

Proceedings of the 22nd International Stroke Genetics Consortium Workshops

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Introduction and welcome

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The 22nd Workshop of the International Stroke Genetics Consortium (ISGC) was held on November 2–3 in Utrecht, the Netherlands, and was hosted by Ynte Ruigrok and Yoichiro Kamatani. The Workshops are a semiannual tradition of the ISGC, where ISGC scientists meet to share their ideas and results. The ISGC is an international collaboration of physicians and scientists who have agreed to pool resources and expertise in an effort to unravel the genetic basis of stroke and its comorbidities (<http://www.strokegenetics.org>). It was formed in 2007 by a small group of scientists and has since grown to over 200 members representing over 50 countries in North and South America, Europe, Australia, and Africa. The success of this initiative stems from the collaboration and engagement of its members who pursue their own research as well as come together under the ISGC banner to conduct larger, collaborative studies. Herein, we present the Proceedings and official published abstracts of the 22nd Workshop of the ISGC.

The workshop held over 2 days included abstract sessions, working group reports on the progress of the scientific projects and new ideas, as well as invited lectures, all on the state-of-the-art complex disease genetics of stroke and its comorbidities. The ultimate goal of the ISGC is to improve the prevention and treatment of stroke and cerebrovascular disease by its genetic discoveries. The ISGC is proud of its junior members and therefore many of the abstracts in these Proceedings reflect the contributions of active junior investigators of the ISGC.

At the ISGC Workshop of 2017 many important ISGC themes were followed-up: results of joint analyses of large repositories of multi-ethnic stroke samples from investigators all over the globe, and the continuing initiative to make the data and results of ISGC analyses publicly available through the NINDS-funded “Platform for Accelerating Genetic Discovery for Cerebrovascular Disease.” During recent workshops new members joining from Biobank Japan, the China-Kadoorie Biobank, and UK Biobank were already welcomed and during this 22nd workshop we additionally welcomed new members, including from Nigeria, Africa.

On behalf of the ISGC Steering Committee and its many members, we hope that you enjoy reviewing our Proceedings and we welcome any opportunities for collaborative growth.

Acknowledgment: Steering Committee—Daniel Woo, MD and Stéphanie Debette, MD; Scientific Committee—Christopher D. Anderson, MD, MMSc; Outreach Committee—Jennifer Majersik, MD; Analysis Committee—Rainer Malik, PhD; Imaging Committee—Natalia Rost, MD, MSc; Translational Research Committee—Christopher D. Anderson, MD, MMSc.

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1. A stroke gene panel for next generation sequencing

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Objective We aimed a comprehensive panel of stroke genes, which may be used in clinical or research situations. **Background** Comprehensive analyses of known monogenic causes of stroke by whole exome or whole genome sequencing is technically possible today. Interpretation of large amount of generated data can be difficult. **Design/Methods** A systematic search of publicly available databases, Online Mendelian Inheritance in Man or PubMed was performed. Pathogenic or putatively pathogenic stroke genes reported in at least one person with stroke were selected. A subsequent description of stroke phenotype for each of these genes was performed based on reports on databases or original reports. Stroke phenotypes selected for clinical classification were: large artery atherosclerotic, large artery non-atherosclerotic (tortuosity, dolichoectasia, aneurysm, non-atherosclerotic dissection or occlusion), cerebral small vessel diseases, cardio-embolic (arrhythmia, heart defect, cardiomyopathy), coagulation dysfunctions (venous thrombosis, arterial thrombosis, bleeding tendency), intracerebral haemorrhage, vascular malformations (cavernoma, arteriovenous malformations) and metabolic (mitochondrial/mitochondrial-like disease). In a second part we included genes from the database search that were related to intermediate phenotypes that may plausibly cause stroke but without a documented stroke patient description. In a third section, we added single nucleotide polymorphisms, significantly associated with stroke as previous studies have shown. **Results** We identified 99 genes associated with stroke and 67 genes associated with different intermediary phenotypes. In addition, genes from recent genome-wide association studies that might be related to stroke were included. We describe these genes and the clinical stroke subtype(s) associated with each of these genes. **Conclusions** The panel can be used in next generation sequencing research studies on mendelian stroke. The pathogenicity of novel variants in these genes may be evaluated based on panel's clinical subtype description. The panel may be considered for clinical use to examine possible monogenic causes of stroke.

