PharmGKB
Pharmacogenomics Knowledge Base

Pharmacogenomics & personal genomics

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Stanford University

PharmGKB, http://www.pharmgkb.org/

Today's topics

1. The Pharmacogenomics Knowledgebase (PharmGKB)
2. Applying the PharmGKB to a human genome
3. Look at PharmGKB
4. Do some personal exercises.

PharmGKB
Pharmacogenomics Knowledge Base

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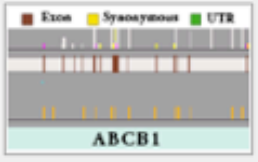
Our Mission: To collect, encode, and disseminate knowledge about the impact of human genetic variations on drug response. We curate primary genotype and phenotype data, annotate gene variants and gene-drug-disease relationships via literature review, and summarize important PGx genes and drug pathways.

Find Data By Type

You can find what you're looking for by browsing or searching the four major data types we store. If you need a pointer, check out our tutorial. You can also do a general search in the search box at the top of the page.

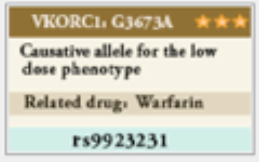
Genes



- Important PGx genes
- Pharmacokinetic genes
- Pharmacodynamic genes
- Genotyped genes

find genes examples

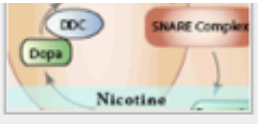
Variants



- Annotated SNPs by gene
- Annotated SNPs by drug
- Annotated SNPs by disease
- Download all annotated SNPs

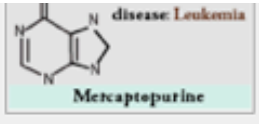
find variants examples

http://www.pharmgkb.org/



- Pharmacokinetic pathways
- Pharmacodynamic pathways
- All pathways

find pathways examples
hint: enter a gene, drug, disease



- Drugs with genetic information
- Drugs with data

find drugs examples
hint: enter a gene, rsid, drug, disease

Diseases

- Diseases with genetic information
- Diseases with curated information
- All diseases

find diseases examples
hint: enter a gene, rsid, drug, disease

Opportunities to Contribute:

Seeking Input on PGx Drug Relabeling Opportunities

PGx Toolbox

- PharmGKB Downloads and Web Services

Useful Links

- PharmGKB Tutorials

Curators' Favorite Papers

- Effect of single nucleotide polymorphisms within the interleukin-4 promoter on aspirin intolerance in asthmatics and interleukin-4 promoter activity FA GN
- ABCB1 gene polymorphisms are associated with the severity of major depressive disorder and its response to escitalopram treatment GN
- Association analysis of

See the archives for more.

PGx in the News

- Comments on Genetic Testing Registry Highlight Wide Range of Stakeholder Concerns
- AMA Makes Progress on Final CPT Codes for Molecular Diagnostics, But Job Far from Done
- OncoMethylome Becomes MDxHealth, Sharpens Focus on Molecular Dx for Cancer
- Study Suggests Infinity's NSCLC Hsp90 Chaperone Inhibitor May Be Effective in Genetic Subpopulation

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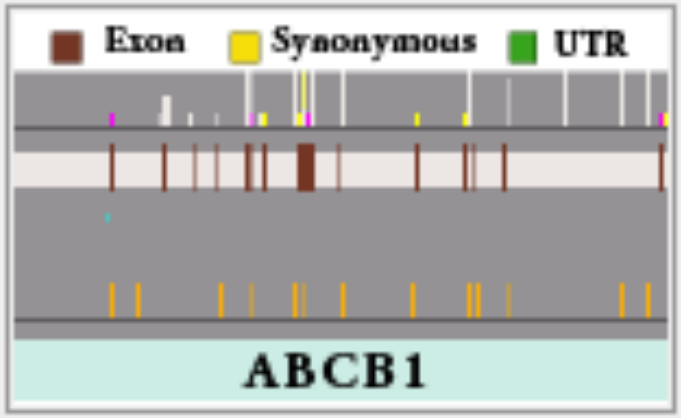
Find Data By Type

You can find what you're looking for by bro
pointer, check out our **tutorial**. You can a

Genes



- Important PGx genes
- Pharmacokinetic genes
- Pharmacodynamic genes
- Genotyped genes

