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Supplemental Information

Genetic Interaction-Based Biomarkers Identification for Drug Resistance and Sensitivity in Cancer Cells

Yue Han, Chengyu Wang, Qi Dong, Tingting Chen, Fan Yang, Yaoyao Liu, Bo Chen, Zhangxiang Zhao, Lishuang Qi, Wenyuan Zhao, Haihai Liang, Zheng Guo, and Yunyan Gu

Supporting information

Table S1. Statistics of the SV and SL interactions from other studies

Source (PMID)	SL	SV
27438146	107	
26427375	843	
27453043	5065	
24025726	98	
23728082	100	
26516187	19952	
24104479	200	
26227665	23	40
28319113	168	10
26451775	1309	
Boettcher et al.	57	80
28481362	95	178
26781748	846	
27557495	464	
23563794	211	199
28319085	30	

Table S2. Quantitative scores assigned to SV and SL according to the experimental methods annotated by evidence sources

Method	Score
Mutant & Mutant	0.9
CRISPR	0.9
Low-throughput	0.8
RNA interference & Mutant	0.75
Bi-specifie RNA interference	0.5
RNA interference & Drug inhibition	0.5
High-throughput	0.5

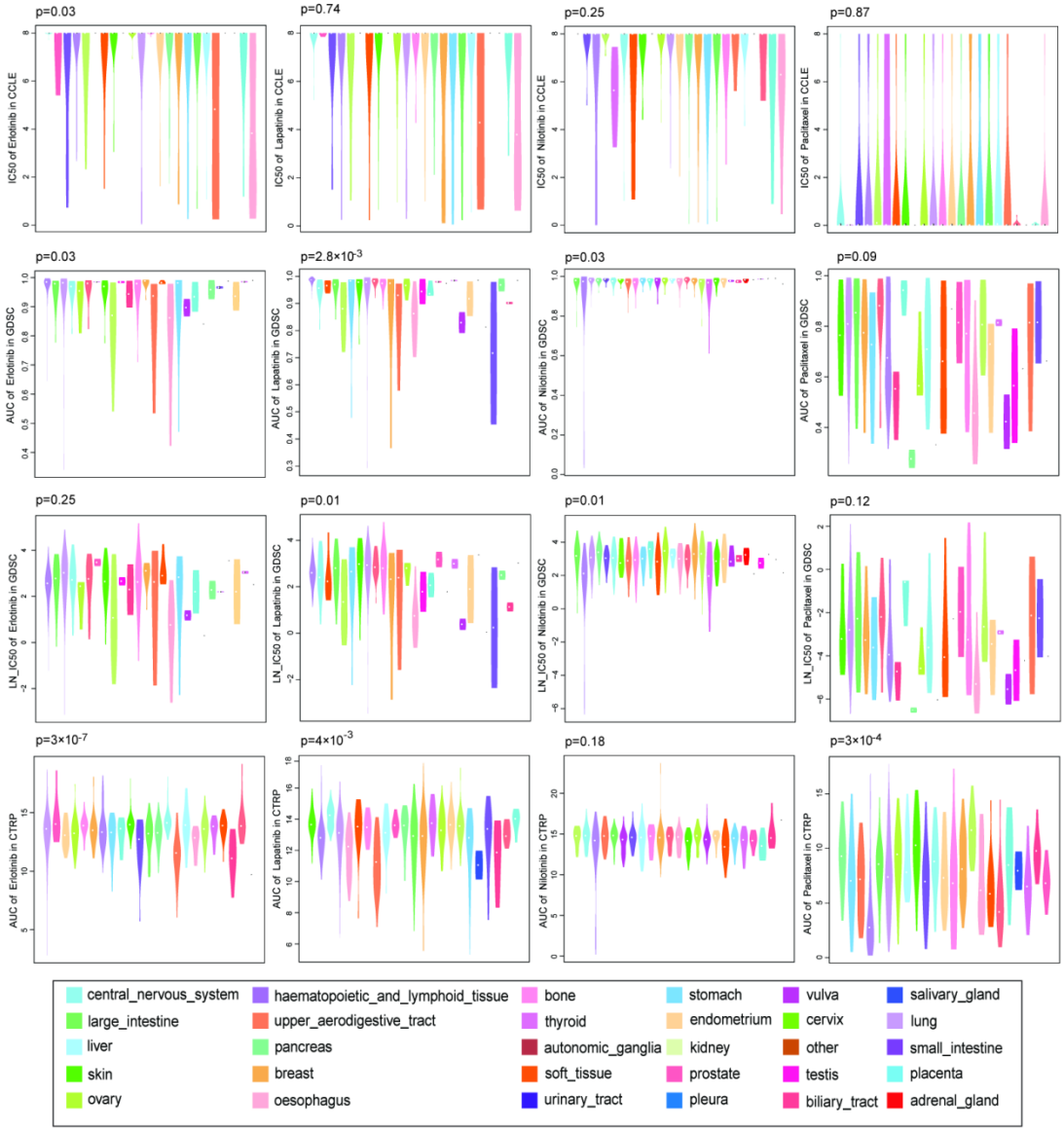


Figure S1. Distribution of drug sensitivity scores among tissues from CCLE, GDSC and CTRP.

