Curation and Analysis of Pharmacogenomics data of Dermatological Disorders

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD

OF THE DEGREE

OF

MASTER OF TECHNOLOGY

IN

BIOINFORMATICS

SUBMITTED BY

RUCHI SHARMA

(2K16/BIO/06)

UNDER THE SUPERVISION

OF

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CANDIDATE'S DECLARATION

I, **Ruchi Sharma**, Roll no. 2K16/BIO/06, student of **M.Tech (Bioinformatics)**, hereby declare that the project Dissertation titled "**Curation and Analysis of Pharmacogenomics data of dermatological Disorders**" which is submitted by me to the Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Technology, is original and not copied from any source without proper citation. This work has not previously formed the basis for the award of any Degree, Diploma Associate ship, Fellowship or other similar title or recognition.

Place: Delhi

Date:

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CERTIFICATE

I, hereby certify that the Project Dissertation titled "**Curation and Analysis of Pharmacogenomics data of Dermatological Disorders**" which is submitted by **Ruchi Sharma**. 2K16/BIO/06, Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Technology, is a record of the project work carried out by the student under my supervision. To the best of my knowledge this work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere.

Place: Delhi

Date:

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Supervisor
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ABSTRACT

A significant proportion of patients with skin disease do not respond to treatment and adverse drug reactions are a common problem. Genetic factors are important determinants for both drug efficacy and toxicity. The fields of pharmacogenetics and pharmacogenomics examine inter-individual variations in the DNA sequences that are related to drug efficacy and toxicity. The notion of treating the patient, and not the particular disease, has been emphasized by physicians for some time. In the past decade, this idea advanced with the human genome project, and has been taken further with the advent of personalized dermatology, or using genetics to drive pharmacological treatment. Although some dermatological conditions such as melanoma are being targeted with gene-specific therapy, the idea of choosing a drug based on the genetic makeup to treat other dermatologic conditions might be relevant, since it may increase drug efficacy or decrease adverse drug events. This concept of pharmacogenomics could be applied throughout the field of dermatology. Online libraries have been developed to guide drug efficacy, dose prediction and adverse events. We provide a list of current systemic dermatologic drugs in which the pharmacokinetics and pharmacodynamics have been studied. It would be beneficial to guide patient treatment with these drugs, if we can better understand their pharmacogenomics.

ACKNOWLEDGEMENT

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LIST OF ABBREVIATIONS

BioPAX	Biological Pathway Exchange
CPIC	Clinical Pharmacogenetics Implementation Consortium
DNA	Deoxyribonucleic Acid
EGFR	Epidermal Growth Factor receptor
EMA	European Medicines Agency
FDA	Food and Drug Administration
GPML	Gaussian Processes for Machine Learning
GWAS	Genome-wide Association Studies
HCSC	Health care Service Corporation
HGNC	HUGO gene Nomenclature Committee
MS	Mass Spectrometry
NCBI	National Center for Biotechnology
NMR	Nuclear magnetic Resonance
OMIM	Online Mendelian Inheritance of Man
PharmGKB	Pharmacogenomics Knowledge base
PD	Pharmacodynamics
PK	Pharmacokinetics
PGx	Pharmacogenomics
PMDA	Pharmaceuticals and Medical Devices agency
TSV	Tab-separated Value
USA	United States of America
VIPs	Very important pharmacogenes

Chapter-1 INTRODUCTION

Every person has different effects on medication because of their variation in genomic structure. How the drugs respond at germ line and somatic level can be predicted through a study known as pharmacogenetics. Development of pharmacogenetics is based on how the genes identified and their allelic variants affects drug response. While PGx is a new field that explains the identification of human genes, their products, and their variation express and how they function. Pharmacogenomics used these data to predict right treatment for patients and helps in development of new drugs. Main difference between pharmacogenetics and pharmacogenomics is that pharmacogenetics used to study single genes and their effect on individual while pharmacogenomics used in broader context i.e. for study the whole genome in respect to all genes function and their interactions and it is caused by pharmacokinetics and pharmacodynamics or both. Study that helps in knowing individual's genetic behavior in response to drugs is known as pharmacogenomics [Berlin DS et al. 2010]. It is a very new field in science that combines two fields i.e. Pharmacology and Genomics. Pharmacology is defined as the study of drugs while genomics is used for study of genes and their functions. It means pharmacogenomics deals with both study of genes and drugs and how they work. Hence, it is widely used to make new drugs that are more effective and safe according to patient's genetic makeup. Drugs that are available in market follow "one size fits all" theorem i.e. one medication is used for several diseases but they are not fit for all individual who are taking it. This becomes very difficult task to prove which medication is perfect for which individual and do not cause any side effects. These effects are known as adverse drug reactions because of these reactions there are more chances for hospitalization and death of an individual [Nelson MR et al. 2009]. After the discovery of Human Genome Project, we can learn genetic differences are affected any patient's response to any medication. These differences help to predict right medication according to patient's genetic makeup [Whirl-Carrillo M, et al. 2012]. As we know, genes are responsible for making of human proteins, enzymes, their receptors and other molecules that are involved in drug and pathways of diseases. Pharmacogenomics can differentiate patients and diseases with the help of variants present in these genes on the basis of their genetic tests and

prescribe a drug that is effective for whom and in what dose it should be given [Evans WE et al. 2003]. We can say that pharmacogenomics helps to design new drugs and in identification of drugs effectiveness before symptoms are apparent. Pharmacogenomic helps companies to bring their drugs that are FDA approved more quickly in the market because it reduces the risk of clinical trials failures by giving exact knowledge of people's genetic behavior and drugs that are effective for them at genetic level. Pharmacogenomics also reduces time and number of trials to prove drugs efficacy and safety with respect to patient's genetic makeup.

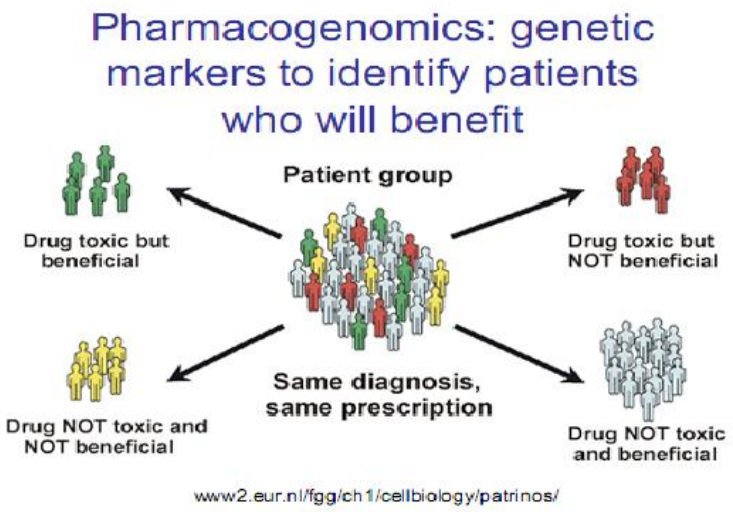

Figure1: Pharmacogenomics – Genetics markers to identify patients who will benefit.

Chapter-2 REVIEW OF LITERATURE

2.1 Pharmacogenetics and Pharmacogenomics

In human genomic sequence, the first major clinical application in advances is pharmacogenetics. There are so many responsibilities to these advances in pharmacology which include maximizing drug efficacy, minimizing toxicity and providing selective medication to patient according to their genetic makeup [Whirl-Carrillo M et al. 2012]. Advancement in pharmacogenetics results into pharmacogenomics. Pharmacogenomics include studies of monogenic to polygenic traits and make genomic science to genome-wide studies. Their effects are classified as those which alter factors that influence the drug concentration reaches to its target, hence called pharmacokinetics factors. Those effects that involve the target itself, known as pharmacodynamics factors. Properties of drug that influence pharmacokinetics include their absorption, distribution, metabolism and excretion. Recently, the main focus in pharmacogenomics is increasing on pathways that include both pharmacokinetic and pharmacodynamics [Giacomini KM et al. 2007].

