KSBi-BIML 2023

Bioinformatics & Machine Learning(BIML)
Workshop for Life Scientists, Data Scientists,
and Bioinformatians

생물정보학&머신러닝 워크샵(온라인)

Pharmacogenomics in drug discovery and development

남호정 _ GIST

SBi 한국생명정보학회
Korean Society for Bioinformatics

본 강의 자료는 한국생명정보학회가 주관하는 BIML 2023 워크샵 온라인 수업을 목적으로 제작된 것으로 해당 목적 이외의 다른 용도로 사용할 수 없음을 분명하게 알립니다.

이를 다른 사람과 공유하거나 복제, 배포, 전송할 수 없으며 만약 이러한 사항을 위반할 경우 발생하는 **모든 법적 책임은 전적으로 불법 행위자 본인에게 있음을 경고**합니다.

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안녕하십니까?

한국생명정보학회가 개최하는 동계 교육 워크샵인 BIML-2023에 여러분을 초대합니다. 생명정보학 분야의 연구자들에게 최신 동향의 데이터 분석기술을 이론과 실습을 겸비해 전달하고자 도입한 전문 교육 프로그램인 BIML 워크샵은 2015년에 시작하여 올해로 9차를 맞이하게 되었습니다. 지난 2년간은 심각한 코로나 대유행으로 인해 아쉽게도 모든 강의가 온라인으로 진행되어 현장 강의에서만 가능한 강의자와 수강생 사이에 다양한 소통의 기회가 없음에 대한 아쉬움이 있었습니다. 다행히도 최근 사회적 거리두기 완화로 현장 강의가 가능해져 올해는 현장 강의를 재개함으로써 온라인과 현장 강의의 장점을 모두 갖춘 프로그램을 구성할 수 있게 되었습니다.

BIML 워크샵은 전통적으로 크게 인공지능과 생명정보분석 두 개의 분야로 구성되었습니다. 올해 AI 분야에서는 최근 생명정보 분석에서도 응용이 확대되고 있는 다양한 심층학습(Deep learning) 기법들에 대한 현장 강의가 진행될 예정이며, 관련하여 심층학습을 이용한 단백질구조예측, 유전체 분석, 신약개발에 대한 이론과 실습 강의가 함께 제공될 예정입니다. 또한 싱글셀오믹스 분석과 메타유전체분석 현장 강의는 많은 연구자의 연구 수월성 확보에 큰 도움을 줄 것으로 기대하고 있습니다. 이외에 다양한 생명정보학 분야에 대하여 30개 이상의 온라인 강좌가 개설되어 제공되며 온라인 강의의 한계를 극복하기 위해서 실시간 Q&A 세션 또한 마련했습니다. 특히 BIML은 각 분야 국내 최고 전문가들의 강의로 구성되어 해당 분야의 기초부터 최신 연구 동향까지 포함하는 수준 높은 내용의 강의가 될 것입니다.

이번 BIML-2023을 준비하기까지 너무나 많은 수고를 해주신 BIML-2023 운영위원회의 남진우, 우현구, 백대현, 정성원, 정인경, 장혜식, 박종은 교수님과 KOBIC 이병욱 박사님께 커다란 감사를 드립니다. 마지막으로 부족한 시간에도 불구하고 강의 부탁을 흔쾌히 허락하시고 훌륭한 현장 강의와 온라인 강의를 준비하시는데 노고를 아끼지 않으신 모든 연사분께 깊은 감사를 드립니다.

2023년 2월

한국생명정보학회장 이 인 석

강의개요

Pharmacogenomics in drug discovery and development

약물유전체학이란(pharmacogenomics) 유전체(genome) 수준에서 염기서열의 차이 또는 유전자 발현 차이를 분석하여 개개인이 갖는 약물 반응의 차이를 규명하는 연구분야이다. 본 수업에서는 이러한 개인별 약물 반응성을 고려한 약물 개발 과정에 대하여 알아보고 또한 개인별 유전자에 따른 약물 반응을 연구/예측하는데 필요한 생명정보학적 접근 방식을 알아본다. 구체적으로는 약물유전체학에 대한 기본 개념을 이해하고, 연구에 필요한 다양한 데이터베이스와 기본적인 생명정보학적 알고리즘들에 대해서 다룬다.

강의는 다음의 내용을 포함한다:

- Pharmacogenomics 기본 개념
- Drug discovery and development 기본 개념
- Protein representation features
- Molecular representation features
- 개인별 유전자 정보를 이용한 다양한 약물 개발 연구 소개

* 교육생준비물:
강의 동영상 플레이가 가능한 컴퓨터

* 강의 난이도: 중급

* 강의: 남호정 교수 (광주과학기술원 전기전자컴퓨터공학부)

Curriculum Vitae

Speaker Name: Hojung Nam, Ph.D.

▶ Personal Info

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Title	Associate Professor
Affiliation	Gwangju Institute of Science and Technology (GIST)

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Research Interest

Bioinformatics, Systems Biology, Cheminformatics, Machine learning

Educational Experience

2001	B.S. in Computer Science, Sogang Univ., Seoul, Korea.
2003	M.S. in Computer Science, KAIST, Daejeon, Korea.
2009	Ph.D. in Bio and Brain Engineering, KAIST, Daejeon, Korea.

Professional Experience

2009-2013	Postdoctoral Researcher, Bioengineering, University of California, San Diego, CA USA
2013-2018	Assistant Professor, Gwangju Institute of Science and Technology (GIST)
2018-	Associate Professor, Gwangju Institute of Science and Technology (GIST)

Selected Publications (5 maximum)

1. Hyunho Kim, Eunyoung Kim, Ingoo Lee, Bongsung Bae, Minsu Park, Hojung Nam*, " Artificial Intelligence in Drug Discovery: A Comprehensive Review of Data-Driven and Machine Learning Approaches", Biotechnology and Bioprocess Engineering, volume 25, pages895–930(2020).
2. Hyunho Kim, Hojung Nam*, "hERG-Att: Self-Attention-Based Deep Neural Network for Predicting hERG Blockers", Computational Biology and Chemistry, Available online 19 May 2020, 107286.
3. Soobok Joe , Hojung Nam*, "Prediction model construction of stem cell pluripotency using CpG and non-CpG DNA methylation markers", BMC Bioinformatics, 2020 21:175.
4. Heeyeon Choi, Soobok Joe, Hojung Nam*, "Development of Tissue-Specific Age Predictors Using DNA Methylation Data", Genes 2019, 10(11), 888.
5. Ingoo Lee, Jongsoo Keum, Hojung Nam*, "DeepConv-DTI: Prediction of drug-target interactions via deep learning with convolution on protein sequences", PLoS Computational Biology 15(6): e1007129. https://doi.org/10.1371/journal.pcbi.1007129

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Pharmacogenomics in drug discovery and development

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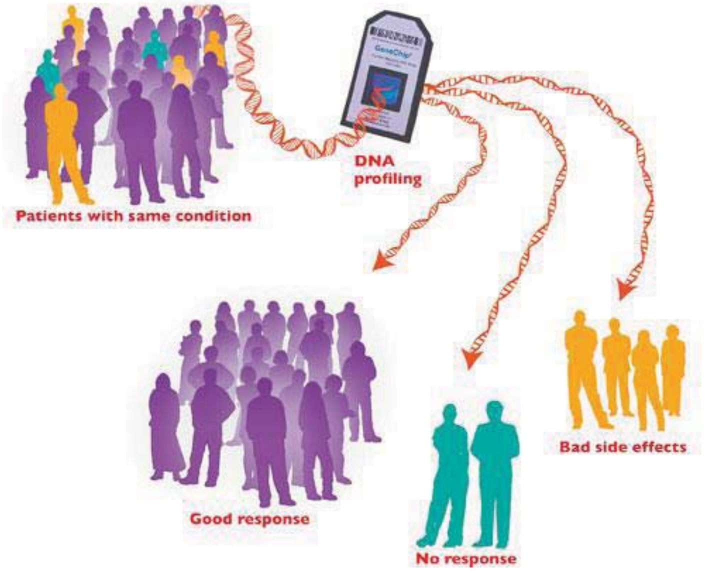
INTRODUCTION TO PHARMACOGENOMICS

Pharmacogenomic

- The term **pharmacogenetics** was coined in the 1950s and captures the idea that large effect size DNA variants contribute importantly to variable drug actions in an individual (single gene-drug).
- The term **pharmacogenomics** is now used by many to describe the idea that multiple variants across the genome that can differ across populations affect drug response. The International Conference on Harmonisation, a worldwide consortium of regulatory agencies, has defined **pharmacogenomics as the study of variations of DNA and RNA characteristics as related to drug response.**

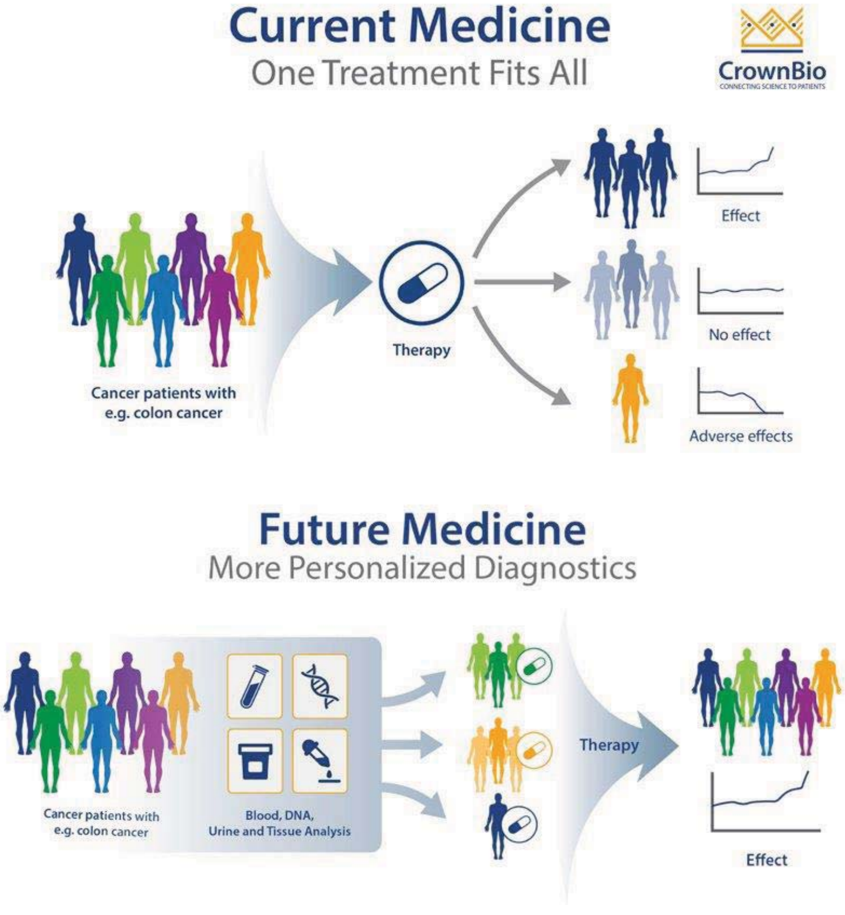
Dan M Roden et al., Lancet . 2019 Aug 10;394(10197):521-532.



Look for genetic variants that affect drug response used to treat the condition. The analysis will yield results that allow physicians to determine if their patient will have a positive response to the drug treatment.
[National Human Genome Research Institute]

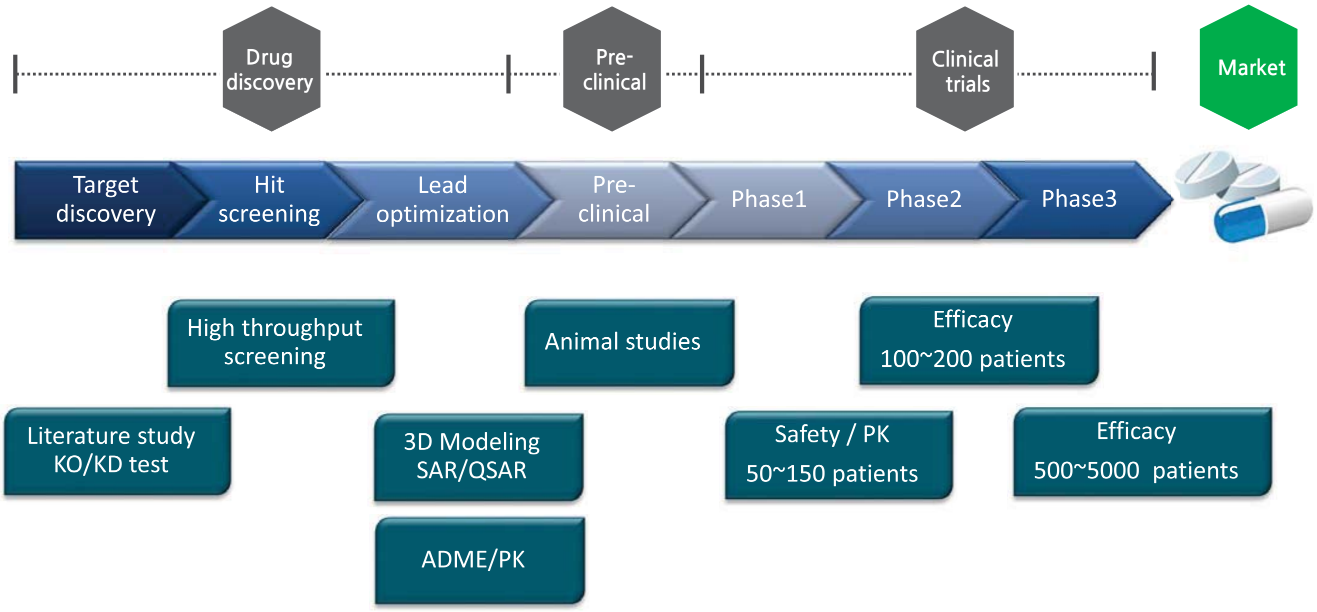
Pharmacogenomics Adds Precision to the Practice of Medicine, June 15, 2015 (Vol. 35, No. 12)

https://www.genengnews.com/magazine/249/pharmacogenomics-adds-precision-to-the-practice-of-medicine/



https://blog.crownbio.com/pdx-personalized-medicine#_

Drug discovery and development



Drug discovery

Pre-clinical

Clinical trials

Market

Target discovery

Hit screening

Lead optimization

Pre-clinical

Phase1

Phase2

Phase3

High throughput screening

Animal studies

Efficacy 100~200 patients

Literature study KO/KD test

3D Modeling SAR/QSAR

Safety / PK 50~150 patients

Efficacy 500~5000 patients

ADME/PK

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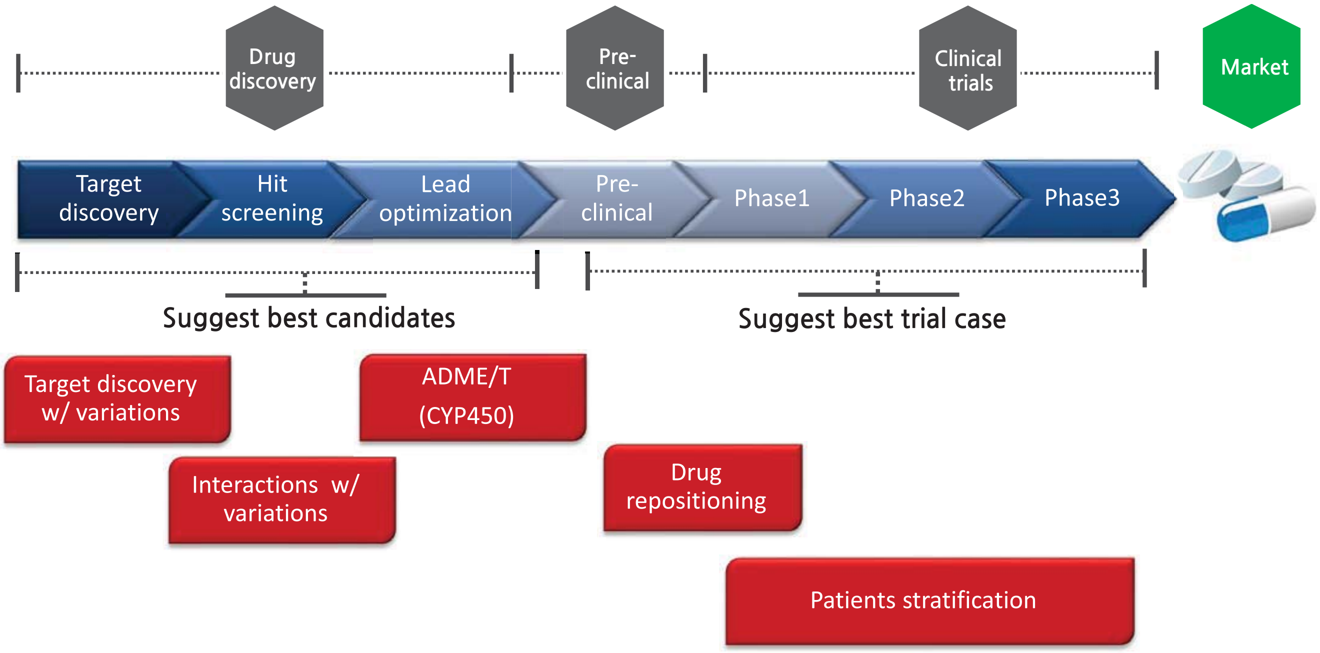
Pharmacogenomics in drug discovery and development



Drug discovery

Pre-clinical

Clinical trials

Market

Target discovery

Hit screening

Lead optimization

Pre-clinical

Phase1

Phase2

Phase3

Suggest best candidates

Suggest best trial case

Target discovery w/ variations

ADME/T (CYP450)

Interactions w/ variations

Drug repositioning

Patients stratification

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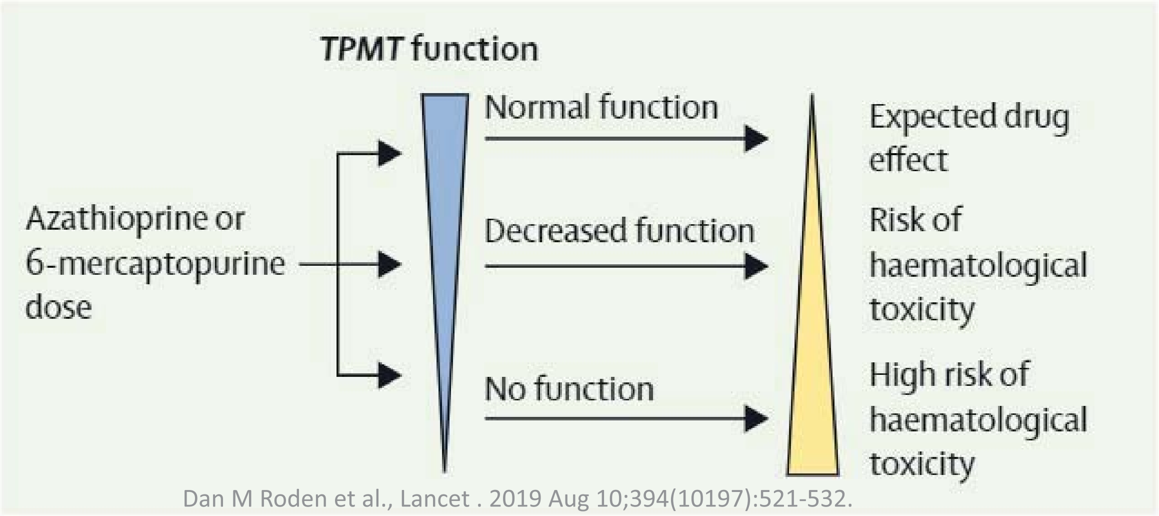
Example 1 – TPMT

Pharmacogenetics in Oncology

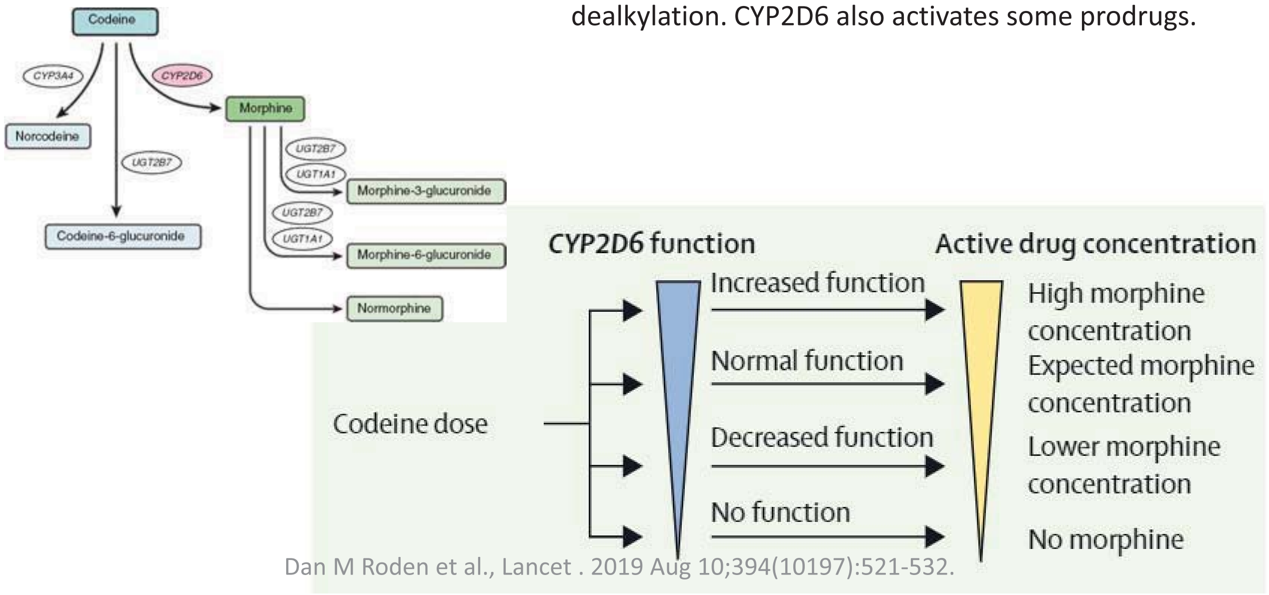
- The thiopurine S-methyltransferase (TPMT) is a metabolizer of chemotherapeutic agents 6MP and azothiopurine (used mainly in blood-based malignancies)
- TPMT deficiency leads to severe toxicity associated with treatment (potential mortality)


TPMT function
Azathioprine or 6-mercaptopurine dose
Normal function
Decreased function
No function
Expected drug effect
Risk of haematological toxicity
High risk of haematological toxicity

Dan M Roden et al., Lancet . 2019 Aug 10;394(10197):521-532.

Example 2 – CYP2D6

- Cytochrome P450 2D6 (CYP2D6) is an enzyme that in humans is encoded by the CYP2D6 gene. CYP2D6 is primarily expressed in the liver.
- In particular, CYP2D6 is responsible for the metabolism and elimination of approximately 25% of clinically used drugs, via the addition or removal of certain functional groups – specifically, hydroxylation, demethylation, and dealkylation. CYP2D6 also activates some prodrugs.



Dan M Roden et al., Lancet . 2019 Aug 10;394(10197):521-532.

- PART1
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  - Key data sources
  - Representations of proteins, chemicals

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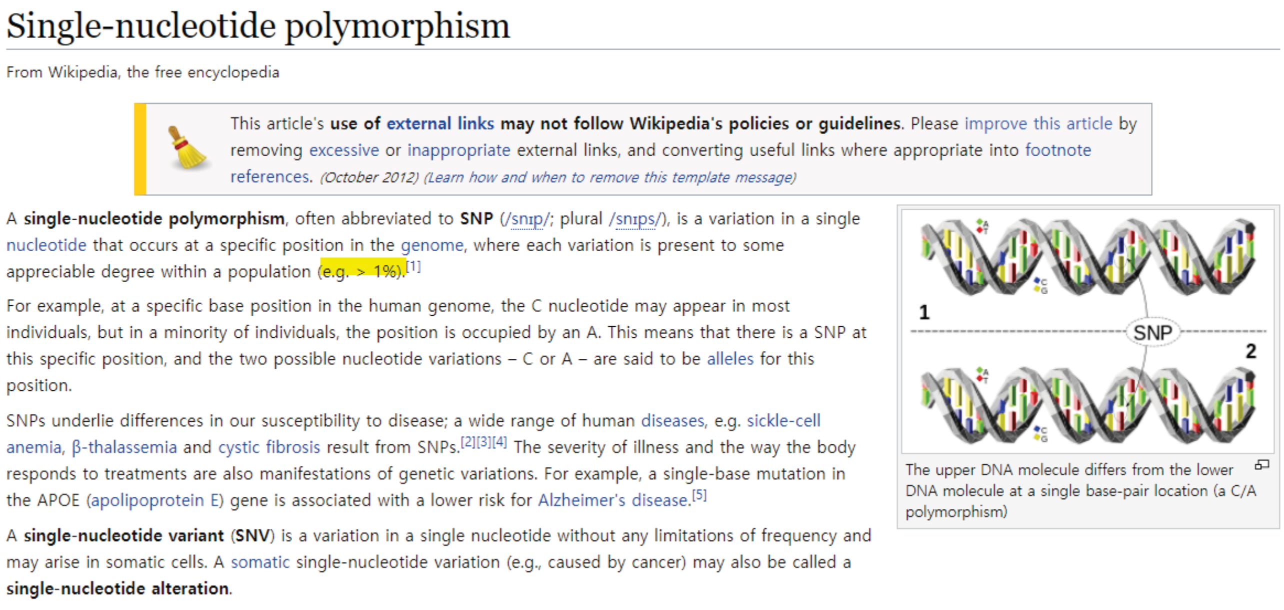
KEY DATA RESOURCES

SNP (단일염기다형성)



Single-nucleotide polymorphism

From Wikipedia, the free encyclopedia

This article's **use of external links may not follow Wikipedia's policies or guidelines**. Please improve this article by removing excessive or inappropriate external links, and converting useful links where appropriate into footnote references. *(October 2012) (Learn how and when to remove this template message)*

A **single-nucleotide polymorphism**, often abbreviated to **SNP** (/snɪp/; plural /snɪps/), is a variation in a single nucleotide that occurs at a specific position in the genome, where each variation is present to some appreciable degree within a population (e.g. > 1%).[1]

For example, at a specific base position in the human genome, the C nucleotide may appear in most individuals, but in a minority of individuals, the position is occupied by an A. This means that there is a SNP at this specific position, and the two possible nucleotide variations – C or A – are said to be alleles for this position.

