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Recommendations from the International Stroke Genetics Consortium, Part 1: Standardized Phenotypic Data Collection

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INTRODUCTION

Risk and clinical outcome of stroke, as for nearly all complex conditions, is polygenic.[1] Discovering influential genetic variants offers the promise of new and personalized treatments that will substantially reduce the devastating effects of stroke on global health. Adequate power to detect multiple genetic risk alleles requires large sample sizes. Although stroke is the second leading cause of death worldwide and a major contributor to adult disability,[2] no individual center can collect sufficient samples on its own. Recognizing this challenge, in 2007 stroke researchers from around the world formed the International Stroke Genetics Consortium (ISGC, www.strokegenetics.org). The ISGC mission is to identify genetic factors influencing stroke risk, prognosis, and treatment response by studying patients enrolled at centers around the globe. Though there has been notable early success,[3–5] much work remains to achieve the ultimate goal of personalized medicine in stroke: not only finding genetic risk alleles but, more importantly, to develop comprehensive stroke risk assessments with actionable clinical results.[6] Judging from developments in other complex diseases such as diabetes and coronary artery disease, sample sizes of the order of 100,000–200,000 will be needed in order to identify the full range of genetic variation involved in stroke. Achieving such sample sizes requires even larger collaboration.

We propose a standard methodology for data collection in stroke genetics studies to establish a best practice approach, sharing lessons learned through the ISGC. We outline the appropriate selection of case and control subjects and delineate the phenotypic data to collect, including minimum and preferred data points. “Minimum” requirements are prerequisites for inclusion in basic stroke genetic studies. “Preferred” data elements enable centers to participate in a broader variety of collaborations, such as those exploring gene-environment interactions, imaging endophenotypes such as white matter hyperintensities (WMH), and functional outcomes after stroke. While we do not propose a uniform case report form, we strongly encourage the collection of the described data elements in order to facilitate future global meta-analyses with a minimum of heterogeneity.[7, 8] Biostatistical methods required for genome wide association analysis are not unique to the stroke population and are well-described elsewhere.[9] Our companion paper[10]describes the processes and infrastructure necessary for establishment of a genetic biorepository specific to stroke patients.

STUDY DESIGN

Genetic association studies typically utilize a case-control[11] or a cohort[12] design. Generally, patients with stroke are ascertained when they present to the hospital or outpatient clinic. For individuals enrolled in prospective cohorts that do not require a particular diagnosis for entry, stroke cases become defined when they develop a stroke during follow up. *Regardless of the study design, cases and controls must be clearly and consistently defined*.

Cases should be patients who have suffered an ischemic stroke (IS) or hemorrhagic stroke - intracerebral hemorrhage (ICH) or subarachnoid hemorrhage (SAH). For IS and ICH, stroke is defined as a sudden onset of a focal neurological deficit consistent with a vascular cause and either confirmatory pathologic or imaging evidence (CT or MRI) and with other etiologies excluded.[13] Imaging or pathologic confirmation is critical for genetic studies to reliably distinguish between IS and ICH. The diagnosis of aneurysmal SAH (aSAH) is based on the presence of extravasated blood in the basal cisterns on head CT (HCT) or MRI, or—if imaging is negative—by cerebrospinal fluid xanthochromia. For patients with normal brain imaging and xanthochromia, proof of an intracranial aneurysm (IA) is a prerequisite for inclusion as aSAH. Diagnosis of aSAH can also be made by autopsy.

Controls should be clinically stroke-free (brain imaging *not* required). They should be of similar sex, age, and race/ethnicity distribution as cases (minimal) and preferably ascertained from a comparable geographic region and over a similar time period as cases. Imbalances in vascular risk factors can be accounted for during data analysis. The recruitment strategy for controls should reflect the study aim and minimize bias. Controls chosen via population-based methods (random recruitment from the entire population) are more representative of the background genetic risk than either hospital-based controls (with higher co-morbidities and vascular disease) or spouses (who share environmental exposures). Regardless of the way controls are chosen, the method should be carefully described and possible bias acknowledged.

To facilitate pooling of individual studies for meta-analysis, the following information should be provided to collaborators (minimal): inclusive recruitment dates, study design including recruitment strategy, study population including region/country, inclusion/exclusion criteria for cases and controls, and the process used to determine data element content particularly including case/control status. Supplementary Table I, http://stroke.ahajournals.org, summarizes study-wide information to report.

