

# PharmGED: Pharmacogenetic Effect Database

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Received August 15, 2006; Revised and Accepted October 10, 2006

## ABSTRACT

**Prediction and elucidation of pharmacogenetic effects is important for facilitating the development of personalized medicines. Knowledge of polymorphism-induced and other types of drug-response variations is needed for facilitating such studies. Although databases of pharmacogenetic knowledge, polymorphism and toxicogenomic information have appeared, some of the relevant data are provided in separate web-pages and in terms of relatively long descriptions quoted from literatures. To facilitate easy and quick assessment of the relevant information, it is helpful to develop databases that provide all of the information related to a pharmacogenetic effect in the same web-page and in brief descriptions. We developed a database, Pharmacogenetic Effect Database (PharmGED), for providing sequence, function, polymorphism, affected drugs and pharmacogenetic effects. PharmGED can be accessed at <http://bidd.cz3.nus.edu.sg/phg/> free of charge for academic use. It currently contains 1825 entries covering 108 disease conditions, 266 distinct proteins, 693 polymorphisms, 414 drugs/ligands cited from 856 references.**

## INTRODUCTION

Individual response to drugs often differs significantly and these drug-response variations are frequently associated with polymorphisms of pharmacologically related proteins (1–5). Pharmacogenetic study of these proteins and their regulatory sites is important for the understanding of molecular mechanism of drug responses and for the development of personalized medicines (1,6–9). Resources that provide information about molecular mechanism of drug-response variations are useful for facilitating pharmacogenomics study and the development of personalized medicine (10). There have been calls and efforts for developing such resources (11) and the related informatics tools (12,13). A number of freely accessible web-based resources have been

developed for providing information about genetic and clinical pharmacogenetic information (14), polymorphisms in drug-related proteins (15–20) and toxicogenomics data (21).

Although pharmacogenetic knowledge, polymorphism and toxicogenomic information are provided in these databases, some of the reported pharmacogenetic effects are given in web-pages separate from that of other important information such as protein and drug information, and are often given by relatively long descriptions quoted from literatures. To facilitate easy and quick assessment of the relevant information, it is helpful to develop databases that provide all the information related to a pharmacogenetic effect in the same web-page. We developed Pharmacogenetic Effect Database (PharmGED) with the aim to provide the information about the effects of a particular protein polymorphism, non-coding region mutation, splicing alteration or expression variation on the response of a particular drug. It currently contains 1825 entries covering 108 disease conditions, 266 distinct proteins, 693 polymorphisms, 414 drugs/ligands cited from 856 references.

## DATABASE STRUCTURE AND ACCESS

PharmGED has a web interface at <http://bidd.cz3.nus.edu.sg/phg/>. The entries of this database were derived from a comprehensive search of published literatures (via Medline) by using a similar search and evaluation procedure as we have used for developing other databases of drug-related proteins (15–18). Entries of this database are searchable by several methods. These methods include the search of protein name, drug/ligand name, disease name (extracted from the related terms described in the relevant publications) and drug class (derived based on the related terms described in the relevant publications). Full list of protein names, drug/ligand names, disease names and drug classes are separately provided in the PharmGED main web-page for facilitating the search of particular entries.

Moreover, keyword-based text search is also supported. The search is case insensitive and wildcards are supported. In a query, a user can specify full name or any part of the name in a text field. Wild character of '\*' and '?' is allowed in text field. Here, '?' represents any single character

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and '\*' represents a string of characters of any length. For example, input of 'dehydrogenase' in the field of protein/gene name enables the finding of all entries containing 'dehydrogenase' in the protein name, such as 3-oxo-5-alpha-steroid 4-dehydrogenase 2, Alcohol dehydrogenase 1B, Alcohol dehydrogenase 1C, Fatty aldehyde dehydrogenase, Glucose-6-phosphate 1-dehydrogenase, NAD(P)H dehydrogenase

(quinone) 1, etc. On the other hand, input of Fatty\* dehydrogenase enables the finding of all dehydrogenases whose names start with 'Fatty'.