warfarin

examples

hint: enter a gene, rsid, drug, disease

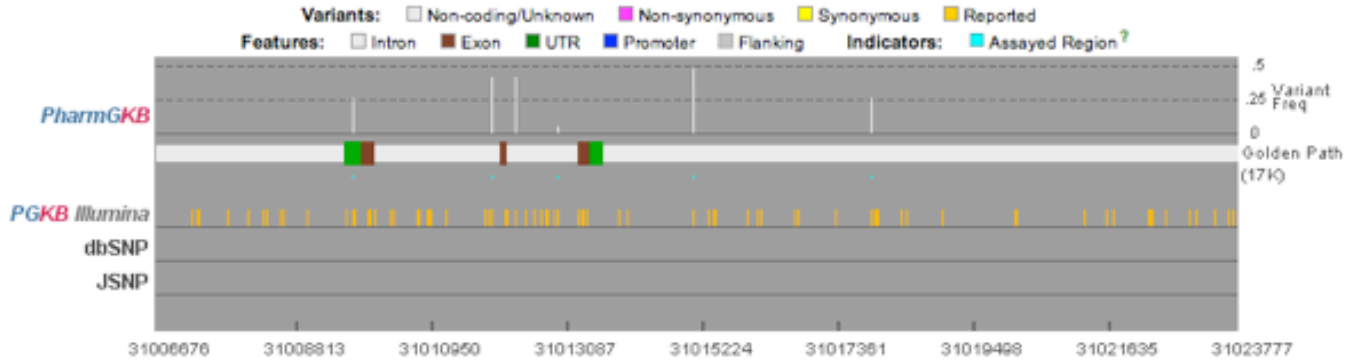
	Gene: PROC Name: protein C (inactivator of coagulation factors Va and VIIIa) Alternate symbols: PC, PROC1
	Gene: PROS1 Name: protein S (alpha) Alternate symbols: PROS, PS21, PS22, PS23, PS24, PS25, PSA
	Gene: F7 [variants] Name: coagulation factor VII (serum prothrombin conversion accelerator) Alternate symbols:
VIP	Gene: VKORC1 [VIP annotation] [variants] [genetics] Name: vitamin K epoxide reductase complex, subunit 1 Alternate symbols: EDTP308, FLJ00289, IMAGE3455200, MGC2694, MST134, MST576, UNQ308, VKCFD2, VKOR
	Gene: BGLAP Name: bone gamma-carboxyglutamate (gla) protein Alternate symbols: BGP, OC, PMF1
	Gene: GGCX Name: gamma-glutamyl carboxylase Alternate symbols: FLJ26629, VKCFD1
	Gene: F9 Name: coagulation factor IX Alternate symbols: FIX, Factor IX, HEMB, MGC129641, MGC129642, PTC

GENE:

VKORC1

vitamin K epoxide reductase complex, subunit 1

Overview | VIP | Variants | Genetics | Related Genes | Pathways | Related Drugs | Related Diseases | Datasets | Downloads/LinkOuts



Expand Variants View | Comparative Genomics

PharmGKB Non-Array Variant Data

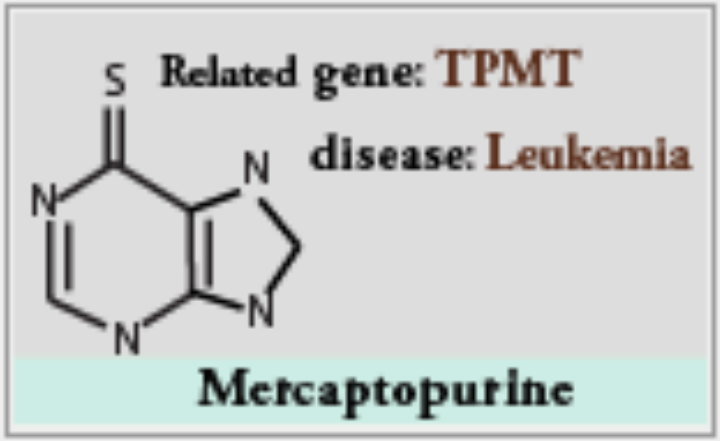
All features below come from the default feature set. Alleles are reported on the strand the gene is on, the minus strand. Note that not all variants in dbSNP or known variants may be listed here.

view legend

GP Position (hg18)	dbSNP Id (build 130)	Variant	Feature	Amino Acid Translation	Annotated Variant Curation Level
chr16:31009822	rs7294	G/A	3' UTR		★★★ [view]
chr16:31010090	rs7200749				★★ [view]
chr16:31011297	rs2359612				★★ [view]
chr16:31012010	rs8050894	G/C	Intron		★★ [view]
chr16:31012379	rs9934438	A/G	Intron		★★★ [view]
chr16:31012854	rs17708472				★★ [view]
chr16:31013055	rs2884737	T/G	Intron		
chr16:31013380	rs28940304				★★ [view]
chr16:31013418	rs28940303				★★ [view]
chr16:31013467	rs28940302				★★ [view]
chr16:31015190	rs9923231	T/C	NA		★★★ [view]
chr16:31018002	rs17880887	C/A	Intron		

Export options: CSV | Excel | XML

Drugs & Small Molecules



- Drugs by therapeutic categories
- Drugs with genetic information
- Drugs with data

