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Database issue

VARIDT 3.0: the phenotypic and regulatory variability of drug transporter

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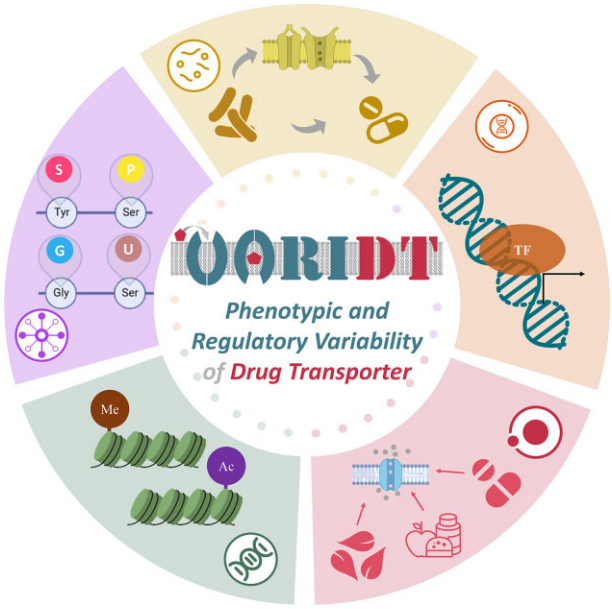
Abstract

The phenotypic and regulatory variability of drug transporter (DT) are vital for the understanding of drug responses, drug-drug interactions, multidrug resistances, and so on. The ADME property of a drug is collectively determined by multiple types of variability, such as: *microbiota influence* (MBI), *transcriptional regulation* (TSR), *epigenetics regulation* (EGR), *exogenous modulation* (EGM) and *post-translational modification* (PTM). However, no database has yet been available to comprehensively describe these valuable variabilities of DTs. In this study, a major update of VARIDT was therefore conducted, which gave 2072 MBIs, 10 610 TSRs, 46 748 EGRs, 12 209 EGMs and 10 255 PTMs. These variability data were closely related to the transportation of 585 approved and 301 clinical trial drugs for treating 572 diseases. Moreover, the majority of the DTs in this database were found with multiple variabilities, which allowed a collective consideration in determining the ADME properties of a drug. All in all, VARIDT 3.0 is expected to be a popular data repository that could become an essential complement to existing pharmaceutical databases, and is freely accessible without any login requirement at: https://idrblab.org/varidt/.

Graphical abstract



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Introduction

The phenotypic and regulatory variabilities of drug transporters (DTs) have attracted extensive attentions in recent years, and a variety of such data have been found to significantly modify the ADME properties of drugs by inducing substantial variabilities on their corresponding DTs (1–3). These variabilities include: *Microbiota Influence* (MBI) on DTs that is key for understanding the transportation of drugs among various organs (4); *Post-Translational Modification* (PTM) of DTs that is indispensable for drug disposition (5) and the revealing of the mechanisms underlying disease progression (6); *Transcriptional Regulation* (TSR) of DTs that is essential for reversing multidrug resistance (7) and discovering new therapy (8); *Epigenetic Regulation* (EGR) of DTs that is crucial for the development of drug resistance and the optimization of clinical treatment (9) and *Exogenous Modulation* (EGM) of DTs that can change the disposition of studied drug (10) and is crucial for revealing the mechanisms underlying drug-drug interactions (11–14). Since the ADME property of a drug is reported to be collectively determined by multiple types of DT's phenotypic and regulatory variabilities (1,3), a database describing all aspects of such variability data is highly demanded.

So far, several data repositories have been constructed, and are still active to provide transporter-related data (15–24). Some of them, such as TCDB (15), TransportDB (16), METscout (17) and HMPAS (18), provide general classification and categorization of transporter protein, but do not describe phenotypic and regulatory variability information of DTs; some others, such as UniProt (19), TTD (20), DrugBank (21), UCSF-FDA (22), Transformer (23) and Metrabase (24), offer EGM data of DT as one part of the broader collection of biological/pharmacological data. VARIDT 2.0 is the only database that provides information on both EGR and EGM (25–28). However, to the best of our knowledge, no database has yet been available, to comprehensively describe five aspects of DT's phenotypic and regulatory variability. In other words, it is urgently needed for the current ADME study to have the data describing these multiple aspects of such variability for any studied DT.

In this study, the VARIDT was therefore significantly updated to its version 3.0 by systematically collecting and providing DT's phenotypic and regulatory variabilities data (illustrated in Figure 1) of MBI, PTM, TSR. Particularly, 2072 MBI data of 145 DTs influenced by 124 microbe species were described, and the relative abundances of these microbe species across 76 diseases were systematically provided using 16S/metagenomic experiments; 10 255 PTM data of 418 DTs that were related to 24 PTM types (such as phosphorylation, ubiquitination, glycosylation and acetylation) were also collected, and the graphical illustrations on 9717 experimentally-validated PTM sites and their impacts on DTs' expression/function, were explicitly described; 10 610 TSR data of 381 DTs that were regulated by 357 transcription factors (TFs) were collected, and the differential expression profiles of these TFs across 59 organs and 106 diseases were given based on the transcriptomic data from 21 781 disease/health individuals. Furthermore, the DT's *epigenetic regulation* (EGR) and *exogenous modulation* (EGM) data were significantly enriched compared with that of the existing databases (including VARIDT 2.0). Particularly, a total of 46 748 EGR data for 287 DTs relevant to 3 types of EGM (DNA methylation, histone modification & ncRNA regulation) were provided, and 12 209 EGMs for 419 DTs modulated by 1717 exogenous factors (such as dietary constituent, mycotoxin, biotoxin and medication) were described. As a result, these data of five categories collected to VARIDT 3.0 were found to be closely related to the transportation of 585 approved and 301 clinical trial drugs, which involved widely in treating 572 diseases. The majority (91%) of those DTs in VARIDT had the phenotypic and regulatory variabilities data from multiple aspects (MBI, PTM, TSR, EGR and EGM), which allowed the collective consideration when determining the ADME property of a studied drug.

