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VARIDT 1.0: variability of drug transporter database

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ABSTRACT

The absorption, distribution and excretion of drugs are largely determined by their transporters (DTs), the variability of which has thus attracted considerable attention. There are three aspects of variability: epigenetic regulation and genetic polymorphism, species/tissue/disease-specific DT abundances, and exogenous factors modulating DT activity. The variability data of each aspect are essential for clinical study, and a collective consideration among multiple aspects becomes crucial in precision medicine. However, no database is constructed to provide the comprehensive data of all aspects of DT variability. Herein, the *Variability of Drug Transporter Database* (VARIDT) was introduced to provide such data. *First*, 177 and 146 DTs were confirmed, for the first time, by the transporting drugs approved and in clinical/preclinical, respectively. *Second*, for the confirmed DTs, VARIDT comprehensively collected all aspects of their variability (23 947 DNA methylations, 7317 noncoding RNA/histone regulations, 1278 genetic polymorphisms, differential abundance profiles of 257 DTs in 21 781 patients/healthy individuals, expression of 245 DTs in 67 tissues of human/model organism, 1225 exogenous factors altering the activity of 148 DTs), which allowed mutual connection between any aspects. Due to huge amount of accumulated data, VARIDT made it possible to generalize characteristics to reveal disease etiology and optimize clinical treatment, and is freely accessible at: https://db.idrblab.org/varidt/ and http://varidt.idrblab.net/.

INTRODUCTION

Drug transporter (DT) is acknowledged to be one of the main determinants governing drug absorption, excretion, and, in many cases, the extent of drug entry into target organs (1). Therefore, the variability of DTs has attracted considerable attention and widespread interest (2–4). There are three aspects of variability: (a) epigenetic regulation and genetic polymorphism of DT that are key in drug resistance (5) and clinical treatment optimization (6); (b) species-, tissue- and disease-specific DT abundances that are vital in bridging preclinical study with clinical trial (7), balancing efficacy and safety (8) and predicting disease-drug interaction (9), respectively; (c) exogenous factors (environmental substance, dietary constituent, bio/mycotoxin, pharmaceutical excipient/chemical, *etc*.) modulating DT activity and altering the disposition of DT's endogenous substrate/transported drugs (10,11). These variability data are essential for preclinical and clinical studies (1,12), and the accumulation of such data can lay the foundation for *big data*-driven precision medicine (13–16).

Due to the extreme complexity of drug disposition in living organisms, the interplays among different aspects of DT variability attracts great interest and have emerged to be promising research directions (5,17,18). Particularly, one of the common mechanisms of cancer multidrug resistance (MDR) is the *overexpression* of particular efflux DTs (18) or *low abundance* of some uptake DTs (5) in cancer cells, and thus, several strategies (based on the interplays between the abnormal abundances of DT proteins and other aspect of variability) have been proposed to reverse cancer MDR successfully (5,18). These strategies include the discovery of *exogenous chemical* to inhibit the efflux of certain DT (17–19), the *demethylation* of corresponding DTs (5) or regulation of *histone acetylation* to restore DT abundances (20), and the *combination* of the multiple strategies reported above (21). In other words, besides the key role played by each aspect of DT variability in clinical study (1,12), the interplays among different aspects become increasingly impor-

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tant, which makes the variability data of multiple aspects essential for revealing disease etiology and further optimizing clinical treatment.

