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ORIGINAL ARTICLE

Exploring genetic targets of psoriasis using genome wide association studies (GWAS) for drug repurposing

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Abstract

Psoriasis is a chronic inflammatory disease causing itching in the body and pain in the joints. Currently, no permanent cure is available at a commercial level for this disease. Genome wide association studies (GWAS) provide a deeper insight that helps in better understanding this disease and further possible cure of this disease. The major goal of the present study is to identify potent genetic targets of psoriasis disease using GWAS approach and identify drugs for repurposing. The methods used include GWAS catalogue, GeneAnalytics, canSAR protein annotation tool, VarElect, Drug bank, Proteomics database, ProTox software. By exploring GWAS catalogue, 126 psoriasis associated genes (PAG) were identified. 68 genes found to be druggable were obtained from canSAR protein annotation tool. Localization results depict that maximum genes are present in cytoplasmic cellular components. The superpathways obtained from GeneAnalytics resulted in involvement of these genes in the immune system, Jak/Stat pathway, Th17 and Wnt pathways. Two genes Interleukin 13 (IL13) and POLI are Food and Drug Administration (FDA) approved targets. Small compounds for these targets were analysed for drug-likeliness, toxicity and mutagenecity properties. The FDA approved drug pandel was found to possess desirable properties. The medications used for psoriasis causes mild to severe side effects and does not work well always. Hence we propose drug repurposing strategy to use existing drugs for new therapies. Therefore, the drug pandel could be explored further and repurposed to treat psoriasis.

Keywords Chronic disease · Pathways · Gene ontology · Mutagenicity · Toxicity

Introduction

Psoriasis is a chronic inflammatory disease which affects the skin and joints of the human body that leads to substantive inflammation and epidermal hyperplasia resulting in skin lesions (Sundarrajan et al. 2015). Psoriatic arthritis is an inflammatory arthropathy associated with psoriasis disease (Chimenti et al. 2013a, b; Helliwell and Wright 1997). The itching caused by this disease leads to the acreage amount of irritation in the patient's body (Yang and Yang 2015). The inflammation produced by this disease is extremely threatening to the patient's life (Richards et al. 2001; Rapp et al. 1997). The patients experience pain and joint tenderness which produce a reduced function of regulatory systems in the body (Strand et al. 2012). When psoriasis develops, the skin cells mature quicker in 3–6 days and move to the surface of the skin. The skin cells pile up causing the visible lesions. Psoriatic lesions are well-defined erythematous indurated plaques with silvery white scales. Autoimmune diseases like vitiligo, lichen planus, bullous pemphigoid and

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alopecia areata are also known to be associated in psoriatic patients (Velappan et al. 2019).

A review survey depicts that psoriasis is more prevalent in patients having mental stress and psychiatric disorders (Kurd et al. 2010; Gupta and Gupta 2003). The depression and mental health problems in patients suffering from psoriasis are supremely caused due to inflammation and discomfort caused by visible skin rashes and appearance. Genetics and immune system involvement are the two theories involved in the physiology of this disease. T-cell subsets related to autoimmune diseases include Th17 and T-regulatory cells. A greater ratio of Th17 to T regulatory cells is observed in case of pregnancy (Bandoli et al. 2010). Psoriasis is primarily a Th17 disease with T helper cells involvement. Psoriasis affects pregnancy conditions as it functions to downregulate the Th17 cells (Porter et al. 2017). Psoriasis arthritis is an exaggerated inflammatory response associated with psoriasis (Chimenti et al. 2013a, b). It affects nearly 0.16–0.25% of the world's population (Gelfand et al. 2005; Gladman et al. 2005; Haroon et al. 2013; Lofvendahl et al. 2014). The disease is mainly characterized by synovial hyperplasia. The major pathways in this disease include immune cells infiltration and cytokines release (Fitzgerald and Winchester 2009). The central T-cell inflammatory cytokines involved in arthritis are IL-22 and IL-23/Th 17 (Wolk et al. 2009; Sabat et al. 2007) The association of this disease is with four clinical phenotypes: synovial predominant, entheseal predominant, axial predominant and mutilans which are determined by genotype (Fitzgerald et al. 2015). Common medications comes with its own possible side effects which includes, topical corticosteroids (hypertension, osteoporosis, cataracts, glaucoma, and diabetes) and retinoids (teratogenicity, serum lipid and transaminase elevations, mucocutaneous toxicity, hair loss, and skeletal changes) vitamin D analogues (skin irritation and photosensitivity) and other biologics in combination with phototherapy (Ayala-Fontánez et al. 2016). Meta-analysis of psoriasis expression data provides insight in to associated comorbidities with the prominent one being type 2 diabetes (T2DM) followed by rheumatoid arthritis, obesity, Alzheimers disease and myocardial infarction (Sundarrajan and Arumugam 2016).

