



# ISGC NEWSLETTER

## ISSUE 7- OCTOBER 2010

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If you'd like to suggest a topic or article for a future newsletter, or if you'd like to give general feedback, please contact:

Lynelle Cortellini  
([lcortellini@partners.org](mailto:lcortellini@partners.org)).

# Introduction

This is the seventh issue of the bi-monthly newsletter for the International Stroke Genetics Consortium. The ISGC newsletter will serve to keep investigators updated on ongoing projects, new project proposals, meetings, and publications.

The newsletter will be sent to participants on the 1st of even months (or nearest workday) as an email attachment.

All Investigators are invited and encouraged to submit content for the newsletter. Please send content suggestions to Lynelle Cortellini (lcortellini@partners.org).

# ISGC Founding Principles

Cerebrovascular disease is a complex disorder influenced by variation in many genetic and non-genetic exposures, each of which contributes only a small influence to disease risk. Therefore large (larger than any single center can assemble on its own) well-characterized samples will be necessary to discover these exposures.

## Principles of Collaboration:

- 1) The ISGC is open to all who can contribute
- 2) All contributions will be fairly recognized in publications
- 3) We work together in a spirit of cooperation and open communication in order to promote the best science in the present and the best science in the future.

# ISGC Project Updates

## New Projects:

### **Replication of associations detected in a the Meta-stroke meta-analysis of genome-wide studies in ischaemic stroke**

Contact: Hugh Markus

Date Proposed: September 2010

Aims: Replication of findings from the initial MetaStroke collaboration in novel cohorts of Caucasian and other ethnic groups.

## Ongoing Projects:

### **Wellcome Trust Case Control Consortium Ischemic Stroke GWAS**

Contact: Hugh Markus

Date Proposed: July 2007

Aims: Determine whether there are genetic determinants of ischemic stroke that can be identified using GWAS and whether these determinants predispose individuals to specific subtypes of stroke.

Status: Genotyping of Phase I completed, replication in European cohort on Illumina ImmunoChip underway.

### **NIH-funded ICH GWAS**

Contact: Jonathan Rosand

Date Proposed: January 2008

Aims: This multi-center genome-wide association study (GWAS) is designed to identify genetic determinants of:

- 1) Risk of intracerebral hemorrhage (ICH) using a case-control design
- 2) Clinical course of ICH using a cohort design of individuals who have suffered an ICH.

Status: Genotyping in progress, meta-analysis with U Cincinnati group in progress.

# ISGC Project Updates

## Ongoing Projects (continued):

### **A genome-wide association study of early onset ischemic stroke**

Contact: Braxton Mitchell, Steven Kittner

Date Proposed: January 2008

Aims: To carry out a GWAS of early onset stroke

- 1) Conduct a staged GWAS in the U of Maryland sample
- 2) Replicate associations detected in Aim 1 in an independent set of young-onset stroke cases controls from collaborators in the ISGC.
- 3) Determine if SNPs robustly associated with early onset stroke in both the Maryland and IGSC cohorts are also associated with older onset stroke.

Status: A first phase GWAS has been completed for ischemic stroke in the GEOS cohort with genotyping carried out as part of the GENEVA Consortium. Additional analyses are ongoing based on stroke subtype and to detect SNPs whose associations with stroke are modified by smoking. Through supplemental funding, GENEVA is providing support to GWAS 1,200 young onset ischemic stroke cases from Danish Saleheen s Pakistan cohort as a replication study. Sample plating is currently underway. GENEVA has also agreed to support GWAS genotyping an additional 1,000 young stroke cases from Arndt Rolfs as a second replication sample.

### **Replication of Chr. 9q21 region in stroke cases and matched controls in Chinese population**

Contacts: Xingyu Wang, Lisheng Liu

Date Proposed: March 2008

Aims: To replicate the findings of the Chromosome 9p21 projects of the ISGC within a Chinese cohort.

Status: Manuscript being drafted.

# ISGC Project Updates

## Ongoing Projects (continued):

### **International Validation of a Computerized Algorithm for Etiologic Classification of Ischemic Stroke: The Causative Classification of Stroke System (CCS)**

Contact: Hakan Ay, Jonathan Rosand

Date Proposed: March 2008

Aims: This is an ISGC-wide study to validate a computerized system for etiologic classification of ischemic stroke.

