ISGC May Madness 2026

Virtual Workshop Series

Stroke Genomics Across the Globe

May 4/5 • May 11/12 • May 18/19 • May 25/26, 2026

International Stroke Genomics Consortium – www.strokegenetics.org

Register here >

WELCOME

Dear colleagues,

On behalf of the International Stroke Genomics Consortium (ISGC) and the Early Career Researcher committee of the ISGC, we are pleased to welcome you to the **ISGC May Madness Virtual Workshop Series 2026**.

Following the transition of ISGC to a single in-person workshop each year, this virtual series was developed to maintain momentum, visibility, and collaboration across the consortium throughout the year.

Over four weeks in May, ISGC Working Groups will present recent findings, discuss emerging themes, and explore opportunities for collaboration. The sessions are designed to mimic the spirit of the ISGC annual meeting: short scientific talks combined with interactive discussion.

The program also highlights interdisciplinary collaborations and the importance of expanding genomic research to diverse populations worldwide.

We hope this series fosters new collaborations and helps advance stroke genomics research globally.

Mark Bakker, PhD
May Madness Committee lead
Vice Chair, International Stroke Genomics Consortium

Organization

May Madness Committee

Chad Aldridge, Virginia, USA
Mark Bakker, Utrecht, The Netherlands
Michael Chong, Hamilton, Canada
John Cole, Baltimore, USA
Quentin le Grand, Paris, France
Shraddha Mainali, Richmond, USA
Alice Man, Hamilton, Canada

Early Career Researcher Committee

Alexis Simpkins; Anne-Katrin Giese; Ben Gaastra; Chad Aldridge; Cristina Gallego; Danit Saks; Dearbhla Kelly; Eric Harshfield; Jeong-Yoon Lee; Josefin Kaufmann; Kara Tai; Kristiina Rannikmae; Kristina Schlicht; Mark Bakker; Olayinka Adebayo; Quentin Le Grand; Rohan Arora; Savvina Prapiadou; Seon-Kyu (Bosco) Yang; Shraddha Mainali; Bracky Mitchel; Brad Worrall; Carlos Cruchaga; Christopher Anderson; Dan Woo; Israel Fernandez; Jemma Hopewell; John Cole; Myriam Fornage; Natalia Rost; Steven Kittner.

ISGC Steering Committee

Chair: Dr. Amy Brodtmann, Melbourne, Australia
Vice Chair: Dr. Mark Bakker, Utrecht, The Netherlands
Immediate Past Chair: Dr. Brad Worrall, Virginia, USA
Dr. Yoichiro Kamatani, Tokyo, Japan
Dr. Steven Kittner, Baltimore, USA
Dr. Aniket Mishra, Bordeaux, France
Dr. Ynte Ruigrok, Utrecht, The Netherlands
Dr. Si Cheng, Beijing, China
Dr. Michael Chong, Hamilton, Canada
Dr. Stacie Demel, Cincinnati, USA
Dr. Cristina Gallego-Fabrega, Barcelona, Spain
Dr. Liisa Tomppo, Helsinki, Finland

Contributing ISGC working groups

Imaging working group
Cognition working group
Global Alliance working group
Rare Variants working group
Intracerebral Hemorrhage working group
Translational working group
Biological Sex Differences working group
Intracranial Aneurysms working group
Early-Onset Stroke working group

PROGRAMME OVERVIEW

The sessions last **1 hour**, except for the extended May 11/12 sessions.

Session	Date	Topics	Time						
			Los Angeles	New York	London	Central Europe	Beijing	Tokyo	Sydney
S1	**May 4**	Imaging • Cognition • Stroke Outcome	00:00	03:00	**08:00**	**09:00**	**15:00**	**16:00**	**17:00**
S2	**May 4/5**	Imaging • Cognition • Stroke Outcome	**07:00**	**10:00**	**15:00**	**16:00**	22:00	23:00	00:00 (May 5)
S3	**May 11**	Rare Variants • ICH • Translational	06:00	**09:00**	**14:00**	**15:00**	**21:00**	22:00	23:00
S4	**May 11/12**	Rare Variants • ICH • Translational	**16:00**	**19:00**	00:00 (May 12)	01:00 (May 12)	**07:00 (May 12)**	**08:00 (May 12)**	**09:00 (May 12)**
S5	**May 18**	Sex Differences • Intracranial Aneurysm • Early-Onset Stroke	00:00	03:00	**08:00**	**09:00**	**15:00**	**16:00**	**17:00**
S6	**May 18/19**	Sex Differences • Intracranial Aneurysm • Early-Onset Stroke	**08:00**	**11:00**	**16:00**	**17:00**	23:00	00:00 (May 19)	01:00 (May 19)
S7	**May 25/26**	Interdisciplinary Collaborations • Diverse Populations	**16:00**	**19:00**	00:00 (May 26)	01:00 (May 26)	**07:00 (May 26)**	**08:00 (May 26)**	**09:00 (May 26)**
S8	**May 26**	Interdisciplinary Collaborations • Diverse Populations	00:00	03:00	**08:00**	**09:00**	**15:00**	**16:00**	**17:00**

The sessions last **1 hour**, except for the extended May 11/12 sessions which last 1h30m and 1h45m, respectively.

SESSION S1

Imaging, cognition, and stroke outcome (1/2)

Date: May 4

Session host: Mark Bakker, University Medical Center Utrecht, The Netherlands

https://uvahealth-org.zoom.us/j/96800299350?pwd=bbybfzDkhyHVWHsQLjxvajRaI1nD7w.1
Meeting ID: 968 0029 9350
Passcode: 47289541

Session time across timezones:

Los Angeles	New York	London	Central Europe	Beijing	Tokyo	Sydney
02:00	03:00	08:00	09:00	15:00	16:00	17:00

Programme

1. Introduction by the working group leads
2. Abstract S1.1. ***DNA Methylation in Post-Stroke Cognitive Impairment Across African and European Ancestries: An Exploratory Study***. Motunrayo Coker. College of Medicine, University of Ibadan, Nigeria.
3. Abstract S1.2. ***Brain Communication Modes Shape Cognition after Stroke.*** Nicholas Parsons. School of Translational Medicine, Monash University, Melbourne Australia.
4. Abstract S1.3. Si Cheng. Beijing Tiantan Hospital, China.
5. General discussion + closing remarks

SESSION S2

Imaging, cognition, and stroke outcome (2/2)