Our work aims to extract data from genome wide association studies (GWAS) and was used to create a working list of psoriasis associated genes (PAG). GWAS is a combination of pathway and meta-analysis systems to find out the gates responsible for a complex disease (Solovieff et al. 2013). Psoriasis is a burning issue around the globe which affects the people leading to emotional stress and pain. It becomes very crucial for treating this disease. Studying the characterization of PAG helps to find a potential cure of the disease at a clinical level. We have used gene ontology and pathway profiles to study PAG. FDA approved drugs and experimental drug list for PAG were obtained from drug bank and further studied for its drug-likeliness properties. These drugs could probably offer a therapeutic benefit to psoriasis patients.

Methods

Creation of PAG list

Various bioinformatics and proteomics tools were explored to extract and create a working list of PAG. The working list of PAG was obtained using NHGRI-EBI GWAS catalogue (Welter et al. 2014) with p value less than 0.05 which is considered to be a significant value. The genomic, transcriptomic, proteomic, genetic, clinical and functional annotation of these genes were performed using Human gene database—GeneCards. This include the two powerful tools GeneALaCart and GeneAnalytics. GeneALaCart provides a methodical and comprehensive information of gene lists achieved from differential expression, transcriptional regulation, siRNA screens or genome-wide genetic association studies (GWAS) whereas GeneAnalytics provides gene expression analysis and function-based analysis (Safran et al. 2010). VarElect (variant election application for disease/phenotype-dependent gene variant) is a comprehensive phenotype-dependent variant/gene prioritizer, which combines information and details of Gene cards, MalaCards and the human genome map database. In this manner, 126 PAG were obtained from the GWAS catalogue.

Gene ontology, pathway, localization analysis

Gene ontology (GO) is typically an outline which defines the concepts used to describe the gene function along with their hierarchical structure across species. In addition, it also provides the characterization of genes of a particular disease (The Gene Ontology Consortium 2008). The GO information on PAG which are significantly involved in the pathophysiology of this disease were obtained from GeneALaCart meta-analysis tool from GeneCards (Harel et al. 2009). The information about proteins, biological processes, cellular components, molecular functions, pathways and interactions were mined for each PAG from GeneALaCart meta-analysis tool. Meta-analysis tool GeneALaCart and GeneAnalytics from GeneCards were utilized to establish superpathways associated with psoriasis genes.

Chemogenomics analysis of PAG

In addition to the gene analysis, protein annotation was also performed. Protein annotation describes in detail the sites of interest and localization in the protein sequence such as post-translational modifications, binding sites, and enzymes action, secondary and tertiary structure of different

proteins. canSAR 3.0 is an updated and fully integrated cancer research and drug discovery database. It provides information on biological annotation, chemical screening, expression amplification and 3D structural data (Halling-Brown et al. 2012) The protein expression studies were verified using proteomics database (Wilhelm et al. 2014) Protein is considered as druggable if it is able to recognize and bind to a drug like small ligand and can get its activity modulated. 68 genes out of 126 PAG were found to have druggable property. Information about Zinc ID, structures, Rule of five (RO5) property and druggability score of the compounds against these targets were obtained (Lipinski et al. 2001; Lipinski 2004; Oprea et al. 2001).

Gene mutations and disorder analysis

PAG were subjected to mutational and disorder analysis. VarElect is an application for disease/phenotype-dependent gene variant prioritization. The different variants and disorders of the PAG were obtained using VarElect tool from gene cards (Law et al. 2014). 30 genes out of 126 PAG were found to have an indirect association with mutational variants and 6 genes were found to have a direct association with various disorders whereas 23 genes were indirectly associated with different disorders.

Creation of the list of FDA drugs

Drug repurposing is an innovative method to find out promising existing drugs for other diseases. The information about various approved drugs for PAG was obtained from the DrugBank (Stelzer et al. 2016). The chemical structures of the drugs were obtained from Zinc database (Bulusu et al. 2014). The list of drugs obtained from drug bank was compared with FDA database to find out existing drugs having the same composition.

Toxicity analysis

canSAR compound link for genes provides diverse information including Lipinski's RO5, bioactivity and assay profiles and molecular weight of compounds. Highest stringency was chosen for RO5 violation (value = 0), protein 3D structural homology was set to 100%. The ligand based drug ability score was chosen as > 60% confidence limit. Drugs with IC50 values and inhibitory activities were chosen as < 100 nM. The toxicity studies of the drugs were done by ProTox software (Drwal et al. 2014). ProTox is a web server for the prediction of median oral lethal doses ("LD50" values) and toxicity classes in rodents. The prediction method is based on the analysis of the two-dimensional (2D) similarity to compounds with known "LD50" values and the identification of fragments over represented in toxic compounds. Based on the "LD50" value of the different FDA approved drugs, there is a division of drugs into various classes. Classes 5 and 6 were chosen as safe and non-toxic drugs. The range of class 5 may be harmful if swallowed ($2000 < LD50 \leq 5000$ mg/kg) and Class 6 is non-toxic ($LD50 > 5000$ mg/kg). The entire methodology followed in this study is depicted as a flowchart in Fig. 1.