To date, a variety of databases have been developed to provide DT-related data, the majority of which are still active and are freely accessible. Some of these databases (including UniProt (22), PDB (23), KEGG (24), ChEMBL (25), DrugBank (26) and TTD (27)) contain transporter information as part of a broader collection of biological and pharmacological data, and some others (including TCDB (28), TransportDB (29), HMPAS (30) and METscout (31)) include general classification and categorization for human transporters. Since the above databases do not focus on describing DT variability, several databases are designed to provide (i) the association between disease and the genetic polymorphism of a single transporter (like ABCA4Database (32) and SCN1A Variant Database (33)) or transporters (like PharmGKB (34), IUPHAR-DB (35), OMIM.org (36) and SLC TABLES (37)) or (ii) exogenous chemicals modulating the activity of ∼50 DTs (like UCSF-FDA (38), Transformer (39) and Metrabase (40)). However, few epigenetic regulation data of DTs (DNA methylation, histone modification and noncoding RNA regulation) are provided by current available knowledge bases, and no database has been constructed to simultaneously describe the multiple aspects of variability for DT(s). Due to the great importance of the interplay among different variability aspects (as was discussed in the previous paragraph) and the *big data* of variability that is essential for precision medicine (13,41), it is crucial to develop a new database that comprehensively describes all aspects of DT variability.

In this study, an open-accessible database, *Variability of Drug Transporter Database* (VARIDT) was introduced. *First*, a comprehensive literature review on all (>1800) drugs approved by the U.S. FDA and >1000 drugs in clinical trial or preclinical study was conducted. Different from the small number of DTs (∼20) that were well characterized in previous publication (42), 177 DTs were confirmed, for the first time, to transport approved drugs, and 146 DTs were to transport drugs in clinical/preclinical study. *Second*, for these newly confirmed DTs, VARIDT comprehensively provided all three aspects of their variability (a: epigenetic regulation and genetic polymorphism of DT; b: species-, tissue- and disease-specific protein abundance of DT; c: exogenous factors modulating DT activity; as shown in Figure 1), which allowed the mutual connection or interplay between any two aspects and could thus facilitate the study of disease etiology and the optimization of clinical treatment.

FACTUAL CONTENTS, DATA ACCESS AND INFORMATION RETRIEVAL

Confirmation and collection of DTs by comprehensive literature review

The DTs that were collected in this study were confirmed by the drugs that are of clinical importance (all drugs were either approved or in clinical/preclinical test). Particularly, a comprehensive literature review on all the drugs that were approved by the U.S. FDA (1875 drugs collected from FDA website) and 1268 drugs that were in clinical/preclinical test (collected from *ClinicalTrials.gov* and TTD (43)) was conducted to confirm their corresponding DT by searching the PubMed. As a result, 177 and 146 DTs were confirmed to transport 585 approved drugs and 246 clinical/preclinical drugs, respectively (57 out of these above DTs were able to transport both approved and clinical/preclinical drugs, which resulted in a total of 266 DTs confirmed by the drugs of clinical importance). These 266 DTs belonged to diverse transporter families (38 families in total defined by the TCDB (28)), and the *top-5* popular DT families were *Major Facilitator* (55 DTs), *ATP-binding Cassette* (24 DTs), *Mitochondrial Carrier* (18 DTs), *Neurotransmitter:sodium Symporter* (17 DTs) and *Amino Acid/auxin Permease* (16 DTs). The affinities of experimentally assessed kinetic parameters based on *Michaelis–Menten* steady-state analysis between 151 drugs (121 approved and 30 clinical trial) and 78 DTs in 186 types of cell line were also collected via literature review and were provided in the VARIDT.

Moreover, since the discovery of a new drug that hitchhiked on a transporter was inspired frequently by the corresponding endogenous substrate of that transporter (44), the transporters with endogenous substrates were considered to be more feasible in becoming a DT than those without (44). This made these transporters potential DTs (PDTs). Herein, the endogenous substrates of all human transporters (769 in total collected from TCDB (28)) were thus systematically reviewed and collected. In addition to the 266 DTs that were confirmed by at least one drug of clinical importance, 150 PDTs were further identified to transport 118 endogenous substrates. The transporter families that were covered by these 150 PDTs were also very diverse (33 families in total), and the *top-5* popular PDT families included the *Drug/metabolite Transporter* (18 PDTs), *Mitochondrial Carrier* (18 PDTs), *Major Facilitator* (16 PDTs), *Voltage-gated Ion Channel* (14 PDTs), and *Monovalent Cation:proton Antiporter-1* (13 PDTs). The biological function of all DTs and PDTs was provided, and the multiple aspects of DT variability were further collected for a total of 416 DTs and PDTs.

