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OPEN DATABASES FOR P-GLYCOPROTEIN. APPLICATIONS IN DRUG RESEARCH

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ABSTRACT

P-glycoprotein is a membrane protein that acts as a transporter, often involved in drug resistance by expelling drugs from cells. This protein is frequently considered in research studies in the fields of pharmacology and medicine. This study focuses on how P-glycoprotein data are made available to researchers through public, open-access databases that contain data on the genetic, structural, and functional characteristics of P-glycoprotein. The study illustrates how these databases are used for these purposes, discusses how this information promotes a better understanding of the role of P-glycoprotein in drug research. Their contribution to advancing further research in designing drugs that can bypass P-glycoprotein efflux or modulate its function for medical benefits is also emphasized.

KEY WORDS*: NCBI, UniProt, PDB, AlphaFold, DrugBank*

1. INTRODUCTION

P-glycoprotein, also known as permeability glycoprotein (abbreviated as P-gp, Pgp or PGP), multidrug resistance protein 1 (MDR1) or ATP-binding cassette sub-family B member 1 (ABCB1) is a membrane-bound transporter that plays a crucial role in drug resistance. It is found in animals, fungi, and bacteria, and it probably developed as a protective response to harmful substances as it acts as a pump that expels foreign substances out of the cells and reduces the efficacy of some pharmaceutical drugs (Löscher & Potschka, 2005). This action makes P-gp a critical factor in pharmacokinetics and drug efficacy, especially in the treatment of multidrug-resistant diseases.

P-gp is found in several tissues in humans: epithelial cells of intestine, liver, kidney, lungs and blood-brain barrier (Thiebaut *et al*., 1987; Cordon-Cardoet *et al*., 1989). Its presence in these important tissues highlights its protective and detoxifying

roles across various organ systems and also its critical role in drugs absorption and transport. Due to its ability to expel drugs out of cells and its presence in intestines, P-gp may reduce the bioavailability of oral administrated drugs. Furthermore, its overexpression in cancer cells may lead to resistance to chemotherapeutic drugs (Nanayakkara *et al.*, 2018).

P-gp is known to have polymorphic variants that can affect how effectively it transports various xenobiotics across cell membranes and leads to changes in ADMET (absorption, distribution, metabolism, excretion, toxicity) profiles of substrates (Wolking *et al.*, 2015). Consequently, information about the P-gp polymorphisms and the implications is important for understanding interindividual variability in drug response being especially relevant in the field of pharmacogenomics.

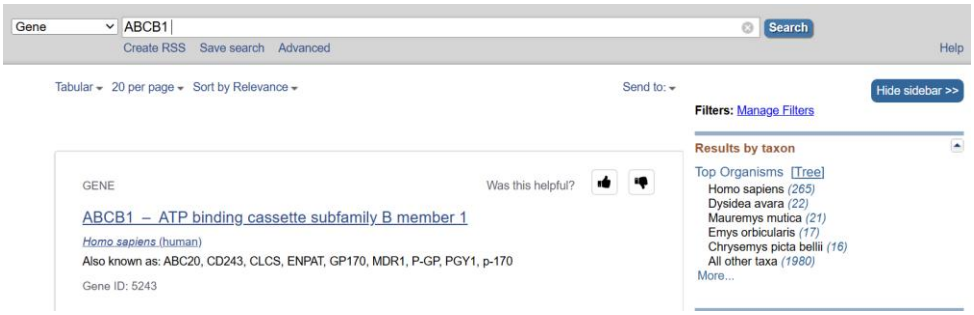
Open access tools usually play a significant role in drug research and in academic area, offering various benefits that enhance efficiency, collaboration, and knowledge dissemination (Isvoran, 2015; Isvoran 2016; Pujicic & Isvoran, 2024). Online open resources provide comprehensive chemical and biological data, which are essential for identifying drug candidates, understanding molecular structures, and exploring existing drug information. Furthermore, online free available computational modeling tools enable researchers to simulate molecular interactions, visualize protein-ligand interactions and predict molecular behavior. All these help in drug design and optimization without the need for costly physical experiments (Wang & Durrant, 2022; Niazi & Mariam, 2023).

