ISGC Newsletter
Issue 14 - December 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:

Valerie Valant (valant@chgr,mgh.harvard.edu).

Introduction

This is the fourteenth 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 Valerie Valant (valant@chgr.mgh.harvard.edu).

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 Plasma Fibrinogen

Contact: Christopher O'Donnell

Date Proposed: November 2011

Aims: To conduct a meta-analysis of GWA studies on plasma levels of fibrinogen with the goal of identifying novel loci that underlie variation in plasma fibrinogen concentration.

Pharmacogenomics GWAS of tPA-induced Haemorrhagic Transformation

Contact: Chris Levy

Date Proposed: November 2011

Aims: To identify SNPs associated with haemorrhagic transformation of acute ischemic stroke after intravenous tPA therapy using a pharmacogenomic-focused 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: 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: Beginning to genotype warfarin related ICH cases. Meta-analysis of GOCHA and GERFHS data in all ICH and ICH subtypes (lobar and deep ICH) showed a significant association between all ICH and SNPs on chromosome 11 and several promising stacks on other chromosomes. Currently outlining replication steps. Also Exome chip genotyping will begin at the beginning of 2012 to test the rare variant risk hypothesis of ICH.

ISGC Project Updates

Ongoing Projects (continued):

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: Genotyping for last set of replication samples just completed; analyses are being finalized.

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

Contacts: 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.

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: Recent phase of WMH GWAS meta-analysis including the ISGC (MGH, ISGS, SWISS and ASGS) and WTCCC cohorts did not demonstrate genome-significant associations. Efforts to further normalize the phenotypic data and to increase the power are ongoing

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.

ISGC Project Updates

Ongoing Projects (continued):

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: BEAST - a GWA study for cerebrovenous thrombosis (CVT). This is an internationally collaborative project which seeks to recruit and analyze patients with CVT. The recruitment is mainly retrospective. At the most recent teleconference it was agreed that genotyping would commence in the Spring of 2012 in the first 500 cases. If you would like to join this endeavor or think you will be able to contribute to the 500 cases, please contact pankaj.sharma@imperial.ac.uk

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

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

ISGC Project Updates

Ongoing Projects (continued):

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.

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: The examination of rare variants in ischemic stroke in collaboration with the NHLBI Exome Sequencing Project (ESP) has made significant progress. The ESP Executive Committee has approved the use of 3,000 case samples and 3,000 control samples to be genotyped with the ExomeChip, a custom 300,000 SNP array (as designed by Illumina) with rare variants residing in exomes and additional content. These samples will be split with WHI and the ISGC, and restricted to those samples with existing GWAS data (for imputation), deep phenotyping (for use with other targeted traits), and both cases and controls from the same sites, with IRB approval for extensive sharing of information and deposition of data into dbGaP. The two studies that had samples meeting these criteria and immediately available for shipment to the University of Washington (the ESP genotyping site for ischemic stroke) were GEOS and ISGS. These samples are being sent for evaluation with anticipated completion of genotyping in Q1 2012.

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.

Status: No update at this time.

ISGC Project Updates

Ongoing Projects (continued):

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 .

Status: No update at this time.

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.

Status: Carotid plaque and stenosis genome wide study. The international collaborators seek to undertake a meta-analysis of GWAS data in stroke patients in whom carotid data is available. The analysis will be both qualitative and quantitative for carotid plaque. At present we are characterizing the discovery dataset and will then require summary statistics from the replication sets. If you have GWAS data on stroke patients with carotid imaging (MRA/CTA/Doppers) and would like to participate in this project, please contact pankaj.sharma@imperial.ac.uk

Genome-wide Heritability of Ischemic Stroke in Caucasians.

Contact: Braxton Mitchell

Date Proposed: August 2011

Aims: Examine the heritability of ischemic stroke using genome wide SNPs for early vs. late onset IS and determining stroke subtype

Status: No update at this time.

GWAS of Stroke/TIA in Patients with Atrial Fibrillation

Contact: Mina Chung, Sudha Seshadri

Date Proposed: October 2011

Aims: Perform a GWAS meta-analysis of stroke/TIA within AF cases

Status: No update at this time.