Date: May 4/5

Session host: Shraddha Mainali, Virginia Commonwealth University School of Medicine, Richmond, USA

https://uvahealth-org.zoom.us/j/98446693092?pwd=wlTaXiKeobI2PbdS4CULvzCXzNPgK1.1
Meeting ID: 984 4669 3092
Passcode: 07868925

Session time across timezones:

Los Angeles	New York	London	Central Europe	Beijing	Tokyo	Sydney
07:00	10:00	15:00	16:00	22:00	23:00	00:00 (May 5)

Programme

1. Introduction by the working group leads
2. Abstract S2.1. ***Proteomic study identifies inflammatory plasma proteins associated with 3-month functional outcome after ischemic stroke***. Kara Tai, University of Gothenburg, Sweden; and Laia Llucià Carol, Sant Pau Research Institute, Barcelona, Spain.
3. Abstract S2.2. ***Comparative Plasma Proteomics in Cerebral Amyloid Angiopathy and Alzheimer's Disease: A Discovery Study***. Joan Jiménez Balado, Hospital del Mar, Barcelona, Spain.
4. Abstract S2.3. ***Image-based prediction of stroke outcomes***. Anna K. Bonkhoff, Massachusetts General Hospital, Harvard Medical School, Boston, USA.
5. General discussion + closing remarks

SESSION S3

Rare variants, intracerebral hemorrhage, and translational research (1/2)

Date: May 11

Duration: 1 h 45 min

Session host: Alice Man & Michael Chong, McMaster University, Hamilton, Canada

Please click this URL to start or join. https://monash.zoom.us/j/89285397305?pwd=s4QNgXSMp8rVDHLsqYfLC2me7WGHgI.1
Or, go to https://monash.zoom.us/join and enter meeting ID: 892 8539 7305 and passcode: 238973
Ensure your device has a dedicated microphone and webcam.

Join from a dial-in phone:
Dial: +61 3 990 59666 [+61 3 9905 ZOOM] or +61 2 8015 2088
Meeting ID: 892 8539 7305
International numbers available: https://monash.zoom.us/u/kew3zF97eA

Session time across timezones:

Los Angeles	New York	London	Central Europe	Beijing	Tokyo	Sydney
06:00	09:00	14:00	15:00	21:00	22:00	23:00

Programme

1. Introduction by hosts
2. Abstract S3.1. ***From Variant to Vessel: How PAR4 Genetics Shapes Stroke Outcomes.*** Frederik Denorme, Laboratory for Cell Biology and Histology, University of Antwerp, Belgium.
3. Abstract S3.2. ***Advancing the therapeutic potential of ADAMTS13 in Stroke***. Colin Kretz, McMaster University, Hamilton, Canada.
4. Abstract S3.3. ***Epigenome Wide Association Study in ICH, with sex stratification and sex interaction.*** Cristina Gallego, Stroke Pharmacogenomics and Genetics Group, Institut de Recercat Sant Pau, Barcelona, Spain.
5. Abstract S3.4. ***Quantifying the Contribution of Rare Coding Variants to Stroke Risk Factors with RARity.*** Nazia Pathan, Population Health Research Institute, Hamilton, Ontario.
6. Abstract S3.5. ***Making the most of whole-genome sequencing data for rare variant association tests using the RAVA-FIRST approach.*** Ozvan Bocher, Université de Bretagne Occidentale, Brest, France.
7. General discussion + closing remarks

SESSION S4

Rare variants, intracerebral hemorrhage, and translational research (2/2)

Date: May 11/12

Duration: 1 h 30 min

Session host: Alice Man & Michael Chong, McMaster University, Hamilton, Canada

Please click this URL to start or join. https://monash.zoom.us/j/88317799611?pwd=y3QvexaHlmpp4t1SlQyFYywvKMofpE.1
Or, go to https://monash.zoom.us/join and enter meeting ID: 883 1779 9611 and passcode: 522277
Ensure your device has a dedicated microphone and webcam.

Join from a dial-in phone:
Dial: +61 3 990 59666 [+61 3 9905 ZOOM] or +61 2 8015 2088
Meeting ID: 883 1779 9611
International numbers available: https://monash.zoom.us/u/kvLDJFds3

Session time across timezones:

Los Angeles	New York	London	Central Europe	Beijing	Tokyo	Sydney
16:00	19:00	00:00 (May 12)	01:00 (May 12)	07:00 (May 12)	08:00 (May 12)	09:00 (May 12)

Programme

1. Introduction by hosts
2. Abstract S4.1. ***Implementing rare variant genetic risk scores to predict onset of complex disease.*** Ricky Lali, Department of Health Research Methodology, Evidence, and Impact, McMaster University, Hamilton, Canada.
3. Abstract S4.2. ***How an Emergency Medicine physician ended up in Translational Research.*** Laura Heitsch, Washington University in St. Louis, St. Louis, USA.
4. Abstract S4.3. ***Peripheral Methylation Status Recovers in Young but not Aged Animals after Photothrombic Stroke.*** Miguel Madeira, Department of Neurology, Renaissance School of Medicine at SUNY Stony Brook, New York, USA.
5. Abstract S4.4. ***Assessing colchicine as a treatment for ICH.*** Aristeidis Katsanos, McMaster University, Hamilton, Canada.
6. General discussion + closing remarks

SESSION S5

Sex differences, intracranial aneurysms, and early-onset stroke (1/2)

Date: May 18

Session host: Quentin Le Grand, Bordeaux Population Health Research Center, INSERM, France.

Please click this URL to start or join. https://monash.zoom.us/j/89892698887?pwd=YmnUepe8cOpSh4d4sIaFByjTFA4aC6.1
Or, go to https://monash.zoom.us/join and enter meeting ID: 898 9269 8887 and passcode: 251767
Ensure your device has a dedicated microphone and webcam.

Join from a dial-in phone:
Dial: +61 3 990 59666 [+61 3 9905 ZOOM] or +61 2 8015 2088
Meeting ID: 898 9269 8887
International numbers available: https://monash.zoom.us/u/kep7NhJLQI

Session time across timezones:

Los Angeles	New York	London	Central Europe	Beijing	Tokyo	Sydney
00:00	03:00	08:00	09:00	15:00	16:00	17:00

Programme

1. Introduction by the working group leads
2. Abstract S5.1. ***Sex-stratified GWAS-XWAS in ischemic stroke***. Paula Boldo, Hospital de Sant Pau, Barcelona, Spain.
3. Abstract S5.2. ***Mechanistic clusters of intracranial aneurysm-associated genetic variants define pathogenic mechanisms and clinical associations***. Mark Bakker, University Medical Center Utrecht, The Netherlands.
4. Abstract S5.3. ***Family history of stroke and cardiovascular diseases and interaction with cardiovascular risk burden in early-onset cryptogenic ischemic stroke***. Maximilian Sihvo, Helsinki University Central Hospital and University of Helsinki, Finland.
5. General discussion + closing remarks

SESSION S6

Sex differences, intracranial aneurysms, and early-onset stroke (2/2)

Date: May 18/19

Session host: John Cole, Baltimore VA Medical Center and University of Maryland School of Medicine, USA.

