User Manual

Table of Contents

User Manual	1
Introduction	2
Using the website	2
Analysis	3
Drug	
Gene	5
Disease	8
Batch prediction	
Help	
Download	

Introduction

Genetic disease genes are considered a promising source of drug targets. Most diseases are caused by more than one pathogenic factor; thus, it is reasonable to consider that chemical agents targeting multiple disease genes are more likely to have desired activities. This is supported by a comprehensive analysis on the relationships between agent activity/druggability and target genetic characteristics. The therapeutic potential of agents increases steadily with increasing number of targeted disease genes, and can be further enhanced by strengthened genetic links between targets and diseases. By using the multi-label machine-learning models for genetics-based drug activity prediction, we provide universal tools for prioritizing drug candidates.

To facilitate the use of the machine-learning prediction models, we developed a web server SCG-Drug (Systems Chemical Genetics-Drug, http://zhanglab.hzau.edu.cn/scgdrug) that allows a quick and intuitive access to the background information and predicted results.

Using the website

SCG-Drug is a web service that can help researchers to predict potential activities of drugs of interest with respect to their genetic information using the systems chemical genetics method.

Currently, SCG-Drug contains 5,759 agents, 703 diseases and 19,238 genes derived from various databases. By retrieving SCG-Drug, researchers can detect the complex relationships between agents, genes, and diseases, which are definitely helpful to evaluate the agent activity and druggability.

Analysis

The SCG-Drug web interfaces allow users to explore medicinal information related to a given drug or gene through three interfaces: "Drug", "Gene", "Disease" and "Batch prediction". By inputting the target information of any agents into SCG-Drug, one can use the established machine-learning models to predict the potential activities of the agents. In addition, all of the information for documented drugs (with normalized indications) and targets/genes (with normalized disease annotations) can be downloaded from the server. The data and the machine-learning models will be updated regularly.

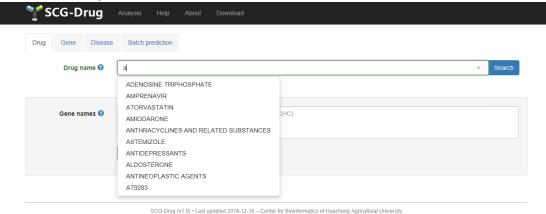
Drug

The "Drug" interface allows users to submit a single drug to retrieve target genes and potential activities of the query drug.

🌱 SCG-Drug	Analysis Help About Download	
Drug Gene Disea	ase Batch prediction	
Drug name 😯	Type in a drug name	Search
Gene names 🕄	Type in gene names, separated by comma.(e.g. SDC3,SDHC)	
	Predict	
	—	

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When you submit a single drug in the dropdowns, the drug will be searched in the database directly.



If it is unable to find any matches for the search term, the user will be asked to input the corresponding target genes of the drug.

🍸 S	CG-Dru	ıg	Analysis Help	About	Download					
Drug	Gene [Disease	Batch prediction							
	Drug nam	e 😧 🗍	abcd							Search
	Gene name	es 🕜	Type in gene name	es, separate	ed by comma.(e.g.	g. SDC3,SDHC)	;)			
			Predict							

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Then, the system will call the prediction module automatically.

				Sing	
Drug	Gene	Disease	Batch prediction		
	Drug n	ame 🕄	abcd		Search
	Gene na	mes 😯	SDC3, SDHC		
			Predict		

The predicted results will be present on the website and sorted by prediction score of MLKNN. And it can be downloaded as excel file.

🦿 sco	-Drug Analysis Help About Download	
Drug G	ene Disease Batch prediction	
C	rug name 9 abcd	Search
Ge	ne names 🛛 SDC3, SDHC	
	Predict	
	energia.	
	Total record count:667 Download as excel	
<< .	1 2 3 4 5 >	
NO.	Disease	MLKNN
1	LEUKEMIA	0.402121
2	NEOPLASMS	0.395604
3	LYMPHOMA	0.360891
4	HAMARTOMA SYNDROME, MULTIPLE	0.358616
5	SARCOMA	0.358502
6	LEUKEMIA, LYMPHOID	0.178994
7	LYMPHOMA, NON-HODGKIN	0.161389
8	LYMPHOMA, T-CELL	0.158737
9	LYMPHOMA, B-CELL	0.158521
10	LEUKEMIA, HAIRY CELL	0.146795

Gene

The "Gene" interface allows users to explore gene-related diseases and drugs only by submitting a gene name or an Entrez ID, which have been documented in the server. In addition, users can download overall information.