warfarin

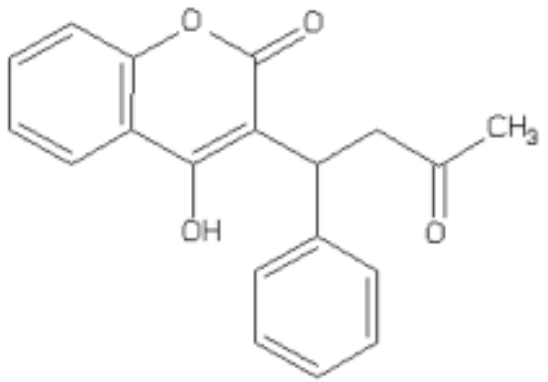
examples

hint: enter a gene, rsid, drug, disease

DRUG:
warfarin

Overview

Generic Names:	Warfarin sodium
IUPAC Name:	2-hydroxy-3-(3-oxo-1-phenylbutyl)chromen-4-one
Trade Names:	Athrombin; Athrombin-K; Athrombine-K; Brumolin; Co-Rax; Coumadin; Coumafen; Coumafene; Coumaphen; Coumaphene; Coumarins; Coumefene; D-Con; Dethmor; Dethnel; Dicusat E; Frass-Ratron; Jantoven; Kumader; Kumadu; Kumatox; Kypfarin; Latka 42; Mar-Frin; Marevan; Maveran; Panwarfin; Place-Pax; Prothromadin; RAX; Rosex; Sofarin; Solfarin; Sorexa Plus; Temus W; Tintorane; Tox-Hid; Vampirinip II; Vampirinip III; Waran; Warf 42; Warfarat; Warfarin Plus; Warfarin Q; Warfarine; Warficide; Warfilone; Zoocoumarin
PharmGKB Accession Id:	PA451906



Description

An anticoagulant that acts by inhibiting the synthesis of vitamin K-dependent coagulation factors. Warfarin is indicated for the prophylaxis and/or treatment of venous thrombosis and its extension, pulmonary embolism, and atrial fibrillation with embolization. It is also used as an adjunct in the prophylaxis of systemic embolism after myocardial infarction. Warfarin is also used as a rodenticide. [PubChem]

Indication

For the treatment of retinal vascular occlusion, pulmonary embolism, cardiomyopathy, atrial fibrillation and flutter, cerebral embolism, transient cerebral ischaemia, arterial embolism and thrombosis.

Therapeutic Category

- B01AA:Vitamin K antagonists

DRUG/SMALL MOLECULE:
warfarin

Enable Edit Mode

Overview | Properties | Genetics | Related Genes | Pathways | Related Drugs | Related Diseases | Datasets | Downloads/LinkOuts

The following drugs are in curated knowledge about this drug.

view legend

	Drug	Relationship	Evidence
	acetaminophen		Publications
	allopurinol		Publications
	amiodarone	PD	Publications
	aspirin	CO PD	Publications
	azathioprine		Publications
	capecitabine	PK	Publications
	carbamazepine		Publications
	cefazolin		Publications
	chloramphenicol		Publications
	cimetidine		Publications
	dicloxacillin		Publications
	disulfiram		Publications

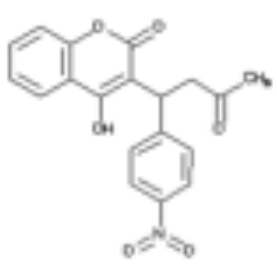
A list of non-curated publications that mention this drug along with other drugs is available.

Structurally Similar Drugs

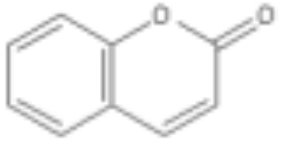
These are the top 8 structurally similar drugs found in the PharmGKB database. Structure similarity was calculated using Daylight® chemical information systems.

Structurally Similar Drugs

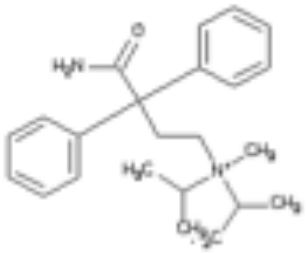
These are the top 8 structurally similar drugs found in the PharmGKB database. Structure similarity wa
systems.



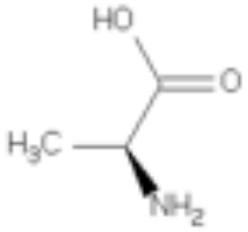
acenocoumarol



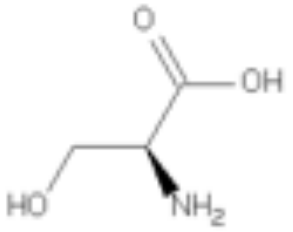
coumarin



isopropamide

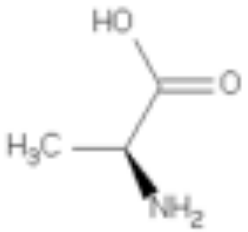


l-alanine

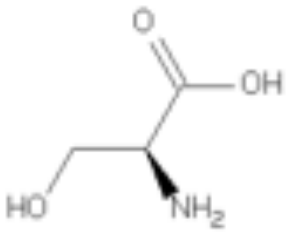


l-serine

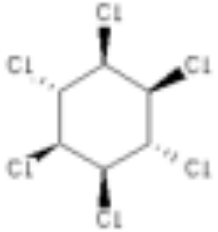
PharmGKB database. Structure similarity was calculated using Daylight® chemical information