Open access databases are valuable tools for researchers working to understand and address these issues and make information about P-gp accessible to researchers worldwide. Considering the known molecular activity of P-gp and to overcome the phenomenon of multidrug resistance and/or increase the bioavailability of some oral drugs, it is necessary to understand the structural, functional and pharmaceutical properties of P-gp. Accordingly, the aim of this study is to present how several open access databases can be used to obtain valuable information on the structural and functional properties of P-gp and how this information can be useful for drug design research. Some major databases where genetic, structural, functional and pharmacological information about P-gp can be found include: National Center for Biotechnology Information (NCBI) Gene database (Sayers *et al.*, 2023), NCBI Single Nucleotide Polymorphism database (dbSNP, Phan *et al.*, 2025), NCBI ClinVar database (Landrum *et al.*, 2018), Universal Protein Knowledgebase (UniProt) (The UniProt Consortiun, 2025), Protein Data Bank (Berman *et al.*, 2000), AlphaFold (Jumper *et al.*, 2021), DrugBank (Knox *et al.*, 2024).

2. OPEN DATABASES FOR P-GLYCOPROTEIN

2.1. NCBI Gene database

The National Center for Biotechnology Information (NCBI) Gene database (https://www.ncbi.nlm.nih.gov/home/genes/ - accessed on 17 February 2025, Sayers *et al.*, 2023) is a resource helping understanding the genetic basis of diseases. In the case of P-glycoprotein, by typing "ABCB1" in the search bar, NCBI Gene database provides detailed genetic information about P-gp, including the location of the ABCB1 gene, its gene structure, its exons and introns, alternative splicing variants, gene expression, mutations and polymorphism, etc. (Figure 1). All information related to human P-glycoprotein existing in the NCBI Gene database can be accessed at https://www.ncbi.nlm.nih.gov/gene/5243 (accessed on 17 February, 2025). This information is useful for researchers because it allows them to understand how variations in this gene affect the function of P-glycoprotein.



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Name/Gene ID	Description	Location	Aliases	MIM
ABCB1 ID: 5243	ATP binding cassette subfamily B member 1 [*Homo sapiens* (human)]	Chromosome 7, NC_000007.14 (87503017..87713295, complement)	ABC20, CD243, CLCS, ENPAT, GP170, MDR1, P-GP, PGY1, p-170	171050

b

FIG. 1. Accessing information about P-glycoprotein in the NCBI Gene database: (a) general information about P-glycoprotein (b) information about human P-glycoprotein.

This database also provides data on: (i) how the ABCB1 gene is expressed in different tissues and becomes important for understanding the role of this protein in drug resistance in different organs; (ii) how polymorphisms of this protein influence drug

metabolism and drug resistance. In addition, by using the NCBI Gene database, it is possible to identify whether a particular P-glycoprotein mutation is linked to treatment failure or adverse drug reactions in a patient population. This may help in the development of genetic tests for personalizing drug therapy.

2.2. NCBI ClinVar database

NCBI ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/ -accessed on 17 February 2025) is a public archive containing comprehensive data on the genetic variants and interpretations of their significance for human health (Landrum *et al.*, 2018). For detailed information on specific genetic variants in the ABCB1 gene and their clinical significance, there is possible to search the ClinVar directly by typing "ABCB1" in the search bar and information is provided (Figure 2).

Variation	Gene (Protein Change)	Type (Consequence)	Condition	Classification, Review status
GRCh38/hg38 7p22.3-q36.3(chr 7:54185-159282390)x1	CUL1, CUX1 +4737 more	Copy number loss	See cases	Pathogenic ☆
GRCh38/hg38 7q21.11-21.3(chr 7:84002634-95228883)x1	LOC129998788, LOC129998789 +227 more	Copy number loss	See cases	Pathogenic ☆
GRCh38/hg38 7q21.12-21.2(chr 7:87379476-91731873)x1	**ABCB1**, ABCB4 +78 more	Copy number loss	See cases	Likely pathogenic ☆
NM_001348946.2(**ABCB1**):c.*424C>T	**ABCB1**	Single nucleotide variant (3 prime UTR variant)	Tramadol response	drug response ☆
NM_001348946.2(**ABCB1**):c.*421T>C	**ABCB1**	Single nucleotide variant (3 prime UTR variant)	Tramadol response	drug response ☆
NM_001348946.2(**ABCB1**):c.*420C>G	**ABCB1**	Single nucleotide variant (3 prime UTR variant)	Tramadol response	drug response ☆
NM_001348946.2(**ABCB1**):c.*394G>A	**ABCB1**	Single nucleotide variant (3 prime UTR variant)	Tramadol response	drug response ☆