As an emerging area in current DT researches, the role of a given DT in the 'handling' of a range of endogenous metabolites (45) was frequently discovered using (i) *in vivo* DT knockout mice/rats (46), (ii) cell lines over/low expressing DT (47) or (iii) clinical data of the patients with DT polymorphisms (48). To collect such valuable data on endogenous metabolites for each DT, a comprehensive literature review on all DTs was conducted by searching the PubMed, which identified 73 DTs with endogenous metabolite available. Among these 73 DTs, 24 (32.9%), 30 (41.1%) and 7 (9.6%) were discovered by *in vivo* DT knockout mice/rats, cell lines over/low expressing DT, and clinical data of the patient with DT polymorphisms, respectively. All these data were fully downloadable and could be viewed in the page of 'Drug Transporter (DT) Information'.

Epigenetic regulations and genetic polymorphisms of DTs

Epigenetic regulation of DT was one of the key mediators of drug resistance/toxicity in diseases such as cancer and infection (5,49), which included DNA methylation, histone modification and noncoding RNA (ncRNA) regulation (50,51).

Figure 1. Multiple aspects and sub-aspects of variability described in VARIDT. (**A**) ERGPDT (red): epigenetic regulations and genetic polymorphisms of DT; (**B**) DSTSPA (dark blue): disease-, species- and tissue-specific protein abundance of DT; (**C**) EFMDTA (gray): exogenous factors modulating DT activity. The leaf of the corresponding sub-aspect indicated its typical/potential application.

Overexpression of efflux DTs in the acquired resistance to cancer therapy was reported to be closely associated with DNA methylation (52) and histone acetylation (53), and the ncRNAs were found to sensitize the carcinoma cells to chemotherapy by downregulating DT expression (54,55). Moreover, the genetic polymorphisms of a DT could alter its function, which, in turn, significantly affected the pharmacokinetics of its transporting drug (6). Thus, knowledge of both the epigenetic regulation and genetic polymorphism of DTs were important (shown in Figure 1) for understanding the interindividual variations of treatments (6,56), guiding the optimization of medical products (57), and realizing the promise of precision medicine (58).

Since the epigenetic regulation information of all DTs was largely dispersed in the literature, PubMed database was systematically searched for their corresponding DNA methylation, histone modification and ncRNA regulation using the combination of the keywords 'methylation'/'histone modification'/'microRNA'/'miR'/'lncRNA'/'noncoding RNA' and the name/synonyms of each DT/PDT. The discovered publications were assessed manually to retrieve any epigenetic regulation data of DTs. The collected data included the epigenetic types (DNA methylation, histone acetylation/methylation, ncRNA regulation, *etc.*); the location, prevalence, resulting alteration in RNA/protein expression and detail description of each epigenetic phenomenon; the experimental methods (microarray, proteomics, immunohistochemistry, etc.) and materials (various disease cell lines, tissues, *etc.*) adopted to validate each phenomenon; and the studied phenotype (species, habits, treatments, ages, organs, diseases, *etc.*). Moreover, the DNA methylation data for all DTs in VARIDT were further collected by the following process. *First*, microarray datasets of 16 disease indications covered by VARIDT were collected from Gene Expression Omnibus (59), which included GSE47915 (prostate cancer), GSE48684 (colorectal cancer), GSE66695 (breast cancer), GSE42752 (colon adenocarcinoma), GSE84745 (celiac disease), GSE67751 (HIV), GSE52955 (bladder cancer), GSE85845 (lung adenocarcinoma), GSE61441 (renal cell carcinoma), GSE59250 (system lupus erythematosus), GSE54503 (hepatocellular carcinoma), GSE97466 (papillary thyroid cancer), GSE49149 (pancreatic ductal adenocarcinoma), GSE70460 (atypical teratoid rhabdoid tumor), GSE102468 (panic disorder) and GSE113725 (depression). All the datasets were generated using Illumina HumanMethylation450 BeadChip with 1821 samples in total. *Second*, for

DT with multiple methylation beta values, the median was calculated and assigned as the methylation value of that particular DT. To assess the change in DT abundances between sample groups, Student's *t*-test was adopted, and the *Z*-score and fold change were calculated. Corresponding epigenetic regulation data of DT could be assessed by different types of search strategies within the 'Home' page or the menu of 'Genetic/Epigenetic Variability' (as shown in Figure 2).