Please click this URL to start or join. https://monash.zoom.us/j/84635016892?pwd=WT3feHNSN3r1NvtICs2aYcPpsmRYBw.1
Or, go to https://monash.zoom.us/join and enter meeting ID: 846 3501 6892 and passcode: 727959
Ensure your device has a dedicated microphone and webcam.

Join from a dial-in phone:
Dial: +61 3 990 59666 [+61 3 9905 ZOOM] or +61 2 8015 2088
Meeting ID: 846 3501 6892
International numbers available: https://monash.zoom.us/u/kdoHhu90m9

Session time across timezones:

Los Angeles	New York	London	Central Europe	Beijing	Tokyo	Sydney
08:00	11:00	16:00	17:00	23:00	00:00 (May 19)	01:00 (May 19)

Programme

1. Introduction by the working group leads
2. Abstract S6.1. ***Sex heterogeneity loci associated with atrial fibrillation risk***. Jara Cárcel-Márquez, Hospital de Sant Pau, Barcelona, Spain.
3. Abstract S6.2. ***Genome-wide association study of intracranial aneurysms reveals 60 risk loci and marked sex-specificity***. Qi Chang Lin, University Medical Center Utrecht, The Netherlands.
4. Abstract S6.3. ***New insights into the genetic determinants of cervical artery dissection by leveraging large biobanks***. Quentin Le Grand, Bordeaux Population Health Research Center, INSERM, France.
5. General discussion + closing remarks

SESSION S7

Stroke genomics in diverse populations

Date: May 25/26

Session host: Amy Brodtmann, School of Translational Medicine, Monash University, Mebourne, Australia

Please click this URL to start or join. https://monash.zoom.us/j/88307135044?pwd=a4hiQ7Wlox8JWRcx9eDguJLtHjrXOx.1
Or, go to https://monash.zoom.us/join and enter meeting ID: 883 0713 5044 and passcode: 387668
Ensure your device has a dedicated microphone and webcam.

Join from a dial-in phone:
Dial: +61 3 990 59666 [+61 3 9905 ZOOM] or +61 2 8015 2088
Meeting ID: 883 0713 5044
International numbers available: https://monash.zoom.us/u/kemJL8bjyh

Session time across timezones:

Los Angeles	New York	London	Central Europe	Beijing	Tokyo	Sydney
16:00	19:00	00:00 (May 26)	01:00 (May 26)	07:00 (May 26)	08:00 (May 26)	09:00 (May 26)

Programme

1. Introduction by the working group leads
2. Abstract S7.1. ***The Formosa Stroke Genetic Consortium (FSGC): A Multicenter Stroke Registry in Taiwan***. Sung-Chun Tang, Department of Neurology, National Taiwan University Hospital, Taiwan.
3. Abstract S7.2. **Genetics of Latin American Diversity (GLAD) project and generative models to share data from under-researched groups**. Timothy O'Connor, University of Maryland, Baltimore, USA.
4. Abstract S7.3. Katrina Claw, University of Colorado Anschutz, Aurora, USA.
5. General discussion + closing remarks

SESSION S8

Advancing stroke genomics through interdisciplinary ties

Date: May 26

Session host: Mark Bakker, University Medical Center Utrecht

Please click this URL to start or
join. https://monash.zoom.us/j/83655264822?pwd=gWKoPScbH07d7jVP5Afc2IGuYP3RE6.1
Or, go to https://monash.zoom.us/join and enter meeting ID: 836 5526 4822 and passcode: 863070
Ensure your device has a dedicated microphone and webcam.

Join from a dial-in phone:
Dial: +61 3 990 59666 [+61 3 9905 ZOOM] or +61 2 8015 2088
Meeting ID: 836 5526 4822
International numbers available: https://monash.zoom.us/u/kB1H5j8nr

Session time across timezones:

Los Angeles	New York	London	Central Europe	Beijing	Tokyo	Sydney
00:00	03:00	08:00	09:00	15:00	16:00	17:00

Programme

1. Introduction by the host
2. Abstract S8.1. ***ENIGMA Stroke Recovery: International Collaborations on Brain Imaging and Opportunities for Genetics.*** Sook-Lei Liew, University of Southern California, Los Angeles, USA.
3. Abstract S8.2. ***BIOSTROKE – a platform for stroke biomarker research***. Steffen Tiedt, Ludwig-Maximilians-University Hospital, Munich, Germany.
4. Abstract S5.3. **AFGen -** ***Rare coding variant architecture and gene discovery from 130,000 sequenced cases of atrial fibrillation***. Sean Jurgens, University of Amsterdam, The Netherlands.
5. General discussion + closing remarks

ABSTRACTS

Session S1

Abstract S1.1. ***DNA Methylation in Post-Stroke Cognitive Impairment Across African and European Ancestries: An Exploratory Study***. Motunrayo Coker. College of Medicine, University of Ibadan, Nigeria.

Post-stroke cognitive impairment (PSCI) contributes substantially to long-term disability, affecting ~27% to >90% within three months across ancestries. Yet, molecular studies are largely Eurocentric, limiting discovery of ancestry-specific mechanisms. DNA methylation may bridge genetic and environmental influences underlying PSCI heterogeneity. This study utilized the EpiCogFAST cohort, of 80 stroke survivors from the SIREN study in West Africa and the CogFAST study in the United Kingdom. Participants were classified as cognitively impaired or unimpaired at three months post-stroke using neuropsychological assessments with groups matched by age, sex, and ethnicity. Epigenome-wide association analyses were performed to identify DNA methylation profiles associated with PSCI. Top-ranking CpG sites were identified in genes related to immune and neuronal functions, including loci within *GPR78* in the European cohort and *IL1RAPL2* in the West African cohort. However, no CpG sites attained statistical significance after multiple testing correction (FDR $q \leq 0.05$), and no overlap was observed between the top loci across cohorts, suggesting potential ancestry-specific methylation patterns. Gene enrichment analysis in the West African cohort revealed overrepresentation of immune-related pathways, particularly those involving major histocompatibility complex and antigen presentation. Meta-analysis across both cohorts showed consistent directions of effect for top CpG sites, despite the absence of statistically significant associations. These findings highlight converging neuroimmune mechanisms underlying PSCI while emphasizing the importance of population diversity in epigenetic studies. The lack of significant associations reflects limited statistical power and underscores the need for larger, well-powered studies in diverse populations.