RECOMMENDED BASIC DEMOGRAPHIC INFORMATION

Demographics

The following minimal demographic information should be recorded for each subject: case or control status; date of biosample draw; birth year; and sex. For cases, age at or date of first (minimal) and recurrent (preferred) strokes or other follow-up events should also be recorded. For all subjects, record age or date at initial determination of status of case vs control and end of data collection (preferred).

Although self-reported race and ethnicity often do not reflect genetic ancestry, particularly in highly admixed populations,[14] analyses of genotype data can correct for population stratification, making complete capture of race less necessary than in traditional epidemiologic studies. Still, investigators should record the subject's self-reported race and ethnicity (preferred). Race categories depend upon the studied population; investigators should provide their specific definitions (preferred). For example, studies funded by the US National Institutes of Health (NIH) require reporting based upon five, broad US census categories,[15] but studies in Asian populations may utilize more refined race categories.

Vascular Risk Factors

One of the most significant lessons we have learned through the conduct of numerous collaborative genetic association studies is that the need for large numbers of cases and controls outweighs the need for numerous covariates. Nonetheless, information on vascular risk factors is helpful. We strongly encourage use of standard definitions such as those provided by the PhenX Toolkit[8] or the NIH[7] in order to ease subsequent homogenization across studies and facilitate meta-analysis. Investigators should record their risk factor definitions (minimal). Although it is acceptable to record risk factors as dichotomous variables (yes/no/unknown) (minimal), for inclusion in the broadest set of analyses, it is preferable to record as much detail as possible by using quantitative measures (continuous or ordinal variables). For example, anthropometric assessments can be recorded as body mass index and tobacco use as pack-years.

Supplementary Table II, http://stroke.ahajournals.org, provides a complete list of stroke risk factors to collect, however the specific risk factors collected may vary for unique populations or study types. For example, smokeless tobacco use should be characterized in populations with frequent use and requires separate definitions from smoked tobacco. Similarly, studies of pediatric stroke genetics should include data elements that capture etiologies more common in children, [16, 17] including: IS arteriopathies, infectious/parainfectious causes, cardiac diseases, thrombophilias, and vascular malformations. Participation in pharmacogenomic and genetic expression studies will at a minimum require record of medications (name and dose) taken at the time of stroke; the latter also requires meticulous recording of the timing between biosample draw and events of interest (e.g. stroke onset, thrombolytic administration, IA rupture).

RECOMMENDED PHENOTYPIC INFORMATION BY STROKE SUBTYPE

Ischemic Stroke (IS) and Transient Ischemic Attack (TIA)

IS/TIA Subtypes and Etiology—IS is a heterogeneous disorder of multiple subtypes with differing risk factors, etiologies, preventative strategies, and outcomes. In order to elucidate pathophysiologic mechanisms, it is critical that genetic studies accurately classify IS cases into the constituent stroke subtypes, preferably with graded certainty and good reproducibility.

IS cases are often classified according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) system into five causative categories.[18] TOAST has only moderate inter-rater reliability and assigns up to half of patients into "undetermined causes." Undetermined cases

are rarely used in genetic analysis, resulting in significant loss of information and study efficiency.[19] Newer classification systems such as A-S-C-O Phenotypic System and the Causative Classification System (CCS) provide graded certainty and are mechanistic. The Oxfordshire Community Stroke Project is also widely used and avoids assumptions about risk factors. CCS offers an automated web-based interface that retains and standardizes individual data points, allowing flexible analysis and further stratification of stroke phenotypes.[20] CCS also allows for identification of the most likely source when multiple etiologies are found. The US NIH has recently invested substantial resources to classify roughly 18,000 US and European IS cases according to CCS.[21] Despite the limitations of TOAST, it is widely used and can be utilized effectively in genetic studies[6] and so we consider it a minimum requirement. However, we recommend using a more stringent and mechanistic classification system with limited assignments to "undetermined" categories for prospective studies if possible (preferred).

Generally, stroke and TIA cases are not combined in stroke genetics studies. To be classified as TIA, cases must have symptom resolution within 24 hours. We strongly recommend TIA case adjudication by a stroke physician and imaging proximal to symptom onset (MRI strongly preferred) to exclude non-vascular mimics and acute infarct (i.e. stroke) in this oft-misdiagnosed category.[22, 23] We encourage biosampling of less common IS etiologies (e.g. Fabry's, cervical artery dissection) but caution that such patients should be categorized by their specific etiologies, not combined into an "other" category.

