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# dbGAPs: A comprehensive database of genes and genetic markers associated with psoriasis and its subtypes

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ABSTRACT

Psoriasis is a systemic hyperproliferative inflammatory skin disorder, although rarely fatal but significantly reduces quality of life. Understanding the full genetic component of the disease association may provide insight into biological pathways as well as targets and biomarkers for diagnosis, prognosis and therapy. Studies related to psoriasis associated genes and genetic markers are scattered and not easily amendable to data-mining. To alleviate difficulties, we have developed dbGAPs an integrated knowledgebase representing a gateway to psoriasis associated genomic data. The database contains annotation for 202 manually curated genes associated with psoriasis and its subtypes with cross-references. Functional enrichment of these genes, in context of Gene Ontology and pathways, provide insight into their important role in psoriasis etiology and pathogenesis. The dbGAPs interface is enriched with an interactive search engine for data retrieval along with unique customized tools for Single Nucleotide Polymorphism (SNP)/indel detection and SNP/indel annotations. dbGAPs is accessible at http://www.bmicnip.in/dbgaps/.

## 1. Introduction

Psoriasis is a chronic inflammatory autoimmunodermatosis that affects 1.3–2.2% of the world population [1]. Although the disease condition is not typically lethal, but it leads to physical discomfort and psychological stress, that in due course affects the professional and social life of an individual [2,3]. It is a complex multifactorial disease that has features of polygenic inheritance. The complex genetic background involves multiple genes encoding multiple different proteins that have significant functions in the regulation of the pathophysiology of the disease [4]. To date, number of Genome-wide association studies (GWAS) have been carried out using large psoriasis cohorts from various populations and have collectively identified numerous susceptibility loci for psoriasis [5–9]. Besides this, for complete characterization of the genetic architecture of psoriasis and its subtypes; other strategies being used such as meta-analysis [10], deep sequencing [11], copy number variants detection [12,13]. These mounting genetic association studies assert their role in the resultant phenotypic variations among individuals with an endeavor towards disease diagnosis, prognosis and treatment [14].

The expanding genetic data on psoriasis could result in commensurate gains in new investigation on disease diagnosis, prognosis and therapeutic front; provided these data are being systematically integrated to make it available for researchers [15–17]. Database such as GWAS Central [18], GWAS catalog [19], ClinVar [20] and Human Gene Mutation Database [21] store genetic variation data of many human diseases. However, GWAS central and GWAS catalog house data from genome-wide association studies only. Stenson et al. stated that ClinVar lacks depth (in terms of variant and literature coverage) and contains unpublished (i.e. non-peer reviewed) data which causes problems pertaining to data quality, submission, provenance and consent [21]. The Human Gene Mutation Database provides free access to only less up-to-date version (minimum of 3.5 years out of date) [21]. Nevertheless, a unified repository for psoriasis associated genes and related genetic variations, is not yet developed.

In this study, we report the first such unified repository named

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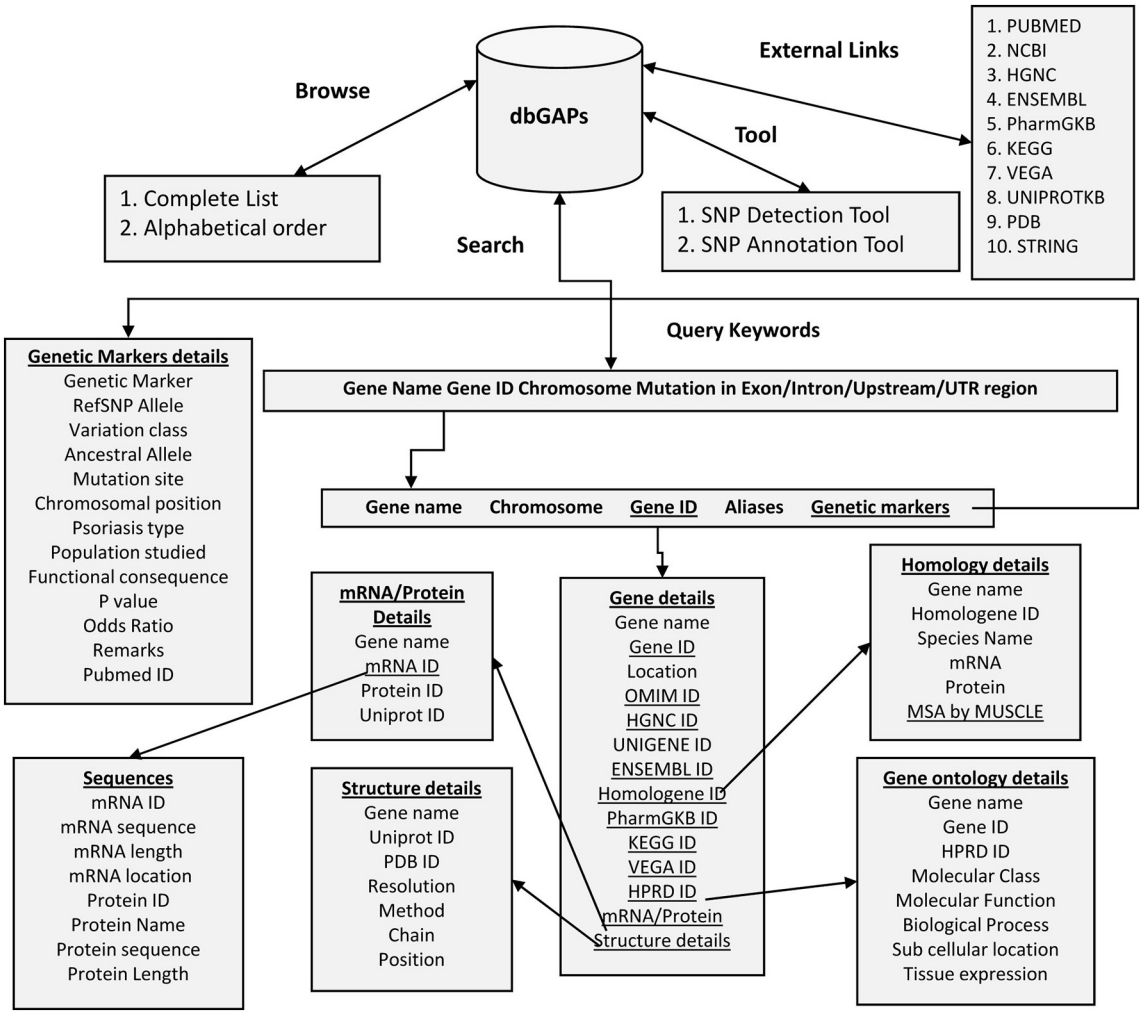