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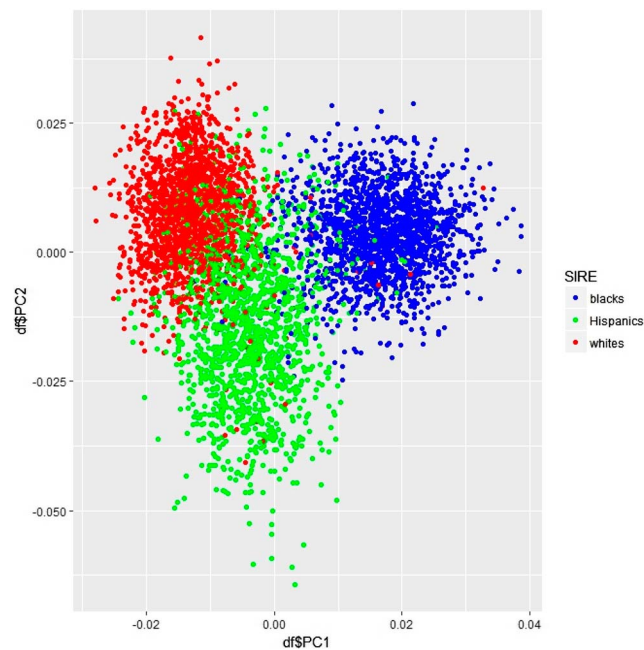
2. Estimate of non-genetic risk for intracerebral hemorrhage: Comparing genetically-defined and self-identified ancestry

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Objective We investigated whether DNA-based ancestry informative markers (AIMs), provided additional information compared with self-identified race/ethnicity (SIRE) and therefore improved risk modeling across racial/ethnic groups. **Background** The natural history of intracerebral hemorrhage (ICH) differs substantially across race/ethnicity. Resolving the degree to which these differences arise through nature, environment or both is likely to yield opportunities for reducing the impact of the disease. **Design/Methods** Using data from the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study (a multi-center case-control study of ICH in whites, blacks, and Hispanics), we utilized few AIMs to perform principal component (PC) analysis using variance-standardized relationship matrix dimension reduction. Multivariate logistic regression and tests for independent samples (X² and Mann-Whitney U tests) were used to compare AIM-defined ancestry and SIRE in tests of association with vascular risk factors (VRFs) for stroke. We then compared the performance of models for ICH risk that included AIM and SIRE. **Results** Among 4,935 subjects (median age 61, interquartile range 52–72), 34.7% were black, 35.1% white, and 30.2% Hispanic by SIRE. Within each self-reported population, AIM-defined ancestry remained associated with VRFs ($p < 0.001$) demonstrating that by SIRE did not account for the effect of genetically-defined ancestry. Regression of AIM-derived against VRFs confirmed independent associations of AIMs with hypertension across all SIRE ($p < 0.01$) and with diabetes, hypercholesterolemia, coronary artery disease and atrial fibrillation within each population defined by SIRE. Akaike information criterion (6294 vs 6286) and likelihood ratio test ($p < 0.001$) verified that AIMs significantly improved the ICH risk prediction model over SIRE alone. **Conclusions** In conclusion, AIMs provide a more detailed assessment of risk exposure in

representative U.S. populations than SIRE. Particularly among Hispanics and blacks, using AIMs adds value over self-reported ancestry in controlling for genetic and environmental exposures within these populations. These results confirm that, in ICH populations, self-defined race-ethnicity cannot be substituted for genetically defined ancestry.



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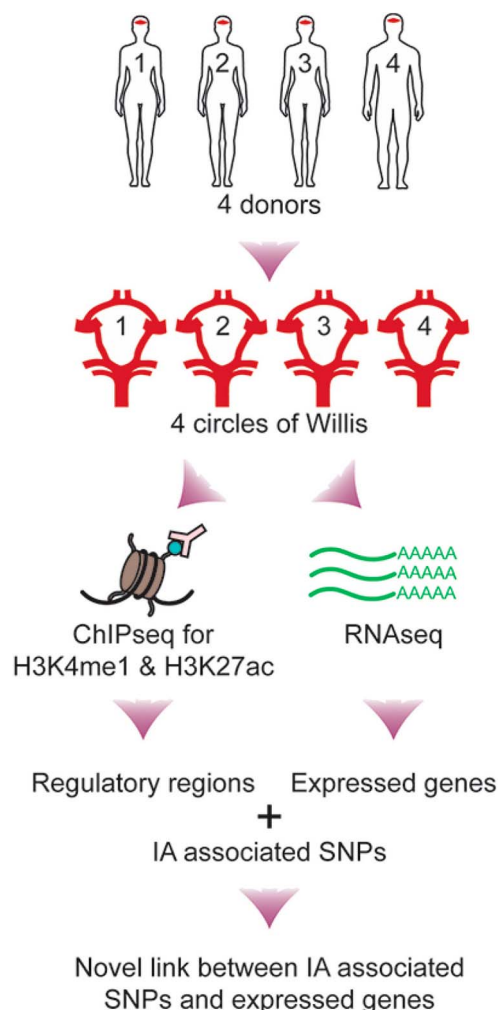
3. Intracranial aneurysm associated genetic variants alter non coding regulatory DNA within the human circle of Willis