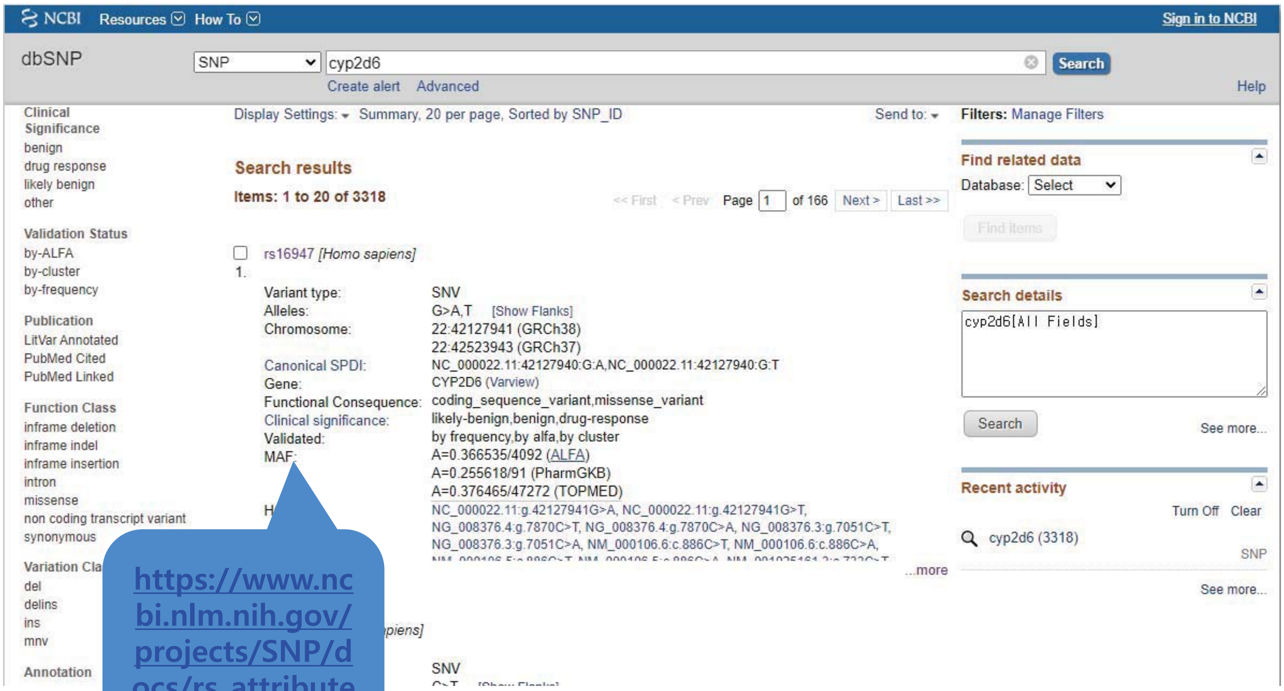
SNPs underlie differences in our susceptibility to disease; a wide range of human diseases, e.g. sickle-cell anemia, β-thalassemia and cystic fibrosis result from SNPs.[2][3][4] The severity of illness and the way the body responds to treatments are also manifestations of genetic variations. For example, a single-base mutation in the APOE (apolipoprotein E) gene is associated with a lower risk for Alzheimer's disease.[5]

A **single-nucleotide variant** (**SNV**) is a variation in a single nucleotide without any limitations of frequency and may arise in somatic cells. A somatic single-nucleotide variation (e.g., caused by cancer) may also be called a **single-nucleotide alteration**.

The upper DNA molecule differs from the lower DNA molecule at a single base-pair location (a C/A polymorphism)

https://en.wikipedia.org/wiki/Single-nucleotide_polymorphism

NCBI dbSNP



cyp2d6

Clinical Significance
benign
drug response
likely benign
other

Validation Status
by-ALFA
by-cluster
by-frequency

Publication
LitVar Annotated
PubMed Cited
PubMed Linked

Function Class
inframe deletion
inframe indel
inframe insertion
intron
missense
non coding transcript variant
synonymous

Variation Cla
del
delins
ins
mnv

Annotation

Display Settings: Summary, 20 per page, Sorted by SNP_ID

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Search results

Items: 1 to 20 of 3318

<< First < Prev Page 1 of 166 Next > Last >>

1. rs16947 *[Homo sapiens]*

Variant type: SNV
Alleles: G>A,T [Show Flanks]
Chromosome: 22:42127941 (GRCh38)
22:42523943 (GRCh37)
Canonical SPDI: NC_000022.11:42127940:G:A,NC_000022.11:42127940:G:T
Gene: CYP2D6 (Varview)
Functional Consequence: coding_sequence_variant,missense_variant
Clinical significance: likely-benign,benign,drug-response
Validated: by frequency,by alfa,by cluster
MAF: A=0.366535/4092 (ALFA)
A=0.255618/91 (PharmGKB)
A=0.376465/47272 (TOPMED)
H NC_000022.11:g.42127941G>A, NC_000022.11:g.42127941G>T,
NG_008376.4:g.7870C>T, NG_008376.4:g.7870C>A, NG_008376.3:g.7051C>T,
NG_008376.3:g.7051C>A, NM_000106.6:c.886C>T, NM_000106.6:c.886C>A,
...more

piens]

SNV

Filters: Manage Filters

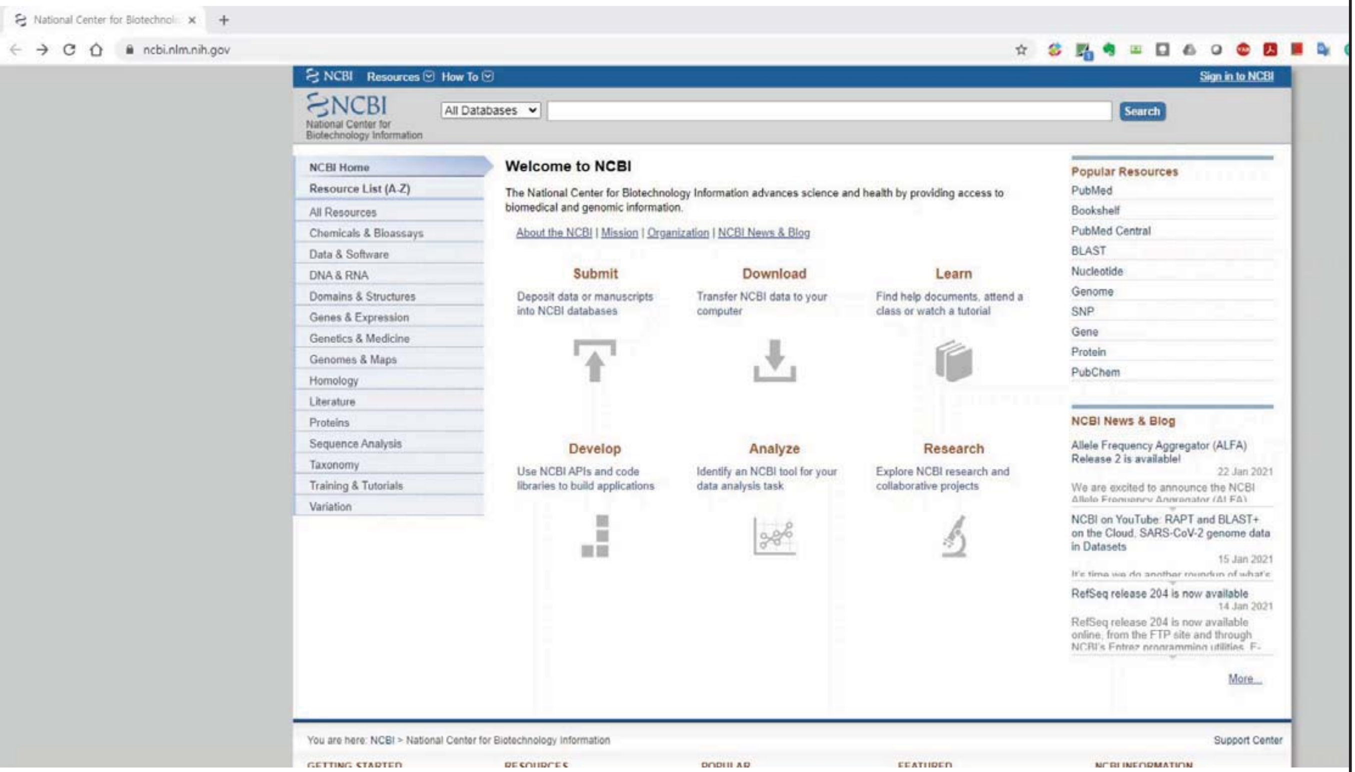
Find related data
Database: Select
Find items

Search details
cyp2d6[All Fields]
Search
See more...

Recent activity
Turn Off Clear
cyp2d6 (3318)
SNP
See more...

https://www.ncbi.nlm.nih.gov/projects/SNP/docs/rs_attributes.html#gmaf

https://www.ncbi.nlm.nih.gov/snp/?term=cyp2d6



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Variation

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NCBI News & Blog

Allele Frequency Aggregator (ALFA) Release 2 is available!
22 Jan 2021
We are excited to announce the NCBI Allele Frequency Aggregator (ALFA)

NCBI on YouTube: RAPT and BLAST+ on the Cloud, SARS-CoV-2 genome data in Datasets
15 Jan 2021
It's time we do another roundup of what's

RefSeq release 204 is now available
14 Jan 2021
RefSeq release 204 is now available online, from the FTP site and through NCBI's Entrez programming utilities, E-

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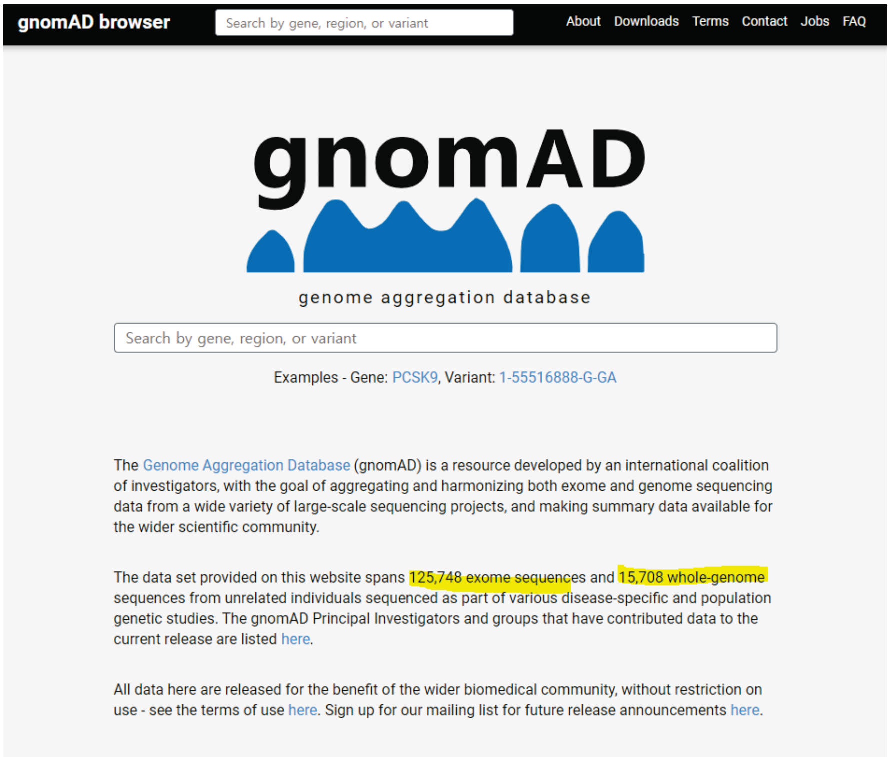
GETTING STARTED RESOURCES POPULAR FEATURED NCBI INFORMATION

gnomAD


gnomAD browser
Search by gene, region, or variant
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Downloads
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Jobs
FAQ
gnomAD
genome aggregation database
Search by gene, region, or variant

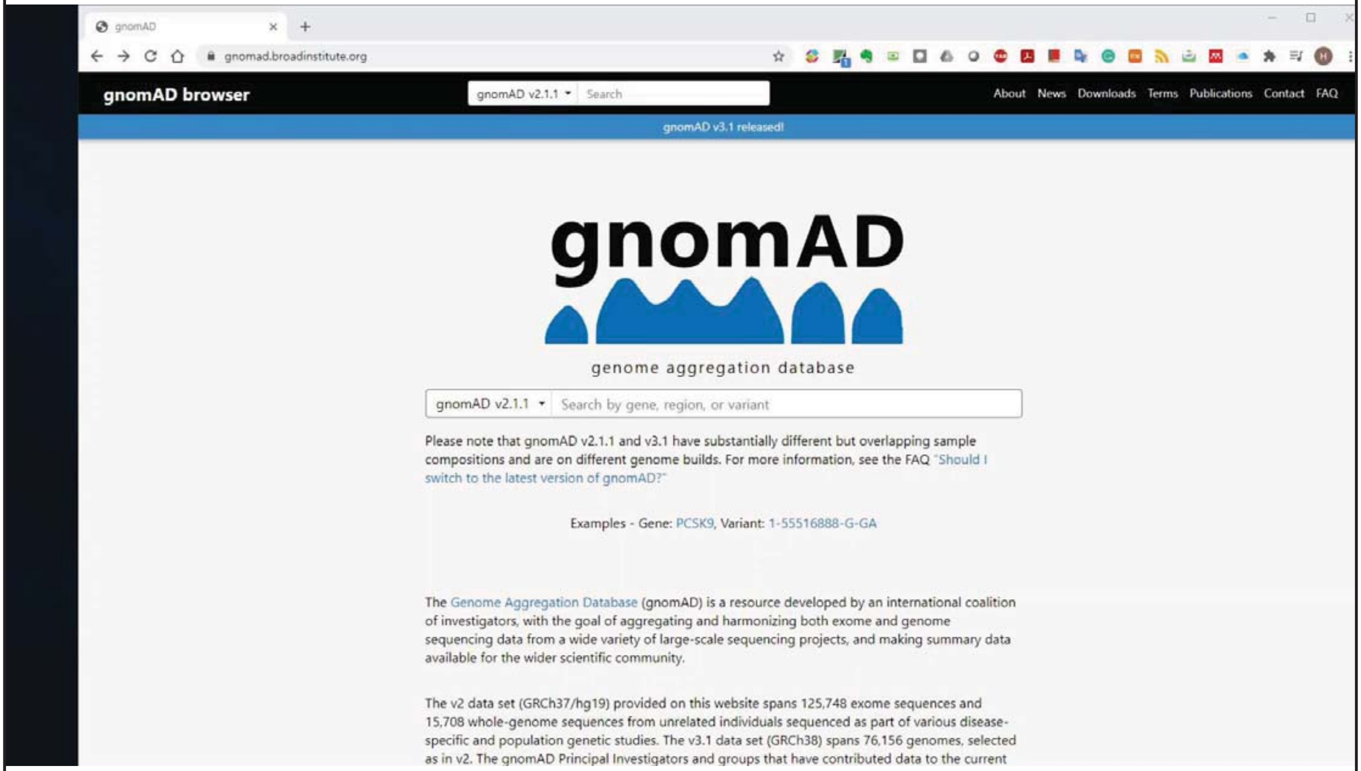
Examples - Gene: PCSK9, Variant: 1-55516888-G-GA

The Genome Aggregation Database (gnomAD) is a resource developed by an international coalition of investigators, with the goal of aggregating and harmonizing both exome and genome sequencing data from a wide variety of large-scale sequencing projects, and making summary data available for the wider scientific community.

The data set provided on this website spans 125,748 exome sequences and 15,708 whole-genome sequences from unrelated individuals sequenced as part of various disease-specific and population genetic studies. The gnomAD Principal Investigators and groups that have contributed data to the current release are listed here.

All data here are released for the benefit of the wider biomedical community, without restriction on use - see the terms of use here. Sign up for our mailing list for future release announcements here.

https://gnomad.broadinstitute.org/



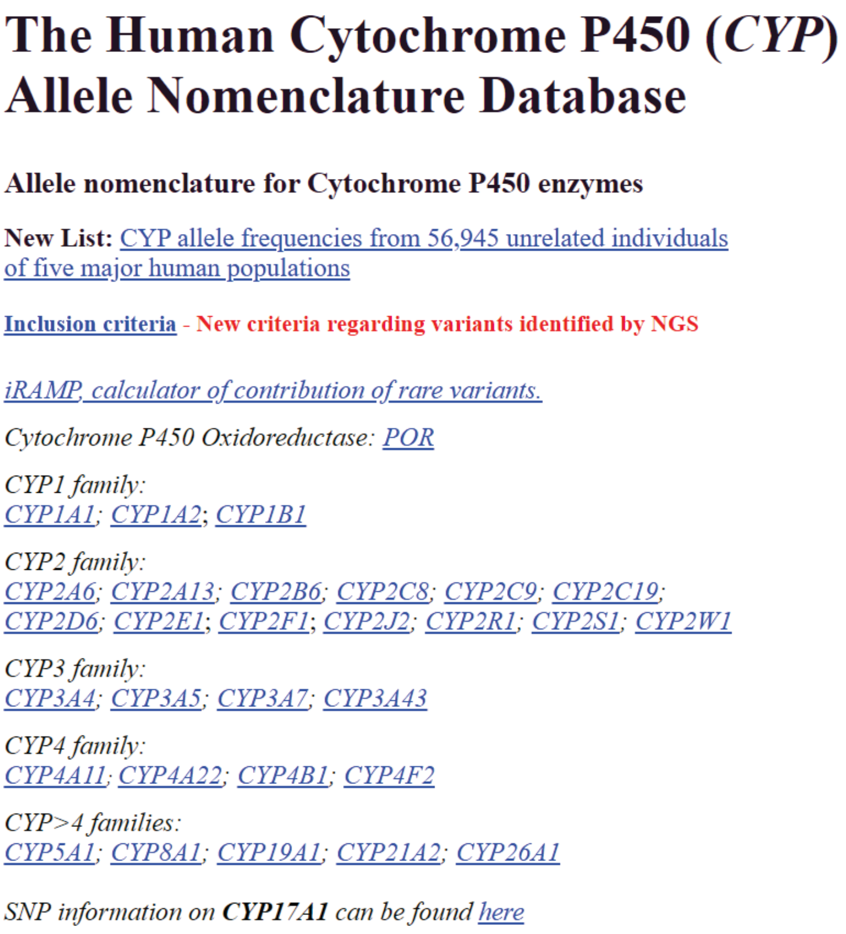
Please note that gnomAD v2.1.1 and v3.1 have substantially different but overlapping sample compositions and are on different genome builds. For more information, see the FAQ "Should I switch to the latest version of gnomAD?"

Examples - Gene: PCSK9, Variant: 1-55516888-G-GA

The Genome Aggregation Database (gnomAD) is a resource developed by an international coalition of investigators, with the goal of aggregating and harmonizing both exome and genome sequencing data from a wide variety of large-scale sequencing projects, and making summary data available for the wider scientific community.

The v2 data set (GRCh37/hg19) provided on this website spans 125,748 exome sequences and 15,708 whole-genome sequences from unrelated individuals sequenced as part of various disease-specific and population genetic studies. The v3.1 data set (GRCh38) spans 76,156 genomes, selected as in v2. The gnomAD Principal Investigators and groups that have contributed data to the current

https://gnomad.broadinstitute.org/



The Human Cytochrome P450 (*CYP*) Allele Nomenclature Database

Allele nomenclature for Cytochrome P450 enzymes

New List: CYP allele frequencies from 56,945 unrelated individuals of five major human populations

Inclusion criteria - **New criteria regarding variants identified by NGS**

iRAMP, calculator of contribution of rare variants.

Cytochrome P450 Oxidoreductase: POR

CYP1 family:
CYP1A1; *CYP1A2*; *CYP1B1*

CYP2 family:
CYP2A6; *CYP2A13*; *CYP2B6*; *CYP2C8*; *CYP2C9*; *CYP2C19*; *CYP2D6*; *CYP2E1*; *CYP2F1*; *CYP2J2*; *CYP2R1*; *CYP2S1*; *CYP2W1*

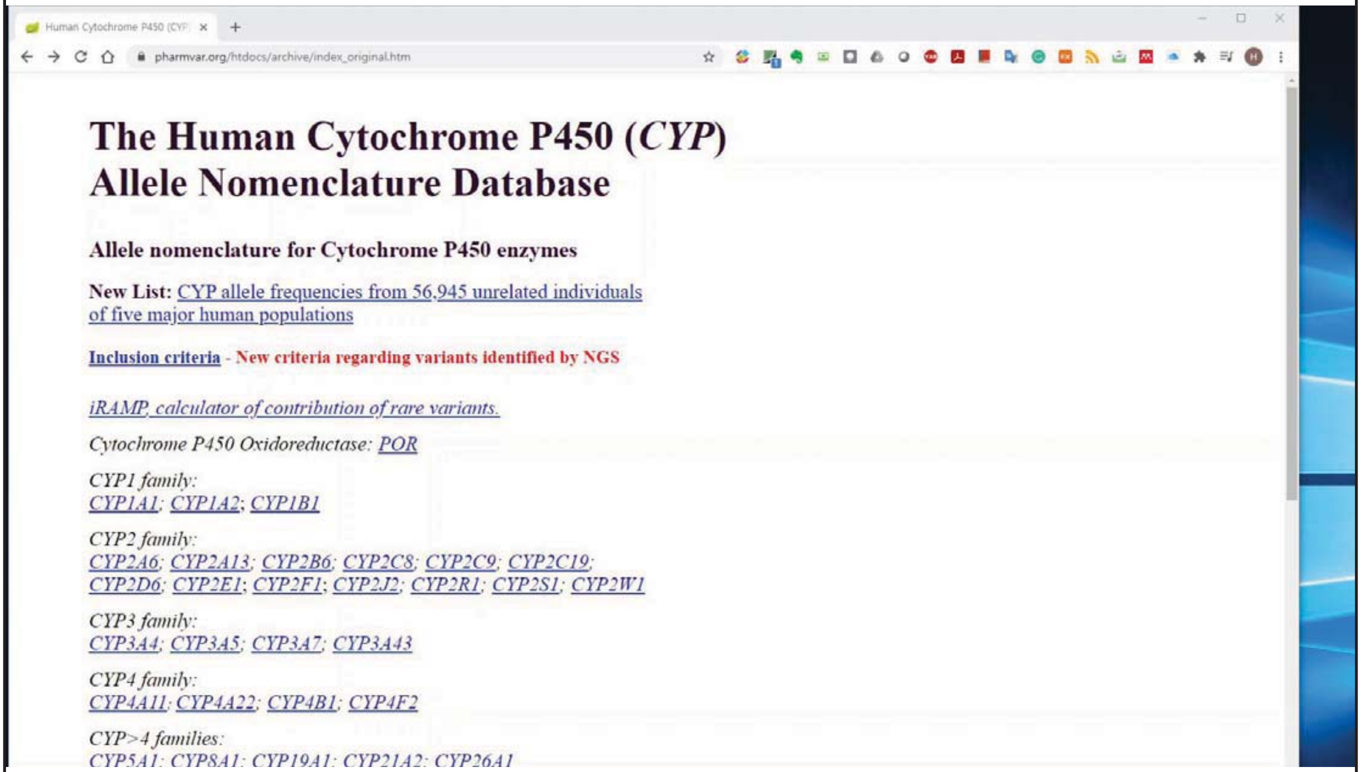
CYP3 family:
CYP3A4; *CYP3A5*; *CYP3A7*; *CYP3A43*

CYP4 family:
CYP4A11; *CYP4A22*; *CYP4B1*; *CYP4F2*

CYP>4 families:
CYP5A1; *CYP8A1*; *CYP19A1*; *CYP21A2*; *CYP26A1*

SNP information on ***CYP17A1*** *can be found here*

https://www.pharmvar.org/htdocs/archive/index_original.htm



Human Cytochrome P450 (CYP ×
+
pharmvar.org/htdocs/archive/index_original.htm

The Human Cytochrome P450 (*CYP*) Allele Nomenclature Database

Allele nomenclature for Cytochrome P450 enzymes

New List: CYP allele frequencies from 56,945 unrelated individuals of five major human populations

Inclusion criteria - **New criteria regarding variants identified by NGS**

iRAMP, calculator of contribution of rare variants.

Cytochrome P450 Oxidoreductase: POR

CYP1 family:
CYP1A1; *CYP1A2*; *CYP1B1*

CYP2 family:
CYP2A6; *CYP2A13*; *CYP2B6*; *CYP2C8*; *CYP2C9*; *CYP2C19*; *CYP2D6*; *CYP2E1*; *CYP2F1*; *CYP2J2*; *CYP2R1*; *CYP2S1*; *CYP2W1*

CYP3 family:
CYP3A4; *CYP3A5*; *CYP3A7*; *CYP3A43*

CYP4 family:
CYP4A11; *CYP4A22*; *CYP4B1*; *CYP4F2*

CYP>4 families:
CYP5A1; *CYP8A1*; *CYP19A1*; *CYP21A2*; *CYP26A1*

https://www.pharmvar.org/htdocs/archive/index_original.htm

PharmVar

The Human CYP Allele Nomenclature Database
PharmVar
PharmGKB

After more than 15 years the Human Cytochrome P450 (*CYP*) Allele Nomenclature Database has transitioned…

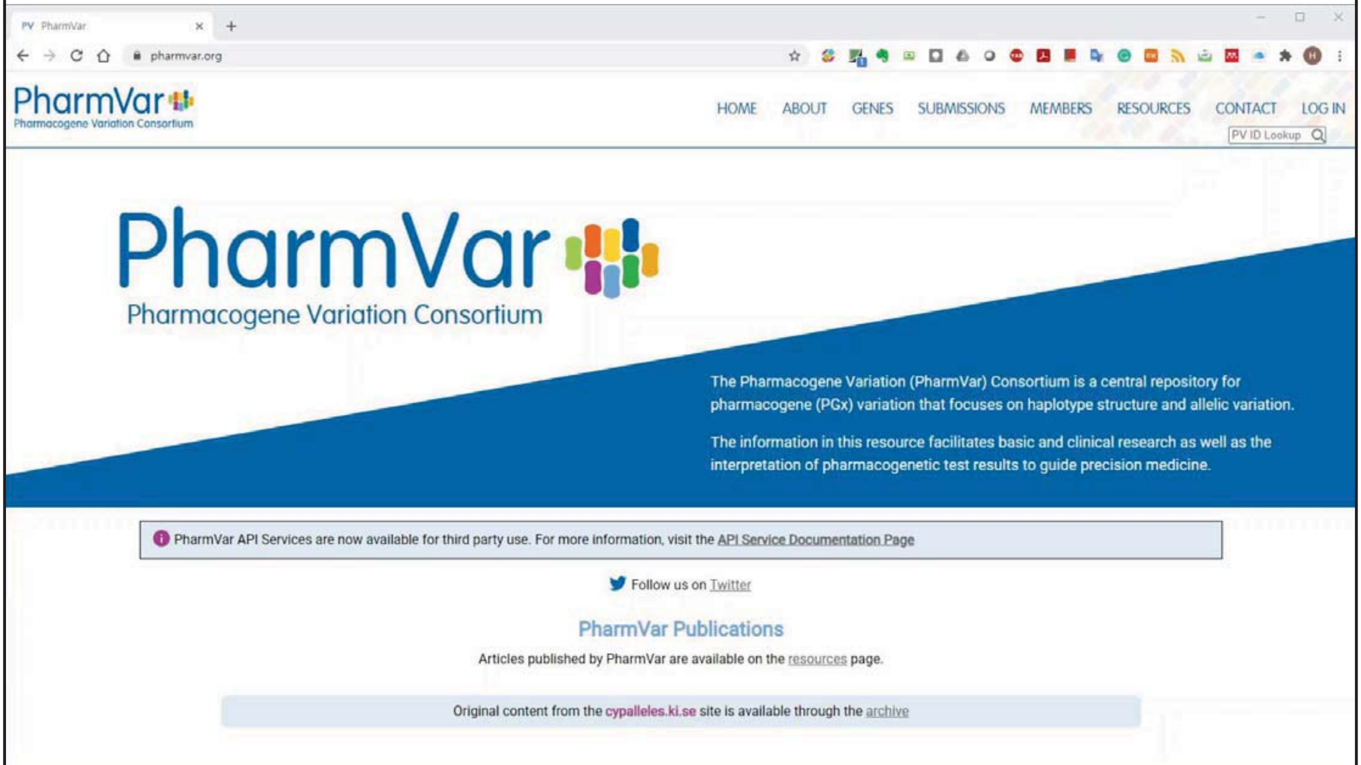
…to the **Pharm**acogene **Var**iation (**PharmVar**) Consortium at www.PharmVar.org

PharmVar will serve as a central repository for pharmacogene variation to facilitate allele (haplotype) designation and the interpretation of pharmacogenetic test results to guide precision medicine

PharmVar is a PGRN resource funded by NIGMS.

