ICH GWAS Monthly Newsletter
Issue 8 - July 2009

In this issue:

This is the eighth 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).

Currently Active ICH GWAS Sub-projects

This section of the ICH GWAS Newsletter will list all sub-project that have been proposed from Investigators. Contact information for each specific subproject will also be listed. Sub-project proposal for the ICH GWAS can be submitted for evaluation by all ICH GWAS Investigators that have already contributed samples. The ICH GWAS Sub-project proposal form can be obtained from the ICH GWAS section of the ISGC website or by contacting the Coordinating Center (see contact info for this topic).

Currently active Sub-Projects

ApoE Candidate Gene Study in ICH

Aims: Investigate the role of ApoE in ICH using a large-scale candidate-gene approach.

Current Status:

Genotyping has been completed on approximately 500 ICH cases and healthy controls.

Interim data analysis will be carried out and further genotyping performed in the next few months.

Requirements for Participation:

In silico ApoE genotype data or ICH samples eligible for ApoE genotyping.

Required phenotype data points are identical to the ICH GWAS minimal and additional requirements.

Contact: Jonathan Rosand, MD MSc
Massachusetts General Hospital
jrosand@partners.org

Consent Status in the determination of the phenotype spectrum in hemorrhagic stroke genetic research

Aims: Investigate the impact of consent status (self-consent, enrollment by proxy authorization, or waiver of consent because subject died prior to inclusion) in the ICH phenotypic spectrum in GOCHA / ICH GWAS

Current Status:

Currently available data was obtained from approximately 550 individuals (169 self-consented, 142 enrolled post mortem, and 239 enrolled via surrogate) from 7 sites. Analysis will be focused on preliminary comparisons among the 3 groups in relation to demographics (sex, race, age), risk factors, warfarin status, INR, and hemorrhage characteristics.

Requirements for Participation:

As discussed at the ICH GWAS Investigator Meeting in Munich, one group not currently represented in the data consists of eligible that declined participation. We anticipate being able to generate basic demographics on "refusers" from the MGH and UVA sites. If other individual sites have reasonably complete data on individuals who refused participation they are welcome to submit them for analysis.

Contact: Bradford B. Worrall, MD, MSc
University of Virginia Health System
bbw9r@virginia.edu

For further info on this topic please contact:
Lynelle Cortellini, M.Sc.
lcortellini@partners.org

ICH GWAS Investigators Meeting - Presentations

In an effort to keep the ISGC website current, Steve Bevan and Lynelle Cortellini will be collecting slides presented at the Munich ICH GWAS Investigators Meeting. All investigators willing to have slides posted in the ICH GWAS Members Only section of the ISGC website are invited to send a copy of their presentation to either Steve Bevan or Lynelle Cortellini (see contact info for this topic). If there are particular slides within a presentation that investigators would prefer not to be posted, please delete them from the presentation before sending it to the ISGC website team.

All presentations from the Munich ICH GWAS Investigators Meeting will be made available on the ICH GWAS section of the ISGC website shortly.

For further info on this topic please contact:

Lynelle Cortellini, M.Sc. lcortellini@partners.org

Steve Bevan, BSc PhD sbevan@sgul.ac.uk

Recruitment Updates

Sites recruiting prospectively as part of GOCHA

Study site	Period	Warfarin		Non Warfarin		Total
		Case	Control	Case	Control	
Mass General Hospital	April 2009	3	-	9	7	**19**
	May 2009	1	-	3	3	**7**
	June 2009	1	-	5	-	**6**
University of Michigan	April 2009	-	-	1	-	**1**
	May 2009	-	1	-	-	**1**
	June 2009	-	-	1	1	**2**
University of Virginia	April 2009	-	-	1	3	**4**
	May 2009	2	-	2	3	**7**
	June 2009	-	-	3	-	**3**
Mayo Clinic - Jacksonville	April 2009	-	-	1	-	**1**
	May 2009	-	-	1	3	**4**
	June 2009	-	-	2	1	**3**
University of Florida	April 2009	-	-	1	-	**1**
	May 2009	-	-	-	-	**-**
	June 2009	-	-	-	-	**-**
Beth Israel Deaconess Medical Center	April 2009	-	-	-	-	**-**
	May 2009	-	-	-	-	**-**
	June 2009	-	-	1	-	**1**
Totals		**7**	**1**	**31**	**21**	**60**