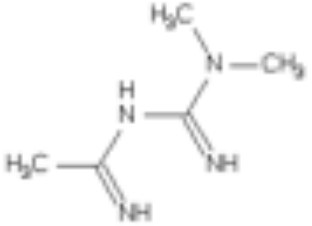
l-alanine



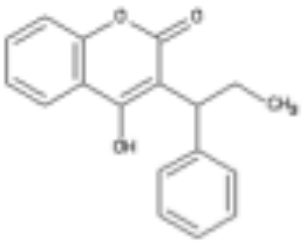
l-serine



lindane



metformin



phenprocoumon

Pathways

- Pathways by therapeutic categories
- Pharmacokinetic pathways
- Pharmacodynamic pathways
- All pathways

warfarin

examples

hint: enter a gene, drug, disease

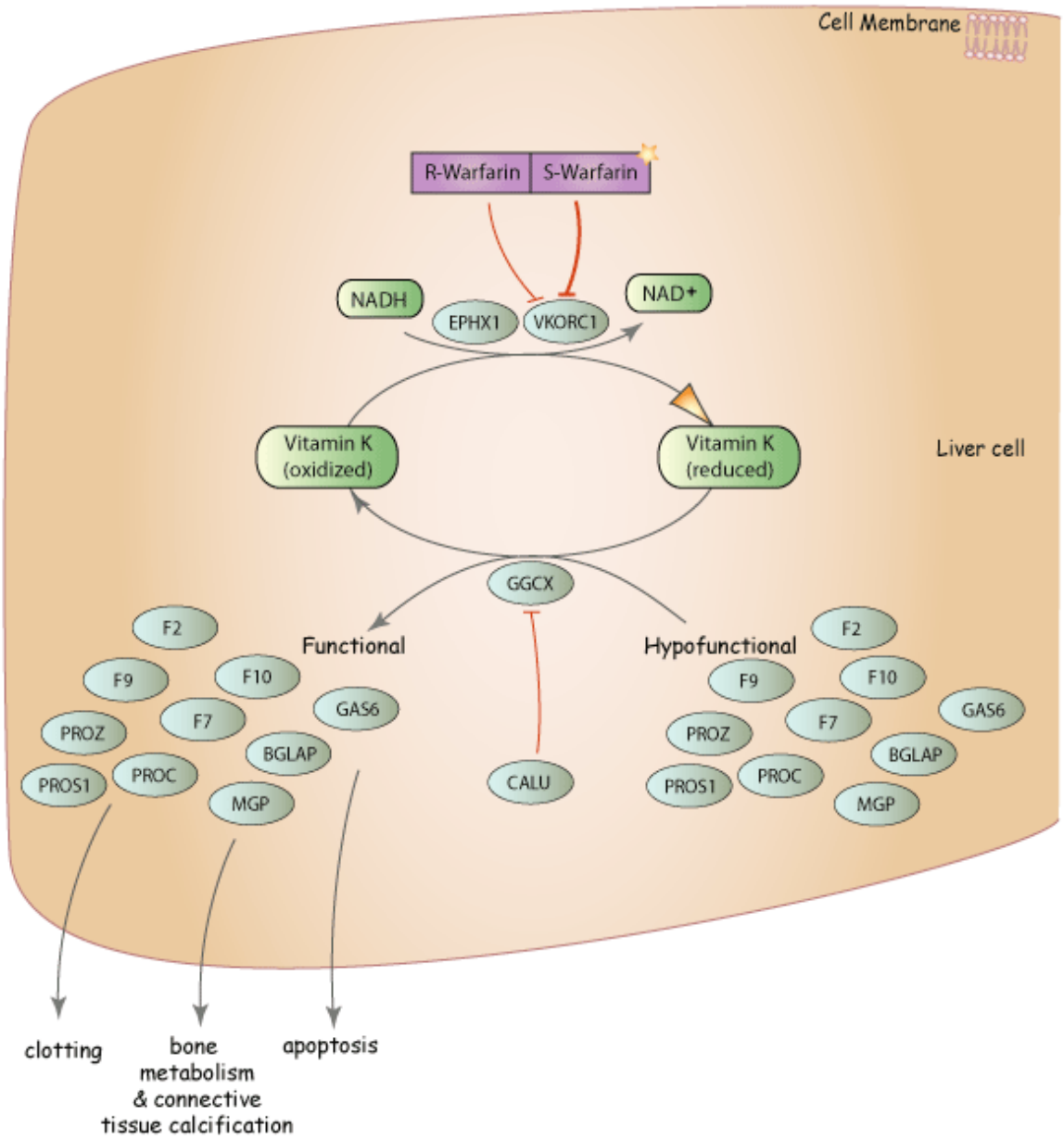
Warfarin Pathway

UNDER REVIEW

Pharmacodynamics:

Simplified diagram of the target of warfarin action and downstream genes and effects.

Legend



All Pathways

PD

Go

RELATED genes

- CYPYF2

DOWNLOADS

- Supporting Evidence (xls)