All in all, because of the significance of DT's phenotypic and regulatory variabilities in pharmaceutical, biological, chemical and medical sciences, and the urgent needs for collective consideration among multiple aspects (29,30), the comprehensive data describing all aspects of DT's variability in VARIDT 3.0 were expected to emerge to be the popular data repository and essential complement to the existing pharmaceutical databases. The latest version of VARIDT could be freely accessed without login requirement by all users at: https://idrblab.org/varidt/

Factual content and data retrieval

Microbiota influence (MBI) on drug transporters (DTs)

Microbiota influence (MBI) on DTs is key for in-depth understanding of the various processes involved in drug transport (30). Particularly, microbiota can modulate efficacy and availability of therapeutic drugs through direct bioaccumulation of drugs (4), or by regulating the expression and function of DT via the biosynthesis of microbial metabolites (31–33), the biotransformation of exogenous substances (34) and other mechanisms (e.g. modulation of transcriptional processes of host DTs) (35), as shown in Figure 2. Furthermore, there is mounting evidence indicating that the abundance of microbiota in different diseases significantly impacts the expression levels of multiple transporters. This ultimately results in individual variations in drug response (36). Therefore, gaining a comprehensive understanding of how the microbiota influences DTs (as shown in Figure 2) is crucial for accurately predicting the distribution of drugs within the body (37) and for developing personalized treatment strategies (38).

Since the microbiota influence information of all DTs was largely scattered in literatures, their corresponding microbiota influence was systematically searched in the PubMed database using keyword combinations such as 'microbe' + 'drug transporter', 'microbe' + 'sequester', 'microbe' + 'bioaccumulate', 'microbe' + 'transporter expression', 'microbial metabolite' + 'transporter', 'microbe'/ 'microbiota'/ 'microorganism'+ the name/synonyms of each DT. Those publications identified were manually evaluated to retrieve the data on any microbiota influence on DTs. The collected data included the microbiota species classification with a total of 124 species belonging to 3 kingdoms, 26 phyla, 21 classes, 31 orders, 56 families and 85 genera, *in-vivo* and *in-vitro* experimental models (such as rat small intestine epithelial cells (IEC-6), human colon adenocarcinoma cells (Caco-2) and mouse white adipose tissue preadipocytes cells (3T3-L1)), the studied tissues (such as kidney, ileum and small intestine), the studied phenotypes, detailed mechanism of action of each microbiota influence and resulting DT changes (the exact mechanism as shown