Analysis of Variance(ANOVA) was used to test whether the the drug sensitivity score are different among kinds of tissue specific cells.

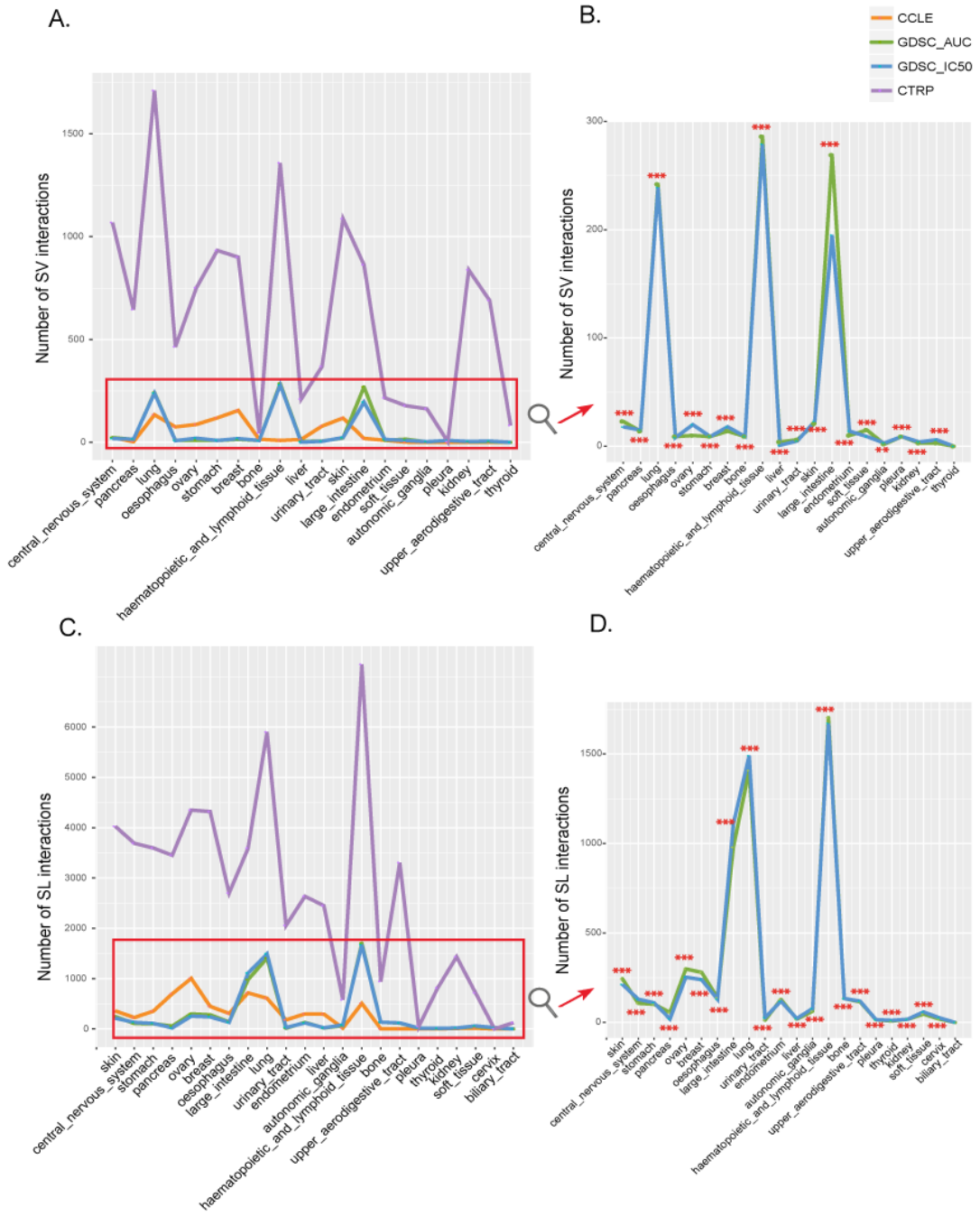


Figure S2. Statistics of the SV and SL interactions in tissue-specific cell lines. (A) Statistics of SV interactions related to drug resistance in 20 tissues. (B) Statistics of SV interactions identified by GDSC (AUC) and GDSC (LN_IC50). Red asterisks represent significant overlapping of SV interactions between GDSC (AUC) and GDSC (LN_IC50) (*P* <0.001, hypergeometric test). (C) Statistics of

SL interactions related to drug sensitivity in 22 tissues. (D) Statistics of SL interactions identified by GDSC (AUC) and GDSC (LN_IC50). Red asterisks represent significant overlapping of SL interactions between GDSC (AUC) and GDSC (LN_IC50) (*P* <0.001, hypergeometric test).