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Objective We aimed to identify regulatory regions in the human circle of Willis (CoW) and to investigate whether intracranial aneurysm (IA) associated genetic variants are enriched in these regulatory regions. **Background** Genome wide association studies show significant association of IA with genetic variants in 6 genomic loci. Follow up studies on

these variants have largely been lacking. **Design/Methods** We performed chromatin immunoprecipitation and sequencing for histone modifications H3K4me1 and H3K27ac to identify regulatory regions in four human CoWs and investigated their biological meaning. We analyzed whether these regulatory regions overlap IA associated variants. In addition, we analyzed gene expression of the same CoWs by RNA sequencing. By combining our results with publicly available data, we linked the identified non-coding regulatory regions to potential target genes. **Results** CoW distal enhancers are enriched around genes that were implicated in IA disease pathogenesis in previous studies. Gene ontology analysis also revealed an enrichment of cell adhesion and extracellular matrix related terms, for both the distal enhancers and the expressed genes. IA associated SNPs from genome wide association studies are significantly enriched in CoW regulatory regions. Within regulatory distance of these regulatory regions are 102 genes that are expressed in the CoW and among these genes are likely the ones that are involved in IA pathogenesis. **Conclusions** In conclusion, our data suggest that regulatory regions from the CoW may link genetic variants associated with IA to genes with a potential role in the development of the disease. These data provide a substantial resource from which candidates for follow-up studies can be prioritized.



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4. Polygenic Risk to Estimate Cardioembolic Stroke from Atrial Fibrillation (PRECISE-AF) study protocol

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Objective PRECISE-AF will develop and implement a clinical genetic test that will enable personalized Atrial Fibrillation (AF) risk estimation in patients with ischemic stroke. **Background** AF affects over 34 million individuals worldwide, and is a major risk factor for stroke. Occult AF underlies 10–30% of ischemic strokes, and effective treatment exists if it can be detected. Currently, no standardized AF risk stratification paradigm exists to inform the use of cardiac rhythm monitoring or anticoagulation in the absence of documented AF. **Design/Methods** This study will prospectively enroll 500 ischemic stroke patients at a single center, and perform CLIA-certified genotyping of 166 DNA variants using a next-generation sequencing platform for calculation of genetic risk scores (GRS) by individual. Enrolled subjects will be followed for 1 year, with primary endpoints of test turnaround time and technical validity, and secondary endpoints of clinical AF detection, recurrent stroke and vital status, and resource utilization in association with GRS by quintile. **Results** The preliminary data motivating this proposal demonstrates that patients in the highest quintile of AF genetic risk as measured by the 166 SNP GRS have >2.8-fold higher risk of cardioembolic stroke subtype assignment, after adjustment for clinical risk factors in an available retrospective genetic data set ($p = 2 \times 10^{-5}$). The study protocol will examine the performance of this test in a prospective and clinically viable fashion. **Conclusions** PRECISE-AF will deliver an optimized polygenic test for AF genetic risk in a clinical environment with prospective performance metrics, and will inform future efforts for dissemination of polygenic test results to patients and providers to guide clinical decision-making.

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5. Unraveling the Genetic Architecture of Stroke in Africans: Updates from the SIREN project

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Objective To discover significant associations of novel genetic variants with stroke and its subtypes among indigenous Africans. **Background** Stroke has attracted global attention as 1 in 6 people worldwide will experience a stroke in their lifetime and the burden is growing in Africa as a result of demographic transition and lifestyle changes. While people in Africa carry a disproportionately higher burden of stroke compared to the rest of the world, the exact contributions of genomic factors to this disparity are unknown. Unraveling the genomic contributions to stroke occurrence, type, severity and outcome in people of African ancestry will deepen our understanding of the unique pathways involved in the neurobiology of stroke and provide valuable targets for prevention and treatment. The Stroke Investigative Research and Educational Network (SIREN) project is a component of the Human Health and Heredity in Africa (H3 Africa) Consortium. SIREN aims to explore genomic and environmental risk factors of stroke in populations of African ancestry. **Design/Methods** Twenty-three previously identified single nucleotide polymorphisms (SNPs) in 14 genes of relevance to the neurobiology of ischemic stroke were investigated. Logistic regression models adjusting for known cardiovascular disease risk factors were constructed to assess the associations of the 24 SNPs in rigorously phenotyped cases (N = 429) of ischemic