Abstract S1.2. ***Brain Communication Modes Shape Cognition after Stroke***. Nicholas Parsons. School of Translational Medicine, Monash University, Melbourne Australia.

Cognitive functioning relies on communication across large-scale neural networks, yet it remains unclear whether information transfer is governed by a single dominant strategy or multiple distinct modes of signal propagation across the connectome. Most network models conceptualize brain communication as routing-based, with information traveling along selective, efficient pathways between regions. Here we asked whether cognition following focal brain injury depends on selective routing along efficient pathways or on distributed communication across multiple indirect routes. Using ischemic stroke as an empirical perturbation of neural networks, we analyzed longitudinal multimodal MRI and cognitive data from 118 participants assessed over three years, including individuals with stroke and

matched healthy controls. Routing-based and diffusion-based communication capacities were estimated across more than 1,000 cortical, subcortical, and cerebellar regions and related to performance across tasks spanning processing speed, working memory, and executive function. Routing-based communication supported performance broadly across domains, particularly for speed-dependent and attentionally constrained tasks. In contrast, diffusion-based communication exhibited selective associations that increased with cognitive complexity, preferentially supporting integrative and executive processes. These effects were expressed across both ipsilesional and contralesional cortices and remained stable across recovery. Together, these findings reveal a structured division of labor between network communication modes, in which efficient routing supports rapid, constrained processing while distributed diffusion increasingly supports flexible, integrative cognition. By leveraging focal brain injury as an empirical perturbation of large-scale brain networks, this work provides evidence that the human brain deploys complementary communication strategies to sustain cognition when structural pathways are disrupted.

Abstract S1.3. Si Cheng. Beijing Tiantan Hospital, China.

Session S2

Abstract S2.1. ***Proteomic study identifies inflammatory plasma proteins associated with 3-month functional outcome after ischemic stroke***. Kara Tai, University of Gothenburg, Sweden; and Laia Llucià Carol, Sant Pau Research Institute, Barcelona, Spain.

Background:
The inflammatory response in acute ischemic stroke (AIS) is complex and not fully understood. We recently identified inflammatory plasma proteins associated with functional outcome after AIS in a young Swedish cohort.1 Here, we profiled the same set of proteins for associations with outcome in two older cohorts with different case mixes.

Methods:

This study included AIS cases from *SAHLSIS phase 2* (*SAHLSIS2*; n=482, median 69 years) and *PREVICTUS* (n=376, median 74 years). Blood was drawn at median 2 days post-stroke in *SAHLSIS2* and within 6 hours of stroke onset in *PREVICTUS*. Plasma protein levels were measured using proximity extension assays (Olink®). Functional outcome was assessed by the modified Rankin Scale (mRS) at 3-month follow-up, dichotomized into favorable (mRS 0-2) and unfavorable (mRS 3-6). Associations between protein levels and outcome were assessed by logistic regressions. Mendelian randomization (MR) was used to identify proteins with potential causal effects.

Results:

In univariable analyses, elevated levels of 23 proteins were significantly associated with outcome in both cohorts (FDR <0.05). After adjustment for age, sex, and diabetes mellitus, 6 proteins remained significantly associated with outcome in both cohorts. In addition, MR analyses suggested causal effects of 3 proteins.

Conclusions:

We identified candidate plasma proteins associated with outcome after AIS. Some may have causal roles in processes related to outcome, supporting potential as therapeutic targets. Angerfors A, Brännmark C, Lagging C, Tai K, Svedberg RM, Andersson B, Jern C, Stanne TM. *J Neuroinflammation*. 2023;20(1):224.

Abstract S2.2. ***Comparative Plasma Proteomics in Cerebral Amyloid Angiopathy and Alzheimer's Disease: A Discovery Study***. Joan Jiménez Balado, Hospital del Mar, Barcelona, Spain.

Aims

We compared plasma proteomic profiles between patients with cerebral amyloid angiopathy (CAA) and Alzheimer's disease (AD) and examined their associations with MRI markers of CAA.

Methods

We included 26 AD^+ (A^+T^+) and 42 CAA (Boston 2.0) participants (21 with concomitant AD, CAA^+AD^+, and 21 with pure CAA, CAA^+AD^-) from the ANGMAR cohort (Hospital del Mar). Plasma samples collected at diagnosis were analyzed using the Illumina Protein Prep 9.5K SomaScan platform (10,895 proteins). Data were log-transformed and analyzed using multivariable linear models adjusted for age and sex. Proteins with $p<5\times10^{-3}$ and consistent effects in CAA with and without AD co-pathology were further tested for associations with MRI markers (cortical superficial siderosis, lobar cerebral microbleeds [lCMBs], centrum semiovale enlarged perivascular spaces, and white matter hyperintensities).