Results

Creation of PAG working list

The GWAS catalogue was utilised to ascertain the essential genes involved in psoriasis. p value < 0.05 was then applied as the filter for genes to consider them as significant. The results showed identification of 126 PAG which includes protein coding genes, noncoding RNA and genes with druggable action. While comparing the molecular functions of these PAG, largest group were found to possess protein binding functions (DDX58, STAT2, and TNFAIP3). Other molecular functions of genes include DNA binding, receptor binding (interleukin, growth hormone, cytokine, tumor necrosis factor) followed by RNA binding (Fig. 2).

Gene ontology, pathway and localization analysis

Psoriasis is thought to exhibit in patients with altered immune system leading to chronic inflammatory dermatosis. A plethora of evidence suggests the role of genetic factors in the disease progression and hence by determining the superpathways involved and the associated genes helped to undermine the pathogenicity of this disease. The PAG were found to play a role in the pathways like immune system, apoptosis, endocrine secretions, signalling pathways like JAK/Stat pathway, NF kappa B pathway and Wnt pathway (Table 1). A number of genes common to these pathways were found to involve in type III interferon signalling, cytokine signalling in the immune system, adaptive immune system, non-canonical and canonical Wnt signalling pathway, two of the genes were found to cause Salmonella infection and 12 genes were associated with influenza A infection (Fig. 3) (Takeshita et al. 2017). The venn diagram representing the common superpathways by the three important PAG viz, DDX58, STAT2, and TNFAIP3 is represented in Fig. 4. The localization studies of the genes were done using GeneALaCart meta-analysis tool from GeneCards (Fig. 5). The Gene Ontology analysis affirmed the specific subcellular locations of PAG including cytoplasmic, nuclear, cytosolic, nucleoplasm and intracellular locations.