stroke (Men = 198; Women = 231) and stroke-free (N = 483) controls (Men = 236; Women = 247). **Results** Interleukin-6 (IL6) rs1800796 (C minor allele; frequency: West Africans = 8.6%) was significantly associated with ischemic stroke in men (OR = 2.006, 95% CI = [1.065–3.777], $p = 0.031$) with hypertension in the model but not in women. In addition, rs2383207 in CDKN2A/CDKN2B (minor allele A with frequency: West Africans = 1.7%) was also associated with ischemic stroke in men (OR = 2.550, 95% CI = [1.027–6.331], $p = 0.044$) with primary covariates in the model, but not in women. Polymorphisms in other genes did not show significant association with ischemic stroke. For subjects with symptomatic small vessel disease (SVD) ischemic stroke, Apolipoprotein L1 (APOL1) rs73885319 (OR = 1.52; CI: 1.09–2.13, p -value = 0.013), rs2383207 in CDKN2A/CDKN2B (OR = 3.08; CI: 1.15–8.26, p -value = 0.026) and rs2107595 (OR = 1.70; CI: 1.12–2.60, p -value = 0.014) and rs28688791 (OR = 1.52; CI: 1.03–2.26, p -value = 0.036) in HDAC9 gene were associated with SVD stroke at 0.05 significance level. Polymorphisms in other genes did not show significant associations. **Conclusions** Polymorphisms rs1800796 in IL6 gene and rs2383207 in CDKN2A/CDKN2B gene have significant associations with ischemic stroke in indigenous West African men while the association of Apolipoprotein L1 (APOL1) rs73885319 with SVD ischemic stroke is the first report of a specific association of APOL1 with a stroke subtype. Further research is needed to confirm these initial findings and deepen understanding of the genetics of stroke in people of African ancestry with possible implications for other ancestries since all humans originated from Africa.

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6. Genetic susceptibility loci for coronary artery disease and large artery stroke are associated with human atherosclerotic plaque characteristics

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Objective We studied the impact of sequence variation on plaque characteristics, and tissue-specific gene expression by combining data from independent biobanks comprising patients with clinically significant arterial stenosis. **Background** Tens of genetic susceptibility loci associate with large artery ischemic stroke (LAS) and coronary artery disease (CAD), but deciphering their underlying mechanisms to identify putative therapeutic targets is challenging. Atherosclerosis is cardinal to cardiovascular diseases (CVD) and histological studies have identified plaque characteristics that associate with clinical outcome. To what extent common variation associated with CVD relates to these characteristics remains unknown. **Design/Methods** We genotyped 1,439 patients from Athero-Express, 127 patients from BiKE, and 109 patients from STAGE. We tested 61 CVD susceptibility loci for association to 7 plaque characteristics, and gene expression using regression modeling, correcting for age, sex, 10 principal components, and study specific covariates. **Results** We report a ~5.2-fold enrichment of CAD variants associated with plaque characteristics ($p = 3.6 \times 10^{-8}$, 16 out of 61 variants). The CAD risk reducing alleles of rs12539895 and a nearby deletion (chr7:106,901,393 TG > T) on 7q22 associated with less fat in plaques ($p < 5.1 \times 10^{-6}$), and lower circulating LDL levels. Circularized chromosome conformation capture in monocytes revealed many regional genes physically interacting with rs12539895. Additional analyses revealed tissue-specific effects on *HBPI*, *COG5*, and *GPR22*

expression, further prioritizing the list of 11 regional genes for future studies. **Conclusions** Our study supports the view that genetic loci conferring susceptibility to CAD and LAS, play a role in the underlying pathophysiology of the atherosclerotic plaque.

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7. Genome-wide study of 100,000 participants from the China Kadoorie Biobank identifies novel variants for stroke sub-types

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Objective To identify genetic variants associated with stroke sub-types in the China Kadoorie Biobank study. **Background** China Kadoorie Biobank (CKB) is a prospective study of 512,000 adults, recruited at age 30–79 years from 10 diverse regions of China in 2004–2008. Detailed questionnaire data and physical measurements were recorded at baseline and at subsequent resurveys, and blood samples were stored for DNA extraction and genotyping. Follow-up using linkage with death and disease registries and with national health insurance systems identified incident stroke in 53,566 individuals, including 7,427 intracranial haemorrhage (ICH) and 36,112 ischaemic stroke (IS) cases in those with no prior history of cardiovascular disease (CVD). Ongoing validation and classification of IS and ICH stroke events, by review of clinical records, has confirmed the diagnosis for 93% of reported ICH cases and has identified 379 lobar and 1,899 non-lobar cases. **Design/Methods** Affymetrix Axiom arrays, custom-designed for Chinese populations, were used to genotype 102,783 CKB participants, including all ICH cases without prior CVD. After QC, 100,597 data sets were imputed into the 1000 genomes Phase 3 reference using SHAPEIT3 and IMPUTE4, yielding genotypes for 10.2M variants with MAF >0.005, including 8.6M with info >0.8. Associations with stroke subtypes used mixed models (BOLT-LMM v2.3) with adjustment for sex, age, age², region, array type, and 8 principal components. For each outcome (any stroke, IS, ICH, lobar and non-lobar ICH) analyses included all participants or subsets without any CVD prior to the censor date. **Results** Preliminary analyses identified novel associations at genome-wide significance ($p < 5 \times 10^{-8}$) for each of IS, ICH, lobar ICH and non-lobar ICH. There was no

overlap between the loci identified for different stroke sub-types, nor with previously reported stroke loci. **Conclusions** GWAS of stroke in Chinese individuals identified multiple novel loci, confirming the value of performing association studies in populations of different ancestries. Discovery of different variants associated with lobar and non-lobar ICH sub-types highlights the different genetic architectures and distinct aetiologies of ICH sub-types.