FIG. 2. Screenshot illustrating what information the ClinVar database contains for P-glycoprotein

As Figure 2 shows, this database contains entries for genetic variants in the ABCB1 gene that have been linked to various health conditions, including inflammatory diseases and multidrug resistance in cancer. These variants can influence P-gp expression and function, affecting drug efficacy and toxicity.

2.3. NCBI Single Nucleotide Polymorphism database (dbSNP)

Single nucleotide polymorphisms (SNPs) are a specific type of genetic variants and are one of the most common types of variations in the human genome. A SNP refers

to a variation at a single position in a DNA sequence, a single nucleotide (A, T, C, or G) being replaced by a different nucleotide at a specific position in the genome. The NCBI Single Nucleotide Polymorphism database (dbSNP, https://www.ncbi.nlm.nih.gov/snp/ - accessed on 18 February 2025) provides valuable information on genetic variations, the clinical significance of specific single nucleotide polymorphisms (SNPs) for proteins (Phan *et al.,* 2025). For a comprehensive list of SNPs in the ABCB1 gene and detailed information on each variant, the dbSNP database can be accessed directly by searching for "ABCB1" (Figure 3). For every SNP there is information regarding its location, allele frequencies, potential clinical impact (likely benign, benign, drug response, likely pathogenic or pathogenic) and a link toward PubMed scientific database for identifying the publication(s) where additional information can be obtained.

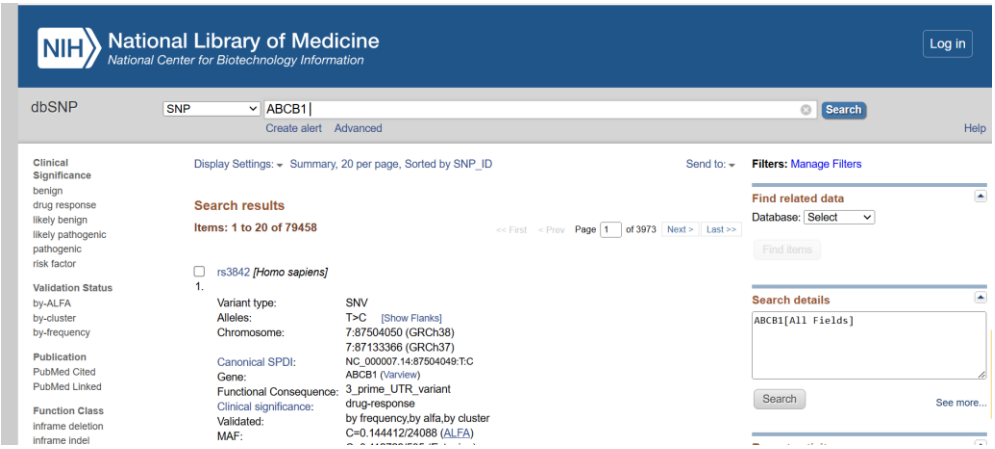


FIG. 3. Screenshot illustrating what information is found in NCBI SNP database for P-glycoprotein