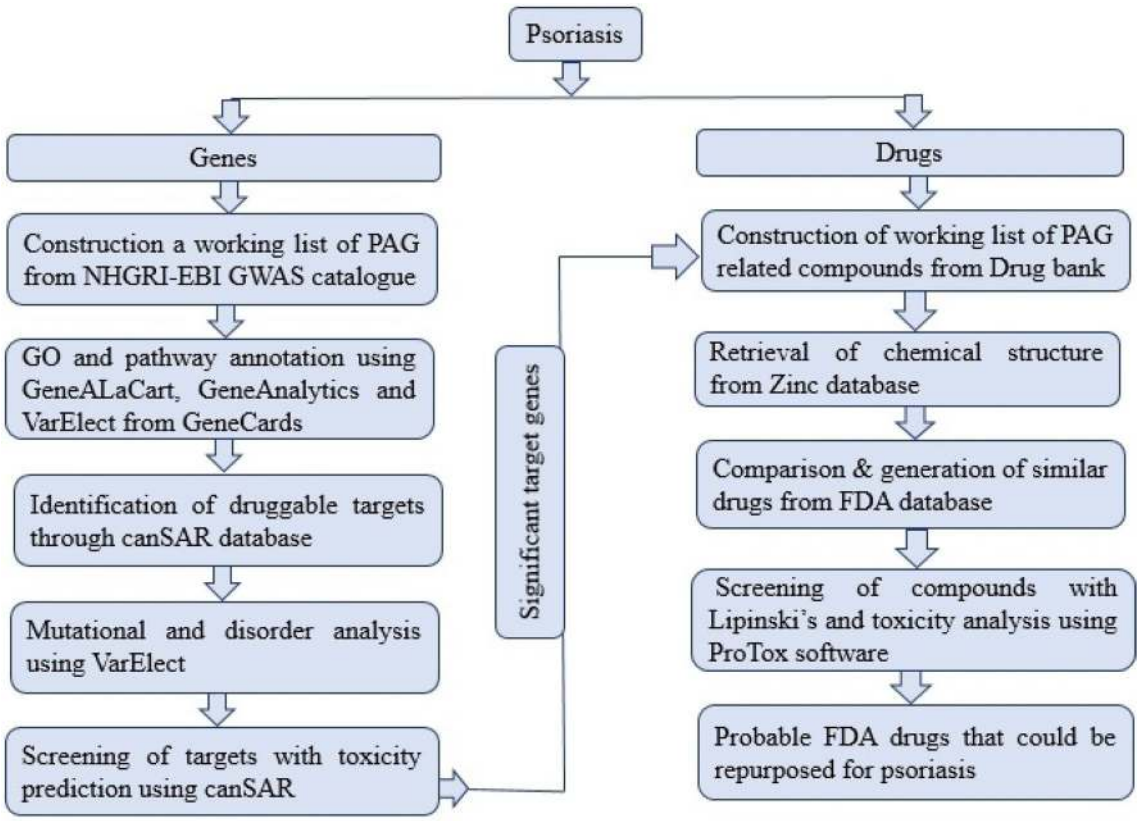

Fig. 1 Workflow of the present study

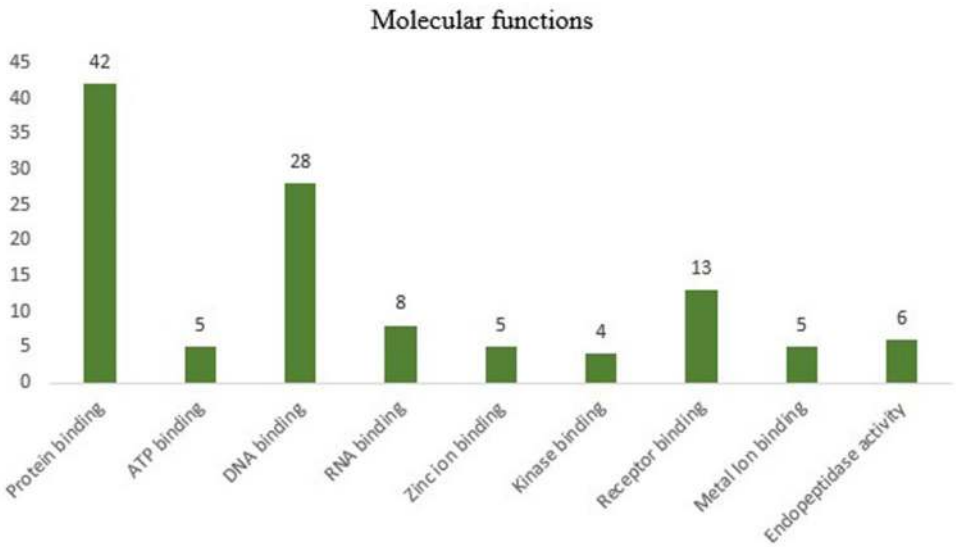

Fig. 2 The different molecular functions of psoriasis associated genes

Chemogenomics analysis of PAG

With the systematic screening of small molecules against the drug target families, it is possible to identify novel drug and drug targets. Sixty eight psoriasis proteins were found to have a key role in drug action by canSAR protein annotation tool. These targets comprised of enzymes and receptors. Small molecular weight compounds were analysed for targeting psoriasis proteins. By applying the

Table 1 The different super pathways of PAG obtained from gene analytics

Super pathways (gene analytics)	Psoriasis associated genes
Immune system	
Interleukin 3,5 signalling	DDX58,STAT2, IL23R, ELMO1, TSC1, TYK2, IFNLR1, PSMA6, CAMK2G
Cytokine signalling	IL13, IL23R, IFNLR1
Interleukin 11 signalling	TYK2
Infection	
Influenza A	DDX58, STAT2, IL13, TNFAIP3, TYK2, IFIH1, POU2F3
Hepatitis C	DDX58, STAT2, TYK2
Salmonella infection	NOS2
Spinal cord injury	NOS2
Endometrial cancer	RUNX1
Prostate cancer	TSC1
Endocrine	
Insulin secretion	NOS2, EXOC2, TSC1, PSMA6, CAMK2G
Apoptosis	
Apoptosis	IL13, PSMA6, TNIP1, TP63
Apoptosis and autophagy	TNFAIP3
Ubiquitin dependent degradation of cyclin	PSMA6
TNFR1 signalling	ERAP1
Intrinsic pathway of apoptosis	TP63
Signaling	
NF-kappa B signaling	DDX58, TNFAIP3
Interferon gamma signaling	DDX58, STAT2, TYK2, CAMK2G
Beta signaling	STAT2, IL13, RUNX1, TYK2
ERK signaling	STAT2, IL13, IL23R, NOS2, TSC1, TYK2, ETS1, PSMA6, CAMK2G
Toll-like signaling	DDX58, STAT2, IL13, NOS2, IFIH1
Jak/STAT signaling	STAT2, TYK2
Akt	STAT2, IL13, IL23R, TSC1
Ras signalling	TNFAIP3
CD40 ligand signaling	ELMO1, POLI, REV3L, EXOC2, PTRF, TYK2, ETS1, PSM6, CAMK2G, PSMA6, SDC4