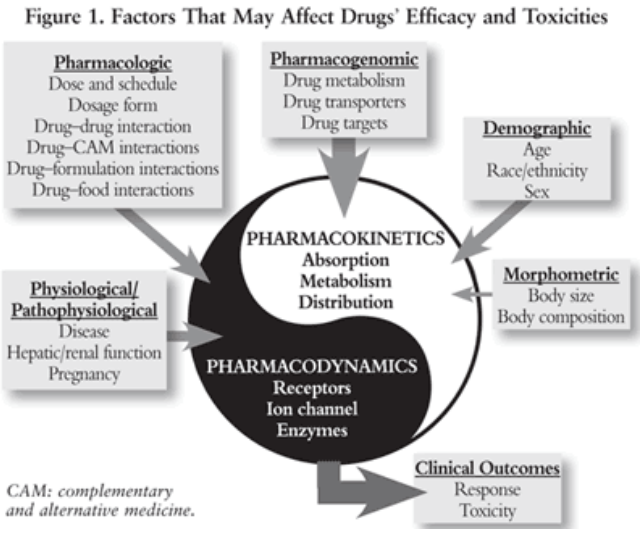

Figure2: factors that may affect drug efficacy and drug toxicities

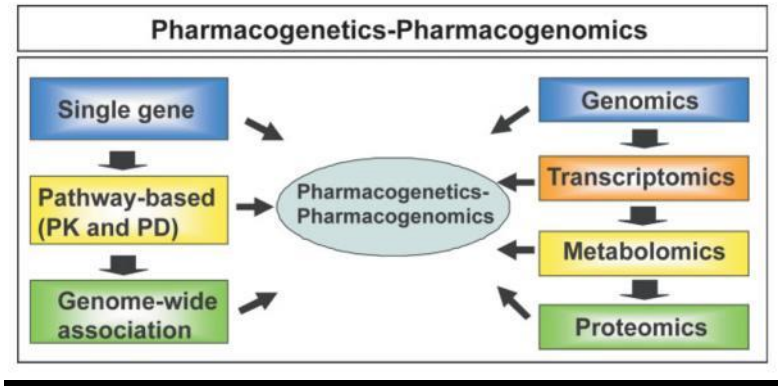

Figure3: pharmacogenetics-pharmacogenomics

2.2 Genome-wide association studies (GWAS)

It is the studies that measures and analyze DNA sequence variation in whole genome so as to identify genetic risk factors that are most common in population [Crowley JJ et al. 2009]. The main goal of GWAS is to use genetic risk factors to predict the risk and identify disease susceptibility for developing new prevention and treatment analyses [Yee SW, et al. 2016]. The success of pharmacogenomics GWAS depends on allelic frequency of genetic variants, their effect size that influence traits. There are so many advantages of GWAS in pharmacogenomics that includes:

1. GWAS provides that information that is not available to genetic contribution of pharmacogenomics traits.
2. Pharmacogenomics GWAS directly investigate the role of genetic variation on clinical trials results.

2.3 Other resources

2.3.1 PharmGKB

Previously there was no standard format to store and describe genotypic and phenotypic data that was collected from pharmacogenetics studies. In 2000, a database as started as one of the first 'post-genomic' databases known as PharmGKB [Klein TE et al. 2001]. The main challenge of PharmGKB is to maintain the data quality without compromising privacy of subject [Klein TE et al. 2001]. It presents the data in a new way with increasing volumes of data. PharmGKB built new relationships with other known resources like drugbank, Biopax, university of California Santa Cruz (CA, USA) genome browser [Altman RB et al. 2013]. The main motive to make new relations is to enhance the knowledge to pharmacogenomics. At present, PharmGKB collects and annotate pharmacogenomics data from different sources and data can access from related gene, drug and disease tabs [Owen RP et al. 2008].

The PharmGKB Knowledge Pyramid provides users with is an overview of the different types of information found in our knowledgebase and shows how this information is acquired and integrated together. PGx knowledge is accumulated at the bottom of the pyramid, to the implementation of PGx in the clinic at the top.

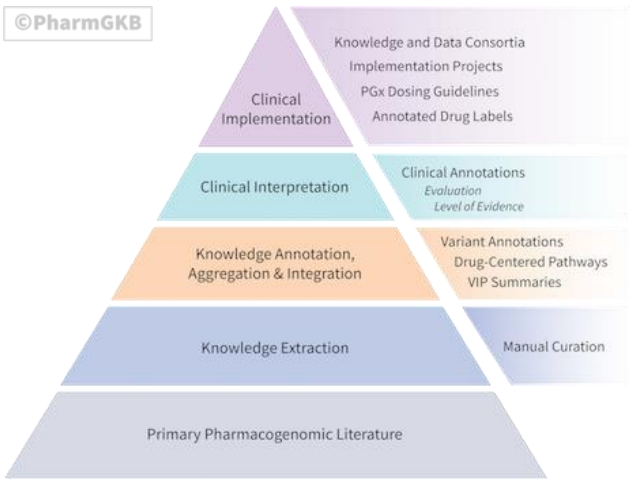

Figure4: PharmGKB pyramid

2.3.2 Drugbank

A unique bioinformatics/chemiinformatics resource that provides complete data about drug and their targets information is called DrugBank. It contains approximately >4100 drug entries that includes >800 FDA approved drug, >14000 protein or drug targets sequences [Knox C et al. 2011]. Its main focus is on quantitative, analytic or molecular-scale information about drugs and their targets. It is a fully searchable web-based resource that contains many built-in tools and features that allow us to view, sort and extract drug or drug targets data [Wishart DS et al. 2016]. The aim of Drugbank is to provide comprehensive resources on drugs that provide their pharmacological actions, biochemical information, their mechanism and targets. It is a database of drugs that facilitate in-silico design of drug, drug targets discovery, prediction of drug metabolism, their interaction etc.

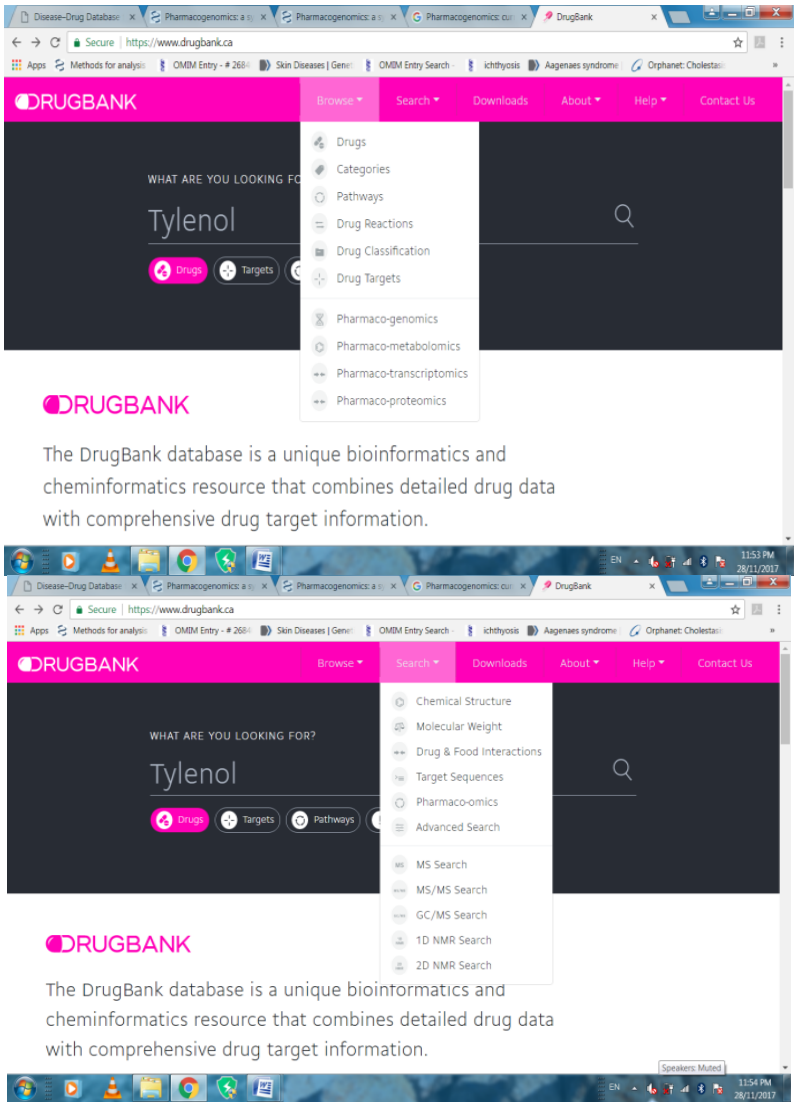

Figure5: Screenshot of DrugBank homepage.