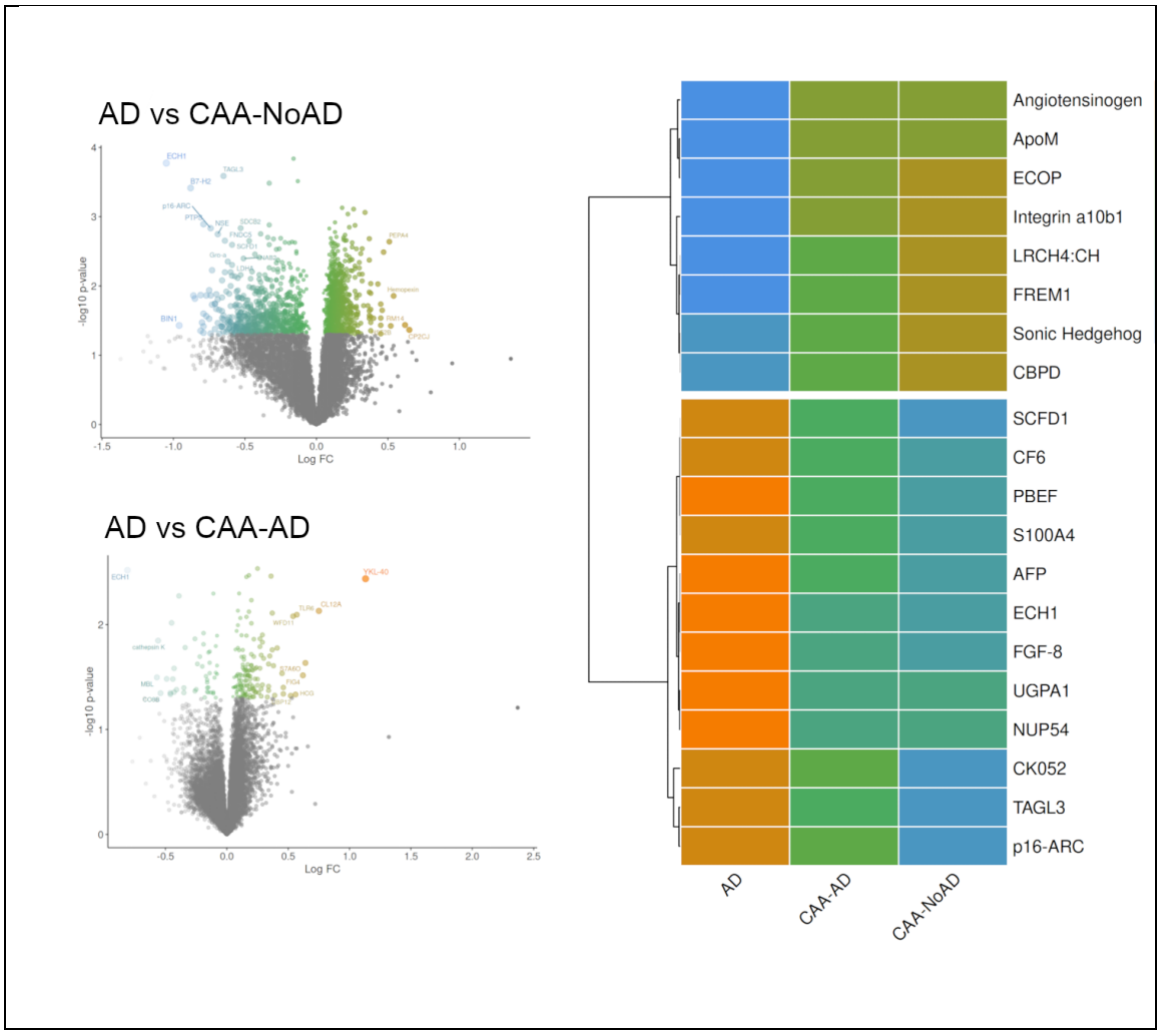
Results

Participants had a mean age of 74.0 years (71.0-77.0), and 50.8% were female. Volcano plots (Figure 1, left panels) showed more pronounced differences between CAA^-AD^+ and CAA^+AD^-, with attenuated but consistent effects in CAA^+AD^+.

Although no proteins passed the multiple testing threshold, 20 proteins showed consistent nominal associations ($p<5\times10^{-3}$) in CAA^+AD^- compared with CAA^-AD^+, with similar effect directions in CAA^+AD^+ (Figure 1, right panel). Among these, APOM abundance was associated with higher lCMB in CAA+ patients (≥5 lCMBs; p=0.01, d=0.9). On the other hand, ITGB1 was associated with greater global CAA MRI burden (score ≥3; p=0.04, d=0.69).

Conclusions

Plasma proteomics suggests a distinct molecular signature in CAA compared with AD. The identified proteins, including APOM and ITGB1, show exploratory associations with MRI markers of CAA severity.



Abstract S2.3. ***Image-based prediction of stroke outcomes***. Anna K. Bonkhoff, Massachusetts General Hospital, Harvard Medical School, Boston, USA.

Accurate prediction of individual outcomes after stroke is a central goal of precision medicine, with neuroimaging-derived lesion information emerging as a key data source. Across recent work, we demonstrate that stroke outcome prediction benefits from integrating multi-level representations of lesion anatomy, including lesion volume, voxel-wise location, and network-level disconnection measures. In a large-scale, multi-cohort analysis, models incorporating structural and functional disconnection – which captures remote network effects beyond focal injury – consistently outperformed approaches based on lesion volume or location alone, particularly when trained on large and multicenter datasets, highlighting the importance of both feature richness and sample size for generalizable prediction.

Complementing these findings, generative modeling approaches reveal that stroke lesions can be decomposed into biologically interpretable patterns ("lesion atoms") that differentially contribute to domain-specific cognitive outcomes, with distinct hemispheric contributions to

language, memory, and visuospatial deficits. These approaches move beyond single-region inference toward probabilistic, multivariate representations of lesion–symptom relationships.

Methodologically, prediction performance scales with data size and model complexity: while linear models perform robustly in small samples, non-linear and deep learning approaches increasingly capture complex lesion–outcome relationships as datasets grow, suggesting the presence of higher-order interactions within lesion topology.

Together, these findings support a shift from localized lesion-based inference toward network-informed, data-driven prediction frameworks. Future progress will depend on large, harmonized datasets and careful validation across independent cohorts to enable clinically meaningful, individualized prognostication after stroke.

Session S3

Abstract S3.1. ***From Variant to Vessel: How PAR4 Genetics Shapes Stroke Outcomes.*** Frederik Denorme, Laboratory for Cell Biology and Histology, University of Antwerp, Belgium.

Abstract S3.2. ***Understanding the VWF and ADAMTS13 Axis in Stroke***. Colin Kretz, McMaster University, Hamilton, Canada.

Abstract S3.3. ***Epigenome Wide Association Study in ICH, with sex stratification and sex interaction.*** Cristina Gallego, Stroke Pharmacogenomics and Genetics Group, Institut de Recercat Sant Pau, Barcelona, Spain.

Abstract S3.4. ***Quantifying the Contribution of Rare Coding Variants to Stroke Risk Factors with RARity.*** Nazia Pathan, Population Health Research Institute, Hamilton, Ontario.

