ICH GWAS Monthly Newsletter
Issue 20 - October 2010

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Please fill in the Doodle with preferred time and date for the call
http://www.doodle.com/6p3fiar75tzqg2d4

ICH GWAS Monthly Newsletter Issue 20 - October 2010

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;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.

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 have submitted data for analysis.

Final analyses in progress. A preliminary draft of the paper will be circulated to participating Investigators shortly.

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 if still willing to join this collaborative effort (see below).

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: November 2010

The next ICH GWAS Conference Call will be held in **November 2010**. All ICH GWAS Principal Investigators and Study Personnel are welcome to join.

Available time and dates are listed below. Please note that all times are Eastern US Time.

- Thursday November 11 at 11:00 am
- Thursday November 11 at 12:00 pm
- Monday, November 22 at 12:00 pm
- Tuesday, November 30 at 11:00 am

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.

In order to indicate your availability for this call, please visit the poll website below:

http://www.doodle.com/6p3fiar75tzqg2d4

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

Li Y, Vinckenbosch N, Tian G et al.

Resequencing of 200 human exomes identifies an excess of low-frequency non-synonymous coding variants.

Nat Genet. 2010 Oct 3.

ABSTRACT

Targeted capture combined with massively parallel exome sequencing is a promising approach to identify genetic variants implicated in human traits. We report exome sequencing of 200 individuals from Denmark with targeted capture of 18,654 coding genes and sequence coverage of each individual exome at an average depth of 12-fold. On average, about 95% of the target regions were covered by at least one read. We identified 121,870 SNPs in the sample population, including 53,081 coding SNPs (cSNPs). Using a statistical method for SNP calling and an estimation of allelic frequencies based on our population data, we derived the allele frequency spectrum of cSNPs with a minor allele frequency greater than 0.02. We identified a 1.8-fold excess of deleterious, non-syonomyous cSNPs over synonymous cSNPs in the low-frequency range (minor allele frequencies between 2% and 5%). This excess was more pronounced for X-linked SNPs, suggesting that deleterious substitutions are primarily recessive.

Spotlight: Article

Mulle JG, Dodd AF, McGrath JA et al.

Mutations in GRIN2A and GRIN2B encoding regulatory subunits

of NMDA receptors cause variable neurodevelopmental phenotypes.

Nat Genet. 2010 Oct 3.

ABSTRACT

N-methyl-D-aspartate (NMDA) receptors mediate excitatory neurotransmission in the mammalian brain. Two glycine-binding NR1 subunits and two glutamate-binding NR2 subunits each form highly Ca(2+)-permeable cation channels which are blocked by extracellular Mg(2+) in a voltage-dependent manner. Either GRIN2B or GRIN2A, encoding the NMDA receptor subunits NR2B and NR2A, was found to be disrupted by chromosome translocation breakpoints in individuals with mental retardation and/or epilepsy. Sequencing of GRIN2B in 468 individuals with mental retardation revealed four de novo mutations: a frameshift, a missense and two splice-site mutations. In another cohort of 127 individuals with idiopathic epilepsy and/or mental retardation, we discovered a GRIN2A nonsense mutation in a three-generation family. In a girl with early-onset epileptic encephalopathy, we identified the de novo GRIN2A mutation c.1845C>A predicting the amino acid substitution p.N615K. Analysis of NR1-NR2A(N615K) (NR2A subunit with the p.N615K alteration) receptor currents revealed a loss of the Mg(2+) block and a decrease in Ca(2+) permeability. Our findings suggest that disturbances in the neuronal electrophysiological balance

during development result in variable neurological phenotypes depending on which NR2 subunit of NMDA receptors is affected.