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8. Gene expression profile of cervical artery dissection by time of event

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Objective Aim 1: Demonstrate if patients with cervical artery dissection (CeAD) have a distinct gene expression profile in whole blood at time-of-event compared to healthy controls. Aim 2: Demonstrate if patients with CeAD have a distinct gene expression profile in whole blood at time-of-event compared to convalescent profiles at 3–6 months. **Background** Dissection of the carotid and vertebral arteries is a prevalent cause of stroke in young adults. While the pathogenesis of incident CeAD remains poorly understood, clinical and genetic associations suggest a systemic arteriopathy at time of event. **Design/Methods** We enrolled 37 consecutive patients with carotid or vertebral artery dissection (with and without ischemic stroke) from 2013 to 2016, excluding concurrence of major trauma. Cases were age and sex matched to non-CeAD ischemic stroke controls (n = 16) and healthy controls (n = 11). Whole blood samples were collected within 4 weeks from time of event, and again at 3–6-month follow-up. We used IlluminaHT-12 microarrays to assess differential gene expression at time of CeAD relative to controls, and relative to gene expression at >3 months follow-up within CeAD cases. Mixed effects regression models included relevant covariates of age, sex, race/ethnicity, time of enrollment, and occurrence of stroke. We used a False Discovery Rate (FDR) cutoff of 5% to account for multiple testing as well as a 1.5-fold change cutoff to identify robust, differential gene expression. **Results** We identified 538 differentially expressed genes between CeAD patients and healthy controls with 30 of these genes reaching our predetermined 1.5x fold change limit. Within CeAD cases, 1,238 genes showed differential expression at a 5% FDR

compared to time points at 3–6 months follow-up, with 31 genes showing at least a 1.5 fold change. Overlapping the 2 comparisons, including CeAD vs controls and convalescent profiles, 11 genes were significant using the 5% FDR and 1.5-fold change cutoffs: AHSP, HBD, HBG1, HBG2, HBM, YBX3P1, RBM38, SELENBP1, SLC25A37, SNCA, TESC. **Conclusions** In this consecutive series of individuals with CeAD, we identified a distinct gene expression profile associated with incident dissection. These data are limited by small sample size and results are hypothesis generating. Replication in larger, independent cohorts is warranted.

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9. Estonian young stroke registry

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Objective The aim of the current study is to determine the epidemiology, etiology, risk-factors, life-style indicators, biomarkers and genetic determinants of young stroke patients.

Background: The Estonian Young Stroke Registry was established in January 2013. Detailed data is collected prospectively from patients admitted to the Department of Neurology and Neurosurgery, University of Tartu with the diagnosis of stroke (ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage) or transient ischemic attack (TIA) aged 18–54. **Design/Methods** Using prospective design, detailed data of every patient is collected and registered. Clinical data consists of detailed medical history, risk factors, neurologic symptoms, NIHSS stroke scale (upon admission, 1st and 7th day/discharge, 3 months and 1 year), mRS (before stroke, 7th day/discharge, 3 months and 1 year), cardiac data (echocardiography, electrocardiogram, 24 hour cardiac monitoring), blood tests, computed tomography (CT), CT-angiography, magnetic resonance imaging (MRI), used medications, self-reported health-behavior data (before stroke, at 3 months and 1 year). All strokes are subtyped according to TOAST (Trial of Org 10172 in Acute Stroke) and CCS (Causative Classification of Stroke) classifications. In addition, to routine blood tests, profound biochemical profiling is done (measurement of interleukins, atherosclerosis and oxidative stress markers in plasma) upon admission, 3 months and 1 year after stroke. DNA (upon admission) and RNA (upon admission and at 1 year) is collected (with informed consent only) and stored for further analyses. **Results**

There are over 500 patients in the registry: 300 ischemic stroke patients, 88 patients with subarachnoid or intracerebral hemorrhage and >100 patients with TIA. The registry is ongoing. The DNA samples from 250 ischemic stroke patients have been tested using the Affymetrix chips (containing 902,675 SNPs). No genotype-phenotype association analyses have been done yet. **Conclusions** The Estonian Young Stroke Registry comprises a profound database and enables to analyze detailed data of young stroke patients. We hope that our registry helps to determine the causes and possible biochemical and clinical markers of stroke in the young.