2.3.3 CPIC

A shared project was started in late 2009 between Pharmacogenomics knowledge base and pharmacogenomics research network (PGRN) is named as Clinical Pharmacogenetics Implementation Consortium (CPIC). It is an international consortium in which an individual person volunteers and staff containing very small number of peoples who are dedicated to their work are come [Relling MV et. Al. 2011]. These staff members are facilitated to use pharmacogenetics tests for patient care. Its main targets is to translate genetic laboratory test results into taking decisions for drug prescription by provide all the information about gene/drug clinical practice guidelines and make them freely available and updatable data.

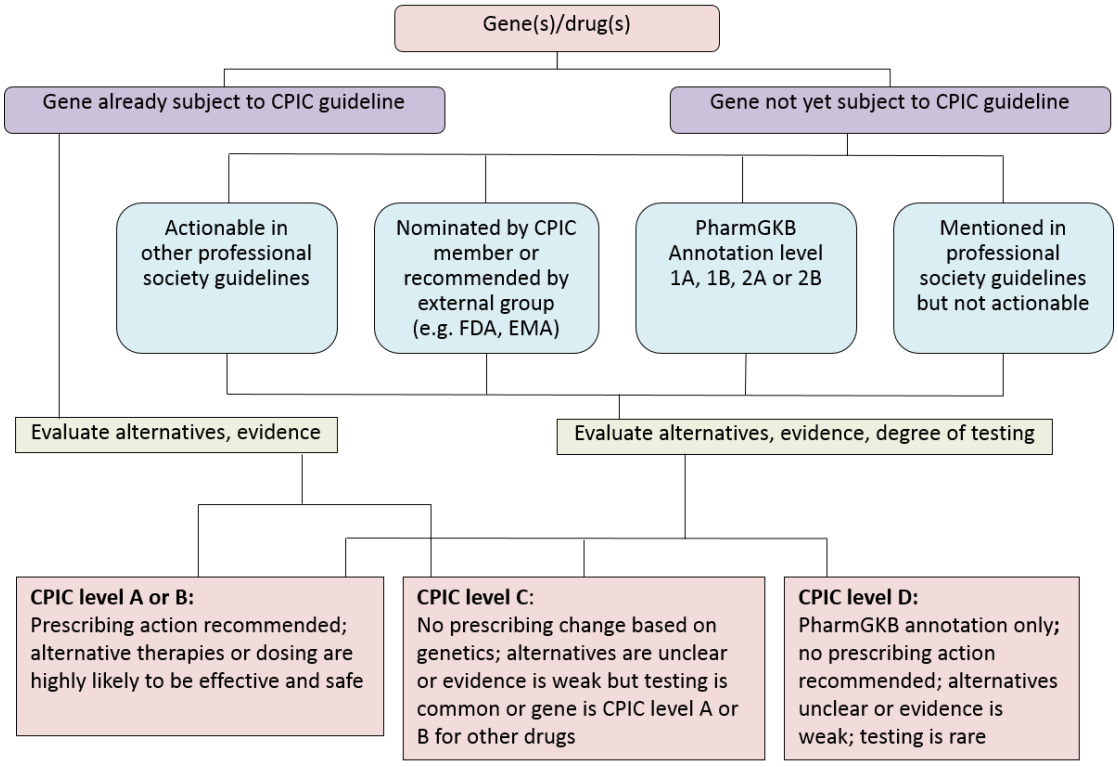

Figure6: CPIC levels for drugs

Chapter-3 MATERIAL AND METHOD

3.1 Data curation

3.1.1 PharmGKB

PharmGKB is a tool that provides access to all the pharmacogenetics and pharmacogenomics data. It contains information in a fully structured format [Sangkuhl K et al. 2008]. In the homepage of PharmGKB, we can search by using disease name, drug, variant or combination. Some tabs are also present where we can search for clinical pharmacogenomics, PGx research, overview, VIPs, haplotypes, pathways etc. as shown in figure given below[Thorn CF et al. 2009].

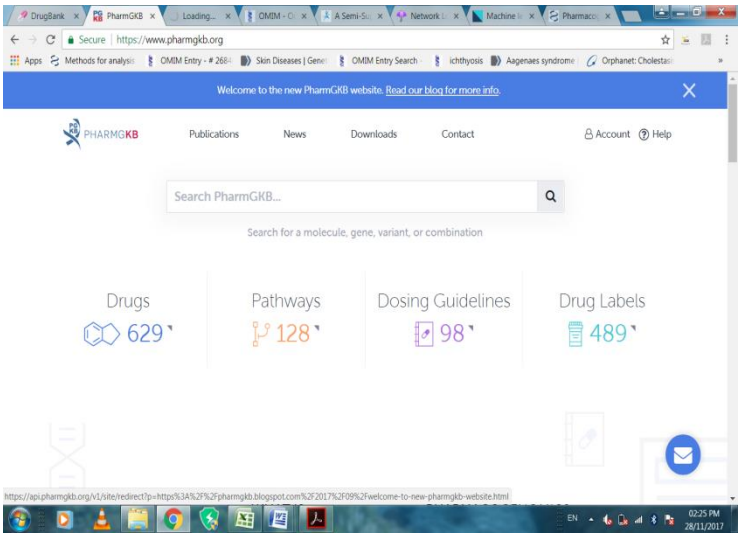

Figure7: Homepage of PharmGKB

- From PharmGKB tool, we opt for pathways, clinical annotation, variant annotation, gene location. Pathways that are present in PharmGKB are evidence-based diagrams that depict the PK and PD of a drug [Hodge AE et al. 2007]. Drugs that are used in PharmGKB pathways are taken from various other sources. It also contains other important PGx related information. We can easily download all the information present in pathways in the format of TSV, BioPAX and GPML.
- Clinical annotation provides information about variant-drug relations. In clinical annotation, phenotype for known genotype can be related to other genotypes that are associated. The figure below contains different level of clinical annotations. For viewing clinical annotation, one can use search box at the top of the page and search for their interested gene or drug. A new page is open where you can click on “clinical annotation” tab in left-hand menu. Each row represents single clinical annotation. From clinical annotation we choose here levels, variants, molecules and their types.
- Variant annotation provides information about the association between variant and phenotype information that are present here, are directly taken from publication. To search for variant annotation, click on “variant annotation” tab in left-hand menu on gene page.