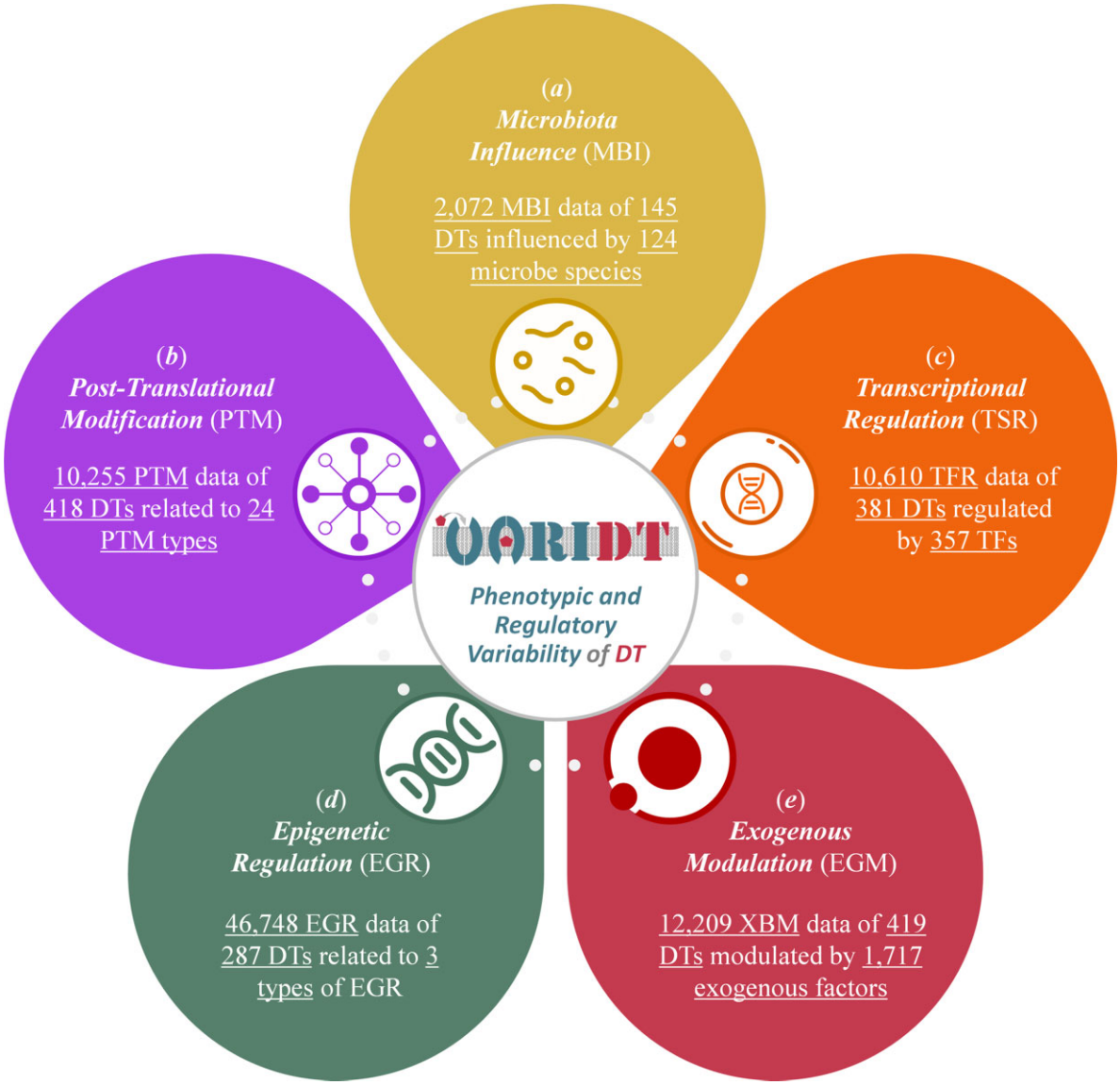

Figure 1. The phenotypic and regulatory variability data of drug transporters (DTs) provided in VARIDT 3.0. (**a**) the microbiota influence (MBI) on DTs; (**b**) the post-translational modification (PTM) of DTs; (**c**) the transcriptional regulation (TSR) of DTs; (**d**) the epigenetic regulation (EGR) of DTs; and (**e**) the exogenous modulation (EGM) of DTs. Statistics were also provided.

in Figure 2), and the drug affected by microbiota influence phenomenon.

Additionally, the relative abundances of these collected microbes across 76 disease classes based on 16S/metagenomic experiments were collected. This invaluable data provides insights into the relative expression of microbes in various disease classes (ADHD with hypertension, clostridium infection, autoimmune disease, cardiovascular disease, colorectal neoplasm, diarrhea, infant low short bowel syndrome, stomach neoplasms, and many others. To further assist users in exploring and understanding the relationship between microbiota and DT, VARIDT offered various search strategies within the '*Home*' page or the '*Microbiota Influence*' menu. These search strategies allow researchers and clinicians to access the corresponding microbiota influence data of DTs in the database. Overall, 2072 MBI data of 145 DTs regulated by 124 microbe species were collected and were provided in the VARIDT 3.0 (the detailed information is shown in Table 1).

Post-translational modification (PTM) of drug transporters (DTs)

PTM of DT is mostly reversible and dynamic and has been demonstrated to directly or indirectly modulate DT's expression, efficiency, function, structure, and more (39), which are critical for their transport kinetics and ability to transport drugs (40). In addition to single regulatory PTM, there are also PTMs that function in orchestrated manners. For instance, the balance between phosphorylation-palmitoylation of the sodium-dependent dopamine transporter (SLC6A3) has been reported to determine its transport capacity (41). This suggests that the interplay between different PTMs is key for the overall regulation of DT activity. Understanding the specific PTMs and their effects on DTs is essential for accurate prediction of drug disposition *in vivo* (5,39) and revealing disease progression (42). By collecting such regulations, researchers can uncover the mechanisms by which PTMs modulate the activity or expression of DTs, which in turn can lead to the devel-

