



# ISGC NEWSLETTER

## ISSUE 5- JUNE 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)**.

# Introduction

This is the fifth 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:

### **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 this association will be modified by the presence/duration/severity of hypertension.

### **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.

## 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: Further developments include: 1. GWAS analysis underway: 1M SNPs genotyped on Illumina Omni Quad platform through the NHGRI-sponsored GENEA Consortium. Collaboration established with two additional early onset stroke cohorts for a combined meta-analysis: (a) 1,500 cases from Pakistan (Dr. Danish Saleheen); and (b) 1,000 cases from Germany (Dr. Arndt Rolf).  
2. Genotyping completed for 50K Illumina CVD chip for analysis of common and rare SNPs in CVD candidate genes proceeding.

### **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.

### **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 under review

# ISGC Project Updates

## Ongoing Projects (continued):

### **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 under review

### **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 cohorts is complete. Genome-wide genotyping of the replication cohorts close to completion. Analyses in progress.

### **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: Ethics Committee submission in progress.

# ISGC Project Updates

## Ongoing Projects (continued):

### **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.

### **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

# ISGC Project Updates

## Ongoing Projects (continued):

**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: Recently completed genotyping of 3600 patients and 2500 controls regarding 66 candidate SNP's from the above areas of interest.

## **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 late Spring.

# 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 under review

## 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 Discover for Warfarin-Related Intracerebral Hemorrhage (ICH GWAS)
- Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH)
- NINDS Ischemic Stroke Genetics Consortium

## ISGC Publications

Gschwendtner A, Bevan S, Cole JW, Plourde A, Matarin M, Ross-Adams H, Meitinger T, Wichmann E, Mitchell BD, Furie KL, Slowik A, Rich SS, Syme PD, Macleod MR, Meschia JF, Rosand J, Kittner SJ, Markus H, Müller-Myhsok B, Dichgans M, on behalf of the International Stroke Genetics Consortium. Sequence variants on chromosome 9p21.3 confer risk of atherosclerotic stroke. *Ann Neurol.* 2009; 65(5): 531-539

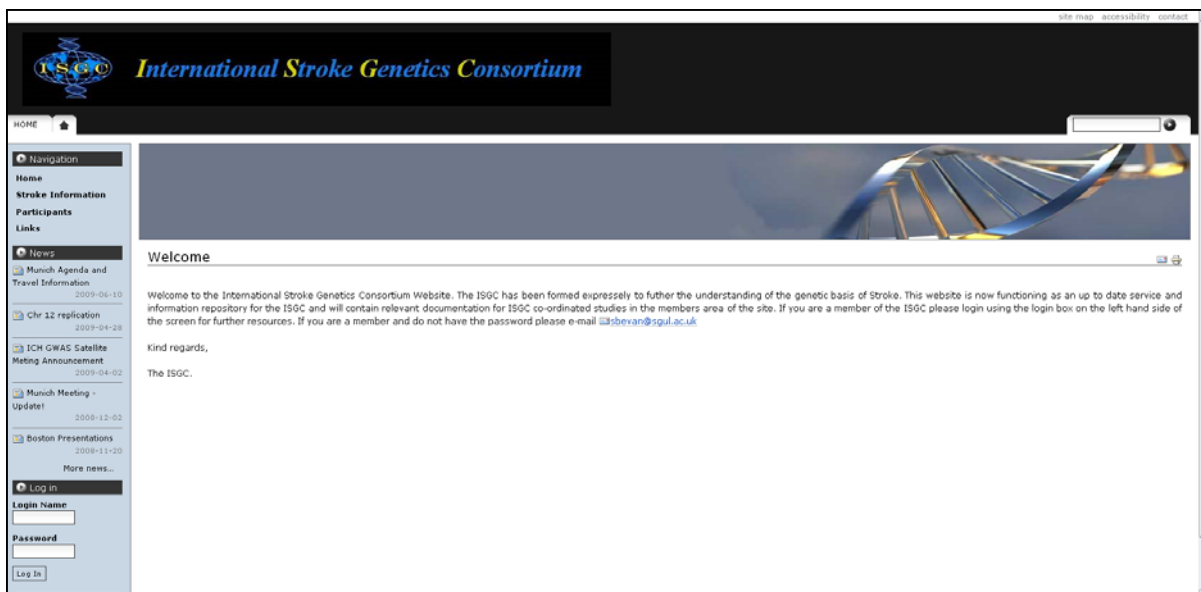
Nalls M, Biffi A, Matarin M, Anderson CD, Chasman DI, Bevan S, Spencer CA, Gschwendtner A, Sale MM, Wu L, Salaheen D, Deary IJ, Lagenfeld C, Peddareddygari LR, Cole JW, Arapelli SK, Aucutt-Walter N, Brott TG, Broderick JP, Brown DL, Brown M, Brown RD, Buring JE, Cortellini L, Danesh J, Deka R, Elias 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.* *Ne England Journal of Medicine.* 2010;362:1547-1550.

# 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!



# 7th International Workshop: Edinburgh, Scotland

Our upcoming ISGC European Workshop will take place on June 17 and 18, 2010. This meeting will be hosted by Cathie Sudlow (cathie.sudlow@ed.ac.uk) and Brad Worrall (bbw9r@virginia.edu).

Although the hotel booking deadline has passed, you can still register for the meeting online at the following website:

[https://www.epay.ed.ac.uk/browse/extra\\_info.asp?compid=1&modid=2&prodid=274&deptid=75](https://www.epay.ed.ac.uk/browse/extra_info.asp?compid=1&modid=2&prodid=274&deptid=75)

**\*PLEASE NOTE:** The Workshop registration deadline is **Monday, May 31**. If you do not register in advance, you will be unable to attend this meeting.



# 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)) and European Co-Chair (TBA at the Edinburgh workshop).

Additional details will be sent out as they are received.