Additionally, the genetic polymorphism data of all DTs was searched in PubMed by combining the keywords 'gene polymorphism'/'gene variability'/'genetic variant'/'gene mutation'/'genetic polymorphism' with the name/synonym of each DT/PDT. The discovered literatures were checked manually to identify genetic polymorphism information of the DTs. The collected data included the polymorphism types (single nucleotide polymorphism, deletion mutation, insertion mutation, etc.); the polymorphism sites in human chromosome; the minor allele frequency; the drugs affected by the polymorphism together with the corresponding disease; and the detail phenotypes correlated with this polymorphism (drug responses, survival, disease risk, adverse reactions, etc.). All in all, 23 947 DNA methylations, 92 histone modifications, 7225 ncRNA regulations and 1,278 genetic polymorphisms of 251 DTs and 129 PDTs were collected and were provided in the VARIDT.

Disease-, species- and tissue-specific protein abundances of DTs

Protein abundance of DT was always a critical issue in various aspects of drug development, such as clinical pharmacokinetics, adverse reaction assessments and drug-drug interactions (60). Particularly, the gene homology and differential abundance of DT between model organism and human should be considered before moving from preclinical to clinical (7); tissue-specific DT abundances determined the varied drug concentrations among different tissues, which were thus essential for maintaining the delicate balance between drug efficacy and safety (8); disease-associated variations in DT abundances could influence the drug pharmacokinetics and thus lead to drug toxicity (9). Since these variabilities in DT abundance were crucial in biomedical researches, the relevant data should be accumulated and further analyzed to promote modern drug discovery (60).