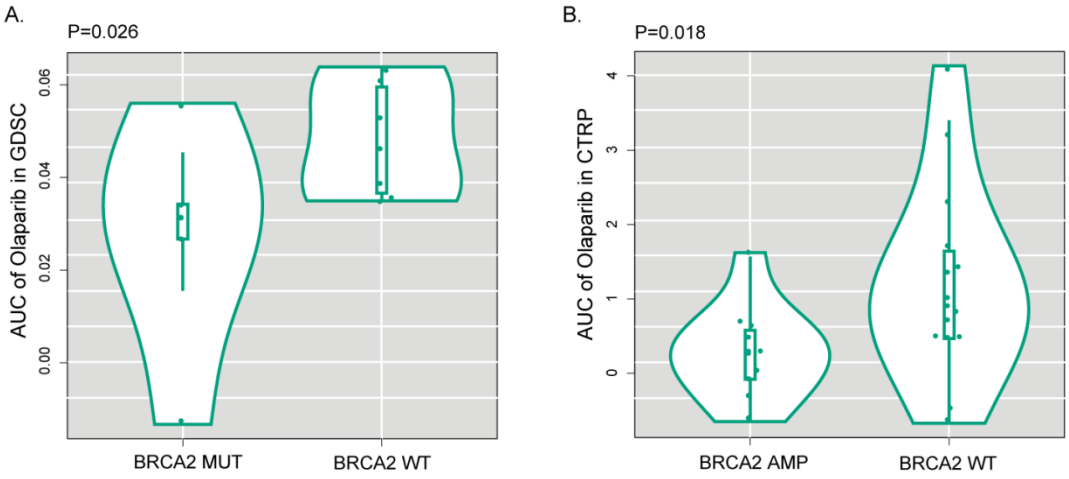


Figure S3. *BRCA2* alterations were related to olaparib sensitivity in cancer cell lines. (A) Cell lines with *BRCA2* mutations are sensitive to olaparib in GDSC. The difference of AUC between the cell lines with or without mutations in *BRCA2* was tested by one-sided Wilcoxon rank sum test (*P*=0.026). (B) Cell lines with *BRCA2* mutations are sensitive to olaparib in CTRP (*P*=0.018, Wilcoxon rank sum test).

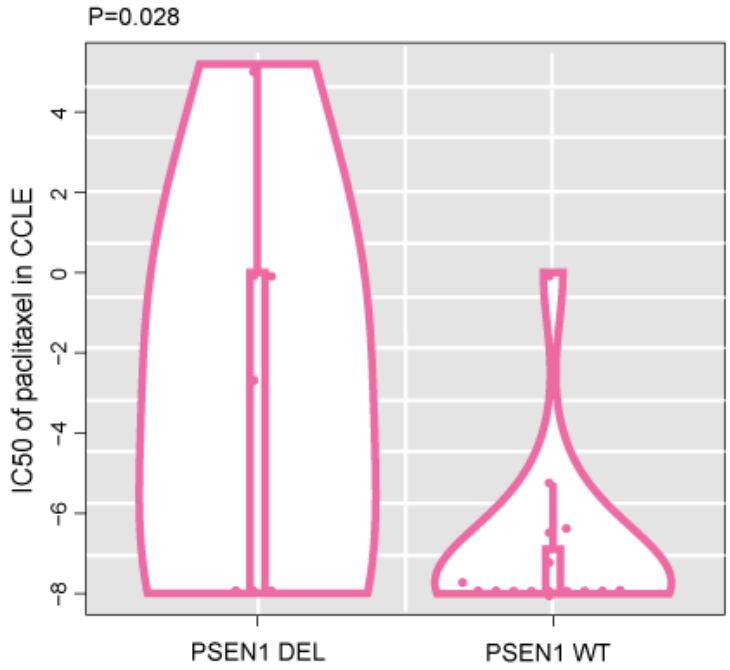


Figure S4. ***PSEN1*** **deletions were related to paclitaxel resistance in CCLE (*P*=0.028, Wilcoxon rank sum test).**

