GEPHE SUMMARY

Gephebase Gene

CYP2C9 (https://www.gephebase.org/search-criteria?/and+Gene Gephebase=^CYP2C9^#gephebase-summary-title)

Entry Status

Published

GepheID

GP00000200

Main curator

Martin

PHENOTYPIC CHANGE

Trait Category

Physiology (https://www.gephebase.org/search-criteria?/and+Trait Category=^Physiology^#gephebase-summary-title)

Trait

Xenobiotic resistance (anti-coagulant drug response) (https://www.gephebase.org/search-criteria?/and+Trait=^Xenobiotic resistance (anti-coagulant drug response)^#gephebase-summary-title)

Trait State in Taxon A

Homo sapiens - Caucasians and Japanase

Trait State in Taxon B

Homo sapiens - Caucasians and Japanase

Ancestral State

Data not curated

Taxonomic Status

Intraspecific (https://www.gephebase.org/search-criteria?/and+Taxonomic Status=^Intraspecific^#gephebase-summary-title)

Taxon A

Latin Name

Homo sapiens (https://www.gephebase.org/search-criteria?/and+Taxon and Synonyms=^Homo sapiens^#gephebase-summary-title)

Common Name

human

Synonyms

human; man; Homo sapiens Linnaeus, 1758; Home sapiens; Homo sampiens; Homo sapeins; Homo sapian; Homo sapians; Homo sapien; Homo sapience; Homo sapiense; Homo sapients; Homo sapines; Homo spaiens; Homo spiens; Humo sapiens

Rank

species

Lineage

cellular organisms; Eukaryota; Opisthokonta; Metazoa; Eumetazoa; Bilateria; Deuterostomia; Chordata; Craniata; Vertebrata; Gnathostomata; Teleostomi; Euteleostomi; Sarcopterygii; Dipnotetrapodomorpha; Tetrapoda; Amniota; Mammalia; Theria; Eutheria; Boreoeutheria; Euarchontoglires; Primates; Haplorrhini; Simiiformes; Catarrhini; Hominoidea; Hominidae; Homininae; Homo

Parent

Homo () - (Rank: genus) (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 9605)

NCBI Taxonomy ID

9606 (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 9606)

is Taxon A an Infraspecies?

No

Taxon B

Latin Name

Homo sapiens (https://www.gephebase.org/search-criteria?/and+Taxon and Synonyms=^Homo sapiens^#gephebase-summary-title)

Common Name

human

Synonyms

human; man; Homo sapiens Linnaeus, 1758; Home sapiens; Homo sampiens; Homo sapeins; Homo sapian; Homo sapians; Homo sapien; Homo sapience; Homo sapiense; Homo sapients; Homo sapines; Homo spaiens; Homo spiens; Humo sapiens

Rank

species

Lineage

cellular organisms; Eukaryota; Opisthokonta; Metazoa; Eumetazoa; Bilateria; Deuterostomia; Chordata; Craniata; Vertebrata; Gnathostomata; Teleostomi; Euteleostomi; Sarcopterygii; Dipnotetrapodomorpha; Tetrapoda; Amniota; Mammalia; Theria; Eutheria; Boreoeutheria; Euarchontoglires; Primates; Haplorrhini; Simiiformes; Catarrhini; Hominoidea; Hominidae; Homininae; Homo

Parent

Homo () - (Rank: genus) (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 9605)

NCBI Taxonomy ID

9606 (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 9606)

is Taxon B an Infraspecies?

No

GENOTYPIC CHANGE

Generic Gene Name

CYP2C9

Synonyms

CPC9; CYP2C; CYP2C10; CYPIIC9; P450IIC9

String

9606.ENSP00000260682 (http://string-db.org/newstring_cgi/show_network_section.pl?identifier=9606.ENSP00000260682)

Sequence Similarities

Belongs to the cytochrome P450 family.

GO - Molecular Function

GO:0016491 : oxidoreductase activity (https://www.ebi.ac.uk/QuickGO/term/GO:0016491)
GO:0020037 : heme binding (https://www.ebi.ac.uk/QuickGO/term/GO:0020037)
GO:0005506 : iron ion binding (https://www.ebi.ac.uk/QuickGO/term/GO:0005506)

UniProtKB Homo sapiens

P11712 (http://www.uniprot.org/uniprot/P11712)

GenebankID or UniProtKB

M21939 (https://www.ncbi.nlm.nih.gov/nuccore/M21939)

GO:0004497 : monooxygenase activity
(https://www.ebi.ac.uk/QuickGO/term/GO:0004497)
GO:0034875 : caffeine oxidase activity
(https://www.ebi.ac.uk/QuickGO/term/GO:0034875)
GO:0016712 : oxidoreductase activity, acting on paired donors, with incorporation or
reduction of molecular oxygen, reduced flavin or flavoprotein as one donor, and
incorporation of one atom of oxygen (https://www.ebi.ac.uk/QuickGO/term/GO:0016712)
GO:0008392 : arachidonic acid epoxygenase activity
(https://www.ebi.ac.uk/QuickGO/term/GO:0008392)
GO:0008144 : drug binding (https://www.ebi.ac.uk/QuickGO/term/GO:0008144)
GO:0008395 : steroid hydroxylase activity
(https://www.ebi.ac.uk/QuickGO/term/GO:0008395)