After September 26, 2017, please visit www.PharmVar.org to access content of the original P450 Nomenclature Database

http://www.cypalleles.ki.se/



The Pharmacogene Variation (PharmVar) Consortium is a central repository for pharmacogene (PGx) variation that focuses on haplotype structure and allelic variation.

The information in this resource facilitates basic and clinical research as well as the interpretation of pharmacogenetic test results to guide precision medicine.

PharmVar API Services are now available for third party use. For more information, visit the API Service Documentation Page

Follow us on Twitter

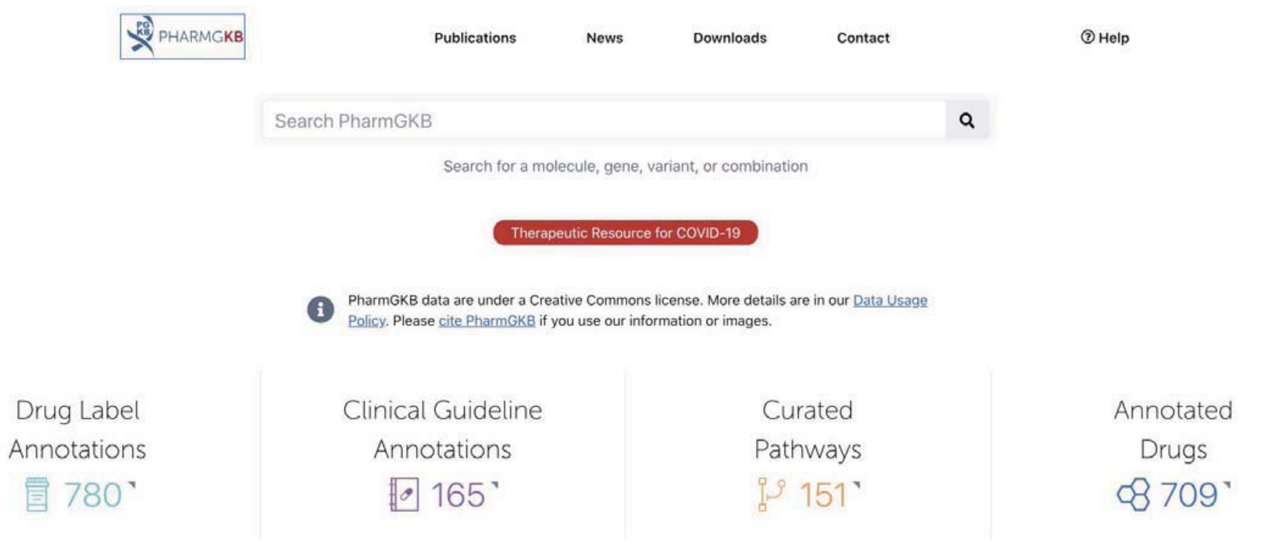
PharmVar Publications

Articles published by PharmVar are available on the resources page.

Original content from the cypalleles.ki.se site is available through the archive

https://www.pharmvar.org/

PHARMGKB



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Therapeutic Resource for COVID-19

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Drug Label Annotations	Clinical Guideline Annotations	Curated Pathways	Annotated Drugs
780	165	151	709

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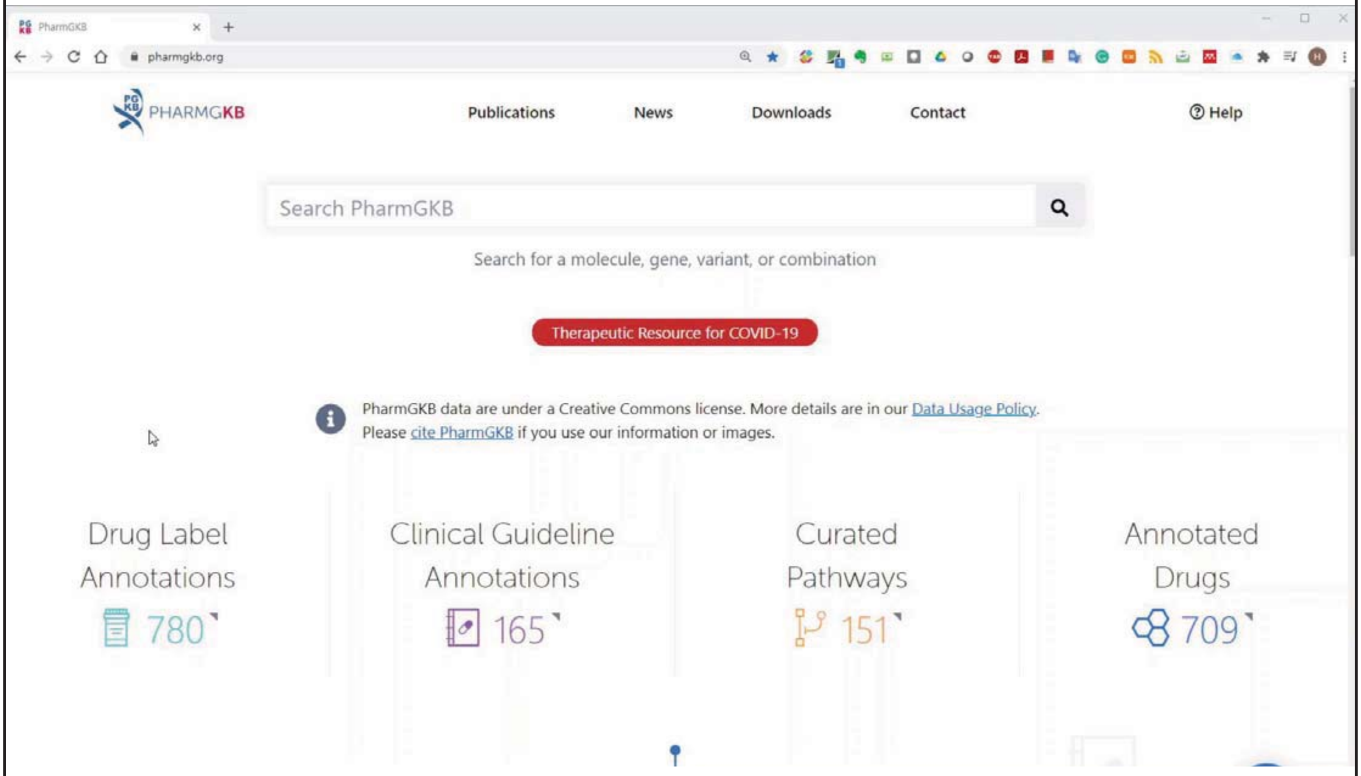

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https://www.pharmgkb.org/

Resources for pan-cancer genomics profiles and tools

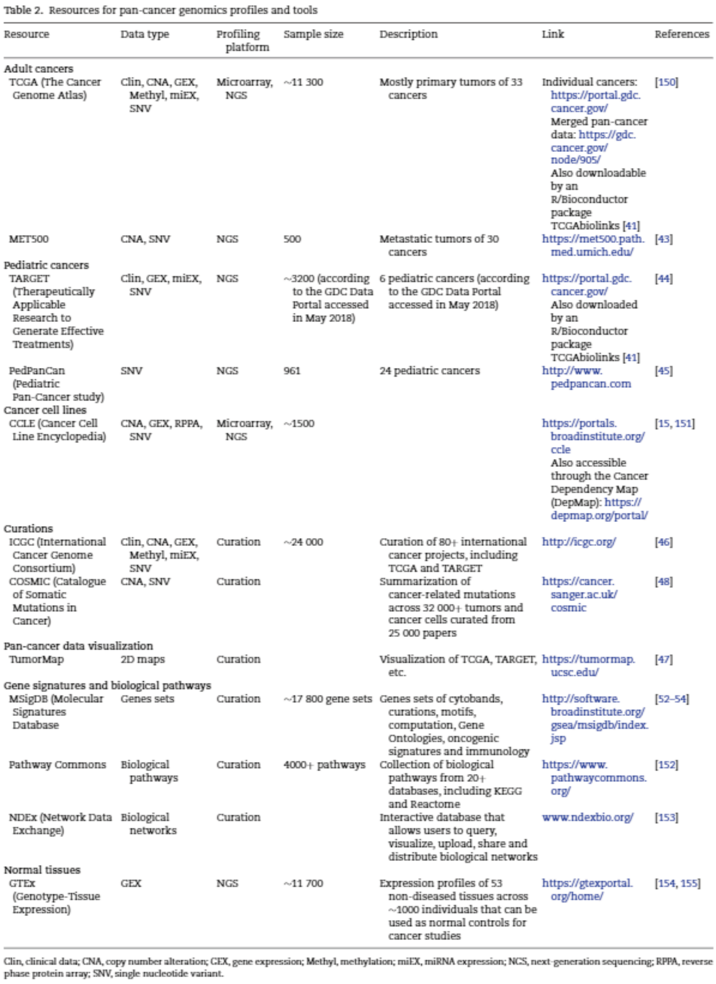


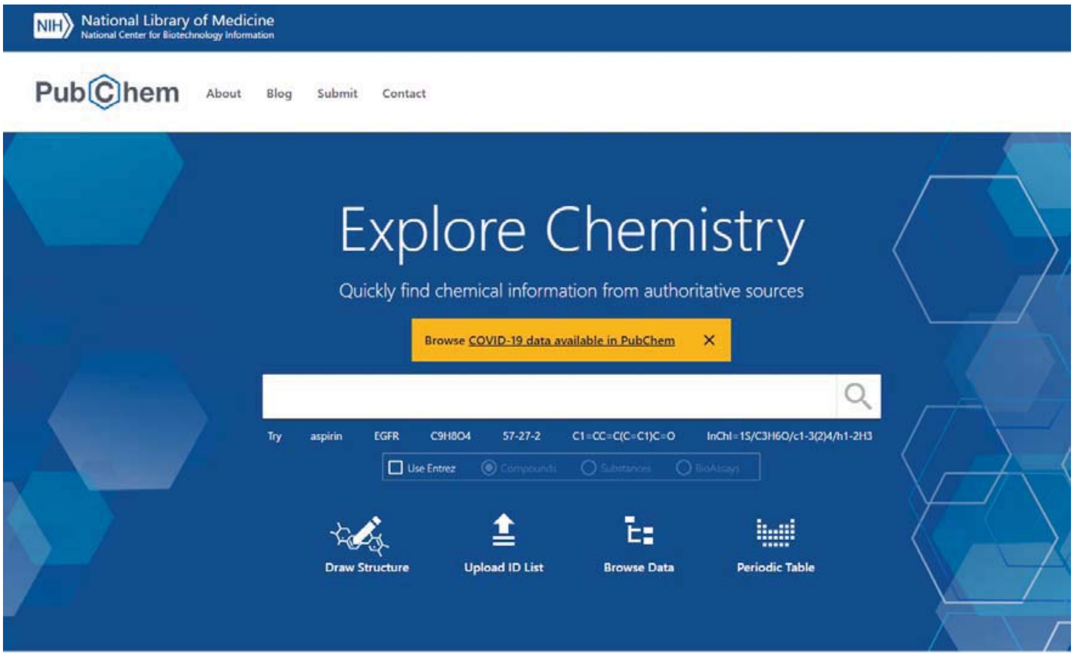
Table 2. Resources for pan-cancer genomics profiles and tools

Resource	Data type	Profiling platform	Sample size	Description	Link	References
Adult cancers						
TCGA (The Cancer Genome Atlas)	Clin, CNA, GEX, Methyl, miEX, SNV	Microarray, NGS	~11 300	Mostly primary tumors of 33 cancers	Individual cancers: https://portal.gdc.cancer.gov/ Merged pan-cancer data: https://gdc.cancer.gov/node/905/ Also downloadable by an R/Bioconductor package TCGAbiolinks [41]	[150]
MET500	CNA, SNV	NGS	500	Metastatic tumors of 30 cancers	https://met500.path.med.umich.edu/	[43]
Pediatric cancers						
TARGET (Therapeutically Applicable Research to Generate Effective Treatments)	Clin, GEX, miEX, SNV	NGS	~3200 (according to the GDC Data Portal accessed in May 2018)	6 pediatric cancers (according to the GDC Data Portal accessed in May 2018)	https://portal.gdc.cancer.gov/ Also downloaded by an R/Bioconductor package TCGAbiolinks [41]	[44]
PedPanCan (Pediatric Pan-Cancer study)	SNV	NGS	961	24 pediatric cancers	http://www.pedpancan.com	[45]
Cancer cell lines						
CCLE (Cancer Cell Line Encyclopedia)	CNA, GEX, RPPA, SNV	Microarray, NGS	~1500		https://portals.broadinstitute.org/ccle Also accessible through the Cancer Dependency Map (DepMap): https://depmap.org/portal/	[15, 151]
Curations						
ICGC (International Cancer Genome Consortium)	Clin, CNA, GEX, Methyl, miEX, SNV	Curation	~24 000	Curation of 80+ international cancer projects, including TCGA and TARGET	http://icgc.org/	[46]
COSMIC (Catalogue of Somatic Mutations in Cancer)	CNA, SNV	Curation		Summarization of cancer-related mutations across 32 000+ tumors and cancer cells curated from 25 000 papers	https://cancer.sanger.ac.uk/cosmic	[48]
Pan-cancer data visualization						
TumorMap	2D maps	Curation		Visualization of TCGA, TARGET, etc.	https://tumormap.ucsc.edu/	[47]
Gene signatures and biological pathways						
MSigDB (Molecular Signatures Database	Genes sets	Curation	~17 800 gene sets	Genes sets of cytobands, curations, motifs, computation, Gene Ontologies, oncogenic signatures and immunology	http://software.broadinstitute.org/gsea/msigdb/index.jsp	[52–54]
Pathway Commons	Biological pathways	Curation	4000+ pathways	Collection of biological pathways from 20+ databases, including KEGG and Reactome	https://www.pathwaycommons.org/	[152]
NDEx (Network Data Exchange)	Biological networks	Curation		Interactive database that allows users to query, visualize, upload, share and distribute biological networks	www.ndexbio.org/	[153]
Normal tissues						
GTEx (Genotype-Tissue Expression)	GEX	NGS	~11 700	Expression profiles of 53 non-diseased tissues across ~1000 individuals that can be used as normal controls for cancer studies	https://gtexportal.org/home/	[154, 155]

Clin, clinical data; CNA, copy number alteration; GEX, gene expression; Methyl, methylation; miEX, miRNA expression; NGS, next-generation sequencing; RPPA, reverse phase protein array; SNV, single nucleotide variant.

Brief Bioinform . 2020 Dec 1;21(6):2066-2083. doi: 10.1093/bib/bbz144.

NCBI PubChem



Explore Chemistry

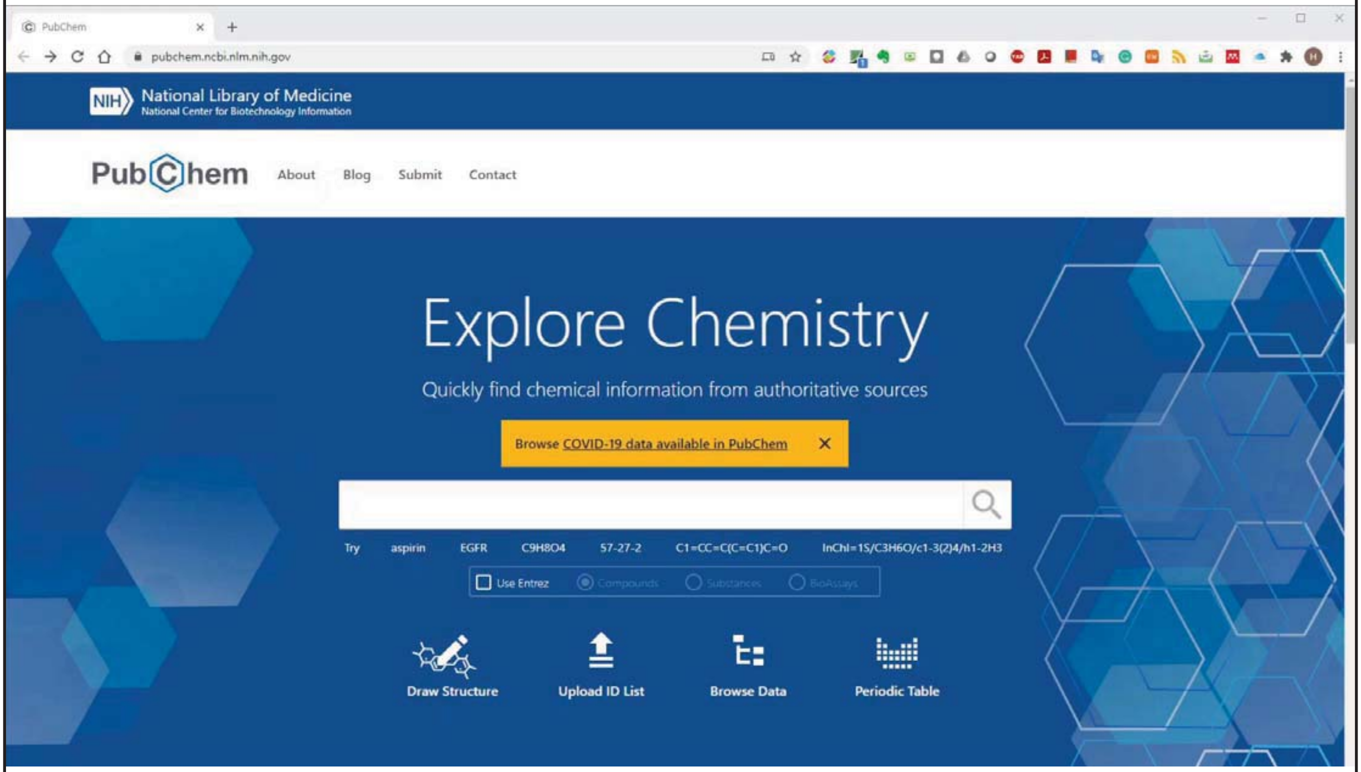
Quickly find chemical information from authoritative sources

Browse COVID-19 data available in PubChem ✕

Try aspirin EGFR C9H8O4 57-27-2 C1=CC=C(C=C1)C=O InChI=1S/C3H6O/c1-3(2)4/h1-2H3

□ Use Entrez ● Compounds ○ Substances ○ BioAssays

https://pubchem.ncbi.nlm.nih.gov/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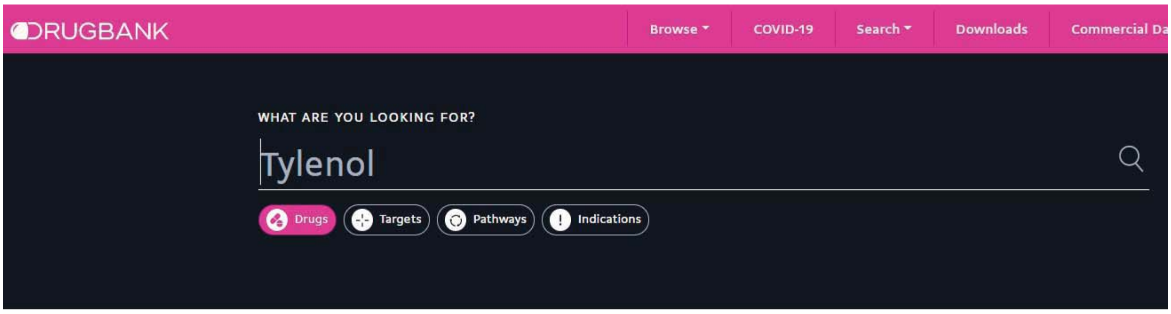
Quickly find chemical information from authoritative sources

Browse COVID-19 data available in PubChem ✕

Try aspirin EGFR C9H8O4 57-27-2 C1=CC=C(C=C1)C=O InChI=1S/C3H6O/c1-3(2)4/h1-2H3
□ Use Entrez ○ Compounds ○ Substances ○ BioAssays
Draw Structure
Upload ID List
Browse Data
Periodic Table

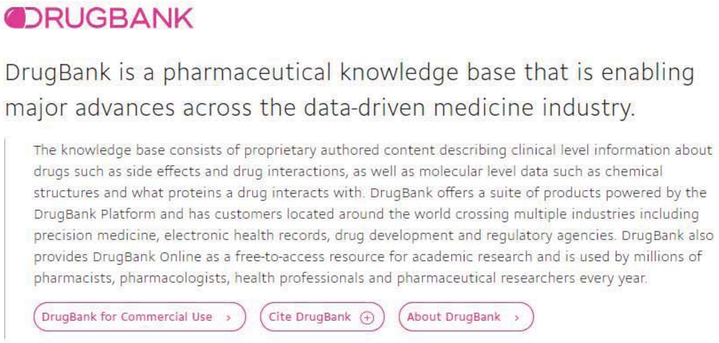
https://pubchem.ncbi.nlm.nih.gov/

DrugBank



WHAT ARE YOU LOOKING FOR?

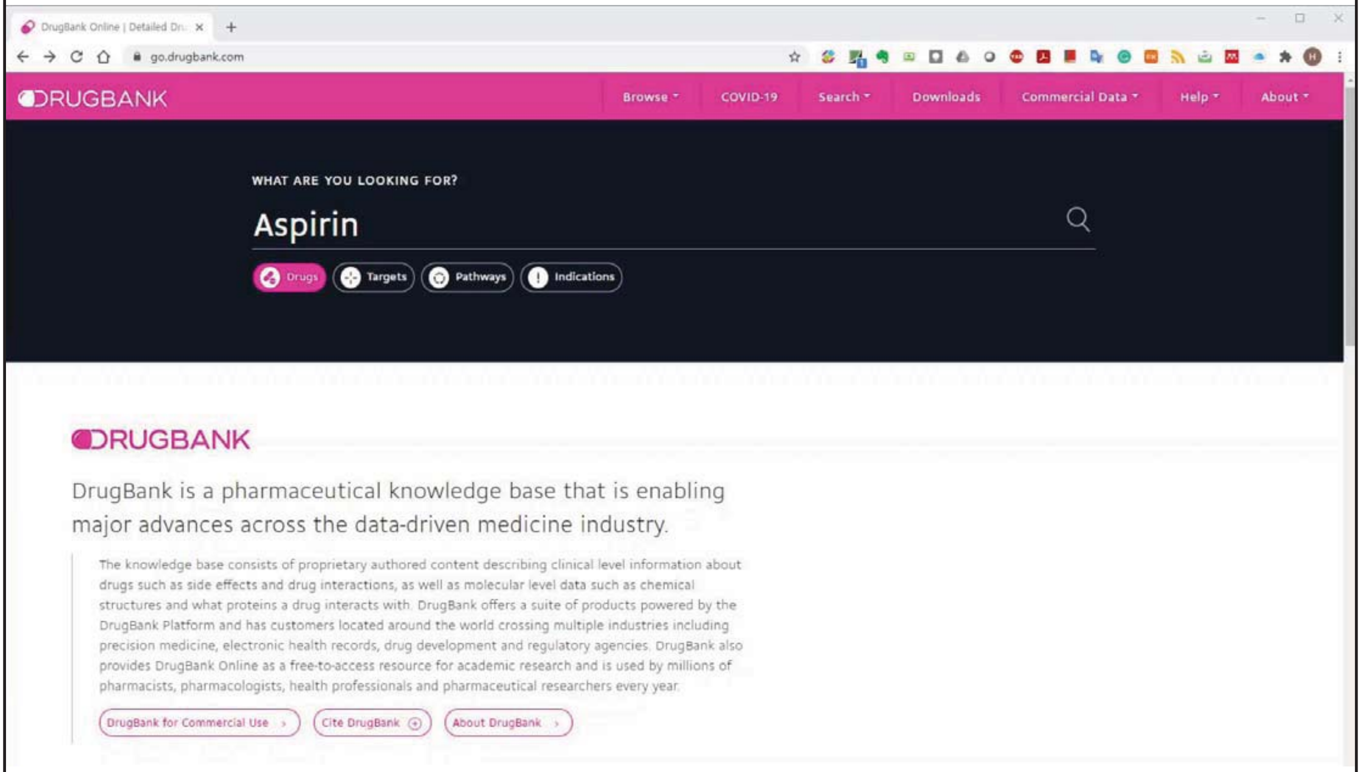
Tylenol



DrugBank is a pharmaceutical knowledge base that is enabling major advances across the data-driven medicine industry.