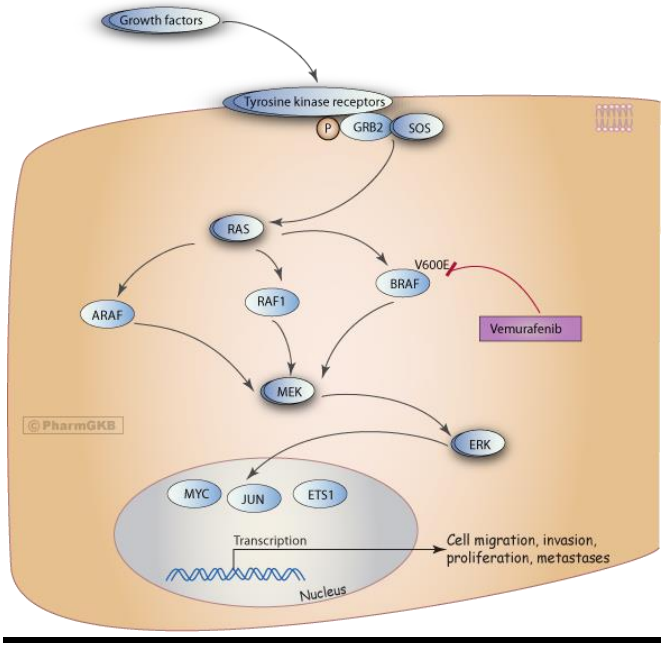

Figure8: the Vemurafenib Pathway for EGFR gene

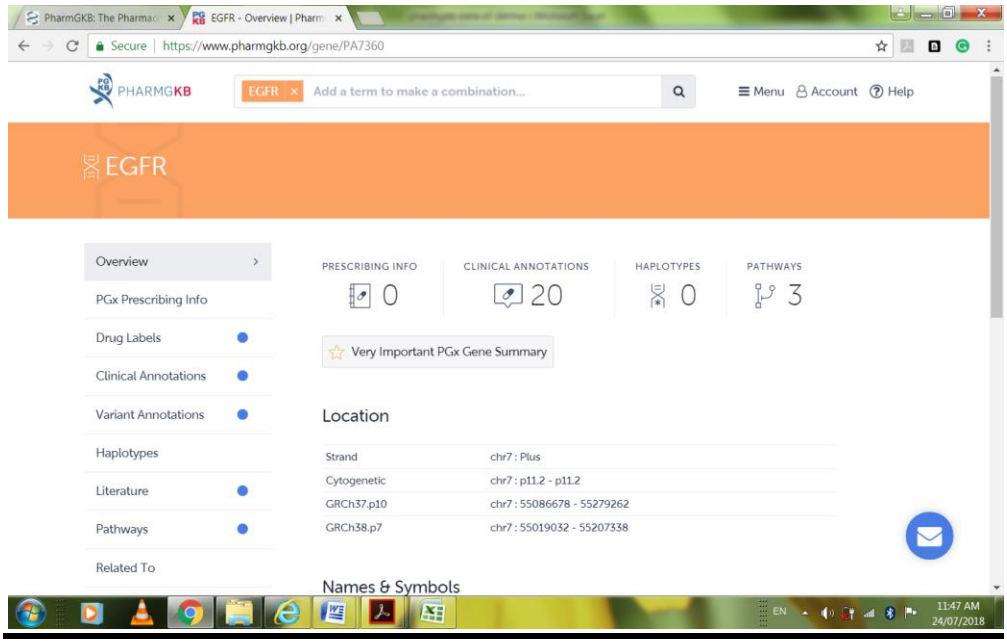

Figure9: the EGFR gene overview page that shows links to different attributes.

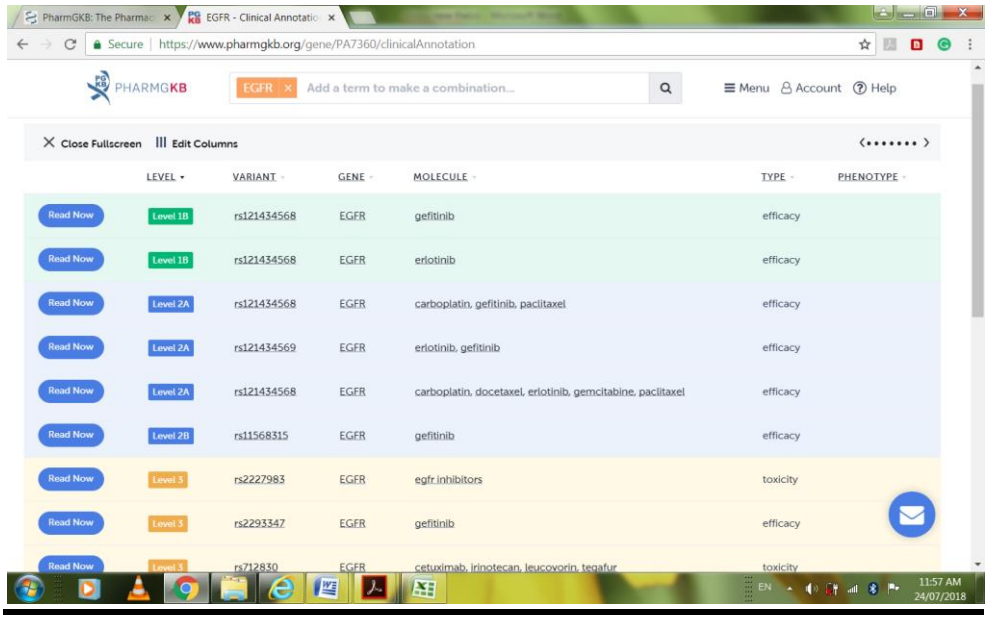

Figure10: screenshot showing clinical annotation for EGFR gene

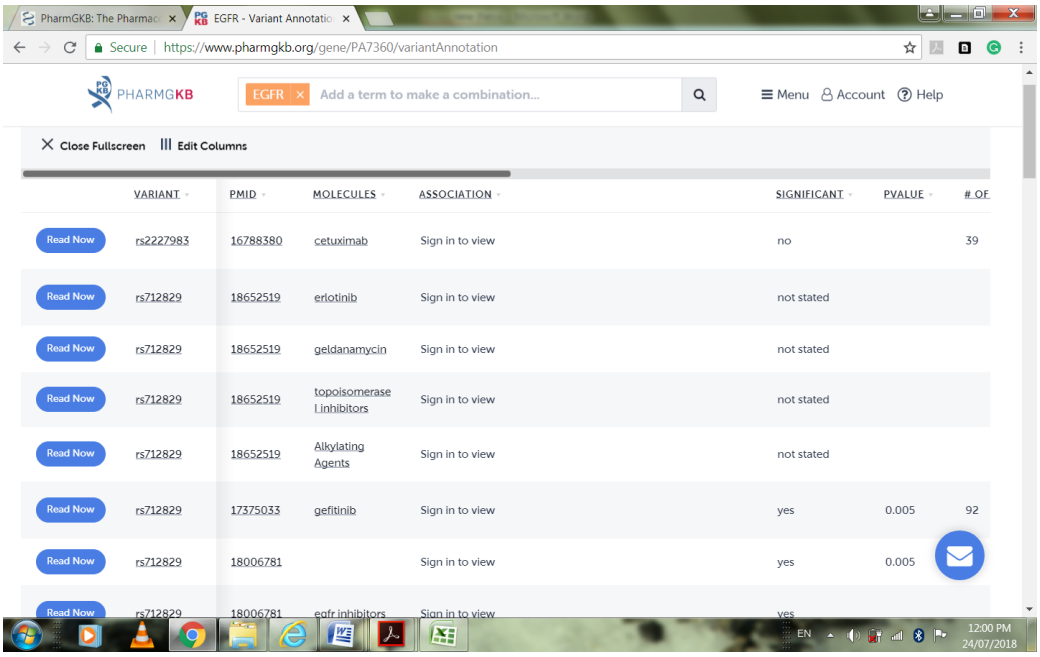

Figure11: screenshot showing variant annotation of EGFR gene

3.1.2 DrugBank

Drugbank is a resource which is used to search information about drug structure and their targets, their metabolism, actions, side-effects, cost and we can also identify drug by their MS or NMR spectra. It is also used for repurpose existing drugs and to design new drugs based on the information that it provides [Wishart DS et al. 2017]. On the DrugBank homepage, we have different tabs for browse, search, downloads, about, help and contact us. From browse we can search any drug on the basis of their category, pathways etc. from the data available on Drugbank we use here drug, drug group, their targets and enzymes.