**Fig. 1.** Architecture of dbGAPs.

"database of Genes Associated with Psoriasis" (dbGAPs). The genes and genetic alterations of psoriasis and its subtypes' are compiled from varying literature resources including candidate gene studies, GWAS, meta-analysis etc. dbGAPs will enable user to explore psoriasis associated genetic alterations, their functional consequences (pathogenicity of missense variants, mRNA and protein sequences, protein-protein networks, homology, enrichment according to Gene Ontology (GO) terms biological process and molecular function, pathways) both at sequence and structure level.

## 2. Results

dbGAPs is developed to cater a unified resource for psoriasis associated genes and genetic markers. The database currently houses 202 non-redundant genes which were found to be associated with psoriasis and its subtypes. The database architecture is shown in (Fig. 1).

### 2.1. Utility of dbGAPs

The data in the dbGAPs can be easily accessed through search and browsing facilities. The database can be queried by gene symbol, gene ID, chromosome or mutation in exonic, intronic, upstream, untranslated regions (UTR), which will return the gene or genetic marker-centered information. The gene details page provides the basic information and cross-references for gene symbol, gene ID, gene name, contig, gene location, OMIM ID, HGNC ID, UniGene ID, Ensembl ID, Homologene ID, PharmGKB ID, KEGG ID, VEGA ID, HPRD ID, mRNA-Protein Seq, UniProt ID and genetic markers.

Accessing specific IDs in the database retrieves information (Fig. 2) on 1) Gene ID – NCBI unique Entrez Identifier 2) Homologene - provides details of similar mRNA and protein sequences that are present in other eukaryotic genomes which are linked to NCBI multiple sequence alignment pages. 3) HPRD - displays gene ontology details including molecular class, molecular function, biological process, subcellular localization and tissue expression. 4) mRNA-protein - stores mRNA and protein sequence details. 5) structural detail - provides information on wild type and mutant structures (if missense variant) and display it through an interactive Jmol plug-in 6) Genetic marker - displays information about refSNP allele, variation class, ancestral allele, mutation site, chromosomal position, psoriasis type, population studied, functional consequence, *p*-value, OR with 95% CI and cross-linked to bibliographic reference (PubMed ID). For each non-synonymous SNP (nsSNP) (only with reported rsID), pathogenicity and tolerant or deleterious effect on protein structure is predicted through SIFT (Sorting Intolerant From Tolerant) [22], PolyPhen (Phenotyping Polymorphism) [23], PANTHER (Protein Analysis Through Evolutionary Relationships) [24], SNAP2 (Prediction of functional effects of sequence variants) [25] and details incorporated within genetic marker reference table. Additionally, polymorphisms in the 3′UTR of genes are known for their ability to affect miRNA binding