The knowledge base consists of proprietary authored content describing clinical level information about drugs such as side effects and drug interactions, as well as molecular level data such as chemical structures and what proteins a drug interacts with. DrugBank offers a suite of products powered by the DrugBank Platform and has customers located around the world crossing multiple industries including precision medicine, electronic health records, drug development and regulatory agencies. DrugBank also provides DrugBank Online as a free-to-access resource for academic research and is used by millions of pharmacists, pharmacologists, health professionals and pharmaceutical researchers every year.

https://go.drugbank.com/



WHAT ARE YOU LOOKING FOR?

Aspirin

DRUGBANK

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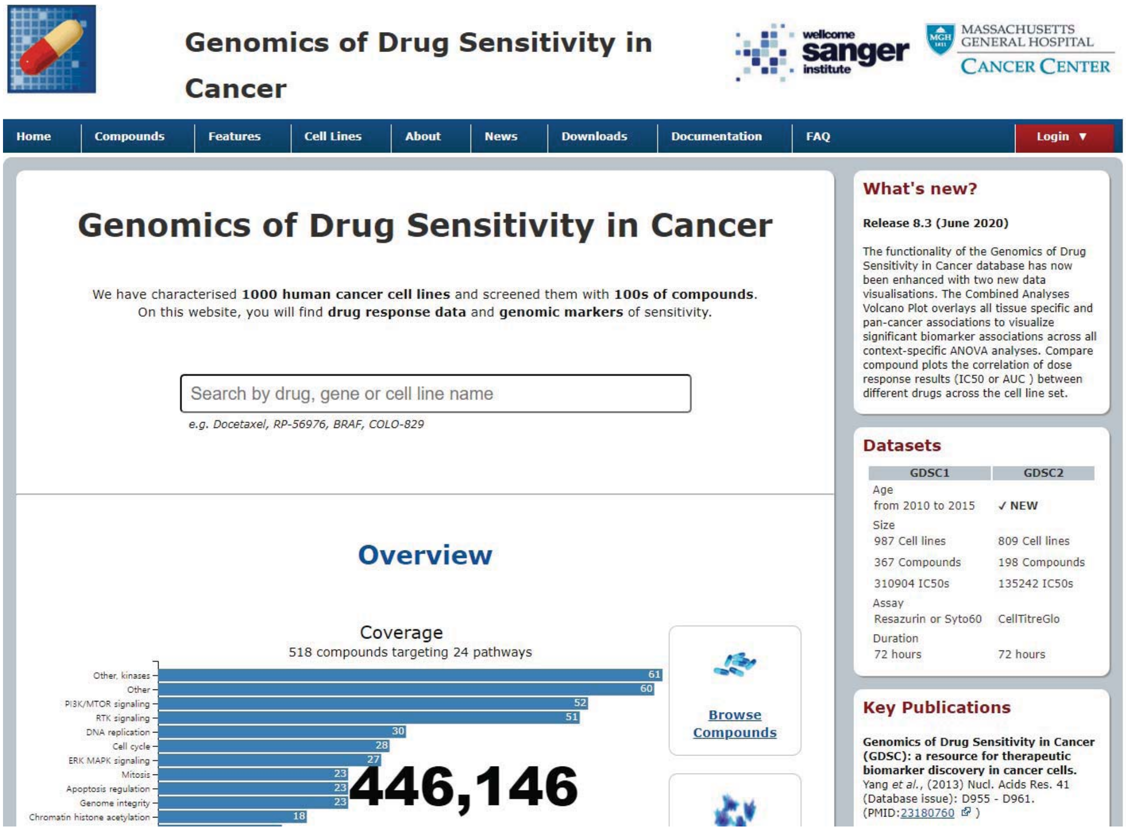
https://go.drugbank.com/

Genomics of Drug Sensitivity in Cancer (GDSC)



Genomics of Drug Sensitivity in Cancer

We have characterised **1000 human cancer cell lines** and screened them with **100s of compounds**. On this website, you will find **drug response data** and **genomic markers** of sensitivity.

Search by drug, gene or cell line name

e.g. Docetaxel, RP-56976, BRAF, COLO-829

Overview

Coverage

518 compounds targeting 24 pathways

What's new?

Release 8.3 (June 2020)

The functionality of the Genomics of Drug Sensitivity in Cancer database has now been enhanced with two new data visualisations. The Combined Analyses Volcano Plot overlays all tissue specific and pan-cancer associations to visualize significant biomarker associations across all context-specific ANOVA analyses. Compare compound plots the correlation of dose response results (IC50 or AUC) between different drugs across the cell line set.

Datasets

	GDSC1	GDSC2
Age	from 2010 to 2015	✓ NEW
Size	987 Cell lines	809 Cell lines
	367 Compounds	198 Compounds
	310904 IC50s	135242 IC50s
Assay	Resazurin or Syto60	CellTitreGlo
Duration	72 hours	72 hours

Key Publications

Genomics of Drug Sensitivity in Cancer (GDSC): a resource for therapeutic biomarker discovery in cancer cells. Yang *et al.*, (2013) Nucl. Acids Res. 41 (Database issue): D955 - D961. (PMID:23180760)

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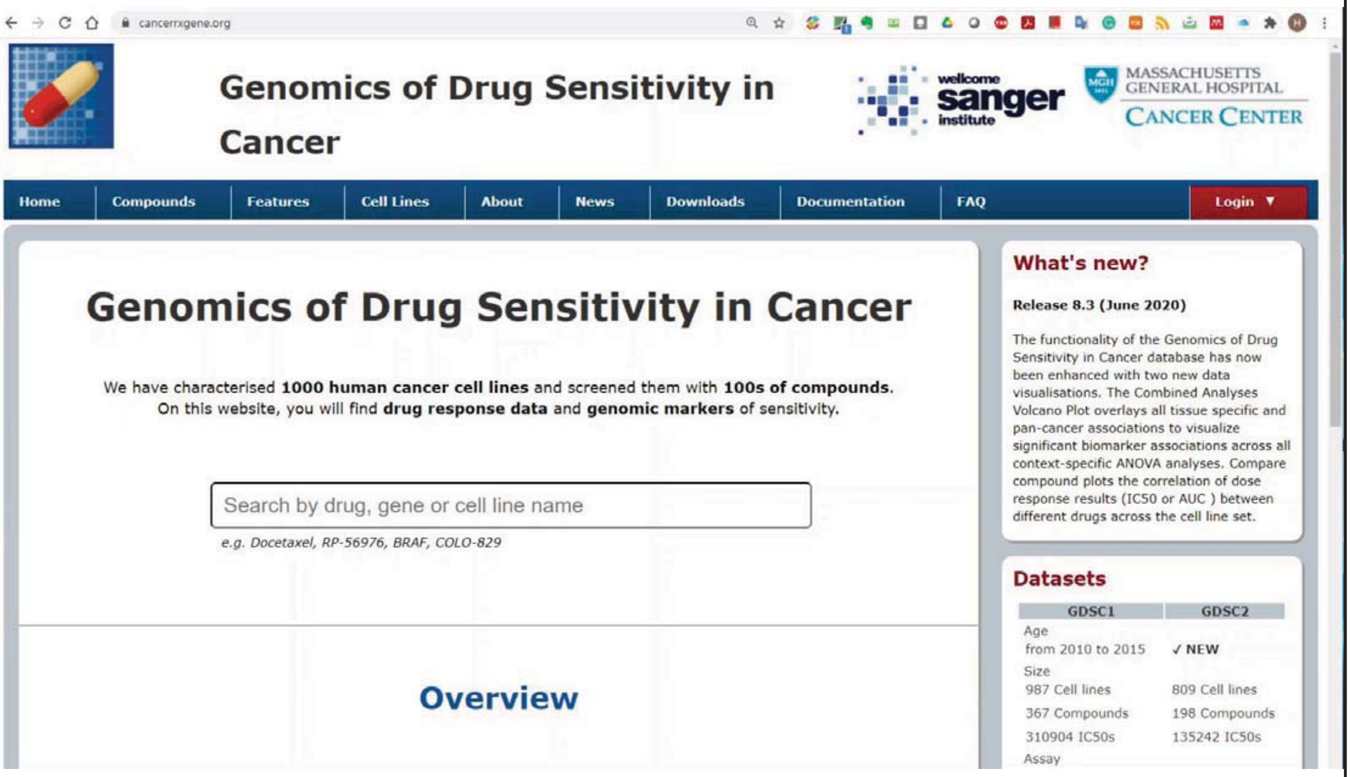
https://www.cancerrxgene.org/



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https://www.cancerrxgene.org/

- PART1
  - Introduction to pharmacogenomics
    - Drug discovery and development
  - Key data sources
  - Representations of proteins, chemicals
- PART2
  - Studies related to pharmacogenomics based on machine learning

PROTEIN REPRESENTATIONS

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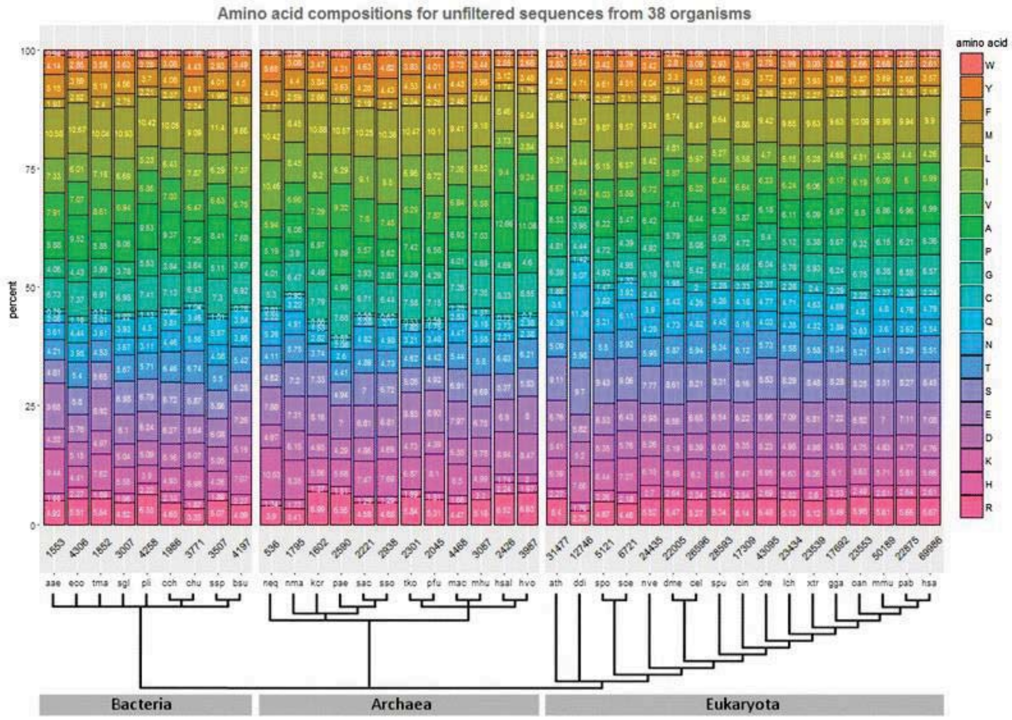
Why protein representations are necessary?

Representation of proteins for machine-learning features that fully captured wide ranges of properties of the target molecule

Types of protein representations

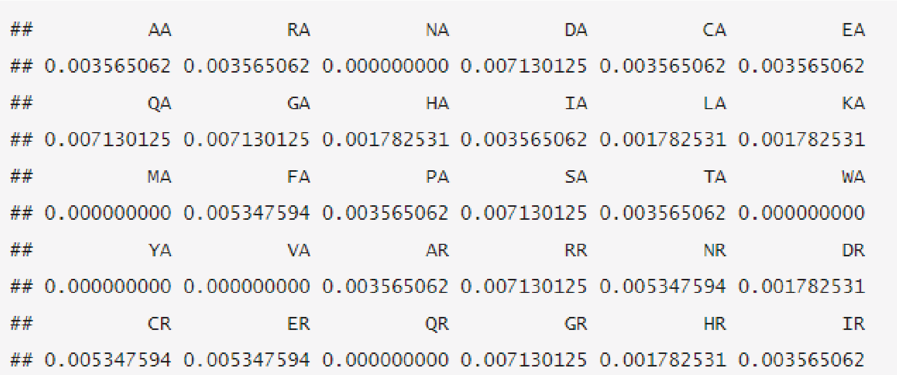
- Protein descriptors
  - Amino Acid Composition (AAC) - 20D
  - Dipeptide Composition Descriptor - 400D
  - Tripeptide Composition Descriptor - 8000D
  - Composition, Transition and Distribution (CTD) - 147D
- Protein embedding

Amino Acid Composition –AAC (20D)

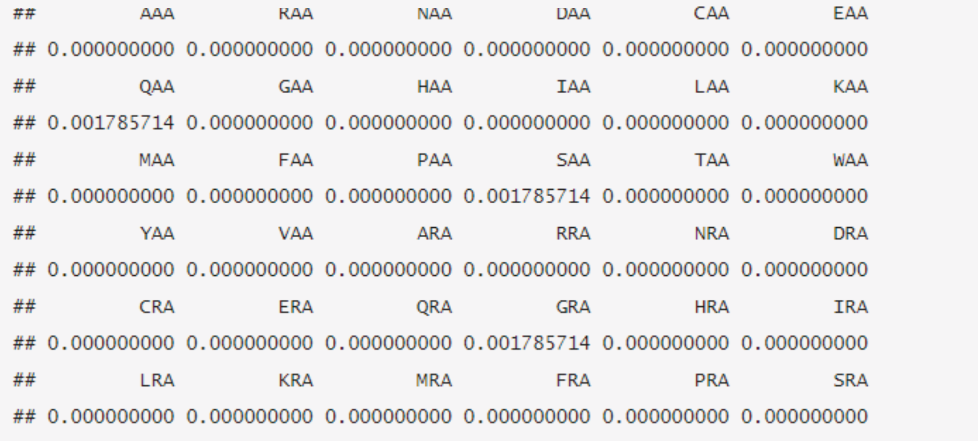


BMC Research Notes volume 11, Article number: 117 (2018)

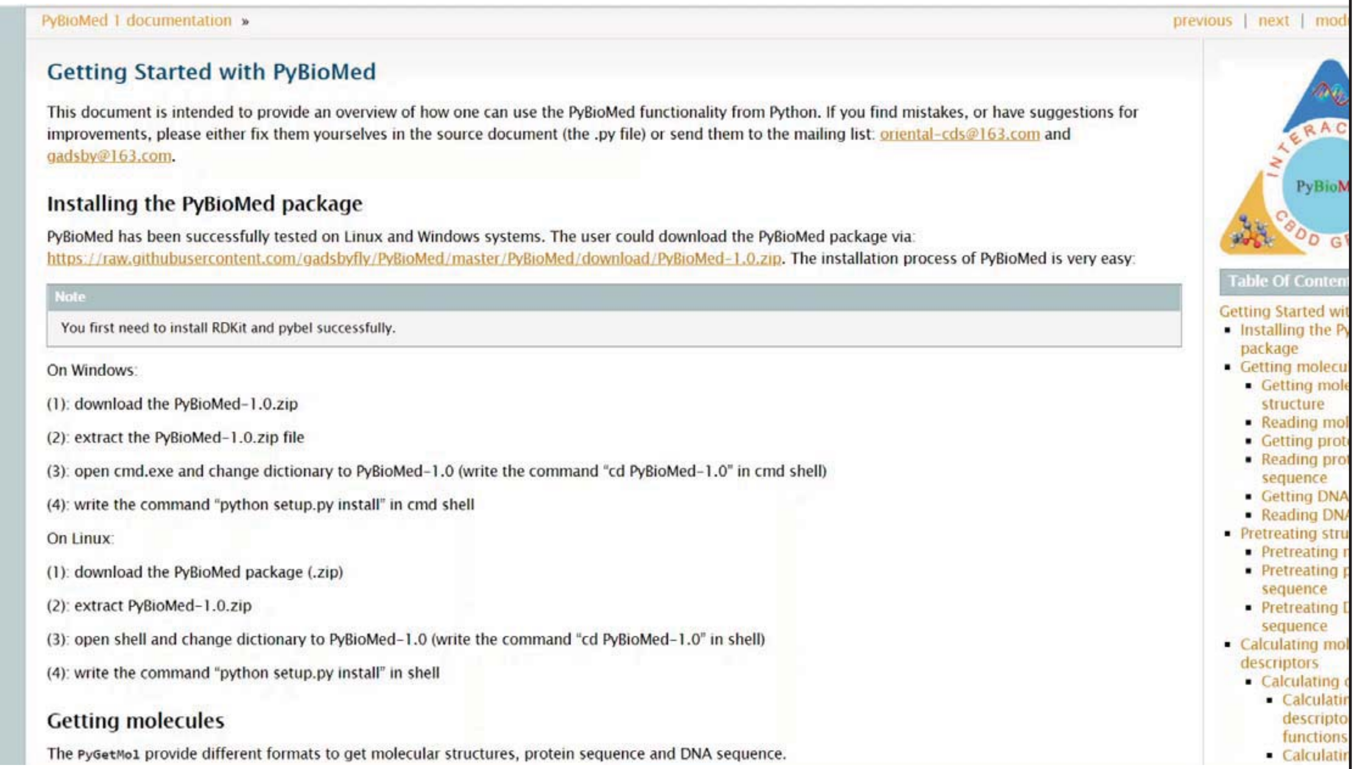
Dipeptide (400D) / Tripeptide (8000D) Composition



```
##          AA          RA          NA          DA          CA          EA
## 0.003565062 0.003565062 0.000000000 0.007130125 0.003565062 0.003565062
##          QA          GA          HA          IA          LA          KA
## 0.007130125 0.007130125 0.001782531 0.003565062 0.001782531 0.001782531
##          MA          FA          PA          SA          TA          WA
## 0.000000000 0.005347594 0.003565062 0.007130125 0.003565062 0.000000000
##          YA          VA          AR          RR          NR          DR
## 0.000000000 0.000000000 0.003565062 0.007130125 0.005347594 0.001782531
##          CR          ER          QR          GR          HR          IR
## 0.005347594 0.005347594 0.000000000 0.007130125 0.001782531 0.003565062
```



```
##         AAA         RAA         NAA         DAA         CAA         EAA
## 0.000000000 0.000000000 0.000000000 0.000000000 0.000000000 0.000000000
##         QAA         GAA         HAA         IAA         LAA         KAA
## 0.001785714 0.000000000 0.000000000 0.000000000 0.000000000 0.000000000
##         MAA         FAA         PAA         SAA         TAA         WAA
## 0.000000000 0.000000000 0.000000000 0.001785714 0.000000000 0.000000000
##         YAA         VAA         ARA         RRA         NRA         DRA
## 0.000000000 0.000000000 0.000000000 0.000000000 0.000000000 0.000000000
##         CRA         ERA         QRA         GRA         HRA         IRA
## 0.000000000 0.000000000 0.000000000 0.001785714 0.000000000 0.000000000
##         LRA         KRA         MRA         FRA         PRA         SRA
## 0.000000000 0.000000000 0.000000000 0.000000000 0.000000000 0.000000000
```



PyBioMed 1 documentation » | previous | next | mod

Getting Started with PyBioMed

This document is intended to provide an overview of how one can use the PyBioMed functionality from Python. If you find mistakes, or have suggestions for improvements, please either fix them yourselves in the source document (the .py file) or send them to the mailing list: oriental-cds@163.com and gadsby@163.com.

Installing the PyBioMed package

PyBioMed has been successfully tested on Linux and Windows systems. The user could download the PyBioMed package via: https://raw.githubusercontent.com/gadsbyfly/PyBioMed/master/PyBioMed/download/PyBioMed-1.0.zip. The installation process of PyBioMed is very easy:

Note

You first need to install RDKit and pybel successfully.

On Windows:

(1): download the PyBioMed-1.0.zip

(2): extract the PyBioMed-1.0.zip file

(3): open cmd.exe and change dictionary to PyBioMed-1.0 (write the command "cd PyBioMed-1.0" in cmd shell)

(4): write the command "python setup.py install" in cmd shell

On Linux:

(1): download the PyBioMed package (.zip)

(2): extract PyBioMed-1.0.zip

(3): open shell and change dictionary to PyBioMed-1.0 (write the command "cd PyBioMed-1.0" in shell)

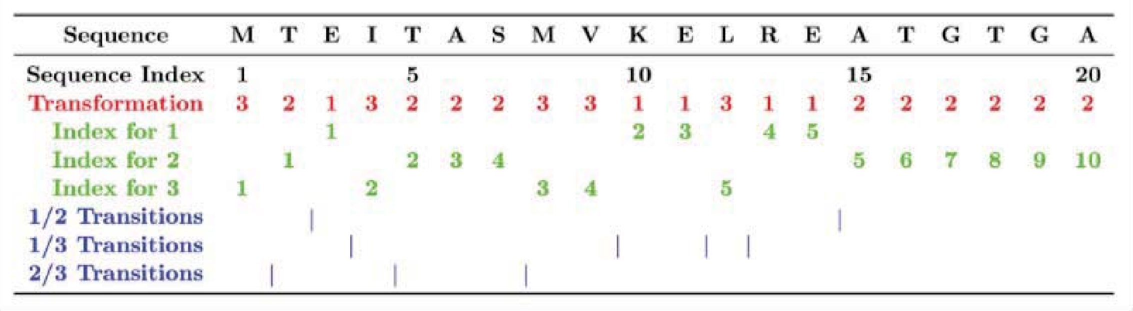
(4): write the command "python setup.py install" in shell

Getting molecules

The `PyGetMol` provide different formats to get molecular structures, protein sequence and DNA sequence.

Table Of Conten

Composition, Transition and Distribution (CTD), 147D

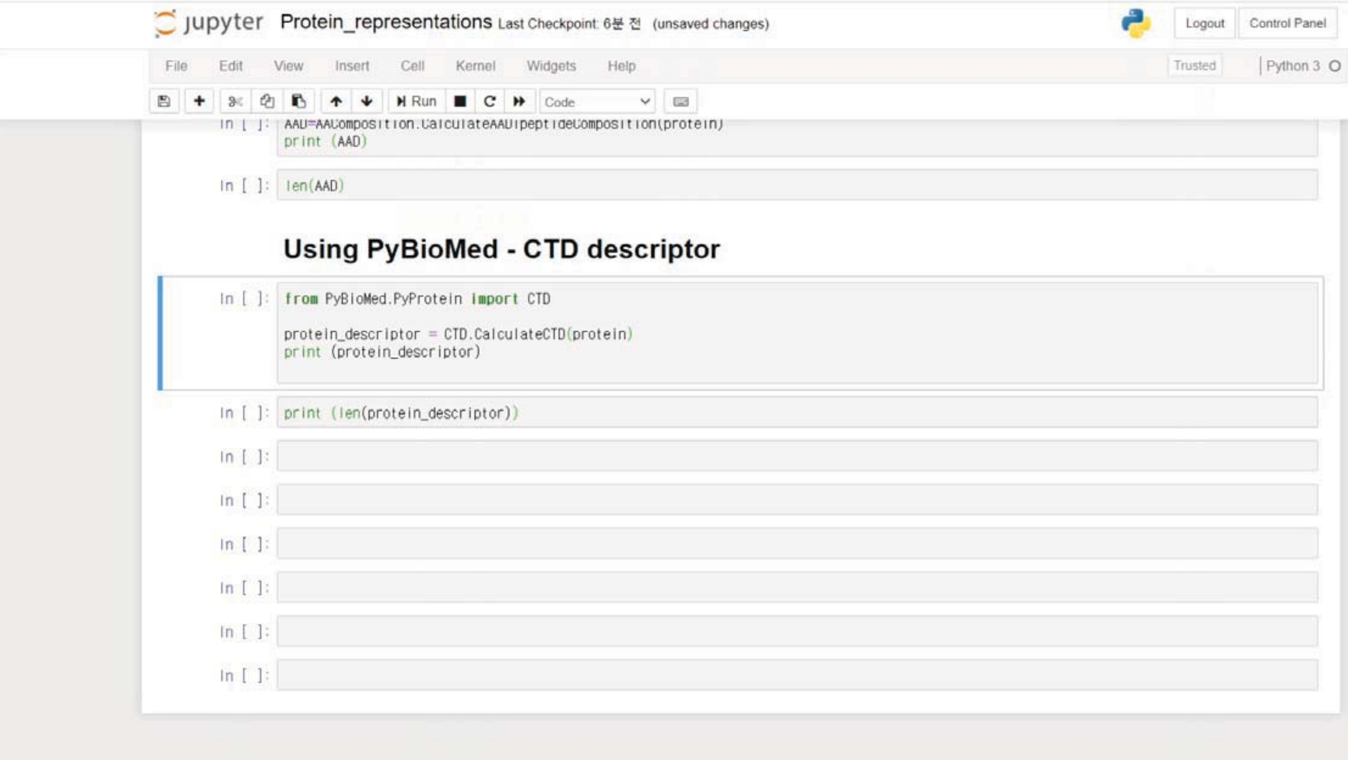


Sequence	M	T	E	I	T	A	S	M	V	K	E	L	R	E	A	T	G	T	G	A
Sequence Index	1				5					10					15					20
Transformation	3	2	1	3	2	2	2	3	3	1	1	3	1	1	2	2	2	2	2	2
Index for 1			1							2	3		4	5						
Index for 2		1			2	3	4								5	6	7	8	9	10
Index for 3	1			2				3	4			5								
1/2 Transitions			∣												∣					
1/3 Transitions				∣						∣		∣	∣							
2/3 Transitions		∣			∣			∣												

Table 1: Amino acid attributes, and the three-group classification of the 20 amino acids by each attribute

	Group 1	Group 2	Group 3
Hydrophobicity	Polar	Neutral	Hydrophobicity
	R, K, E, D, Q, N	G, A, S, T, P, H, Y	C, L, V, I, M, F, W
Normalized van der Waals Volume	0-2.78	2.95-4.0	4.03-8.08
	G, A, S, T, P, D, C	N, V, E, Q, I, L	M, H, K, F, R, Y, W
Polarity	4.9-6.2	8.0-9.2	10.4-13.0
	L, I, F, W, C, M, V, Y	P, A, T, G, S	H, Q, R, K, N, E, D
Polarizability	0-1.08	0.128-0.186	0.219-0.409
	G, A, S, D, T	C, P, N, V, E, Q, I, L	K, M, H, F, R, Y, W
Charge	Positive	Neutral	Negative
	K, R	A, N, C, Q, G, H, I, L, M, F, P, S, T, W, Y, V	D, E
Secondary Structure	Helix	Strand	Coil
	E, A, L, M, Q, K, R, H	V, I, Y, C, W, F, T	G, N, P, S, D
Solvent Accessibility	Buried	Exposed	Intermediate
	A, L, F, C, G, I, V, W	R, K, Q, E, N, D	M, S, P, T, H, Y

https://mran.microsoft.com/snapshot/2017-12-06/web/packages/protr/vignettes/protr.html