Stroke risk factors are heritable traits influenced by both common and rare genetic variants. While common variants are well studied, the contribution of rare coding variants (MAF<1%) to these traits remains poorly understood. We developed RARity (Rare variant heritability estimator), a scalable and computationally efficient framework to quantify the contribution of rare variants (RVs) to complex trait heritability (*h*2RV) without assuming a specific genetic architecture. Applying RARity to over 167,348UK Biobank participants across 31 continuous traits, we showed that gene-level RV aggregation suffers from 79% (95% CI: 68-93%) loss of *h*2RV. Using unaggregated variants, we demonstrate that RVs make a significant contribution to key stroke risk factors (*h*2RV > 5%), including BMI, LD, HDL, triglycerides, total cholesterol and systolic and diastolic blood pressure, among which, BMI has the highest *h*2RV at 9.9% (95% CI: 7.0-12.8%). The total heritability, including common and rare variants, approaches pedigree-based estimates in these traits, suggesting that a substantial portion of the missing heritability resides in the rare variant. RARity also enables gene-level estimation, identifying 11 previously unreported gene–phenotype associations, and consequently a tool for gene-target prioritization. In conclusion, the trait variance explained

by RVs makes it imperative to continue to invest in the study of RVs and understand their impact on health and disease.

Abstract S3.5. ***Making the most of whole-genome sequencing data for rare variant association tests using the RAVA-FIRST approach.*** Ozvan Bocher, Université de Bretagne Occidentale, Brest, France.

Rare variant association tests (RVAT) are essential for studying the contribution of rare variants to complex traits, which often lack statistical power in genome-wide association studies. While high-throughput sequencing technologies have made whole-genome data widely accessible, RVAT are typically limited to coding regions, leaving much of the genome unexplored. This limitation stems from the need to aggregate and filter rare variants into testing units, a process that is straightforward in exomes (using genes as natural units and filtering based on consequences of variants on proteins) but challenging in non-coding regions. Existing solutions, such as the STAAR pipeline, use sliding windows and multiple annotations, but can be computationally intensive and difficult to interpret. To address these challenges, we developed RAVA-FIRST (RAre Variant Association using Functionally-InfoRmed Steps, doi: 10.1371/journal.pgen.1009923), a three-step approach based on: (1) defining whole-genome testing units based on functionally-adjusted CADD scores from gnomAD ("CADD regions"); (2) applying region-dependent filtering to retain rare variants representing functional variation tolerated in the general population; (3) implementing a functionally-informed burden test that considers genomic categories within CADD regions. We validated RAVA-FIRST using simulations and real-world datasets. The method is freely available in the R package *Ravages*. The RAVA-FIRST strategy, its recent update supporting build 38, and future directions and enhancements will be presented.

Session S4

Abstract S4.1. ***Implementing rare variant genetic risk scores to predict onset of complex disease.*** Ricky Lali, Department of Health Research Methodology, Evidence, and Impact, McMaster University, Hamilton, Canada.

Abstract S4.2. Laura Heitsch, Washington University in St. Louis, St. Louis, USA.

Abstract S4.3. ***Peripheral Methylation Status Recovers in Young but not Aged Animals after Photothrombic Stroke.*** Miguel Madeira, Department of Neurology, Renaissance School of Medicine at SUNY Stony Brook, New York, USA.

Abstract S4.4. ***Assessing colchicine as a treatment for ICH.*** Aristeidis Katsanos, McMaster University, Hamilton, Canada.

Session S5

Abstract S5.1. ***Sex-stratified GWAS-XWAS in ischemic stroke***. Paula Boldo, Hospital de Sant Pau, Barcelona, Spain.

Background and Aims

Ischemic stroke (IS) is a complex disease influenced by genetic, environmental, and sex-related factors. However, sex-stratified genome-wide association studies (GWAS), particularly including the X chromosome, remain limited. We aimed to identify sex-specific genetic variants associated with IS and its TOAST subtypes.

Methods

We analyzed 8,064,232 autosomal and X-chromosome variants after TOPMed imputation. Association analyses were performed using models specifically adapted for the X chromosome, accounting for different assumptions of X-chromosome inactivation and allowing both sex-stratified and combined analyses. Testing was conducted under an additive framework, adjusting for age and the first 6 principal components. Both autosomal and X-chromosome variants were evaluated across IS and its main TOAST subtypes. Functional annotation analyses were planned to prioritize candidate genes and pathways.

Results

The study included 6,731 men (2,276 cases) and 6,618 women (1,899 cases). Sex-stratified analyses revealed differences in genetic signals between sexes. Several loci showed associations at both suggestive and genome-wide significance levels in combined and sex-stratified analyses across autosomes and the X chromosome. Consistent signals were observed on chromosome 6, while additional suggestive associations were identified on the X chromosome, although none reached genome-wide significance.

Conclusions

These findings highlight the contribution of both autosomal and X-chromosome variation to IS and support the use of sex-stratified approaches to better capture its genetic architecture. Accounting for X-inactivation and sex-specific effects may improve the identification and interpretation of genetic associations.

Abstract S5.2. ***Mechanistic clusters of intracranial aneurysm-associated genetic variants define pathogenic mechanisms and clinical associations***. Mark Bakker, University Medical Center Utrecht, The Netherlands.

Background and Aims

Rupture of an intracranial aneurysm (IA) causes aneurysmal subarachnoid hemorrhage. Recently, we identified 60 independent genetic risk variants through genome-wide association study (40,427 cases; 2,898,910 controls). Here, we investigated through which pathogenic mechanisms these variants act, and their relationship with clinically relevant patient- and aneurysm characteristics.

Methods

Sixty IA-associated variants were clustered according to their associations with 30 traits (putatively) linked to IA including stroke subtypes and conventional risk factors, derived from independent genome-wide association studies.

We created genetic scores representing participants' liability to each cluster, and all clusters combined. Associations between these scores and patient- and aneurysm characteristics (N=6,151 IA patients), were assessed using logistic regression, adjusting for sex, cohort, and genetic background.

Results

Five clusters (7-31 variants each) were found, representing distinct pathogenic mechanisms underlying IA. Clusters were related to cardiovascular risk factors (cluster 1 [CL1]), ischemic stroke-protective mechanisms (CL3), hypertension (CL4) and inflammation (CL5).

Overall genetic liability correlated with positive family history (Odds ratio [OR] per standard deviation=1.11, p=0.002) and number of IAs (OR=1.06, $p=3.7\times10^{-8}$). Cluster-specific associations included:

- CL4 with: hypertension (OR=1.07, p=0.013), IAs located at the posterior communicating (Pcom; OR=1.11, p=0.008) and basilar artery (OR=1.24, $p=6.2\times10^{-5}$).
- CL1 with: anterior communicating artery IAs (Acom; OR=0.90, $p=6.0\times10^{-4}$).
- Middle cerebral artery (MCA) IAs showed higher CL2/3/5, and lower CL4 scores (each $p<0.05$).