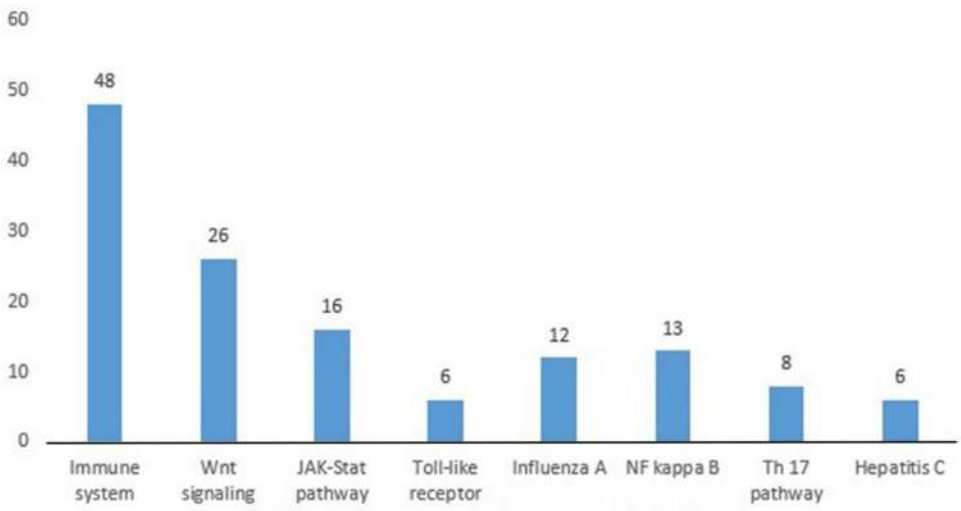

Fig. 3 Super pathways of psoriasis associated genes

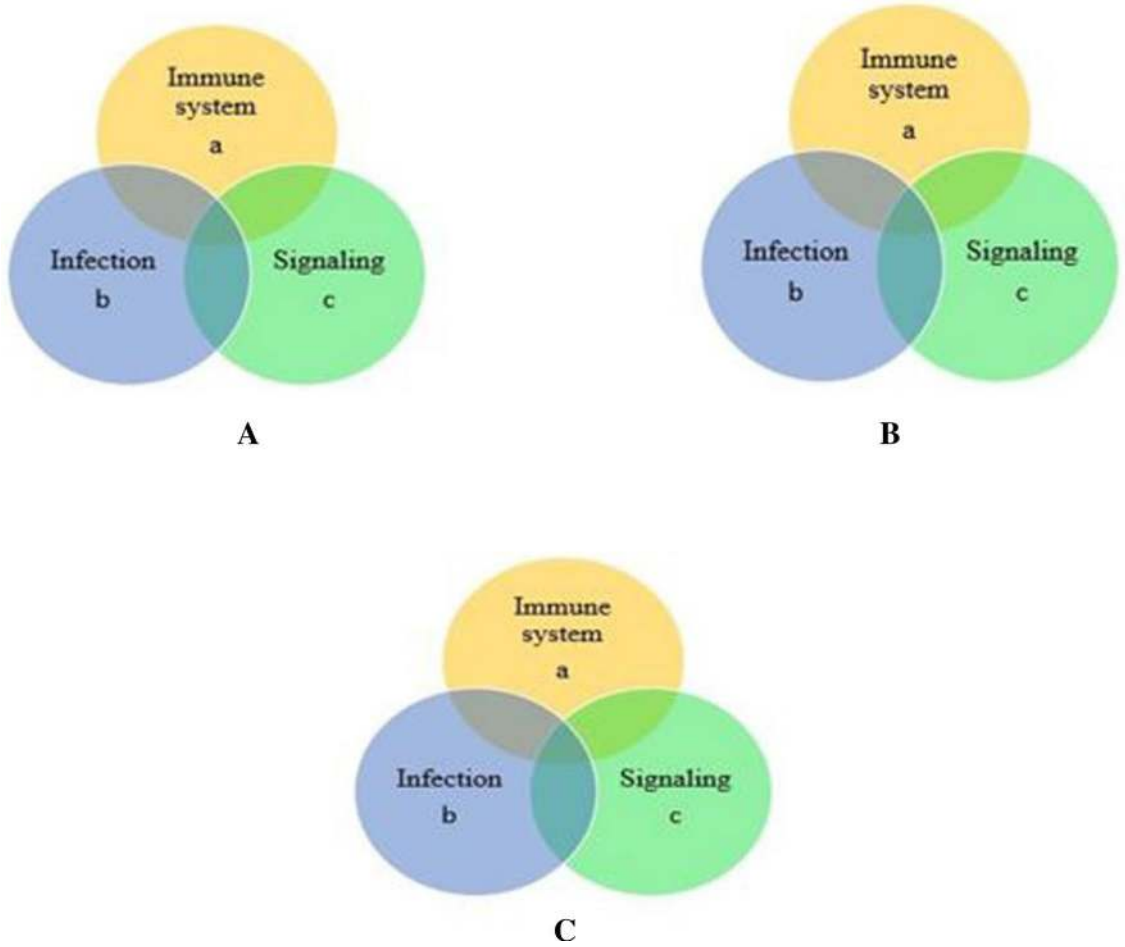

Fig. 4 **A** Common super Pathways of gene DDX5 a: Interleukin 3,5 signaling b: Influenza A and Hepatitis C c: NF-kappa B signalling, Interferon gamma signalling and Toll-like signalling. **B** Common super Pathways of gene STAT2 a: Interleukin 3,5 signalling b: Influenza A and Hepatitis C c: Interferon gamma signalling, Beta signalling, ERK signalling, JAk/Stat signalling and Akt signaling. **C** Common super pathways of IL13 a: Cytokine signalling b: Influenza A c: Beta signalling, ERK signalling, Toll like signalling, Akt signalling

