

Life Sciences Reporting Summary

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► Experimental design

1. Sample size

Describe how sample size was determined.

No pre-defined power analysis was carried out. We used all currently available stroke samples and controls for this study, therefore reaching the maximum sample size possible.

2. Data exclusions

Describe any data exclusions.

Inclusion and exclusion criteria for each study in MEGASTROKE are given in the Supplementary Material, Section 3, pages 64-97. Due to the extensive nature of our analysis, we cannot provide all details in this form.

3. Replication

Describe whether the experimental findings were reliably reproduced.

Experimental replication was not performed

4. Randomization

Describe how samples/organisms/participants were allocated into experimental groups.

Cases were defined as ischemic stroke (IS) or intracerebral hemorrhage (ICH) based on clinical and imaging criteria. IS was further subdivided into the following categories mostly using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria: i) large vessel ischemic stroke (LV-IS); ii) cardioembolic ischemic stroke (CE-IS); iii) small vessel ischemic stroke (SV-IS). Subarachnoid hemorrhages were excluded from all analyses. Controls were stroke-free. Where possible, cases and controls were matched for relevant covariates. Association models were additionally corrected for relevant covariates.

5. Blinding

Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

Blinding was not relevant for this study, as group allocation was based on clinical and imaging criteria

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or the Methods section if additional space is needed).

n/a Confirmed

- ☐ ☒ The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
- ☐ ☒ A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly.
- ☒ ☐ A statement indicating how many times each experiment was replicated
- ☐ ☒ The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
- ☐ ☒ A description of any assumptions or corrections, such as an adjustment for multiple comparisons
- ☐ ☒ The test results (e.g. p values) given as exact values whenever possible and with confidence intervals noted
- ☐ ☒ A summary of the descriptive statistics, including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
- ☐ ☒ Clearly defined error bars

See the web collection on [statistics for biologists](#) for further resources and guidance.

► Software

Policy information about [availability of computer code](#)

7. Software

Describe the software used to analyze the data in this study.

R 3.2.5 (<https://www.r-project.org/>)
 VEGAS2 (<https://vegas2.qimrberghofer.edu.au/>)
 METAL (<http://csg.sph.umich.edu/abecasis/metal/>)
 MANTRA
 LD score regression (<https://github.com/bulik/ldsc>)
 epigwas (<http://archive.broadinstitute.org/mpg/epigwas/>)
 DEPICT (<https://github.com/perslab/depict>)
 Ingenuity Pathway Analysis (<https://www.qiagenbioinformatics.com/products/ingenuity-pathway-analysis/>)
 gwas-pw (<https://github.com/joepickrell/gwas-pw>)
 GCTA (<http://cns.genomics.com/software/gcta/>)
 RiVIERA beta (<https://yueli-compbio.github.io/RiVIERA-beta/>)
 GenABEL (<http://www.genabel.org>)
 gtx 0.0.8 (<https://cran.r-project.org/web/packages/gtx/index.html>)
 matSpDlite (<http://neurogenetics.qimrberghofer.edu.au/matSpDlite/>)
 TwoSampleMR (<https://github.com/MRCIEU/TwoSampleMR>)

For all studies, we encourage code deposition in a community repository (e.g. GitHub). Authors must make computer code available to editors and reviewers upon request. The *Nature Methods* [guidance for providing algorithms and software for publication](#) may be useful for any submission.

► Materials and reagents

Policy information about [availability of materials](#)

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.

No unique materials were used

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).

No antibodies were used

10. Eukaryotic cell lines

- State the source of each eukaryotic cell line used.
- Describe the method of cell line authentication used.
- Report whether the cell lines were tested for mycoplasma contamination.
- If any of the cell lines used in the paper are listed in the database of commonly misidentified cell lines maintained by [ICLAC](#), provide a scientific rationale for their use.

No eukaryotic cell lines were used

No eukaryotic cell lines were used

No eukaryotic cell lines were used

No cell lines were used

► Animals and human research participants

Policy information about [studies involving animals](#); when reporting animal research, follow the [ARRIVE guidelines](#)

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.

No animals were used

Policy information about [studies involving human research participants](#)

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

Ascertainment criteria for each study in MEGASTROKE are given in the Supplementary Note, Section 3.1. An overview of population characteristics for each study can be seen in Supplementary Table 2. Due to the extensive nature of these data, please refer to this table.