GO - Biological Process

GO:0055114 : oxidation-reduction process
(https://www.ebi.ac.uk/QuickGO/term/GO:0055114)
GO:0042737 : drug catabolic process (https://www.ebi.ac.uk/QuickGO/term/GO:0042737)
GO:0017144 : drug metabolic process (https://www.ebi.ac.uk/QuickGO/term/GO:0017144)
GO:0019373 : epoxygenase P450 pathway
(https://www.ebi.ac.uk/QuickGO/term/GO:0019373)
GO:0042738 : exogenous drug catabolic process
(https://www.ebi.ac.uk/QuickGO/term/GO:0042738)
GO:0042759 : long-chain fatty acid biosynthetic process
(https://www.ebi.ac.uk/QuickGO/term/GO:0042759)
GO:0032787 : monocarboxylic acid metabolic process
(https://www.ebi.ac.uk/QuickGO/term/GO:0032787)
GO:0016098 : monoterpenoid metabolic process
(https://www.ebi.ac.uk/QuickGO/term/GO:0016098)
GO:0097267 : omega-hydroxylase P450 pathway
(https://www.ebi.ac.uk/QuickGO/term/GO:0097267)
GO:0070989 : oxidative demethylation
(https://www.ebi.ac.uk/QuickGO/term/GO:0070989)
GO:0006805 : xenobiotic metabolic process
(https://www.ebi.ac.uk/QuickGO/term/GO:0006805)
GO:0043603 : cellular amide metabolic process
(https://www.ebi.ac.uk/QuickGO/term/GO:0043603)
GO:0006082 : organic acid metabolic process
(https://www.ebi.ac.uk/QuickGO/term/GO:0006082)
GO:0008202 : steroid metabolic process
(https://www.ebi.ac.uk/QuickGO/term/GO:0008202)
GO:0019627 : urea metabolic process (https://www.ebi.ac.uk/QuickGO/term/GO:0019627)

GO - Cellular Component

GO:0005737 : cytoplasm (https://www.ebi.ac.uk/QuickGO/term/GO:0005737)
GO:0043231 : intracellular membrane-bounded organelle
(https://www.ebi.ac.uk/QuickGO/term/GO:0043231)
GO:0005789 : endoplasmic reticulum membrane
(https://www.ebi.ac.uk/QuickGO/term/GO:0005789)
GO:0031090 : organelle membrane (https://www.ebi.ac.uk/QuickGO/term/GO:0031090)

Presumptive Null

No (https://www.gephebase.org/search-criteria?/and+Presumptive Null=^No^#gephebase-summary-title)

Molecular Type

Coding (https://www.gephebase.org/search-criteria?/and+Molecular Type=^Coding^#gephebase-summary-title)

Aberration Type

SNP (https://www.gephebase.org/search-criteria?/and+Aberration Type=^SNP^#gephebase-summary-title)

SNP Coding Change

Nonsynonymous

Molecular Details of the Mutation

I359L

Experimental Evidence

Association Mapping (https://www.gephebase.org/search-criteria?/and+Experimental Evidence=^Association Mapping^#gephebase-summary-title)

	Taxon A	Taxon B	Position
Codon	-	-	-
Amino-acid	-	-	-

Main Reference

A genome-wide association study confirms VKORC1, CYP2C9, and CYP4F2 as principal genetic determinants of warfarin dose. (2009) (https://pubmed.ncbi.nlm.nih.gov/19300499)

Authors

Takeuchi F; McGinnis R; Bourgeois S; Barnes C; Eriksson N; Soranzo N; Whittaker P; Ranganath V; Kumanduri V; McLaren W; Holm L; Lindh J; Rane A; Wadelius M; Deloukas P

Abstract

We report the first genome-wide association study (GWAS) whose sample size (1,053 Swedish subjects) is sufficiently powered to detect genome-wide significance (p<1.5 x 10(-7)) for polymorphisms that modestly alter therapeutic warfarin dose. The anticoagulant drug warfarin is widely prescribed for reducing the risk of stroke, thrombosis, pulmonary embolism, and coronary malfunction. However, Caucasians vary widely (20-fold) in the dose needed for therapeutic anticoagulation, and hence prescribed doses may be too low (risking serious illness) or too high (risking severe bleeding). Prior work established that approximately 30% of the dose variance is explained by single nucleotide polymorphisms (SNPs) in the warfarin drug target VKORC1 and another approximately 12% by two non-synonymous SNPs (*2, *3) in the cytochrome P450 warfarin-metabolizing gene CYP2C9. We initially tested each of 325,997 GWAS SNPs for association with warfarin dose by univariate regression and found the strongest statistical signals (p<10(-78)) at SNPs clustering near VKORC1 and the second lowest p-values (p<10(-31))

emanating from CYP2C9. No other SNPs approached genome-wide significance. To enhance detection of weaker effects, we conducted multiple regression adjusting for known influences on warfarin dose (VKORC1, CYP2C9, age, gender) and identified a single SNP (rs2108622) with genome-wide significance (p = 8.3 x 10(-10)) that alters protein coding of the CYP4F2 gene. We confirmed this result in 588 additional Swedish patients (p<0.0029) and, during our investigation, a second group provided independent confirmation from a scan of warfarin-metabolizing genes. We also thoroughly investigated copy number variations, haplotypes, and imputed SNPs, but found no additional highly significant warfarin associations. We present power analysis of our GWAS that is generalizable to other studies, and conclude we had 80% power to detect genome-wide significance for common causative variants or markers explaining at least 1.5% of dose variance. These GWAS results provide further impetus for conducting large-scale trials assessing patient benefit from genotype-based forecasting of warfarin dose.

Additional References

Genome-wide association study identifies genetic determinants of warfarin responsiveness for Japanese. (2010) (https://pubmed.ncbi.nlm.nih.gov/20833655)

RELATED GEPHE

Related Genes

4 (alcohol dehydrogenase (ADH1B), CYP4F2, MDR1, Vkorc1) (https://www.gephebase.org/search-criteria?/or+Taxon ID=^9606^/and+Trait=Xenobiotic resistance/and+groupHaplotypes=true#gephebase-summary-title)

Related Haplotypes

No matches found.

EXTERNAL LINKS

COMMENTS