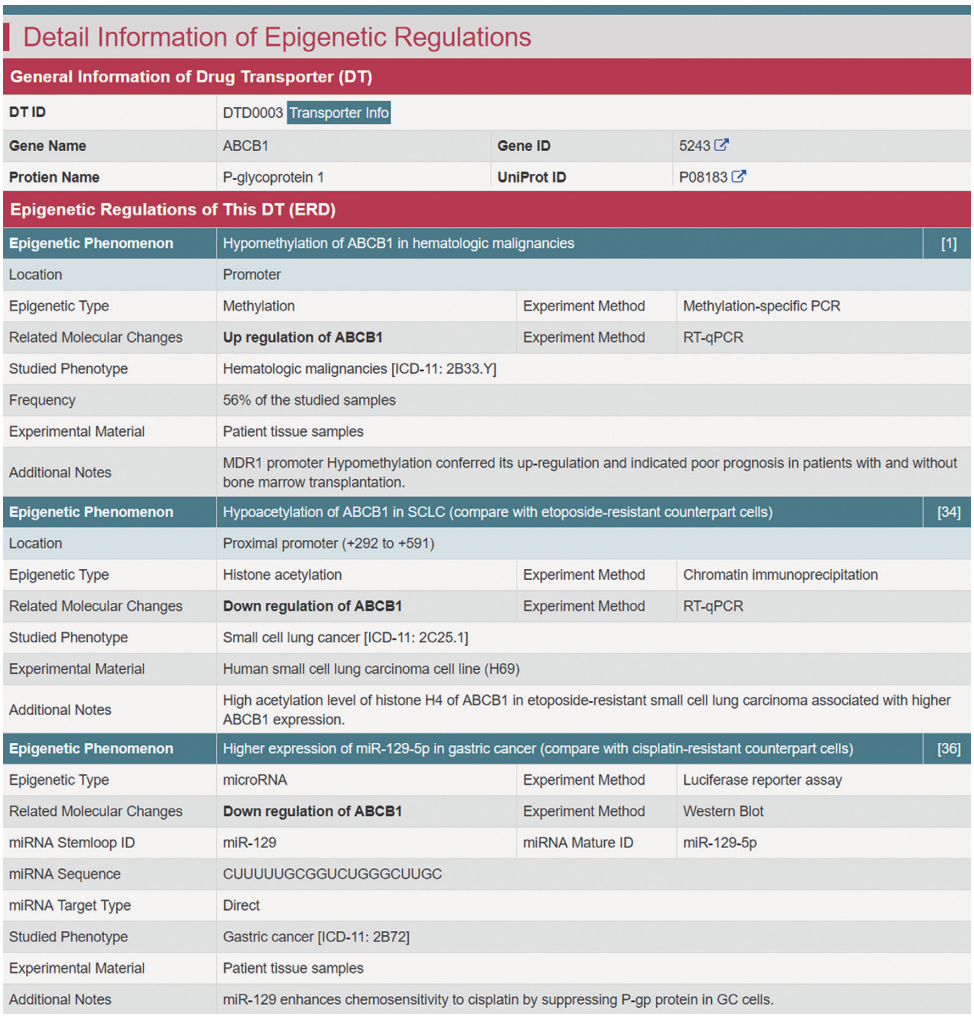
The disease-specific DT abundance data were collected by the following processes. *First*, 2812 series records of human microarray generated using the platform of HG-U133 Plus 2.0 were identified from Gene Expression Omnibus (59), and the tissue distribution together with the related disease indication were also collected. By comparing to the tissue and disease of the DTs in VARIDT, 436 series records of 108 diseases and 61 tissues covered by VARIDT were selected to analyze the expression profile of DTs. *Second*, normalization and log-transformation were used to preprocess all the collected records (61), which resulted in 21 781 samples. *Third*, the expression data from the same tissue and the same disease were integrated and further processed by perfect match correction, quantile, robust multiarray average and median polish (62). *Fourth*, a comparison between the cases and controls across samples was conducted by defining a baseline of DT expression that had median intensities and then all the samples were normalized to that baseline (63). To assess the variation in DT abundances between the different sample groups, Student's *t*-test was applied, and the *Z*-score and fold change were calculated. The analyzed groups in the VARIDT included: (i) DT expression in the normal tissue adjacent to the diseased tissue of patients (blue color), (ii) DT expression in the diseased tissue of patients (red color), (iii) DT expression in the normal tissue of healthy individuals (green color) and (iv) DT expression in tissue other than the diseased tissue of patients (orange color). *Finally*, DT expression plot across all samples was drawn based on *ggplot2* in the ***R*** environment, and a box plot illustrating the abundance variations between two studied groups was further generated based on the *pandas* module in ***Python*** 3.7.4. The plots drawn above could not only be viewed online (illustrated in Figure 3) but were also freely downloadable from website.

Species- and tissue-specific data of the DT abundances were collected by the following process. *First*, three benchmark microarray datasets containing the expression information across various tissues of human (GSE2361), mouse (GSE10246) and rat (GSE63362) were downloaded from Gene Expression Omnibus (59). *Second*, for the DT with multiple expression intensities (detected by multiple probes), the median of these intensities was calculated and assigned as the expression value of that DT. *Finally*, a DT expression plot across all tissues was drawn by *ggplot2* in the ***R*** environment, which could also be viewed online and was directly downloadable from the website. Overall, the VARIDT covered and provided the differential abundance profiles of 257 DTs and 115 PDTs in 21,781 patients and healthy individuals of 61 tissues and 108 diseases. Additionally, the expression profiles of 245 DTs and 101 PDTs in 67 tissues of *Homo sapiens* and the model organisms (*Mus musculus* and *Rattus norvegicus*) were collected and provided. All the data could be directly downloaded from the VARIDT website.