🍸 SCG-Drug	Analysis Help About Download	
Drug Gene Disease	Batch prediction	
Gene name 🚱	Type in a gene name or entrez ld	Search
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When you submit a single gene in the dropdowns, the drug will be searched in the database directly.

🍸 SCG-Drug	Analysis Help Abou	Download			
Drug Gene Disease	Batch prediction				
Gene name 🕄	abd			×	Search
	ABCA1				
	ABCC4				
	ABCB4				
	ABCB1				
	ABCA13				
	ABCA12				
	ABCG2				
	ABCG8				
	ABCC1				
	ABCA7				

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The searched result of gene will be present on the website.

,	Drug /	nalysis He	lp About	Download	
Orug Gene	Disease	Batch predict	ion		
Gen	e name 😯	ABCA1			Searc
Gene Infoma	ation				
Gene Infoma Gene name	ation Gene Entrez	d Summary			

The related disease will be present separately on the website and sorted by the druggability score. Meanwhile the related drugs will also be presented on the website on another page and sorted by the source of database. And they can be downloaded as excel file.

Re	Related diseases Related dru Total record count:97	igs		
	< < 1 2 3 4	5 > >> ± Disease Description	Source	Score 📀
1	GUILLAIN-BARRE SYNDROME	An acute inflammatory autoimmune neuritis caused by T cell- mediated cellular immune response directed towards peripheral myelin. Demyelination occurs in peripheral nerves and nerve roots. The process is often preceded by a viral or bacterial infection, surgery, immunization, lymphoma, or exposure to toxins. Common clinical marifestations include progressive weakness, loss of sensation, and loss of deep tendon reflexes. Weakness of respiratory muscles and autonomic dysfunction may occur. (From Adams et al., Principles of Neurology, 6th ed, pp1312-1314)	Clinvar; GAD; OMIM; Orphanet; HGMD; GWASdb; DisGeNET	33
2	WISKOTT-ALDRICH SYNDROME	A rare, X-linked immunodeficiency syndrome characterized by ECZEMA; LYMPHOPENIA; and, recurrent pyogenic infection. It is seen exclusively in young boys. Typically, IMMUNOGLOBULIN M levels are low and IMMUNOGLOBULIN A and IMMUNOGLOBULIN E levels are elevated. Lymphoreticular malignancies are common.	HGMD; DisGeNET	7
3	RETINAL DISEASES	NA	GAD; DisGeNET	3
4	RADIATION INJURIES	Harmful effects of non-experimental exposure to ionizing or non-ionizing radiation in VERTEBRATES.	GAD; DisGeNET	3
5	SUPRANUCLEAR PALSY, PROGRESSIVE	A degenerative disease of the central nervous system characterized by balance difficulties; OCULAR MOTILITY DISORDERS (supranuclear ophthalmoplegia); DYSARTHRIA; swallowing difficulties; and axial DYSTONIA. Onset is usually in the fifth decade and disease progression occurs over several years. Pathologic findings include neurofibrillary degeneration and neuronal loss in the dorsal MESENCEPHALON; SUBTHALAMIC NUCLEUS; RED NUCLEUS; Pallidum; dentate nucleus; and vestibular nuclei. (From Adams et al., Principles of Neurology, 6th ed, pp1076-7)	GAD; DisGeNET	3
6	BEHCET SYNDROME	Rare chronic inflammatory disease involving the small blood vessels. It is of unknown etiology and characterized by mucocutaneous ulceration in the mouth and genital region and uveitis with hypopyon. The neuro-ocular form may cause blindness and death. SYNOVITIS; THROMBOPHLEBITIS; gastrointestinal ulcerations; RETINAL VASCULITIS; and OPTIC ATROPHY may occur as well.	GAD; DisGeNET	3
7	GLOMERULONEPHRITIS	Inflammation of the renal glomeruli (KIDNEY GLOMERULUS) that can be classified by the type of glomerular injuries including antibody deposition, complement activation, cellular proliferation, and glomerulosclerosis. These structural and functional abnormalities usually lead to HEMATURIA; PROTEINURIA; HYPERTENSION; and RENAL INSUFFICIENCY.	GAD; DisGeNET	3
8	SMALL CELL LUNG CARCINOMA	A form of highly malignant lung cancer that is composed of small ovoid cells (SMALL CELL CARCINOMA).	GAD; DisGeNET	3
9	PULMONARY DISEASE, CHRONIC OBSTRUCTIVE	A disease of chronic diffuse irreversible airflow obstruction. Subcategories of COPD include CHRONIC BRONCHITIS and PULMONARY EMPHYSEMA.	GAD; DisGeNET	3
10	DIABETES COMPLICATIONS	Conditions or pathological processes associated with the disease of diabetes mellitus. Due to the impaired control of BLOOD GLUCOSE level in diabetic patients, pathological processes develop in numerous tissues and organs including the EYE, the KIDNEY, the BLOOD VESSELS, and the NERVE TISSUE.	GAD; DisGeNET	3



