ICH GWAS Monthly Newsletter
Issue 17 - July 2010

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Sub-project Proposal
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APOE, ICH Volume and ICH Outcome:
A Genetic Association Study


Contact: Alessandro Biffi, MD
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ICH GWAS Monthly Newsletter Issue 17 - July 2010

This is the 17th 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).

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 ongoing in additional US samples.

Additional Participating Institutions are invited to join.

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

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	
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

Yang J, Benyamin B, McEvoy BP et al.

Common SNPs explain a large proportion of the heritability for human height.

Nat Genet. 2010;42(7):565-569.

ABSTRACT

SNPs discovered by genome-wide association studies (GWASs) account for only a small fraction of the genetic variation of complex traits in human populations. Where is the remaining heritability? We estimated the proportion of variance for human height explained by 294,831 SNPs genotyped on 3,925 unrelated individuals using a linear model analysis, and validated the estimation method with simulations based on the observed genotype data. We show that 45% of variance can be explained by considering all SNPs simultaneously. Thus, most of the heritability is not missing but has not previously been detected because the individual effects are too small to pass stringent significance tests. We provide evidence that the remaining heritability is due to incomplete linkage disequilibrium between causal variants and genotyped SNPs, exacerbated by causal variants having lower minor allele frequency than the SNPs explored to date.

Spotlight: Article

Park JH, Wacholder S, Gail MH et al.

Estimation of effect size distribution from genome-wide association studies and implications for future discoveries.

Nat Genet. 2010;42(7):570-575.

ABSTRACT

We report a set of tools to estimate the number of susceptibility loci and the distribution of their effect sizes for a trait on the basis of discoveries from existing genome-wide association studies (GWASs). We propose statistical power calculations for future GWASs using estimated distributions of effect sizes. Using reported GWAS findings for height, Crohn's disease and breast, prostate and colorectal (BPC) cancers, we determine that each of these traits is likely to harbor additional loci within the spectrum of low-penetrance common variants. These loci, which can be identified from sufficiently powerful GWASs, together could explain at least 15-20% of the known heritability of these traits. However, for BPC cancers, which have modest familial aggregation, our analysis suggests that risk models based on common variants alone will have modest discriminatory power (63.5% area under curve), even with new discoveries.