ICH GWAS Monthly Newsletter
Issue 5 - April 2009

In this issue:

This is the fifth issue of the monthly newsletter for the ICH GWAS Study Group. This newsletter is meant to be a tool to keep investigators participating in the ICH GWAS updated on all aspects of this project, including phenotyping, genotyping, data analysis and logistics.

The newsletter will be sent out to participants on the 15th of each month (or nearest workday) as an email attachment from the Program Manager at the Coordinating Center.

If you want to add topics relevant to all investigators involved in the ICH GWAS to the next newsletter, or you'd like to give general feedback to the Newsletter Design Team please contact:
Lynelle Cortellini (lcortellini@partners.org).

Please do not forget to mark your calendars with the date for the next ICH GWAS Conference Call:

Tuesday, May 19th 2009
10-11 am, Eastern USA time

Recruitment Updates

Sites recruiting prospectively as part of GOCHA

Study site	Period	Warfarin		Non Warfarin		Total
		Case	Control	Case	Control	
Mass General Hospital	January 2009	4	2	4	-	**10**
	February 2009	2	4	5	-	**11**
	March 2009	1	2	5	0	**8**
University of Michigan	January 2009	-	-	-	2	**2**
	February 2009	1	2	1	1	**5**
	March 2009	-	3	1	2	**6**
University of Virginia	January 2009	-	-	5	-	**5**
	February 2009	-	-	-	-	**-**
	March 2009	-	2	2	25	**29**
Mayo Clinic - Jacksonville	January 2009	1	-	1	-	**2**
	February 2009	-	-	1	-	**1**
	March 2009	-	-	2	-	**2**
University of Florida	January 2009	1	-	-	1	**2**
	February 2009	-	-	-	-	**-**
	March 2009	-	-	-	1	**1**
Beth Israel Deaconess Medical Center	January 2009	-	-	2	-	**2**
	February 2009	-	5	1	1	**7**
	March 2009	-	-	1	1	**2**
Total		10	20	31	34	**95**

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Sites recruiting prospectively as part of ICH GWAS

Principal Investigator		Institution	Country of Origin	Status
Last Name	First Name			
Majersik	Jennifer	University of Utah	US	Joining
Thjis	Vincent	Leuven	Belgium	Joining
Slowik	Agnieszka	Jagiellonian University, Krakow	Poland	Joined
Dichgans	Martin	Munich	Germany	Joined

Sites recruiting retrospectively as part of ICH GWAS

Principal Investigator		Institution	Country of Origin	Number of Cases	Number of Controls	Samples received by Genotyping Center
Last Name	First Name					
Lindgren	Arne	University Hospital, Lund	Sweden	250	250	
Markus	Hugh	St. George's, University of London	UK	200	200	
Melander	Olle	Malmo University Hospital	Sweden	100	300	
Montaner	Joan	Vall d'Hebron Hospital	Spain	185	270	
Roquer	Jaume	Hospital del Mar	Spain	200	200	
Schmidt	Reinhold	Medical University Graz	Austria	400	1000	
Slowik	Agnieszka	Jagiellonian University	Poland	350	430	**Yes**

Data presented in the table above are estimates of the number of samples each participating center has pledged to provide for the ICH GWAS. Actual numbers of samples analyzed will vary depending on DNA and phenotype quality.

For further info on this topic please contact:

Alessandro Biffi, M.D.

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Spotlight: Article

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.

A Genome-Wide Association Study Confirms *VKORC1*, *CYP2C9*, and *CYP4F2* as Principal Genetic Determinants of Warfarin Dose

PLoS Genet. 2009;5(3):e1000433. Epub 2009 Mar 20

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 ($p<1.5\times10^{-7}$) 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 ~30% of the dose variance is explained by single nucleotide polymorphisms (SNPs) in the warfarin drug target *VKORC1* and another ~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 ($p=8.3\times10^{-10}$) 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.

ICH GWAS Conference Calls: Schedule and Information

Please mark your calendars with dates for the next ICH GWAS Conference Calls:

Tuesday, May 19 2009
10-11 am, Eastern USA time

As previously announced via email to all Investigators, we will be moving to a web-based conferencing system for the next ICH GWAS Conference Call. This means that we will be using Internet Connections and a Voice over IP provider. Still, we have arranged for Investigators who prefer to use a telephone line to join to be able to do so.

To get more information on the service we will be using you can visit:
http://www.paetec.com/

Please do not hesitate to contact us if you have any questions about the equipment needed for the Web-Conferencing (see box).

For further info on this topic please contact:
Alessandro Biffi, M.D.
abiffi@partners.org

EQUIPMENT NEEDED

In order to participate to the Conference Call over the Web.
Investigators will need:

- **Internet Connection**
- **Mac or PC computer**
- **Communication set**
  This typically consists of a headset: unlike music headsets, these also include a built-in microphone for conversations. They are commercially available and can be bought both online and at electronics retail stores for extremely low prices.
  Alternatively, users can use speakers on their computers to listen to conversations and buy a separate stand-alone microphone to talk. However, this solution is technically not recommended. Moreover most stand-alone microphones are only available in packages that also include a web-cam, specifically intended for use in video-conferencing.