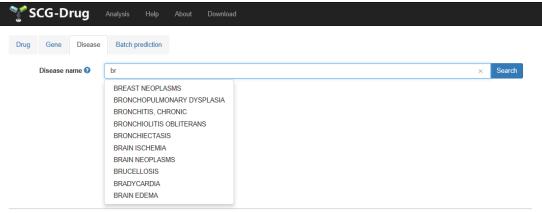
NO.	Drug name	Drug Description	Source
1	HMG COA REDUCTASE INHIBITORS	NĂ	DGIdb
2	ADENOSINE TRIPHOSPHATE	DB00171:An adenine nucleotide containing three phosphate groups esterified to the sugar moiety. In addition to its crucial roles in metabolism adenosine triphosphate is a neurotransmitter. [PubChem] & TTDS00350:Dietary shortage	Drugbank; DGIdb
3	PROBUCOL	DB01599:A drug used to lower LDL and HDL cholesterol yet has little effect on serum-triglyceride or VLDL cholesterol. (From Martindale, The Extra Pharmacopoeia, 30th ed, p993). & TTDS00278:Coronary artery disease	Drugbank; DGldb
4	GLYBURIDE	DB01016:Glyburide is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It belongs to the sulfonylurea class of insulin secretagogues, which act by stimulating β cells of the pancreas to release insulin. Sulfonylureas increase both basal insulin secretion and meal-stimulated insulin release. Medications in this class differ in their dose, rate of absorption, duration of action, route of elimination and binding site on their target pancreatic β cell receptor. Sulfonylureas also increase peripheral glucose utilization, decrease hepatic gluconeogenesis and may increase the number and sensitivity of insulin receptors. Sulfonylureas are associated with weight gain, though less so than insulin. Due to their mechanism of action, sulfonylureas may cause hypoglycemia and require consistent food intake to decrease this risk. The risk of hypoglycemia is increased in elderly, debilitated and manourished individuals. Glyburide has been shown to decrease fasting plasma glucose, postprandial blood glucose and glycosolated hemoglobin (HbA1c) levels (reflective of the last 8-10 weeks of glucose control). Glyburide appears to be completely metabolites, its incompleted in the liver. Although its metabolites are excreted in urine and feces in approximately equal proportions. The half-life of glyburide appears to be unaffected in those with a creatinine clearance of greater than 29 ml/min/1.73m ²	Drugbank; DGIdb

Disease

The "Disease" interface allows users to obtain relevant disease genes with druggability score, and database source by querying standardized disease descriptions of MeSH.

🍸 SCG-Drug	Analysis Help About Download	
Drug Gene Disease	Batch prediction	
Disease name 🕄	Type in a disease name s	Search
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When you submit a single disease name in the dropdowns, the drug will be searched in the database directly.



