ICH GWAS Monthly Newsletter
Issue 10 - October 2009

In this issue:

Currently Active ICH GWAS Subprojects 3

Recruitment Updates 5

Enrollment status for ICH GWAS participating sites
recruiting prospectively and retrospectively

Spotlight: Article 7

Genome-wide association study identifies 19p13.3 (UNC13A) and 9p21.2
as susceptibility loci for sporadic amyotrophic lateral sclerosis

Spotlight: Article 8

Genome-wide association study identifies variants at CLU and PICALM
associated with Alzheimer's disease

Spotlight: Article 9

Genome-wide association study identifies variants at CLU and CR1
associated with Alzheimer's disease

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

Tuesday, November 17th 2009
10 - 11 AM, Eastern USA time

This is the ninth 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 completed.
Further genotyping performed in the next month.
Additional data from several ICH GWAS Investigators ready for meta-analysis.

Requirements for Participation:

In silico ApoE genotype data (raw genotyped data preferred).
Required phenotype data points are identical to the ICH GWAS
minimal and additional requirements.

Contact: Alessandro Biffi, MD
Massachusetts General Hospital
abiffi@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

Recruitment Updates

Sites recruiting prospectively as part of GOCHA

Study site	Period	Warfarin		Non Warfarin		Total
		Case	Control	Case	Control	
Mass General Hospital	July 2009	-	1	4	-	**5**
	August 2009	0	1	7	0	**8**
	September 2009	4	0	11	0	**15**
University of Michigan	July 2009	-	-	-	-	**-**
	August 2009	-	-	-	-	**-**
	September 2009	-	-	-	-	**-**
University of Virginia	July 2009	-	-	1	-	**1**
	August 2009	-	-	1	-	**1**
	September 2009	-	-	1	3	**4**
Mayo Clinic - Jacksonville	July 2009	1	1	2	2	**6**
	August 2009	-	1	2	1	**4**
	September 2009	-	-	-	2	**2**
University of Florida	July 2009	-	-	-	-	**-**
	August 2009	1	1	-	-	**2**
	September 2009	-	1	-	-	**1**
University of Washington	July 2009	-	-	-	-	**-**
	August 2009	2	-	-	-	**2**
	September 2009	-	-	-	-	**-**
Beth Israel Deaconess Medical Center	July 2009	-	1	-	-	**1**
	August 2009	-	-	-	-	**-**
	September 2009	-	-	-	-	**-**
Totals		**8**	**7**	**29**	**8**	**52**

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
Thijs	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	153	167	**Yes**
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	169	176	**Yes**
Rothwell	Peter	Oxford	UK	40	40	
Roquer	Jaume	Hospital del Mar	Spain	200	200	**Yes**
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: Article

van ES MA., Veldink JH., Saris CG., et al.

Genome-wide association study identifies 19p13.3 (UNC13A) and 9p21.2 as susceptibility loci for sporadic amyotrophic lateral sclerosis

Nat Genet. 2009 Oct;41(10):1083-87.

ABSTRACT

We conducted a genome-wide association study among 2,323 individuals with sporadic amyotrophic lateral sclerosis (ALS) and 9,013 control subjects and evaluated all SNPs with P < 1.0 x 10(-4) in a second, independent cohort of 2,532 affected individuals and 5,940 controls. Analysis of the genome-wide data revealed genome-wide significance for one SNP, rs12608932, with P = 1.30 x 10(-9). This SNP showed robust replication in the second cohort (P = 1.86 x 10(-6)), and a combined analysis over the two stages yielded P = 2.53 x 10(-14). The rs12608932 SNP is located at 19p13.3 and maps to a haplotype block within the boundaries of UNC13A, which regulates the release of neurotransmitters such as glutamate at neuromuscular synapses. Follow-up of additional SNPs showed genome-wide significance for two further SNPs (rs2814707, with P = 7.45 x 10(-9), and rs3849942, with P = 1.01 x 10(-8)) in the combined analysis of both stages. These SNPs are located at chromosome 9p21.2, in a linkage region for familial ALS with frontotemporal dementia found previously in several large pedigrees.

Spotlight: Article

Harold D., Abraham R., Hollingworth P., et al.

Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease

Nat Genet. 2009 Oct;41(10):1088-93.

ABSTRACT

We undertook a two-stage genome-wide association study (GWAS) of Alzheimer's disease (AD) involving over 16,000 individuals, the most powerful AD GWAS to date. In stage 1 (3,941 cases and 7,848 controls), we replicated the established association with the apolipoprotein E (APOE) locus (most significant SNP, rs2075650, P = 1.8 x 10(-157)) and observed genome-wide significant association with SNPs at two loci not previously associated with the disease: at the CLU (also known as APOJ) gene (rs11136000, P = 1.4 x 10(-9)) and 5' to the PICALM gene (rs3851179, P = 1.9 x 10(-8)). These associations were replicated in stage 2 (2,023 cases and 2,340 controls), producing compelling evidence for association with Alzheimer's disease in the combined dataset (rs11136000, P = 8.5 x 10(-10), odds ratio = 0.86; rs3851179, P = 1.3 x 10(-9), odds ratio = 0.86).

Spotlight: Article

Lambert JC., Heath S., Even G., et al.

Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease

Nat Genet. 2009 Oct;41(10):1094-99.

ABSTRACT

The gene encoding apolipoprotein E (APOE) on chromosome 19 is the only confirmed susceptibility locus for late-onset Alzheimer's disease. To identify other risk loci, we conducted a large genome-wide association study of 2,032 individuals from France with Alzheimer's disease (cases) and 5,328 controls. Markers outside APOE with suggestive evidence of association (P < 10(-5)) were examined in collections from Belgium, Finland, Italy and Spain totaling 3,978 Alzheimer's disease cases and 3,297 controls. Two loci gave replicated evidence of association: one within CLU (also called APOJ), encoding clusterin or apolipoprotein J, on chromosome 8 (rs11136000, OR = 0.86, 95% CI 0.81-0.90, P = 7.5 x 10(-9) for combined data) and the other within CR1, encoding the complement component (3b/4b) receptor 1, on chromosome 1 (rs6656401, OR = 1.21, 95% CI 1.14-1.29, P = 3.7 x 10(-9) for combined data). Previous biological studies support roles of CLU and CR1 in the clearance of beta amyloid (Abeta) peptide, the principal constituent of amyloid plaques, which are one of the major brain lesions of individuals with Alzheimer's disease.