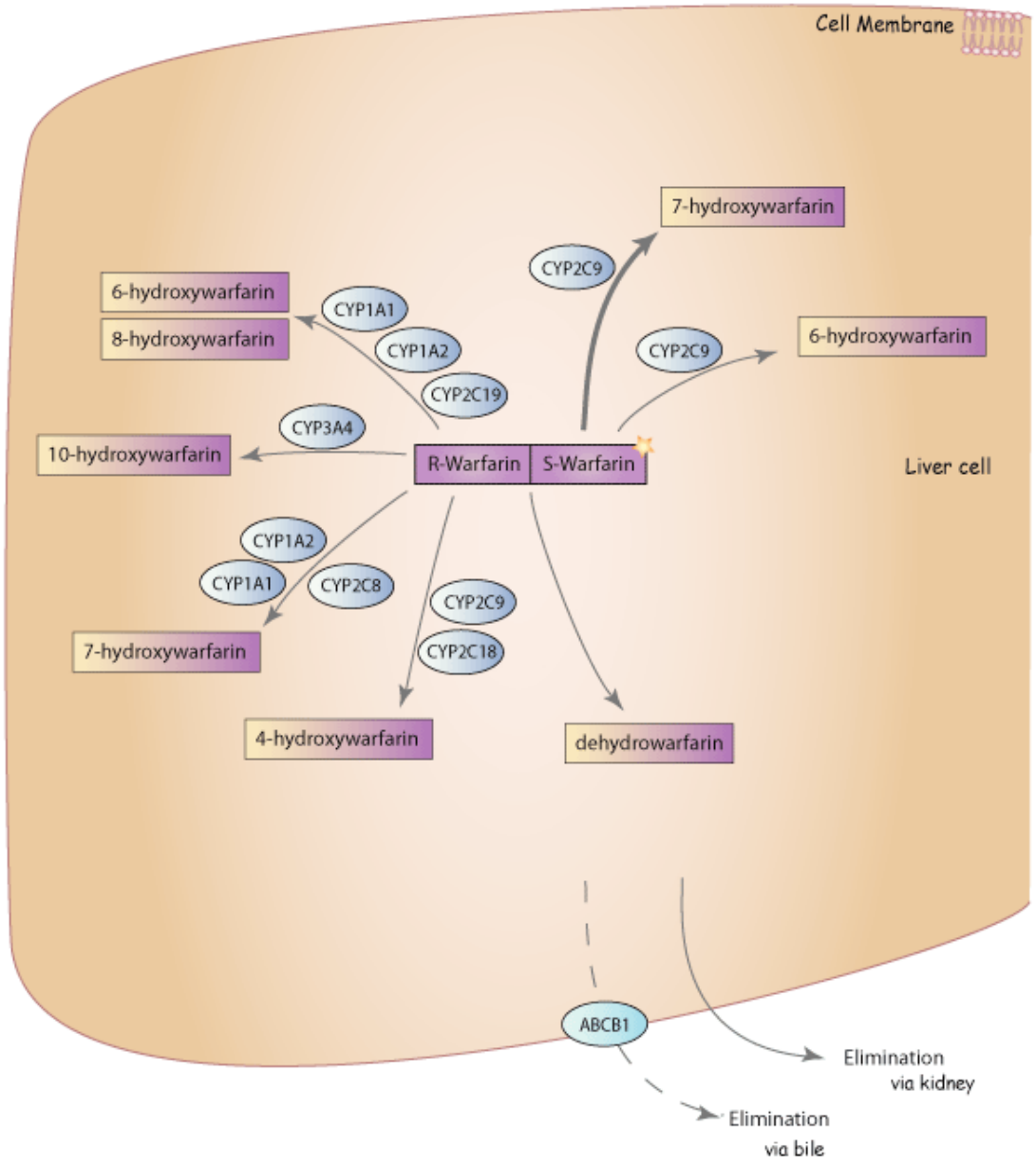
Warfarin Pathway

UNDER REVIEW

Pharmacokinetics :

Representation of the candidate genes involved in transport, metabolism and clearance of warfarin.

Legend



All Pathways

PK

Go

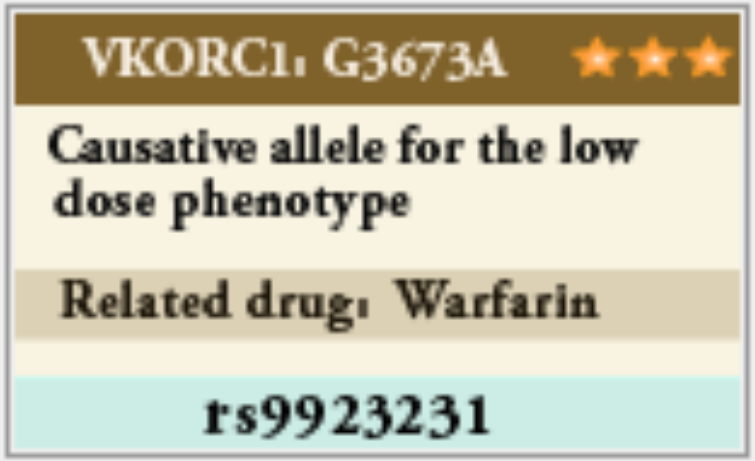
RELATED genes

- CYPYF2

DOWNLOADS

- Supporting Evidence (xls)

Variants



- Annotated SNPs by gene
- Annotated SNPs by drug
- Annotated SNPs by disease
- Download all annotated SNPs

warfarin

examples

hint: enter a gene, rsid, drug, disease

Variant rs1800460 at chr6:18139228 in TPMT

Alleles
A/G

Amino Acid
T/A @ 154

Alternate Names:
TPMT*3B, TPMT:*3B, c.460G>A, g.18247207C>T, g.21147G>A, p.Ala154Thr

VIP Variant

The *TPMT *3B* allele is rare and has only the codon 154 SNP. It is usually in tight linkage disequilibrium with the *3C SNP, resulting in the common allele, *3A*. When expressed in the yeast and in cultured mammalian cells such as COS-1, *3B* is degraded rapidly, resulting in significantly decreased levels of enzyme activity and protein [Article:8561894]. It is also associated with thiopurine drug -related toxicity [Article:8561894].