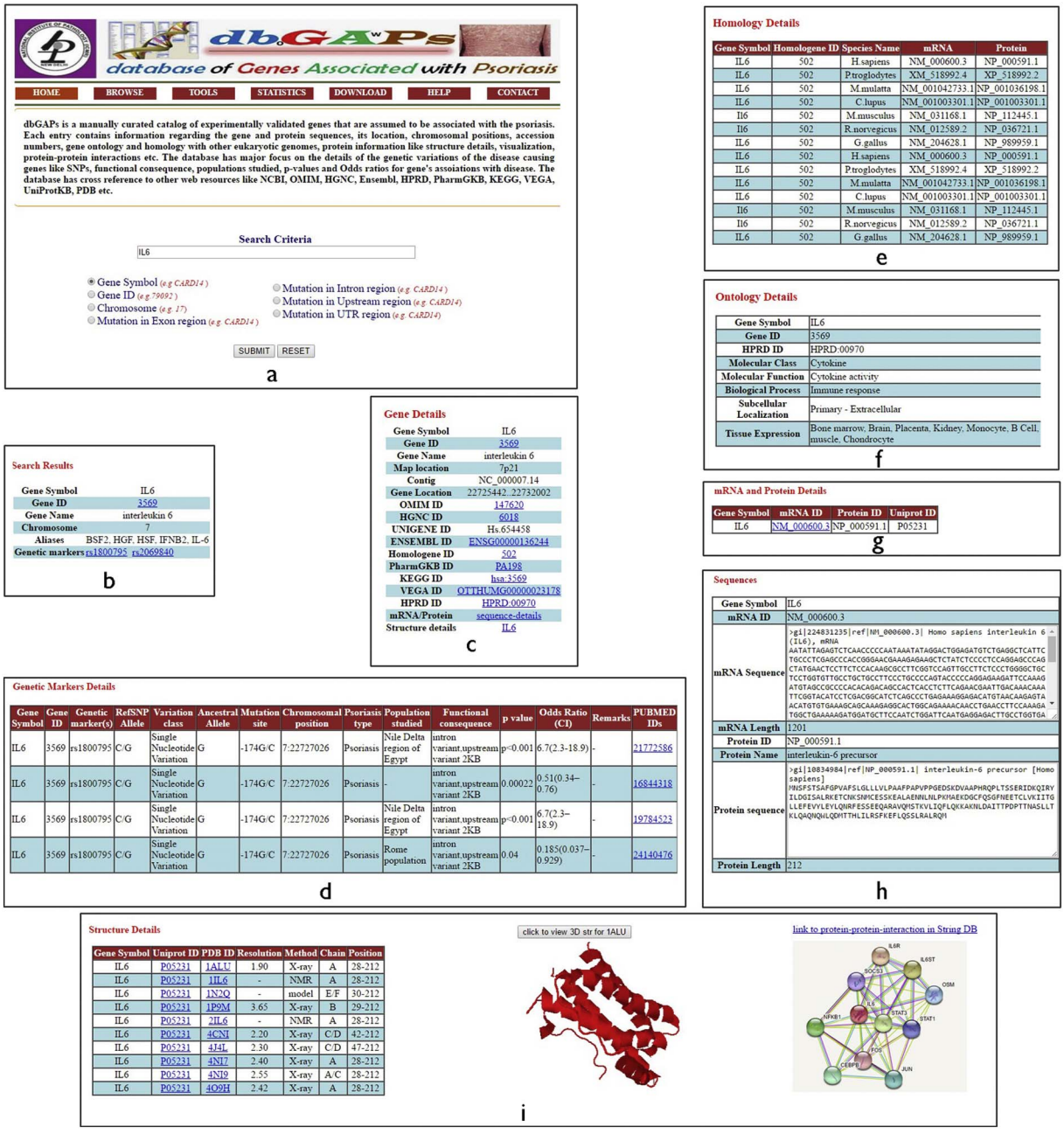


**Fig. 2.** Data retrieval from dbGAPs. (a) Home page displaying dbGAPs search engine. (b) Highlights of search result for specific gene (e.g. IL6) (c) Navigation to Gene details through Gene ID hyperlink in the search result highlights (d) Genetic marker (e.g. rs1800795) associated with the quarried gene (e) Homology details (f) Ontology details (g and h) mRNA and protein description and sequences (i) Protein structure, its description and protein-protein interaction network.

by modulating existing miRNA recognition elements (MREs) or by creating new MREs. SNPs that modulate or create MREs across the 3′UTR [26] (only with reported rsID) of reported genes in the database are identified using MirSNP database [27] and details incorporated within respective genetic marker table.

All genes in the dbGAPs can also be assessed through browse page wherein genes are ordered alphabetically. A summary of the statistics including features such as genes vs references, genetic markers vs genes, chromosome wise gene distribution, gene ontology and pathway enrichment plots are incorporated in statistics page in the database.

### 2.2. Functional enrichment analysis

The gene ontology term enrichment analysis on psoriasis associated genes showed that these genes majorly participates in immunological processes, including defense response to other organism, regulation of immune effector process, positive regulation of JAK-STAT cascade, positive regulation of cytokine production, regulation of inflammatory response and keratinocyte differentiation [28] (Fig. 3) (Supp. Table SS1). These pathways have all been implicated in psoriasis pathogenesis [29] and suggest functional significance of the genes present in the repository. Molecular functions (Supp. Fig. SS1 and Supp. Table SS2) and pathway enrichment (Supp. Fig. SS2 and Supp. Table SS3) of 202

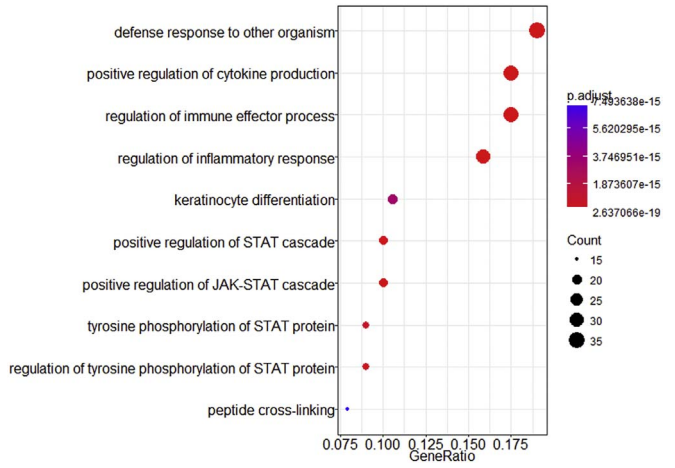


**Fig. 3.** The enriched gene ontology terms (Biological Process) of psoriasis-associated genes. The horizontal axis represents gene ratio, size of dots indicate the count of genes in each term, and different colours correspond to different adjusted *p*-values.

genes further approved their role in psoriasis pathogenesis. The JAK-STAT signaling pathway, cytokine-cytokine receptor interaction pathway, Th17 cell differentiation pathways are among the most significant enriched pathways. Nevertheless, Th17 cells are well known to play major role in psoriasis pathogenesis [30,31].

Functionality of customized tools

a) SNP detection tool: A customized tool has been developed and linked to the dbGAPs that searches a user-provided query sequence against the psoriasis associated sequences available in the database (Fig. 4). The sequence homology search can be useful to detect presence of psoriasis associated SNPs/indels in queried sequence(s). Assuming the query sequences from samples, match with known SNPs/indels in the database; it would have potential clinical application in identifying probable genetic trigger along with other environmental/external factors in the individual patients, thereby to devise a personalized therapeutic strategy.
b) SNP annotation tool: The tool retrieves whether queried SNPs/indels overlaps with existing psoriasis associated genetic variations in the database (Fig. 4). Further, tool provides genomic coordinates, functional consequence, ethnicity, related trait, *p*-values, Odds Ratio with 95% CI, references etc. for the queried SNPs/indels.

### 2.3. Current status and future developments

The current release of dbGAPs contains 202 unique genes that are supported by evidences from > 340 unique PubMed records. The database records such as newly reported mutations, whenever available in literature, will be updated periodically with latest and validated data to ensure the quality and completeness of the information. We would be enriching the database it in terms of both content and functionality and add additional tools which will facilitate users in data analysis and retrieval.

## 3. Discussion

The enormous amount of data has been generated by high throughput genome scale studies which require systematic collection and annotation for discovery of biomarkers and therapeutic targets in pathological conditions [32] including psoriasis. dbGAPs intend to fulfill this purpose by providing a comprehensive and systematic collection of manually curated and validated non-redundant psoriasis associated genes and related variations along with their annotations. Each gene and genetic marker has been manually curated, verified and hyperlinked with reference literature. It also connects to external databases to improve the interoperability of datasets. To the best of our knowledge, till date, no database indexing genes and genetic markers associated with psoriasis and its subtype exists.