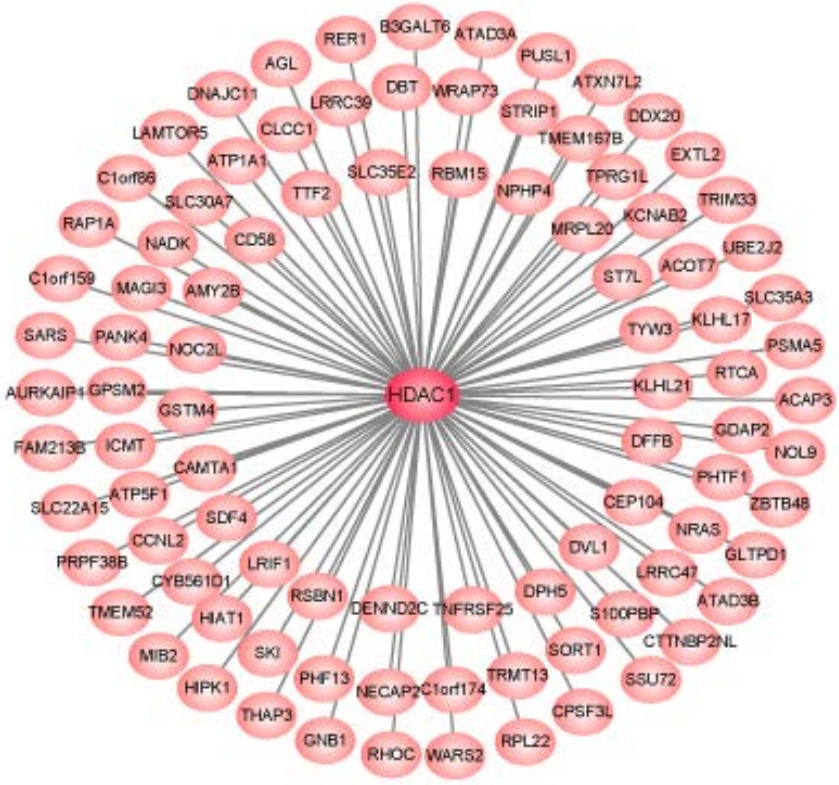


Figure S5. ***HDAC1*** **subnetwork derived from the SV network.**

Dark pink node represents HDAC1 and light pink nodes represent the partner genes of HDAC1 in SV network.

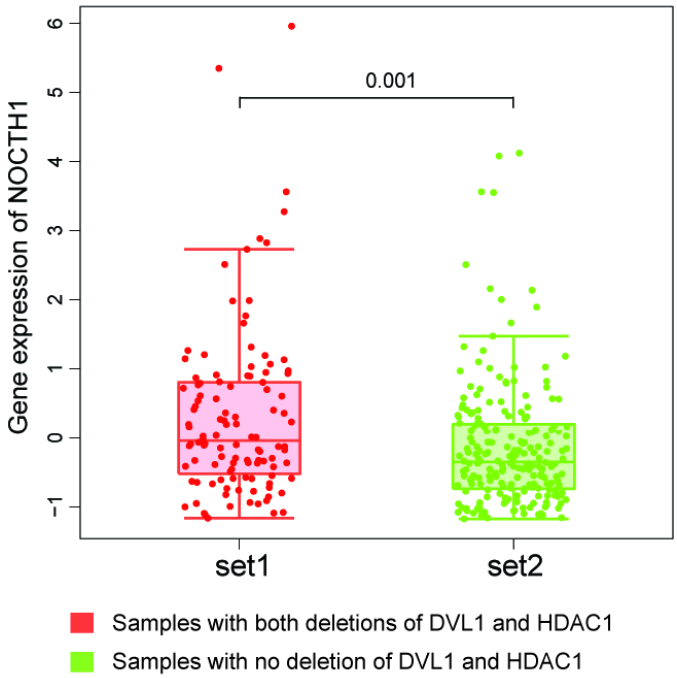


Figure S6. Distribution of ***NOTCH1*** **expression values in liver hepatocellular carcinoma (LIHC). Red points represent the samples with both deletions of DVL1 and HDAC1. Green points represent the samples with no deletion of DVL1 and HDAC1. The difference of expression between the samples with or without deletion in DVL1 and HDAC1 was tested by T-test (*P*=0.001).**