Variant Annotations

Evidence	Paper Discusses	Sentence
19898482		Allele T is associated with increased risk of Deafness when treated with cisplatin in people with Neoplasms as compared to allele C . [disease] [disease]

Study Size	Frequency	Race	Population Characteristics	P-value
53 /		Unknown	Age Group: pediatric	0.022
/ 109		Unknown	Age Group: pediatric	0.046

8561894	PK	Allele T is associated with increased risk of Drug Toxicity when treated with mercaptopurine and purine analogues as compared to genotype CC . [disease] Full text not available see http://www.pharmgkb.org/search/annotatedGene/tpmt/variant.jsp for more information on TPMT*3B.
8561894	PK	Allele T is associated with decreased catalytic activity of TPMT in human liver samples . (Full text not available)
15228163	PK	Allele T is associated with increased risk of toxicity when treated with thiopurines . [toxicity] Please note, this refers to the *3B/*3C genotype, which is also known as the *3A haplotype.

CC Has average risk of toxicity with thiopurine drugs.
CT Is associated with increased risk for toxicity with thiopurine drugs.
TT Is associated with increased risk for toxicity with thiopurine drugs.

Genes: TPMT
Drugs: azathioprine, mercaptopurine, purine analogues, thioguanine
Race:
Strength of Evidence: Level 1
Type: Toxicity/ADR

Clinical Rating

- purine analogues more likely to cause toxicity (by spdavid)

CC Has average risk for hearing loss with cisplatin treatment.
TC May have increased risk for hearing loss with cisplatin treatment.
TT May have increased risk for hearing loss with cisplatin treatment.

Drugs: cisplatin
Diseases: Neoplasms
Race:
Race Notes: Canada
Strength of Evidence: Level 2
Type: Toxicity/ADR

Ashley et al, Lancet, Vol. 175, p1525

Clinical assessment incorporating a personal genome

Euan A Ashley, Atul J Butte, Matthew T Wheeler, Rong Chen, Teri E Klein, Frederick E Dewey, Joel T Dudley, Kelly E Ormond, Aleksandra Pavlovic, Alexander A Morgan, Dmitry Pushkarev, Norma F Neff, Louanne Hudgins, Li Gong, Laura M Hodges, Dorit S Berlin, Caroline F Thorn, Katrin Sangkuhl, Joan M Hebert, Mark Woon, Hersh Sagreiya, Ryan Whaley, Joshua W Knowles, Michael F Chou, Joseph V Thakuria, Abraham M Rosenbaum, Alexander Wait Zaranek, George M Church, Henry T Greely, Stephen R Quake, Russ B Altman

Summary

Background The cost of genomic information has fallen steeply, but the clinical translation of genetic risk estimates remains unclear. We aimed to undertake an integrated analysis of a complete human genome in a clinical context.

Methods We assessed a patient with a family history of vascular disease and early sudden death. Clinical assessment included analysis of this patient's full genome sequence, risk prediction for coronary artery disease, screening for causes of sudden cardiac death, and genetic counselling. Genetic analysis included the development of novel methods for the integration of whole genome and clinical risk. Disease and risk analysis focused on prediction of genetic risk of variants associated with mendelian disease, recognised drug responses, and pathogenicity for novel variants. We queried disease-specific mutation databases and pharmacogenomics databases to identify genes and mutations with known associations with disease and drug response. We estimated post-test probabilities of disease by applying likelihood ratios derived from integration of multiple common variants to age-appropriate and sex-appropriate pre-test probabilities. We also accounted for gene-environment interactions and conditionally dependent risks.

Lancet 2010; 375: 1525–35

See Comment page 1497

See Online/Viewpoint

DOI:10.1016/S0140-6736(10)60599-5

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nature biotechnology

LETTERS

Published online August 10, 2009

Single-molecule sequencing of an individual human genome

Dmitry Pushkarev[1,2], Norma F Neff[1,2] & Stephen R Quake[1]

Recent advances in high-throughput DNA sequencing technologies have enabled order-of-magnitude improvements in both cost and throughput. Here we report the use of single-molecule methods to sequence an individual human genome. We aligned billions of 24- to 70-bp reads (32 bp average) to ~90% of the National Center for Biotechnology Information (NCBI) reference genome, with 28× average coverage. Our results were obtained on one sequencing instrument by a single operator with four data collection runs. Single-molecule sequencing enabled analysis of human genomic information without the need for cloning, amplification or ligation. We determined ~2.8 million single nucleotide polymorphisms (SNPs) with a false-positive rate of less than 1% as validated by Sanger sequencing and 99.8% concordance with SNP genotyping arrays. We identified 752 regions of copy number variation by analyzing coverage depth alone and validated 27 of these using digital PCR. This milestone should allow widespread application of genome sequencing to many aspects of genetics and human health, including personal genomics.

on a surface can be extended asynchronously, thereby allowing substantial flexibility in the kinetics of sequencing chemistry. Previous reports of single-molecule sequencing have been proofs of principle[11–13], and their sequencing throughput has not been competitive with alternative approaches. Generally, read lengths have been relatively short and error rates have been dominated by deletions; it has not been clear whether the resulting sequence quality is suitable for human genome sequencing applications.