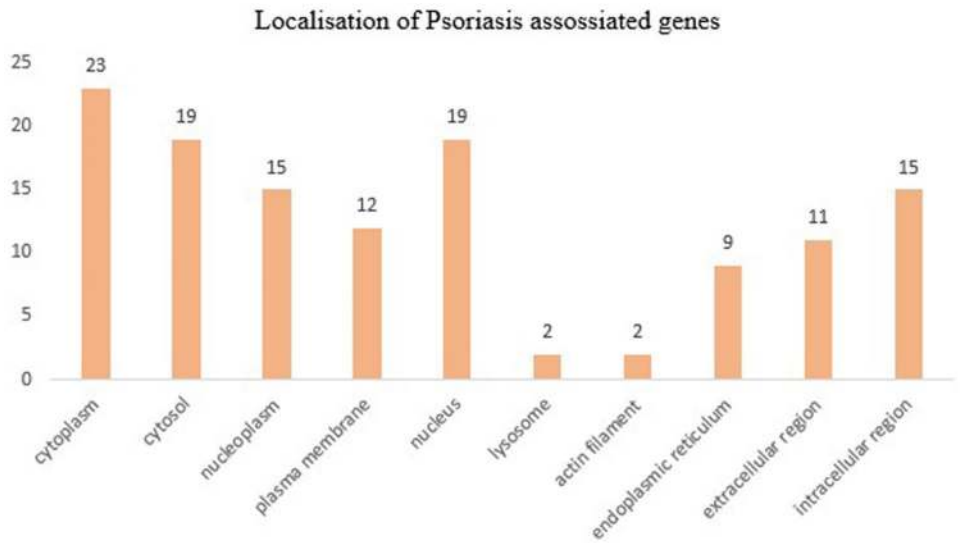

Fig. 5 Cellular locations of Psoriasis Associated Genes

filter of Lipinski's RO5 the POLI, NOS2, PSMA6 and IL13 were found to possess the compounds with desirable property. Most of these genes were found to be associated with interleukin-13, tumor protein-63 and nitric oxide synthase activities (Figs. 6, 7).

Creation of FDA drug list and toxicity prediction

The concept of drug repurposing is becoming a rising consideration as it opens up avenues for new therapeutic implications. The FDA database identified POLI and IL13 as the predictive genetic targets of psoriasis. The specific drugs obtained from DrugBank for POLI are Hydrocortisone (DB00741) and for IL13 are Fletikumab (DB12356), Rilonacept (DB06372), Interleukin-10 (DB12880), Anakinra (DB00026), Oprelvekin (DB00038), Binetrakin (DB12182) and humanized SMART Anti-IL-12 Antibody (DB05848). These drugs obtained from DrugBank were compared with FDA database drugs on the basis of the same composition and structure (Table 2). A total of 58 FDA approved drugs were similar to hydrocortisone and 2 FDA approved drugs viz. Arcalyst and Kineret are similar to Rilonacept and Oprelvekin respectively. Most of the drugs are categorized as class 5 which may be harmful and only one drug, i.e. pandel has been categorized as class 6 which is considered to be safe. The molecular properties and toxicity end points of pandel is represented in Table 3.

Discussion

Psoriasis is a chronic disease of skin, which includes inflammation and itching in the dermal layers of the skin (Torre and Shahriari 2017). Though not life threatening, the disease

