ISGC ICH Bi-Monthly Newsletter
Issue 27 - May 2012

In this issue:

ICH GWAS Investigators Meeting:

To be held during the ISGC Workshop in Krakow, Poland (Date TBA)

Please contact Valerie (vvalant@partners.org) or Sarah Gramann (gramansc@UCMAIL.UC.EDU) for additional details

ISGC ICH Bi-Monthly Newsletter Issue 27 - May 2012

This is the 27th issue of the ISGC ICH bi-monthly newsletter. This newsletter is a tool for updating all members of the ISGC on aspects of projects relating to Intracerebral Hemorrhage. In addition to project updates, this will also include information on phenotyping, genotyping, data analysis and other logistics.

The newsletter will be sent out bi-monthly on the 15th of each release month (or nearest workday) as an email attachment from the Coordinating Center at Massachusetts General Hospital. Both Dr. Jonathan Rosand of Massachusetts General Hospital and Dr. Daniel Woo of The University of Cincinnati oversee this Newsletter. For study specific questions, please contact either Valerie Valant or Sarah Gramann who can direct your inquiry toward the investigating researcher.

If you would also like to add topics to the next newsletter, or provide feedback on the current newsletter, please contact Valerie Valant.

Valerie Valant
Massachusetts General Hospital
vvalant@partners.org

Sarah Gramann
The University of Cincinnati
gramansc@UCMAIL.UC.EDU

Study Updates

ERICH (Ethnic and Racial Variation in Intracerebral Hemorrhage)

Contact Site: University of Cincinnati

Aims: The ERICH study is a multi-center, prospectively recruited case-control study of spontaneous intracerebral hemorrhage. Site selection for enrollment targeted minority populations of African-American and Hispanic populations with a goal of recruiting 1000 cases in each ethnic minority as well as 1000 cases among non-Hispanic Whites. Controls are identified from the same region as the cases through random-digit dialing and all subjects undergo a direct interview and cases undergo an additional chart abstraction, 3, 6 and 12 month follow-up. Centralized neuroimaging review is performed on all cases and every fifth subject has a study-MRI performed.

Status: Case recruitment is now at 96% of target for this time point and control recruitment is at 52% of target enrollment for an overall rate of 78.8% of target. We have 931 cases of ICH enrolled plus 315 controls. Our first abstract regarding AED use after ICH was presented as an oral platform presentation at the AAN. The abstract found that AED use was still common but in our study, was not associated with an increased mortality rate which may be related to a higher Keppra use than prior studies which were predominately Dilantin based.

GERFHS: Genetic and Environmental Risk Factors for Hemorrhagic Stroke

Contact Site: University of Cincinnati

Aims: The GERFHS study is a population-based, prospectively recruited case-control study of spontaneous intracerebral hemorrhage. Demographically mached controls are identified by random digit dialing and a direct interview and chart abstraction is performed on enrolled cases and a chart abstraction on all cases of ICH within the region. Aims: To perform a genome-wide association study of ICH using Affymetrix 6.0 array to identify common variants associated with ICH.

Status: Case enrollment is in final stages. Affymetrix 6.0 genotyping on final sample set to be completed later this year. Working on next phase of the project in conjunction with Dr. Rosand.

ICH GWAS (Intercerebral Hemorrhage – Genome Wide Association Study)

Contact Site: Massachusetts General Hospital and University of Cincinnati

Aims: This multi-center genome-wide association study (GWAS) is designed to identify genetic determinants of:

1) Risk of intracerebral hemorrhage (ICH) using a case-control design
2) Clinical course of ICH using a cohort design of individuals who have suffered an ICH.

Status: No update as of January 2012 (MGH): *We are currently in the process of genotyping warfarin related ICH cases and controls. Currently outlining replication steps as described below in "Chromosome 11: Taqman Replication."*

ICH Meta-Analysis

Contact Site: Massachusetts General Hospital

Aims: To identify and uncover the common genetic determinants of risk of non-warfarin intracerebral hemorrhage.