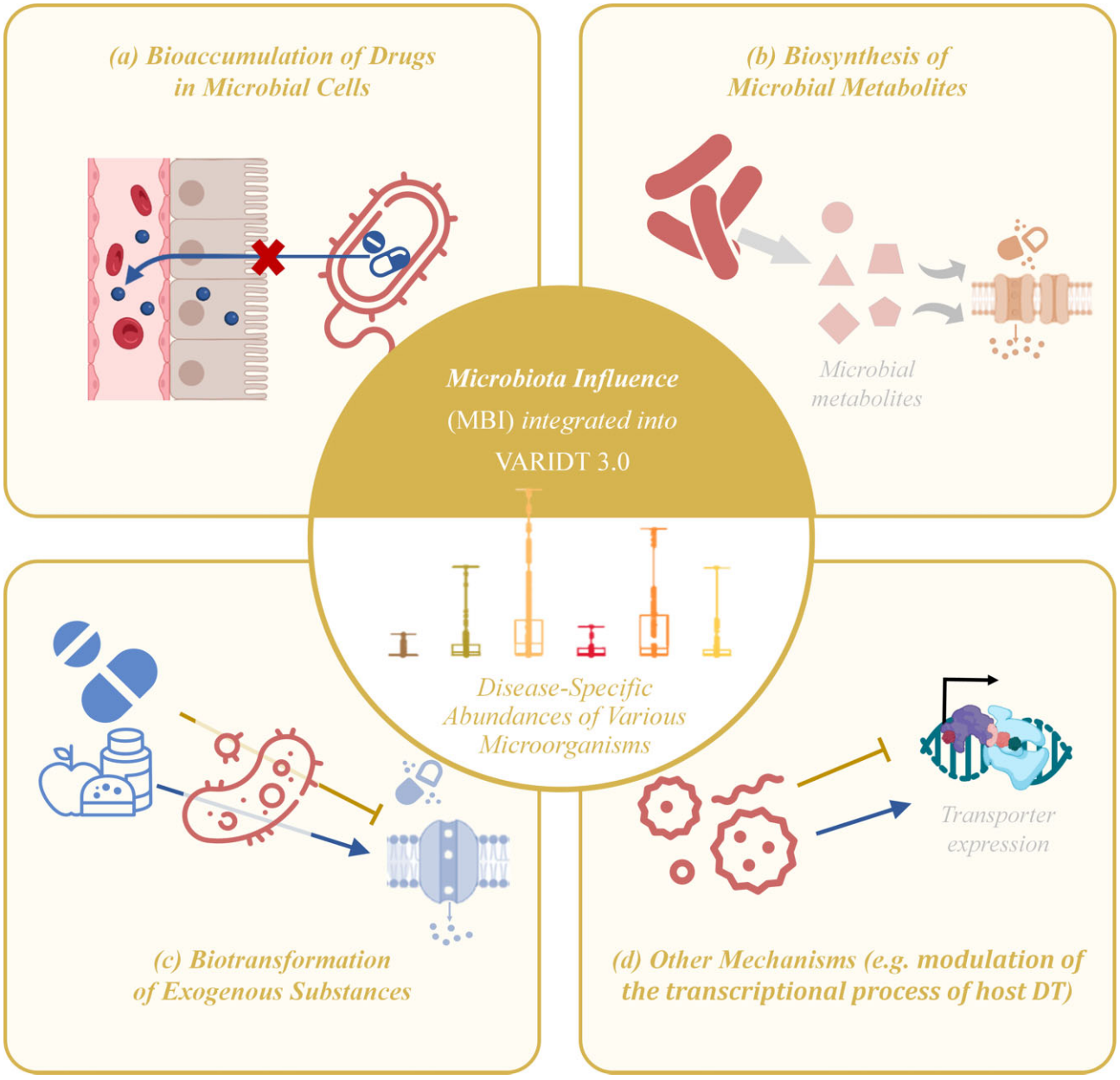

Figure 2. Detailed mechanism underlying microbiota influence (MBI) on DTs. The microbiota modulates the availability and efficacy of drugs through (**a**) direct bioaccumulation of drugs, (**b**) biosynthesis of microbial metabolites to regulate DT expression/function, (**c**) biotransformation of exogenous substances to alter DT expression/function, (**d**) other mechanisms (e.g. modulation of the transcriptional processes of the studied DTs).

opment of new therapeutic strategies and the identification of potential biomarkers for drug response and disease prognosis.

Therefore, the post-translational modifications that regulated DT expression and activities were systematically reviewed in PubMed based on the combination of keywords: 'post-translational modification', 'PTM', 'phosphorylation', 'glutathionylation', 'glycosylation', 'palmitoylation', 'acetylation', 'nitrosylation', 'sulfenylation', 'ubiquitination', 'succinylation' and the DT names. The discovered literature was then evaluated manually to find any PTM regulating DTs. The collected data included amino acid residue modification sites, modification types (such as acetylation, glutathionylation, malonylation, methylation, oxidation, phosphorylation, S-glutathionylation and ubiquitination), the detail description of each PTMs phenomenon and its related DT & drugs variation, PTM-related modifying enzymes, experimental methods and materials are described in detail under each PTM. Overall, the 10 255 PTM data of 418 DTs that were related to 24 PTM types and graphical illustrations on 9717 experimentally-validated PTM sites and their impacts on DTs' expression & function (as shown in Figure 3), were explicitly described in VARIDT 3.0 (the detailed information as shown in Table 1).

Transcriptional regulation (TSR) of drug transporters (DTs)

TFs bind to DT's specific DNA sequences and activate or repress the transcription of DT genes, thus affecting the pharmacokinetic profile and distribution in the body of its substrate

Table 1. Statistics of five major contents updated to the latest version of VARIDT

		No. of DTs	No. of DT families	No. of drugs (approved / clinical Trial)	No. of disease classes	Additional description on the phenotypic and regulatory variabilities of DT
Overall Statistics of DTs' Phenotypic and Regulatory Variabilities		422	55	886 (585 / 161)	418	Five types of DT phenotypic and regulatory variabilities were updated as shown in Figure 1
Five Types of Phenotypic and Regulatory Variabilities of DT	*a. Microbiota Influence* (MBI)	145	34	821 (562 / 143)	254	Relative abundances of 124 microbes across 76 disease classes based on 16S or metagenomic experiments
	b. Post-Translational Modification (PTM)	418	55	875 (575 / 152)	280	Illustration of 9717 experimentally-validated PTM sites and their impacts on DTs' expression and function
	c. Transcriptional Regulation (TSR)	381	51	881 (583 / 148)	278	Differential expression profiles of 357 TFs across 59 organs and 106 diseases based on transcriptomic data
	d. Epigenetic Regulation (EGR)	287	45	562 (370 / 98)	154	Three types of EGR, including DNA methylation, histone modification and ncRNA regulation
	e. Exogenous Modulation (EGM)	419	55	885 (585 / 155)	281	A total of 1717 exogenous factors, such as medications, biotoxins, mycotoxins, and dietary constituents

These five major contents included: microbiota influence (MBI), post-translational modification (PTM), transcriptional regulation (TSR), epigenetic regulation (EGR), and exogenous modulation (EGM).