Conclusions

Clustering IA-associated variants revealed five pathogenic mechanisms, linked to clinically relevant patient- and IA characteristics. We highlight a polygenic component underlying familial IAs, and that IA characteristics vary according to genetic liability for distinct pathogenic mechanisms.

Abstract S5.3. ***Family history of stroke and cardiovascular diseases and interaction with cardiovascular risk burden in early-onset cryptogenic ischemic stroke***. Maximilian Sihvo, Helsinki University Central Hospital and University of Helsinki, Finland.

Background and aims: We examined the association between family history (FH) of stroke and cardiovascular diseases with early-onset cryptogenic ischemic stroke (eCIS), and whether the accumulation of modifiable stroke risk factors influences these associations.

Methods: We included 508 CIS patients aged 18–49 years and 520 matched controls from the SECRETO multicenter case–control study. Family history of stroke, venous thromboembolism (VTE), coronary artery disease (CAD), and aneurysms in first-degree relatives (FDR) and grandparents was assessed by questionnaire. Associations were examined using multivariable logistic regression with interaction analyses for risk-factor burden.

Results: FH of stroke was independently associated with eCIS among FDR (OR 1.50; 95% CI 1.04–2.16) and grandparents (1.50; 1.12–1.99), with stronger associations for FH of early-onset stroke in FDR (2.36; 1.11–5.04) and grandparents (3.03; 1.01–9.12). FH of early-onset VTE among FDR was associated with eCIS (3.45; 1.47–8.13). FH of CAD and aneurysms were not associated with eCIS. A significant negative interaction was observed between FH of VTE among FDR and traditional stroke risk factors (p-value for interaction = 0.024). In contrast, non-traditional risk-factor burden showed a significant positive interaction with FH of stroke in FDR (p-value for interaction = 0.004).

Conclusions: FH of stroke and VTE are independently associated with eCIS, with stronger effects for early-onset disease. The burden of modifiable stroke risk factors may modify these associations: familial thrombotic susceptibility appears strongest in low-risk individuals; familial stroke risk on the other hand synergises with non-traditional pathogenic mechanisms.

Session S6

Abstract S6.1. ***Sex heterogeneity loci associated with atrial fibrillation risk***. Jara Cárcel-Márquez, Hospital de Sant Pau, Barcelona, Spain.

Background
Atrial fibrillation (AF) exhibits notable sex differences in epidemiology and outcomes. This study investigates biological sex-specific differences in AF through sex-stratified genome-wide association studies (GWAS) and proteomic related analyses.

Methods
We performed a sex-stratified GWAS meta-analysis using data from the UK Biobank study: 4,375 male AF cases and 162,645 controls; 1,981 female AF cases and 192,193 controls. Significant loci and sex-specific associations were identified, and sex heterogeneity was assessed. Replication was done in an independent cohort of 12,614 individuals (1,207 AF cases, 55% female). Plasma proteomic analyses in 46,724 subjects assessed genotype–sex interactions stratifying by atrial fibrillation status. Heritability estimates and sex-specific polygenic risk scores (PRS) were also calculated.

Results
Two male-specific loci: *CFL2* and *ATXN1* were identified. The meta-analysis identified additional 22 known AF loci. Sex heterogeneity was found in 6 of the 24 loci, with *TTN* and *SPATS2L* showing stronger effects in females, and *NTMT2*, *PITX2*, *GBF1*, and *CFL2* stronger effects in males. Heritability estimation liability was higher in females (h^2=0.19) than in males (h^2=0.12). PRS performance was similar across sexes (AUC=0.60–0.63). Replication confirmed heterogeneity for *PITX2* and *CFL2*, with *CFL2* variant associated with AF only in males. Proteomics analyses suggested nominals association such as: myosin light chain 1/3 (MYL1) and biogenesis of lysosomal organelles complex 1 subunit 2 (BLOC1S2). Key associated pathways included SCF-KIT signaling, prolactin signaling, and the RAC1/PAK1/p38/MMP2.

Conclusions
Our findings indicate significant sex-based heterogeneity in the effects of well-known AF-associated loci. Proteomic-genetic integration suggested sex-specific differences and candidate pathways. Despite this heterogeneity, a sex-specific approach did not significantly enhance PRS prediction, underscoring the need for adequately powered sex-specific GWAS.

Abstract S6.2. ***Genome-wide association study of intracranial aneurysms reveals 60 risk loci and marked sex-specificity***. Qi Chang Lin, University Medical Center Utrecht, The Netherlands.

Abstract S6.3. ***New insights into the genetic determinants of cervical artery dissection by leveraging large biobanks***. Quentin Le Grand, Bordeaux Population Health Research Center, INSERM, France.

Background and aims:
Cervical artery dissection (CeAD) is a leading cause of ischemic stroke in young adults. The first and only genome-wide association study (GWAS) of CeAD was conducted in 2015 (N=1,393/14,416). Here, we aimed to explore the genetic determinants of CeAD by conducting a new CeAD GWAS leveraging large biobanks.

Methods:
We leveraged data from four biobanks. CeAD was defined using the following ICD-10 codes: I77.71 and I77.74. We conducted a GWAS in these biobanks and meta-analyzed results with the first CeAD GWAS (N=2,287/22,982). We performed single-variant look-ups and genetic correlation analyses with known CeAD-related traits. Finally, we performed a multi-trait GWAS (MTAG), leveraging the pairwise genetic correlation of CeAD with fibromuscular dysplasia (FMD) and spontaneous coronary artery dissection (sCAD).

Results:
Our CeAD GWAS meta-analysis identified three genome-wide significant loci (*PHACTR1*, *LRP1*, *ZBBX*). Of these, *LRP1* and *PHACTR1* were already identified in the previous GWAS, with *PHACTR1* being the only locus previously replicated. In single-variant look-ups, these two loci were associated with several traits, including sCAD, FMD and migraine. We showed significant ($p<0.05$) genetic correlations between CeAD and blood pressure, sCAD,

intracranial aneurysms and stroke. MTAG analyses with FMD and sCAD identified four novel genome-wide significant loci requiring further investigation.

Conclusions:
In conclusion, by leveraging large biobanks, our results provide new insights into the genetic determinants of CeAD, confirming previously identified loci and pointing to novel pathways. Further research is needed to confirm these findings and decipher the underlying biological mechanisms.

Session S7

Abstract S7.1. ***The Formosa Stroke Genetic Consortium (FSGC): A Multicenter Stroke Registry in Taiwan***. Sung-Chun Tang, Department of Neurology, National Taiwan University Hospital, Taiwan.