Status: No update as of January 2012: *Meta-analysis of GOCHA and GERFHS data in all ICH and ICH subtypes (lobar and deep ICH) showed a significant association between all ICH and SNPs on chromosome 11 and several promising stacks on other chromosomes. Further investigation has shown these SNPs on chromosome 11 lie on an uncategorized pseudo-gene, which is also a CNV region. We are currently performing a CNV analysis of the GOCHA and GERFHS subjects as well as running Taqman replication of the top two SNPs from the meta-analysis (described below in "Chromosome 11: Taqman Replication.")*

Chromosome 11: Taqman Replication

Contact Site: Massachusetts General Hospital

Aims: To replicate association of chromosome 11 SNPs from GOCHA-GERFHS meta-analysis.

Status: No update as of January 2012: *GOCHA and GERFHS have selected top SNPs from chromosome 11 for replication in previously non-genotyped samples. MGH is replicating the top chromosome 11 SNP from the ICH meta-analysis using Taqman Assay to look for an association between the subjects' genotype and incidence of ICH. The assay is being run on 408 cases and 160 controls. Projected completion is Friday, March 3rd.*

ExomeChip Genotyping

Contact Site: Massachusetts General Hospital and University of Cincinnati

Aims: To test the rare variant risk hypothesis of ICH in samples which have already completed genotyping through GWAS.

Status: No update as of March 2012*: Samples have been submitted and chips have been received by Broad Institute. Currently in the process of plating samples to be genotyped. Results are to be received in spring 2012.*

A Genetic Score Analysis: Common Genetic Variants (CGVs) for Hypertension and Risk of Intracerebral Hemorrhage

Contact Site: Massachusetts General Hospital

Aims: 1) To examine whether increasing numbers of common genetic variants associated with hypertension influence the risk of ICH.

Hypothesis: Increasing numbers of CGVs associated with HTN produce additive increases in ICH risk.

2) To examine whether increasing numbers of common genetic variants associated with hypertension influence the radiological features and clinical outcome of ICH.

Hypothesis: Increasing numbers of CGVs associated with HTN produce larger hematomas, as measured upon at admission and at 24 hours, and worsens clinical outcome.

Status: Data analysis completed. Manuscript under review.

Risk Variants for White Matter Hyperintensity (WMH) influence risk of Intracerebral Hemorrhage (ICH)

Contact Site: Massachusetts General Hospital

Aims: 1) To examine whether increasing numbers of common genetic variants associated with hypertension influence the risk of ICH.

Hypothesis: Increasing numbers of CGVs associated with HTN produce additive increases in ICH risk.

2) To examine whether increasing numbers of common genetic variants associated with hypertension influence the radiological features and clinical outcome of ICH.

Hypothesis: Increasing numbers of CGVs associated with HTN produce larger hematomas, as measured upon at admission and at 24 hours, and worsens clinical outcome.

Status: Data analysis completed. Manuscript in preparation.