The Heliscope Single Molecule Sequencer (Helicos Biosciences) is the first commercial release of a single-molecule sequencing instrument. It allows one to follow ~1 billion individual molecules as they are sequenced over the course of a week—a throughput that is practical for human genome sequencing. There have been several technical improvements to the platform since the reported sequencing of a viral genome[12], including more than a 1,000-fold improvement in parallelism, a new generation of sequencing reagents that allows digital measurement of homopolymer sequences, and a new software algorithm, IndexDP, for performing alignments to the entire human genome.

We used two of the instrument's 50 flow-cell channels to resequence

PharmGKB Annotation Method

- Evaluate 2500 SNP annotations for direct drug relevance to patient 0
- Evaluate CNVs in known important genes (VIP, PK, PD)
- Evaluate novel SNPs in known important genes (VIP, PK, PD)

Variant annotation highlights

- Patient is heterozygous for a null mutation of CYP2C19 (metabolizing enzyme)
- CYP2C19 critical for metabolism of:
  - proton pump inhibitors (lansoprazole, omeprazole, pantoprazole, rabeprazole)
  - antiepileptics (diazepam, norphenytoin,phenobarbitone)
  - Amitryptyline, citalopram, chloramphenicol, clopidogrel, indomethacin, nelfinavir, propranolol, R-warfarin, imipramine...

Summary of Pharmacogenetic Good News

Drug	Summary	Level of Evidence	PMID	Gene	rsID
HMG CoA Reductase Inhibitors (statins)	No increased risk of myopathy	High	18650507	SLCO1B1	rs4149056
Statins	No increased risk of myopathy	High	12811365	SLCO1B1	rs4149056
Desipramine; Fluoxetine	Depression may improve more than average	Medium	19414708	BDNF	rs61888800
Fluvastatin	Good response	Medium	18781850	SLCO1B1	rs11045819
Metoprolol and other CYP2D6 substrates	Normal CYP2D6 metabolizer.	Medium	19037197	CYP2D6	rs3892097/ rs1800716
Pravastatin	May have good response	Medium	15199031	HMGCR	rs17238540
Pravastatin, Simvastatin	No reduced efficacy	Medium	15199031	HMGCR	rs17244841
Caffeine	No increased risk of heart problems with caffeine	Low	16522833	CYP1A2	rs762551
Calcium channel blockers	No increased risk of Torsades de Pointe	Low	15522280	KCNH2	rs36210421
Carbamazepine	SNP is part of protective haplotype for hypersensitivity to carbamazepine	Low	16538175	HSPA1A	rs1043620
Neviraprine	Reduced risk of hepatoxicity	Low	16912957	ABCB1	rs1045642
Efavirenz; Nevirapine	Reduced risk of hepatoxicity	Low	16912956	ABCB1	rs1045642
Epoetin Alfa	Lower dose of iron and epo required	Low	18025780	HFE	rs1799945
Fexofenadine	Average blood levels expected	Low	11503014	ABCB1	rs1045642
Irbesartan	Irbesartan may work better than beta-blocker	Low	15453913	APOB	rs1367117
Lithium	Increased likelihood of response	Low	18408563	CACNG2	rs5750285

Summary of Pharmacogenetic Bad News

Drug	Summary	Level of Evidence	PMID	Gene	rsID
Clopidogrel & CYP2C19 substrates	CYP2C19 poor metabolizer, many drugs may need adjustment.	High	19106084	CYP2C19	rs4244285
Warfarin	Requires lower dose	High	15888487	VKORC1	rs9923231
Warfarin	Requires lower dose	High	19270263	CYP4F2	rs2108622
Metformin	Less likely to respond	Medium	18544707	CDKN2A/B	rs10811661
Troglitazone	Less likely to respond	Medium	18544707	CDKN2A/B	rs10811661
Cisplatin	Increased risk of nephrotoxicity	Low	19625999	SLC22A2	rs316019
Citalopram	May increase risk of suicidal ideation during therapy	Low	17898344	GRIA3	rs4825476
Escitalopram; Nortriptyline	Depression may not respond as well	Low	19365399	NR3C1	rs10482633
Morphine	May require higher dose for pain relief	Low	17156920	COMT	rs4680
Paclitaxel	Cancer may respond less well	Low	18836089	ABCB1	rs1045642
Pravastatin	May require higher dose	Low	15116054	SLCO1B1	rs2306283
Talinolol	May require higher dose	Low	18334920	ABCC2	rs2273697
Sildenafil	May not respond as well	Low	12576843	GNB3	rs5443

Copy Number Variations

No interpretable CNVs for drug response

No CNVs in CYP2D6, CYP2C9, CYP3A4, CYP3A5

So any variation in these is due to SNPs.