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	University Hospital Leuven	Belgium	Joining
Slowik	Agnieszka	Jagiellonian University, Krakow	Poland	Joined
Schmidt	Reinhold	Medical University Graz	Austria	Joined
Dichgans	Martin	Ludwig Maximilians University, 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					
Dichgans	Martin	Munich	Germany	50	50	
Lindgren	Arne	University Hospital, Lund	Sweden	250	250	
Macleod	Marie	University of Aberdeen	GB	40	40	
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	**Yes**
Rothwell	Peter	Oxford	UK	40	40	
Roquer	Jaume	Hospital del Mar	Spain	200	200	
Schmidt	Reinhold	Medical University Graz	Austria	42	400	**Yes**
Slowik	Agnieszka	Jagiellonian University	Poland	224	420	**Yes**
Sudlow	Cathie	Western General, Edinburgh	GB	40	40	

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.

abiffi@partners.org

Spotlight: Study

Genetic and Environmental Risk Factors for Hemorrhagic Stroke Study

The Genetic and Environmental Risk Factors for Hemorrhagic Stroke Study began in 1997 as a pilot project from the Center for Environmental Genetics to collect DNA on cases of hemorrhagic stroke that were being enrolled into the Yale Hemorrhage Study. Since that time, the project has enrolled over 1000 cases of hemorrhagic stroke and 2000 population-based controls

Through the first two iterations of the project, 600 cases of intracerebral hemorrhage (ICH) and 400 cases of subarachnoid hemorrhage were collected. Among the 600 cases of ICH, approximately 500 were among whites and had sufficient DNA available for further genotyping. The project was then resubmitted as a genome-wide association study of intracerebral hemorrhage among whites. With approval, the project restarted in July 2008. Throughout the first four years of the project, additional cases of ICH and controls will be recruited. But parallel to the recruitment effort, genotyping using the Affymetrix 6.0 genechip is being performed on the existing 500 cases and 500 population-based controls.

The study recruits cases from 16 area hospitals in a 50 mile radius from the University of Cincinnati including urban, suburban and rural regions. Controls are identified using random digit dialing and are matched to cases by age (+/- 5years), race and gender.

The genotyping facility at the Kettering Laboratory directed by Dr. Ranjan Deka performs DNA extraction, sample preparation, genotyping and genotyping calls for the study. The laboratory is the genotyping center for the NIH Funded multi-center Familial Intracranial Aneurysm study for which over 600 cases and controls have been genotyped using the Affymetrix 6.0 genechip. The study also includes a statistical center at Wake Forest University headed by Dr. Carl Langefeld. Dr. Langefeld's center has extensive experience in large scale genome-wide association studies including participation in analyses of stroke as a phenotype. In addition, statistical genetics core exists at Cincinnati Children's Hospital where quality control measures and data handling are performed.

The first year of recruitment included 114 cases of ICH of which 100 were among whites. At the current rate of recruitment, an expected 900 total cases of ICH among whites will be recruited along with 1800 controls to be genotyped. Combined with the efforts of the ISGC ICH GWAS

study, this sample size will make identification of moderate to smaller effect sizes possible. The unique opportunity and scientific responsibility in advancing our understanding of the molecular genetics of ICH is of paramount importance to principal investigators and participating staff in both studies.