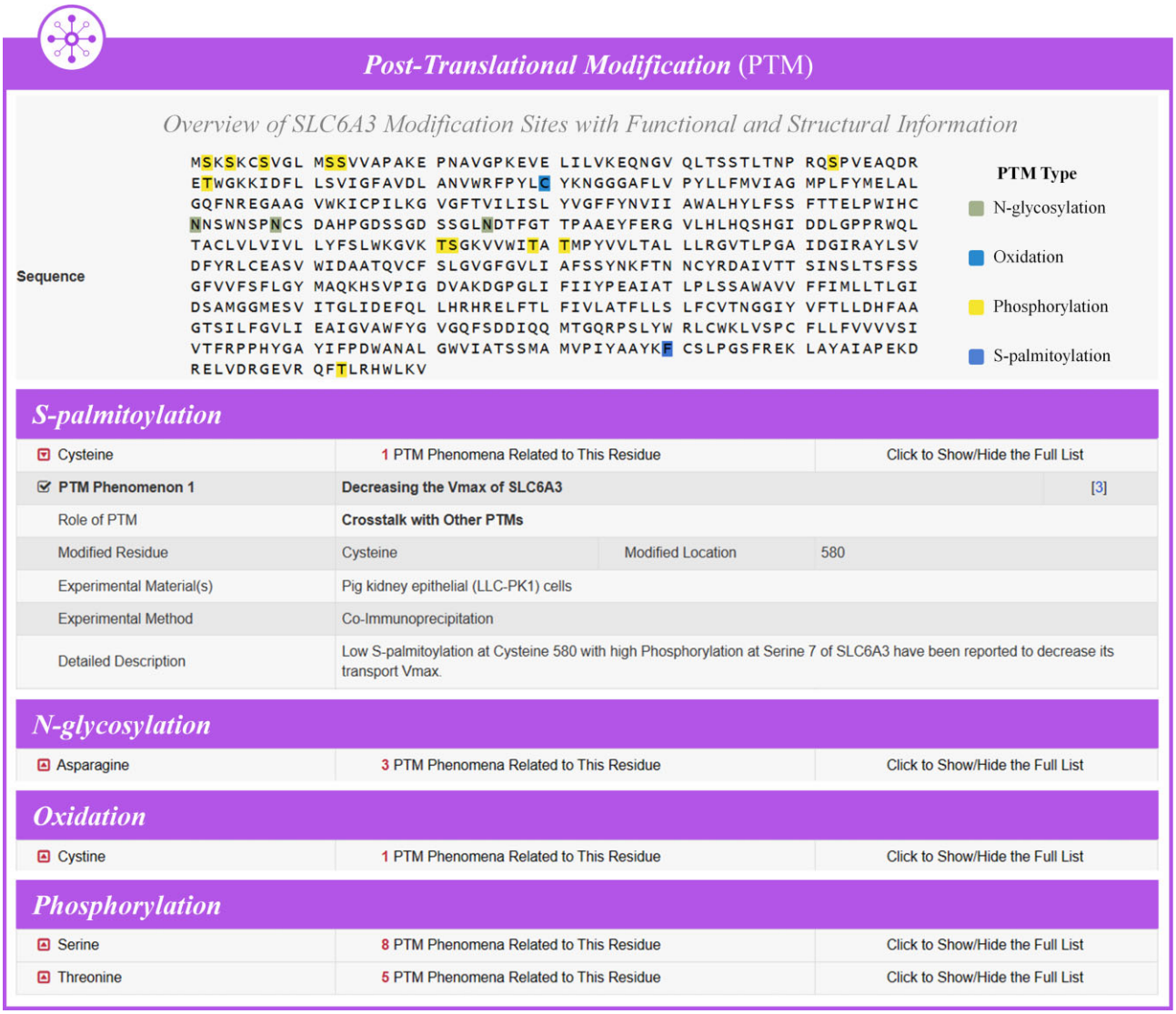

Figure 3. A typical page providing the post-translational modification (PTM) information of DT. The graphical illustrations of the DT's modification sites with function and structure information was provided at the top. The detailed information of each PTM, including the amino acid residue modification site, modification type (such as phosphorylation, ubiquitination, glycosylation and acetylation), PTM-related modifying enzymes, experimental method, experimental material.

drugs (43). In particular, multidrug resistance caused by overexpression of the permeability-glycoprotein (P-gp) encoded by ATP-binding cassette subfamily B member 1 (ABCB1) was reported to be reversed by the transcription factor BHLHE40 (Basic helix-loop-helix family member e40), which regulated drug resistance by directly binding to and transcriptionally inactivating the ABCB1 promoter. This discovery presents a novel mechanism for overcoming multidrug resistance (44–46). Thus, a thorough understanding of transcriptional regulation of drug transporter is indispensable for overcoming multidrug resistance (47), guiding new therapeutic strategies (48), and identifying adequate dosages for administration (49).

The identification of data on the regulation of DTs by transcription factors involved conducting a comprehensive literature search by various combinations of keywords, such as 'transcriptional regulation' + 'DT name/synonyms', 'transcription factor' + 'DT name/synonyms' and 'transcriptional regulation' + 'DT name/synonyms'. The discovered literature was evaluated manually to extract any information on the transcriptional regulation of DTs. The data gathered included the identification of specific transcription factors involved and their corresponding families or subfamilies, the specific mechanisms of DT regulated by transcription factors (such as activation, regression and direct binding), the studied phenotype tissue, the experimental material and a detailed description of each TSR phenomenon.

Additionally, the disease-specific TF expressions in VARIDT 3.0 were collected and calculated. *Initially*, 5608 series records generated from Gene Expression Omnibus (GEO) (50) using the Affymetrix HGU133 Plus 2.0 microarray platform were obtained, and the related disease indication together with their tissue were also accumulated. *Second*, collected records underwent sequential preprocessing steps, including data normalization, transformation, integration, perfect match correction, quantile normalization, robust multiarray average, and median polish (51). *Third*, differential expression analysis (52) was performed by comparing the abundance of transcription factors (TFs) among sample groups. *Fourth*, a TF expression plot was generated using ggplot2 in the R environment, and a box plot, based on the *pandas* module in Python 3.8, was used to illustrate abundance variations between the two studied groups. The four different types of TF expression were described in detail: (i) TF expression in normal tissue adjacent to the diseased tissue of patients (blue color), (ii) TF expression in the diseased tissue of patients (red color), (iii) TF expression in the normal tissue of healthy individuals (green color) and (iv) TF expression in tissue other than the diseased tissue of patients (orange color). Overall, a total of 10 610 TSR data of 381 DTs regulated by 357 TFs were collected. The differential expression profiles of these TFs across 59 organs and 106 diseases, based on transcriptomic data from 21 781 disease/health individuals, were provided and are downloadable from the website (as illustrated in Figure 4), the detailed information as shown in Table 1.