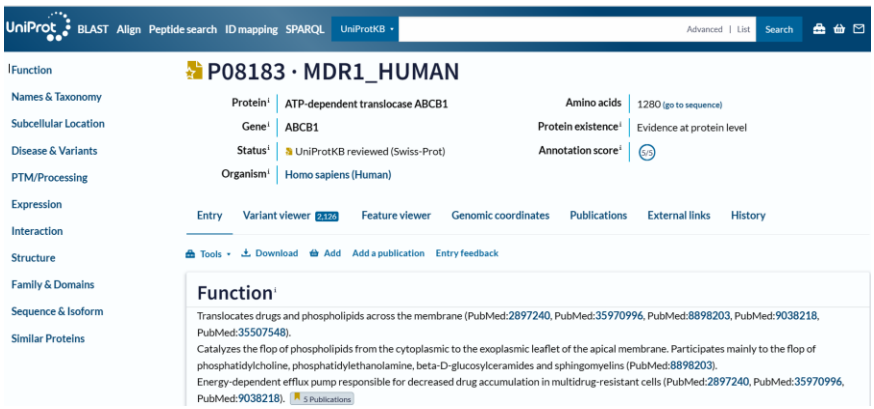
In the case of P-glycoprotein, dbSNP catalogs numerous SNPs within the ABCB1 gene. Among these, several have been extensively studied due to their potential impact on P-gp activity (Robinson&Tiriveedhi, 2020): (i) rs1045642 (3435T>C), a synonymous SNP resulting in an Ile1145Ile amino acid change and associated with altered P-gp expression levels that may influence drug bioavailability and response; (ii) rs2032582 (2677T>G/A), a SNP leading to amino acid substitutions at position 893 (Ser893Ala/Thr) and being associated with altered P-gp function, affecting the transport of various substrates; (iii) rs1128503 (1236T>C) that results in a Gly412Gly amino acid change, a variant that has been studied in conjunction with other SNPs to understand

the possible combined effect on P-gp activity. These SNPs, among others, contribute to the genetic variability observed in P-gp function across different populations. Understanding these variations is essential for predicting individual responses to drugs and for the development of personalized medicine strategies.

2.4. Universal Protein Knowledgebase (UniProt)

UniProt (https://www.uniprot.org/ - accessed on 12 March 2025) is a leading global data resource for protein sequences and functional data being frequently used by researchers for analyzing proteins. There are data for both a reviewed set of protein entries (that are experimentally verified, or computationally predicted) and the unreviewed set of proteins, where entries are computationally annotated by automated systems (The UniProt Consortiun, 2025). UniProt provides detailed and essential information about P-gp, as it is presented below.

The entry code of P-gp in UniProt database is P08183. The use of UniProt database for P-gp conducts to (Figure 4): (i) names and taxonomy; (ii) sequence information as UniProt provides the complete amino acid sequence for P-gp which is crucial for understanding its structure and function; (iii) subcellular location; (iv) protein domains in the protein that might be involved in drug binding or ATP hydrolysis, important for its role as a transporter; (v) known mutations in the P-glycoprotein gene and their impact on drug resistance or functional activity, which can help in drug development; (vi) links to other databases and scientific studies that discuss the P-gp role in diseases.



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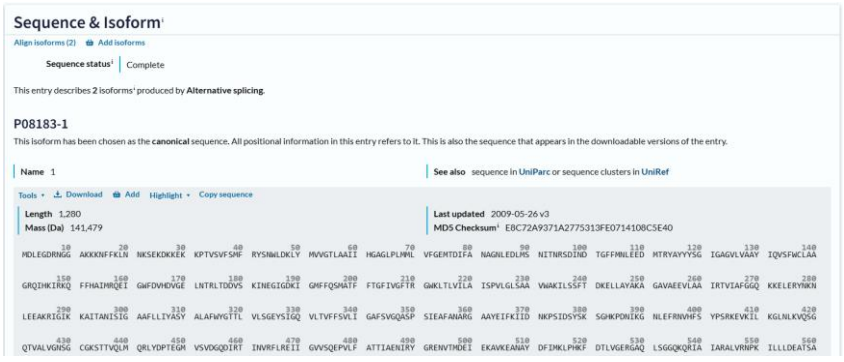