The result of a typical search is illustrated in Figure 1. In this interface, all entries that satisfy the specified search criteria are listed along with protein name, polymorphism rules, drug/ligand name, drug classification, disease name

You searched for: 5-hydroxytryptamine 2A receptor

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Protein Name	Gene Name	Polymorphism Rules	Drug/Ligand Name	Drug Classification	Disease Name	Links to related entries
<a href="#">5-hydroxytryptamine 2A receptor</a>	HTR2A	HTR2A T102C	Paroxetine	Antidepressants [SSRIs]	Affective disorders	<a href="#">Find all entries related to this protein</a>
<a href="#">5-hydroxytryptamine 2A receptor</a>	HTR2A	HTR2A T102C	Risperidone	Antipsychotics [Atypical]	psychotic disorders	<a href="#">Find all entries related to this protein</a>
<a href="#">5-hydroxytryptamine 2A receptor</a>	HTR2A	HTR2A I197V	Loxapine	Antipsychotics [Dibenzoxazepine]	psychotic disorders	<a href="#">Find all entries related to this protein</a>
<a href="#">5-hydroxytryptamine 2A receptor</a>	HTR2A	HTR2A I197V	Serotonin	Endogenous chemical		<a href="#">Find all entries related to this protein</a>
<a href="#">5-hydroxytryptamine 2A receptor</a>	HTR2A	HTR2A A447N	Serotonin	Endogenous chemical		<a href="#">Find all entries related to this protein</a>
<a href="#">5-hydroxytryptamine 2A receptor</a>	HTR2A	HTR2A His452Tyr (H452Y)	Serotonin	Endogenous chemical		<a href="#">Find all entries related to this protein</a>
<a href="#">5-hydroxytryptamine 2A receptor</a>	HTR2A	HTR2A T25N	Serotonin	Endogenous chemical		<a href="#">Find all entries related to this protein</a>
<a href="#">5-hydroxytryptamine 2A receptor</a>	HTR2A	HTR2A A447N	Loxapine	Antipsychotics [Dibenzoxazepine]		<a href="#">Find all entries related to this protein</a>

**Figure 1.** The interface displaying a search result on PharmGED. All entries that satisfy the specified search criteria are listed along with protein name, polymorphism rules, drug/ligand name, drug classification, disease name and links to other related entries in this database.

**Bioinformatics & Drug Design group [BIDD]****PharmGED: PharmacoGenetic Effect Database**

PharmGED is intended to specifically provide information about the effects of a particular protein polymorphism, non-coding region mutation, splicing alteration, or expression variation on the response of a particular drug. PharmGED currently contains 1,825 entries covering 266 distinct proteins, 693 polymorphisms, 414 drugs/ligands cited from 856 references.

