ISGC Newsletter
Issue 20 - December 2012

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 twentieth 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 posted as a PDF document to the ISGC website on the 1st of even months (or nearest workday) and can either be viewed online or downloaded as an 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

There are no new projects to report at this time.

Ongoing Projects:

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: MGH (GOCHA and ISGC), University of Cincinnati (GERFHS), and University of Pennsylvania (Pakistani ICH Study) have imputed their data to the latest release of 1000 genomes (1000 genomes phase I integrated variant set) using IMPUTE2 and run GWA in their respective case-control subject pool. We are currently exchanging summary results and performing a meta-analysis across all 3 studies.

Looking for genetic risk factors of cervical artery dissections

Contact: Stéphanie Debette and 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: The manuscript was newly submitted in early November. We are currently awaiting response from reviewers.

ISGC Project Updates

Ongoing Projects (continued):

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.

White Matter Hyperintensity GWAS

Contacts: Natalia Rost, Jonathan Rosand

Date Proposed: July 2009

Aims: To discover genetic markers of WMH severity using available genome-wide data and WMH volumes measured on MRI in patients with acute ischemic stroke.

Status: Preliminary data demonstrating association between: (a) Chr 17q25 locus and WMH severity in stroke patients (Poneh Adib-Samii - PI); (b) WMH-based genetic score and incident ischemic stroke risk (Natalia Rost - PI); and (c) population-based WMH genetic risk score and risk of lacunar stroke (William Devan - PI) were submitted as abstracts to the 2012 American Neurological Association meeting.

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: Samples have now been received by Imperial College and are in the process of being extracted prior to genotyping.

ISGC Project Updates

Ongoing Projects (continued):

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.

Status: No update at this time.

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.

ISGC Project Updates

Ongoing Projects (continued):

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.

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: Individual Investigators are being approached to determine the extent of phenotyping available.

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

Ongoing Projects (continued):

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.

Status: No update at this time.

Pharmacogenomics GWAS of tPA-induced Haemorrhagic Transformation

Contact: Christopher Levi

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.

Status: No update at this time.

Genome-wide association study of incident stroke-wave 2

Contact: Stéphanie Debette, Will Longstreth, and Sudha Seshadri on behalf of the CHARGE Consortium

Date Proposed: June 2012

Aims: Our aim is to perform a second wave Incident Stroke GWAS meta-analysis within the CHARGE consortium, including a larger number of cohorts, using 1000G imputation, and including extension to other ethnic groups if large enough samples can be collected.

Status: Analyses in discovery cohorts have started, current deadline for uploading results Nov 30, 2012.

GRECAS Project: Genotyping Risk and Efficacy of Clopidogrel or Aspirin following Stroke

Contact: Israel Fernandez-Cadenas and Joan Montaner

Date Proposed: September 2012

Aims: Replication Study. This is a pharmacogenomic study, the main objective is: to find genetic risk factors associated with Aspirin or Clopidogrel clinical resistance, considering clinical resistance as new vascular recurrences during a follow up of one year.

Status: No update at this time, recruitment of replication cohort ongoing.

ISGC Project Updates

Completed 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 accepted and in press at Nature Genetics

*Bellenguez C, Bevan S, Gschwendtnew A, et al., on behalf od the International Stroke Genetics Consortium (ISGC) & the Wellcome Trust Case Control Consortium 2 (WTCCC2). Genome-wide association study identifies a variant in HDAC9 associated with large vessel ischemic stroke. *Nature Genetics* (in press).

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*. 2011 Nov 1; 1(6):505-514.

ISGC Project Updates

Completed 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 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.

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.

ISGC Project Updates

Completed Projects (continued):

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.

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; 42(1):214-6.

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

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

METASTROKE
Contact: Martin Dichgans

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

Falcone GJ, Biffi A, Devan WJ, et al, on behalf on the GOCHA investigators. Burden of Blood Pressure -Related Alleles is Associated with Larger Hematoma Volume and Worse Outcome in Intracerebral Hemorrhage. *Stroke* 2012. In press.

Traylor M, Farrall M, Holliday EG, et al, on behalf of the International Stroke Genetics Consortium. Genetic risk factors for ischaemic stroke and its subtypes (the METASTROKE Collaboration): a meta-analysis of genome-wide association studies. *Lancet Neurol.* 2012 Nov;11(11):951-962.

Holliday EG, Maguire JM, Evans TJ, et al, on behalf of the International Stroke Genetics Consortium. Common variants at 6p21.1 are associated with large artery atherosclerotic stroke. *Nat Genet.* 2012 Oct;44(10):1147-51.

Falcone GJ, Biffi A, Devan WJ, et al, on behalf of the International Stroke Genetics Consortium. Burden of Risk Alleles for Hypertension Increases Risk of Intracerebral Hemorrhage. *Stroke.* 2012 Nov;43(11):2877-2883.

Cheng YC, Anderson CD, Bione S, et al, on behalf of the International Stroke Genetics Consortium. Are myocardial infarction—associated single-nucleotide polymorphisms associated with ischemic stroke? *Stroke.* 2012;43(4):980-986.