Enriched epigenetic regulations (EGRs) and exogenous modulations (EGMs) of DTs

During this update, the EGR and EGM data of DTs have been substantially upgraded. As mentioned in VARIDT 1.0, the EGR of DTs is key to the development of drug resistance and the optimization of clinical treatment (9,53), and EGM of DTs can alter the disposition of drugs (54) and is of great importance for deciphering the mechanism underlying drug-drug interaction (55–57). Thus, the epigenetic regulation data in VARIDT 3.0 have been significantly expanded. This update includes the methylation differences of DT in a variety of diseases were expanded from 51 ICD-standardized disease classes in VARIDT 2.0 to 101 classes in 3.0. These newly added classes included: diffuse midline glioma, esthesioneuroblastoma, craniopharyngioma. Furthermore, the number of exogenous factors modulating the DTs has increased from 822 to 1717, which is helping to further advance the understanding of DT-mediated drug-drug interaction and improve individual healthcare. Overall, the enriched data on EGR and EGM in VARIDT 3.0 will greatly advance our understanding of the mechanisms underlying drug resistance and drug-drug interactions. This knowledge will ultimately contribute to improving individualized healthcare and developing more effective treatment strategies.

All in all, a total of 46 748 EGRs (DNA methylation, histone modification & ncRNA regulation) of 287 DTs were collected, and 12 209 EGMs of 419 DTs modulated by 1717 exogenous factors (such as drug, natural product, mycotoxins, environmental toxicant, acute toxic substance and carcinogen) were described. Epigenetic regulation and exogenous modulation data of DT could be assessed by different types of search strategies within the '*Home*' page or the menu of '*Epigenetic Regulation*' (as shown in Figure 5) and '*Exogenous Modulation*' (as shown in Figure 6).

Standardization, access and retrieval of data

To make the access and analysis of VARIDT3.0 data convenient for all users, the collected raw data were carefully cleaned up and then were systematically standardized including the disease standardization using the latest version of the International Classification of Diseases (ICD-11), microbe species according to the Taxonomy database, transcription factors classification and crosslink to various reference databases. Further information about each DT and its corresponding drug(s) could be accessed via the crosslinks to CAS Registry Number (58), ChEBI (59), ClinicalTrials.gov (60), DrugMAP (61), Drugs@FDA (62), Ensembl (63), HGNC (64), ICD-11 (65), INTEDE (66), JASPAR (67), NCBI Gene (68), NCBI Taxonomy (69), PubChem (70), TCDB (15), TTD (20), UniProtKB (19) and so on. The latest version of VARIDT is freely accessible without login requirement by all users at: https://idrblab.org/varidt/

Conclusion and perspectives

Drug transporters are widely recognized as key determinants of the absorption, distribution, and excretion of many exogenous substances (drugs) and endogenous compounds (hormone, nutrient) that can directly or indirectly influence drug efficacy and safety (71–76). The variability of DTs plays a key role in drug resistance (11,77), clinical treatment optimization (9,78), and is essential for bridging preclinical study with clinical trial (79), balancing efficacy & safety (80–82), and predicting disease-drug interaction (83–85), and DT-related variability data can lay the foundation for big data-driven precision medicine. Therefore, VARIDT has been continuously featured in the NAR database issues (25,26) and has been found 'effective' in identifying the transporters of new therapy (86) and very supportive to the broad audiences who worked in pro-