The Formosa Stroke Genetic Consortium (FSGC) was established in 2006 as a multicenter prospective registry enrolling patients within 10 days of stroke onset. Comprehensive data collection includes detailed clinical information, blood samples (plasma and DNA), and functional outcomes up to 3 months after stroke. The main research focus of the FSGC is to identify biological markers associated with stroke mechanisms and prognosis. In addition to studies on clinical characteristics and stroke epidemiology, previous work has included plasma protein profiling and metabolomics analyses to investigate stroke mechanisms and predict outcomes. In the field of genetics, we have examined candidate single nucleotide polymorphisms (SNPs), including the association between aldehyde dehydrogenase 2 (ALDH2) genotypes and stroke risk, as well as the prevalence of monogenic disorders such as NOTCH3 R544C across different stroke subtypes. Furthermore, genome-wide association studies (GWAS) have been conducted to explore novel genetic determinants of stroke, although these efforts have been limited by sample size. We welcome opportunities for further international collaboration.

Abstract S7.2. **Genetics of Latin American Diversity (GLAD) project and generative models to share data from under-researched groups**. Timothy O'Connor, University of Maryland, Baltimore, USA.

Important resources for personalized genomic medicine have not been developed for all people, and as a result, have created research disparities. Added to that is an explosion of data that has been siloed to protect the consent of the participants, but with the side effect of decreasing the breadth of benefit to biomedical science. By abstracting and de-identifying the data, we can make it available to any researcher, thereby expanding its use. We have developed two projects that resolve this issue using data science and machine learning. First, the Genetics of Latin American Diversity (GLAD) project is the first of our projects and has combined genome-wide data from 53,738 individuals across 39 studies representing 46 geographical regions. We developed GLAD-match, a simulated annealing algorithm, to match the genetic background of external samples to our GLAD-database, sharing summary statistics

(i.e., allele and haplotype frequencies) without transferring individual-level genotypes. This creates a means of sharing ancestry-matched controls for many different genetic epidemiological focuses. In our second project, we demonstrate that when combined with plentiful data and with population-specific selection criteria, deep generative models can produce synthetic genomes and cohorts that closely model the original populations. These modeled samples can be shared as references to other investigators without revealing individual data from the original participants. The goal of our projects is to utilize the momentum gained in personalized genomic medicine and make it applicable to a greater number of people.

Abstract S7.3. Katrina Claw, University of Colorado Anschutz, Aurora, USA.

Session S8

Abstract S8.1. ***ENIGMA Stroke Recovery: International Collaborations on Brain Imaging and Opportunities for Genetics.*** Sook-Lei Liew, University of Southern California, Los Angeles, USA.

The ENIGMA Stroke Recovery working group is comprised of over 100 international researchers across 15 countries who, together, have created a database of over 2000 high-resolution stroke MRIs with detailed behavioral outcomes (https://enigma.ini.usc.edu/ongoing/enigma-stroke-recovery/). In this brief talk, I will introduce the ENIGMA Stroke Recovery group, including our initial goals and motivation, our process for harmonizing retrospective datasets across sites, and our key findings, especially regarding global brain health, over the past 10 years. I will conclude with a discussion of opportunities for incorporating genetic data into these analyses, which has been done extensively in other ENIGMA working groups (https://enigma.ini.usc.edu/).

Abstract S8.2. ***BIOSTROKE – a platform for stroke biomarker research***. Steffen Tiedt, Ludwig-Maximilians-University Hospital, Munich, Germany.

BIOSTROKE is an emerging platform aiming to accelerate stroke biomarker research across the full clinical stroke-care continuum – from pre-hospital triage and hyperacute treatment decisions to recovery and secondary prevention. The initiative was launched at the 1st BIOSTROKE meeting in Munich (7-8 November 2024), which brought together ~50 invited international experts to discuss shared challenges, identify gaps, and define specific next steps for the field. Building on this foundation, the 2nd BIOSTROKE meeting has just concluded, expanded to 120 participants through open registration and abstract submission, and enabling scientific exchange and collaboration on pressing, unresolved challenges in clinical decision-making (www.biostroke.org).
A central output of BIOSTROKE has been a structured Delphi process that was used to define consensus research priorities and to develop minimum reporting datasets for stroke biomarker studies. The Delphi work spans key domains along the stroke continuum, including pre-hospital care, ischemic stroke progression and recovery, atrial cardiopathy, atherosclerosis, and intracerebral hemorrhage, with the overarching goal of moving

biomarker research from exploratory associations toward clinically deployable tools with specific contexts of use – patient stratification, pharmacodynamic monitoring, and surrogate endpoint development. This work has been accepted for publication in *The Lancet Neurology*. BIOSTROKE is still at an early stage: while scientific motivation and community momentum are strong, formal structures, governance, and shared resources are only beginning to take shape.

Abstract S5.3. **AFGen -** ***Rare coding variant architecture and gene discovery from 130,000 sequenced cases of atrial fibrillation***. Sean Jurgens, University of Amsterdam, The Netherlands.

Rare coding genetic variants have been linked to atrial fibrillation (AF), yet their contribution to disease architecture and their utility in gene prioritization remain limited by inadequate sample sizes. Here, using data from the AFGen consortium, we performed a massive-scale rare variant association study (RVAS) - analyzing over 1.1 million sequenced participants among which 130,000 with AF. Through a multi-mask burden testing approach, we identified 15 genes significantly associated with AF through rare large-effect variation. Integrative analyses revealed strong convergence between genes implicated by rare and common variation, and highlighted instances where RVAS data may aid in gene prioritization from standard genome-wide association studies (GWAS). Nevertheless, several RVAS genes were not among GWAS loci (*ENTREP1*, *ACTC1*, *FNIP1*, *FBN1*), or were not nominated through contemporary GWAS prioritization methods (*KDM5B*, *ZFP36L2*). Finally, we observed that ultra-rare protein-disrupting variants - concentrated in a small number of large-effect size genes - explained at least 2% of AF susceptibility across European and African ancestry groups. These findings refine the genetic architecture of AF, show the complementarity of RVAS and GWAS, and highlight the value and cost of large-scale sequencing for genomic discovery in common diseases.

CONTACT

International Stroke Genomics Consortium www.strokegenetics.org

Get in touch! https://www.strokegenetics.org/committee/early-career-researcher-committee/

Registration for this event: https://forms.cloud.microsoft/e/wtE5z0wdqd

Join our in-person meeting in San Antonio, October 8-10, 2026! More info:
https://www.strokegenetics.org/upcoming-workshops/