ISGC Newsletter
Issue 12- August 2011

Contents

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 twelfth 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.

<u>Principles of Collaboration:</u>

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

GWA meta-analysis of carotid plaque and intima-media thickness (IMT)

Contact: Pankaj Sharma

Date Proposed: June 2011

Aims: Meta-analysis of existing GWA data in those subjects who have had carotid imaging in order to use carotid disease as a surrogate for vascular disease.

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: Manuscript submitted to Nature Genetics

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 of non-warfarin related ICH cases completed. Genotyping of warfarin related ICH to begin in the fall. 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. GENEVA is also 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. 9q21region 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.

Looking for genetic risk factors of cervical artery dissections

Contact: Stéphanie Debette, Didier Leys, on behalf of the CADISP group

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: Analyses in final stage; additional replication samples are being collected .

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. Project underway.

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):

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 underway. Additional project proposal for replication cohorts sent out to ISGC in September.

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: Ethical documentation has now been prepared and delivered to all sites that have expressed an interest. Following an international teleconference, the agreed plan is to retrospectively recruit cases with CVT (and local controls). Currently 26 investigators from 13 countries are involved. We are actively seeking other sites and if you are interested please email: pankaj.sharma@imperial.ac.uk

ISGC Project Updates

Ongoing Projects (continued):

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

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: Manuscript submitted

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.

Status: Analysis in progress

Consortium of Minority Population genomewide-Association Studies of Stroke (COMPASS)

Contact: Brad Worrall

Date Proposed: December 2010

Aims: Meta-analysis of cohorts and case-control studies with GWAS data for individuals of African descent and other minority groups.

ISGC Project Updates

Ongoing Projects (continued):

Validation of a clinical and genetic decision rule for ischaemic stroke risk

Contact: John Attia, Chris Levi, Jane Maguire

Date Proposed: December 2010

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.

Replication of Ischemic Stroke Genes Discovered from Exome Sequencing

Contact: Steve Rich

Date Proposed: March 2011

Aims: Replication of genes discovered in NHLBI Exome Sequencing Project in ischemic stroke cases with small or large vessel strokes.

Status: As part of the NHLBI Exome Sequencing Project, 526 (of 600) samples of early-onset ischemic stroke (small vessel or large vessel subtype only) have been received by the sequencing center; complete exome sequencing and variant calling has been completed for 242 cases and 48 affected sibling pairs (SWISS); another 100 cases have been sequenced but await variant calls. Comparison group will be 1,000 exomes from a 'deeply phenotyped reference' (DPR) group, randomly selected from over 100,000 subjects. Replication planning is underway, with follow-up in ~3,000 stroke cases using an "Exome Chip" composed of ~200,000 variants identified from ~10,000 exome samples. Selection of follow-up samples is underway.

Genetic studies of recurrent stroke

Contact: Brad Worrall, Michele Sale, Keith Keene

Date Proposed: February 2011

Aims: Meta-analysis and replication of GWAS in recurrent ischemic stroke.

Next Generation Sequencing in Lacunar Stroke and Small Vessel Disease

Contact: Anna Bersano

Date Proposed: April 2011

Aims: Perform Next-Generation Sequencing on subjects with lacunar stroke and small vessel disease. Novel mutations will be replicated via direct genotyping in an additional 1000 cases and 1000 controls .

ISGC Project Updates

Completed Projects:

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 published-

*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.

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, 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 Jul 29. [Epub ahead of print]PMID: 20671249.

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

Completed 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: Manuscript regarding Chromosome 12p13 in press.

*Olsson S, Melander O, Jood K, Smith JG, Lövkvist H, Sjögren M, Engström G, Norrving B, Lindgren A, Jern C, the International Stroke Genetics Consortium (ISGC). A genetic variant on chromosome 12p13 does not show association to ischemic stroke in three Swedish case-control studies. *Stroke* 2010.

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 submitted, project not funded at this time.

Next Generation Sequencing in Cerebral Amyloid Angiopathy

Contact: Jonathan Rosand, Lynelle Cortellini

Date Proposed: February 2011

Aims: Next-generation sequencing project aimed at identifying rare DNA sequence variants associated with CAA. Replication cohorts through the ISGC will be used in targeted sequencing and candidate gene analyses.