Status: Manuscript accepted for publication

### **Relationship of genetic markers for common risk factors for stroke with ischemic cerebrovascular disease**

Contact: Vincent Thijs

Date Proposed: June 2008

Aims: Determine whether SNPs associated with well known risk factors for ischemic stroke like diabetes, elevated LDL, myocardial infarction and atrial fibrillation are associated with ischemic cerebrovascular disease using a case control design.

Status: Manuscript published.

\*Lemmens R, Buysschaert I, Geelen V, Fernandez I, Montaner J, Schmidt H, Schmidt R, Attia J, Maguire J, Levi C, Jood K, Blomstrand C, Jern C, Wnuk M, Slowik A, Lambrechts D, Thijs V; International Stroke Genetics Consortium. The Association of the 4q25 Susceptibility Variant for Atrial Fibrillation With Stroke Is Limited to Stroke of Cardioembolic Etiology. *Stroke*. 2010 Jul 29. [Epub ahead of print]PMID: 20671249.

### **Looking for genetic risk factors of cervical artery dissections**

Contact: Stéphanie Debette on behalf of Didier Leys

Date Proposed: February 2009

Aims: A replication study to test whether the polymorphisms associated with CAD in the GWAS within the CADISP-consortium are also associated with CAD in other independent populations, in order to exclude spurious associations.

Status: Genome-wide genotyping of the discovery and replication cohorts is complete. Analyses in progress.

# ISGC Project Updates

## Ongoing Projects (continued):

### **The International Stroke Genetics Consortium Informatics Platform: A tool for Efficient Collaboration and Rapid Discovery**

Contacts: Lynelle Cortellini, Steve Bevan, Jonathan Rosand

Date Proposed: February 2009

Aims: 1) Compile a publically-available web-based catalog of all clinical characteristics, radiographic studies, genetic data and available biological samples collected for subjects with ischemic stroke and controls.

2) Enrich characterization of stroke patients by classifying all subjects according to the biologically-based Causative Classification of Stroke System and creating a central repository of de-identified neuroimaging data on patients with stroke.

Status: Imaging repository function will be a part of the NINDS-ISGC collaborative U01 grant. Phenotypic and genotypic functionality to be added as a part of a BioInformatics Research Network ARRA grant.

### **National Institute of Neurological Disorders and Stroke Ischemic Stroke GWAS**

Contacts: Steven Kittner

Date Proposed: March 2009

Aims: Funding of an ischemic stroke genetics consortium in order to perform a genome wide association study in ischemic stroke patients and matched controls.

Status: Grant awarded.

### **Chromosome 12 and risk of ischemic stroke: A replication study**

Contacts: James Meschia, Andrew Singleton, Jonathan Rosand

Date Proposed: April 2009

Aims: Replication effort through the ISGC of the CHARGE discovery of two SNPs on chromosome 12 that were over-represented among cases with ischemic stroke, compared to controls.

Status: Manuscript published-

\*International Stroke Genetics Consortium; Wellcome Trust Case-Control Consortium  
2. Failure to validate association between 12p13 variants and ischemic stroke.  
New England Journal of Medicine. 2010;362(16):1547-1550.

# ISGC Project Updates

## Ongoing Projects (continued):

### **White Matter Hyperintensity GWAS**

Contacts: Natalia Rost, Jonathan Rosand

Date Proposed: July 2009

Aims: Perform a meta-analysis of the white matter hyperintensity volumes in patients with acute ischemic stroke and available GWAS data in order to achieve the necessary power to discover genetic associations between WMH volume and risk of stroke.

Status: Genotyping in progress, new sites joining.

### **Are established candidate gene polymorphisms for blood pressure, coronary heart disease, atrial fibrillation, lipid metabolism and hemostatic and inflammatory pathways also related to ischemic stroke risk in populations from the Southwest of Sweden?**

Contacts: Arne Lindgren, Christina Jern, Olle Melander

Date Proposed: July 2009

Aims: To examine if SNPs related to phenotypes are related to ischemic stroke risk in a homogenous population sample from the Southwest of Sweden.

Status: Manuscript regarding Chromosome 12p13 in press.

### **MetaStroke; A meta-analysis of genome-wide studies in ischaemic stroke**

Contact: Hugh Markus

Date Proposed: December 2009

Aims: Meta-Analysis of genome-wide data in ischemic stroke

Status: Meta-analysis to begin in the Fall. Additional project proposal for replication cohorts sent out to ISGC in September.