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The searched result of gene will be present on the website.

🍸 SCG-Drug 🛛	Analysis Help About	Download
Drug Gene Disease	Batch prediction	
Disease name 🕄	BREAST NEOPLASMS	Search
Disease Information		
Disease name		MeSH Description

The related drugs will be present separately on the website and sorted by the druggability score. Meanwhile the related genes will also be presented on the website on another page and sorted by the source of database. And they can be downloaded as excel file.

	lated drugs Related ge Total record count		
NO.	Drug Name	Drug Description	Source
1	111IN-HEGF	NA	TTD
2	177LU-AMBA	NA	TTD
3	17-DMAG	DB03080:	ClinicalTrials; TTD
4	2-METHOXYESTRADIOL	DB02342.2-Methoxyestradiol (2ME2) is a drug that prevents the formation of new blood vessels that tumors need in order to grow (angiogenesis). It has undergone Phase 1 clinical trials against breast cancers. Preclinical models also suggest that 2ME2 could also be effective against inflammatory diseases such as rheumatoid arthritis. [Wikipedia]	ClinicalTrials; Drugbank
5	99MTC-14 F7 MAB	DB05867:99mTc 14F7 Mab has strong anti tumor activity against myeloma cells in vivo. Growth inhibition and prolonged survival of the myeloma tumor were obtained as evidences of anti tumor effect after treatment with 99mTc 14F7 Mab.	Drugbank
6	ABIRATERONE ACETATE	NA	ClinicalTrials
7	ABT-888	NA	ClinicalTrials; TTD
8	AC480	NA	ClinicalTrials
9	ADH-1	DB05485:Adherex's biotechnology compound, ADH-1, targets N-cadherin, a protein present on certain tumor cells and established tumor blood vessels. ADH-1 is currently in clinical development in a combination program with a range of chemotherapeutic agents to investigate the synergistic effects noted in our preclinical models. At the end of 2006, the Company also completed patient enrollment in our single-agent Phase Ib/II and Phase II trials of ADH-1.	ClinicalTrials
10	AE37	NA	ClinicalTrials