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10. Genetic association study in 8,448 UK Biobank individuals identifies a variant in VCAN associated with white matter microstructural integrity

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Objective In 8,448 population-based individuals in UK Biobank we performed a genome-wide analysis to identify common variants associated with microstructural integrity of the cerebral white matter. In addition we aimed to elucidate the relationships of white matter microstructural integrity with stroke, major depressive disorder and Alzheimer's disease and to compare these relationships with white matter hyperintensity volumes (WMH). **Background** Microstructural tissue alterations underlying the cerebral white matter are associated with cerebral small vessel disease markers and predictive of cognitive decline. However, there exist only few published genome-wide association studies with a limited sample size that investigate the microstructural integrity of the white matter. **Design/Methods** Microstructural integrity was measured as fractional anisotropy (FA) and mean diffusivity (MD) derived parameters on diffusion tensor images, WMH was assessed on T2-FLAIR images. **Results** We identified one novel locus at genome-wide significance ([VCAN]: rs13164785, $p = 3.7 \times 10^{-18}$ for MD and rs67827860, $p = 1.3 \times 10^{-14}$ for FA. LD score regression showed a significant genome-wide correlation between FA, MD and WMH (FA-WMH $r_G -0.39$ [SE 0.15]; MD-WMH $r_G 0.56$ [SE 0.19]). In polygenic risk score analysis FA, MD and WMH were

significantly associated with lacunar stroke, MD with major depressive disorder and WMH with Alzheimer's disease. **Conclusions** We identified 2 loci that were genome-wide associated with microstructural integrity of the white matter in the brain measured as FA and MD. The results suggest that mechanisms underlying white matter alterations are shared with cerebrovascular disease, and highlight that inherited differences in white matter microstructure, possibly age-related, impact on Alzheimer's disease and major depressive disorder.

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11. Genetic imbalance is associated with poorer outcome after ischemic stroke

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Objective We explored the impact of genetic imbalance with and without ohnologs on outcome after ischemic stroke (IS) in 2 independent study samples. **Background** Genetic imbalance occurs when a protein-coding gene has more or fewer copies than the 2 copies of a normal diploid genome. Such imbalance may occur in healthy subjects, but has been associated with various disease phenotypes. Ohnologs are genes with pronounced dose-sensitivity. **Design/Methods** Copy number variation was detected by PennCNV analysis of GWAS-microarrays. Findings were individually inspected after noise reduction (<http://noise-free-cnv.sourceforge.net/>). True findings were mapped on the human genome (<http://www.ensembl.org/index.html>) and the ohnolog repository (<http://ohnologs.curie.fr/>). Genetic imbalance was studied in IS patients with favorable (mRS 0–2) and unfavorable (mRS 3–6) outcome after 3 months from the CADISP (Cervical artery dissection and ischemic stroke patients) study (n = 816; age = 44 ± 10 years). To validate the findings, similar analyses were performed in IS patients from 7 SiGN centers (n = 2,498; age = 68 ± 14 years). Propensity scores

were used to adjust for age, sex, stroke severity (NIHSS), stroke subtype (TOAST) and center of recruitment. **Results** Genetic imbalance was analyzed as a continuous variable by counting the number imbalanced protein-coding genes per patient. The number of imbalanced genes was associated with unfavorable outcome in CADISP (p = 0.004; OR = 0.88; 95% CI = 0.83–0.96) as well as in SiGN (p = 0.002; OR = 0.95; 95% CI = 0.91–0.98). In a next step, we focused on imbalances that were specific to ohnologs. Imbalance including ohnologs was clearly associated with unfavorable outcome in the SiGN sample (p = 0.004; OR = 0.92; 95% CI = 0.89–0.66) as well as in the CADISP sample (p = 0.002; OR = 0.88; 95% CI = 0.81–0.95). In contrast, imbalances that did not affect ohnologs were not associated with outcome in both studies (SiGN p = 0.6, CADISP p = 0.3). **Conclusions** Genetic imbalance is an independent predictor of unfavorable outcome 3 months after stroke.

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12. Platelet supervillin protects against shear-dependent thrombus formation and offers a possible therapeutic target to reduce risk of large artery ischaemic stroke

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Objective To identify targets for shear-dependent platelet activation that can be used to reduce risk of large artery ischaemic stroke. **Background** Shear force can promote platelet adhesion to result in thrombus formation. A single nucleotide polymorphism in the SVIL (supervillin) gene that lower mRNA levels has been associated at genome-wide significance with increased shear-dependent platelet activation in African Americans. Shear-dependent platelet activation underlies the pathophysiology of large artery ischaemic stroke. An association of this genetic variant with risk of large artery stroke would further evidence a possible therapeutic target. **Design/Methods** The rs7070678 SNP in the SVIL gene is used here as an instrument for shear-dependent platelet activation mediated by expression of supervillin. The National Institute of Neurological Disorders Stroke Genetics Network international consortium have made discovery stage GWAS meta-analysis summary estimates for ischemic stroke subtypes defined by the TOAST classification system publicly available. We test for any association of the rs7070678 SNP with risk of large artery stroke across all ethnicities, and

compare against other stroke subtypes as negative controls to assess the specificity of this target. **Results** Polymorphisms in the rs7070678 SNP of the SVIL gene that increase mRNA levels to reduce shear-dependent platelet activation are associated with lower risk of large artery stroke ($p = 0.04$). No association was found in the other stroke subtypes that were studied as negative controls (cardioembolic, $p = 0.49$; small artery occlusive, $p = 0.59$). **Conclusions** This genetic evidence supports the conclusion that platelet supervillin expression reduces risk of large artery stroke, and thus highlights a potential therapeutic opportunity. The specificity of this approach may in turn minimize possible adverse effects, most notably increased bleeding risk.

