in inflammation and autoimmunity". Autoimmunity Reviews 12.12 (2013): 1160-1165.
- Jimenez SA and Piera-Velazquez S. "Potential role of human-specific genes, human-specific microRNAs and human-specific noncoding regulatory RNAs in the pathogenesis of systemic sclerosis and Sjogren's syndrome". *Autoimmunity Reviews* 12.11 (2013): 1046-1051.
- 11. Schonthaler HB., *et al.* "Targeting inflammation by modulating the Jun/AP-1 pathway". *Annals of the Rheumatic Diseases* 70.1 (2011): i109-i112.
- 12. McGuffin LJ., *et al.* "IntFOLD: an integrated server for modelling protein structures and functions from amino acid sequences". *Nucleic Acids Research* 43.1 (2015): W169-W173.
- 13. WH Shin., et al. "Prediction of Protein Structure and Interaction by GALAXY protein modeling programs". Bio Design 2.1 (2014): 1-11.
- Roche DB., et al. "The FunFOLD2 server for the prediction of protein-ligand interactions". Nucleic Acids Research 41 (2013): W303-W307.

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