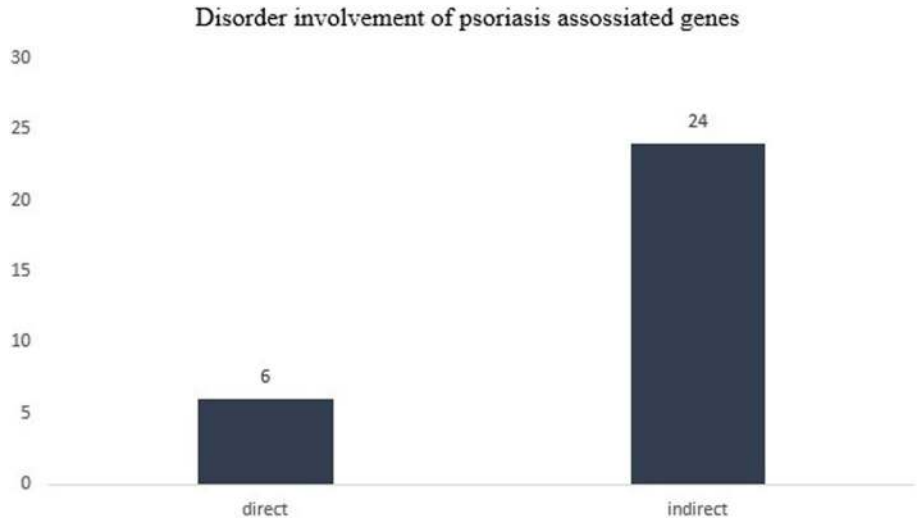

Fig. 6 Number of genes involved in causing disorders

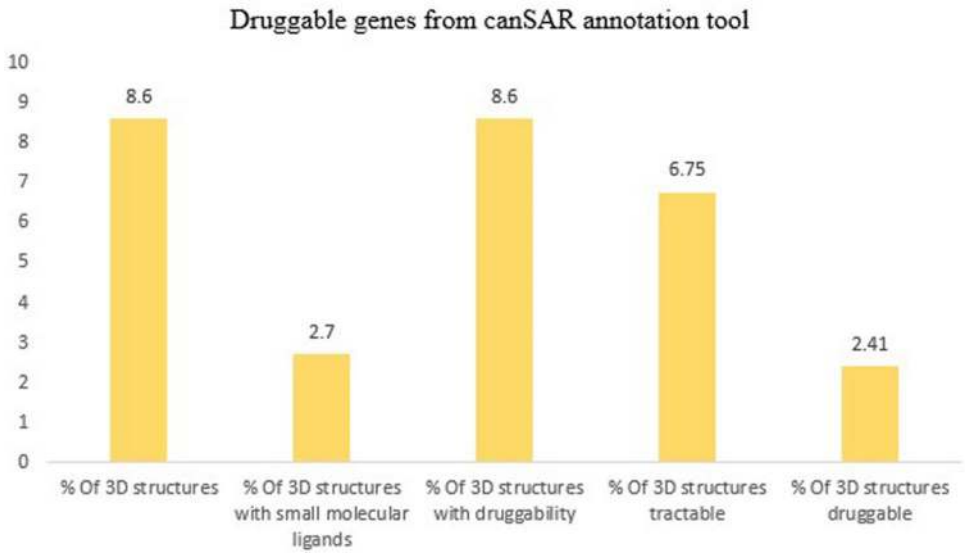

Fig. 7 Percentage of druggable genes of psoriasis disease obtained from canSAR annotation tool

Table 2 The different drugs obtained from FDA database for psoriasis

S. no	Genetic target	ProTox prediction					
		Drug bank	FDA approved drug			LD 50 value (mg/kg)	Class of drug
1	POLI	Hydrocortisone	A-hydrocort	3267	5	3267	5
			Acetasol HC	5000	5	5000	5
			Acetic acid	4	1	4	1
			Achromycin	4400	4	4400	4
			Acticort	5000	5	5000	5
			Aeroseb-HC	5000	5	5000	5
			Ala-Scalp	5000	5	5000	5
			Alphaderm	5000	5	5000	5
			Anusol HC	5000	5	5000	5
			Hydrocortisone acetate	3267	5	3267	5
			Balneol-HC	5000	5	5000	5
			Beta-HC	5000	5	5000	5
			Calmurid HC	1860	4	1860	4
			Carmol HC	3267	5	3267	5
			Cetacort	5000	5	5000	5
			Chloromycetin	1500	4	1500	4
			Cipro HC	4336	4	4336	4
			Colocort	5000	5	5000	5
			Cor-Oticin	5000	5	5000	5
			Cort-Dome	5000	5	5000	5
			Cortef	5000	5	5000	5
			Cortef acetate	3267	5	3267	5
			Cortenema	5000	5	5000	5
			Cortisporin	5000	5	5000	5
			Cortril	5000	5	5000	5
			Dermacort	5000	5	5000	5
			Eldecort	5000	5	5000	5
			Epicort	5000	5	5000	5
			Epifoam	3267	5	3267	5
			Flexicort	5000	5	5000	5
			Glycort	5000	5	5000	5
			H-cort	5000	5	5000	5
			HI-Cor	5000	5	5000	5
			Hydro-RX	5000	5	5000	5
			Hydrocortisone acetate	3267	5	3267	5
			Hydrocortisone butyrate	3000	5	3000	5
			Hydrocortisone sodium phosphate	3950	5	3950	5
			Hydrocortisone sodium succinate	3267	5	3267	5
			Hydrocortisone valerate	3000	5	3000	5
			Hytone	5000	5	5000	5
			Neo-Cort-Dome	5000	5	5000	5
			Neo-cortef	5000	5	5000	5
			Nutracort	5000	5	5000	5
			Orlex HC	5000	5	5000	5
			Otobiotic	5000	5	5000	5
			Otocort	5000	5	5000	5
			Pandel	5120	6	5120	6
			Pediotic	5000	5	5000	5

Table 2 (continued)

S. no	Genetic target	ProTox prediction					
		Drug bank	FDA approved drug			LD 50 value (mg/kg)	Class of drug
			Penecort	5000	5	5000	5
			Protocort	5000	5	5000	5
			Proctofoam HC	3267	5	3267	5
			Solu-cortef	3000	5	3000	5
			Synacort	5000	5	5000	5
			Terra-cortril	5000	5	5000	5
			Texacort	5000	5	5000	5
			Westcort	3000	5	3000	5
			Zinc bacitracin	200	3	200	3
			Neomycin sulfate	2275	4	2275	4
2	IL13	Fletikumab					
		Rilonacept	Arcalyst			NA	NA
		Interleukin-10					
		Anakinra	Kineret			NA	NA
		Oprelvekin					
		Binetrakin					
		Humanized SMART anti-IL-12 antibody					

NA not available in ProTox

is spreading throughout the population and infecting around 2–3% of the people in the world (Nast et al. 2008). Even though the etiology of the disease still remains unclear, various theories were put forward for the establishment of the disease. The major problem faced by people suffering from psoriasis includes stress, depression and poor self-esteem (Tu et al. 2016).