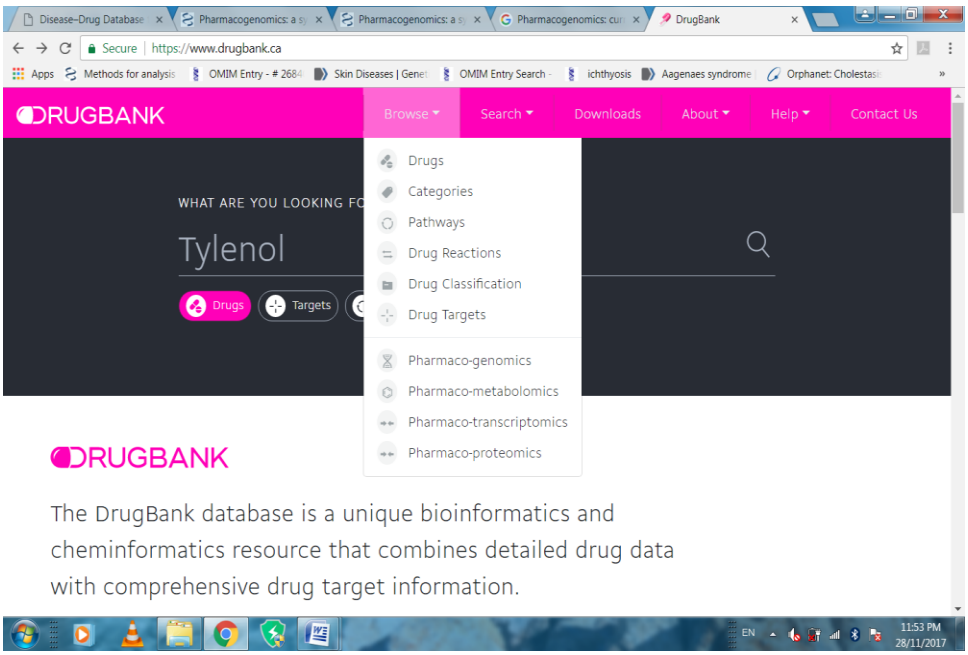

Figure12: detailed page of DrugBank homepage showing browsing details.

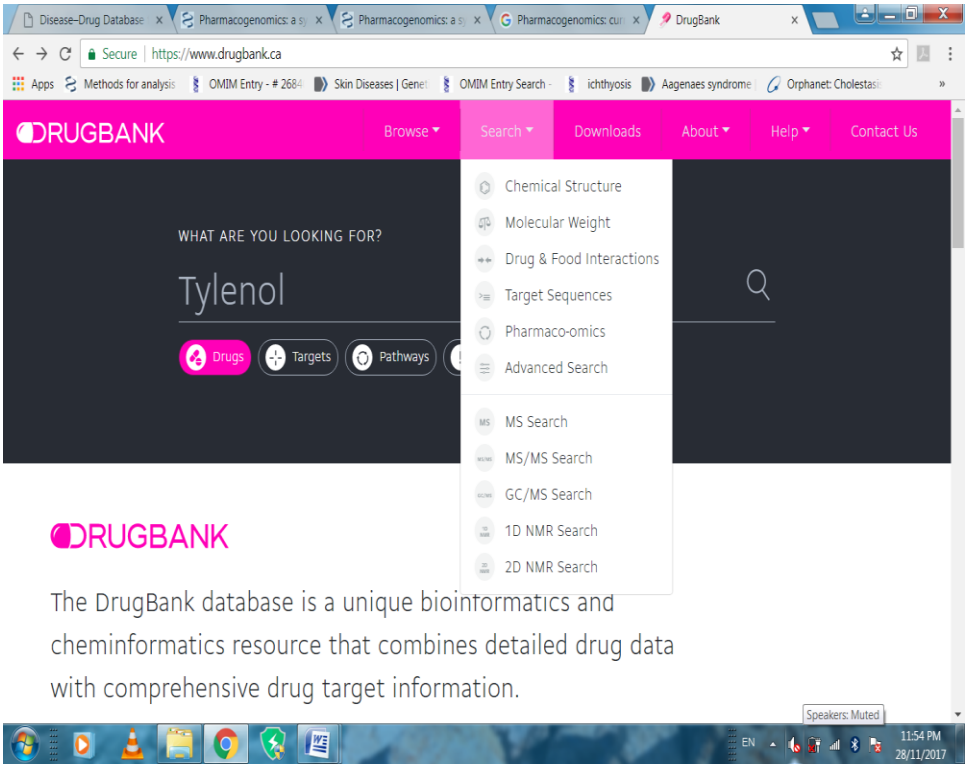

Figure13: detailed page of Drugbank homepage showing searching details.

3.1.3 OMIM

Online Mendelian Inheritance in Man (OMIM) is a complete, reliable and punctual knowledgebase of human genes and genetic disorders that are assemble to support human genetics research and education as well as clinical genetics practices. Each OMIM entry contains full abstract of a genetically determined phenotype and/or gene and it contains number of links to other genetic databases such as DNA and protein sequence [Amberger J et al. 2009]. OMIM is an easy, simple and straight portal to the expand information in human genetics. We can search OMIM from its homepage or from any other page in the NCBI Entrez suite of databases.

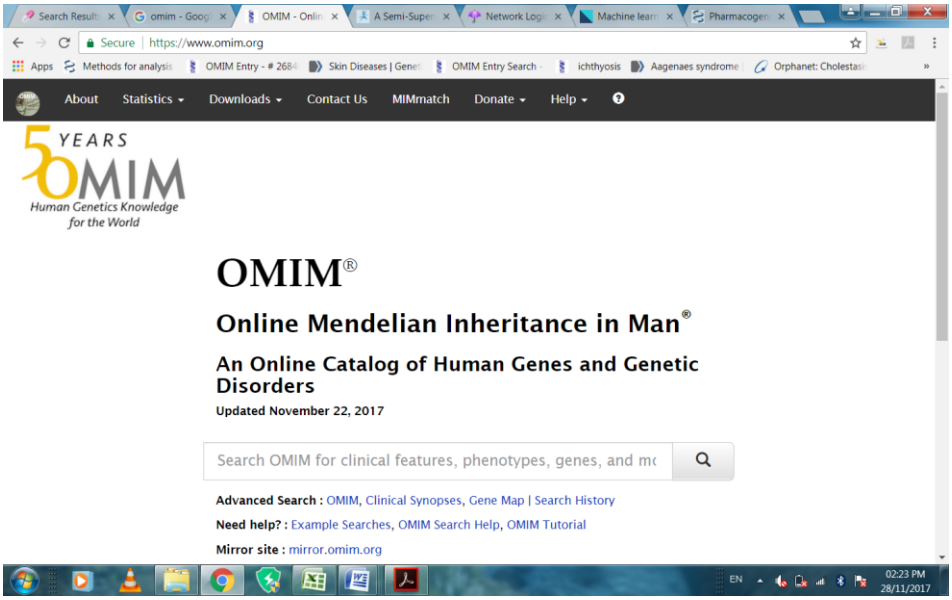

Figure14: User interface of OMIM.

Table 1.

Number of gene and phenotype entries in OMIM as on September 13, 2004

	Autosomal	X-linked	Y-linked	Mitochondrial	Total
* Gene with known sequence	9318	414	47	37	9816
+ Gene with known sequence and phenotype	356	36	0	0	392
# Phenotype description, molecular basis known	1462	134	1	25	1622
% Mendelian phenotype or locus, molecular basis unknown	1288	130	4	0	1422
Other, mainly phenotypes with suspected mendelian basis	2185	154	2	0	2341
Total	14 609	868	54	62	15 593

Figure15: number of gene and phenotype entries in OMIM

3.1.4 Orphanet

The nomenclature of rare disorders used by Orphanet, the reference resource for information on rare diseases and ORPHAN drugs. Since 1997 Orphanet maintains and inventory of rare diseases. Orphanet indexes any disease describe at least two patient s and in less than 50 per 100,000 persons in the General European Population. To search for a particular disease or several diseases and to identify their corresponding ORPHA numbers several options are available. The web-based Orphanet information portal allows you to search for one disease at a time. Now on entering the gene name that we wish to consult click on search represented with the list of results that could interest, we select the gene you wish to consult then we will arrive on the page concerning the gene. We will find the name symbol of the gene, at the top of the page we will then find the gene identity card with the synonyms previous symbols and names of the gene type of gene and chromosome location. We also provide cross reference with other nomenclature and resources such as OMIM, HGNC, uniprot, ensembl, etc.