International Stroke Genetics Consortium (ISGC); Wellcome Trust Case Control Consortium 2 (WTCCC2), Bellenguez C, et al. Genome-wide association study identifies a variant in HDAC9 associated with large vessel ischemic stroke. *Nature Genetics.* 2012;44(3):328-333.

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.

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, 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.

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.

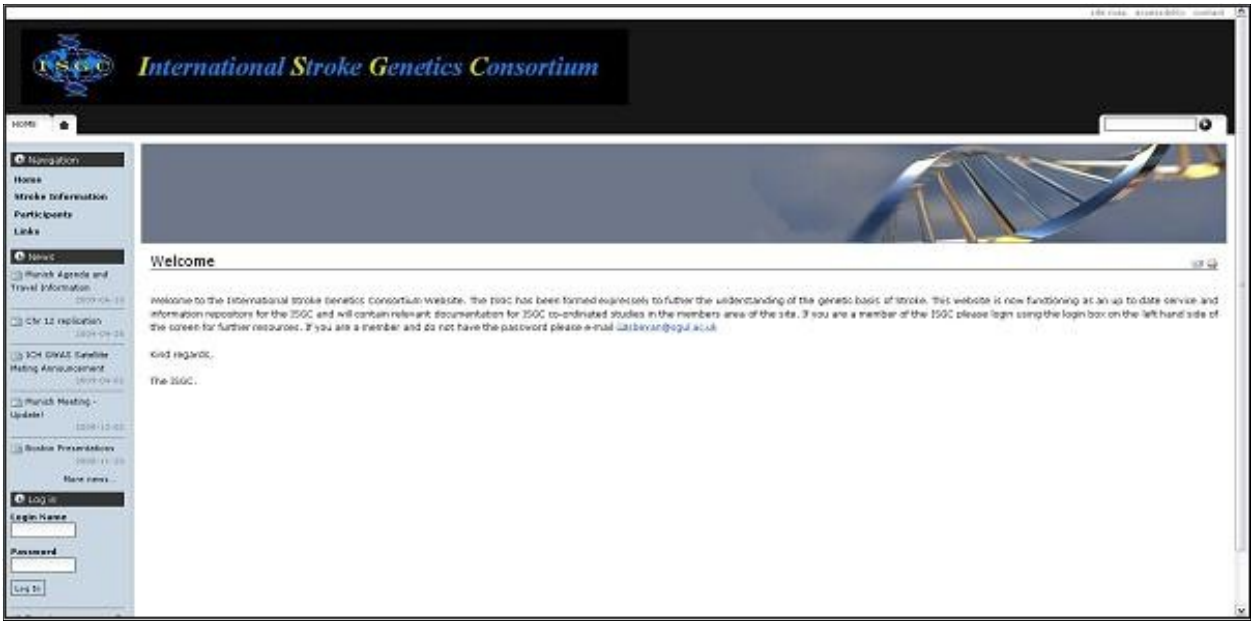
Anderson CD, Biffi A, Rahman R, et. al, on behalf of the International Stroke Genetics Consortium. Common mitochondrial sequence variants in ischemic stroke. *Ann Neurol.* 2011; 69(3):471-80.

Website Update

The ISGC website can be found at www.strokegenetics.org. Please consider submitting a short bio and a picture for the website! If you are interested, please 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!



Upcoming Conference Deadlines

2013

International Stroke Conference

Abstract Deadline: N/a
Meeting Date: February 6-9, 2013
Meeting Location: Honolulu, HI

American Academy of Neurology

Abstract Deadline: N/a
Meeting Date: March 16-23, 2013
Meeting Location: San Diego, CA

International Stroke Genetics Consortium Meeting

Meeting Date: April 25-26, 2013
Meeting Location: Charlottesville, VA

European Stroke Conference

Abstract Deadline: January 13, 2013
Meeting Date: May 21-31, 2013
Meeting Location: London, United Kingdom

American Society of Human Genetics

Abstract Deadline: June 4, 2013
Meeting Date: October 22-26, 2013
Meeting Location: Boston, MA

American Neurological Association

Abstract Deadline: TBA
Meeting Date: October 13-15, 2013
Meeting Location: New Orleans, LA

12th International Workshop: Krakow, Poland

Thank you to Agnieszka Słowik, Joanna Pera, and Steven Kittner, for putting together a successful ISGC Workshop in Krakow!

The 12th International Workshop of the ISGC took place on November 15-16, 2012 in Krakow, Poland.

13th International Workshop: Charlottesville, Virginia (USA)

The 13th International Workshop of the ISGC will take place on April 25-26, 2013 in Charlottesville, Virginia (USA), and will be hosted by Brad Worrall (BBW9R@hscmail.mcc.virginia.edu) and Christina Jern (Christina.Jern@neuro.gu.se).

Please refer to the event website for more detailed information regarding event programs and travel arrangements.

Event Website: http://www.medicine.virginia.edu/ISGC