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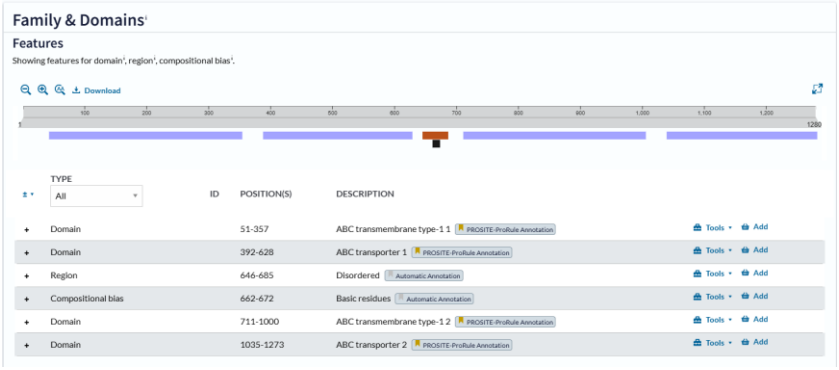

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FIG. 4. Successive screenshots illustrating information found in UniProt database for P-glycoprotein

The sequence data for P-gp are useful in drug design to model the 3D structure of the protein, or identify potential therapeutic targets. Information regarding its domains can directly influence how drugs are designed, how effective they are, and how they are metabolized. There also is information regarding the genetic variations in the ABCB1 gene that can lead to differences in the activity of P-gp by affecting drug response (including sensitivity to chemotherapy or certain medications) or altering P-gp expression levels and function, which may impact disease progression or the response to treatments.

2.5. Protein Data Bank (PDB)

The Protein Data Bank (PDB, www.rcsb.org/ - accessed on 20 March 2025) is a global repository that provides publicly available 3D structural data for macromolecules: proteins, DNA, RNA, and other complex molecules (Berman *et al.*, 2000). The database serves as a critical resource for structural biology, bioinformatics, and computational modeling, allowing the investigation of protein folding mechanisms, enzymatic activity, molecular interactions, and the structural consequences of genetic mutations being freely accessible. PDB contains structural data obtained through various experimental techniques (X-ray crystallography, nuclear magnetic resonance spectroscopy, and cryo-electron microscopy). These structures provide crucial insights into biomolecular function, interactions, and conformational changes, aiding in the study of disease mechanisms and drug discovery. Each PDB entry contains detailed atomic coordinates, structural annotations, and references to relevant scientific literature, facilitating analysis of macromolecular structures (Berman *et al.*, 2000).

The PDB allows scientists to visualize and analyze these structures in 3D, which is vital for understanding how molecules function in biological systems, being a crucial resource for biomedical research and drug design. The use of PDB in P-gp research consists in the structural data for P-glycoprotein that it contains (Table 1).

These structural data allow researchers to investigate the specific regions on P-gp that are involved in drug binding, helping to identify new drug candidates that could bypass or inhibit P-gp function, to visualize how drugs might interact with the protein at the molecular level. Furthermore, as PDB contains 3D structures for other ABC transporters, it allows comparative studies, helping to design drugs that are specific to P-gp. Consequently, PDB structural data on P-gp can be used in drug design to model drug interactions with P-gp such as to design molecules that either avoid being pumped out by P-gp or block its function to improve drug retention inside cells.

TABLE 1. Structural files of human P-glycoprotein present in Protein Data Bank

PDB ID	**Method**	**Resolution** (Å)	**Description of structural file**	**Missing residues**	**Reference**
6C0V	Electron microscopy	3.40	P-gp in complex with ligands: adenosine-5'-triphosphate and magensium ion	1- 34 81- 104 631-694 1277- 1289	Kim&Chen, 2018
6FN1	Electron microscopy	3.58	P-gp in complex with UIC2 Antigen Binding Fragment Light chain (*Mus musculus*), UIC2 Antigen Binding Fragment Heavy Chain (*Mus musculus*) and ligands 1,2-Distearoyl-sn-glycerophosphoethanolamine and 2-acetamido-2-deoxy-beta-D-glucopyranose	630- 692 1276- 1279	Alam&Locher, 2018
6FN4	Electron microscopy	4.14	P-gp in complex in complex with Antigen binding fragment of UIC2 light chain (Mus musculus) and heavy chain (*Mus musculus*)	1-30 630- 692 1275- 1279	
6QEX	Electron microscopy	3.60	P-gp in complex with UIC2 Fab lightchain (*Mus musculus*) and UIC2 Fab heavy chain (*Mus musculus*) and ligands taxol, 1,2-Distearoyl-sn-glycerophosphoethanolamine, cholesterol and 2-acetamido-2-deoxy-beta-D-glucopyranose	1-31 631- 693 1277-1280	Alam&Locher, 2019
7A65	Electron microscopy	3.90	P-gp in complex with MRK16 Fab-fragment light chain (*Mus musculus*) and MRK16 Fab-fragment heavy chain (*Mus musculus*) and ligand cholesterol	1-31 86-103 204- 208 631- 693 1277-1280	. Nosol&Locher, 2020
7A69	Electron microscopy	3.20	P-gp in complex with MRK16 Fab-fragment light chain (*Mus musculus*) and MRK16 Fab-fragment heavy chain (*Mus musculus*) and ligands vincristine and cholesterol	1-31 86-103 204- 208 631- 693 1277-1280	