R	lated drugs To	<u>;</u>	ted genes 4 count:936		
Ŀ	~ <	1 2	3 4 5 > >> 4		
NO.	Gene Name	Entrez Id	Gene Descriptor	Source	Score 😌
1	HSD17B3	3293	This isoform of 17 beta-hydroxysteroid dehydrogenase is expressed predominantly in the testis and catalyzes the conversion of androstenedione to testosterone. It preferentially uses NADP as cofactor. Deficiency can result in male pseudohermaphroditism with gynecomastia. [provided by RefSeq, Jul 2008]	Clinvar; GAD; OMIM; Orphanet; HGMD; DisGeNET	29
2	XRCC3	7517	This gene encodes a member of the RecA/Rad51-related protein family that participates in homologous recombination to maintain chromosome stability and repair DNA damage. This gene functionally complements Chinese hamster ins1SF, a repair-deficient mutant that exhibits hypersensitivity to a number of different DNA-damaging agents and is chromosomally unstable. A rare microsatellite polymorphism in this gene is associated with cancer in patients of varying radiosensitivity. Alternatively spliced transcript variants encoding the same protein have been identified. [provided by RefSeq, Jul 2008]	Clinvar; GAD; OMIM; HGMD; GWASdb; DisGeNET	28
3	HMMR	3161	The protein encoded by this gene is involved in cell motility. It is expressed in breast tissue and together with other proteins, it forms a complex with BRCA1 and BRCA2, thus is potentially associated with higher risk of breast cancer. Alternatively spliced transcript variants encoding different isoforms have been noted for this gene. [provided by RefSeq, Dec 2008]	Clinvar; GAD; OMIM; HGMD; GWASdb; DisGeNET	28
4	CDH1	999	This gene encodes a classical cadherin of the cadherin superfamily. Alternative splicing results in multiple transcript variants, at least one of which encodes a preproprotein that is proteolytically processed to generate the mature glycoprotein. This calcium-dependent cell-cell adhesion protein is comprised of five extracellular cadherin repeats, a transmembrane region and a highly conserved cytoplasmic tail. Mutations in this gene are correlated with gastric, breast, colorectal, thyroid and ovarian cancer. Loss of function of this gene is thought to contribute to cancer progression by increasing proliferation, invasion, and/or metastasis. The ectodomain of this protein mediates bacterial adhesion to mammalian cells and the cytoplasmic domain is required for internalization. This gene is present in a gene cluster with other members of the cadherin family on chromosome 16. [provided by RefSeq, Nov 2015]	Clinvar; GAD; OMIM; HGMD; GWASdb; DisGeNET	28
5	твхз	6926	This gene is a member of a phylogenetically conserved family of genes that share a common DNA-binding domain, the T-box T-box genes encode transcription factors involved in the regulation of developmental processes. This protein is a transcriptional repressor and is thought to play a role in the anterior/posterior axis of the tetrapod forelimb. Mutations in this gene cause ulnar-mammary syndrome, affecting limb, apocrine gland, tooth, hair, and genital development. Alternative splicing of this gene results in three transcript variants encoding different isoforms; however, the full length nature of one variant has not been determined. [provided by RefSeq, Jul 2008]	Clinvar; OMIM; Orphanet; HGMD; DisGeNET	27
6	TSG101	7251	The protein encoded by this gene belongs to a group of apparently inactive homologs of ubiquitin-conjugating enzymes. The gene product contains a coiled-coil domain that interacts with stathmin, a cytosolic phosphoprotein implicated in tumorigenesis. The protein may play a role in cell growth and differentiation and act as a negative growth regulator. In vitro steady-state expression of this tumor susceptibility gene appears to be important for maintenance of genomic stability and cell cycle regulation. Mutations and alternative splicing in this gene occur in high frequency in breast cancer and suggest that defects occur during breast cancer tumorigenesis and/or progression. [provided by RefSeq, Jul 2008]	Clinvar; OMIM; HGMD; GWASdb; DisGeNET	26
7	RB1CC1	9821	The protein encoded by this gene interacts with signaling pathways to coordinately regulate cell growth, cell proliferation, apoptosis, autophagy, and cell migration. This tumor suppressor also enhances retinoblastoma 1 gene expression in cancer cells. Alternative splicing results in multiple transcript variants encoding distinct isoforms. [provided by RefSeq, Nov 2009]	Clinvar; OMIM; HGMD; GWASdb; DisGeNET	26
8	RAD51C	5889	This gene is a member of the RAD51 family. RAD51 family members are highly similar to bacterial RecA and Saccharomyces cerevisiae Rad51 and are known to be involved in the homologous recombination and repair of DNA. This protein can interact with other RAD51 paralogs and is reported to be important for Holiday junction resolution. Mutations in this gene are associated with Fanconi anemia-like syndrome. This gene is one of four localized to a region of chromosome 17q23 where amplification occurs frequently in breast tumors. Overexpression of the four genes during amplification has been observed and suggests a possible role in tumor progression. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Jul 2013]	Clinvar; GAD; OMIM; DisGeNET	18
9	NQO1	1728	This gene is a member of the NAD(P)H dehydrogenase (quinone) family and encodes a cytoplasmic 2-electron reductase. This FAD-binding protein forms homodimers and reduces quinones to hydroquinones. This protein's enzymatic activity prevents the one electron reduction of quinones that results in the production of radical species. Mutations in this gene have been associated with tardive dyskinesia (TD), an increased risk of hematotoxicity after exposure to benzene, and susceptibility to various forms of cancer. Altered expression of this protein has been seen in many turnors and is also associated with Alzheime's disease (AD). Alternate transcriptional splice variants, encoding different isoforms, have been characterized. [provided by RefSeq, Jul 2008]	GAD; OMIM; HGMD; DisGeNET	16
10	ERBB4	2066	This gene is a member of the Tyr protein kinase family and the epidermal growth factor receptor subfamily. It encodes a single-pass type I membrane protein with multiple cysteine rich domains, a transmembrane domain, a tyrosine kinase domain, a phosphotidylinositol-3 kinase binding site and a POZ domain binding molff. The protein binds to and is activated by neuregulins and other factors and induces a variety of cellular responses including mitogenesis and differentiation. Multiple proteolytic events allow for the release of a cytoplasmic fragment and an extraoellular fragment. Mutations in this gene have been associated with cancer. Alternatively spliced variants which encode different protein isoforms have been described; however, not all variants have been fully characterized. [provided by RefSeq, Jul 2008]	HGMD; GWASdb; DisGeNET	11