ICH Publications

- Jeanne M, Labelle-Dumais C, Jorgensen J, Kauffman WB, Mancini GM, Favor J, Valant V, Greenberg SM, Rosand J, Gould DB. COL4A2 Mutations Impair COL4A1 and COL4A2 Secretion and Cause Hemorrhagic Stroke. Am J Hum Genet. 2012 Jan 13;90(1):91-101.
- Biffi A, Battey TW, Ayres AM, Cortellini L, Schwab K, Gilson AJ, Rost NS, Viswanathan A, Goldstein JN, Greenberg SM, Rosand J. Warfarin-related intraventricular hemorrhage: imaging and outcome. Neurology. 2011 Nov 15;77(20):1840-6.
- Biffi A, Cortellini L, Nearnberg CM, Ayres AM, Schwab K, Gilson AJ, Rost NS, Goldstein JN, Viswanathan A, Greenberg SM, Rosand J. Body mass index and etiology of intracerebral hemorrhage. Stroke. 2011;42:2526-30.
- Adeoye O, Haverbusch M, Woo D, Sekar P, Moomaw CJ, Kleindorfer D, Stettler B, Kissela BM, Broderick JP, Flaherty ML. Is Emergency Department Disposition Associated with Intracerebral Hemorrhage Mortality? Am J Emerg Med. 2011;29:391-395.
- Adeoye O, Woo D, Haverbusch M, Sekar P, Moomaw C, Broderick J, Flaherty M. Surgical Management and Case-Fatality Rates of Intracerebral Hemorrhage in 1988 and 2005. Neurosurgery 2008;63:1113-1118 DOI:1227/01.NEU.0000330414.56390.DE PMCID:PMC 100360
- Biffi A, Anderson CD, Jagiella JM, Schmidt H, Kissela B, Hansen BM, Jimenez-Conde J, Pires CR, Ayres AM, Schwab K, Cortellini L, Pera J, Urbanik A, Romero JM, Rost NS, Goldstein JN, Viswanathan A, Pichler A, Enzinger C, Rabionet R, Norrving B, Tirschwell DL, Selim M, Brown DL, Silliman SL, Worrall BB, Meschia JF, Kidwell CS, Broderick JP, Greenberg SM, Roquer J, Lindgren A, Slowik A, Schmidt R, Woo D, Rosand J; on behalf of the International Stroke Genetics Consortium. APOE genotype and extent of bleeding and outcome in lobar intracerebral haemorrhage: a genetic association study. Lancet Neurology. 2011;10:702-9.
- Flaherty M, Tao H, Haverbusch M, Sekar P, Kleindorfer D, Kissela B, Khatri P, Stettler B, Adeoye O, Moomaw C, Broderick J, Woo D. Warfarin use leads to larger intracerebral Hematomas. Neurology 2008;71:1084-1089.
- Biffi A, Devan WJ, Anderson CD, Ayres AM, Schwab K, Cortellini L, Viswanathan A, Rost NS, Smith EE, Goldstein JN, Greenberg SM, Rosand J. Statin use and outcome after intracerebral hemorrhage: case-control study and meta-analysis. Neurology. 2011;76:1581-8.
- Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the tipping point: the decision to anticoagulate *patients with atrial fibrillation.* Circulation: Cardiovascular Quality and Outcomes. 2011;4:14-21.
- Biffi A, Plourde A, Shen Y, Onofrio R, Smith EE, Frosch M, Prada CM, Gusella J, Greenberg SM, Rosand J. *Screening for Familial APP Mutations in Sporadic Cerebral Amyloid Angiopathy*. PLoS ONE 2010; 5: e13949.
- Biffi A, Sonni A, Anderson CD, Kissela B, Jagiella JM, Schmidt E, Jimenez-Conde J, Hansen BM, Fernandez-Cadenas I, Cortellini L, Ayres A, Schwab K, Juchniewicz K, Urbanik A, Rost NS, Viswanathan A, Seifert-Held T, Stoegerer E, Tomás M, Rabionet R, Estivill X, Brown DL, Silliman SL, Selim M, Worrall BB, Meschia JF, Montaner J, Lindgren A, Roquer J, Schmidt R, Greenberg SM, Slowik A, Broderick JP, Woo D, Rosand J. *Variants at APOE Influence Risk of Deep and Lobar Intracerebral Hemorrhage*. Annals of Neurology 2010;68:934-43.