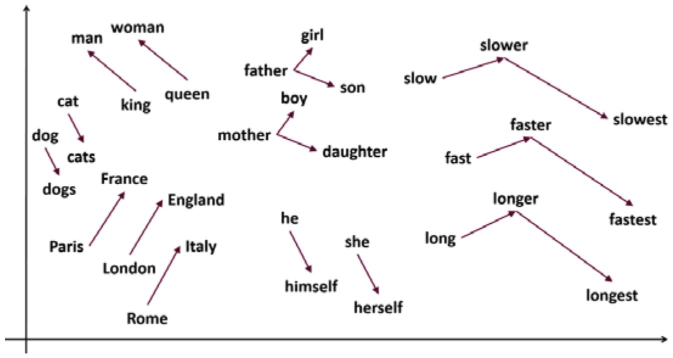
```
In [ ]: AAD=AAComposition.CalculateAADipeptideComposition(protein)
        print (AAD)

In [ ]: len(AAD)
```

Using PyBioMed - CTD descriptor

```
In [ ]: from PyBioMed.PyProtein import CTD

        protein_descriptor = CTD.CalculateCTD(protein)
        print (protein_descriptor)

In [ ]: print (len(protein_descriptor))

In [ ]:

In [ ]:

In [ ]:

In [ ]:

In [ ]:

In [ ]:
```

ProtVec (Asgari et al. ,PLoS ONE 10(11): e0141287, 2015)

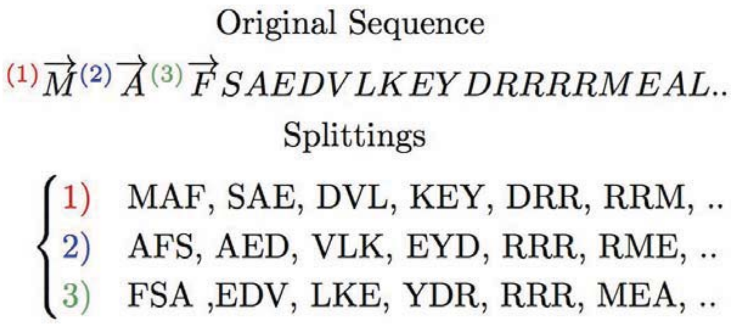
- Continuous distributed representation of biological sequences for deep proteomics and genomics
  - ProtVec: “unsupervised data-driven distributed representation for biological sequences”
  - Each sequence represented as n-dimensional vector
    - Characterizes biophysical and biochemical properties
    - Determined using neural networks



Apply to proteins as well? → ProtVec

ProtVec

- Use large corpus of sequences to train representation
  - E.g.) Swiss-Prot with 546,790 manually annotated and reviewed sequences
  - Break sequences into subsequences (i.e. biological words)
  - Training of the embedding through the Skip-gram neural network
    - for protein sequences: usage of a vector size of 100 and a context size of 25
    - → every 3-gram is represented as a vector of size 100



Original Sequence

$^{(1)}\overrightarrow{M}^{(2)}\overrightarrow{A}^{(3)}\overrightarrow{F}SAEDVLKEYDRRRRMEAL..$

Splittings

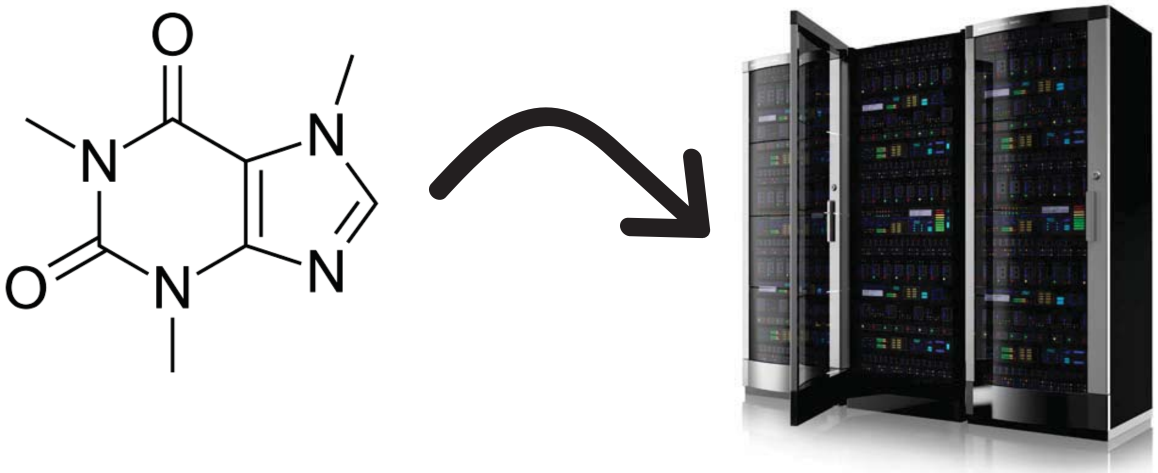
1) MAF, SAE, DVL, KEY, DRR, RRM, ..
2) AFS, AED, VLK, EYD, RRR, RME, ..
3) FSA ,EDV, LKE, YDR, RRR, MEA, ..

Asgari et al. ,PLoS ONE 10(11): e0141287, 2015

- PART1
  - Introduction to pharmacogenomics
    - Drug discovery and development
  - Key data sources
  - Representations of proteins, chemicals
- PART2
  - Studies related to pharmacogenomics based on machine learning

MOLECULAR REPRESENTATION

Why molecular representations are necessary?



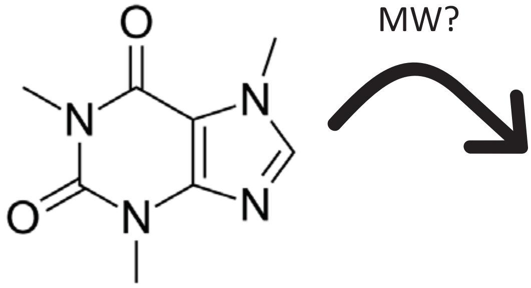
Representation of chemical compounds for machine-learning features that fully captured wide ranges of chemical and physical properties of the target molecule

Types of molecular representations

- Molecular descriptors
- Molecular fingerprints

Molecular descriptors

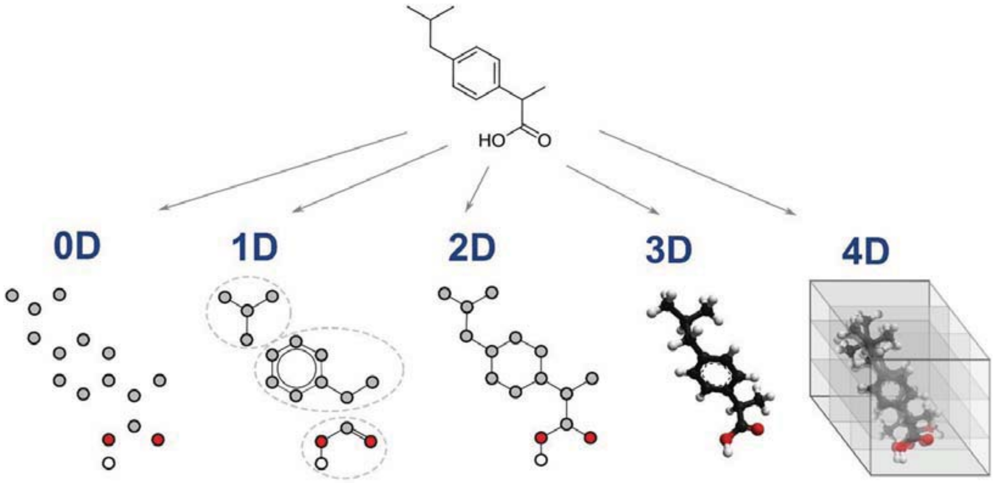
- Molecular descriptors are numerical values that characterize properties of molecules
- The goal of a molecular descript is to provide a numerical representation of molecular structure
- There are numbers of molecular descripts vary in complexity of encoded information



MW?

194.08

Molecular descriptors

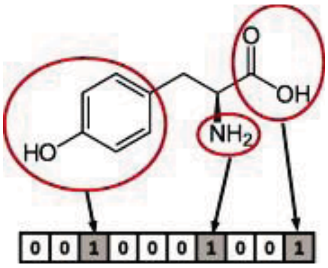


1) **0D-descriptors** (Molecular formula, i.e. Molecular weights, atom counts, bond counts),
2) **1D-descriptors** (Chemical graph, i.e. Fragment counts, functional group counts),
3) **2D-descriptors** (Structural topology, i.e. Wiener index, Balaban index, Randic index, BCUTS),
4) **3D-descriptors** (Structural geometry, i.e. WHIM, autocorrelation, 3D-MORSE, GETAWAY),
5) **4D-descriptors** (Chemical conformation, i.e. Volsurf, GRID, Raptor)

Grisoni F., Ballabio D., Todeschini R., Consonni V. (2018) Molecular Descriptors for Structure–Activity Applications: A Hands-On Approach. In: Computational Toxicology. Methods in Molecular Biology, vol 1800.

Molecular fingerprints

- Fingerprint representations of molecular structure and properties are a particularly complex form of descriptors. Fingerprints are typically encoded as binary bit strings whose settings produce, in different ways, a bit "pattern" characteristic of a given molecule.
- Fingerprints are designed to account for different sets of molecular descriptors, structural fragments, possible connectivity pathways through a molecule, or different types of pharmacophores.



https://doi.org/10.1016/j.ymeth.2014.08.005

Types of fingerprints

Class	Type	Examples
Structural based	Pattern-based FP	MACCS, PubChem, FP3, FP4
Topological	Path-based FP	Daylight, FP2
	Circular FP	ECFP2, ECFP4, ECFP6
	Pharmacophore FP	2D pharmacophore
Neural network based	Graph-based representation	GNN (graph convolutional network (GCN), graph attention network (GAT), gated graph neural network (GGNN), …)
	Molecular embedding	seq2seq, mol2vec

Pattern based fingerprints

SMARTS pattern

- 특정 SMARTS pattern 구조를 기반으로 한 지문표현자 생성 방법

Key position	Key description	Annotation
11	*1~*~*~*~1	4M Ring
12	[Cu,Zn,Ag,Cd,Au,Hg]	Group IB, IIB
13	[#8]~[#7](~[#6])~[#6]	ON(C)C
14	[#16] - [#16]	S-S
⋮	⋮	⋮

MACCS fingerprint SMARTS pattern 기준표

✓ MACCS fingerprints (166 keys)
✓ FP3, FP4 fingerprints from OpenBabel

PubChem Fingerprint

- PubChem에서 제시한 하위 구조를 기반으로 한 지문표현자 (881 bit vector)

Sections	Description
Section 1 (#0~#114)	Hierarchic element counts
Section 2 (#115~#262)	Rings in a canonic Extended Smallest Set of Smallest Rings ring set
Section 3 (#263~#326)	Simple atom pairs
Section 4 (#327~#415)	Simple atom nearest neighbors
Section 5 (#416~#459)	Detailed atom neighborhoods
Section 4 (#460~#712)	Simple SMARTS patterns
Section 4 (#713~#880)	Complex SMARTS patterns

PubChem fingerprints bit별 description

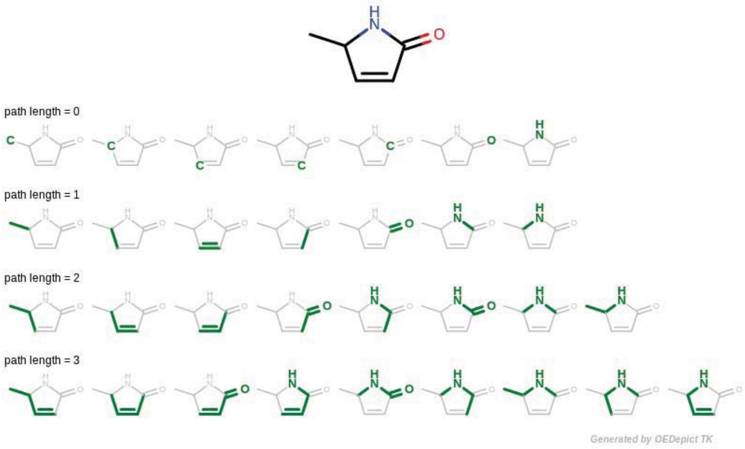
- **특징점**
- 이미 정의된 하위 구조의 유무를 판단하여 생성되는 지문표현자로 하위 구조 검색에 유용하나 이외의 구조를 표현할 수 없음
- 상대적으로 벡터의 길이가 짧음

Path-based fingerprints

- 원자를 기준으로 모든 linear fragment 를 고려하는 방식으로 화합물 구조 그래프를 표현함
- 해싱(hashing) 알고리즘을 사용함

- 관련 Fingerprints
  ✓ FP2 fingerprints (1,021 bit vector)
  ✓ RDK fingerprints, Layered fingerprints (RDKit), CDK fingerprints (CDK)

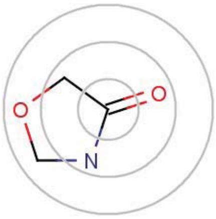
- **특징점**
- 해싱 알고리즘을 사용하여 다양한 하위 구조를 표현할 수 있고 사용자가 길이 조절할 수 있음
- 하위 구조의 사전지식이 필요 없음
- 지문표현자의 resolution은 해싱 알고리즘에 따라 달라질 수 있음
- Bit collision과 bit space 낭비를 고려한 길이의 지문표현자를 찾는 것이 어려움



길이에 따른 fragment 추출 예시

https://docs.eyesopen.com/toolkits/python/graphsimtk/fingerprint.html#section-fingerprint-path

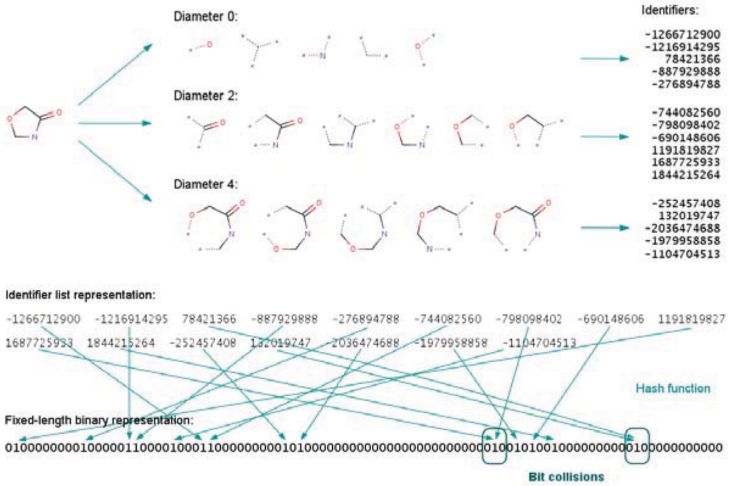
Morgan/Circular fingerprints



- 하나의 원자를 기준으로 주어진 반경 내의 하위 구조 정보를 순차적으로 탐색하는 기법
- 해싱(hashing) 기법을 사용하여 특정 길이 내의 지문표현자로 반환하여 사용함

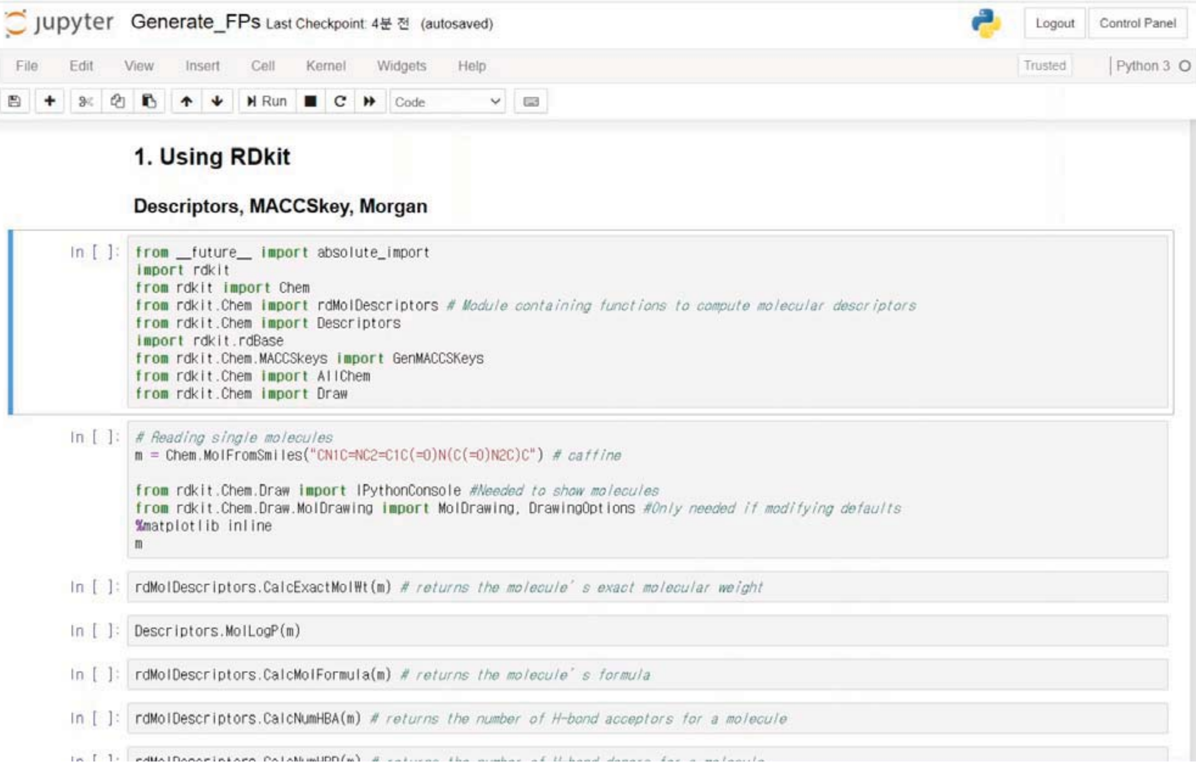
- 관련 Fingerprints
  - ✓ Morgan/Circular fingerprints
  - ✓ ECFPs (ECFP4, ECFP6), FCFPs

- **특징점**
- 이미 정의된 구조가 아닌 하위 구조에 대한 표현이 가능함
- 계산 속도가 빠름
- 전체적인 구조 정보를 표현하는데 유용하나 하위 구조 검색에는 적합하지 않음
- 유사성 검색에 적합함



ECFP fingerprint의 산출 절차

https://docs.chemaxon.com/display/docs/Extended+Connectivity+Fingerprint+ECFP



1. Using RDkit

Descriptors, MACCSkey, Morgan

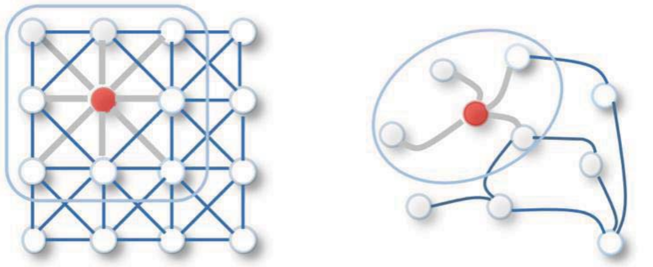
```
In [ ]: from __future__ import absolute_import
        import rdkit
        from rdkit import Chem
        from rdkit.Chem import rdMolDescriptors # Module containing functions to compute molecular descriptors
        from rdkit.Chem import Descriptors
        import rdkit.rdBase
        from rdkit.Chem.MACCSkeys import GenMACCSKeys
        from rdkit.Chem import AllChem
        from rdkit.Chem import Draw

In [ ]: # Reading single molecules
        m = Chem.MolFromSmiles("CN1C=NC2=C1C(=O)N(C(=O)N2C)C") # caffine

        from rdkit.Chem.Draw import IPythonConsole #Needed to show molecules
        from rdkit.Chem.Draw.MolDrawing import MolDrawing, DrawingOptions #Only needed if modifying defaults
        %matplotlib inline
        m

In [ ]: rdMolDescriptors.CalcExactMolWt(m) # returns the molecule' s exact molecular weight

In [ ]: Descriptors.MolLogP(m)

In [ ]: rdMolDescriptors.CalcMolFormula(m) # returns the molecule' s formula

In [ ]: rdMolDescriptors.CalcNumHBA(m) # returns the number of H-bond acceptors for a molecule

In [ ]: rdMolDescriptors.CalcNumHBD(m) # returns the number of H-bond donors for a molecule
```

GNN

- Graph neural networks (GNNs) are connectionist models that capture the dependence of graphs via message passing between the nodes of graphs.
  - – Extract features by considering the structure of the data
  - – Enables automatic feature extraction from raw inputs

  → can embed the drug(molecule) into vectors which has **topological structure information** with edge and atom features

  - With end to end learning, the model can learn **data driven features**



(a) 2D Convolution. Analogous to a graph, each pixel in an image is taken as a node where neighbors are determined by the filter size. The 2D convolution takes the weighted average of pixel values of the red node along with its neighbors. The neighbors of a node are ordered and have a fixed size.

(b) Graph Convolution. To get a hidden representation of the red node, one simple solution of the graph convolutional operation is to take the average value of the node features of the red node along with its neighbors. Different from image data, the neighbors of a node are unordered and variable in size.

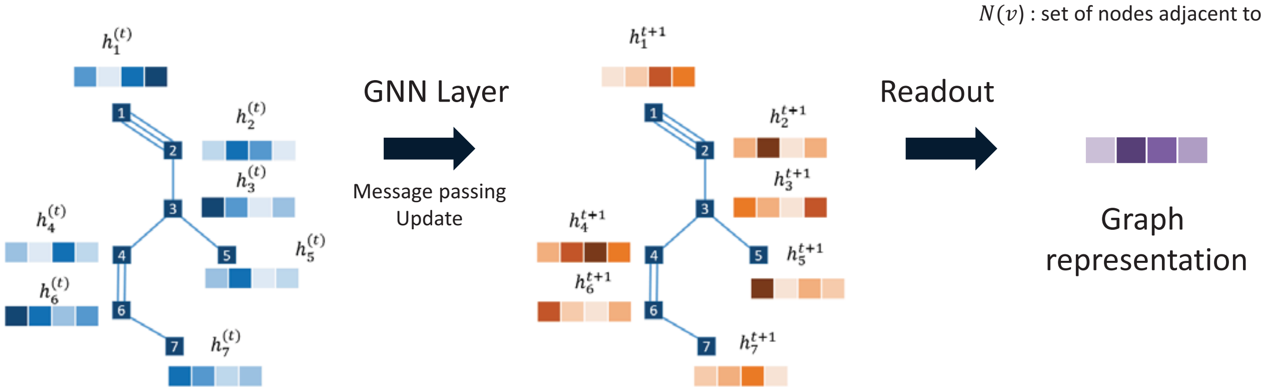
Fig. 1: 2D Convolution vs. Graph Convolution.

https://arxiv.org/abs/1901.00596

Graph Neural Network

- **Message Passing** : aggregate information from neighbors
  - – $m_v^{(t+1)} = message\_passing(\{h_w^{(t)} ,\forall w \in N(v)\})$
- **Update** : with message passing, update the hidden representation
  - – $h_v^{t+1} = update(m_v^{(t+1)}, h_v^{(t)})$
- **Readout** : represent graph with all hidden representations
  - – $h_G^{t+1} = readout(h_v^{t+1}, \forall v \in G)$

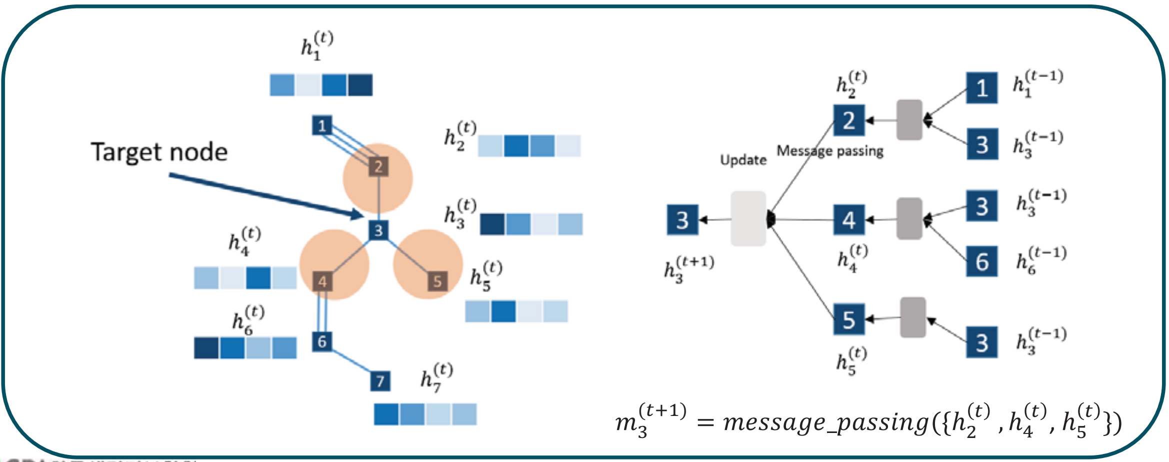
$h_v^0 = X_v$
$N(v)$: set of nodes adjacent to v



h_v^t : hidden embedding vector of node v at t-th GNN layer

Graph Neural Network

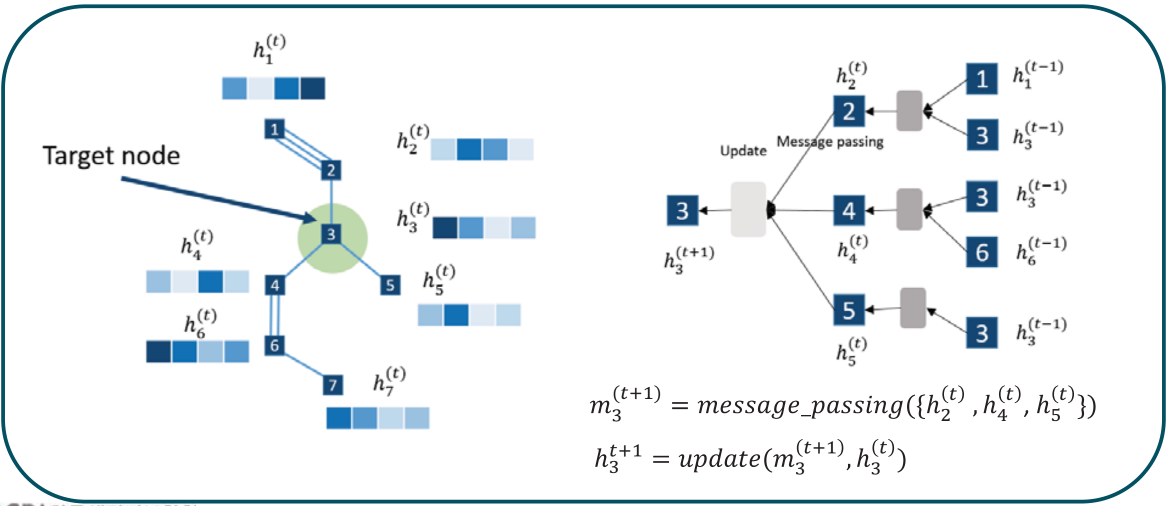
- **Message passing**
  - Message : Information that flows between neighbors and the target node
  - $message\_passing$: function that aggregate neighbor information of target node at t time step with propagation rule
  - $m_v^{(t+1)} = message\_passing(\{h_w^{(t)}, \forall w \in N(v)\})$



$$m_3^{(t+1)} = message\_passing(\{h_2^{(t)}, h_4^{(t)}, h_5^{(t)}\})$$

Graph Neural Network

- **Update**
  - $update$: function that update the t+1 time step hidden representation with t time step node representation and message passing
  - $h_v^{t+1} = update(m_v^{(t+1)}, h_v^{(t)})$

