



# METASTROKE **update**

International Stroke Genetics Consortium  
(ISGC) Meeting  
Salt Lake City, April 2014

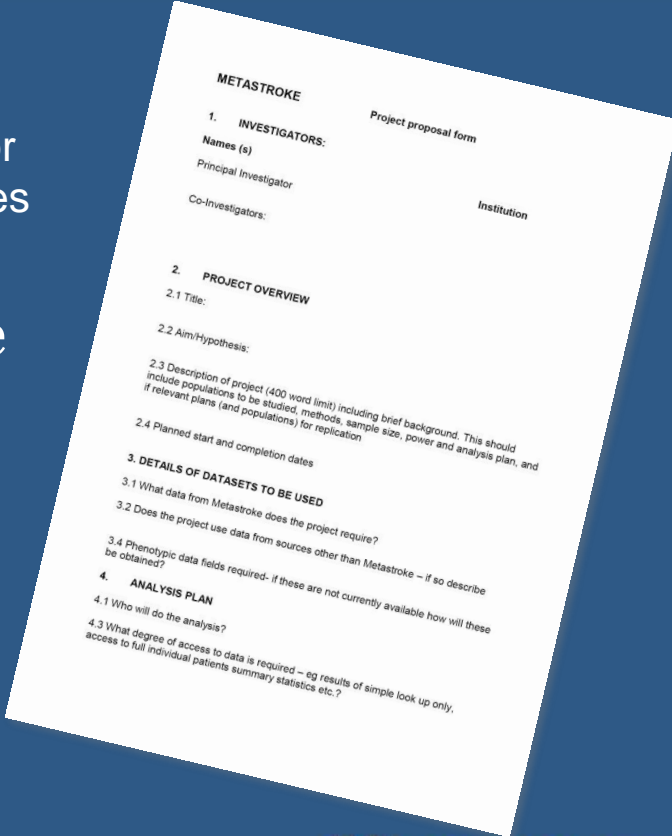
**Martin Dichgans**  
**Bradford B Worrall**





# METASTROKE | Opportunity

- Individual study samples with GWAS data from
  - $\geq 500$  cases for cross-sectional studies or
  - $\geq 300$  cases for prospective cohort studies
- Proposals to access data may be entertained from outside group
- Process of accessing the data:
  - Submission of project proposal
  - Review by the SC
  - Authorship negotiated
  - Approval, rejection, or modification
  - Degree of data access
  - Access to database by custodian



**METASTROKE** Project proposal form

**1. INVESTIGATORS:**  
Names (s)  
Principal Investigator  
Co-Investigators: Institution

**2. PROJECT OVERVIEW**  
2.1 Title:  
2.2 Aim/Hypothesis:  
2.3 Description of project (400 word limit) including brief background. This should include populations to be studied, methods, sample size, power and analysis plan, and if relevant plans (and populations) for replication  
2.4 Planned start and completion dates

**3. DETAILS OF DATASETS TO BE USED**  
3.1 What data from Metastroke does the project require?  
3.2 Does the project use data from sources other than Metastroke – if so describe  
3.4 Phenotypic data fields required- if these are not currently available how will these be obtained?

**4. ANALYSIS PLAN**  
4.1 Who will do the analysis?  
4.3 What degree of access to data is required – eg results of simple look up only, access to full individual patients summary statistics etc.?



# METASTROKE | News

- METASTROKE Collaboration continues to be very fruitful
  - Monthly calls
  - Review new project proposals (both internal and external)
  - Discuss status updates for all active/ open project
  - Up dates from the other consortia
  - Up dates from the analysis committee



# METASTROKE | Leadership

- Martin Dichgans → Immediate Past Chair
  - Hearty thanks to Martin for his leadership over the past two years
- Brad Worrall → Chair
- Sudha Seshadri → Chair Elect
  - We welcome Sudha to the leadership team



# METASTROKE | Papers

- Multilocus genetic risk score associates with ischemic stroke in case-control and prospective cohort studies. Malik R, et al. Stroke. 2014 Feb;45(2):394-402
- Shared genetic susceptibility to ischemic stroke and coronary artery disease: a genome-wide analysis of common variants. Dichgans M, et al. Stroke. 2014 Jan;45(1):24-36



# METASTROKE | Papers

- Meta-analysis in over 17,900 cases of ischaemic stroke reveals a novel association at 12q24.12. Kilarski, *et al.* accepted in *Neurology*.
- Replication of MMP region identified in age-at-onset informed analysis of TCCC2 + ImmunoChip. Traylor *et al* in revisions at *PLoS Genetics*.