ISGC Project Updates

Completed Projects:

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: Manuscript in press at G3: Genes, Genomes, Genetics

*Cheng Y-C, O'Connell JR, Cole, JW, Stine OC, Dueker N, McArdle PF, Sparks MJ, Shen J, Laurie CC, Nelson S, Doheny KF, Ling H, Pugh EW, Bott TG, Brown Jr. RD, Meschia JF, Nalls M, Rich SS, Worrall B, Andreson CD, Biffi A, Cortellini L, Furie KL, Rost NS, Rosand J, Manolio TA, Kittner SJ, Mitchell BD. Genome-wide association analysis of ischemic stroke in young adults. G3: Genes, Genomes, Genetics (in press).

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.

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: The project has been stalled due to a lack of sample collection.

ISGC Project Updates

Completed 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 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.

ISGC Project Updates

Completed Projects (continued):

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 accepted for publication in Stoke.

*Yu-Ching Cheng, PhD; Christopher D. Anderson, MD; Silvia Bione, PhD; Keith Keene, PhD; Jane M. Maguire PhD, RN; Michael Nalls, PhD; Asif Rasheed, MBBS; Marion Zeginigg, MSc; John Attia, PhD, MD, FRCPC, FRACP; Ross Baker, FRACP, FRCPA; Simona Barlera, MSc; Alessandro Biffi, MD; Ebony Bookman, PhD; Thomas G. Brott, MD; Robert D. Brown Jr., MD; Fang Chen, PhD; Wei-Min Chen, PhD; Emilio Ciusani, PhD; John W. Cole, MD; Lynelle Cortellini, MSc; John Danesh, FRCP; Kimberly Doheny, PhD; Luigi Ferrucci, MD, PhD; Maria Grazia Franzosi, PhD; Philippe Frossard, PhD, DSc; Karen L. Furie, MD, MPH; Jonathan Golledge, MChir, FRACS; Graeme J. Hankey, MD, FRACP, FRCP, FRCPE; Dena Hernandez, MS; Elizabeth G. Holliday, PhD; Fang-Chi Hsu, PhD; Jim Jannes, PhD, BMBS BMBS FRACP; Ayeesha Kamal, MD, FAHA, ABVN; Muhammad Saleem Khan, MSc; Steven J. Kittner, MD; Simon A. Koblar, PhD, BMBS FRACP; Martin Lewis, PhD; Lisa Lincz, PhD; Antonella Lisa, PhD; Mar Matarin, PhD; Pablo Moscato, PhD; Josyf C. Mychaleckyj, DPhil; Eugenio A. Parati, MD; Silvia Parolo; Elizabeth Pugh, PhD; Natalia S. Rost, MD; Michael Schallert MSc; Helena Schmidt, MD,PhD; Rodney J. Scott, PhD, PD, FRCPath, FHGSA; Jonathan W. Sturm, PhD, MD; Sunaina Yadav, MSc; Moazzam Zaidi, MBBS; GARNET Collaborative Research Group; GENEVA Consortium; Giorgio B. Boncoraglio, MD; Christopher Royce Levi, MD, FRACP, RACP; James F. Meschia, MD; Jonathan Rosand, MD, MSc; Michele Sale, PhD; Danish Saleheen, MBBS, PhD; Reinhold Schmidt, MD; Pankaj Sharma, MD PhD FRCP; Bradford Worrall, MD, MSc; Braxton D. Mitchell, PhD; on behalf of the International Stroke Genetics Consortium

ISGC Project Updates

Completed Projects (continued):

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 .