Rare/Novel nonsyn. damaging SNPs

SNP_loc	Ref	pt0	Coding	PK/ PD?	Gene	related drugs
1:33251518	G	CG	H191D	**PK**	AK2	**adefovir dipivoxil; tenofovir;**
16:49303700	G	AG	V793M	PD	CARD15	**infliximab;**
12:54774480	C	CT	H578Y	PD	ERBB3	**trastuzumab; erlotinib; gefitinib; lapatinib; PHA-665752; chloroquine; cisplatin; gemcitabine; cetuximab;**
3:124923809	T	AA	I485F	PD	MYLK	**mercaptopurine; methotrexate;**
13:98176691	T	CT	Y21C	**PK**	SLC15A1	**atorvastatin; fluvastatin; hmg coa reductase inhibitors; lovastatin; pravastatin; rosuvastatin; simvastatin;**
9:86090799	G	AG	S443F	**PK**	SLC28A3	**cladribine; fludarabine; uridine; mercaptopurine; thioguanine; antineoplastic agents; gemcitabine; azathioprine; folic acid;**
20:32342227	G	AG	P246L	PD	AHCY	**antimetabolites; mercaptopurine; methotrexate; adenosine; antineoplastic agents; azathioprine; folic acid; thioguanine;**
16:49302615	C	CT	S431L	PD	CARD15	**infliximab;**
6:32593811	G	TT	T262K	PD	HLA-DRB5	**clozapine;**
6:31484467	T	CT	I14T	PD	MICA	**mercaptopurine; methotrexate;**
11:62517376	C	CT	R534Q	**PK**	SLC22A8	**cimetidine; estrone; antiinflammatory and antirheumatic products, non-steroids; ibuprofen; indomethacin; ketoprofen; methotrexate; phenylbutazone; piroxicam; probenecid; atorvastatin; fluvastatin; hmg coa reductase inhibitors; lovastatin; pravastatin; rosuvastatin; simvastatin; adefovir dipivoxil; tenofovir; antineoplastic agents; cyanocobalamin; folic acid; leucovorin; pyridoxine;**

Lessons Learned

1. Sum total of pharmacogenetics research corpus provides some clinical implications for ~100s of drugs/ individual.
2. Information not perfect, but much of it useful and actionable for physicians.
3. Needs to be delivered in appppropriate way, sensitive to workflow of MDs.

NIH R24 GM092672

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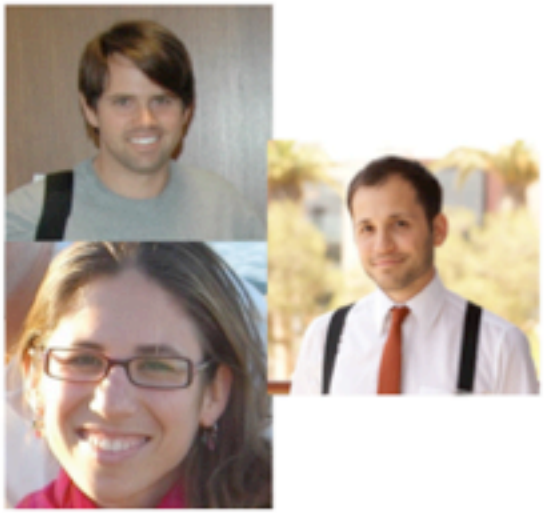
PharmGKB
Pharmacogenomics Knowledge Base



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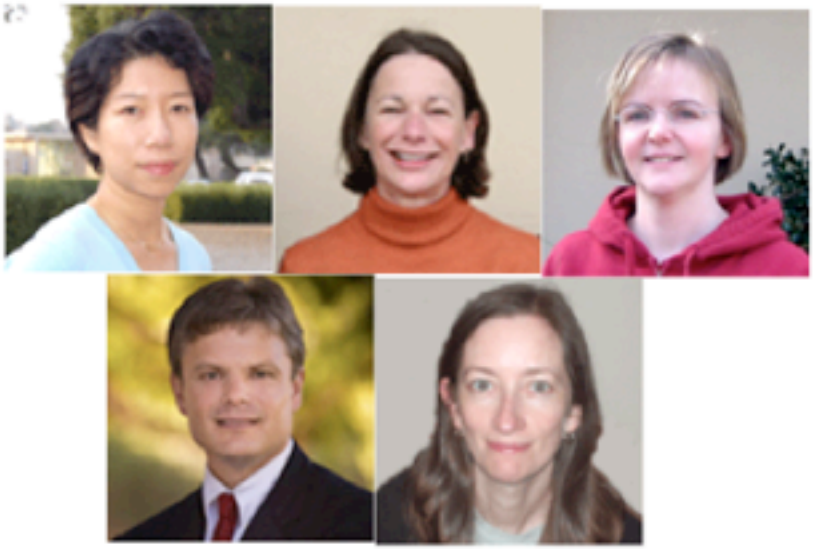

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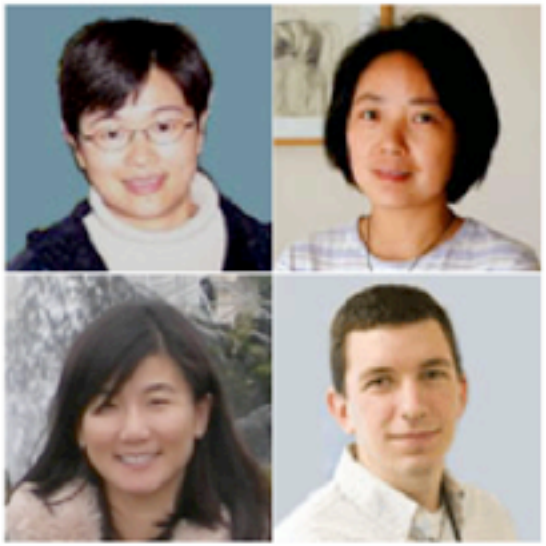

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