Spotlight: Investigator

Daniel Woo, MD MS

Dr. Daniel Woo is the principal investigator of the Genetic and Environmental Risk Factors for Hemorrhagic Stroke study. Completing his residency in neurology from the Cleveland Clinic Foundation, Dr. Woo began a cerebrovascular disorders fellowship at the University of Cincinnati in 1998. During his fellowship year, Dr. Woo submitted a number of grant applications ultimately being funded for the proposal *Genetics of Hypertension in Intracerebral Hemorrhage* in 1999. This small grant examined several genes related to hypertension but was unable to identify a relationship between them and intracerebral hemorrhage. However, the work was important in seeding Dr. Woo's interest in genetics, the limitations of certain genetic epidemiology approaches and the need for a greater understanding of the genetics of stroke.

In 2001, Dr. Woo was also funded for his K-23 award, Familial Aggregation of Stroke with Intracerebral Hemorrhage. Through the course of his K-23, Dr. Woo attended graduate level coursework in molecular genetics which culminated in a masters of science degree in molecular genetics. Also during his K-23, Dr. Woo worked as a special volunteer in Dr. John Hardy's Laboratory of Neurogenetics at the National Institutes of Health/National Institute of Aging during the summer of 2002 and participated in 2005 in the Jackson Laboratory course "Genetics of Complex Trait Analysis". In 2008, Dr. Woo received funding for the competitive renewal of the Genetic and Environmental Risk Factors for Hemorrhagic stroke study. The proposal will perform a genome wide association study of intracerebral hemorrhage.

Dr. Woo has also had a special interest in ethics and compliance. He served as a member of the institutional review board from 2001 to 2004 and was then promoted to medical director of the Post Approval Monitoring Program. In 2008, Dr. Woo was made the Vice-Chair of the Institutional Review board at the University of Cincinnati and most recently, he was awarded academic tenure at the University of Cincinnati. Dr. Woo serves on the editorial board of the journal *Stroke* and was recently inducted into the American Neurological Association.

In addition to his academic life, Dr. Woo is married and has the "two most beautiful girls in the world". Dr. Woo is an avid golfer and an occasional long distance runner.

Spotlight: Article

Purcell S. et al, The International Schizophrenia Consortium

Common polygenic variation contributes to risk of schizophrenia and bipolar disorder.

Nature. 2009 Jul; Epub ahead of print

ABSTRACT

Schizophrenia is a severe mental disorder with a lifetime risk of about 1%, characterized by hallucinations, delusions and cognitive deficits, with heritability estimated at up to 80%. We performed a genome-wide association study of 3,322 European individuals with schizophrenia and 3,587 controls. Here we show, using two analytic approaches, the extent to which common genetic variation underlies the risk of schizophrenia. First, we implicate the major histocompatibility complex. Second, we provide molecular genetic evidence for a substantial polygenic component to the risk of schizophrenia involving thousands of common alleles of very small effect. We show that this component also contributes to the risk of bipolar disorder, but not to several non-psychiatric diseases.

Spotlight: Article

Little J, et al. STrengthening the REporting of Genetic Association Studies.

STrengthening the REporting of Genetic Association Studies (STREGA): an extension of the STROBE statement.

PLoS Med. 2009;3;6(2):e22

Making sense of rapidly evolving evidence on genetic associations is crucial to making genuine advances in human genomics and the eventual integration of this information in the practice of medicine and public health. Assessment of the strengths and weaknesses of this evidence, and hence the ability to synthesize it, has been limited by inadequate reporting of results. The STrengthening the REporting of Genetic Association studies (STREGA) initiative builds on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement and provides additions to 12 of the 22 items on the STROBE checklist. The additions concern population stratification, genotyping errors, modeling haplotype variation, Hardy-Weinberg equilibrium, replication, selection of participants, rationale for choice of genes and variants, treatment effects in studying quantitative traits, statistical methods, relatedness, reporting of descriptive and outcome data, and the volume of data issues that are important to consider in genetic association studies. The STREGA recommendations do not prescribe or dictate how a genetic association study should be designed but seek to enhance the transparency of its reporting, regardless of choices made during design, conduct, or analysis.

Full text and PDF version available at:

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=19192942