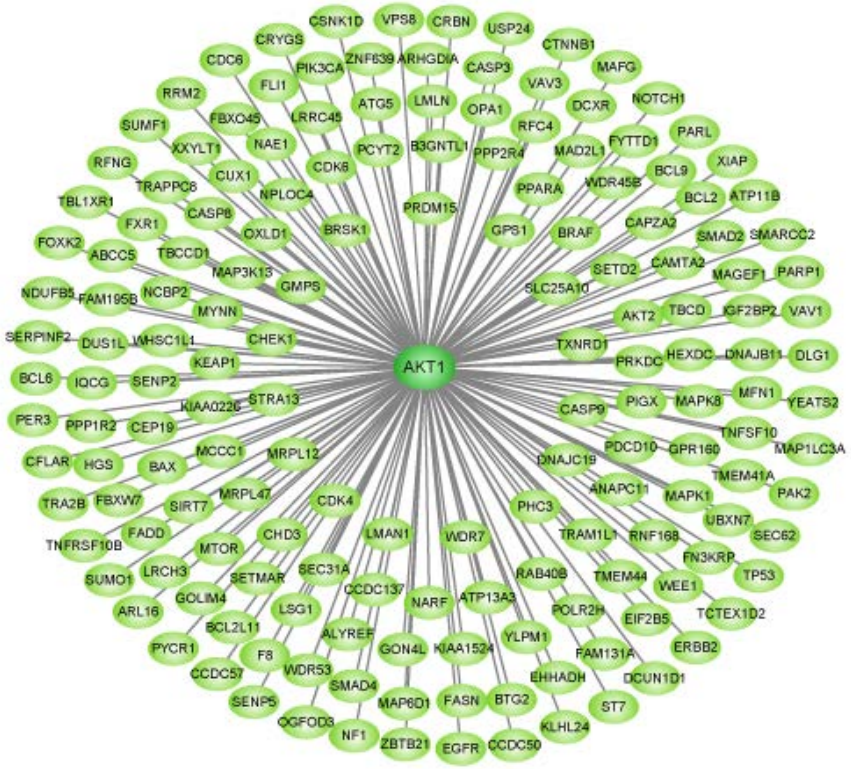


Figure S7. *AKT1* subnetwork derived from the SL network. Dark green node represents AKT1 and light pink nodes represent the partner genes of AKT1 in SL network.

Supplementary methods

Information for other studies

SV or SL interactions were integrated from 16 studies (Table S1). The first main source of data was manually curated SV and SL interactions from a CRISPR screen.[1-4] SV and SL interactions identified from other high-throughput screening experiments, such as shRNA, bispecific shRNA, and combinatorial RNAi/drug screens, were also utilized.[5, 6] Second, several SV and SL interactions were obtained using bioinformatics statistical methods, such as permutation and t-test statistics.[7, 8] Ye *et al.* ranked novel cancer-driving synthetic lethal gene pairs using the Chi-square test [9], and *Kranthi et al.* [10] applied network information centrality . Third, additional SV and SL interactions were identified by applying the DAISY algorithm. DAISY combines multiple approaches into a single screen to identify SL interactions.[11] Several studies have identified SL interactions based on mutual exclusivity of gene alterations accompanied by high-throughput screening experiments, such as shRNA screens.[12, 13] In addition, previous studies have generated strategies to identify SV and SL interactions from other species relying on genetic homology or structure.[14, 15] Finally, SL interactions from SLDB were included in the present study.[16]

Integrative confidence scores

The SV and SL interactions analyzed in the present study were obtained from different types of sources, including computational predictions, biochemical assays, and text mining results. In addition, biochemical assays were based on different experimental technologies and platforms, such as shRNA, CRISPR and drug inhibition. Because multiple types of evidence are conducive to the identification of SV (SL) interactions, an integrative confidence score combining scores from these evidence sources can provide an overall estimation of the reliability of a SV (SL)

interaction. In principle, we supposed that (i) the contribution of experimental evidence to the confidence score is more significant than the contribution of predictive algorithms or text mining and that (ii) the SV (SL) interactions supported by more evidence sources should be beneficial to the confidence score. The scoring procedures were divided into two steps, i.e., quantification and integration. A large number of SV (SL) interactions collected from other studies had only qualitative annotation evidence (such as “high-throughput” or “low-throughput”), or technological descriptions of wet-lab experiments (such as “CRISPR screening” or “shRNA screening”). Thus, it was necessary to assign quantitative scores to these SV (SL) interactions before the calculation of integrative scores. Similar to the scoring scheme from SLDB, the quantitative scores were assigned based on the experimental methods (Table S2). For instance, “Mutant & Mutant” indicated that the pair of SV (SL) genes were disturbed by transgenic or genetic deletions. Moreover, “RNA interference & Mutant” indicated that one gene was perturbed by RNAi and that the other was perturbed via mutation. In summary, the SV (SL) interactions obtained from low-throughput experiments were considered to be more reliable than the results from high-throughput experiments due to the lower false positive rate. Therefore, a higher confidence score was assigned to low-throughput evidence than high-throughput evidence. Compared to other RNA interference experiments (such as shRNA, siRNA and dsRNA), the CRISPR screen had lower off-target effects, which were assigned higher confidence scores similar to mutation and transfection experiments (Table S2).