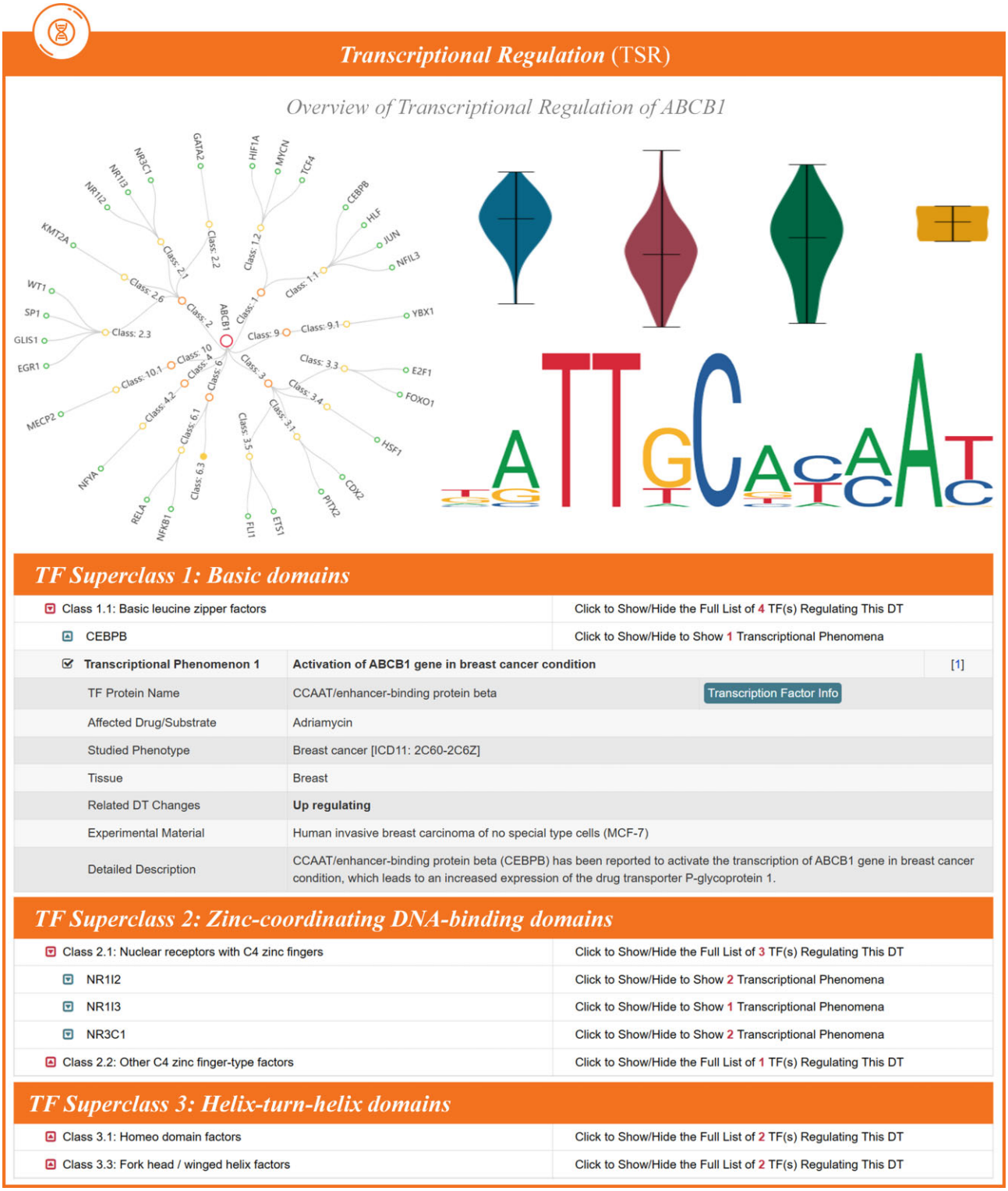

Figure 4. A typical page showing the transcriptional regulation (TSR) data of DT. The names of the transcription factors, as well as the families/subfamilies to which they belong, the specific mechanisms of DT regulation by transcription factors (such as activation, regression and direct binding), the studied phenotype tissue, the experimental material, and the detailed description of each TSR phenomenon were described for each DT. Moreover, the disease-specific expression profiles and binding frequency matrix were also provided for each TF.

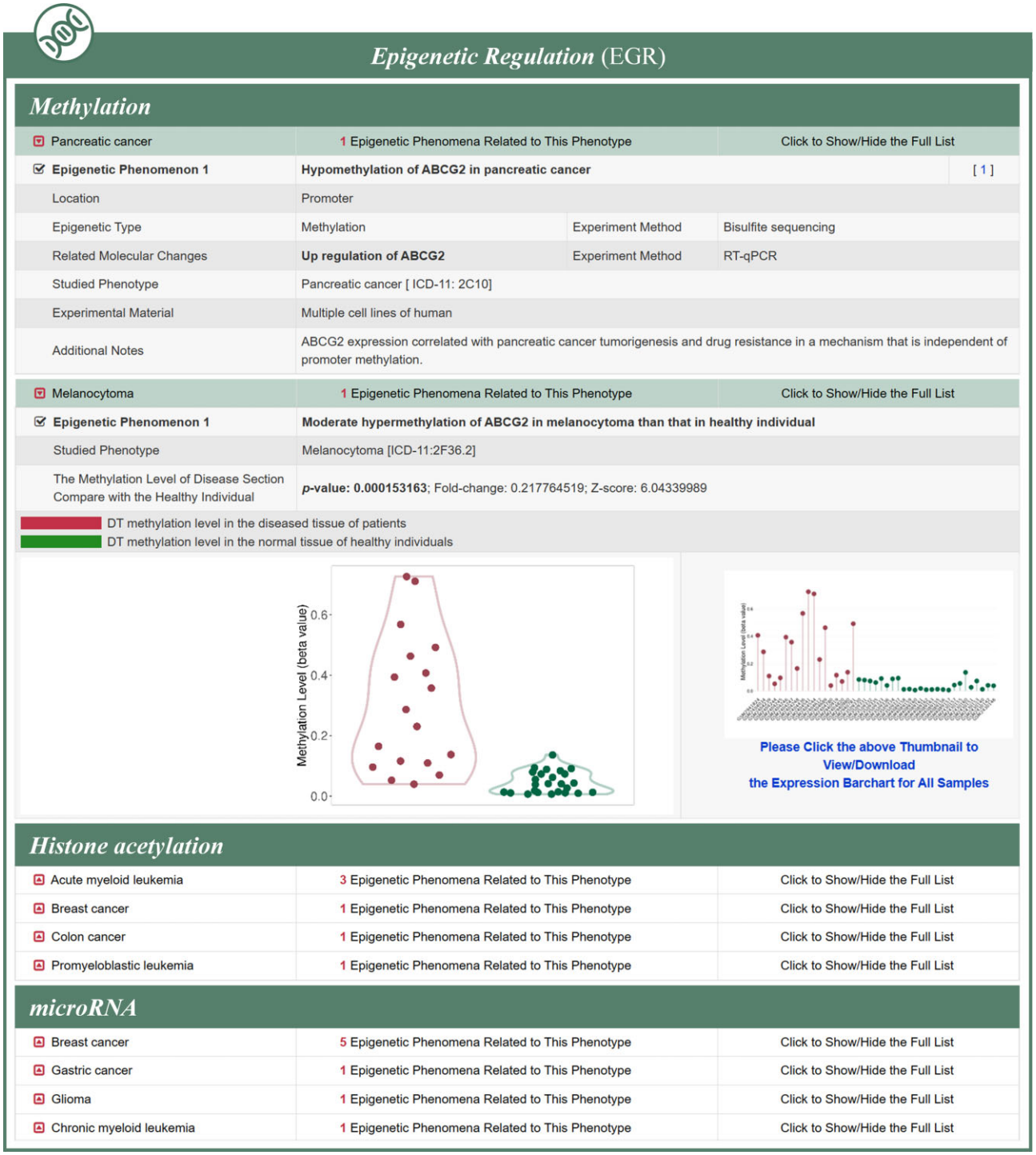

Figure 5. A typical page illustrating epigenetic regulation (EGR) data of DTs. In this update, the methylation differences of DT in a variety of diseases were expanded from 51 ICD-standardized disease classes in VARIDT 2.0 to 101 classes in 3.0. These newly added classes included: diffuse midline glioma, esthesioneuroblastoma, craniopharyngioma. A total of 46748 EGRs (DNA methylation, histone modification, and ncRNA regulation) of 287 DTs were collected.

tein function prediction (87), drug discovery (88), etiological analysis (89), and so on.