Exogenous factors modulating the activity/expression of DTs

The activity or expression of DTs could be inhibited or induced by exogenous factors, which, in turn, affected the pharmacokinetics, efficacy and safety of drugs or the tissue level of drugs/substrates that were transported by the corresponding DTs (42). These exogenous factors that were reported by the previous publication (64) included the following: (i) environmental factors (bio/mycotoxin, pesticide residue, etc.); (ii) medications (investigative chemical, drug, pharmaceutical excipient, etc.); and (iii) dietary constituents (natural product, beverage, etc.). Since these exogenous factors were expected to facilitate the understanding of the mechanism underlying DT-mediated drug-drug interactions (60,65) and improve individual health care (13), it was critical to collect such factors and to clarify their effect on modulating the activity or expression of DTs.

Thus, the exogenous factors that modulated DT activities were systematically reviewed by searching literatures in PubMed based on the combination of the keywords 'exogenous factor', 'environmental factor', 'biotoxin', 'mycotoxin', 'pesticide residue', 'dietary constituent', 'medica-



Detail Information of Epigenetic Regulations

General Information of Drug Transporter (DT)			
DT ID	DTD0003 Transporter Info		
Gene Name	ABCB1	**Gene ID**	5243
Protien Name	P-glycoprotein 1	**UniProt ID**	P08183

Epigenetic Regulations of This DT (ERD)				
Epigenetic Phenomenon	Hypomethylation of ABCB1 in hematologic malignancies			[1]
Location	Promoter			
Epigenetic Type	Methylation	Experiment Method	Methylation-specific PCR	
Related Molecular Changes	**Up regulation of ABCB1**	Experiment Method	RT-qPCR	
Studied Phenotype	Hematologic malignancies [ICD-11: 2B33.Y]			
Frequency	56% of the studied samples			
Experimental Material	Patient tissue samples			
Additional Notes	MDR1 promoter Hypomethylation conferred its up-regulation and indicated poor prognosis in patients with and without bone marrow transplantation.			
Epigenetic Phenomenon	Hypoacetylation of ABCB1 in SCLC (compare with etoposide-resistant counterpart cells)			[34]
Location	Proximal promoter (+292 to +591)			
Epigenetic Type	Histone acetylation	Experiment Method	Chromatin immunoprecipitation	
Related Molecular Changes	**Down regulation of ABCB1**	Experiment Method	RT-qPCR	
Studied Phenotype	Small cell lung cancer [ICD-11: 2C25.1]			
Experimental Material	Human small cell lung carcinoma cell line (H69)			
Additional Notes	High acetylation level of histone H4 of ABCB1 in etoposide-resistant small cell lung carcinoma associated with higher ABCB1 expression.			
Epigenetic Phenomenon	Higher expression of miR-129-5p in gastric cancer (compare with cisplatin-resistant counterpart cells)			[36]
Epigenetic Type	microRNA	Experiment Method	Luciferase reporter assay	
Related Molecular Changes	**Down regulation of ABCB1**	Experiment Method	Western Blot	
miRNA Stemloop ID	miR-129	miRNA Mature ID	miR-129-5p	
miRNA Sequence	CUUUUUGCGGUCUGGGCUUGC			
miRNA Target Type	Direct			
Studied Phenotype	Gastric cancer [ICD-11: 2B72]			
Experimental Material	Patient tissue samples			
Additional Notes	miR-129 enhances chemosensitivity to cisplatin by suppressing P-gp protein in GC cells.			

Figure 2. A typical page in VARIDT providing the epigenetic regulation information of DT. The DNA methylations, histone modifications and ncRNA regulations were collected and provided for each DT. Location, prevalence, resulting alterations in RNA/protein expression and detail description of each epigenetic phenomenon, experimental method (immunohistochemistry, microarray, etc.) and material (disease cell line, tissue, etc.) used to validate each phenomenon, together with the studied phenotype (species, habit, treatment, age, organ, disease, etc.) were described for each DT.

tion', 'inducer', 'inhibitor', 'drug', 'natural product' and the name of each DT/PDT. The discovered literatures were evaluated manually to find any exogenous factor affecting DTs. The collected data included the name of exogenous factor, the modulation types (inducer, inhibitor, etc.), the modulation activity (measured by IC50 or K_i value) and the affected cell systems. All in all, the VARIDT provided a total of 1225 exogenous factors that modulated the activity or expression of 148 DTs and 25 PDTs.