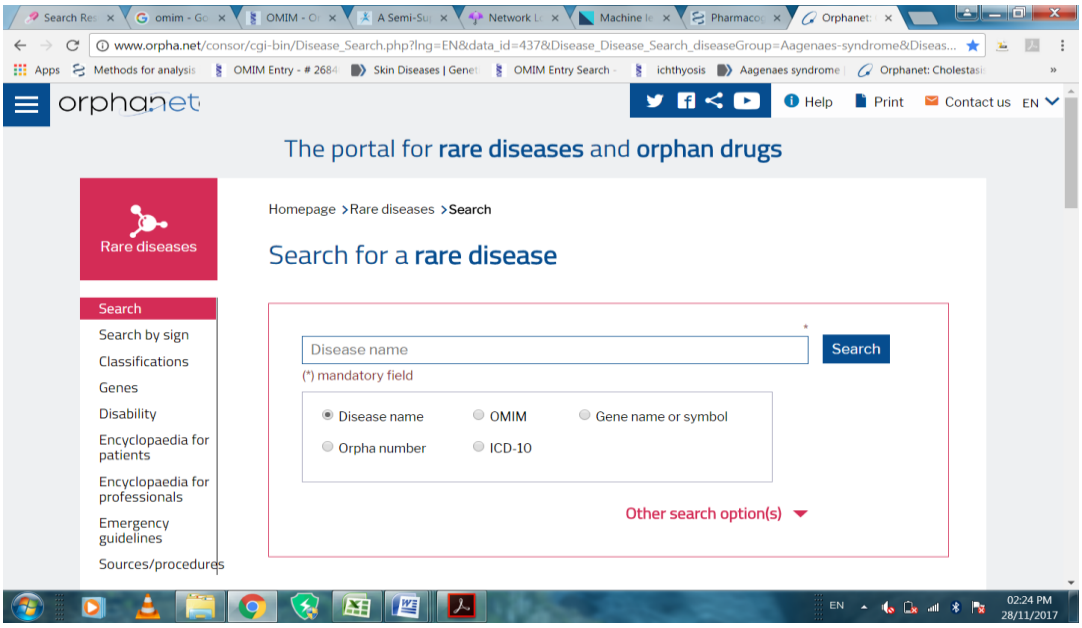

Figure16: Orphanet homepage

3.2 Cleaning data

Now we are going to clean-up the raw data that isn't exactly perfect for analyzing. Some of the data are not present for all genes so we exclude that data. Genes whose data is not present we remove that gene from our citation process.

3.3 Data analysis

We have around 1532 genes of approximately 214 diseases that are taken from mesh browser. Through OMIM we found attributes of 176 diseases out of 214 diseases and we curate them. From all the data present in PharmGKB, we analysis that total of 65 VIPs gene's data are present in PharmGKB out of which only 29 VIPs gene are for our dermatological disorders which we are taken here.

There are 501 drug labels entries in PharmGKB, from which only 49 drug labels are for our dermatological disorders present. From these drug labels we found 24 drugs whose targets we had taken from drugbank database.

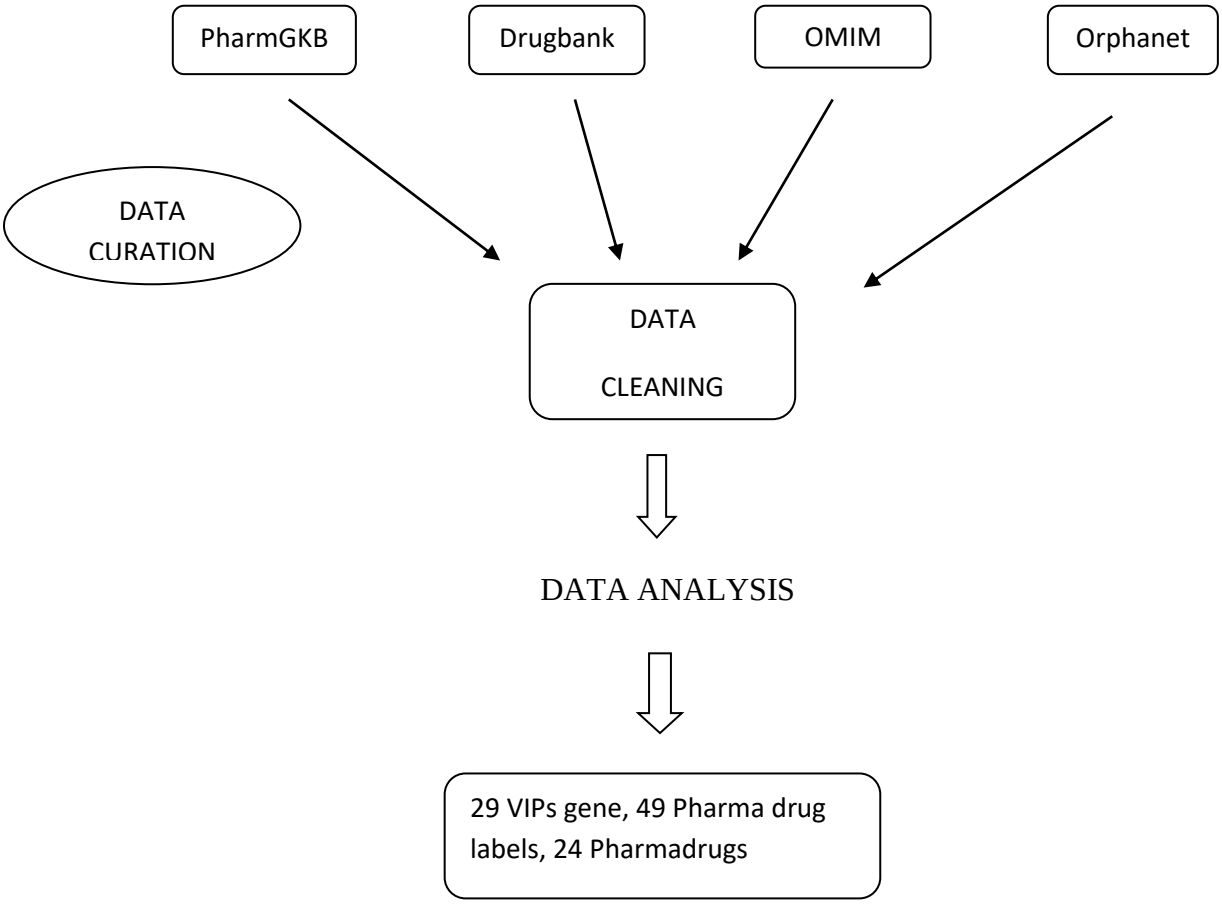

Figure17: flow chart of methodology

Chapter- 4 RESULT AND DISCUSSION

- From the above methods that are mentioned, we found different drugs that contain PGx information approved by FDA, EMA, PMDA and HCSC. There are around 501 drug labels on PharmGKB, from which around 49 drug labels are for dermatological disorders. Table containing all the drug labels of dermatological disorders.

Table1: Drug labels of dermatological disorders approved by different associations.