7A6C	Electron microscopy	3.60	P-gp in complex with If kappa light chain (*Mus musculus*) and MRK16 Fab-fragment heavy chain (*Mus musculus*) and ligands elacridar and cholesterol	1-31 86-103 204- 208 631- 693 1277-1280	
7A6E	Electron microscopy	3.60	P-gp in complex with MRK16 Fab-fragment light chain (*Mus musculus*) and MRK16 Fab-fragment heavy chain (*Mus musculus*) and ligands tariquidar and cholesterol	1-31 86-103 204- 208 631- 693 1277-1280	
7A6F	Electron microscopy	3.50	P-gp in complex with MRK16 Fab-fragment light chain (*Mus musculus*) and MRK16 Fab-fragment heavy chain (*Mus musculus*) and ligands zosuquidar and cholesterol	1-31 86-103 204- 208 631- 693 1277-1280	
7O9W	Electron microscopy	3.50 Å	P-gp in complex with UIC2 Fab-fragment light chain (*Mus musculus*) and UIC2 Fab-fragment heavy chain (*Mus musculus*) and ligand ~{N}-[2-[2-[4-[2-(6,7-dimethoxy-3,4-dihydro-1~{H}-isoquinolin-2-yl)ethyl]phenyl]-1,2,3,4-tetrazol-5-yl]-4,5-dimethoxy-phenyl]-4-oxidanylidene-2,3-dihydrochromene-2-carboxamide	1- 31 91- 103 631- 693 1277- 1280	Nosol&Locher,2022
8Y6H	Electron microscopy	2.49 Å	P-gp in complex with UIC2 Fab light chain (*Mus musculus*), UIC2 Fab heavy chain (*Mus musculus*) and ligand elacridar	1- 31 93- 170 372- 695 800- 808 883- 887 901- 912 1015- 1534	Hamaguchi-Suzuki *et al.*, 2024
8Y6I	Electron microscopy	2.52 Å	P-gp in complex with UIC2 Fab light chain (*Mus musculus*), UIC2 Fab heavy chain (*Mus musculus*) and ligand elacridar, 1,2-Distearoyl-sn-glycerophosphoethanolamine and cholesterol	1- 31 45 93- 170 372- 695 800- 808 883- 887 901- 912 1015- 1534	

2.6. AlphaFold database

AlphaFold (https://alphafold.ebi.ac.uk/ - accessed on 24 February 2025) is an advanced artificial intelligence (AI) tool that predicts protein structures with high accuracy. It models the 3D shapes of proteins based on their amino acid sequences even for proteins that are difficult to study experimentally and currently provides open access to over 200 million protein structure predictions (Jumper *et al.*, 2021). In the case of P-gp, AlphaFold can be useful for downloading highly accurate 3D model of P-glycoprotein (Figure 5) and also to analyze the AlphaMissense Pathogenicity Heatmap (Figure 6) (https://alphafold.ebi.ac.uk/entry/P08183 - accessed on 24 February 2025).