The following formula was utilized to combine the individual scores:

$$s = 1 - \prod_{i-1}^{n} (1 - p_i)$$

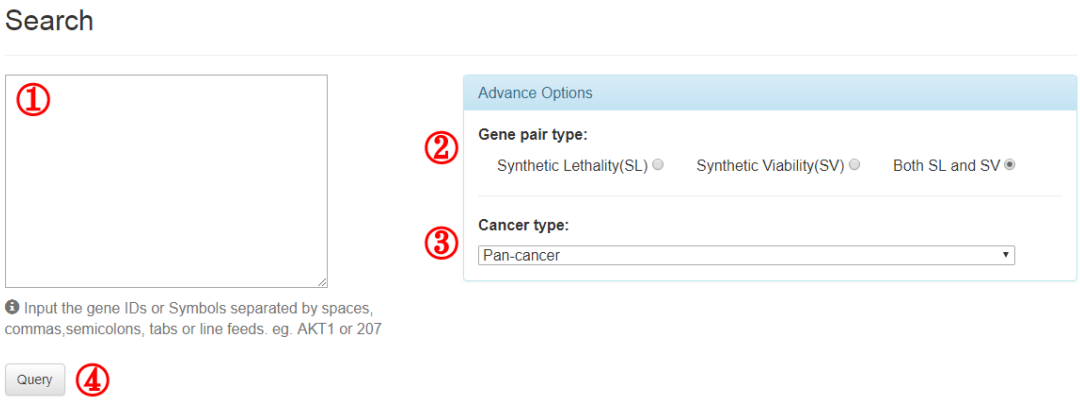
where s represents the integrative score corresponding to the experimental evidence; p_i is the individual score; and n is the total number of experimental supporting evidence.

Database guide

The URL of the database is http://www.medsysbio.org/CGIdb.

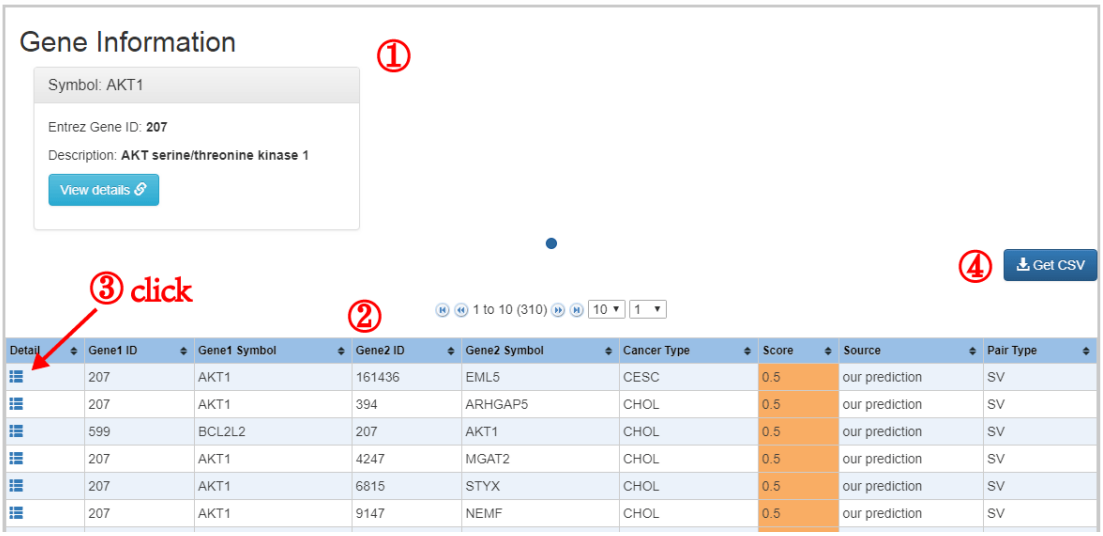
1. Search

In the Search page, users can key in gene ID or symbol to perform a search of corresponding genetic interactions (1), which can be further screened by advance options (2-3).