Batch prediction

The system allows the user to upload a file on the "Batch prediction" interface, in which an agent and corresponding targets are in a single row and the terms in each row are separated by tabs, along with an email address to which the predicted activities of the agents will be sent. Offline prediction automatically starts, and the predicted results will be sent to the user via e-mail.

🍸 sa	CG-D	rug	Analysis	Help	About D	ownload				
Drug	Gene	Disease	Batch p	prediction						
		Email	Type in y	our email a	ldress					
	Upload	i file 😌	Browse. Only text Fi	No file ile is allowe						
			Submit	Downloa	d a template					

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Help

The "Help" interface presents users useful information about the website Server Access and several Frequently Ask Questions (FAQ).

SCG-Drug Analysis Help About Download

Help

Web Server Access

The SCG-Drug web interfaces allow users to explore medical genetic information related to a given drug, disease or gene through four interfaces. Drug, Gene, Disease and Batch prediction

The Drug interface allows users to submit a single drug or a file containing multiple drugs to explore their potential activities. For example, when a user submits a single drug that was shown in the dropdowns, it will search the database directly for this drug. If it is unable to find any matches for the search term, it will ask the user to input the corresponding target genes of the drug. Then, it will call the prediction module.

The Gene interface allows users to explore gene-related diseases and drugs only by submitting a gene name or an Entrez ID, which are included in the server. In addition, users can download overall information

The Disease interface allows users to obtain relevant disease genes with druggability score, and database source by querying standardized disease descriptions of MeSH.

Alternatively, the system allows the user to upload a file on the Batch prediction interface, in which an agent and corresponding targets are in a single row and the terms in each row are separated by tabs, along with an email address to which the predicted activities of the agents will be sent. Offline prediction automatically starts, and the predicted results are sent to the user via e-mail.

FAQ

What is the goal of SCG-Drug?

To help you to predict potential activities of drugs of interest with respect to their genetic information.

What types of drug names/symbols should I use as input?

Any drug names. But there are total 5,759 drugs included in SCG-Drug database. The drug names are listed in the drugs.txt. Therefore, when you submit a drug name that was listed in the text, SCG-Drug will search the database directly for this drug. If it is unable to find any matches for the search term, it will ask you to input the corresponding target genes of the drug. Then, it will call the prediction module.

What types of gene names/symbols should I use as input?

When you want to get the related information of genes at Gene interface, you could type in HGNC gene symbols or Gene Entrez ID. But when you want to predict a drug's potential activities at Drug interface, you should only type in HGNC gene symbols. Or you will get incorrect results!

What types of diseases should I use as input?

The "Disease" interface allows users to obtain relevant disease genes with druggability score, and database source by querying standardized disease descriptions of MeSH.

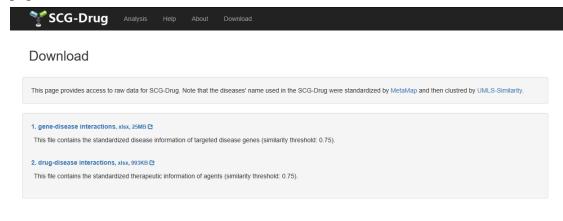
What kind of supported format file should I upload?

The upload file is a TAB delimited file without comment line or header. The first column is a drug name, the following columns are gene symbols:

drug1 IL12A IL10 SLC6A4 CTLA4 drug2 AGGF1 BRK1

Download

Users can obtain the information for documented drugs (with normalized indications) and targets/genes (with normalized disease descriptions) from "Download" page.



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