- Biffi A, Halpin A, Towfighi A, Gilson A, Busl K, Rost NS, Smith EE, Greenberg SM, Rosand J, Viswanathan A. *Antiplatelet Agents and Recurrent Intracerebral Hemorrhage in Cerebral Amyloid Angiopathy*. Neurology. 2010;75:693-698
- Biffi A, Anderson CD, Nalls M, Rahman R, Cortellini L, Rost NS, Greenberg SM, Ross O, Furie KL, Meschia J, Singleton AB, Saxena R, Rosand J. *Principal Component Analysis for Assessment of Population Stratification in Mitochondrial Medical Genetics.* American Journal of Human Genetics 2010;86:904-917.
- Nalls M, Biffi A, Matarin M, Anderson CD, Chasman DI, Bevan S, Spencer CA, Gschwendtner A, Sale MM, Wu L, Salaheen D, Deary IJ, Lagenfeld C, Peddareddygari LR, Cole JW, Arapelli SK, Aucutt-Walter N, Brott TG, Broderick JP, Brown DL, Brown M, Brown RD, Buring JE, Cortellini M, Danesh J, Deka R, Elias GA, Ferrucci L, Frossard P, Furie KL, Gibbs JR, Greenberg SM, Gul M, Hardy J, Harris SE, Hernandez DG, Hsu F, Indugula S, Jackson C, Kissela B, Liu L, Metter EJ, Mitchell BD, Murphy L, Mychaleckyj JC, O'Connell JR, Pare G, Parker AN, Patel RK, Poole D, Rasheed A, Richie A, Rothwell PM, Rose L, Ross OA, Rost NS, Schwab K, Sen S, Silliman SL, Soto-Ortolaza AI, Starr JM, Stine OC, Stamova B, Xu H, Erich Wichmann H, Young LE, Young W, Zaid M, Zhang H, Kittner SJ, Grewal RP, Woo D, Sudlow C, Kamal AK, Wang X, Sharp FR, Worrall BB, Dichgans M, Markus HS, Ridker PM, de Bakker PIW, Singleton A, Meschia J, Rosand J on behalf of the International Stroke Genetics Consortium and the Wellcome Trust Case-Control Consortium 2. *Failure to Validate Associations between Variants on Chromosome 12p13 and Stroke*. New England Journal of Medicine. 2010;362:1547-155
- Eckman MH, Greenberg SM, Rosand J. *Should we test for CYP2C9 before initiating anticoagulant therapy in patients with atrial fibrillation?* J Gen Intern Med. 2009;24:543-549.
- Genes for Cerebral Hemorrhage on Anticoagulation (GOCHA) Collaborative Group. *Exploiting common genetic variation to make anticoagulation safer*. Stroke. 2009;40:S64-66.

US GOCHA Site Recruitment Update

Principal Investigator		Institution	Warfarin Cases Recruited: 3/1/12-4/30/12	Warfarin Control Recruited: 3/1/12-4/30/12
Last Name	First Name			
Brown	Devin	University of Michigan	1	0
Majersik	Jennifer	University of Utah	1	0
Meschia	James	Mayo Clinic, Jacksonville	0	0
Rosand	Jonathan	Massachusetts General Hosp.	5	0
Selim	Magdy	Beth Israel Deaconess Med. Ctr.	0	0
Silliman	Scott	University of Florida	0	1
Tirschwell	David	University of Washington	0	0
Worrall	Brad	University of Virginia	0	0

Sites recruiting prospectively as part of ICH GWAS

Principal Investigator		Institution	Country of Origin	Status
Last Name	First Name			
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

Data presented in the table below 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.

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	**Yes**
Levi	Chris	University of Newcastle	Australia	25		
Lindgren	Arne	University Hospital, Lund	Sweden	153	167	**Yes**
Macleod	Mary	University of Aberdeen	UK	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	**Yes**
Roquer	Jaume	Hospital del Mar	Spain	200	200	**Yes**
Schmidt	Reinhold	Medical University Graz	Austria	42	400	**Yes**
Sharma	Pankaj	Hammersmith Hospitals & Imperial College London	UK	49		**Yes**
Slowik	Agnieszka	Jagiellonian University	Poland	224	420	**Yes**
Sudlow	Cathie	Western General, Edinburgh	UK	100	100	

For further information on these topics please contact either:

Valerie Valant
Massachusetts General Hospital
vvalant@partners.org

Sarah Gramann
The University of Cincinnati
gramansc@UCMAIL.UC.EDU