ICH GWAS Monthly Newsletter
Issue 19 - September 2010

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Upcoming ICH GWAS Conference Call:
The next ICH GWAS Conference Call will be held on:

September 24th 2010
1:00 pm US Eastern Time

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This is the 19th 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 to the next newsletter, or you'd like to give general feedback to the Newsletter Design Team please contact:
Lynelle Cortellini
(lcortellini@partners.org).

ICH GWAS Publications

- 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. In press.
- 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. In press.
- 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.

Currently Active ICH GWAS Sub-projects

This section of the ICH GWAS Newsletter lists all sub-projects proposed by Investigators. Contact information for each specific subproject is listed. All Investigators who have contributed samples are invited to submit proposals. Once submitted, proposals are circulated to all investigators for comment and approval. 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, ICH Volume and ICH Outcome: A Genetic Association Study

Aims: Investigate the role of ApoE in determining ICH volume and functional outcome after hemorrhagic stroke using a large-scale candidate-gene approach.

Current Status:

Initial analysis completed in samples provided by the US ICH GWAS sites.
Replication completed in samples provide by ISGC Investigators
Extension analysis to African-American US ICH GWAS subjects completed.

Additional Participating Institutions are invited to join.

Preliminary results submitted as abstract / oral presentation to the
International Stroke Conference 2011

Requirements for Participation:

ICH cases with available APOE genotype data and the following minimal data points:

- Age
- Gender
- Race / Ethnicity

- ICH Location (lobar / deep / cerebellar)
- History of hypertension, diabetes, coronary artery disease, atrial fibrillation
- Pre-ICH use of ASA / Antiplatelets and Warfarin
- ICH volume at baseline

Additional (optional) data points include:

- ICH volume on follow-up scan
- CAA diagnosis according to the Boston Criteria
- Mortality data (at 30 days and/or 90days)
- Outcome data (Glasgow Outcome Scale or mRS at 30 days and/or 90 days)
- Intraventricular extension and/or Intraventricular Hemorrhage volume (baseline)

***Please note**: participation to the project requires sharing of existing genotype and phenotype data. No additional APOE genotyping is planned as part of this sub-project.*

Deadline: Institutions interested in participating should contact the coordinating center at MGH (see below) no later than **September 30, 2010**.

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. This was presented as a poster at the International Stroke Conference in San Antonio in February.

Requirements for Participation:

As previously discussed, one group not currently represented in the data consists of patients who are eligible but who decline to participate in genetic studies. 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 Conference Call: September 2010

The next ICH GWAS Conference Call will be held on **September 24th 2010 at 1:00 PM Eastern US Time**. All ICH GWAS Principal Investigators and Study Personnel are welcome to join.

The conference call agenda will be circulated separately, but ICH GWAS Investigators are invited to submit topics they would like to be discussed to Lynelle Cortellini (lcortellini@partners.org) for inclusion in the final agenda by Thursday, September 23rd.

As we have done in the past, we will be holding the conference call using the online service Skype. This service requires that each call participant have a user account in order to connect to the call. If you do not already have a Skype account, you can go to the Skype website (http://www.skype.com) and set up a free account by downloading the Skype software and following the instructions to install it onto your computer. Please note that you will either need a headset with microphone or your computer must have a built in microphone in order to connect to this call.

Once you have set up an account with Skype, please email Lynelle Cortellini (lcortellini@partners.org) with your Skype username by Thursday, September 23rd at 3 pm Eastern US time. We will add everyone's usernames to the call contact list and administer the call from Boston (username: "RosandLab"). Once you are added to the contact list, you will be prompted to confirm and add the "RosandLab" to your contact list.

At the start time of the call, please login to your Skype account and wait for the call from "RosandLab". Once you accept the call request, you will be added to the conference call.

Some individuals are not permitted access to Skype at their institutions. If you cannot access Skype and plan to be on the conference call, please email Lynelle the phone number at which you can be reached for the call by Thursday, 9/23 at 3pm and we will call your office phone using the Skype program.

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	**Yes**
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**
Slowik	Agnieszka	Jagiellonian University	Poland	224	420	**Yes**
Sudlow	Cathie	Western General, Edinburgh	UK	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

International Headache Genetics Consortium

Genome-wide association study of migraine implicates a common susceptibility variant on 8q22.1.

Nat Genet. 2010 Aug 29.

ABSTRACT

Migraine is a common episodic neurological disorder, typically presenting with recurrent attacks of severe headache and autonomic dysfunction. Apart from rare monogenic subtypes, no genetic or molecular markers for migraine have been convincingly established. We identified the minor allele of rs1835740 on chromosome 8q22.1 to be associated with migraine (P = 5.38 x 10(-9), odds ratio = 1.23, 95% CI 1.150-1.324) in a genome-wide association study of 2,731 migraine cases ascertained from three European headache clinics and 10,747 population-matched controls. The association was replicated in 3,202 cases and 40,062 controls for an overall meta-analysis P value of 1.69 x 10(-11) (odds ratio = 1.18, 95% CI 1.127-1.244). rs1835740 is located between MTDH (astrocyte elevated gene 1, also known as AEG-1) and PGCP (encoding plasma glutamate carboxypeptidase). In an expression quantitative trait study in lymphoblastoid cell lines, transcript levels of the MTDH were found to have a significant correlation to rs1835740 (P = 3.96 x 10(-5), permuted threshold for genome-wide significance 7.7 x 10(-5)). To our knowledge, our data establish rs1835740 as the first genetic risk factor for migraine.

Spotlight: Article

Mulle JG, Dodd AF, McGrath JA et al.

Microdeletions of 3q29 confer high risk for schizophrenia.

Am J. Hum. Genet. 2010;87(2):229-236

ABSTRACT

Schizophrenia (SZ) is a severe psychiatric illness that affects approximately 1% of the population and has a strong genetic underpinning. Recently, genome-wide analysis of copy-number variation (CNV) has implicated rare and de novo events as important in SZ. Here, we report a genome-wide analysis of 245 SZ cases and 490 controls, all of Ashkenazi Jewish descent. Because many studies have found an excess burden of large, rare deletions in cases, we limited our analysis to deletions over 500 kb in size. We observed seven large, rare deletions in cases, with 57% of these being de novo. We focused on one 836 kb de novo deletion at chromosome 3q29 that falls within a 1.3-1.6 Mb deletion previously identified in children with intellectual disability (ID) and autism, because increasing evidence suggests an overlap of specific rare copy-number variants (CNVs) between autism and SZ. By combining our data with prior CNV studies of SZ and analysis of the data of the Genetic Association Information Network (GAIN), we identified six 3q29 deletions among 7545 schizophrenic subjects and one among 39,748 controls, resulting in a statistically significant association with SZ ($p = 0.02$) and an odds ratio estimate of 17 (95% confidence interval: 1.36-1198.4).

Moreover, this 3q29 deletion region contains two linkage peaks from prior SZ family studies, and the minimal deletion interval implicates 20 annotated genes, including PAK2 and DLG1, both paralogous to X-linked ID genes and now strong candidates for SZ susceptibility.