In recent years, it has been recognized that the phenotypic and regulatory variabilities of drug transporters is highly complex and carefully orchestrated (90,91). The combined effect of various variabilities leads to difference in drug response between healthy individuals and patients in different stages of the disease (1,3). In other words, the balance between these phenotypic and regulatory mechanisms shapes the expression and function of drug transporters, which directly impacts the distribution and disposition of drugs in body (92–95). Therefore, to enable a deeper understanding of the phenotypic and regulatory variabilities of DT and to facilitate cross-analysis between the various aspects of these variabilities, in this update, three new parts (microbiota influence, post-translational modification, and transcriptional regulation) have been in-

Exogenous Modulation (EGM)

Approved Drug

Quinine	7 DT Activity Modulations Related to This Exogenous Factor		Click to Show/Hide the Full List
Cimetidine	5 DT Activity Modulations Related to This Exogenous Factor		Click to Show/Hide the Full List
DT Modulation 1	**Cimetidine inhibits the transportation of N-methylpyridinium by SLC22A2 (IC50 = 120 microM)**		[4]
Affected Drug/Substrate	N-methylpyridinium	Modulation Type	**Inhibition**
Cell System	Human embryonic kidney 293 cells (HEK293)-OCT2		
DT Modulation 2	**Cimetidine inhibits the transportation of Tetraethylammonium by SLC22A2 (IC50 = 373 microM)**		[8]
Affected Drug/Substrate	Tetraethylammonium	Modulation Type	**Inhibition**
Cell System	Oocytes-OCT2		
DT Modulation 3	**Cimetidine inhibits the transportation of YM155 by SLC22A2 (IC50 = 110 microM)**		[6]
Affected Drug/Substrate	YM155	Modulation Type	**Inhibition**
Cell System	Human embryonic kidney 293 cells (HEK293)-OCT2		

Nature Product

Fenamiphos	2 DT Activity Modulations Related to This Exogenous Factor	Click to Show/Hide the Full List
Tetramethrin	1 DT Activity Modulations Related to This Exogenous Factor	Click to Show/Hide the Full List
Cigarette smoke condensate	1 DT Activity Modulations Related to This Exogenous Factor	Click to Show/Hide the Full List
Green tea	1 DT Activity Modulations Related to This Exogenous Factor	Click to Show/Hide the Full List

Environmental toxicant

Fenitrothion	1 DT Activity Modulations Related to This Exogenous Factor	Click to Show/Hide the Full List
DT Modulation 1	**Fenitrothion inhibits the activity of SLC22A2**	[30]

Mycotoxins

Aflatoxin B1	1 DT Activity Modulations Related to This Exogenous Factor	Click to Show/Hide the Full List
Alpha-zearalenol	1 DT Activity Modulations Related to This Exogenous Factor	Click to Show/Hide the Full List
Citrioveridine	1 DT Activity Modulations Related to This Exogenous Factor	Click to Show/Hide the Full List

Acute Toxic Substance

Mercuric Chloride	1 DT Activity Modulations Related to This Exogenous Factor	Click to Show/Hide the Full List
DT Modulation 1	**Mercuric Chloride inhibits the activity of SLC22A2**	[48]
2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine	1 DT Activity Modulations Related to This Exogenous Factor	Click to Show/Hide the Full List

Carcinogen

2-amino-3-methylimidazo(4,5-f)quinoline	1 DT Activity Modulations Related to This Exogenous Factor	Click to Show/Hide the Full List
Benzo(a)pyrene	1 DT Activity Modulations Related to This Exogenous Factor	Click to Show/Hide the Full List

Figure 6. A typical page providing the exogenous modulation (EGM) data of DT. For this update, the number of exogenous factors regulating the DTs has increased from 822 to 1717, and a total of 12 209 EGMs of 419 DTs modulated by 1717 exogenous factors (such as drug, natural product, mycotoxins, environmental toxicant, acute toxic substance, carcinogen) were described.

troduced and two parts of the previous version (epigenetic regulation and exogenous modulation) have been enriched. As a result, the vast majority (91%) of the DTs in VARIDT 3.0 had data from multiple aspects of variabilities, and the number of phenotypic and regulatory variabilities data for each aspect was from thousands to tens of thousands. This wealth of data makes it possible to accurately predict the *in vivo* disposition of a drug and interpret individual differences of drugs, laying the foundation for big data-driven precision medicine.

Although the data collected on DT's phenotypic and regulatory variabilities mentioned above were crucial for the ADME properties of drugs (1–3), it was important to note that these categories were not completely independent or isolated. In fact, they interacted with each other and had a complex interplay in determining DT's expression and activity. For example, a bacterial population containing Bacilli and Clostridia classes could induce the expression of P-gp in the colon. The potential mechanisms involved in this induction include HDAC inhibition, NRF2 activation, and PXR activation (31). Additionally,

the lipid-lowering drug Fenofibrate could upregulate the expression of the drug transporter ABCB1 by promoting transcriptional activation of Peroxisome proliferator-activated receptor alpha (PPARA) (96). Each category contributed in its unique way to the overall understanding of drug response, and the interplay among them plays an important role in shaping a personalized drug response. Therefore, a comprehensive analysis of these variability data in the VARIDT 3.0 could contribute to a comprehensive understanding of intricate dynamics of drug response and inspire personalized treatment strategies. In the VARIDT 3.0, we have incorporated a total of over 300 interplay data between different categories into our database. In the future, we will continue to explore relevant data to continuously improve and expand the information in our database.

Data availability

The data underlying this article are available in the article and in its online supplementary material. The latest version of VARIDT is freely accessible at: https://idrblab.org/varidt/.

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Conflict of interest statement

None declared.

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