

ICH GWAS Monthly Newsletter

Issue 21 - November 2010

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ICH GWAS Subproject:
APOE, ICH Volume and ICH Outcome
PROJECT COMPLETE



ICH GWAS Investigators Meeting:
To be held on Friday, January 14th 2011 during
The ISGC Workshop in Miami FL, USA
Please contact Lynelle (lcortellini@partners.org) for additional details



ICH GWAS Monthly Newsletter Issue 21 - November 2010

This is the 21st 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, 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. Epub ahead of print.
- 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, 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.

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:

All Analyses completed.

A preliminary draft of the paper will be circulated to participating Investigators shortly.

Preliminary results will be featured in an oral presentation at the International Stroke Conference 2011

Deadline: Data gathering complete.

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 2010.

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
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For further info on this topic please contact:

Lynelle Cortellini, M.Sc.

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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

Vissers LE, de Ligt J, Gilissen C et al.

A de novo paradigm for mental retardation.

Nat Genet. 2010 Nov 14.

ABSTRACT

The per-generation mutation rate in humans is high. De novo mutations may compensate for allele loss due to severely reduced fecundity in common neurodevelopmental and psychiatric diseases, explaining a major paradox in evolutionary genetic theory. Here we used a family based exome sequencing approach to test this de novo mutation hypothesis in ten individuals with unexplained mental retardation. We identified and validated unique non-synonymous de novo mutations in nine genes. Six of these, identified in six different individuals, are likely to be pathogenic based on gene function, evolutionary conservation and mutation impact. Our findings provide strong experimental support for a de novo paradigm for mental retardation. Together with de novo copy number variation, de novo point mutations of large effect could explain the majority of all mental retardation cases in the population.

Spotlight: Article

Zawistowski M, Gopalakrishnan S, Ding J, Li Y, Grimm S, Zöllner S

Extending rare-variant testing strategies:

analysis of noncoding sequence and imputed genotypes.

Am J Hum Genet. 2010;12:604-617.

ABSTRACT

Next Generation Sequencing Technology has revolutionized our ability to study the contribution of rare genetic variation to heritable traits. However, existing single-marker association tests are underpowered for detecting rare risk variants. A more powerful approach involves pooling methods that combine multiple rare variants from the same gene into a single test statistic. Proposed pooling methods can be limited because they generally assume high-quality genotypes derived from deep-coverage sequencing, which may not be available. In this paper, we consider an intuitive and computationally efficient pooling statistic, the cumulative minor-allele test (CMAT). We assess the performance of the CMAT and other pooling methods on datasets simulated with population genetic models to contain realistic levels of neutral variation. We consider study designs ranging from exon-only to whole-gene analyses that contain noncoding variants. For all study designs, the CMAT achieves power comparable to that of previously proposed methods. We then extend the CMAT to probabilistic genotypes and describe application to low-coverage sequencing and imputation data. We show that augmenting sequence data with imputed samples is a practical method for increasing the power of rare-variant studies. We also provide a method of

controlling for confounding variables such as population stratification. Finally, we demonstrate that our method makes it possible to use external imputation templates to analyze rare variants imputed into existing GWAS datasets. As proof of principle, we performed a CMAT analysis of more than 8 million SNPs that we imputed into the GAIN psoriasis dataset by using haplotypes from the 1000 Genomes Project.