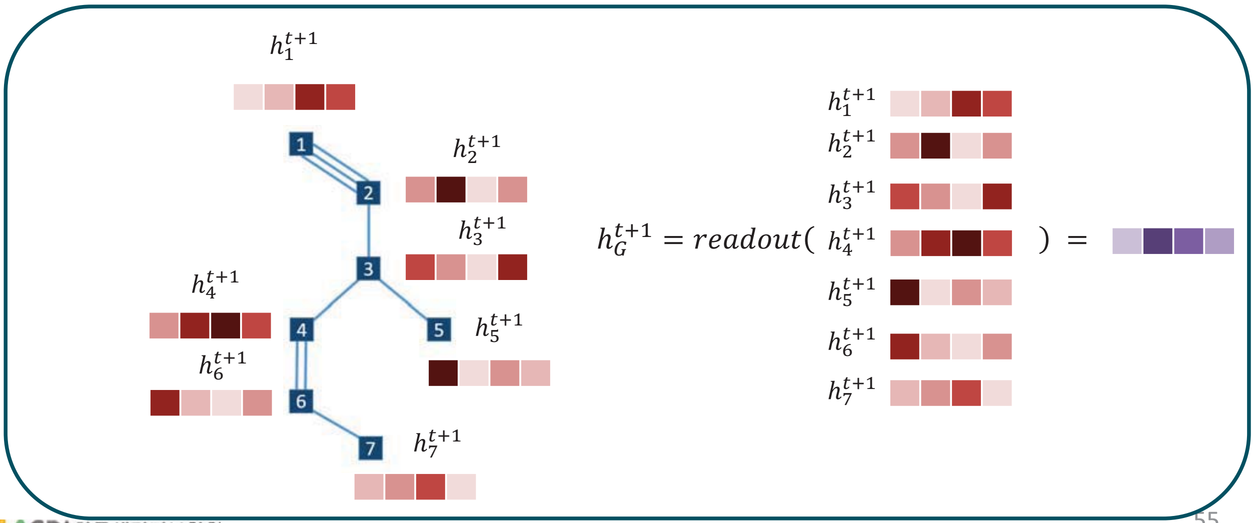


$$m_3^{(t+1)} = message\_passing(\{h_2^{(t)}, h_4^{(t)}, h_5^{(t)}\})$$

$$h_3^{t+1} = update(m_3^{(t+1)}, h_3^{(t)})$$

Graph Neural Network

- **Readout**
  - $readout$: function that represent the graph calculated by all hidden representations
  - $h_G^{t+1} = readout(h_v^{t+1}, \forall v \in G)$


h_1^{t+1}
h_2^{t+1}
h_3^{t+1}
h_4^{t+1}
h_5^{t+1}
h_6^{t+1}
h_7^{t+1}
1
2
3
4
5
6
7
$h_G^{t+1} = readout($ h_1^{t+1} h_2^{t+1} h_3^{t+1} h_4^{t+1} h_5^{t+1} h_6^{t+1} h_7^{t+1} $) =$

Graph Neural Network Models

- Semi –Supervised Classification with Graph Convolutional Networks (**GCN**)
- Inductive Representation Learning on Large Graphs (**GraphSAGE**)
- Neural Message Passing for Quantum Chemistry (**MPNN**)
- Graph Attention Networks (**GAT**)
- How Powerful Are Graph Neural Network? (**GIN**)
- Analyzing Learned Molecular Representations for Property Prediction (**DMPNN**)

→ Various Message passing, Update, Readout function

To be continued.

1. P
2. ~~D~~R
3.

Contents

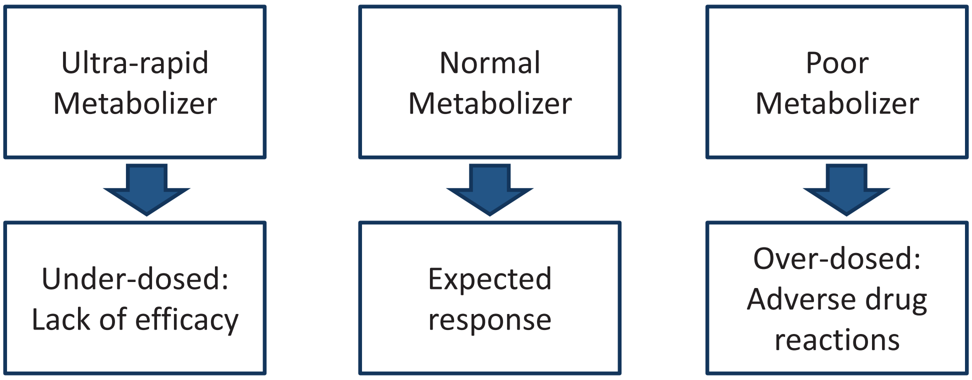
- PART1
  - Introduction to pharmacogenomics
    - Drug discovery and development
  - Key data sources
  - Representations of proteins, chemicals
- PART2
  - Studies related to pharmacogenomics based on machine learning

CYP450 VARIATIONS AND DRUG RESPONSES

SBi 한국생명정보학회 Korean Society for Bioinformatics

Pharmacogenomics and drug metabolism

- A patient's genetic makeup and their response to pharmaceutical drugs are seen with regards to their metabolism


Ultra-rapid Metabolizer → Under-dosed: Lack of efficacy

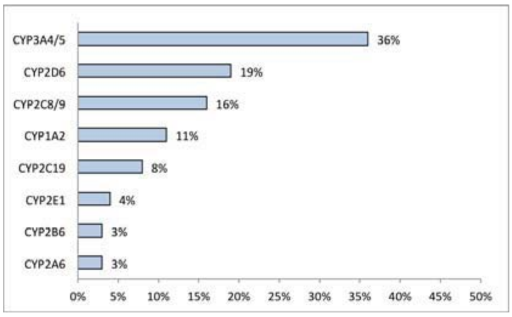
Normal Metabolizer → Expected response

Poor Metabolizer → Over-dosed: Adverse drug reactions

SBi 한국생명정보학회 Korean Society for Bioinformatics

Cytochrome P450 enzymes

- The super-family of cytochrome P450 enzymes has a crucial role in the metabolism of drugs
- CYPs are the major enzymes involved in drug metabolism, accounting for about 75% of the total metabolism
- Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body

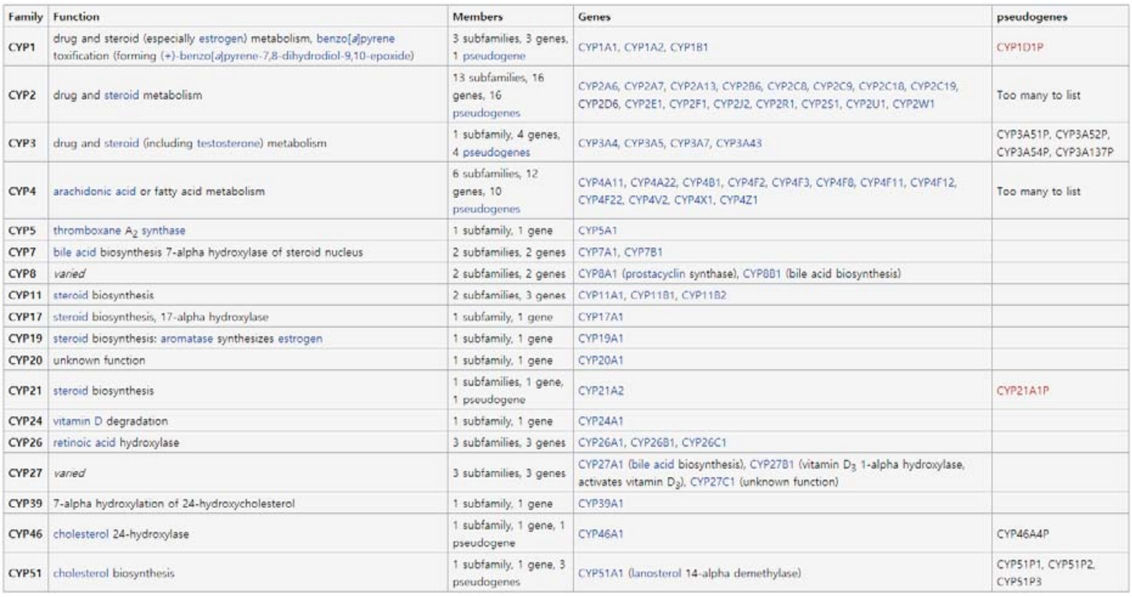


e.g.) Proportion of antifungal drugs metabolized by different families of CYPs.

https://en.wikipedia.org/wiki/Cytochrome_P450#Drug_metabolism

CYP450 isozymes

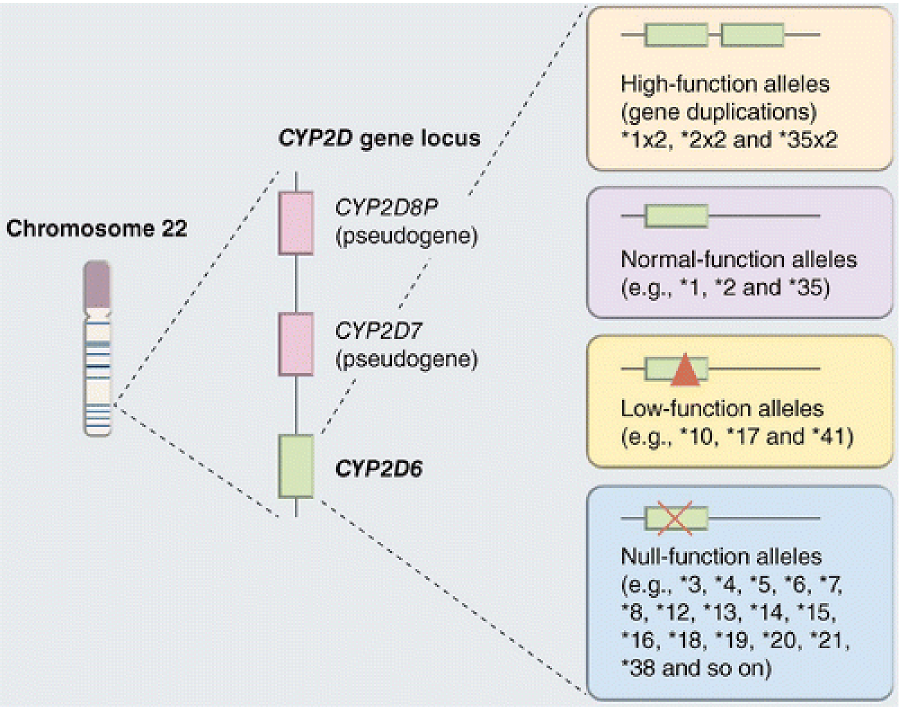
- Humans have 57 genes and more than 59 pseudogenes divided among 18 families of cytochrome P450 genes and 43 subfamilies



Family	Function	Members	Genes	pseudogenes
CYP1	drug and steroid (especially estrogen) metabolism, benzo[*a*]pyrene toxification (forming (+)-benzo[*a*]pyrene-7,8-dihydrodiol-9,10-epoxide)	3 subfamilies, 3 genes, 1 pseudogene	CYP1A1, CYP1A2, CYP1B1	CYP1D1P
CYP2	drug and steroid metabolism	13 subfamilies, 16 genes, 16 pseudogenes	CYP2A6, CYP2A7, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2F1, CYP2J2, CYP2R1, CYP2S1, CYP2U1, CYP2W1	Too many to list
CYP3	drug and steroid (including testosterone) metabolism	1 subfamily, 4 genes, 4 pseudogenes	CYP3A4, CYP3A5, CYP3A7, CYP3A43	CYP3A51P, CYP3A52P, CYP3A54P, CYP3A137P
CYP4	arachidonic acid or fatty acid metabolism	6 subfamilies, 12 genes, 10 pseudogenes	CYP4A11, CYP4A22, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4F22, CYP4V2, CYP4X1, CYP4Z1	Too many to list
CYP5	thromboxane A_2 synthase	1 subfamily, 1 gene	CYP5A1	
CYP7	bile acid biosynthesis 7-alpha hydroxylase of steroid nucleus	2 subfamilies, 2 genes	CYP7A1, CYP7B1	
CYP8	*varied*	2 subfamilies, 2 genes	CYP8A1 (prostacyclin synthase), CYP8B1 (bile acid biosynthesis)	
CYP11	steroid biosynthesis	2 subfamilies, 3 genes	CYP11A1, CYP11B1, CYP11B2	
CYP17	steroid biosynthesis, 17-alpha hydroxylase	1 subfamily, 1 gene	CYP17A1	
CYP19	steroid biosynthesis: aromatase synthesizes estrogen	1 subfamily, 1 gene	CYP19A1	
CYP20	unknown function	1 subfamily, 1 gene	CYP20A1	
CYP21	steroid biosynthesis	1 subfamilies, 1 gene, 1 pseudogene	CYP21A2	CYP21A1P
CYP24	vitamin D degradation	1 subfamily, 1 gene	CYP24A1	
CYP26	retinoic acid hydroxylase	3 subfamilies, 3 genes	CYP26A1, CYP26B1, CYP26C1	
CYP27	*varied*	3 subfamilies, 3 genes	CYP27A1 (bile acid biosynthesis), CYP27B1 (vitamin D_3 1-alpha hydroxylase, activates vitamin D_3), CYP27C1 (unknown function)	
CYP39	7-alpha hydroxylation of 24-hydroxycholesterol	1 subfamily, 1 gene	CYP39A1	
CYP46	cholesterol 24-hydroxylase	1 subfamily, 1 gene, 1 pseudogene	CYP46A1	CYP46A4P
CYP51	cholesterol biosynthesis	1 subfamily, 1 gene, 3 pseudogenes	CYP51A1 (lanosterol 14-alpha demethylase)	CYP51P1, CYP51P2, CYP51P3

https://en.wikipedia.org/wiki/Cytochrome_P450#Drug_metabolism

CYP2D6 alleles



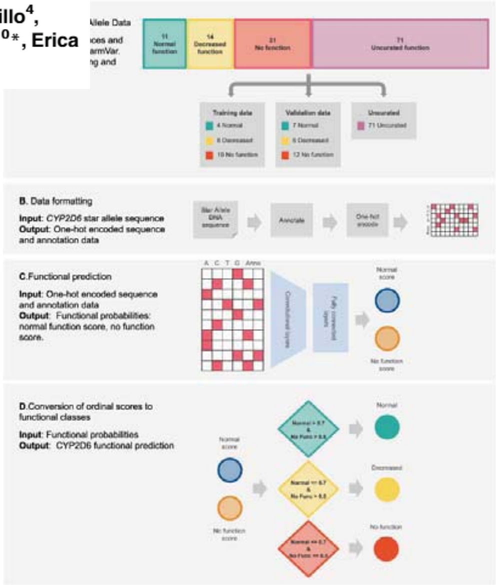
https://www.futuremedicine.com/doi/10.2217/fmeb2013.13.130

Related study:
prediction of CYP2D6 haplotype function

RESEARCH ARTICLE

Transfer learning enables prediction of *CYP2D6* haplotype function

Gregory McInnes[1], Rachel Dalton[2,3], Katrin Sangkuhl[4], Michelle Whirl-Carrillo[4], Seung-been Lee[5], Philip S. Tsao[6,7], Andrea Gaedigk[8,9], Russ B. Altman[4,10]*, Erica L. Woodahl[2]*



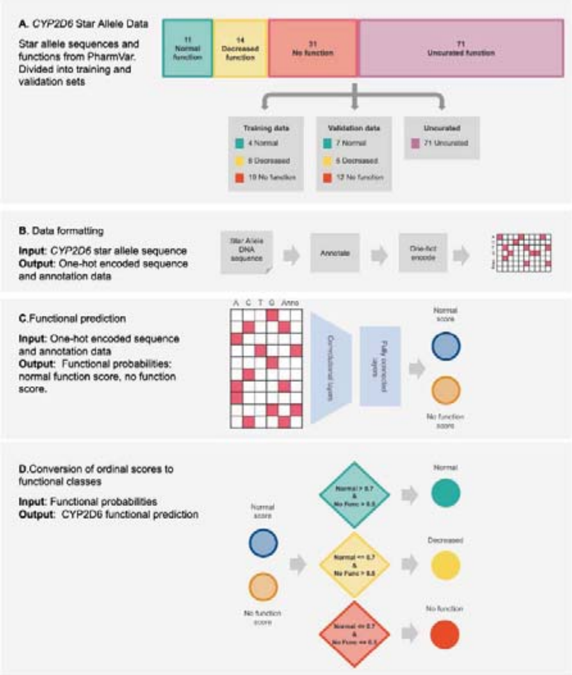
McInnes G, Dalton R, Sangkuhl K, WhirlCarrillo M, Lee S-b, Tsao PS, et al. (2020) Transfer learning enables prediction of CYP2D6 haplotype function. PLoS Comput Biol 16(11): e1008399. https://doi.org/10.1371/journal.pcbi.1008399

Related study: prediction of CYP2D6 haplotype function

- CYP2D6 is an enzyme expressed in the liver that is responsible for metabolizing more than 20% of clinically used drugs
- More than 130 haplotypes comprised of single nucleotide variants (SNVs), insertions and deletions (INDELs), and structural variants (SVs) have been discovered and catalogued in the Pharmacogene Variation Consortium

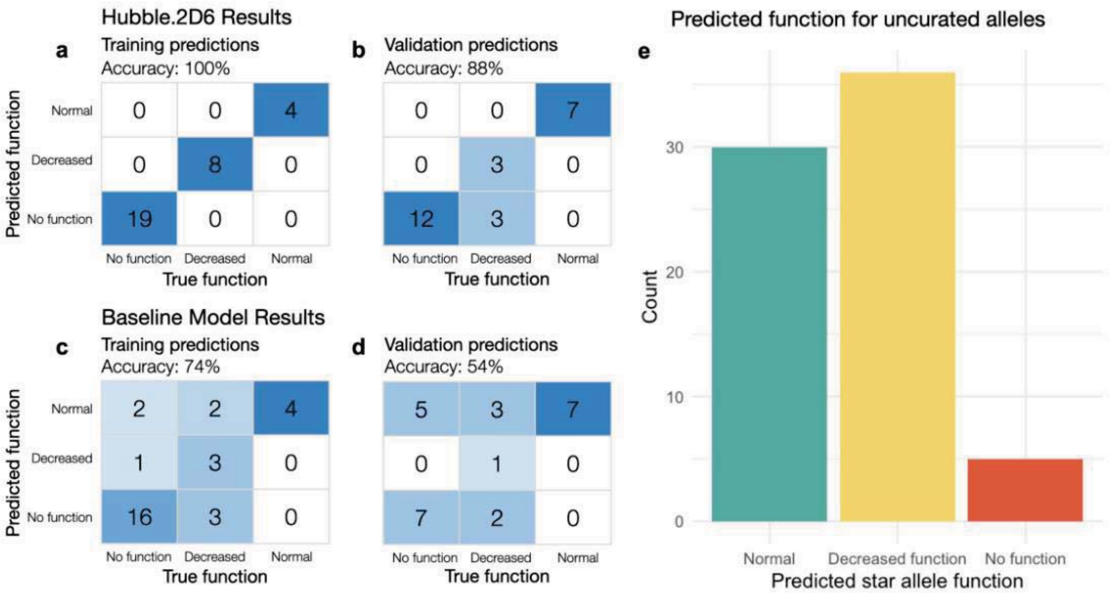
Related study: prediction of CYP2D6 haplotype function

- **Input**
  - CYP2D6 Full genomic sequence (one hot vector)
  - 9 annotations (one hot vector)
    - Coding region, rare variants, deleterious, INDEL, methylation mark, DNase hypersensitivity, TF binding site, eQTL, active site
- **Output**
  - Haplotype activity (No, Reduced, Normal activity)
- **Data**
  - Pre-training with 50,000 randomly selecting a pair of CYP2D6 star alleles with curated function, Pre-training with 314 in vivo data
  - Fine-tuning with PharmVar data
- **Model** – 3 CNN + 2 FC



A. CYP2D6 Star Allele Data
Star allele sequences and functions from PharmVar. Divided into training and validation sets
11 Normal function
14 Decreased function
31 No function
71 Uncurated function
Training data
4 Normal
8 Decreased
19 No function
Validation data
7 Normal
6 Decreased
12 No function
Uncurated
71 Uncurated
B. Data formatting
Input: CYP2D6 star allele sequence
Output: One-hot encoded sequence and annotation data
Star Allele DNA sequence
Annotate
One-hot encode
C.Functional prediction
Input: One-hot encoded sequence and annotation data
Output: Functional probabilities: normal function score, no function score.
A C T G Anno
Convolutional layers
Fully connected layers
Normal score
No function score
D.Conversion of ordinal scores to functional classes
Input: Functional probabilities
Output: CYP2D6 functional prediction
Normal score
No function score
Normal > 0.7 & No Func > 0.5
Normal <= 0.7 & No Func > 0.5
Normal <= 0.7 & No Func <= 0.5
Normal
Decreased
No function

McInnes G, Dalton R, Sangkuhl K, WhirlCarrillo M, Lee S-b, Tsao PS, et al. (2020) Transfer learning enables prediction of CYP2D6 haplotype function. PLoS Comput Biol 16(11): e1008399. https://doi.org/10.1371/journal.pcbi.1008399



a

Predicted function	No function	Decreased	Normal
Normal	0	0	4
Decreased	0	8	0
No function	19	0	0

b

Predicted function	No function	Decreased	Normal
Normal	0	0	7
Decreased	0	3	0
No function	12	3	0

c

Predicted function	No function	Decreased	Normal
Normal	2	2	4
Decreased	1	3	0
No function	16	3	0

d

Predicted function	No function	Decreased	Normal
Normal	5	3	7
Decreased	0	1	0
No function	7	2	0

Fig 2. Star allele classification results. The figure depicts performance metrics for the prediction of star allele function in the training and validation sets; confusion matrices for class prediction in training and validation are shown in (a) and (b), for Hubble.2D6 and in (c) and (d) for the baseline model. (e) shows the frequency of predicted function for uncurated star alleles.

McInnes G, Dalton R, Sangkuhl K, WhirlCarrillo M, Lee S-b, Tsao PS, et al. (2020) Transfer learning enables prediction of CYP2D6 haplotype function. PLoS Comput Biol 16(11): e1008399. https://doi.org/10.1371/journal.pcbi.1008399

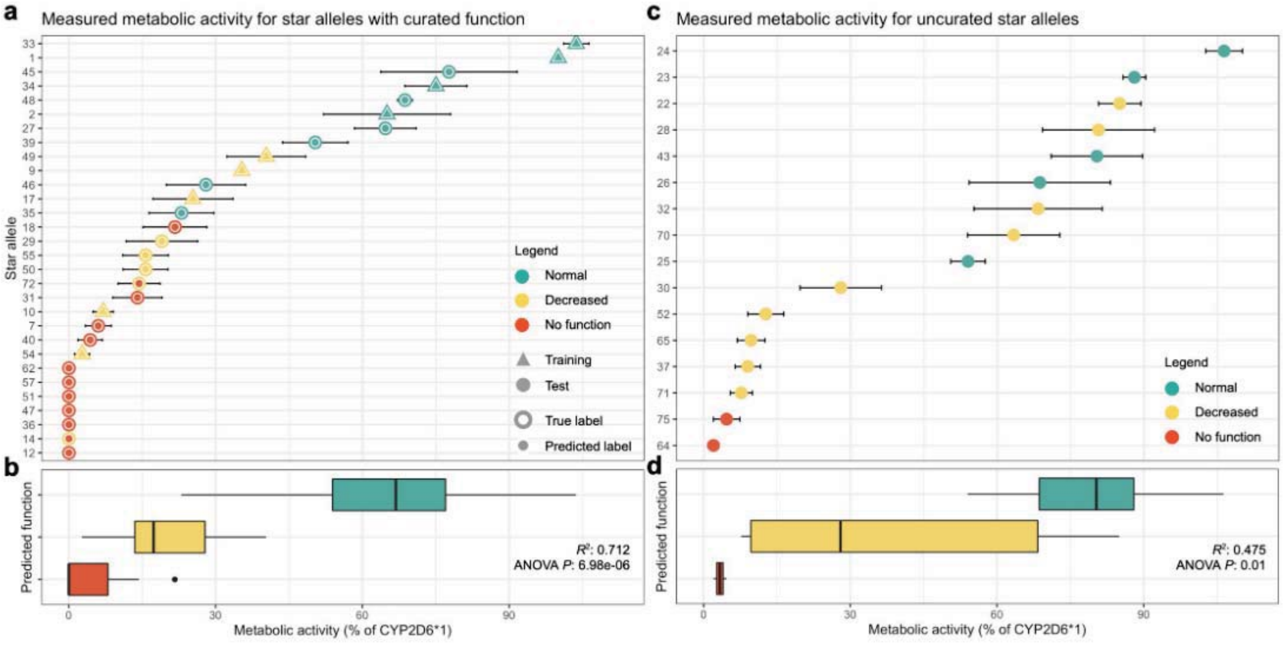


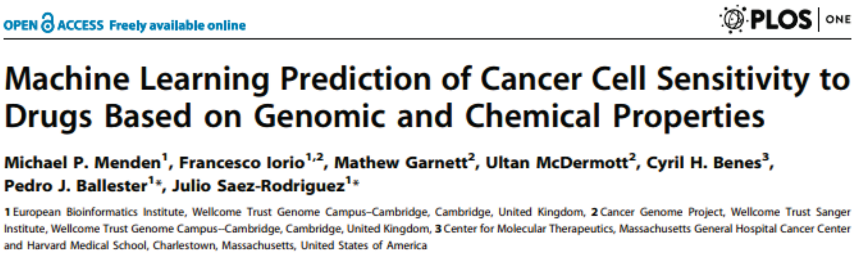
Fig 3. Prediction of star allele function with *in vitro* data. The figures summarize the distribution of metabolic activity measured *in vitro* for star alleles whose function was predicted by Hubble. The distribution of functional activity is shown in (a) and (b) for star alleles with CPIC-assigned clinical function assignments. (a) star alleles included in the training process are depicted with a triangle, and those held for testing are depicted with a circle. Error bars depict the standard error of the measured function. The outer edge of each point indicates the true, curator-assigned phenotype, while the inner color represents predicted function. (b) distribution of values for each predicted functional class for data shown in (a). (c) star alleles without assigned function status; colors represent the predicted function. (d) variance in measured activity of the star alleles for each predicted label for data shown in (c).