Data standardization and their access and retrieval

To make the access and analysis of VARIDT data convenient for all users, the collected raw data were carefully cleaned up and then were systematically standardized. For example, all the diseases in the VARIDT were standardized using the latest version of International Classification of Diseases (ICD-11, officially released by the World Health Organization), which was expected to serve *comprehensive health* management; the functional family of each DT was standardized according to the phylogenetic classification of TCDB (28) by assigning the family/subfamily names; the affinities of experimentally assessed kinetic parameters (K_m value) for drugs transported by their corresponding DTs were unified to the unit of micromolar; 815 (98.0%) out of the 832 drugs that were transported by DTs were with their structures available, and all these structures were drawn using *ChemDraw* and were standardized in the SDF format (both 2D and 3D); further information about each DT and its corresponding drug(s) could be accessed via the crosslinks to UniProtKB (22), TCDB (28), dbSNP (66), Drugs@FDA (67), ClinicalTrials.gov (68), ICD-11 (69), PubChem (70), ChEBI (71), TTD (27), NCBI Gene (72), CAS Registry Number (73) and so on.

VARIDT had been smoothly running for months and been tested from different sites around the world, such as the *United States*, *United Kingdom*, *Germany*, *Singapore* and *China*. All data could be viewed, accessed and downloaded (Figure 4) without any login requirement at: https://db.idrblab.org/varidt/ and http://varidt.idrblab.net/.