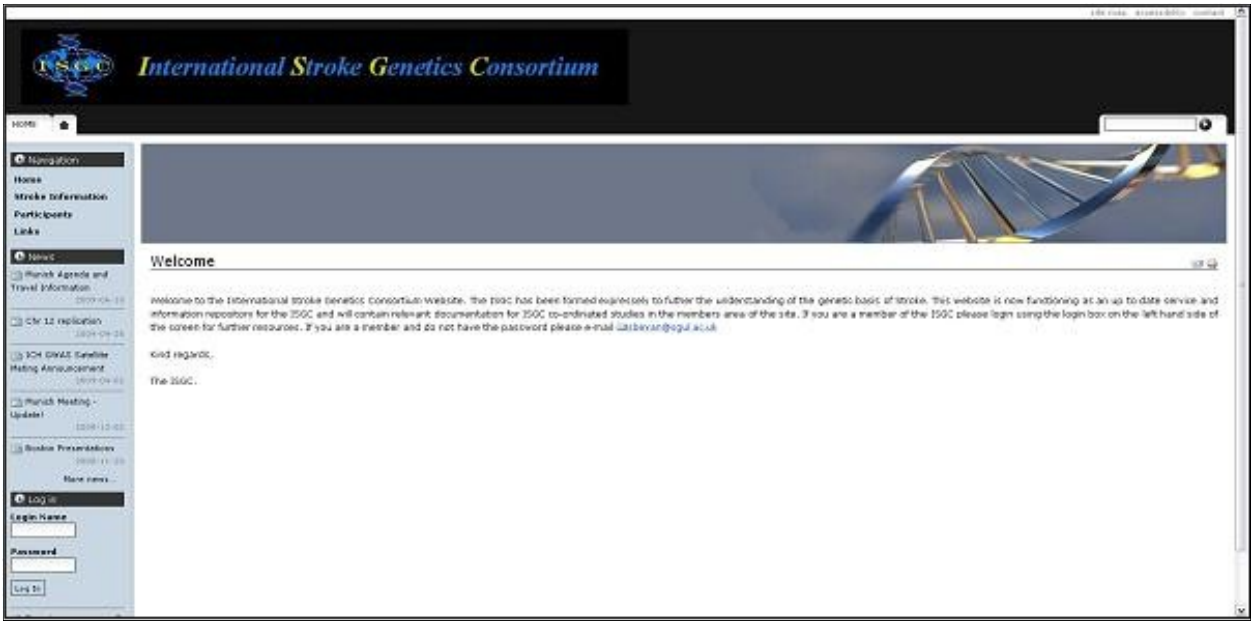
Biffi A, Anderson CD, Jagiella JM, et.al., on behalf of the International Stroke Genetics Consortium. APOE genotype and extent of bleeding and outcome in lobar intracerebral haemorrhage: a genetic association study. *Lancet Neurology*. 2011;10(8):702-709.

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 Steve.

If you have additional website content or layout suggestions, please email Steve Bevan (sbevan@sgul.ac.uk) with your ideas.

Thank you!



10th International Workshop: Jacksonville FL, USA

Thank you to James Meschia (meschia.james@mayo.edu) and Pankaj Sharma (pankaj.sharma@imperial.ac.uk) for putting together a successful ISGC Workshop in Jacksonville!

Congratulations also to the first successful Steering Committee meeting. Please see below for the major conclusions.

ISGC Internal Collaboration

Goal: To harmonize the work of ISGC subgroups to improve information flow. The ISGC works best as a platform for bringing together studies/collaboration. We should both overlap working groups and standardize follow-up data collection for all stroke genetic research.

ISGC External Collaboration

Goal: How can we improve the relationship between ISGC and other international organizations, such as SiGN? For example, international collaboration with SiGN has leveraged the ISGC. Additionally, we should outreach to additional populations, such as junior investigators and translational researchers and also involve more members of the "monogenetic" community.

ISGC Workshops

Goal: To increase member activity during ISGC Workshops. How can we make meetings an "active" experience for every attendee while keeping flexibility so members can join as they please? How can we increase the financial support for travel and exchange? The workshops are the "brain" and the priority of the ISGC. Let's edit the rules of engagement during the workshop so that it is safe to present unpublished data. Ultimately, the workshop should be an extended "lab" meeting, a clearinghouse for technological innovation.

ISGC Mission

Goal: To clarify our mission. How do we reach the goal of curing stroke through genetic discovery? Does focusing our strengths mean continuing the focus on sample size and phenotyping? Should we create a brainstorming group on personalized medicine? We need to both increase and clarify our communications with each other and our collaborators, as well as identify champions for each working group.

11th International Workshop: Newcastle, Australia

The 11th International Workshop of the ISGC will take place on April 12-13, 2012 in Newcastle, Australia, and will be hosted by Chris Levi and John Attia.

All information regarding the meeting venue, travel and hotels, scientific and social programs, conference registration, contact information and other "FAQs" can be found on the conference website: http://www.isgc2012australia.org.au/home/.aspx