McInnes G, Dalton R, Sangkuhl K, WhirlCarrillo M, Lee S-b, Tsao PS, et al. (2020) Transfer learning enables prediction of CYP2D6 haplotype function. PLoS Comput Biol 16(11): e1008399. https://doi.org/10.1371/journal.pcbi.1008399

GENETIC VARIATIONS AND DRUG RESPONSES

Related study: prediction of cancer cell sensitivity to drugs

- Genomic features
  - MSI, variations, CNV
- Simple neural network

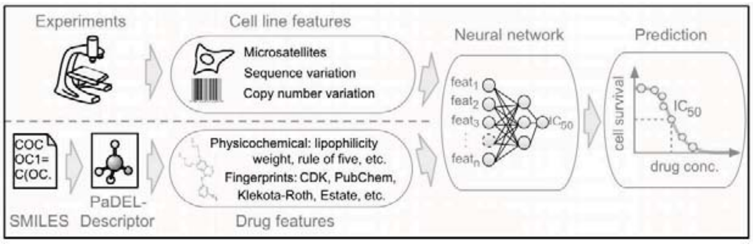


OPEN ACCESS Freely available online PLOS | ONE

Machine Learning Prediction of Cancer Cell Sensitivity to Drugs Based on Genomic and Chemical Properties

Michael P. Menden[1], Francesco Iorio[1,2], Mathew Garnett[2], Ultan McDermott[2], Cyril H. Benes[3], Pedro J. Ballester[1]*, Julio Saez-Rodriguez[1]*

1 European Bioinformatics Institute, Wellcome Trust Genome Campus–Cambridge, Cambridge, United Kingdom, 2 Cancer Genome Project, Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus–Cambridge, Cambridge, United Kingdom, 3 Center for Molecular Therapeutics, Massachusetts General Hospital Cancer Center and Harvard Medical School, Charlestown, Massachusetts, United States of America



Menden, Michael P., et al. "Machine learning prediction of cancer cell sensitivity to drugs based on genomic and chemical properties." PLoS one 8.4 (2013): e61318.

Related study:
prediction of cancer cell sensitivity to drugs

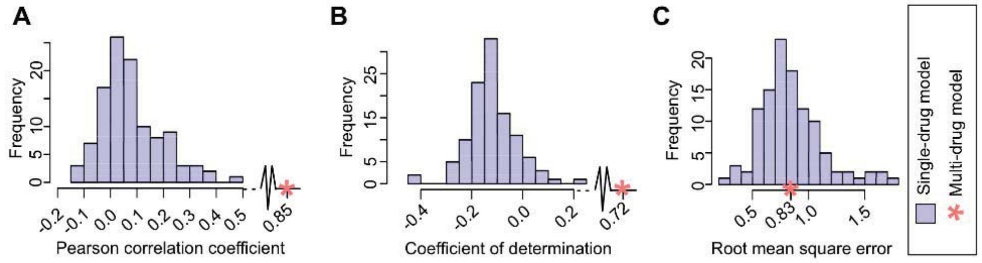
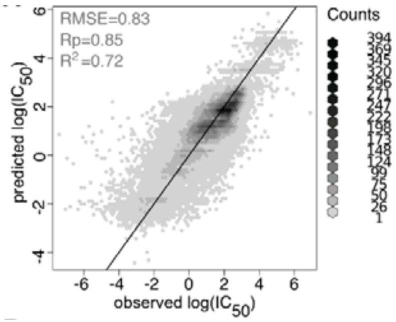


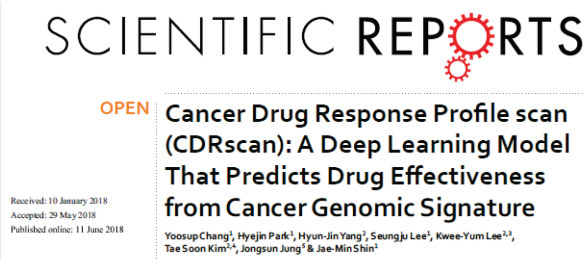
Figure 2. Comparison of single-drug models and the multi-drug model. The performance of the multi-drug model (red asterisk) and the family of 111 single-drug models (blue histogram) is represented using three different metrics: (A) Pearson correlation R_p, (B) coefficient of determination R^2, and (C) root mean square error RMSE.
doi:10.1371/journal.pone.0061318.g002



- Genomics of Drug Sensitivity in Cancer (GDSC) project
- mutational status of 77 oncogenes
- 639 cancer cell lines
- 131 drugs
- 67,488 possible drug response
- 8-fold cross-validation

Menden, Michael P., et al. "Machine learning prediction of cancer cell sensitivity to drugs based on genomic and chemical properties." PLoS one 8.4 (2013): e61318.

Related study:
prediction of cancer cell sensitivity to drugs



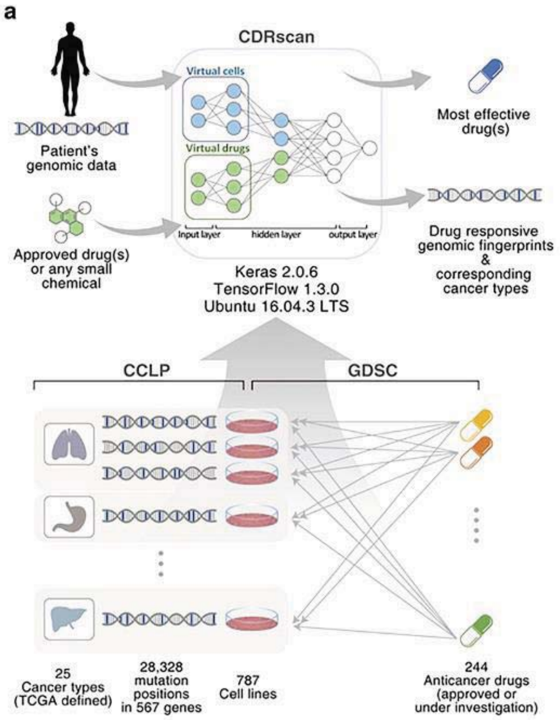
SCIENTIFIC REPORTS

OPEN

Cancer Drug Response Profile scan (CDRscan): A Deep Learning Model That Predicts Drug Effectiveness from Cancer Genomic Signature

Received: 10 January 2018
Accepted: 29 May 2018
Published online: 11 June 2018

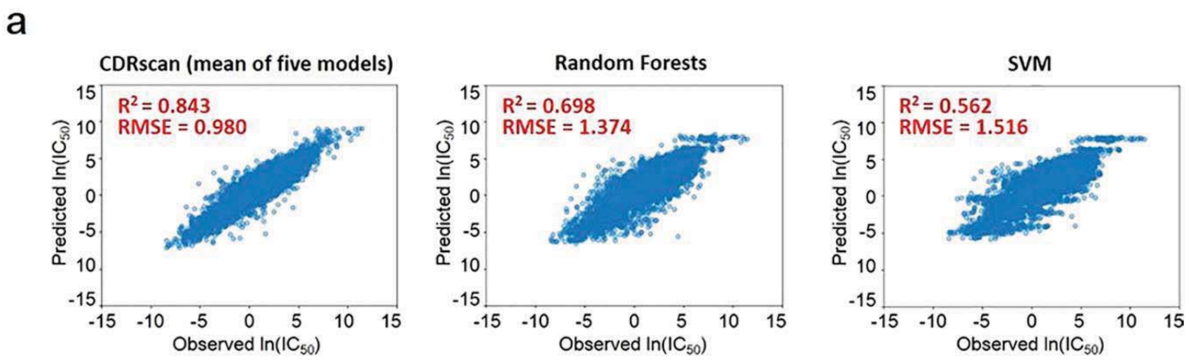
Yoosup Chang[1], Hyejin Park[1], Hyun-Jin Yang[2], Seungju Lee[1], Kwee-Yum Lee[2,3], Tae Soon Kim[2,4], Jongsun Jung[5] & Jae-Min Shin[1]


a
CDRscan
Virtual cells
Virtual drugs
Patient's genomic data
Approved drug(s) or any small chemical
Input layer
hidden layer
output layer
Most effective drug(s)
Drug responsive genomic fingerprints & corresponding cancer types
Keras 2.0.6
TensorFlow 1.3.0
Ubuntu 16.04.3 LTS
CCLP
GDSC
25 Cancer types (TCGA defined)
28,328 mutation positions in 567 genes
787 Cell lines
244 Anticancer drugs (approved or under investigation)

- GDSC
- 28,328 mutation positions in 567 genes
- 787 cell lines
- 244 drugs

Chang, Yoosup, et al. "Cancer Drug Response Profile scan (CDRscan): A Deep Learning Model That Predicts Drug Effectiveness from Cancer Genomic Signature." Scientific reports 8.1 (2018): 8857.

Related study: prediction of cancer cell sensitivity to drugs

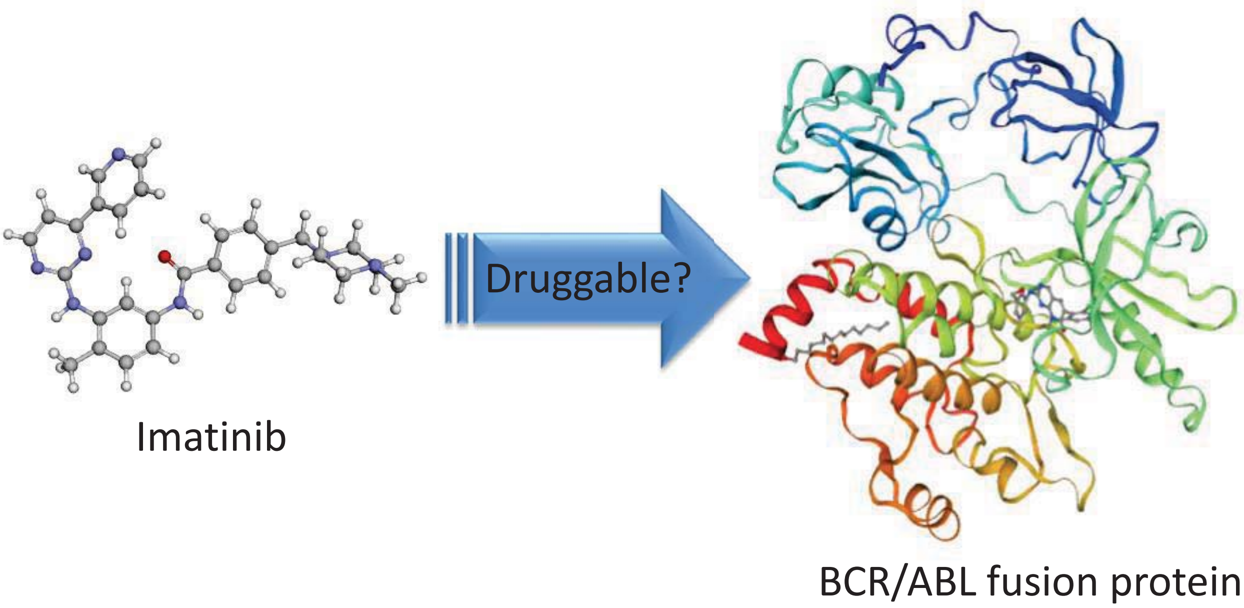


- multi-fold cross validation (five-fold with each fold)

Chang, Yoosup, et al. "Cancer Drug Response Profile scan (CDRscan): A Deep Learning Model That Predicts Drug Effectiveness from Cancer Genomic Signature." Scientific reports 8.1 (2018): 8857.

PROTEIN SEQUENCE AND DRUG INTERACTIONS

Prediction of drug-target interaction



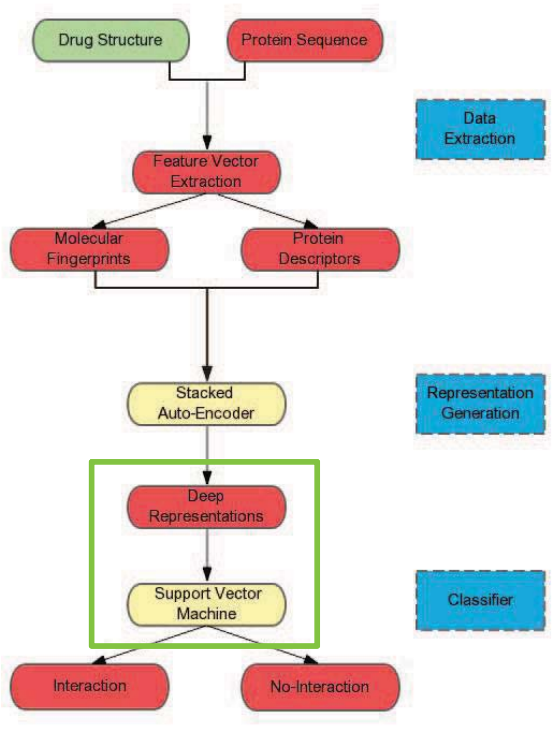
DTI prediction using protein descriptors

Large-Scale Prediction of Drug-Target Interactions from Deep Representations

Peng-Wei Hu Keith C.C. Chan Zhu-Hong You
Department of Computing
Hong Kong Polytechnic University
Hung Hom, Kowloon
Hong Kong
{csphu, cskcchan, csyzhuhong }@comp.polyu.edu.hk

MFDR employed stacked Auto-Encoder(SAE) to abstract original features into a latent representation with a small dimension. With latent representation, they trained a support vector machine(SVM), which performed better than previous methods, including feature-and similarity-based methods.

Chan, Keith CC, and Zhu-Hong You. "Large-scale prediction of drug-target interactions from deep representations." *Neural Networks (IJCNN), 2016 International Joint Conference on*. IEEE, 2016.



Multi-scale features deep representations inferring interactions (MFDR)

DTI prediction using protein descriptors

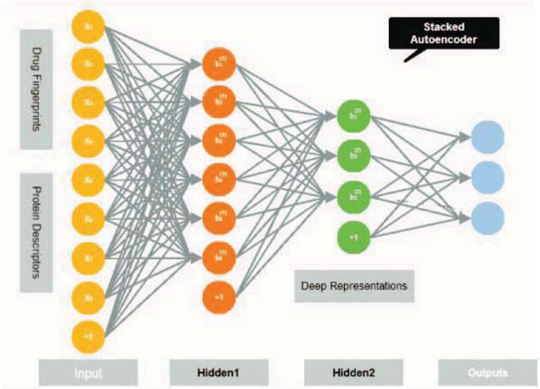
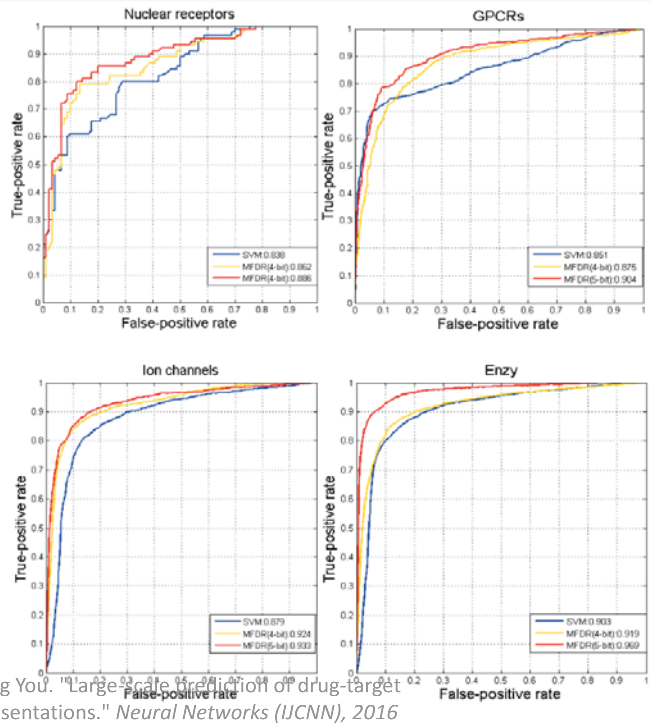


Fig. 2. A Stacked Auto-Encoder composed by two visible layers and two hidden layers

DRUG-TARGET DATA STATISTIC

Type		Ion channel	Enzyme	GPCR	Nuclear receptor
Drugs		210	445	223	54
881 bits					
Target proteins		204	664	95	26
567 Descriptors	1449 Descriptors				
Positive Drug–target Interactions		1476	2926	635	90

5fold cross-validation



Chan, Keith CC, and Zhu-Hong You. "Large-scale prediction of drug-target interactions from deep representations." *Neural Networks (IJCNN), 2016 International Joint Conference on*. IEEE, 2016.

DTI prediction using protein sequence

Bioinformatics, 34, 2018, i821–i829
doi: 10.1093/bioinformatics/bty593
ECCB 2018

OXFORD

DeepDTA: deep drug–target binding affinity prediction

Hakime Öztürk[1], Arzucan Özgür[1,*] and Elif Ozkirimli[2,*]

- **Model**
  - Input – Protein sequence, SMILES
  - Output – Binding affinity
  - Model – CNN for protein, DNN for drug
- **Contribution**
  - first used CNN to learn representations of proteins

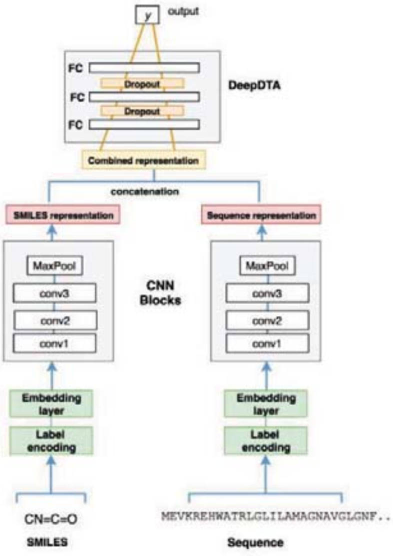
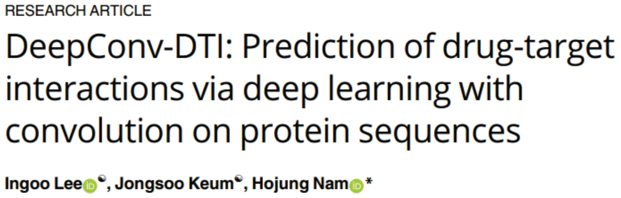


Fig. 2. DeepDTA model with two CNN blocks to learn from compound SMILES and protein sequences

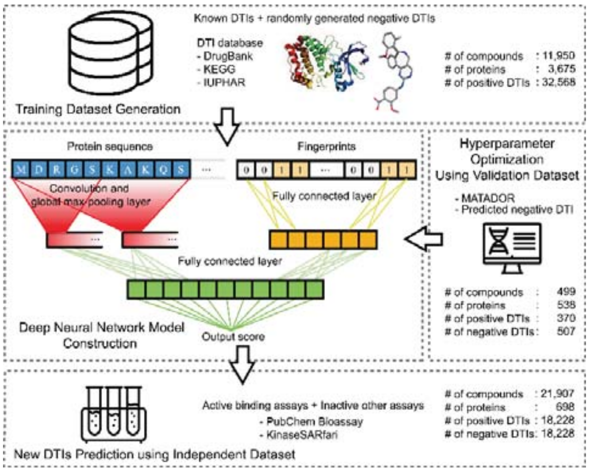
DTI prediction using protein sequence



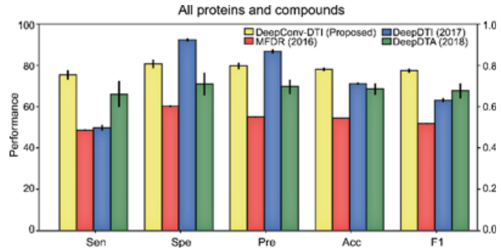
RESEARCH ARTICLE

DeepConv-DTI: Prediction of drug-target interactions via deep learning with convolution on protein sequences

Ingoo Lee, Jongsoo Keum, Hojung Nam*



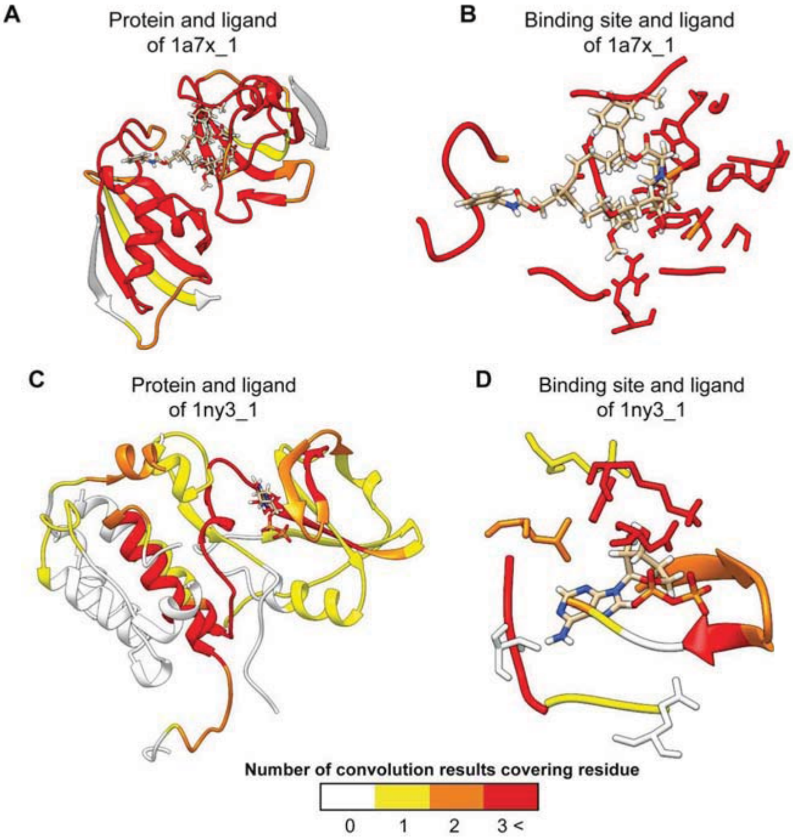
- **Model**
  - Input – Protein sequence, ECFP4
  - Output – Interaction/Non-interaction
  - Model – CNN for protein, DNN for drug



- **Contribution**
  - Embedding representation of protein works well
  - Model can capture local residue patterns

Lee I, Keum J, Nam H (2019) DeepConvDTI: Prediction of drug-target interactions via deep learning with convolution on protein sequences. PLoS Comput Biol 15(6): e1007129. https://doi. org/10.1371/journal.pcbi.1007129

- Compare pooled convolution result with binding sites from sc-PDB



A
Protein and ligand of 1a7x_1
B
Binding site and ligand of 1a7x_1
C
Protein and ligand of 1ny3_1
D
Binding site and ligand of 1ny3_1
Number of convolution results covering residue
0
1
2
3 <

- FKB1A [Enzyme]

- MAPK2 [Kinase]

Lee I, Keum J, Nam H (2019) DeepConvDTI: Prediction of drug-target interactions via deep learning with convolution on protein sequences. PLoS Comput Biol 15(6): e1007129. https://doi. org/10.1371/journal.pcbi.1007129

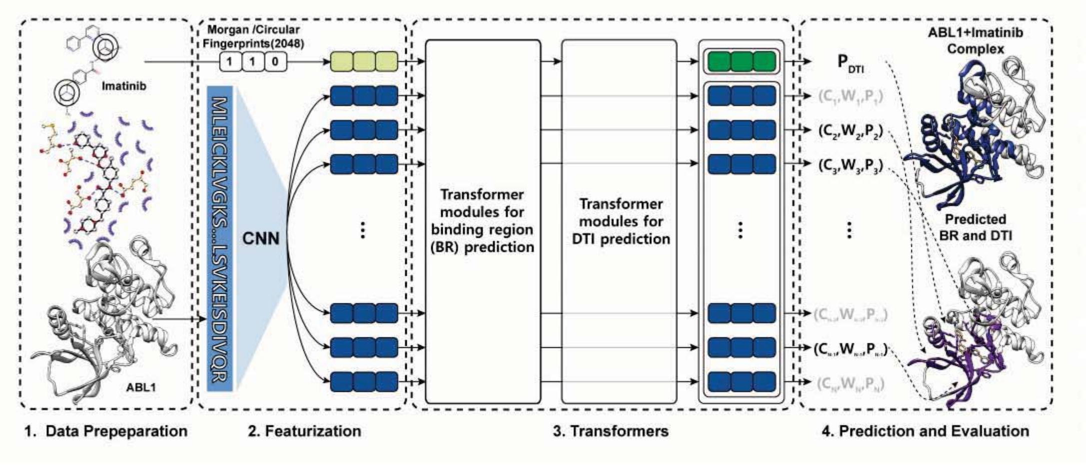
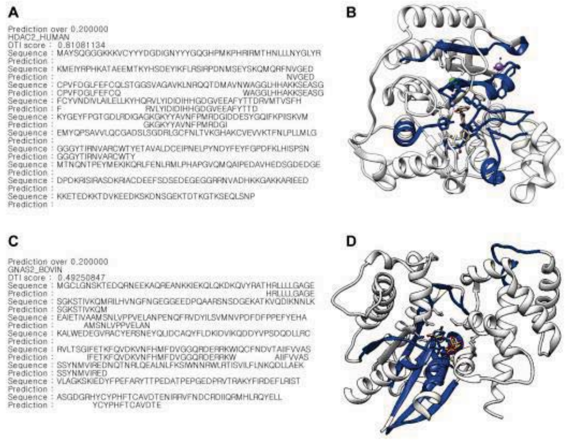

Morgan /Circular Fingerprints(2048)
1
1
0
Imatinib
MLEICLKLVGKS...LSVKEISDIVQR
CNN
ABL1
Transformer modules for binding region (BR) prediction
Transformer modules for DTI prediction
P_{DTI}
(C_1,W_1,P_1)
(C_2,W_2,P_2)
(C_3,W_3,P_3)
$(C_{N-2},W_{N-2},P_{N-2})$
$(C_{N-1},W_{N-1},P_{N-1})$
(C_N,W_N,P_N)
ABL1+Imatinib Complex
Predicted BR and DTI
1. Data Prepeparation
2. Featurization
3. Transformers
4. Prediction and Evaluation

Fig. 1. HoTS model overview. HoTS considers amino acid sequences of individual proteins and Morgan/circular fingerprints of drug compounds. Therefrom, local residue patterns are extracted by a convolutional neural network, and maximum values are pooled from each protein grid. Compound and protein grids are taken into transformers to model interactions between local residue patterns and individual compounds. After passing the transformers, a compound token is used to predict DTIs, and individual protein grids are used to reflect binding regions (BR). For DTI prediction, HoTS calculates a prediction score $\mathbf{P_{DTI}}$ ranging from 0 to 1 and center (C), length (W), and confidence (P) scores for binding regions.

