Clinical Pharmacogenetic Dataset
Transforming scientific data into clinical knowledge

The Clinical Pharmacogenetic (PGx) Dataset provides in-depth analysis of the impact of genetic variants of enzymes and transporters on the PK, PD, and safety of drugs in various populations. Available information comes from publications and NDA reviews describing gene-drug interactions (GDI), ethnicity-drug interactions, and case reports.

- **Detailed study information** regarding design, drug dosing, genetic polymorphisms, population characteristics, PK, PD, and safety results are structured and presented according to the latest PGx scientific consensus. Common metrics for active compounds (percent changes in AUC, plasma concentrations, oral clearance, dose requirements) and metabolites (AUC ratio of metabolite/parent, and formation clearance) are used across all studies to allow metadata analysis of quantitative results.

- **Study results** are categorized according to the overall impact of genetic variants on drug exposure, PD, and safety/efficacy compared to a reference group (non-carriers of variant).

- **Comprehensive PK parameters** for parent drugs and their metabolites are available.

- **Pre-formulated queries** allow users to retrieve an *in vivo* PGx dataset by drug name, gene name, and/or ethnicity.

- **Results** can be viewed, customized, and downloaded, allowing users to compile and organize the large body of information available.
FROM A CITATION OR NDA/BLA REVIEW

The latest, most relevant, peer-reviewed publications and regulatory documents are identified and fully analyzed. Study protocol and results are manually curated to update the knowledgebase on a daily basis.


Song, B. L.¹, Wu, M.², Tang, G.³, Sun, C.¹, Zhu, Y. B.², Linda, N.¹, Fan, H. W.², Zou, J.².

Abstract

PURPOSE: Some studies in the white population have shown that carriers of at least 1 loss-of-function allele in the gene that encodes the cytochrome P-450 2C19 isozyme (CYP2C19) have lower levels of the clopidogrel active metabolite (CAM) and a reduced antiplatelet effect of clopidogrel. However, data are limited regarding the association between CYP2C19 genetic variants and exposure to CAM and on the pharmacodynamic properties of CAM in the Chinese population. Data from the white population cannot be extrapolated to the Chinese population because of the marked interethnic differences in CYP2C19 variants. This study was aimed to investigate the influence of CYP2C19 genetic polymorphisms on the pharmacokinetic properties of CAM and the antiplatelet effect of clopidogrel in healthy Chinese volunteers, and to provide evidence for the role of a CYP2C19 genotyping test in predicting the antiplatelet effect of clopidogrel in the Chinese population.
TO A FULLY CURATED DATASET

Prior to integration, all data are carefully and critically evaluated. The richness of each citation, including relevant insights, is exploited, generating a highly detailed dataset.

CYP2C19 Phenotyping

<table>
<thead>
<tr>
<th>Genotyping Method</th>
<th>Alleles Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPLEX Sequenom MassArray</td>
<td>CYP2C19*3A</td>
</tr>
<tr>
<td></td>
<td>CYP2C19*3G</td>
</tr>
<tr>
<td></td>
<td>CYP2C19*3A</td>
</tr>
<tr>
<td></td>
<td>CYP2C19*3G</td>
</tr>
<tr>
<td></td>
<td>CYP2C19*2</td>
</tr>
<tr>
<td></td>
<td>CYP2C19*3</td>
</tr>
</tbody>
</table>

CYP2C19 Genotyping

- 8 Healthy volunteer(s) (reference)
- CYP2C19*1/*1
- CYP2C19*1/*2
- CYP2C19*1/*3
- CYP2C19 Intermediate Metabolizers
  - Asian
  - Chinese
  - Malay
  - Non-smokers
- 10 Healthy volunteer(s)
- CYP2C19*1/*2
- CYP2C19*1/*3

CYP2C19 Dosing

- clopidogrel 300 mg oral single dose
- Design: Single Dosing, Open-label

Pharmacokinetics

<table>
<thead>
<tr>
<th>CYP2C19 Genotype</th>
<th>Impact of Variant</th>
<th>RUC (mg/L*h) Mean ± SD</th>
<th>AUC% Mean ± SD</th>
<th>Cmax (mg/L) Mean ± SD</th>
<th>D Cmax Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor Metabolizers</td>
<td>Yes</td>
<td>37.67 ± 11.21</td>
<td>27.08 ± 2.72</td>
<td>29.15 ± 7.30</td>
<td>19.58 ± 2.19</td>
</tr>
<tr>
<td>Normal Metabolizers</td>
<td>Yes</td>
<td>37.67 ± 11.21</td>
<td>27.08 ± 2.72</td>
<td>29.15 ± 7.30</td>
<td>19.58 ± 2.19</td>
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</tbody>
</table>

Clopidogrel exposure is significantly impacted in CYP2C19 poor metabolizers.

What other drugs have an AUC change of at least 2-fold in carriers of CYP2C19 loss-of-function alleles?
POWERFUL TOOL FOR DATA INTEGRATION: FROM ONE CITATION TO METADATA ANALYSIS

The data are formatted for immediate use and can be filtered and re-arranged to allow meta-analysis of multiple results.

Query all drugs exhibiting exposure increases of at least 2-fold in CYP2C19 poor metabolizers

Table View of Query Results

Multiple formats for viewing and downloading

Obtain a complete list of drugs that may need dosing adjustment in CYP2C19 poor metabolizers
APPLICATIONS OF THE CLINICAL PGx DATASET

PROVIDES CONTEXT for RESULTS OBTAINED with candidate compounds

HELPS DEVELOP OVERALL REGULATORY STRATEGY and optimize clinical PGx trials:
- Refines inclusion/exclusion criteria
- Helps select dose, duration, and timing of drug administration in the context of PGx
- Provides PK variability data for power calculations
- Quickly identifies known substrates of enzymes/transporters among marketed drugs to understand GDI risk

SUPPORTS STATIC PREDICTIONS and PBPK MODELING with input parameters

ACCESSES REGULATORY GDI STUDIES for recently marketed drugs

PROVIDES REFERENCE RESOURCE for ASSESSMENT of DRUG INTERACTION SAFETY

HELPS IMPLEMENT PERSONALIZED MEDICINE in the context of GDI and gene-DDI

CLINICAL PGX DATASET IN NUMBERS

(as of October 16, 2023)

3,248 in vivo PGx citations / 10,084 in vivo PGx entries

104 in vivo PGx NDAs/BLAs / 275 in vivo PGx entries

Dedicated in vitro PGx queries with 10 possible searches

707 citations on PGx efficacy (PD) / 1,590 entries

714 citations on PGx safety (side effects) / 1,140 entries

307 case reports

725 drugs involved in in vivo PGx

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To learn more, visit www.druginteractionsolutions.org
or email DIDBase@Certara.com

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