# ISGC Project Updates

## Ongoing Projects (continued):

### **Genome-wide association study of deep cerebral phenotypes**

Contact: Dan Woo

Date Proposed: February 2010

Aims: (1) Specific SNPs/gene regions will be associated with deep cerebral phenotypes (deep/periventricular location of ICH, lacunar stroke or white matter disease) and this association will be independent of traditional risk factors including hypertension. (2) Specific SNPs/gene regions will be associated with deep cerebral phenotypes and will be modified by the presence/duration/severity of hypertension.

Status: List of interested studies compiled and in the process of developing a data transfer agreement. In addition, we are awaiting the completion of the Wellcome Trust effort as it would constitute a major contribution of small vessel ischemic strokes.

### **Genetics of cerebral venous thrombosis (CVT)**

Contact: Pankaj Sharma

Date Proposed: May 2010

Aims: To recruit DNA from CVT patients in order to undertake a GWAS.

Status: List of interested groups compiled and contacted. Teleconference to be arranged.

### **Replication of a genetic risk score for ischemic stroke based on polymorphisms associated with diabetes, BMI, cholesterol, atrial fibrillation and coronary artery disease**

Contact: Vincent Thijs

Date Proposed: May 2010

Aims: To replicate the genetic risk score for ischemic stroke that was based upon polymorphisms associated with diabetes, BMI, cholesterol, atrial fibrillation and coronary artery disease studied in a previous ISGC project proposal within a larger ISGC cohort.

Status: Collection of genotype data from collaborators underway

# ISGC Project Updates

## Ongoing Projects (continued):

### **Genes and Response to Aspirin in Secondary Stroke Prevention, GRASSP**

Contact: Agnieszka Slowik, Joanna Pera

Date Proposed: June 2010

Aims: To establish genetic markers of aspirin efficiency, aspirin resistance, aspirin intolerance, and increased risk aspirin-related adverse effects in ischemic stroke patients with different stroke etiologies. To develop clinically useful and cost-effective test(s) allowing predict responses to aspirin treatment, and to avoid/reduce adverse effects .

Status: Grant writing underway.

### **Association of myocardial infarction-associated SNPs with ischemic stroke: a meta-analysis of European Caucasian populations**

Contact: Braxton Mitchell, Yu-Ching Cheng

Date Proposed: July 2010

Aims: The goal of this project is to extend previous work (e.g., the ISGC analysis of the chr 9 SNP on stroke) to determine if: (1) other MI-associated SNPs are associated with ischemic stroke; and (2) if associations of these additional SNPs are dependent on stroke subtype and/or age of stroke onset.

Status: Project Development underway

## Other Projects Involving ISGC Members

### **Genetic and Environmental Risk Factors for Hemorrhagic Stroke**

Contact: Daniel Woo

### **Australian Stroke Genetics Collaborative Group**

Contact: Chris Levi, John Attia

### **NHLBI Initiative on White Matter Disease**

Contact: Paul Nyquist

### **INTERSTROKE**

Contact: Guillaume Pare

### **Mitochondrial Genetics and Risk of Stroke**

Contact: Jonathan Rosand

Status: Manuscript published

## ISGC Grants Awarded

- Wellcome Trust Genome-Wide Association Study for Ischemic Stroke (WTCCC2)
- Australian Stroke Genetics Collaborative Group
- The Baltimore-Washington Young Stroke Study (GEI)
- Gene Discovery for Warfarin-Related Intracerebral Hemorrhage (ICH GWAS)
- Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH)
- NINDS-Stroke Genetics Network (SiGN) Study

# ISGC Publications

Gschwendtner A, Bevan S, Cole JW, et.al., on behalf of the International Stroke Genetics Consortium. Sequence variants on chromosome 9p21.3 confer risk of atherosclerotic stroke. *Annals of Neurology*. 2009; 65(5): 531-539

Nalls M, Biffi A, Matarin M, et. al., 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;362:1547-1550.

Lemmens R, Buysschaert I, Geelen V, et al.; International Stroke Genetics Consortium. The Association of the 4q25 Susceptibility Variant for Atrial Fibrillation With Stroke Is Limited to Stroke of Cardioembolic Etiology. *Stroke*. 2010 Sep;41(9):1850-7 .

Anderson CD, Biffi A, Rahman R, et. al, on behalf of the International Stroke Genetics Consortium. Common mitochondrial sequence variants in ischemic stroke. *Annals of Neurology*. 2010 Sep 13. [Epub ahead of print].