The quick browsing and search option provided by the dbGAPs enables researchers to gain information on psoriasis associated genetic variations with their annotations. A help section is available for the guidance of the accessibility of the database. This database provides useful information regarding genes (proteins) such as ontology, homology, pathway, protein-protein interaction, structure, genetic marker details etc.

GO annotations have been used widely to describe protein functions and to know trends in protein datasets [33]; we have also classified psoriasis associated genes (proteins) according to their molecular function and biological process. The top biological processes depicted in database are mainly associated with immunological processes such as regulation of immune effector process, defense response to other organism, positive regulation of JAK-STAT cascade, and positive regulation of cytokine production. The pathways in dbGAPs are enriched in Th17 cell differentiation pathways, JAK-STAT signaling pathway, and cytokine-cytokine receptor interaction pathway. Functional enrichment of genes with respect to biological processes and molecular pathways may contribute in better understanding of pathogenesis of psoriasis and to design drugs to target pathways rather than a specific gene. This suggests psoriasis is a complex condition, henceforth, each protein in the database is linked with Protein-Protein Interaction (PPI) networks.

Further, genetic markers related information such as significance level (*p*-values), odds ratio with 95% CI, population studied, disease type are added from published literature will definitely make a way for genotype–phenotype researches. dbGAPs has incorporated an exhaustive list of genetic markers including rare/common SNPs, indels, repeat markers, Copy number variations, HLA alleles found to be associated with psoriasis. Most of the genetic markers are supported by multiple literature evidences wherever applicable. Furthermore, screening and identification of highly damaging non-synonymous SNPs (nsSNPs) which are likely to affect the function of their respective proteins significantly has also been mentioned in the database.

From the 202 catalogued genes in the dbGAPs, genetic markers in 64 genes are reported to be associated with plaque psoriasis, 8 genes with pustular psoriasis and 4 genes with guttate psoriasis (Table 1). Genotypic variations in ANGPT2, DEFB123, FCGR3B, IFNG, IL18, MBIP and TLR4 are uniquely associated with plaque psoriasis subtype while that of AP1S3 is seen in guttate psoriasis subtype. Genetic markers in ADAMTS9, BARD1, CTNNA3, DEFB1, DENND1B, PPARG, PSMG3, RNF39, SLC17A2, SLC46A3, TMPRSS11F and TRIM39 are uniquely associated with psoriatic arthritis as that of ADO, FAM27L and LINC00643 are unique to cutaneous psoriasis. Type I psoriasis and Type II psoriasis genetic markers are noticed in 43 and 20 genes, respectively (Table 1). Markers in C17orf51, CCL4L1, CLMN and SMCP distinctively associated with Type I psoriasis whereas IL1R1 is associated Type II psoriasis. The uniquely associated genes might be useful in discriminating psoriasis subtypes based on genotypic variations. None of the 202 genes are reported to harbor genetic markers associated either inverse or erythrodermic psoriasis subtype. Moreover, the catalogued genes missing in Table 1 are not associated with any specific psoriasis subtypes.

dbGAPs also compiles the tertiary structures for each associated gene along with its mutant conformations. The wild type structures are either retrieved from protein databank or predicted through comparative modelling or ab initio method. The sequence and structure information of wild type and mutant psoriasis associated genes would assist in visualizing impact of SNPs on tertiary structure topology