For the past few years, a humongous amount of data related to genes of a specific disease can be generated using GWAS approach (Denny et al. 2013; Gottesman et al. 2013; Postmus et al. 2014; Shungin et al. 2015; Simon-Sanchez and Singleton 2008; Wolpin et al. 2014; Calabrese et al. 2016; McGeachie et al. 2014; Kim et al. 2014). The study aims to retrieve targets of psoriasis using GWAS approach and to identify the potential drug therapies using drug repurposing. Drug repositioning helps to unravel new therapeutic options than the traditionally followed methods. In addition to advancements in technology, it has been very easy to establish protein 3D structures and hence possible to use powerful tools like canSAR for prediction of drug action of different PAG (Kolker et al. 2012; Uhlen et al. 2015).

This work began with creating a working list of PAG from GWAS approach that provides a promiscuous initiating point for novel diagnostics and therapeutics strategies. By the results obtained by the preliminary search, 126 genes that show an association with psoriasis protein coding and non-coding sequences were identified. These putative targets, i.e., PAG included enzymes, transcription factors, regulators, transporters and receptors. A detailed analysis of the genes were studied thereafter. Localization results from GeneALacart showed that most of the genes are located in the cytoplasm and nucleus.

Using chemogenomics approach, the examination of identified PAG shows an association with infections, autoimmune disorders and immune system. Superpathways mapping with GeneAnalytics meta-analysis tool provided evidences for an involvement of the diverse genes in NF-kappa B signalling, Wnt signalling, apoptosis, tumor necrosis factor, prostate cancer and are also found in association with insulin secretion. Developing the inhibitors of these pathway protein can offer a therapeutic approach in treating patients suffering from psoriasis.

In 2019, the AAD (American Academy of Dermatology)/NPF (National Psoriasis Foundation) group published guidelines for psoriasis treatment: they are phototherapy/non-biologics systemic agents (ultraviolet light B, sunlight, psoralen with ultraviolet light A and tanning beds), biologics (tumor necrosis factor-alpha inhibitor, interleukin-12 inhibitor, interleukin-17 inhibitor, T-cell inhibitor and interleukin-23 inhibitor), systemics (acitretin, cyclosporine, methotrexate, off-label systemics) and topicals (topical non-steroids, topical steroids). While a complete cure for psoriasis is currently unavailable at clinical levels, it is therefore possible

Table 3 Molecular property and toxicity prediction for pandel using ProTox

Molecular properties		Prediction
Molweight		488.61
Number of hydrogen bond acceptors		7
Number of hydrogen bond donors		0
Number of atoms		39
Number of bonds		42
Number of rings		4
Number of rotatable bonds		9
Total charge		0
Molecular polar surface area		106.97
Toxicity prediction	Prediction	Probability
Hepatotoxicity	Inactive	0.99
Carcinogenicity	Active	0.51
Mutagenicity	Inactive	0.96
Cytotoxicity	Inactive	0.54

to develop a therapy by repurposing for FDA approved drug for the treatment. A similar study on drug repurposing for vitiligo associated genes has been carried out by Ramaswamy (2015). Chemogenomics approach led to the identification of druggable targets, bioactive compounds, FDA approved drugs and nutraceuticals associated with the vitiligo genome. Pharmaceutical industry has previously done extensive research in this field. The greatest advantage of this research is that toxicity, side effect and structure of the drugs are already available in DrugBank and ProTox database. Thus 58 FDA approved drugs are obtained from the FDA database for POLI and 2 FDA approved drugs for IL13. The toxicity studies of the different drugs suggested that most of the drugs are safe and non-toxic. Some literature has reported that there are no signs of toxicity detected during treatment with hydrocortisone derivatives, Kineret® (Anakinra) (Dehkharghani et al. 2018; van Mierlo et al. 2014). The PAG were found to be associated with a variety of therapeutic drugs and nutraceuticals. Thus, toxicity level testing of these drugs has already been done. However, further clinical trials can be done with combinations of other commercially available regimens in the market. Hence, these drugs provide an alternative way to the existing treatments of psoriasis.

Conclusion

Psoriasis is one of the most long lasting skin disorders which is typically characterized by skin cells that multiply at an uncontrollable rate as compared to normal skin cells. The current challenges of psoriasis treatment is: there are drawbacks in medications and is expensive as well. The major focus of our research work is to find a potential cure of the disease which is not available right now at a commercial level. Hence, we used GWAS and chemogenomics approach to find out FDA approved drugs for prospective treatment of this disease. The results obtained by our research shows that maximum of the genes are involved in immune system super pathways and have indirect involvement in causing various disorders. The genes possessing FDA approved drug action are of interferon Alfa sub-types. The drug pandel against the target POLI shows desirable molecular and toxicity properties. Thus after a methodological animal model study, this drug could be considered as a therapy for psoriasis as a single compound or with a combination of other compounds with or without UVB phototherapy.

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Author contributions AM: Conceived and designed the analysis. HN, NP: Collected data and implemented the analysis. RO: Helped in manuscript writing. JJ: Contributed data or analysis tools.

Compliance with ethical standards

Conflict of interest We declare no conflict of interests. The authors are completely responsible for the content published in the article.

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