

# ISGC ICH Bi-Monthly Newsletter

## Issue 28 - July 2012

### In this issue:

#### Study Updates

|                                           |   |
|-------------------------------------------|---|
| ERICH.....                                | 3 |
| GERFHS.....                               | 3 |
| ICH GWAS.....                             | 3 |
| ICH Meta-Analysis.....                    | 4 |
| ExomeChip.....                            | 4 |
| Risk Variants for WMH.....                | 4 |
| BP-related Genetics Variants.....         | 5 |
| Effect Modification by Admission BP ..... | 5 |

|                               |   |
|-------------------------------|---|
| ICH Related Publications..... | 6 |
|-------------------------------|---|

#### ICH GWAS Recruitment Updates

|                          |   |
|--------------------------|---|
| US Sites.....            | 8 |
| International Sites..... | 9 |

#### ICH GWAS Investigators Meeting:

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

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

# ISGC ICH Bi-Monthly Newsletter Issue 28 - July 2012

This is the 28th 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 15<sup>th</sup> 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](mailto:vvalant@partners.org)

Sarah Gramann  
The University of Cincinnati  
[gramansc@UCMAIL.UC.EDU](mailto: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: The ERICH study celebrated a landmark milestone in June with their one thousandth case of ICH enrolled in under 18 months of active recruitment. The study has a number of abstracts being prepared for the International Stroke Conference.

### **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 matched 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: Genotyping of GERFHS III recruited cases and controls are underway. Case recruitment is at over 500 cases of ICH and should be complete this winter.

### **ICH GWAS (Intracerebral 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: We have successfully completed genotyping of 190 Warfarin-cases and 190 Warfarin-controls and are in the process of submitting another 4 plates for GWAS.

## 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: We were unable to replicate the top hits on chromosome 11 in our additional ICH subjects using Taqman array. Our collaborator Danish Saleheen from University of Pennsylvania was also not able to replicate these findings in his Pakistani ICH cohort. We are planning on including the recently genotyped 190 GOCHA Warfarin-ICH cases and 190 GOCHA Warfarin controls on Illumina OmniExpress into the meta-analysis to better refine our results.

## 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: Samples have been plated and are in queue for ExomeChip genotyping at the Broad Institute. Results expected to be received late summer 2012.

## 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.

## **Effect of blood pressure-related genetic variants on intracerebral hemorrhage volume and outcome**

Contact Site: Massachusetts General Hospital

Aims: 1) To evaluate the effect of blood pressure-related risk alleles on the admission volumes of primary intracerebral hemorrhage  
2) To evaluate the effect of blood pressure-related risk alleles on the admission volumes of warfarin-related intracerebral hemorrhage  
3) To evaluate the effect of blood pressure-related risk alleles on clinical outcome of primary intracerebral hemorrhage  
4) To evaluate the effect of blood pressure-related risk alleles on clinical outcome of warfarin-related intracerebral hemorrhage

Status: Analysis completed. Manuscript in preparation.

## **Effect modification by admission blood pressure of the effect of APOE on ICH admission volumes**

Contact Site: Massachusetts General Hospital

Aims: 1) To assess differences in effect estimates of APOe on first ICH admission volume across strata of admission blood pressure.  
2) To assess differences in effect estimates of APOe on recurrent ICH admission volume across strata of admission blood pressure.  
3) To assess differences in effect estimates of APOe on clinical outcome of first and recurrent ICH across strata of admission blood pressure.

Status: Analysis completed. Manuscript in preparation.

## ICH Publications

- Falcone GJ, Biffi A, Devan W, Jagiella JM, Schmidt H, Kissela K, Hansen BM, Jimenez-Conde J, Giralt-Steinhauer E, Elosua R, Cuadrado-Godia E, Soriano C, Ayres AM, Schwab K, Pera J, Urbanik A, Rost NS, Goldstein JN, Viswanathan A, Pichler A, Enzinger C, Norrving B, Tirschwell DL, Selim M, Brown DL, Silliman SL, Worrall BB, Meschia JF, Kidwell CS, Montaner J, Fernandez-Cadenas I, Delgado P, Broderick JP, Greenberg SM, Roquer J, Lindgren A, Slowik A, Schmidt R, Flaherty ML, Kleindorfer DO, Langefeld CD, Woo D, Rosand J. Burden of risk alleles for Hypertension Increases Risk of Intracerebral Hemorrhage. *Stroke* 2012. In press.
- 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 PMID: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, Salameen D, Deary IJ, Lagenfeld C, Peddareddygar 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.

# ISGC ICH Bi-Monthly Newsletter Issue 28 - July 2012

## US GOCHA Site Recruitment Update

| Principal Investigator |            | Institution                     | Warfarin Cases Recruited:<br>5/1/12-6/20/12 | Warfarin Control Recruited:<br>5/1/12-6/20/12 |
|------------------------|------------|---------------------------------|---------------------------------------------|-----------------------------------------------|
| Last Name              | First Name |                                 |                                             |                                               |
| Brown                  | Devin      | University of Michigan          | 0                                           | 0                                             |
| Majersik               | Jennifer   | University of Utah              | 1                                           | 0                                             |
| Meschia                | James      | Mayo Clinic, Jacksonville       | 1                                           | 0                                             |
| Rosand                 | Jonathan   | Massachusetts General Hosp.     | 3                                           | 0                                             |
| Selim                  | Magdy      | Beth Israel Deaconess Med. Ctr. | 0                                           | 0                                             |
| Silliman               | Scott      | University of Florida           | 0                                           | 0                                             |
| Tirschwell             | David      | University of Washington        | 0                                           | 0                                             |
| Worrall                | Brad       | University of Virginia          | 0                                           | 0                                             |



# ISGC ICH Bi-Monthly Newsletter Issue 28 - July 2012

## 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](mailto:vvalant@partners.org)

Sarah Gramann  
The University of Cincinnati  
[gramansc@UCMAIL.UC.EDU](mailto:gramansc@UCMAIL.UC.EDU)