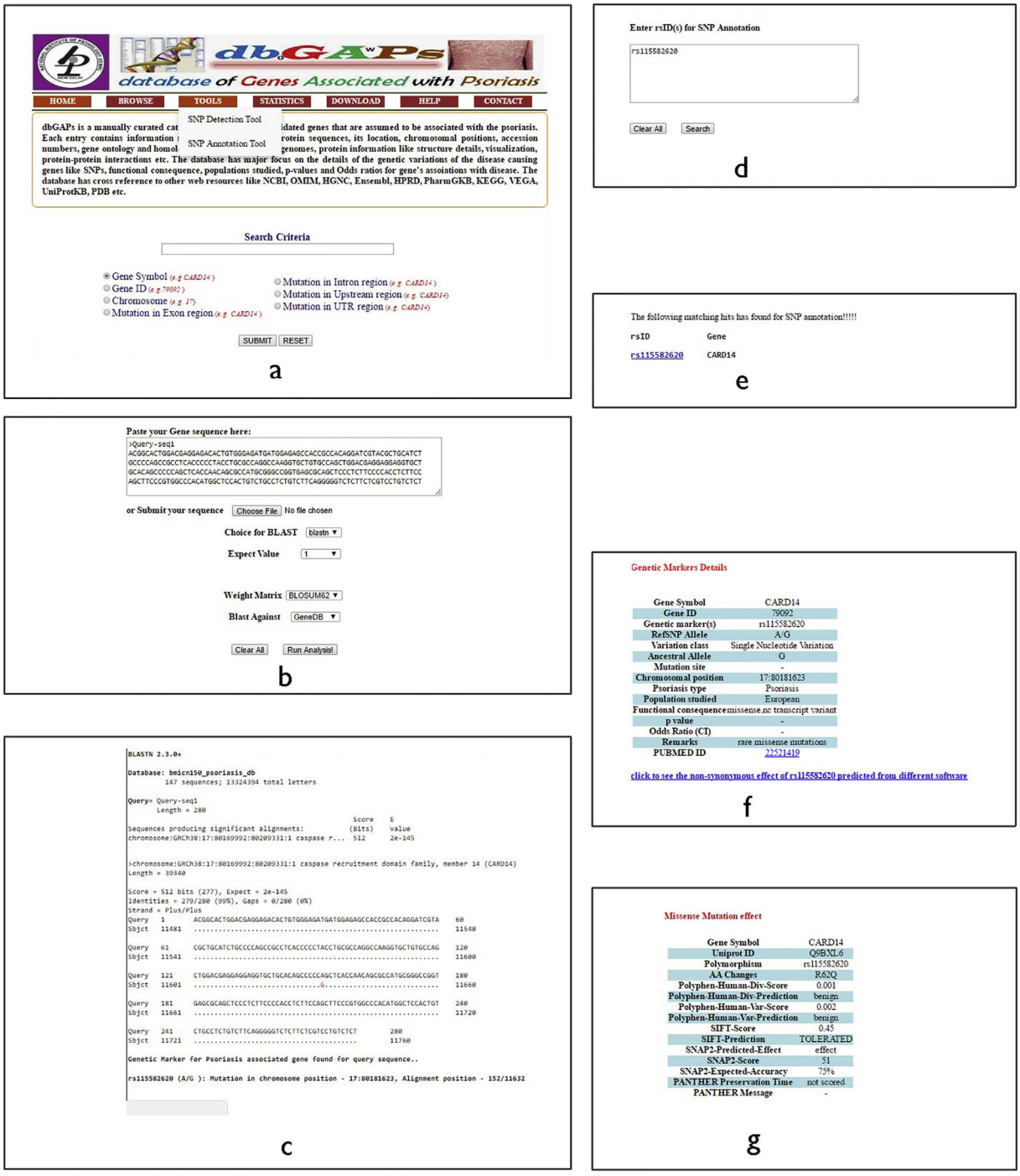


**Fig. 4.** Illustration of tools of dbGAPs (a) Homepage with navigation links for integrated tools in dbGAPs: SNP detection and SNP annotation (b) SNP detection query page (c) Displaying SNP detection tool output (d) Input text box for SNP annotation (e) Annotation tool result (f) Query (genetic marker) details (g) Probable Effect of missense mutation (since query: rs115582620 is non-synonymous SNP).

interactively. Furthermore, mutations mapped to protein 3D structures would reveal the loss and gain of various types of functional attribute, thereby quantifying the impact of disease-causing amino acid substitutions on catalytic activity, metal binding, macromolecular binding, ligand binding, allosteric regulation and post-translational modification [34,21].

Another advantage of this database is the customized SNP detection and SNP annotation tools which provide quick searches for psoriasis associated SNP/indels in a single or set of input gene sequences. The tool can also annotate set of input rsIDs for their possible role in psoriasis. The customized tools being able to detect presence of psoriasis associated SNPs/indels in queried sequence(s), has potential clinical application in identifying probable genetic trigger along with other environmental/external factors in the individual patient thereby to devise a personalized therapeutic strategy. Therefore, dbGAPs serves as a unified resource of psoriasis associated genetic data and an efficient knowledgebase for researchers and clinicians interested in psoriasis. The database will be immensely useful in understanding genetic basis of psoriasis pathogenesis.

**Table 1**
Genes associated with psoriasis subtypes.

| Psoriasis subtypes | Psoriasis associated genes |
|---|---|
| Based on appearance | |
| Plaque psoriasis | ACE, **ANGPT2**, APOE, CAMK2G, CARD14, CCHCR1, CDKAL1, CDSN, COG6, **DEFB123**, ERAP1, FBXL19, **FCGR3B**, GJB2, HLA-A, HLA-B, HLA-C, HLA-DQA1, HLA-DQB1, HLA-DRB1, **IFNG**, IFNLR1, IL12B, IL13, **IL18**, IL1B, IL22, IL23A, IL23R, IL36RN, LCE3A, LCE3B, LCE3D, LCE3E, LTA, **MBIP**, MTHFR, NFKBIA, NFKBIZ, NOS2, PLCL2, POU5F1, PTTG1, REL, REV3L, RNF114, RUNX3, SERPINB8, SLC22A5, **TLR4**, TNF, TNFAIP3, TNIP1, TRAF3IP2, VDR, VEGFA, ZNF816, CD226, TYK2, IL1A, IL20, PTPN22, SLC22A4 |
| Pustular psoriasis | CARD14, CSMD1, HLA-C, IL36RN, LCE3B, TNIP1, **AP1S3**, TRAF3IP2 |
| Guttate psoriasis | APOE, CCHCR1, CDSN, HLA-C |
| Based on age of onset | |
| Type I psoriasis | ACE, ADAM33, **C17orf51**, CARD14, CCHCR1, **CCL4L1**, CD226, CDKAL1, CDSN, **CLMN**, ELMO1, ERAP1, FBXL19, FLG, HLA-A, HLA-B, HLA-C, HLA-DRB1, IFIH1, IL10, IL12B, IL13, IL1B, IL2, IL21, IL22, IL22RA2, IL23R, IVL, LCE3B, NOS2, PTPN22, REL, REV3L, SERPINB8, SLC22A4, **SMCP**, TNF, TYK2, VDR, VEGFA, ZC3H12C, ZNF816 |
| Type II psoriasis | CCHCR1, CD226, CDSN, HLA-A, HLA-B, HLA-C, IFIH1, IL10, IL12B, IL19, IL1B, **IL1R1**, IL2, IL23A, IL23R, MIF, RNF114, TRAF3IP2, VEGFA, ZC3H12C |
| Based on location of psoriatic lesions | |
| Nail psoriasis | HLA-B |
| Palmoplantar psoriasis | CARD14, CCHCR1, CDSN, HLA-C, IL20 |
| Based on joint complaint | |
| Cutaneous psoriasis | **ADO**, **FAM27L**, FBXL19, HLA-C, IL1RN, **LINC00643**, MICA, NOS2, RPS26, SDC4, SMARCA4, TSC1 |
| Psoriatic arthritis | **ADAMTS9**, **BARD1**, CARD14, CCHCR1, **CTNNA3**, **DEFB1**, **DENND1B**, ERAP1, ERAP2, FBXL19, GJB2, HCP5, HLA-A, HLA-B, HLA-C, HLA-DQB1, HLA-DRB1, IFIH1, IFNLR1, IL12B, IL13, IL1A, IL2, IL21, IL23A, IL23R, IL4R, LCE3A, LCE3B, LCE3D, LTA, MICA, MICB, MTHFR, NFKBIZ, NOD2, NOS2, POU5F1, **PPARG**, **PSMG3**, PTPN22, PTTG1, REL, RNF114, **RNF39**, RPS26, RUNX3, SDC4, **SLC17A2**, SLC22A5, **SLC46A3**, SMARCA4, STAT2, STAT3, STAT4, **TMPRSS11F**, TNF, TNFAIP3, TNFRSF9, TNIP1, TRAF3IP2, **TRIM39**, TSC1,TYK2, ZNF816 |

N.B. Genes highlighted in bold are uniquely observed in the specific phenotype.