Ingoo Lee, Hojung Nam*, "Sequence-based prediction of binding regions and drug-target interactions", Under review.



```
Prediction over 0.200000
HDAC2_HUMAN
DTI score  :  0.81081134
Sequence   : MAYSQGGGKKKVCYYYDGDIGNYYYGQGHPMKPHRIRMTHNLLLNYGLYR
Prediction :
Sequence   : KMEIYRPHKATAEEMTKYHSDEYIKFLRSIRPDNMSEYSKQMQRFNVGED
Prediction :                                              NVGED
Sequence   : CPVFDGLFEFCQLSTGGSVAGAVKLNRQQTDMAVNWAGGLHHAKKSEASG
Prediction : CPVFDGLFEFCQ                       WAGGLHHAKKSEASG
Sequence   : FCYVNDIVLAILELLKYHQRVLYIDIDIHHGDGVEEAFYTTDRVMTVSFH
Prediction : F                  RVLYIDIDIHHGDGVEEAFYTTD
Sequence   : KYGEYFPGTGDLRDIGAGKGKYYAVNFPMRDGIDDESYGQIFKPIISKVM
Prediction :                  GKGKYYAVNFPMRDGI
Sequence   : EMYQPSAVVLQCGADSLSGDRLGCFNLTVKGHAKCVEVVKTFNLPLLMLG
Prediction :
Sequence   : GGGYTIRNVARCWTYETAVALDCEIPNELPYNDYFEYFGPDFKLHISPSN
Prediction : GGGYTIRNVARCWTY
Sequence   : MTNQNTPEYMEKIKQRLFENLRMLPHAPGVQMQAIPEDAVHEDSGDEDGE
Prediction :
Sequence   : DPDKRISIRASDKRIACDEEFSDSEDEGEGGRRNVADHKKGAKKARIEED
Prediction :
Sequence   : KKETEDKKTDVKEEDKSKDNSGEKTDTKGTKSEQLSNP
Prediction :
```

```
Prediction over 0.200000
GNAS2_BOVIN
DTI score  :  0.49250847
Sequence   : MGCLGNSKTEDQRNEEKAQREANKKIEKQLQKDKQVYRATHRLLLLGAGE
Prediction :                                         HRLLLLGAGE
Sequence   : SGKSTIVKQMRILHVNGFNGEGGEEDPQAARSNSDGEKATKVQDIKNNLK
Prediction : SGKSTIVKQM
Sequence   : EAIETIVAAMSNLVPPVELANPENQFRVDYILSVMNVPDFDFPPEFYEHA
Prediction :         AMSNLVPPVELAN
Sequence   : KALWEDEGVRACYERSNEYQLIDCAQYFLDKIDVIKQDDYVPSDQDLLRC
Prediction :
Sequence   : RVLTSGIFETKFQVDKVNFHMFDVGGQRDERRKWIQCFNDVTAIIFVVAS
Prediction :       IFETKFQVDKVNFHMFDVGGQRDERRKW        AIIFVVAS
Sequence   : SSYNMVIREDNQTNRLQEALNLFKSIWNNRWLRTISVILFLNKQDLLAEK
Prediction : SSYNMVIRED
Sequence   : VLAGKSKIEDYFPEFARYTTPEDATPEPGEDPRVTRAKYFIRDEFLRIST
Prediction :
Sequence   : ASGDGRHYCYPHFTCAVDTENIRRVFNDCRDIIQRMHLRQYELL
Prediction :        YCYPHFTCAVDTE
```

Fig. 3. Prediction and visualization of binding regions on 3D-complexes. A) Predicted binding regions for drug-target interactions between HDAC2_HUMAN and N-(4-amino-biphenyl-3-yl)benzamide (LLX). **B)** Visualization of predicted binding regions on the 3D complex of human HDAC2 complexed with LLX (Protein Data Bank: 3MAX). **C)** Predicted binding regions between GNAS2_BOVIN and 5'-guanosine-diphosphate-monothiophosphate (GSP). **D)** Visualization of predicted binding regions on the 3D complex of bovine GNAS2 complexed with GSP (Protein Data Bank: 1CUL).

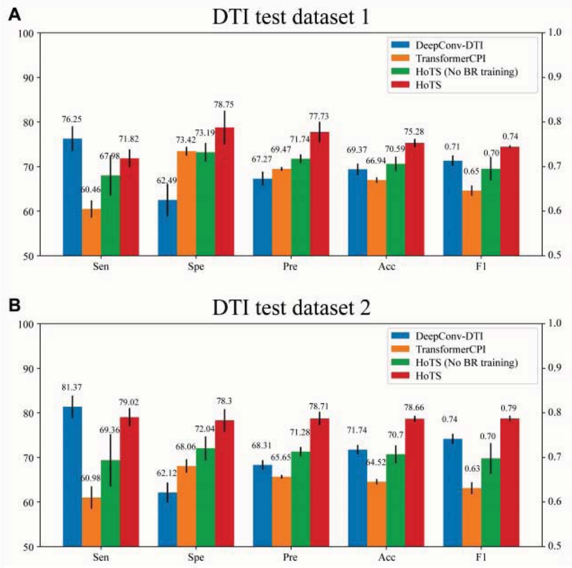


Fig. 4. Prediction performance for drug-target interactions in the independent test datasets.

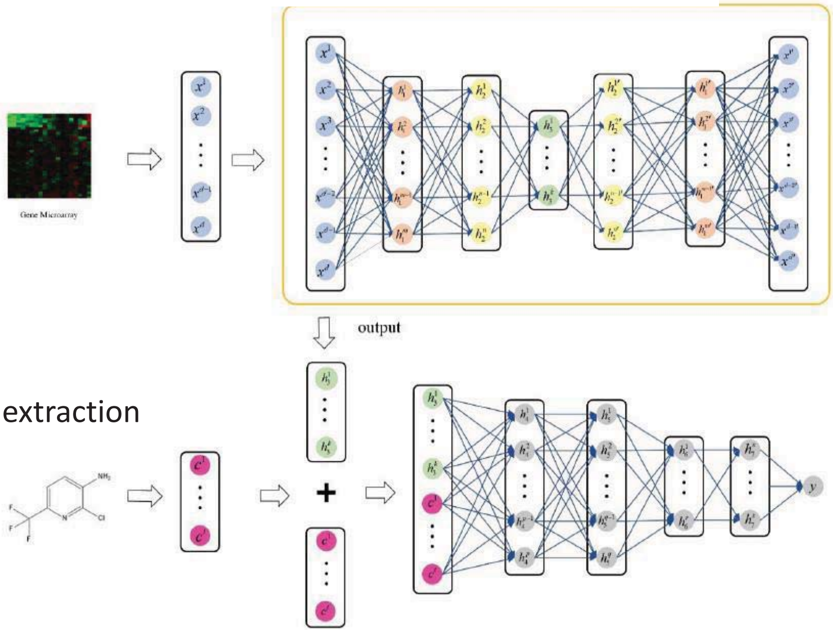
Ingoo Lee, Hojung Nam*, "Sequence-based prediction of binding regions and drug-target interactions", Under review.

GENE EXPRESSION AND DRUG RESPONSE

Related study: prediction of cancer cell sensitivity to drugs

DeepDSC: A Deep Learning Method to Predict Drug Sensitivity of Cancer Cell Lines

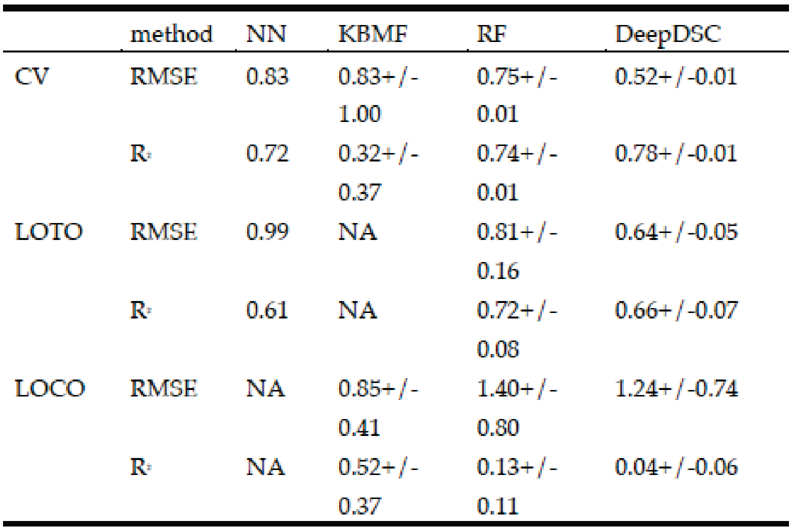
Min Li, Yake Wang, Ruiqing Zheng, Xinghua Shi, Yaohang Li, Fang-Xiang Wu, and Jianxin Wang



- GDSC, CCLE
- Transcriptomic feature
- Morgan fingerprint
- Autoencoder based feature extraction

Li, Min, et al. "DeepDSC: A Deep Learning Method to Predict Drug Sensitivity of Cancer Cell Lines." *IEEE/ACM transactions on computational biology and bioinformatics* (2019).

Related study:
prediction of cancer cell sensitivity to drugs

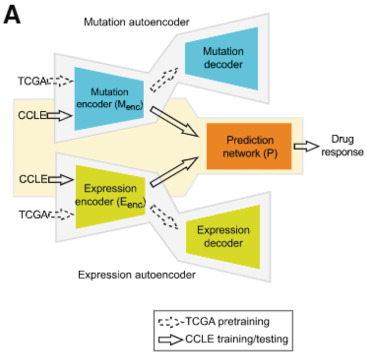


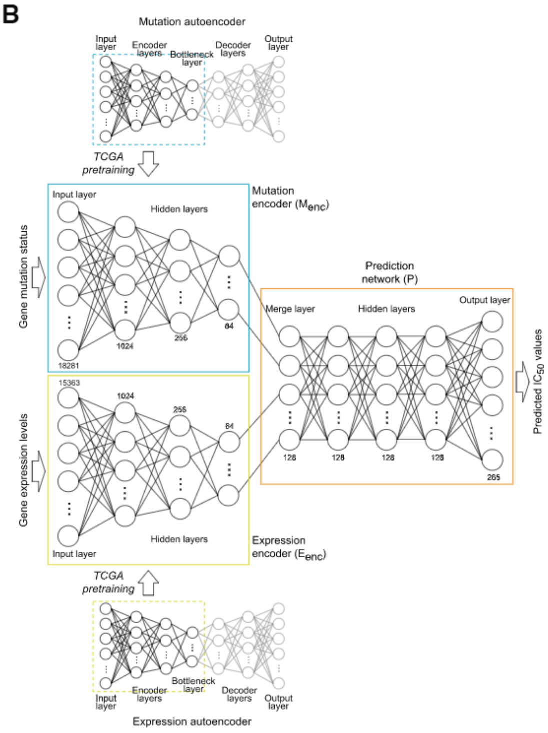
	method	NN	KBMF	RF	DeepDSC
CV	RMSE	0.83	0.83+/-1.00	0.75+/-0.01	0.52+/-0.01
	R^2	0.72	0.32+/-0.37	0.74+/-0.01	0.78+/-0.01
LOTO	RMSE	0.99	NA	0.81+/-0.16	0.64+/-0.05
	R^2	0.61	NA	0.72+/-0.08	0.66+/-0.07
LOCO	RMSE	NA	0.85+/-0.41	1.40+/-0.80	1.24+/-0.74
	R^2	NA	0.52+/-0.37	0.13+/-0.11	0.04+/-0.06

- 10-fold cross-validation
- Better performance than typical machine learning methods
- Deep learning based feature extraction

Li, Min, et al. "DeepDSC: A Deep Learning Method to Predict Drug Sensitivity of Cancer Cell Lines." *IEEE/ACM transactions on computational biology and bioinformatics* (2019).

Related study:
prediction of cancer cell sensitivity to drugs

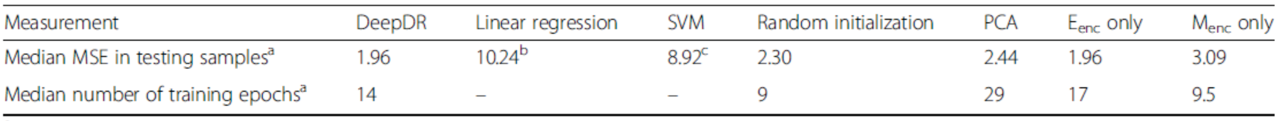




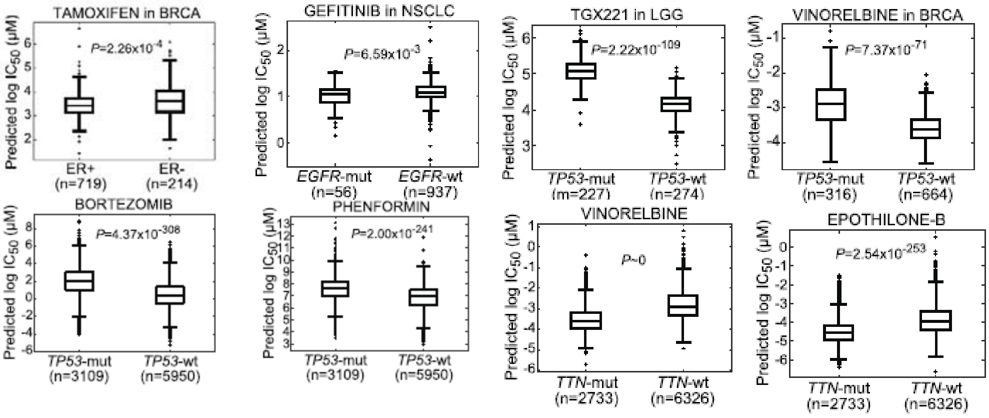
- TCGA for pre-training
- GDSC for response prediction network
- Using both of genomic and transcriptomic feature
- Autoencoder based feature extraction

Chiu, Yu-Chiao, et al. "Predicting drug response of tumors from integrated genomic profiles by deep neural networks." BMC medical genomics 12.1 (2019): 18.

Related study:
prediction of cancer cell sensitivity to drugs



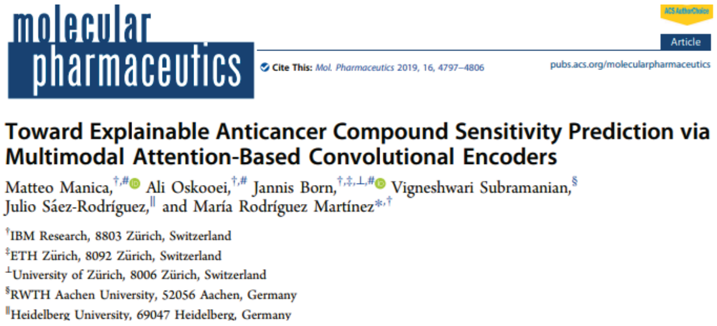
Measurement	DeepDR	Linear regression	SVM	Random initialization	PCA	E_{enc} only	M_{enc} only
Median MSE in testing samples[a]	1.96	10.24[b]	8.92[c]	2.30	2.44	1.96	3.09
Median number of training epochs[a]	14	–	–	9	29	17	9.5



- Samples with mutation showed significantly different result compared to non-mutated samples

Chiu, Yu-Chiao, et al. "Predicting drug response of tumors from integrated genomic profiles by deep neural networks." BMC medical genomics 12.1 (2019): 18.

Related study:
prediction of cancer cell sensitivity to drugs



molecular pharmaceutics

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Article

Cite This: *Mol. Pharmaceutics* 2019, 16, 4797–4806

pubs.acs.org/molecularpharmaceutics

Toward Explainable Anticancer Compound Sensitivity Prediction via Multimodal Attention-Based Convolutional Encoders

Matteo Manica,[†,#] Ali Oskooei,[†,#] Jannis Born,[†,‡,⊥,#] Vigneshwari Subramanian,[§] Julio Sáez-Rodríguez,[‖] and María Rodríguez Martínez[*,†]

[†] IBM Research, 8803 Zürich, Switzerland
[‡] ETH Zürich, 8092 Zürich, Switzerland
[⊥] University of Zürich, 8006 Zürich, Switzerland
[§] RWTH Aachen University, 52056 Aachen, Germany
[‖] Heidelberg University, 69047 Heidelberg, Germany

- Transcriptomic feature
- PPI for feature selection
- SMILES

- Attention based model
  - Interpretable

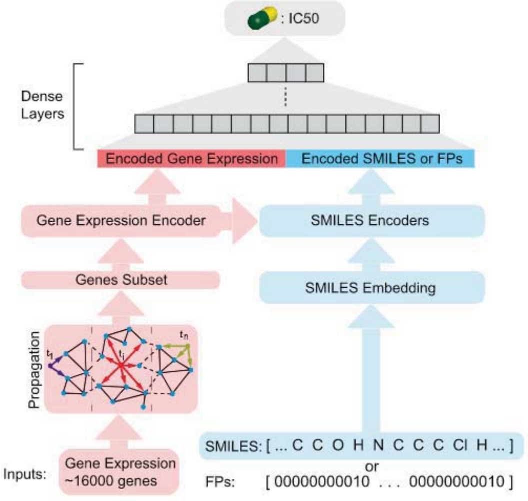
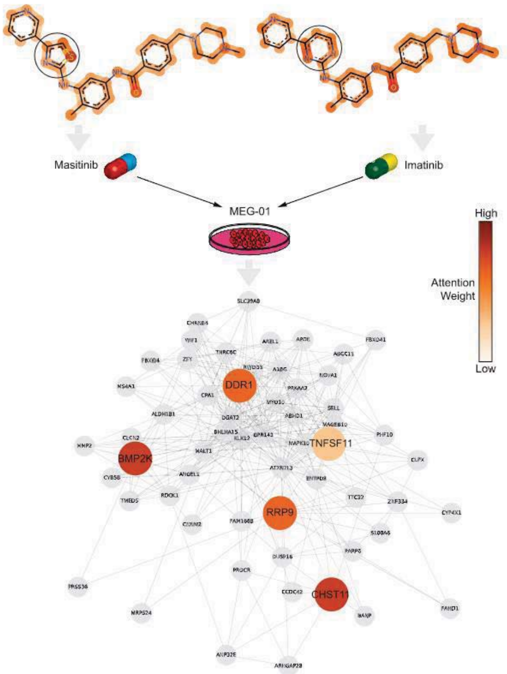
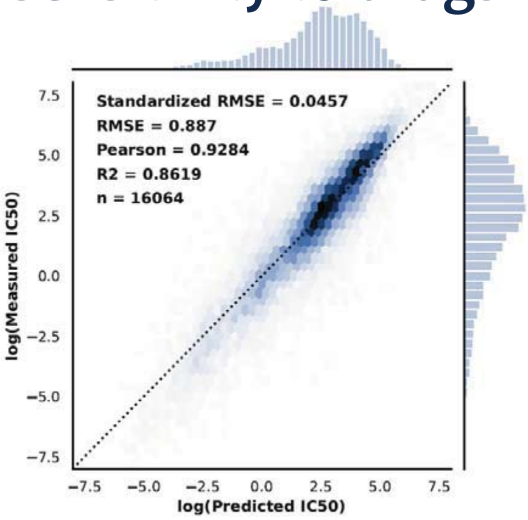


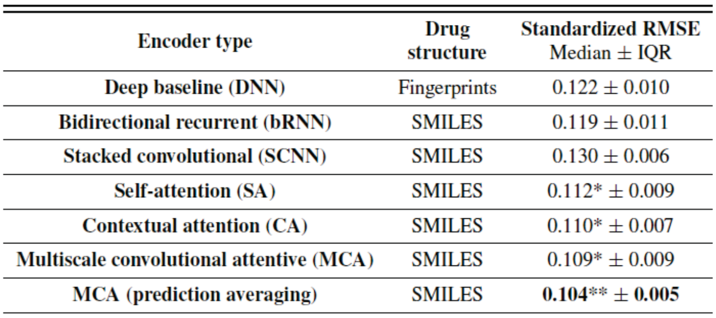
Figure 1. Multimodal end-to-end architecture of the proposed encoders. General framework for the explored architectures. Each model ingests a cell−compound pair and makes an IC50 drug sensitivity prediction. Cells are represented by the gene expression values of a subset of 2128 genes, selected according to a network propagation procedure. Compounds are represented by their SMILES string (apart from the baseline model that uses 512-bit fingerprints). The gene-vector is fed into an attention-based gene encoder that assigns higher weights to the most informative genes. To encode the SMILES strings, several neural architectures are compared (for details see section 2) and used in combination with the gene expression encoder in order to predict drug sensitivity.

Manica, Matteo, et al. "Toward explainable anticancer compound sensitivity prediction via multimodal attention-based convolutional encoders." Molecular Pharmaceutics (2019).

Related study:
prediction of cancer cell sensitivity to drugs



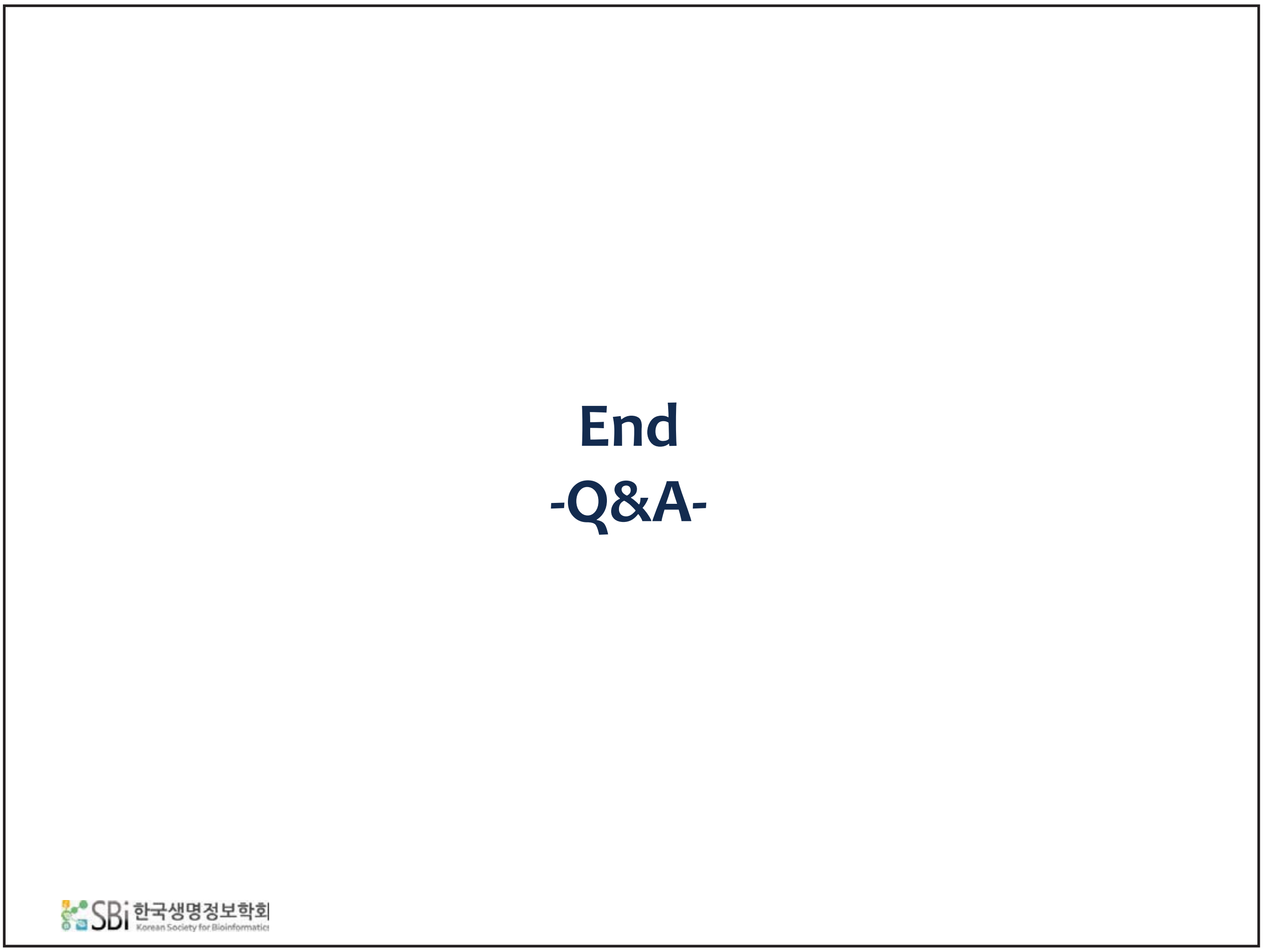




Encoder type	Drug structure	Standardized RMSE Median ± IQR
Deep baseline (DNN)	Fingerprints	0.122 ± 0.010
Bidirectional recurrent (bRNN)	SMILES	0.119 ± 0.011
Stacked convolutional (SCNN)	SMILES	0.130 ± 0.006
Self-attention (SA)	SMILES	0.112* ± 0.009
Contextual attention (CA)	SMILES	0.110* ± 0.007
Multiscale convolutional attentive (MCA)	SMILES	0.109* ± 0.009
MCA (prediction averaging)	SMILES	**0.104**** ± **0.005**

Contents

- PART1
  - Introduction to pharmacogenomics
    - Drug discovery and development
  - Key data sources
  - Representations of proteins, chemicals
- PART2
  - Studies related to pharmacogenomics based on machine learning



End

-Q&A-

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