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13. A human iPSC-based vascular model to study the HDAC9 genetic variant associated with large-vessel stroke

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Objective To study how a specific genetic variant in the HDAC9 gene, which has been identified to be highly associated with large-vessel stroke, is affecting HDAC9 activity and contributing to the development of the blood vessel disease leading to stroke. **Background** A common variant in the Histone Deacetylase 9 (HDAC9) gene has been identified in GWAS study as the strongest genetic risk for large-vessel stroke to date and further associated with promoting carotid atherosclerosis. The mechanism linking HDAC9 variant with increased risk of stroke is still unknown due to the lack of suitable models. Since HDAC9 levels were found up-regulated in carotid plaques, we suggest that the HDAC9 stroke-associated variant may affect gene expression and this may promote vessel damage, which contributes to the pathophysiology of ischaemic stroke. **Design/Methods** To test this hypothesis, we have developed a vascular model using human induced pluripotent stem cells (iPSC), by differentiating iPSC carrying the HDAC9 risk variant into vascular smooth muscle cells (SMC) of neural crest origin, which mimic the blood vessels of the brain, using a well-defined protocol. **Results** Increased expression of HDAC9 was observed in the iPSC line with the HDAC9 stroke-associated variant compared to the WT iPSC used as control. Vascular

SMC, differentiated from the stroke risk iPSC line, also expressed high levels of HDAC9. Moreover, proliferative and apoptotic studies showed that these SMC have lower proliferative rate and increased apoptosis levels compared to WT iPSC-derived SMC. Finally, the use of sodium valproate, which is known to inhibit HDAC activity, was able to reduce the cell death rate of SMC harbouring the HDAC9 risk variant. **Conclusions** Our iPSC-based vascular model has showed that the stroke-associated variant in HDAC9 is likely to cause up-regulation of HDAC9 gene expression, which in turn could affect both cells apoptosis and proliferative activity. This indicates that our human iPSC-derived SMC model can be used as powerful tool to study how HDAC9 stroke-associated variant affects SMC vascular phenotype, with the aim of identifying new pathways/targets for therapeutic development and test existing compounds as well as newly developed drugs in a human system.

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14. Pro-inflammatory gene variants and stroke risk

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Objective To study variation of a “biological process” as risk factor for stroke. **Background** Inflammation plays a fundamental role in the development of atherosclerosis and atherothrombotic stroke. We hypothesized that individuals with a high burden of pro-inflammatory gene variants are more likely to develop atherosclerosis and atherothrombotic stroke. **Design/Methods** Within a population-based stroke registry, we performed a case control study with 466 ischemic stroke patients and 798 control subjects without a history of stroke or recent myocardial infarction, randomly selected from the population. For each subject, the total number of pro-inflammatory alleles of 16 established inflammatory genes (CCL2, CCR5, CD14, CRP, HDAC9, ICAM1, IL1A, IL1B, IL1RN, IL6, IL6R, IL10, SELE, SELS, TGFB1, TNF) was assessed (“16-SNP score”) and associated with occurrence of carotid plaque (in control subjects) and with stroke (in the whole study sample). **Results** Score values of ischemic stroke patients (13.2 ± 2.3) were slightly higher than those of control subjects (13.0 ± 2.4 ; $p = 0.096$). Adjustment for hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation and smoking in a logistic regression model revealed non-significant, but suggestive association between score values and stroke risk ($p = 0.061$, odds for stroke: 1.051 with 95%

confidence interval 0.997–1.108). Score values of stroke subgroups (LVD: 13.1 ± 2.1 ; CE: 13.4 ± 2.1 , SVD: ± 2.4) did not differ significantly among each other. Control subjects with baseline leukocytosis (WBC counts $>10,000/\text{mm}^3$) had higher score values than those with lower WBC counts ($13.7 \pm 2.4/13.0 \pm 2.4$; $p = 0.051$), in particular in the subgroup of non-smoking control subjects ($14.2 \pm 2.2/13.0 \pm 2.4$; $p = 0.008$). Score values of controls with carotid plaque did not differ from those without plaque ($13.1 \pm 2.5/12.9 \pm 2.3$; $p = 0.230$), but young controls with plaque had higher score values than subjects without (≤ 60 years: $13.7 \pm 2.8/12.8 \pm 2.4$; $p = 0.039$; ≤ 50 years: $15.3 \pm 1.5/13.0 \pm 2.2$; $p = 0.011$). **Conclusions** Our data suggest a borderline effect of a higher number of proinflammatory alleles on stroke risk. However, we could not detect a particular association between our proposed 16-SNP score and stroke due to LVD. In younger control subjects, we found evidence for an association between higher score values and carotid atherosclerosis and also with baseline leukocytosis suggesting higher inflammatory response in subjects with higher score values. Our findings need replication in other samples. Moreover, inclusion of additional pro-inflammatory variants may improve the predictive value of the proposed inflammatory gene score.