# METASTROKE | Manuscripts

- Genetic variants associated with plasma homocysteine levels and their effect on stroke risk. Pankaj Sharma & Ioana Cotlarciuc
- The Contribution of Variants in Collagen IV Genes to Common Cerebrovascular Phenotypes. Ready for submission. Kristiina Rannikmae and Cathie Sudlow
- Frequentist and Bayesian Analysis of the Polygenic Architecture of Ischaemic Stroke. Liz Holliday



# METASTROKE | Challenges

- Re-run analyses on data imputed to 1000 Genomes (imputation completed, analysis in progress)
- Meta-Analyse with data from CHARGE (in progress)
- Meta-Analyse with data from COMPASS (imputed to HapMap2, 1000 Genomes underway)
- Meta-Analyse with data from NINDS SIGN (2014?)
- Get additional samples on board
- Move to NGS
- Move to functional studies (Translational science working group)



# METASTROKE | New Projects

- “Is a genetic risk score associated with MI and large artery stroke?” PI: Daniel Freitag
- “GWAS of Early-Onset Ischemic Stroke: a meta-analysis of Caucasians, South Asians and African Americans.” PI: Yu-Ching Cheng
- “Exome sequencing in cardioembolic strokes” PIs: Fernández/Montaner
- “BRIANSTORM - a cross-disorder analysis of common variation in neurological and psychiatric diseases” PI: Martin Dichgans
- “BP SNPs from GWAS in Stroke” PI Patricia Munroe



# METASTROKE |

## Project proposal form

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# Projects | Ongoing

- A Mendelian Randomisation Analysis of Cystatin C and Cardiovascular Disease - PI Folkert Asselbergs
- Atrial Fibrillation Genetic Risk and Ischaemic Stroke - PI Steve Lubitz
- Familial and General Migraine Related Genes and Ischaemic Stroke Risk - PI Andrea Harriott
- Causal Effects of Vitamin D Binding Protein on Cardiovascular and Metabolic Outcomes: A Mendelian Randomisation Analysis - PI Brent Richards
- Look-up of Suggestive Loci for WMH Volume Derived from a GWAS in CADASIL patients - PI: Christian Opherk



# Projects | Ongoing

- The Association Between Polygenic Risk for Ischaemic Stroke & Cognitive Functions Lifetime Cognitive Change & Structural Brain Parameters in Older Age PI: Ian Deary
- Correlating Polygenic Scores From METASTROKE to Subclinical Phenotypes Related to Ischaemic Stroke in the Athero-Express Biobank Study - PI Paul deBakker
- Novel Susceptibility Loci for Atrial Fibrillation - PI Patrick Ellinor
- Replication of Stroke Loci Identified in African Americans from the COMPASS Study in METASTROKE - PI Cara Carty
- Genomewide Association Study of Ischaemic Stroke and Subtypes in Pakistan - PI Danish Selaheen



# Projects | Ongoing

- The 1000 Genomes Imputation of METASTROKE cohorts - PI: Liz Holliday
- Shared Heritability Between Altered Coagulation/Fibrinolysis and Ischaemic Stroke and its Subtypes - PI: Hugh Markus
- Replication of the Association Between a Low Expression Variant of FABP4 and Large Artery Stroke - PI: Perttu Lindsberg
- Mendelian Randomisation Studies of Lipid and Glucometabolic Traits with Stroke and its Subtypes - PI Danish Salaheen:
- Exome Chip Initiative in Large Artery Stroke (ECLAS) - PI Martin Dichgans



# Projects | Ongoing

- White Matter Hyperintensity Burden and Risk of Stroke: A Genetic Score Analysis - PI Natalia Rost
- Genetic Variation in Platelet Aggregation as a Risk Factor for Ischaemic Stroke - PI Nicole Dueker
- Do Genetic Risk Variants Associated with Renal and Retinal Microvascular Disease also Contribute to Stroke Risk? - PI Liz Holliday
- Polymorphisms in the Thrombomodulin - Endothelial Cell Protein C Receptor System and the Risk of Cerebral Infarction - PI John Cole:
- Cross Replication of Susceptibility Loci for Migraine and Ischaemic Stroke and Metaanalysis - PI Martin Dichgans/  
Rainer Malik



# Projects | Ongoing

- Do Alzheimers Disease and Ischaemic Stroke Share Genetic Risk Factors - PI Steve Bevan
- Prognostic Modelling in Ischaemic Stroke - PI Paul de Bakker
- Homocysteine and Stroke: Meta-Analysis of MTHFR Case-Control Studies Avoiding Publication Bias - PI Robert Clarke
- Cross Replication of Susceptibility Loci For Cerebrovascular and Cardiac Phenotypes and Meta-Analysis - PI Martin Dichgans
- Genetic Variants Related to LDL-Cholesterol and Risk of Vascular Disease - PI Jemma Hopewell



# Projects | Ongoing

- **Generation of a Weighted Risk Score for Ischaemic Stroke**  
- PI Rainer Malik
- **Genomewide Pathway Analysis of Ischaemic Stroke** - PI  
Matthew Traylor
- **Analysis of METASTROKE Candidates in Minority Populations: A Project from the COMPASS consortium** - PI  
Brad Worrall
- 11 additional projects have been completed, combined with other projects, or abanded



# EXISTENTIAL ~~THREAT~~

Opportunity

- The proposal for a central database of individual level data – As Jonathan pointed out that there is a lot that more that can be done with individual rather than summary data
- SiGN central database



[www.strokegenetics.net](http://www.strokegenetics.net)



**METASTROKE**

THANKS!