DISEASES	DRUGS	FDA	EMA	HCSC	PMDA
Bullous Congenital Ichthyosiform Erythroderma	Vandetanib	-	Testing recommended	-	-
	Sulfadiazine	Actionable PGx	-	Actionable PGx	Actionable PGx
Harlequin Fetus	peginterferon alfa-2b	Actionable PGx	-	-	-
Ichthyosis Hystrix	Tretinoin	Testing required	-	Testing required	Actionable PGx
Ichthyosis Vulgaris	Tretinoin	Testing required	-	Testing required	Actionable PGx
	Nalidixic Acid	Actionable PGx	-		Actionable PGx
Hereditary Palmoplantar Keratoderma Epidermolytic	Tretinoin	Testing required	-	Testing required	Actionable PGx
Hyperkeratosis	Dabrafenib	Testing required, actionable PGx, informative PGx	Testing required	Testing required	-
	Tretinoin	Testing required	-	Testing required	Actionable PGx
Keratosis Follicularis Spinulosa Decalvans	Tretinoin	Testing required	-	Testing required	Actionable PGx

Pachyonychia Congenita	Quinine	Actionable PGx	-	Actionable PGx	-
	Tretinoin	Testing required	-	Testing required	Actionable PGx
Dyskeratosis Congenita	Quinine	Actionable PGx	-	Actionable PGx	-
Ataxia Telangiectasia	Carisoprodol	Actionable PGx	-	-	-
	Succimer	Informative PGx	-	-	-
	Cerliponase alfa	Testing required	-	-	-
	Fosphenytoin	Actionable PGx	-	Testing recommended	-
	Pantoprazole	Actionable PGx	-	-	-
	Carbamazepine	Testing required, actionable PGx	-	Testing recommended	Actionable PGx
	Diazepam	Actionable PGx	-	-	-
	Imipramine	Actionable PGx	-	-	-
Cutis Marmorata Telangiectatica Congenita	Quinine	Actionable PGx	-	Actionable PGx	-
	Tretinoin	Testing required	-	Testing required	Actionable PGx
Hereditary Hemorrhagic	peginterferon alfa-2b	Actionable PGx	-	-	-
Aplasia Cutis Congenita	Enasidenib	Testing required	-	-	-
	Quinine	Actionable PGx	-	Actionable PGx	-
	Tretinoin	Testing required	-	Testing required	Actionable PGx
Focal Dermal Hypoplasia	Azathioprine	Testing recommended	-	Actionable PGx	Actionable PGx
	Carbamazepine	Testing required, actionable PGx	-	Testing recommended	Actionable PGx
Albright Hereditary Osteodystrophy	Anastrozole	Testing required	-	Testing required	-

Familial Dysautonomia	Evolocumab	Informative PGx	-	-	-
	Lomitapide	Informative PGx	Testing required	Informative PGx	-
	Celecoxib	Actionable PGx has dosing info	-	Actionable PGx	Actionable PGx
	Alirocumab	Informative PGx	-	-	-
	Mipomersen	Informative PGx	-	-	-
	Rosuvastatin	Actionable PGx	-	Actionable PGx	-
Familial Dysautonomia	Simvastatin	Informative PGx	-	-	-
	Atorvastatin	Informative PGx	-	Informative PGx	Informative PGx
Hereditary Lymphedema	Trametinib	Testing required, Actionable PGx, informative PGx	Testing required	Testing required	-
NOMID/CINCA	Donepezil	Actionable PGx	-	-	-
Urticaria Pigmentosa	Desloratadine		Informative PGx	-	-
	Doxepin	Actionable PGx	-	-	-
Epidermal Nevus	Cetuximab	Testing required	Testing required	Testing required	Testing required
	Panitumumab	Testing required	Testing required	Testing required	Testing required
	Lapatinib	Testing required, actionable PGx	Testing required	Testing required	Testing required
	Gefitinib	Testing required, actionable PGx	Testing required	Testing required	Testing required
	Neratinib	Testing required, informative PGx	-	-	-
	Osimertinib	Testing required	-	-	-
	Erlotinib	Testing required	Testing required	Testing required	Testing required
	Pertuzumab	Testing	Testing	Testing	Testing

		required, actionable PGx	required	required	required
	Palbociclib	Testing required	-	-	-
	Vandetanib		Testing recommended	-	-
	Afatinib	Testing required	Testing required	Testing required	-
	Abemaciclib	Testing required	-	-	-
	Brigatinib	Testing required	-	-	-
	Flurbiprofen	Actionable PGx	-	-	-
	Telaprevir	Actionable PGx	Actionable PGx	-	-
Congenital Erythropoietic Porphyria	Vandetanib		Testing recommended	-	-
	Sulfadiazine	Actionable PGx	-	Actionable PGx	Actionable PGx
Familial Cutaneous Amyloidosis	Evolocumab	Informative PGx	-	-	-
	Tauroursodeoxycholic acid	Testing required	-	-	-
	Lomitapide	Informative PGx	Testing required	Informative PGx	-
	Denileukin diftitox	Testing required	-	-	-
	Celecoxib	Actionable PGx	-	Actionable PGx	Actionable PGx
	Alirocumab	Informative PGx	-	-	-
	Mipomersen	Informative PGx	-	-	-
	Rosuvastatin	Actionable PGx	-	Actionable PGx	-
	Simvastatin	Informative PGx	-	-	-
	Vemurafenib	Testing required, actionable PGx	Testing required	Testing required	Testing required
	Atorvastatin	Informative PGx	-	Informative PGx	Informative PGx
	Evolocumab	Informative PGx	-	-	-
	Lomitapide	Informative PGx	Testing required	Informative PGx	-

Familial Mucocutaneous Candidiasis	Celecoxib	Actionable PGx	-	Actionable PGx	Actionable PGx
	Posaconazole	-	Informative PGx	-	-
	Voriconazole	Actionable PGx	Informative PGx	Actionable PGx	Actionable PGx
	Alirocumab	Informative PGx	-	-	-
	Mipomersen	Informative PGx	-	-	-
	Rosuvastatin	Actionable PGx	-	Actionable PGx	-
	Tretinoin	Testing required	-	Testing required	Actionable PGx
	Simvastatin	Informative PGx	-		
	Atorvastatin	Informative PGx	-	Informative PGx	Informative PGx

- VIPs provide an overview of significant gene that is involved in drug metabolism. It includes all the information on the gene that includes any disease association in-depth information on the gene's pharmacogenetics. From this data we curate around 29 VIPs of dermatological disorders from total 65 VIPs whose information is present in PharmGKB.

Table2: Top predictive VIPs for dermatological disorders

S.NO.	VIPs GENES IN PharmGKB	DISEASES
1	ABCG2	Breast Neoplasms
2	ABCB1	Breast Neoplasms
3	AHR	Breast Neoplasms, Dermatitis_ Contact, Hyper pigmentation
4	ALOX5	Drug Eruptions, Urticaria
5	BRAF	LEOPARD SYNDROME 3, Cardiofaciocutaneous syndrome
6	BRCA1	Breast Neoplasms, Breast-Ovarian Cancer familial susceptibility to 1,Hereditary Breast and Ovarian Cancer Syndrome
7	COMT	Breast Neoplasms
8	CYP1A2	Porphyria Cutanea Tarda
9	CYP2E1	Drug Eruptions
10	CYP3A4	Breast Neoplasms
11	DPYD	Breast Neoplasms
12	EGFR	Chloracne, Breast Neoplasms
13	ERBB2	Breast Neoplasms
14	F5	Scleroderma_ Systemic
15	G6PD	Dermatitis_ Contact
16	GSTP1	Breast Neoplasms, Dermatitis_ Contact
17	GSTT1	Skin Neoplasms
18	HLA-B	Dermatitis, Drug Eruptions, Stevens-Johnson Syndrome, Dermatomyositis, Exanthema, Behcet Syndrome
19	KIT	Breast Neoplasms, Mastocytosis_ Systemic, Piebaldism
20	KRAS	Breast Neoplasms, Cardiofaciocutaneous syndrome, Nevus_ Sebaceous of Jadassohn
21	MTHFR	Breast Neoplasms, Drug Eruptions, Alopecia
22	NAT2	Breast Neoplasms, Dermatitis_ Occupational
23	NQO1	Dermatitis_ Contact
24	PTGIS	Stevens-Johnson Syndrome
25	SLC22A1	Breast Neoplasms
26	SLCO1B1	Breast Neoplasms
27	TYMS	Breast Neoplasms
28	UGT1A1	Dermatitis_ Contact
29	VDR	Breast Neoplasms, Alopecia

- DrugBank data releases its latest version that contains 11,678 drug entries which includes 2,606 approved small molecules drugs, 1,079 approved biotech drugs, 128 neutraceuticals and over 5,504 experimental drugs. From drugbank database we curate some Pharmadrugs and their targets [Imming P et al. 2006].

