

GEPHE SUMMARY

	Gephebase Gene		GepheID
CYP4F2 (https://www.gephebase.org/search-criteria?/and+GeneGephebase=~CYP4F2^#gephebase-summary-title)		GP00000203	
	Entry Status	Martin	Main curator
Published			

PHENOTYPIC CHANGE

	Trait Category		
Physiology (https://www.gephebase.org/search-criteria?/and+TraitCategory=~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 Japanese			
	Trait State in Taxon B		
Homo sapiens - Caucasians and Japanese			
	Ancestral State		
Data not curated			
	Taxonomic Status		
Intraspecific (https://www.gephebase.org/search-criteria?/and+TaxonomicStatus=~Intraspecific^#gephebase-summary-title)			
	Taxon A		Taxon B
	Latin Name		Latin Name
Homo sapiens (https://www.gephebase.org/search-criteria?/and+Taxon+and+Synonyms=~Homo+sapiens^#gephebase-summary-title)		Homo sapiens (https://www.gephebase.org/search-criteria?/and+Taxon+and+Synonyms=~Homo+sapiens^#gephebase-summary-title)	
	Common Name		Common Name
human		human	
	Synonyms		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		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		Rank
species		species	
	Lineage		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		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		Parent
Homo () - (Rank: genus) (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id=9605)		Homo () - (Rank: genus) (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id=9605)	
	NCBI Taxonomy ID		NCBI Taxonomy ID
9606 (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id=9606)		9606 (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id=9606)	
	is Taxon A an Intraspecies?		is Taxon B an Intraspecies?
No		No	

GENOTYPIC CHANGE

	Generic Gene Name		UniProtKB Homo sapiens
CYP4F2		P78329 (http://www.uniprot.org/uniprot/P78329)	
	Synonyms		GenebankID or UniProtKB
CPF2		BC067440 (https://www.ncbi.nlm.nih.gov/nuccore/BC067440)	
	String		
9606.ENSPO0000221700 (http://string-db.org/newstring.cgi/show_network_section.pl?identifier=9606.ENSPO0000221700)			
	Sequence Similarities		
Belongs to the cytochrome P450 family.			
	GO - Molecular Function		
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)			
GO:0004497 : monoxygenase activity			

(<https://www.ebi.ac.uk/QuickGO/term/GO:0004497>)
GO:0008392 : arachidonic acid epoxygenase activity
(<https://www.ebi.ac.uk/QuickGO/term/GO:0008392>)
GO:0097259 : 20-aldehyde-leukotriene B4 20-monoxygenase activity
(<https://www.ebi.ac.uk/QuickGO/term/GO:0097259>)
GO:0097258 : 20-hydroxy-leukotriene B4 omega oxidase activity
(<https://www.ebi.ac.uk/QuickGO/term/GO:0097258>)
GO:0018685 : alkane 1-monoxygenase activity
(<https://www.ebi.ac.uk/QuickGO/term/GO:0018685>)
GO:0052871 : alpha-tocopherol omega-hydroxylase activity
(<https://www.ebi.ac.uk/QuickGO/term/GO:0052871>)
GO:0052869 : arachidonic acid omega-hydroxylase activity
(<https://www.ebi.ac.uk/QuickGO/term/GO:0052869>)
GO:0050051 : leukotriene-B4 20-monoxygenase activity
(<https://www.ebi.ac.uk/QuickGO/term/GO:0050051>)
GO:0016709 : oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, NAD(P)H as one donor, and incorporation of one atom of oxygen (<https://www.ebi.ac.uk/QuickGO/term/GO:0016709>)
GO:0052872 : tocotrienol omega-hydroxylase activity
(<https://www.ebi.ac.uk/QuickGO/term/GO:0052872>)

GO - Biological Process

GO:0055114 : oxidation-reduction process
(<https://www.ebi.ac.uk/QuickGO/term/GO:0055114>)
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:0097267 : omega-hydroxylase P450 pathway
(<https://www.ebi.ac.uk/QuickGO/term/GO:0097267>)
GO:0006690 : icosanoid metabolic process
(<https://www.ebi.ac.uk/QuickGO/term/GO:0006690>)
GO:0019369 : arachidonic acid metabolic process
(<https://www.ebi.ac.uk/QuickGO/term/GO:0019369>)
GO:0007596 : blood coagulation (<https://www.ebi.ac.uk/QuickGO/term/GO:0007596>)
GO:0036101 : leukotriene B4 catabolic process
(<https://www.ebi.ac.uk/QuickGO/term/GO:0036101>)
GO:0006691 : leukotriene metabolic process
(<https://www.ebi.ac.uk/QuickGO/term/GO:0006691>)
GO:0001676 : long-chain fatty acid metabolic process
(<https://www.ebi.ac.uk/QuickGO/term/GO:0001676>)
GO:0042361 : menaquinone catabolic process
(<https://www.ebi.ac.uk/QuickGO/term/GO:0042361>)
GO:0032304 : negative regulation of icosanoid secretion
(<https://www.ebi.ac.uk/QuickGO/term/GO:0032304>)
GO:0042376 : phyloquinone catabolic process
(<https://www.ebi.ac.uk/QuickGO/term/GO:0042376>)
GO:0032305 : positive regulation of icosanoid secretion
(<https://www.ebi.ac.uk/QuickGO/term/GO:0032305>)
GO:0003095 : pressure natriuresis (<https://www.ebi.ac.uk/QuickGO/term/GO:0003095>)
GO:0008217 : regulation of blood pressure
(<https://www.ebi.ac.uk/QuickGO/term/GO:0008217>)
GO:0003091 : renal water homeostasis
(<https://www.ebi.ac.uk/QuickGO/term/GO:0003091>)
GO:0055078 : sodium ion homeostasis
(<https://www.ebi.ac.uk/QuickGO/term/GO:0055078>)
GO:0000038 : very long-chain fatty acid metabolic process
(<https://www.ebi.ac.uk/QuickGO/term/GO:0000038>)
GO:0042360 : vitamin E metabolic process
(<https://www.ebi.ac.uk/QuickGO/term/GO:0042360>)
GO:0042377 : vitamin K catabolic process
(<https://www.ebi.ac.uk/QuickGO/term/GO:0042377>)

GO - Cellular Component

GO:0016324 : apical plasma membrane
(<https://www.ebi.ac.uk/QuickGO/term/GO:0016324>)
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

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 ($p < 1.5 \times 10^{-7}$) 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 ($p = 8.3 \times 10^{-10}$) 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), CYP2C9, 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