## 4. Materials and methods

### 4.1. Database architecture and web interface

dbGAPs is a relational database designed using MySQL, Apache server, CGI-Perl, Perl scripts, HTML, JavaScript and CSS. The database is hosted at the Biomedical Informatics Centre, National Institute of Pathology (ICMR) and is accessible at http://www.bmicnip.in/dbgaps/.

### 4.2. Data collection and content

dbGAPs is constructed using text mining followed by manual curation. Extensive literature search of NCBI PubMed database by using specific keywords such as - "[genes] AND [psoriasis]", "[genetics] AND [psoriasis]" was done and search was limited till February 2017. We have retrieved 1794 articles. Abstracts of all research articles are screened to list articles containing experimentally proven psoriasis associated gene and related variation information. Articles are scrutinized to extract information such as gene symbol, genetic marker, SNP ID, *p*-values, odds ratio (OR) with 95% confidence interval (CI), population studied, related trait to prepare a non-redundant list of genes associated with psoriasis. The genes and genetic markers are crosschecked with ClinVar, GWAS catalog, GWAS central, Human Gene Mutation Database and OMIM wherever applicable. To ascertain, association of each genes of non-redundant list with psoriasis, further, literature search of NCBI PubMed database was performed with keywords- "specific genes reported to be associated with psoriasis (e.g. [CARD14] AND [psoriasis])" to extract maximum number of research articles for all 202 genes. The systematic protocol implemented for inclusion of genes and their genetic markers in the database is outlined as (Fig. 5). The inclusion method signifies all selected genes and variations deposited within the database are sufficiently validated as psoriasis associated gene.

Subsequently, annotations for each gene were mined from public databases such as NCBI-Entrez, NCBI-dbSNP, OMIM, HGNC, NCBI-UniGene, Ensembl, PharmGKB, KEGG, VEGA, HPRD etc. with cross references through customized Perl scripts to store in a relational database model. Overall, dbGAPs is divided into seven tables - (i) Gene basic information table, (ii) Gene detail table, which store identifiers for OMIM, HGNC, NCBI-UniGene, Ensembl, PharmGKB, KEGG, VEGA, HPRD, UniProt (iii) The homology table that details orthology relationships extracted from Homologene database, (iv) The Gene Ontology table, that specifies the ontology details derived from HPRD database, (v) the sequence table, contains mRNA and protein sequence details derived from NCBI RefSeq database, (vi) protein structure information table and (vii) Genetic variant details table, which stores the detail information of genetic markers and cross reference to dbSNP identifiers. Human Genome Variation Society (HGVS, www.hgvs.org) guidelines are adopted to represent variations stored in the database along with commonly used aliases [35].

### 4.3. Prediction of 3D structures using MODELLER

dbGAPs provides tertiary structural details for each psoriasis associated genes. The 3D structures are either obtained from the protein databank or predicted through comparative modelling or ab initio methods using MODELLER [36] and I-Tasser (Iterative Threading ASSEmbly Refinement) program [37], respectively. dbGAPs also reports mutant protein structures generated using foldX [38,39].

### 4.4. Functional enrichment analysis

The gene ontology terms and pathway enrichment for all genes listed in the database are carried out using Bioconductor package clusterProfiler [40]. *P*-values were corrected for multiple testing using Benjamini–Hochberg adjustments and corrected *p*-value < 0.01 were considered significant.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygeno.2017.10.003.