Protein Information	
<b>PID</b>	PGD-794
<b>Protein</b>	Cytochrome P450 2D6
<b>Synonymous Gene Name</b>	Cytochrome P450 2D6 (EC 1.14.14.1) (CYP2D6) (P450-DB1) (Debrisoquine 4-hydroxylase).
<b>Wild type sequence</b>	<p>MGLEALVPLAVIVAI FLLLV DLMHRRQRWAARYPPGPLPLPGLGNLLHVD            FQNTPYCFDQLRRRFGDVFSLQLAWTPVVVNLGLAAVREALVTHGEDTAD            RPPVPITQILGFGPRSQGVFLARYGPAWREQRRFSVSTLRNLGLGKKSLE            QWVTEEAACLCAAFANHSGRPFPRPNGLLDKAVSNVIASLTCGRRFEYDDP            RFLRLDLAQEGLKEESGFLREVLNAVVPVLLHIPALAGKVLRFQKAFITQ            LDELLTEHRMTWDPAQPPRDLTEAFLAEMEKAKGNPESSFNENLRIVVA            DLFSAGMVTSTTTLAWGLLLMILHDPVQRRVQEQEIDDVIGQVRRPEMGDQ            AHMPYTTAVIHEVQRFQDIPVPLGVTHMSTRDIEVQGFRIKGTTLITNLS            SVLKDEAVWEKPFRRFHPEHFLDAQGHFVKPEAFLPFSAGRRACLGEPLAR            MELFLFFTSLLQHFSFSVPTGQPRPSHHGVFAFLVSPSPYELCAVPR</p>
<b>Protein Function</b>	Responsible for the metabolism of many drugs and environmental chemicals that it oxidizes. It is involved in the metabolism of drugs such as antiarrhythmics, adrenoceptor antagonists, and tricyclic antidepressants.
Polymorphism and Pharmacogenetic effect	
<b>Polymorphism/Genotype</b>	CYP2D6*4 <a href="#">Cross Link to genotype data description.</a>
<b>Drugs</b>	Haloperidol, Fluphenazine
<b>Drug class</b>	Neuroleptics [Classical]
<b>Pharmacogenetic effect</b>	Higher incidence of Tardive Dyskinesia in patients carrying at least one mutant allele.
<b>Number of Patients with Polymorphism (% of patients showed expected effect)</b>	13:81%
List of References	
Schizophr Res. 1998 Jul 27;32(2):101-6. Genetic polymorphisms for drug metabolism (CYP2D6) and tardive dyskinesia in schizophrenia. <a href="#">Link to Pubmed</a>	

Figure 2. Interface displaying the detailed information of an entry in PharmGED.

and links to other related entries in this database. More detailed information of an entry can be obtained by clicking the corresponding protein name. The result is displayed in an interface shown in Figure 2. From this interface, one finds the accession number, name, sequence and function of protein, pharmacogenetic polymorphism, affected drugs and drug class, corresponding disease condition and pharmacogenetic effect. Moreover, the information about the related references and links to the literature database PUBMED (22) is also provided.

## POTENTIAL APPLICATIONS

Established links between polymorphisms of drug-related proteins and individual drug responses have been used in combination with genetic studies as indicators for predicting individual variations of drug response (23–27). Based on the statistical analysis of the data of polymorphisms and variation of drug response of the participating patients, simple rules may be derived in some cases for predicting individual variations of drug response from polymorphism data (23,24,26,28,29). These simple rules may be collected and used for developing

Table 1. Prediction of specific drug responses from the polymorphisms of ADME-associated proteins by using simple rules

Protein	Drugs and treatment/action	Drug responses	Polymorphism rules and year of report	Number of patients with polymorphism	Reported percentage of patients who have a polymorphism and showed the expected effect
Cytochrome P450 1A2	Antipsychotic agents for schizophrenia patients	Tardive dyskinesia	Bsp1201 (C→A) polymorphism in CYP1A2 gene, 2000 (38)	85	69
Cytochrome P450 2D6	Neuroleptic agents for chronic schizophrenic patients	Tardive dyskinesia	CYP2D6*4 genotype, 1998 (39)	13	81
UDP-glucuronyltransferase	Capecitabine/irinotecan for the treatment of metastatic colorectal cancer	Greater antitumor response with low toxicity	UGT1A7*2/*2 genotype, 2005 (27)	6	100
UDP-glucuronyltransferase I	Tranilast for the prevention of restenosis following coronary revascularization	Hyperbilirubinemia	UGT1A7*3/*3 genotype, 2005 (27) Homozygosity for a (TA) <sub>7</sub> -repeat element within the promotor region of UGT1A1 gene, 2004 (23)	7 146	100 40
N-acetyltransferase 2	Isoniazid for the prophylaxis and treatment of tuberculosis	ADRs such as peripheral neuritis, fever and hepatic toxicity	SA type (NAT2*6/*6, NAT2*6/*7 and NAT2*7/*7), 2002 (25)	6	83
Tryptophan hydroxylase	Fluvoxamine for the treatment of depression	Antidepressant response	A218C A/C phenotypes, 2001 (40)	107	76
Norepinephrine transporter	Milnacipran for the treatment of depression	Antidepressant response	A218C C/C phenotypes, 2001 (40) A218C A/A phenotypes, 2001 (40) T allele of the NET T182C polymorphism, 2004 (26)	70 40 50	81 65 72
Serotonin transporter	Serotonin reuptake inhibitors for the treatment of depression	Antidepressant response	s/s genotype of serotonin transporter gene promoter region, 2000–2004 (1,2,41,42) s/l genotype of serotonin transporter gene promoter region, 2000–2004 (1,2,41,42) l/l genotype of serotonin transporter gene promoter region, 2000–2004 (1,2,41,42) ABCB1 C3435T C/C genotype, 2003 (43)	11–72 2–47 4–16 73	54% at sixth week 55% at sixth week 48% at sixth week 75
Multidrug resistance-associated protein 1	Epileptic drugs for the treatment of epilepsy	Drug-resistant epilepsy	ABCB1 C3435T C/T genotype, 2003 (43) ABCB1 C3435T T/T genotype, 2003 (43) MDR1 C3435T C/C genotype, 2005 (44)	169 73 31	63 53 59
Multidrug resistance-associated protein 1	Combination therapy of nelfinavir, efavirenz and nucleoside reverse transcriptase inhibitors for HIV-1 infected children	Virologic response by week 8	MDR1 C3435T C/T genotype, 2005 (44)	33	91