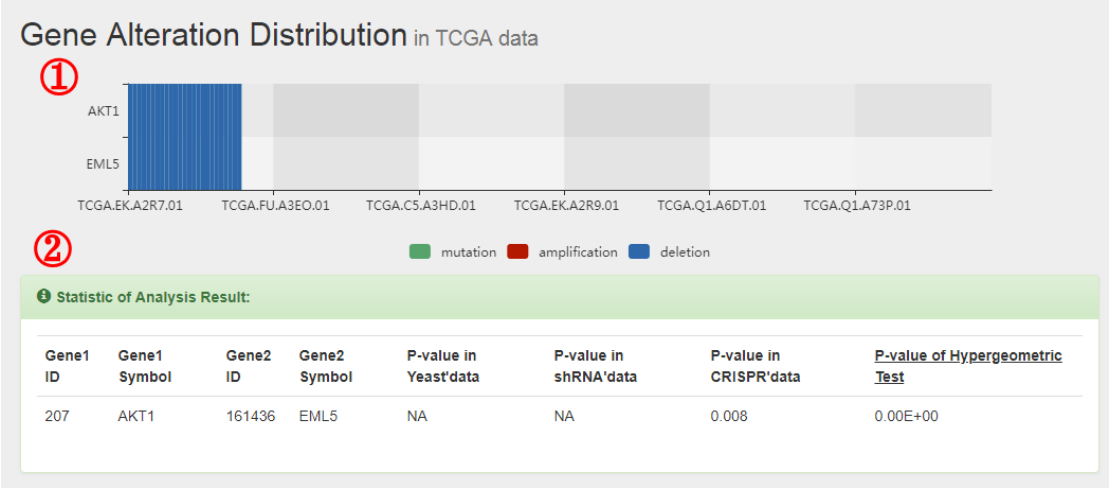
2. Search Results

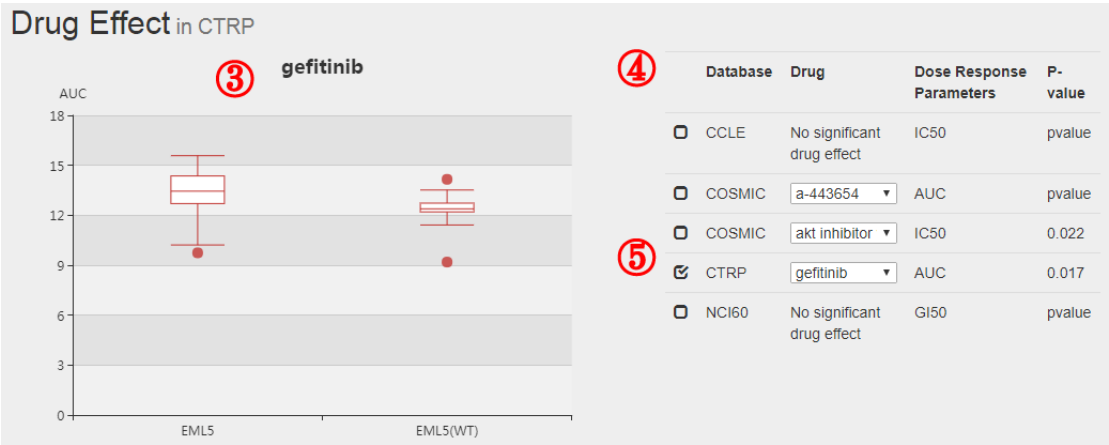
When user queries the genes to the database, the CGIdb will provide search results on this page. The search results are divided into two main parts: (i) information box, which includes the basic information of your selected gene, and the external link to NCBI for more detail (1); (ii) The SL/SV pairs list is provided on the bottom of page (2). And user can click the button (3) to view the details of the gene pairs, including drugs effect and protein-protein interaction network. The results can be exported as CSV format (4).

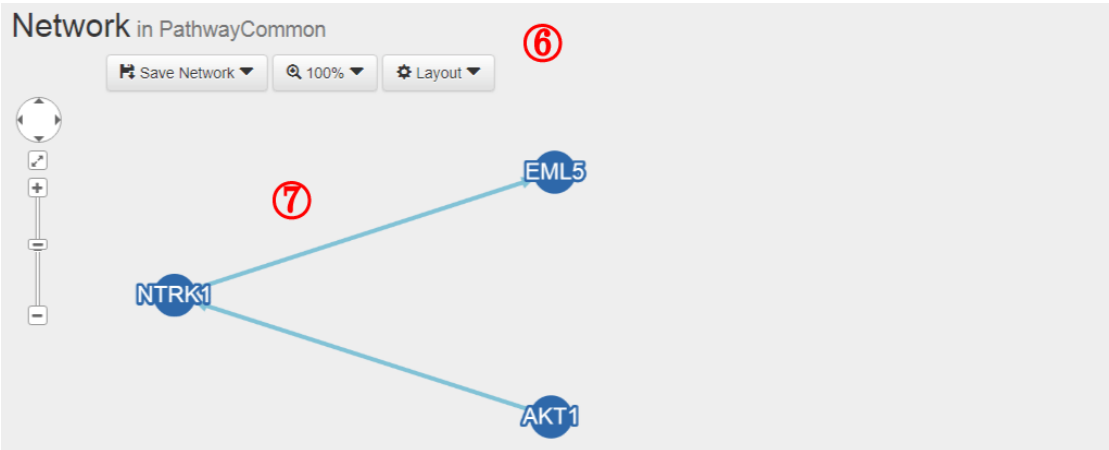


3. Search Details

The details of results are divided in three parts. (i) Distribution of gene alteration in TCGA data are provided. CGIdb shows the altered samples (mutation and copy number alteration) of genes and statistic of analysis results (1-2). (ii) In the middle of page, user can get results of the drug effect. In cell lines with drug targeting the searching gene, a one-sided Wilcoxon rank sum test is used to test whether the drug response measures, such as IC50, are significantly higher or lower in cells lines with and without alterations of the partner genes in the genetic interaction (3). Detailed information about the pharmacodynamic data are shown in the right table (4-5). (iii) On the bottom of the detail page, CGIdb provides the visualized network of protein-protein interactions derived from PathwayCommon. User can export network as jpg or png file (6-7).