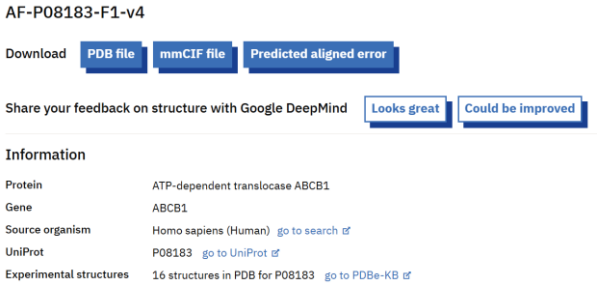

FIG. 5. Illustration of the possibility to extract highly accurate 3D model of P-glycoprotein from AlphaFold database

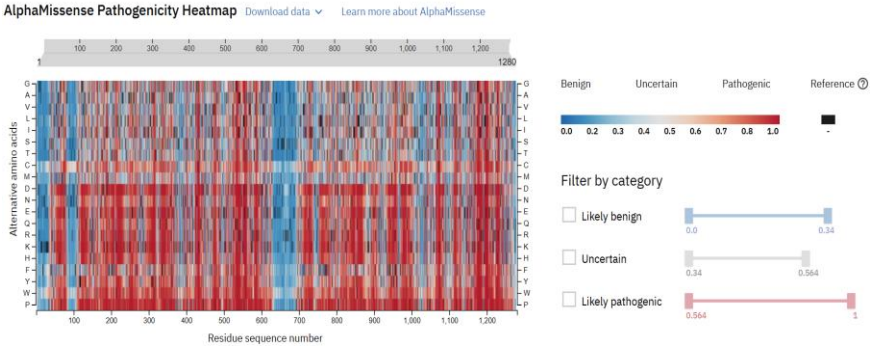

FIG. 6. AlphaMissense Pathogenicity Heatmap for P-glycoprotein: red – likely pathogenic, yellow/orange – neutral or uncertain, blue – likely beningn.

The **AlphaMissense Pathogenicity Heatmap** provides valuable insights into **missense mutations** (changes in a single amino acid in the protein sequence) within **P-gp**. This map visualizes the predicted **pathogenicity scores** for different **missense**

mutations in P-gp. These scores estimate the potential disease-causing effects of **missense mutations** in P-gp. By highlighting which regions of the P-gp structure are affected by missense mutations, the heatmap allows researchers to identify **critical regions** that are important for the protein's function. Some mutations can cause P-glycoprotein to adopt **altered conformations**, which could affect its ability to transport molecules across the cell membrane. Mutations predicted to be highly pathogenic may contribute to multidrug resistance in cancer cells by altering P-gp's ability to pump out chemotherapy drugs. Missense mutations in P-glycoprotein can influence how well the protein **transports** drugs across membranes, affecting **drug efficacy** and **toxicity**. Knowing the effects of missense mutations is helpful in personalized medicine. Some individuals may have mutations in P-gp that affect drug metabolism or resistance and understanding these mutations can help predicting responses to specific drugs or drug combinations.

2.7. DrugBank

DrugBank (https://go.drugbank.com/ - accessed on 5 March 2025) is a unique resource that combines detailed drug information with information about proteins, enzymes, and receptors involved in drug interactions (Knox *et al.*, 2024). In the case of P-gp, in addition to information on synonyms, gene, sequence, function, DrugBank provides information on how different drugs are substrates (drugs that are transported by P-gp), inhibitors (drugs that reduce the transport activity of the protein), modulators (drugs that can either enhance or inhibit P-gp activity, affecting drug transport in a more complex manner) or inducers of this protein (compounds that can induce its expression) (Figure 7), allowing information to be obtained on drugs that are affected by the efflux activity of P-gp, data that is crucial in drug design.

For each P-gp substrate, inhibitor, modulator or inducer, DrugBank provides information on the molecular structure of drugs, the effects of drugs on P-gp (including how they might influence drug transport and efflux), how drugs are absorbed, distributed, metabolized, and eliminated in the presence of P-gp, and descriptions of how drugs interact with P-glycoprotein and how they are transported across cell membranes. DrugBank also provides information on drugs that cross the blood-brain barrier and the role of P-gp in limiting the entry of certain drugs into the central nervous system. In this context, P-gp inhibitors may be explored to enhance the delivery of drugs to the brain for treating neurological diseases.