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15. Clonal mosaicism in blood samples from SiGN patients

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Objective Clonal mosaicism has previously been associated with aging and cancer. This study aims to further investigate the role of clonal mosaicism in stroke patients and healthy controls. **Background** The frequency of mosaic chromosomal abnormalities in blood or buccal samples from healthy donors is low and increasing with age up to 2–3% in subjects >70 years. We study clonal mosaicism in blood samples from SiGN patients and healthy controls. **Design/Methods** The study sample included high-density SNP-microarrays from 1,244 healthy control subjects and 4,622 patients with ischemic stroke from different centres. Mosaicism for aneuploidies >2 Mb of the autosomes and occurring in $>10\%$ of the white blood cells were identified by visual inspection of the samples in the context of CNV validation. Occurrence of mosaicism was associated with

age, sex, center of recruitment and case/control state. **Results** Clonal mosaicism was identified in 101 (1.7%) subjects (8 controls and 93 patients). Subjects with mosaicism were older than those without (73.4 ± 12.1 years vs 64.8 ± 15.6 ; $p < 0.0001$). In a logistic regression model, age was a significant predictor of mosaicism ($p < 0.001$; odds ratio [OR] = 1.041; 95% confidence interval [CI] = 1.023–1.059). The association between age and mosaicism was independent from sex, center and case/control state. Weak, independent associations between mosaicism and center ($p = 0.018$) and between mosaicism and stroke risk ($p = 0.057$) were unexpected observations of this analysis. **Conclusions** Our analysis confirms the finding of clonal mosaicism in blood samples of older individuals. Age was a strong and independent predictor of mosaicism. The significant heterogeneity among the centers with regard to mosaicism remains an unexplained observation of this study.

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16. A genome-wide association study identifies novel susceptibility variants for hypertensive intracerebral hemorrhage in a Han Chinese population

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Objective We sought to identify genetic factors that contribute to hypertensive intracerebral hemorrhage (HICH) stroke in 2 independent samples of Han Chinese individuals. **Background** Previous studies have found genetic associations in the subtypes of ischemic stroke. However, no robust genetic association has been reported for HICH stroke in a Han Chinese population. **Design/Methods** A genome-wide association study (GWAS) was conducted on 363 individuals with HICH stroke and 1,731 controls from a Han Chinese population residing in Taiwan. The study was replicated in an independent Han Chinese population comprising an additional 250 HICH stroke cases and 1,265 controls. **Results** Three SNPs clustered at chromosome 1, with p values lower than 1×10^{-6} , were identified. Other five loci at chromosome 8, 15, and 21 were also identified in the independent Han Chinese population. **Conclusions** To our knowledge, this is the first GWAS for Asian single cohort of HICH stroke conducted in a Han Chinese population. The understanding

of the genetic basis of HICH could be valuable in the development of treatments for specific subtypes of hemorrhage stroke.

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17. The Brazilian Initiative on Precision Medicine (BIPMED): The first publicly available genomic database in Latin America

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Objective Our overall aim is to help implement precision medicine by creating the necessary resources to promote an ethical and responsible sharing of genomic and clinical information. Therefore, we report here the implementation of the first public genomic database in Latin America. **Background** BIPMed is an initiative of five Research Innovation and Dissemination Centers established in the state of Sao Paulo, Brazil, aiming to help implement precision medicine. The BIPMed genomic database is the first product released by our initiative to

fulfill the increasing need for publicly available genetic and genomic information. Our aim is that it becomes a reference for data sharing for different populations in Latin America. BIPMed is also part of the Beacon Project which is a data discovery engine supported by the Global Alliance for Genomics and Health (GA4GH). More recently, BIPMed became the Brazilian Node of the Human Variome Project (HVP). **Design/Methods** BIPMed genomic database is currently based on a software platform, the Leiden Open Variation Database and it was implemented as a fully web-based gene sequence variation database. The design of the database follows the recommendations of the Human Genome Variation Society and the principals and guidelines of the GA4GH for the ethical and responsible sharing of genomic and clinical information. In addition, 2 other databases were designed to store and display information from SNP-arrays and RNA-sequencing data. Furthermore, a platform able to integrate different genomic information is under development. **Results** Currently, the database (www.bipmed.org) contains variants detected using whole exome sequence as well as SNP-genotyping from reference population ascertained based on their geographic origin in Brazil. In this data set we identified over 10 million variants in 20,842 genes. There were 209 variants which were unique to the population studied. In addition, our genomic database has attracted world-wide attention and it has been accessed by an average of 150 users daily from countries all over the globe. **Conclusions** We expect the database to grow fast and include data sets from disease cohorts as well as other types of -omics data. This platform, the first of its kind in Latin America, is intended to be used by clinicians and scientists worldwide, to obtain and share information about various aspects of genomic medicine and human health, as well as to support dissemination and training.

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