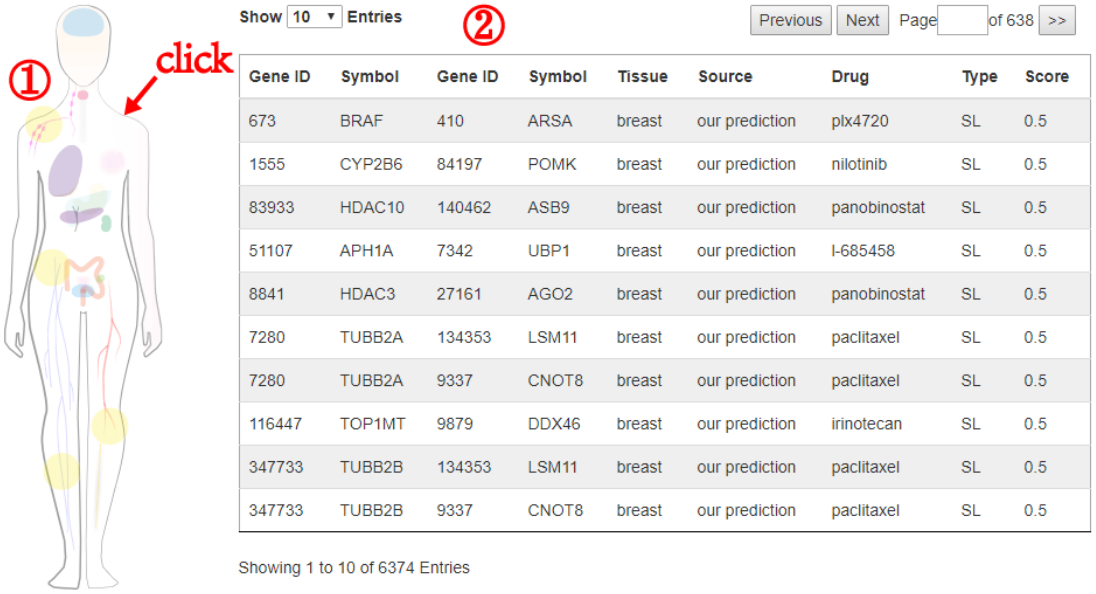




4. Browse

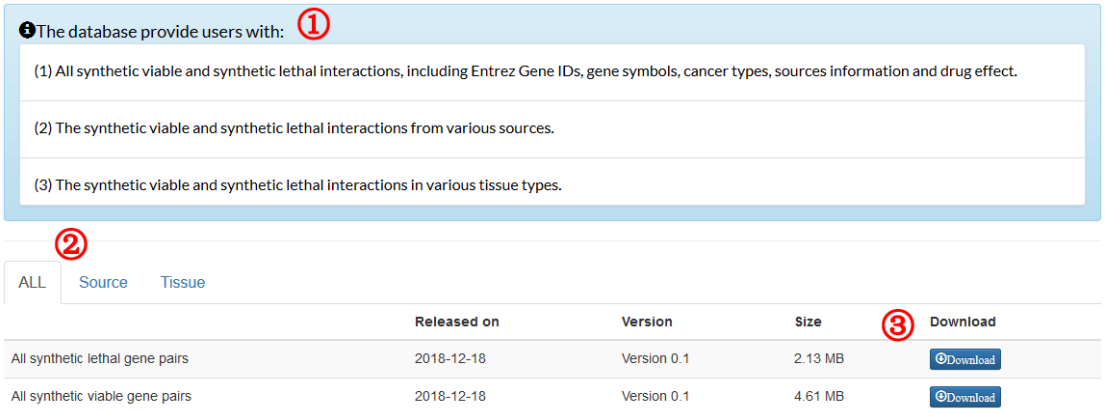
In the Browse page, users can easily filter SV and SL pairs classified by tissue types. The human body on the left includes optional tissue types (1). Click on the tissue on the model to filter the genetic interactions of the tissue. The detailed results are

showed in the right table (2).



5. Data

In the data page, users can download or upload data, We provide all SV and SL pairs, which are classified by different sources and tissue types (1-3).



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