Status: Grant not funded at this time.

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; 41(9):1850-7 .

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; 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.*. 2010; 68(6):934-43.

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*. 2011; 69(3):471-80.

Olsson S, Melander O, Jood K, Smith JG, Lövkvist H, Sjögren M, Engström G, Norrving B, Lindgren A, Jern C, the International Stroke Genetics Consortium (ISGC). A genetic variant on chromosome 12p13 does not show association to ischemic stroke in three Swedish case-control studies. *Stroke*. 2011; 42(1):214-6 .

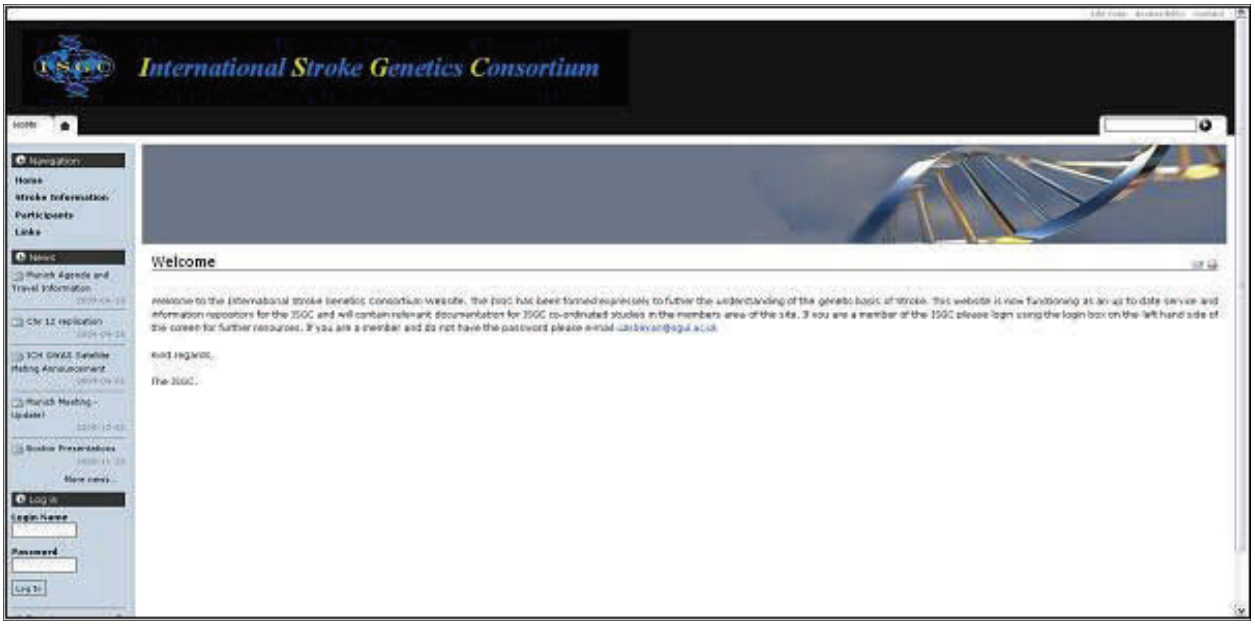
Biffi A, Anderson CD, Jagiella JM, et.al., on behalf of the International Stroke Genetics Consortium. APOE genotype and extent of bleeding and outcome in lobar intracerebral haemorrhage: a genetic association study. *Lancet Neurology*. 2011;10(8):702-709.

Website Update

The ISGC website can be found at 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) or Steve Bevan (sbevan@sgul.ac.uk) with your ideas.

Thank you!



9th International Workshop: Leuven, Belgium

Thank you to our workshop organizers, Vincent Thijs and John Cole!

10th International Workshop: Jacksonville FL, USA

The 10th International Workshop of the ISGC will take place On November 16-17, 2011 in Jacksonville FL, USA, and will be hosted by James Meschia and Pankaj Sharma.

Meeting and Hotel details will be sent around shortly.