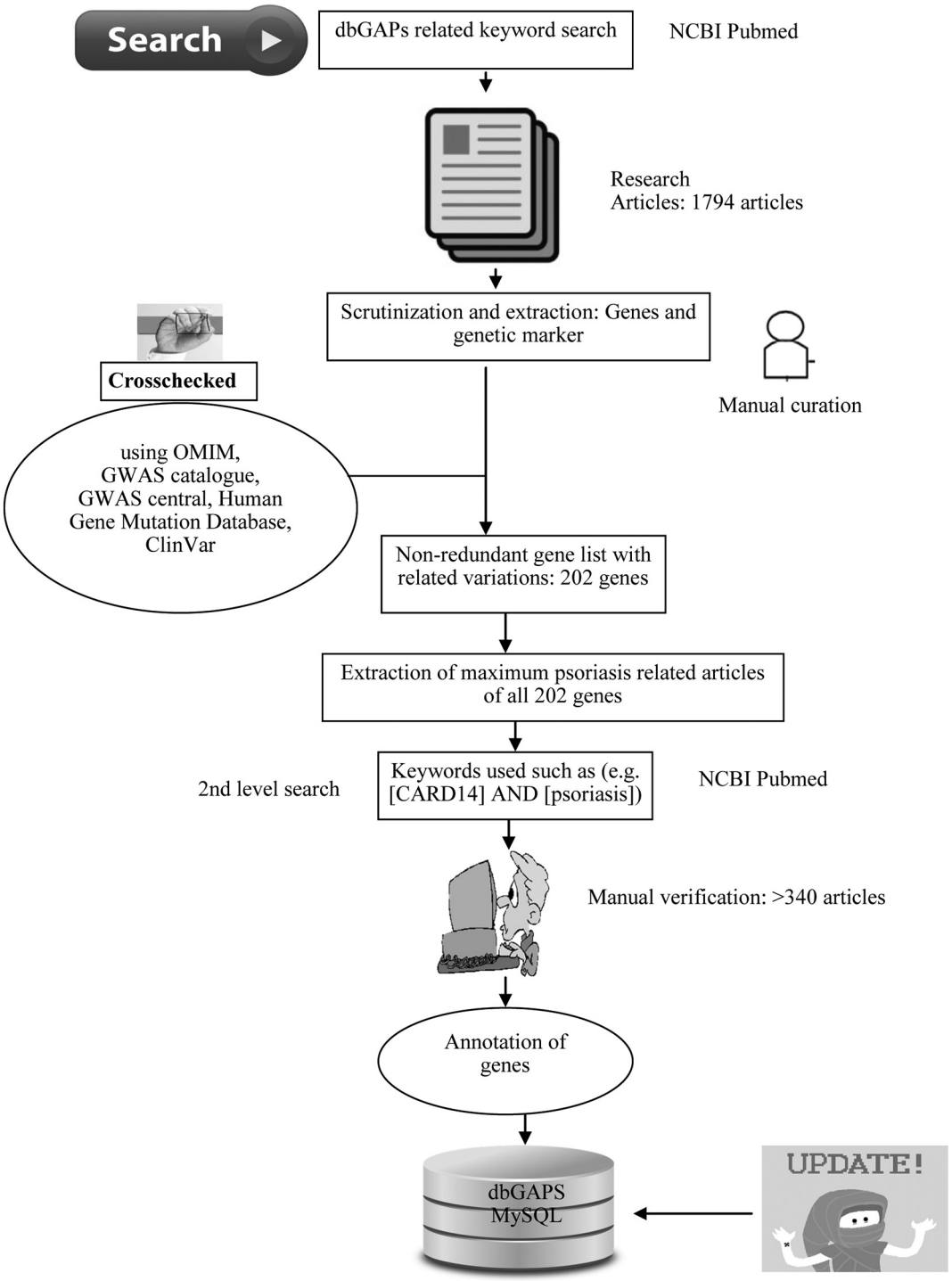


**Fig. 5.** The workflow of psoriasis associated genetic data collection. The genes and genetic makers are extensively validated prior to their inclusion in the dbGAPs.

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S.A. developed the original concept, compiled data and wrote the majority of the manuscript. A.N. designed the database and wrote the data format scripts. D.P. gave suggestions for database architecture and tool development, edited manuscript. R.V. and M.Y. helped in compilation of data. K.P. helped in wild and mutant structure prediction. A.K.J. provided input for database development. All authors read and approved the final manuscript.Additional information

Competing financial interests: The authors declare no competing financial interests.

## References

[1] W. Alwan, F.O. Nestle, Pathogenesis and treatment of psoriasis: exploiting pathophysiological pathways for precision medicine, Clin. Exp. Rheumatol. 33 (5 Suppl 93) (2015 Oct) S2–6.

[2] Y.W. Lee, E.J. Park, I.H. Kwon, K.H. Kim, K.J. Kim, Impact of psoriasis on quality of life: relationship between clinical response to therapy and change in health-related quality of life, Ann. Dermatol. 22 (4) (2010 Nov) 389–396.