Arsava EM, Ballabio E, Benner T et. al.; on behalf of the International Stroke Genetics Consortium. The Causative Classification of Stroke system: An international reliability and optimization study. *Neurology*. 2010 Oct 5;75(14):1277-1284.

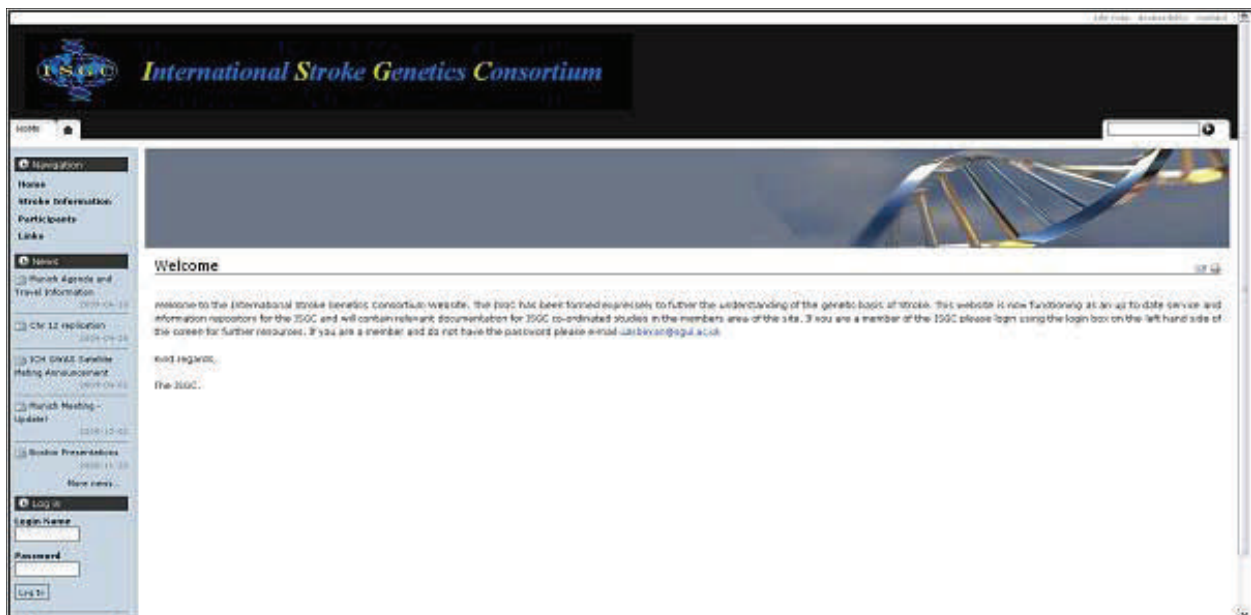
Biffi A, Sonni A, Anderson CD, et al.; on behalf of the International Stroke Genetics Consortium. Variants at APOE Influence Risk of Deep and Lobar Intracerebral Hemorrhage. *Annals of Neurology*. In Press.

# Website Update

The ISGC website can be found at [www.strokegenetics.org](http://www.strokegenetics.org). Thanks to everyone who submitted a short bio and picture for the website! All bios received have been posted. If you would still like to submit a bio and picture, you can email them to either Lynelle or Steve.

If you have additional website content or layout suggestions, please email Lynelle Cortellini ([lcortellini@partners.org](mailto:lcortellini@partners.org)) or Steve Bevan ([sbevan@sgul.ac.uk](mailto:sbevan@sgul.ac.uk)) with your ideas.

Thank you!



# 8th International Workshop: Miami FL, USA

The next US ISGC Workshop will take place on January 13 and 14, 2011. This meeting will be hosted by Ralph L. Sacco ([rsacco@med.miami.edu](mailto:rsacco@med.miami.edu)), Tatjana Rundek ([trundek@med.miami.edu](mailto:trundek@med.miami.edu)), Susan Blanton ([sblanton@med.miami.edu](mailto:sblanton@med.miami.edu)), and Agnieszka Slowik ([slowik@cm-uj.krakow.pl](mailto:slowik@cm-uj.krakow.pl)).

Additional details will be sent out as they are received.



# 9th International Workshop: Leuven, Belgium

The 9th ISGC Workshop will take place in Leuven, Belgium in 2011, date TBD. This meeting will be hosted by Vincent Thijs.

We will send out a poll for meeting dates in the near future.