a computer prediction system in a fashion similar to that of the HIV drug-resistant genotype interpretation systems (30).

Table 1 gives examples of the drug-related proteins in PharmGED with available information about pharmacogenetic polymorphism and drug-response variation from which a reasonably accurate rule have been derived in the literature for predicting responses to a specific drug or drug group. The reported percentage of patients who have a polymorphism and showed the expected effect is also given. Based on the test of the patients described in these reports, most of these rules are capable of predicting drug responses at success rates of 50–100%, which are not too much lower than and in many cases comparable to the accuracies of 81–97% for predicting HIV drug resistance mutations from the HIV-resistant genotype interpretation systems (30). This suggests that these simple rules have certain level of capacity for facilitating the prediction of pharmacogenetic effects and they may be used as the basis for developing more sophisticated interpretation systems similar to those of the HIV-resistant genotype interpretation systems (30).

PharmGED and other databases (14–21) can be potentially used for facilitating the generation of these rules. For instance, one entry of PharmGED describes that patients using classical neuroleptic such as fluphenazine, haloperidol have a higher incidence (81%) of Tardive dyskinesia if they are of the genotype CYP2D6\*4. The corresponding polymorphism can be obtained from a link provided in the database. These data combined with other information in PharmaGED can be used to generate the rule for detecting this pharmacogenetic effect described in Table 1. In a second example, another entry of PharmGED describes that the polymorphism C3435T (Ile1145Ile) of protein MDR1-3435 variant is associated with different virologic response of nelfinavir in HIV-1 infected children. Fifty-nine percent of the 31 C/C genotype and 91% of the 33 C/T genotype show virologic response at eighth week, respectively. These data can then be used to generate the rule for this pharmacogenetic effect as described in Table 1.

## CONCLUDING REMARKS

Knowledge about protein polymorphisms and drug responses appears to have reached a meaningful level for facilitating pharmacogenetic study and for predicting various types of individual variations of drug responses. Specialized pharmacogenetics databases serve as convenient resources for obtaining the relevant information. With the rapid development of genomics (31), pharmacokinetics (32–35) and pharmacogenomics (6,8,9), more information about drug-related proteins, polymorphisms and variations of drug responses are expected to become available. Moreover, progress in the study of proteomics (36) and pathways (37) related to drug-related proteins will further facilitate our understanding of the mechanism of individual variations in drug response.

## ACKNOWLEDGEMENTS

This work was supported in part by grants from Singapore ARF R-151-000-031-112. The Open Access publication charges for this article were waived by Oxford University Press.

*Conflict of interest statement.* None declared.

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