Table3- Pharma drugs with their targets in some dermatological disorders

S.NO.	DRUGS	TARGETS
1	Vandetanib	Vascular endothelial growth factor A, epidermal growth factor receptor, protein-tyrosine kinase 6, angiotensin-1 receptor, proto-oncogene trypsine-protein kinase receptor ret
2	Sulfadiazine	Dihydropteroate synthetase
3	Peg interferon alfa-2b	Interferon alpha/beta receptor 1, Interferon alpha/beta receptor 2
4	Tretinoin	Retinoic acid receptor (RXR-alpha, RXR-beta, RXR-gamma, alpha, beta, gamma), Retinal dehydrogenase (1, 2), Retinoic acid-induced protein 3, Nuclear receptor subfamily 0 group B member 1, Retinoic acid receptor responder protein 1, Lipocalin-1, Odorant-binding protein 2a, Retinol-binding protein 4, [pyruvate dehydrogenase [lipoamide]] kinase isozyme4, cytochrome P450 (26A1, 26B1, 26C1), Hematopoietic prostaglandin D synthase
5	Nalidixic acid	DNA
6	Dabrafenib	Serine/threonine-protein kinase (B-raf, Nek11, SIK1), RAF proto-oncogene serine/threonine-protein kinase, LIM domain kinase 1
7	Quinine	Fe(ll)-protoporphyrin IX, Platelet glycoprotein IX, Intermediate conductance calcium-activated potassium channel protein 4
8	Carisoprodol	Gamma-amino butyric acid receptor subunit (alpha-1,beta-2, gamma-2)
9	Succimer	Lead, Mercury, Cadmium, Arsenic
10	Cerliponase alfa	Cation-independent mannose-6-phosphate receptor
11	Fosphenytoin	Sodium channel protein type 5 subunit alpha
12	Pantoprazole	Potassium-transporting ATPase alpha chain 1
13	Carbamazepine	Sodium channel protein type 5 subunit alpha, Neuronal acetylcholine receptor subunit (alpha-4,beta-2), Neuronal receptor subfamily 1 group I member 2
14	Diazepam	Gamma-amino butyric acid receptor subunit alpha-(1/ 2/ 3/ 5), gamma-amino butyric acid receptor subunit beta-(1/ 2/ 3), gamma-alpha butyric acid receptor subunit gamma-(1/

		2/ 3), gamma-amino butyric acid receptor subunit (delta/ epsilon/ pi/ rho-1/ rho-2/ rho-3/ theta), translocator protein, GABA-A receptor (anion channel) (protein group)
15	Imipramine	Sodium-dependent (noradrenaline/serotonin) transporter, sodium dependent serotonin transporter, 5-hydroxytryptamine receptor-(1A/ 2A/6), histamine H1 receptor, alpha-1a adrenergic receptor, alpha-1d adrenergic receptor, muscarinic acetylcholine receptor (M1/M2/M3/M4/M5), potassium voltage-gated channel subfamily D member (2, 3), 5-hydroxytryptamine receptor-(2C/7), alpha-1B adrenergic receptor, [D(1)/ D(2)] dopamine receptor (protein group), Potassium voltage-gated channel subfamily H member (1,2), sodium dependent dopamine transporter, alpha-1-acid glycoprotein 2
16	Enasidenib	Isocitrate dehydrogenase [NADP], mitochondrial
17	Azathioprine	Hypoxanthine-guanine phosphoribosyltransferase, Ras-related C3 botulinum toxin substrate 1
18	Anastrozole	Cytochrome P450 19A1
19	Evolucumab	-
20	Lomitapide	Microsomal triglyceride transfer protein large subunit
21	Celecoxib	Prostaglandin G/H synthase2, 3-phosphoinositide-dependent protein kinase 1, carbonic anhydrase (2/3), ATP-binding cassette sub-family B member 5, ATP-binding cassette sub-family G member 2, Multidrug resistance protein 1
22	Alirocumab	Proprotein convertase subtilisin/kexin type 9
23	Mipomersen	mRNA of ApoB-100
24	Rosuvastatin	3-hydroxy-3-methylglutaryl-coenzyme A reductase
25	Simvastatin	3-hydroxy-3-methylglutaryl-coenzyme A reductase, Integrin beta-2, Integrin alpha-l
26	Atorvastatin	3-hydroxy-3-methylglutaryl-coenzyme A reductase, Dipeptidyl peptidase 4, Aryl hydrocarbon receptor
27	Tremetinib	-
28	Donepazil	Acetylcholinesterase, 5-hydroxytryptamine receptor 2A
29	Desloratadine	Histamine H1 receptor
30	Doxepin	Histamine (H1/H2/H4) receptor, Sodium-dependent noradrenaline transporter, sodium-dependent serotonin transporter, 5-hydroxytryptine receptor(2A/ 2B/2C), Muscarinic acetylcholine receptor (M1/M2/M3/M4/M5), (Alpha-1A/1B/1D/2A/2B/2C) adrenergic receptor, 5-hydroxytryptamine receptor (1A/6), D(2) dopamine receptor, Potassium voltage-gated channel subfamily H member2
31	Cetuximab	Epidermal growth factor receptor, low affinity immunoglobulin gamma Fc region receptor (II-a/II-b/II-c/III-A/III-B), complement C1r subcomponent, complement C1q subcomponent subunit (A/B/C), complement C1s subcomponent, high affinity immunoglobulin gamma Fc receptor I

32	Panitumumab	Epidermal growth factor receptor
33	Lapatinib	Epidermal growth factor receptor, Receptor tyrosine-protein kinase erbB-2
34	Gefitinib	Epidermal growth factor receptor
35	Neratinib	Epidermal growth factor receptor
36	Osimertinib	Epidermal growth factor receptor
37	Pertuzumab	Receptor tyrosine-protein kinase erbB-2
38	Palbociclib	Cyclin-dependent kinase 4, Cyclin-dependent kinase 6
39	Afatinib	Epidermal growth factor receptor, Receptor tyrosine-protein kinase erbB-2, Receptor tyrosine-protein kinase erbB-4
40	Abemaciclib	Cyclin-dependent kinase 4, Cyclin-dependent kinase 6
41	Brigatinib	ALK tyrosine kinase receptor, Epidermal growth factor receptor, Tyrosine-protein kinase ABL-1, Insulin like growth factor 1 receptor, Receptor-type tyrosine-protein kinase FLT3, Insulin receptor, Hepatocyte growth factor receptor, receptor tyrosine-protein kinase erbB-4, Receptor tyrosine-protein kinase erbB-2
42	Flurbiprofen	Prostaglandin G/H synthase 1, Prostaglandin G/H synthase 2
43	Telaprevir	NS3/4A protein, Solute carrier organic anion transporter family member 1B1, Solute carrier organic anion transporter family member 2B1
44	Tauroursodeoxy cholic acid	-
45	Denileukin diflitox	Interleukin-2 receptor subunit alpha, Interleukin-2 receptor subunit beta, cytokine receptor common subunit gamma
46	Vemurafenib	Serine/threonine-protein kinase B-raf
47	Posaconazole	Lanosterol 14-alpha demethylase
48	Voriconazole	Lanosterol 14-alpha demethylase
49	Erlotinib	Epidermal growth factor receptor, nuclear receptor subfamily 1 group I member 2

Chapter- 5 CONCLUSION

We can conclude that advances in pharmacogenomics will lead to greater significant for clinical improvement in terms of safety and efficiency of medication that increase hundreds of times. Medication which is given to a patient depends on its pharmacokinetics, pharmacodynamics, and pharmacogenetics in combination. Currently, applications of pharmacogenomics in clinical practices are limited but this promise to expand more in future. Pharmacogenomics is used to identify new pharmacological targets and new medications by using biotechnologies such as genomic high-throughput. As the advancement in knowledge has been increasing day by day, this shows that both pharmacogenetics and pharmacogenomics has a great impact on drug research and development, their clinical trials and practices. Current drug databases provide may tool to predict patient's drug effects and also give PK and PD information about so many different drugs. By using this information one can easily increase drug efficacy and using an individual genetic makeup we can provide correct pharmacologic treatments. Although it is not available for all dermatological drugs. It gives an opportunity for doctors to correlate clinical trials with the above-mentioned database and can change the patient treatment in future.

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