ICH GWAS Monthly Newsletter
Issue 16 - June 2010

In this issue:




ICH GWAS
Investigators Meeting

To be held just prior to the start of the ISGC 7th International Workshop Edinburgh, Scotland:

Thursday, June 17th, 2010
8:30-10:00 am

ICH GWAS Monthly Newsletter Issue 16 - June 2010

This is the 15th 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 Candidate Gene Study in ICH

Aims: Investigate the role of ApoE in ICH using a large-scale candidate-gene approach.

Current Status:

Meta-analysis completed. Manuscript drafted and circulated to participating Investigators for review and approval.

Requirements for Participation:

N/A: 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.

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

Seshadri S, Fitzpatrick AL, Ikram MA, et al.

Genome-wide analysis of genetic loci associated with Alzheimer disease.

JAMA. 2010;303(18):1832-1840.

ABSTRACT

CONTEXT: Genome-wide association studies (GWAS) have recently identified CLU, PICALM, and CR1 as novel genes for late-onset Alzheimer disease (AD).

OBJECTIVES: To identify and strengthen additional loci associated with AD and confirm these in an independent sample and to examine the contribution of recently identified genes to AD risk prediction in a 3-stage analysis of new and previously published GWAS on more than 35,000 persons (8371 AD cases).

DESIGN, SETTING, AND PARTICIPANTS: In stage 1, we identified strong genetic associations (P < 10(-3)) in a sample of 3006 AD cases and 14,642 controls by combining new data from the population-based Cohorts for Heart and Aging Research in Genomic Epidemiology consortium (1367 AD cases [973 incident]) with previously reported results from the Translational Genomics Research Institute and the Mayo AD GWAS. We identified 2708 single-nucleotide polymorphisms (SNPs) with P < 10(-3). In stage 2, we pooled results for these SNPs with the European AD Initiative (2032 cases and 5328 controls) to identify 38 SNPs (10 loci) with P < 10(-5). In stage 3, we combined data for these 10 loci with data from the Genetic and Environmental Risk in AD consortium (3333 cases and 6995 controls) to identify 4 SNPs with P < 1.7x10(-8). These 4 SNPs

were replicated in an independent Spanish sample (1140 AD cases and 1209 controls). Genome-wide association analyses were completed in 2007-2008 and the meta-analyses and replication in 2009.

MAIN OUTCOME MEASURE: Presence of Alzheimer disease. RESULTS: Two loci were identified to have genome-wide significance for the first time: rs744373 near BIN1 (odds ratio [OR],1.13; 95% confidence interval [CI],1.06-1.21 per copy of the minor allele; P = 1.59x10(-11)) and rs597668 near EXOC3L2/BLOC1S3/MARK4 (OR, 1.18; 95% CI, 1.07-1.29; P = 6.45x10(-9)). Associations of these 2 loci plus the previously identified loci CLU and PICALM with AD were confirmed in the Spanish sample (P < .05). However, although CLU and PICALM were confirmed to be associated with AD in this independent sample, they did not improve the ability of a model that included age, sex, and APOE to predict incident AD (improvement in area under the receiver operating characteristic curve from 0.847 to 0.849 in the Rotterdam Study and 0.702 to 0.705 in the Cardiovascular Health Study).

CONCLUSIONS: Two genetic loci for AD were found for the first time to reach genome-wide statistical significance. These findings were replicated in an independent population. Two recently reported associations were also confirmed. These loci did not improve AD risk prediction. While not clinically useful, they may implicate biological pathways useful for future research.

Spotlight: Article

Price AL, Kryukov GV, de Bakker PI et al.

Pooled Association Tests for Rare Variants in Exon-Resequencing Studies

Am J Hum Genet. 2010 May 12

ABSTRACT

Deep sequencing will soon generate comprehensive sequence information in large disease samples. Although the power to detect association with an individual rare variant is limited, pooling variants by gene or pathway into a composite test provides an alternative strategy for identifying susceptibility genes. We describe a statistical method for detecting association of multiple rare variants in protein-coding genes with a quantitative or dichotomous trait. The approach is based on the regression of phenotypic values on individuals' genotype scores subject to a variable allele-frequency threshold, incorporating computational predictions of the functional effects of missense variants. Statistical significance is assessed by permutation testing with variable thresholds. We used a rigorous population-genetics simulation framework to evaluate the power of the method, and we applied the method to empirical sequencing data from three disease studies.