[3] A. Chandra, A. Lahiri, S. Senapati, B. Basu, S. Ghosh, I. Mukhopadhyay, et al., Increased risk of psoriasis due to combined effect of HLA-Cw6 and LCE3 risk alleles in Indian population, Sci Rep 6 (2016) 24059.
[4] J. Wu, F. Chen, X. Zhang, Y. Li, H. Ma, Y. Zhou, et al., Association of MIF promoter polymorphisms with psoriasis in a Han population in northeastern China, J. Dermatol. Sci. 53 (3) (2009 Mar) 212–215.
[5] J. Bowes, A. Budu-Aggrey, U. Huffmeier, S. Uebe, K. Steel, H.L. Hebert, et al., Dense genotyping of immune-related susceptibility loci reveals new insights into the genetics of psoriatic arthritis, Nat. Commun. 6 (2015) 6046.
[6] L.C. Tsoi, S.L. Spain, E. Ellinghaus, P.E. Stuart, F. Capon, J. Knight, et al., Enhanced meta-analysis and replication studies identify five new psoriasis susceptibility loci, Nat. Commun. 6 (2015) 7001.
[7] X. Yin, H.Q. Low, L. Wang, Y. Li, E. Ellinghaus, J. Han, et al., Genome-wide meta-analysis identifies multiple novel associations and ethnic heterogeneity of psoriasis susceptibility, Nat. Commun. 6 (2015) 6916.
[8] X. Zuo, L. Sun, X. Yin, J. Gao, Y. Sheng, J. Xu, et al., Whole-exome SNP array identifies 15 new susceptibility loci for psoriasis, Nat. Commun. 6 (2015) 6793.
[9] A. Aterido, A. Julià, C. Ferrándiz, L. Puig, E. Fonseca, E. Fernández-López, et al., Genome-wide pathway analysis identifies genetic pathways associated with psoriasis, J. Invest. Dermatol. 136 (3) (2016 Mar) 593–602.
[10] E. Ellinghaus, P.E. Stuart, D. Ellinghaus, R.P. Nair, S. Debrus, J.V. Raelson, et al., Genome-wide meta-analysis of psoriatic arthritis identifies susceptibility locus at REL, J. Invest. Dermatol. 132 (4) (2012 Apr) 1133–1140.
[11] Y. Sheng, X. Jin, J. Xu, J. Gao, X. Du, D. Duan, et al., Sequencing-based approach identified three new susceptibility loci for psoriasis, Nat. Commun. 5 (2014) 4331.
[12] E.J. Hollox, U. Huffmeier, P.L.J.M. Zeeuwen, R. Palla, J. Lascorz, D. Rodijk-Olthuis, et al., Psoriasis is associated with increased beta-defensin genomic copy number, Nat. Genet. 40 (1) (2008 Jan) 23–25.
[13] A. Julià, J.A. Pinto, J. Gratacós, R. Queiró, C. Ferrándiz, E. Fonseca, et al., A deletion at ADAMTS9-MAGI1 locus is associated with psoriatic arthritis risk, Ann. Rheum. Dis. 74 (10) (2015 Oct) 1875–1881.
[14] C. George Priya Doss, N. Nagasundaram, J. Srajan, C. Chiranjib, LSHGD: a database for human leprosy susceptible genes, Genomics 100 (3) (2012 Sep) 162–166.
[15] K.H. Buetow, Cyberinfrastructure: empowering a “third way” in biomedical research, Science 308 (5723) (2005 May 6) 821–824.
[16] J. Saltz, S. Oster, S. Hastings, S. Langella, T. Kurc, W. Sanchez, et al., caGrid: design and implementation of the core architecture of the cancer biomedical informatics grid, Bioinformatics 22 (15) (2006 Aug 1) 1910–1916.
[17] C. Wang, J. Zhang, M. Cai, Z. Zhu, W. Gu, Y. Yu, et al., DBGC: a database of human gastric cancer, PLoS One 10 (11) (2015) e0142591.
[18] T. Beck, R.K. Hastings, S. Gollapudi, R.C. Free, A.J. Brookes, GWAS central: a comprehensive resource for the comparison and interrogation of genome-wide association studies, Eur. J. Hum. Genet. 22 (7) (2014 Jul) 949–952.
[19] J. MacArthur, E. Bowler, M. Cerezo, L. Gil, P. Hall, E. Hastings, et al., The new NHGRI-EBI catalog of published genome-wide association studies (GWAS catalog), Nucleic Acids Res. 45 (D1) (2017 Jan 4) D896–901.
[20] M.J. Landrum, J.M. Lee, M. Benson, G. Brown, C. Chao, S. Chitipiralla, et al., ClinVar: public archive of interpretations of clinically relevant variants, Nucleic Acids Res. 44 (D1) (2016 Jan 4) D862–868.
[21] P.D. Stenson, M. Mort, E.V. Ball, K. Evans, M. Hayden, S. Heywood, et al., The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies, Hum. Genet. 136 (6) (2017 Jun) 665–677.
[22] P.C. Ng, S. Henikoff, Predicting deleterious amino acid substitutions, Genome Res. 11 (5) (2001 May) 863–874.
[23] I.A. Adzhubei, S. Schmidt, L. Peshkin, V.E. Ramensky, A. Gerasimova, P. Bork, et al., A method and server for predicting damaging missense mutations, Nat. Methods 7 (4) (2010 Apr) 248–249.
[24] P.D. Thomas, M.J. Campbell, A. Kejariwal, H. Mi, B. Karlak, R. Daverman, et al., PANTHER: a library of protein families and subfamilies indexed by function, Genome Res. 13 (9) (2003 Sep) 2129–2141.
[25] Y. Bromberg, B. Rost, SNAP: predict effect of non-synonymous polymorphisms on function, Nucleic Acids Res. 35 (11) (2007) 3823–3835.
[26] V. Vaishnavi, M. Manikandan, A.K. Munirajan, Mining the 3′UTR of autism-implicated genes for SNPs perturbing MicroRNA regulation, Genomics Proteomics Bioinformatics 12 (2) (2014 Apr) 92–104.
[27] C. Liu, F. Zhang, T. Li, M. Lu, L. Wang, W. Yue, et al., MirSNP, a database of polymorphisms altering miRNA target sites, identifies miRNA-related SNPs in GWAS SNPs and eQTLs, BMC Genomics 13 (2012) 661.
[28] I.A. McKay, I.M. Leigh, Altered keratinocyte growth and differentiation in psoriasis, Clin. Dermatol. 13 (2) (1995 Apr) 105–114.
[29] M.A. Lowes, M. Suárez-Fariñas, J.G. Krueger, Immunology of psoriasis, Annu. Rev. Immunol. 32 (2014) 227–255.
[30] A. Blauvelt, New concepts in the pathogenesis and treatment of psoriasis: key roles for IL-23, IL-17A and TGF-β1, Expert. Rev. Dermatol. 2 (1) (2007 Feb 1) 69–78.
[31] E. Fitch, E. Harper, I. Skorcheva, S.E. Kurtz, A. Blauvelt, Pathophysiology of psoriasis: recent advances on IL-23 and Th17 cytokines, Curr. Rheumatol. Rep. 9 (6) (2007 Dec) 461–467.
[32] D. Bhartiya, A. Kumar, H. Singh, A. Sharma, A. Kaushik, S. Kumari, et al., OrCanome: a comprehensive resource for oral cancer, Asian Pac. J. Cancer Prev. 17 (3) (2016) 1333–1336.
[33] S.M. Agarwal, D. Raghav, H. Singh, G.P.S. Raghava, CCDB: a curated database of genes involved in cervix cancer, Nucleic Acids Res. 39 (Database issue) (2011 Jan) D975–979.
[34] J. Lugo-Martinez, V. Pejaver, K.A. Pagel, S. Jain, M. Mort, D.N. Cooper, et al., The loss and gain of functional amino acid residues is a common mechanism causing human inherited disease, PLoS Comput. Biol. 12 (8) (2016 Aug) e1005091.
[35] M. Cruts, J. Theuns, C. Van Broeckhoven, Locus-specific mutation databases for neurodegenerative brain diseases, Hum. Mutat. 33 (9) (2012 Sep) 1340–1344.
[36] A. Sali, T.L. Blundell, Comparative protein modelling by satisfaction of spatial restraints, J. Mol. Biol. 234 (3) (1993 Dec 5) 779–815.
[37] A. Roy, A. Kucukural, Y. Zhang, I-TASSER: a unified platform for automated protein structure and function prediction, Nat. Protoc. 5 (4) (2010 Apr) 725–738.
[38] R. Guerois, J.E. Nielsen, L. Serrano, Predicting changes in the stability of proteins and protein complexes: a study of more than 1000 mutations, J. Mol. Biol. 320 (2) (2002 Jul 5) 369–387.
[39] J. Schymkowitz, J. Borg, F. Stricher, R. Nys, F. Rousseau, L. Serrano, The FoldX web server: an online force field, Nucleic Acids Res. 33 (Web Server issue) (2005 Jul 1) W382–388.
[40] G. Yu, L.-G. Wang, Y. Han, Q.-Y. He, clusterProfiler: an R package for comparing biological themes among gene clusters, OMICS 16 (5) (2012 May) 284–287.