PharmGKB: Update to PGRN members

https://www.pharmgkb.org
PharmGKB: Background

The mission of the PharmGKB is to collect, curate, integrate and disseminate knowledge about how human genetic variation influences drug response. It presents information from the molecular to clinical level, with activities including:

- Collaborative creation of 30 literature-driven genotype-based drug dosing guidelines, and curation of 509 drug labels (265 FDA) to capture PGx information.

- Creation of 132 evidence-based pathways of drug action and metabolism and 65 reviews of key genes involved in drug efficacy and/or toxicity.

- Annotation of >6,300 genetic variants from >14,000 peer reviewed PGx articles.
PharmGKB: Variant Annotations

(1) Summary sentence constructed from standardized terms describing the relationship of the variant with one or more drugs. (2) Additional notes or description of the findings as free text to appear below the summary sentence. (3) Details about the publication source, including a link to the paper on PubMed. (4) Annotations are tagged with broad phenotypic categories of toxicity, dosage, efficacy or metabolism/PK. (5) If the variant annotation has been included as evidence for any clinical annotations, information and a link to the clinical annotation is given here. (6) Key study parameters including study size, allele frequencies (if available in the original publication), statistical analysis results, ethnicity information and any other important details regarding the study population. (7) History section displays when annotation was created and edit events.
PharmGKB: Clinical Annotations

(1) The title indicates variant, genes, drugs and phenotypes have been tagged, and evidence level. (2) The associations between the drug response and the genotypes. It is noted if there are studies showing a lack of association or studies which contradict the association. (3) The level of evidence is displayed; users can click on the ‘?’ icon to see documentation. (4) Clinical annotations can be tagged with phenotypic categories: toxicity, dosage, efficacy and/or metabolism/PK. (5) Each annotation is tagged with gene, variant, relevant drugs and phenotypes. (6) Ethnicity information summarizes which populations are included in the supporting evidence. (7) All of the variant annotations used as evidence are listed. (8) Not shown in this illustration is that (1) clinical annotations which have been submitted to ClinVar contain ClinVar identifiers and links to the ClinVar website, and (2) the history of the creation and edit events for the clinical annotation, is at the bottom of the webpage.
PharmGKB: Impact

• PharmGKB is a highly utilized resource, averaging 70,000 visits/month, providing comprehensive PGx content.

• It has demonstrated remarkable impact in both research and implementation domains
  • it is a highly published and cited resource, with more than 400 publications and a Relative Citation Ratio = 2.92, 80th percentile for all NIH-supported work

• Gene and variant annotations are grouped, evaluated, and summarized to produce drug pathways, gene summaries and clinical interpretations of variants.
PharmGKB: Access & Users

• There are no longer user accounts on PharmGKB.
• PharmGKB is covered under the Creative Commons license which means PharmGKB is freely available to all for use, BUT, PharmGKB cannot be redistributed or sold.
• A large proportion of users are trainees
  • (Self-reported status of users)
• Data types within the resource most helpful
PharmGKB: Collaborative Relationships

- PharmGKB interacts closely (shared staff) with CPIC and shares information with ClinVar, PharmVar and FDA (purple box).
- PharmGKB information is used in some form (hyperlinks, API calls, etc.) by multiple genomics communities, resources and tools (green boxes).
- PharmGKB relies on complimentary data resources for standard vocabularies, unique IDs (e.g., PubMed and dbSNP), allele frequencies, drug labels and other information (blue boxes).
PharmGKB: Highly Curated Knowledge Resource

- Curated clinically relevant/actionable pharmacogenomics information from drug labels, dosing guidelines and related databases
  - 8,966 annotated publications drawn from 860 journals, and associate 1,574 genes to 645 drugs
  - knowledge base associates 6,366 human genetic variants in 20,767 variant-drug annotations (annotations cover 227 diseases)
  - 132 pathways and 65 VIP summaries
    - peer-reviewed and published in Pharmacogenetics & Genomics
  - PharmGKB rating scale for annotations has been adopted as a standard by the scientific community
- 100 dosing guidelines (including 30 CPIC publications) and annotated 509 drug labels from the US, Europe, Japan and Canada (includes 265 FDA labels and 244 labels from European Medicines Agency (EMA), Pharmaceuticals and Medical Devices Agency, Japan (PMDA) or Health Canada (Santé Canada) (HCSC))
PharmGKB: Population Group Remapping

• Different Populations have significantly different frequencies of PGx alleles

• Updated the population tags on all annotation from OMB (US centric) to a new population grouping system that provides improved resolution
  • not intended to replace the need for individualized pharmacogenomic testing, but to more effectively standardize the summary description of PGx studies
  • Used data from the 1000 Genomes Project and the Human Genome Diversity Project
Clinical Pharmacology
& Therapeutics

Article:

Standardized biogeographic grouping system for annotating populations in pharmacogenetic research

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PharmGKB Biogeographical Groups

PharmGKB uses a system of nine biogeographical groups to annotate racial and ethnicity information about participants in pharmacogenetic and pharmacogenomic studies. Seven of the nine groups are based on the geographical distribution of common genetic ancestry pre-colonization and pre-Diaspora, shown in the map below. It is important to realize that the map does not show the present-day distribution of individuals in each of these groups.

In addition to these seven groups, we also have African American/Afro-Caribbean and Latino groups. As these two groups represent populations with a significant degree of post-colonization and post-Diaspora gene flow between distinct geographical populations, they are not shown on the map but are actively used in PharmGKB annotations.
PharmGKB: Other New Initiatives

- Release of beta version of PharmGKB API (see api.pharmgkb.org)
- Updating all FDA approved drug label annotations including changing all links to drugs@FDA
- Adding drug-drug interactions from drug labels
- Added PharmGKB training exercises to the downloads page with additional tutorial videos coming
- Submission of PharmGKB annotations and CPIC dosing guidelines to ClinVar
- Release of PharmCAT annotation tool (with paper) in Winter Quarter 2019

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