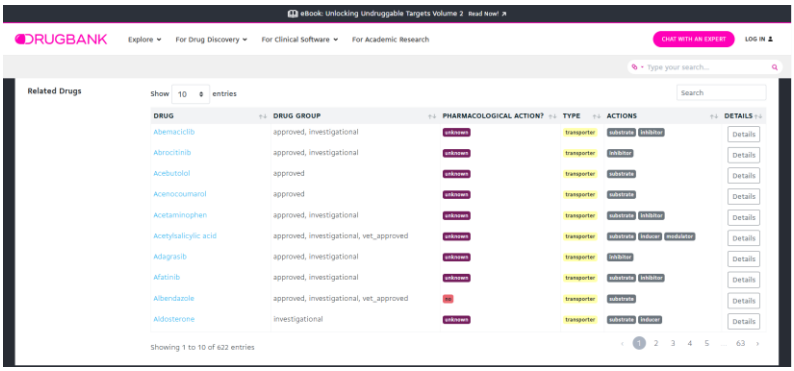

FIG. 7. Screenshot illustrating information found in DrugBank for P-glycoprotein

It should be mentioned that much of the inhibitor/substrate data for P-gp in DrugBank is predicted, not always experimentally validated as DrugBank incorporates QSAR models, docking simulations, and other *in silico* methods to predict P-gp interactions especially for newer or less studied compounds. Furthermore, many drugs are only considered as possible substrates or inhibitors based on structural similarity to known ones, without a direct evidence. In order to avoid this disadvantage, the link toward the scientific publication that is found in DrugBank should be used in order to check the information and correctly appreciate the modulation of P-gp activity by drugs. When the experimental citation is missing, the modulation specified in DrugBank it's likely predictive.

DISCUSSIONS

The availability of P-gp data in open databases helps scientists in various fields, but mainly in pharmacology and drug development. Researchers can access data to identify new drug candidates that can either evade or inhibit P-glycoprotein's drug-export function. Information about the P-gp role in multidrug resistance, its mutations or gene expression, can help to understand the role of this protein in diseases (like cancer or other disorders) improving therapy outcomes. Using open databases, clinical researchers are able to access information on how P-gp might impact drug absorption and effectiveness in different patient populations such as to develop therapies tailored to an individual's genetic makeup, ensuring that P-glycoprotein-related drug resistance is addressed. By understanding the specific binding sites and conformational changes of P-glycoprotein, researchers can design drugs that avoid recognition by P-gp (thus preventing their efflux from cells) or acting as inhibitors of P-gp to increase drug

retention in cells (useful for cancer treatment or overcoming drug resistance). Not at last, the understanding of the structure and function of the domains of P-g allows to optimizing drug design, improving treatment outcomes, and overcoming challenges like drug resistance and toxicity.

There are also challenges in using open databases to study P-gp and its involvement in drug design and development. One of the challenges is the complexity of the data which leads to the need to analyze large data sets to draw meaningful conclusions. This challenge can be overcome by using advanced computational tools to analyze and interpret the available data. Another challenge refers to incomplete or fragmented data which can lead to poor predictions regarding the drugs that may inhibit P-gp and it increases the chances of failing in the early stages of drug development.

CONCLUSIONS

Understanding how P-glycoprotein functions is vital to the field of drug design and discovery, and open databases related to P-gp are important resources to advance understanding of the role of this transporter in drug resistance and its pharmacological implications. Each of the open databases, such as NCBI Gene, NCBI dbSNP, NCBI ClinVar, UniProt, PDB, AlphaFold, and DrugBank, provides unique information on the protein's genetic background, structure, and drug interactions. Combining genetic data from NCBI, structural data from AlphaFold and PDB, and drug interaction data from DrugBank can be complex, but when successfully achieved, can lead to breakthroughs in drug design. These databases enable a global exchange of information that supports drug development, precision medicine, and disease research. These databases are constantly being updated and their content is growing, so we can expect continued improvements in therapies and drug treatments for conditions involving P-glycoprotein, such as cancer and multidrug-resistant infections. By leveraging these resources, researchers can develop more effective treatments to overcome drug resistance and improve drug delivery.

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