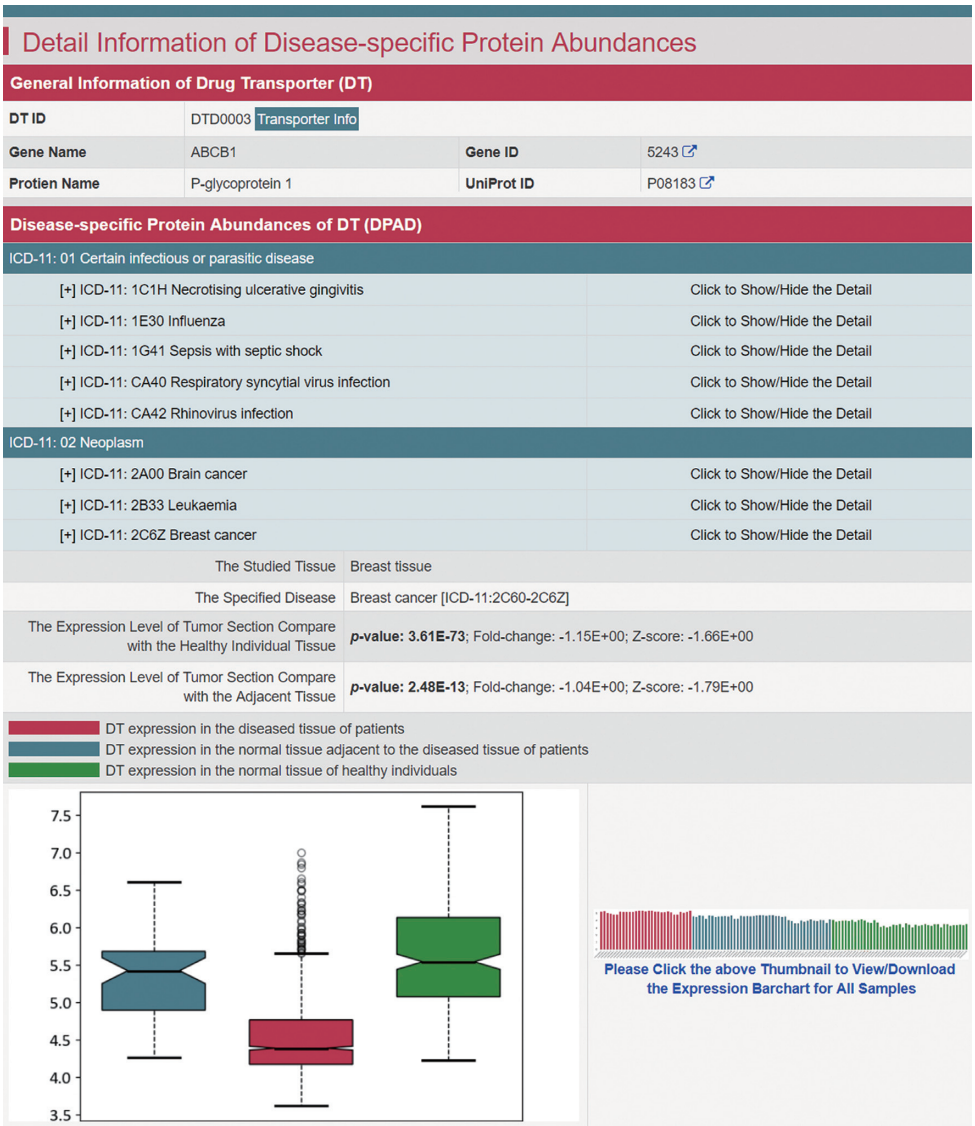


Figure 3. A typical page in VARIDT providing the disease-specific protein abundances of DT. In total, the abundance profile of 96 disease classes defined by ICD-11 was provided for each DT. Abundance variation between groups, *Z*-score and fold change were calculated. *Blue group*: DT expression in the normal tissue adjacent to the diseased tissue of patients; *Red group*: DT expression in diseased tissue of patients; *Green group*: DT expression in the normal tissue of healthy individuals.

INTERPLAY ANALYSIS AMONG MULTIPLE ASPECTS OF VARIABILITY

Although the data of each aspect of DT variability collected above were essential for clinical studies (1,12), the interplays among the different aspects had emerged to be increasingly important due to the extremely complex mechanism underlying drug metabolism (17,18,20). Taking multidrug resistance (MDR) as an example, the loss of the human uptake DT organic cation transporter OCT2 was reported to be responsible for the MDR of chemotherapy (21). Because the DNA hypermethylation and histone hyperacetylation played important roles in repressing OCT2, co-medication with exogenous inhibitor of either DNA methylation (5) or histone deacetylase (21) was found to effectively reverse the MDR (5,21). In other words, the collective consideration (interplay) of multiple variability data (epigenetic regulations *vs* exogenous chemicals) of OCT2 could help to discover new chemotherapeutic regimens. Similar to OCT2, the expressions of many other DTs (such as PCFT (74), OCT1 (75), SLCO1B1 (56), BCRP (76,77) and MRP1 (78)) in VARIDT were altered by their epigenetic/genetic variability, which resulted in drug resistance to mesothelioma (74), cholangiocarcinoma (75), hyperlipidemia (56), lung cancer (76) and renal cell carcinoma (78), respectively. Therefore, the multiple variability data in the VARIDT of these DTs might be able to inspire new strategy to deal with the corresponding resistance.

In order to ensure the multiplicity of DT variability in VARIDT, the corresponding data were carefully collected according to the description that was provided in previous sections. As a result, 244 (91.7%) out of 266 DTs and 91 (60.7%) out of 150 PDTs were described in VARIDT with

Figure 4. The page designed to download the full data of the VARIDT.

multiple variability data. Moreover, the number of variability data for each aspect was from hundreds to tens of thousands, which made it possible to identify the differential features or to generalize the common characteristics from these DT-related 'big data'.

PERSPECTIVES

With increasing movements of modern therapeutics toward stratified and personalized medicines (79), extensive effort has been made to describe the connection among different aspects/sub-aspects of DT variability (17), understand drug-drug interactions (9), optimize therapeutics (6) and overcome drug resistance (80). Thus, the VARIDT and other databases may be further expanded to incorporate newly derived data and novel knowledge to cater the need for the development of novel therapeutics.

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