IS Severity—Capturing initial stroke severity allows determination of genetic associations with severity and outcomes and enables adjustment for severity in analyses. Initial IS severity should be captured via a standardized, validated scale such as the National Institutes of Health Stroke Scale (NIHSS) or the Scandinavian Stroke Scale,[24] in the language of the population being studied (preferred).

Hemorrhagic Stroke: ICH and SAH

Hemorrhagic stroke cases should be separated into ICH and SAH (minimal) and contain separate data collection structures regarding 1) location of the hemorrhage; 2) clinical severity; and 3) imaging characteristics of the hemorrhage (discussed in the imaging section). Traumatic ICH and SAH, subdural hematomas, hemorrhage from cerebral venous thrombosis, and hemorrhage due to neoplasm should be excluded. The discussion below also excludes vascular malformation-related ICH/SAH as secondary causes of hemorrhagic stroke, which are generally not included in large genetic studies of spontaneous ICH or SAH. For both ICH and SAH, record the previously-discussed data elements as well as potential etiologies including: moyamoya syndrome/disease, vasculitis (infectious and autoimmune), drug-related, and oral antithrombotic use (preferred).

ICH Location—ICH should be classified according to its location (minimal): deep; lobar; brainstem; cerebellum; primary intraventricular hemorrhage (IVH); single ICH; and multiple ICH's (definitions in Supplementary Table II, http://stroke.ahajournals.org).

ICH severity should be captured via standard scales, such as the admission GCS[25] (minimum), FUNC score,[26] or the ICH score (both preferred).[27] ICH size is measured as a

continuous variable via the ABC/2 method (preferred).[28] It is ideal to include presence/absence of IVH[29] and the ICH "spot sign."[30]

SAH Subtypes and Etiology—SAH should be minimally classified etiologically as due to aneursymal rupture (aSAH—berry or fusiform) or due to one of the less common subtypes: intracranial dissection, perimesencephalic without identified aneurysm, or cortical SAH without structural cause. ICH caused by an aneurysmal rupture is included with aSAH.

SAH severity can be classified using the Hunt and Hess scale or World Federation of Neurosurgical Societies grading scale (WFNS) (minimal).[24] Initial hemorrhage volume is classified via the Fisher or Hijdra scales (preferred).[20] Investigators should record IA treatment modality, delayed cerebral ischemia complications, IA rebleeding, seizures, and neurological outcomes (preferred).

Investigators studying the genetics of IA (with or without SAH) should also document (preferred except where noted): IA rupture status (ruptured/unruptured) (minimal), IA multiplicity (solitary/multiple), IA location (posterior/anterior), IA size (minimum diameter of largest aneurysm); personal/family history of IA/SAH and aneurysms in other vascular beds; and presence of IA-associated syndromic conditions.

RECOMMENDED NEUROIMAGING PROTOCOLS

The utility of specific neuroimaging modalities depends on the studied phenotype. We consider a HCT that confirms IS, ICH, or SAH to be an acceptable minimum requirement; however, MRI is preferred in all cases with specific sequences discussed next (and Supplementary Table III, http://stroke.ahajournals.org). To participate in multi-center studies, imaging data should be provided for standardized, central adjudication. All relevant MR parameters should be recorded, including diffusion gradients and fractional anisotropy.

We focus only on T1, T2*, T2, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted images, and apparent diffusion coefficient sequences as a minimum set for all MR-based stroke imaging, regardless of time since stroke onset. Inclusion of these six sequences will identify recent (acute/subacute) infarcts of all types, WMH, prior stroke including lacunes of presumed vascular origin, cerebral microbleeds, and non-stroke structural lesions. Both perivascular spaces and WMH are far-better quantified via MRI T2/FLAIR than by CT. We encourage investigators to use standardized terms for imaging findings.[31]

To image spontaneous ICH and SAH, HCT is an acceptable minimum. However, MRI T1/T2* (either GRE or SWI) may facilitate more accurate hemorrhage characterization - and is essential if imaging is delayed more than a few days after stroke onset (preferred). MRI with T2* is also needed to accurately characterize hemorrhagic transformation (HT), superficial siderosis, and petechial hemorrhages (minimal). Inclusion of angiographic studies (of any modality) is required if investigators aim to identify underlying vascular abnormalities.

RECOMMENDED MEASURES OF STROKE OUTCOME

Stroke outcome can be collected at two major time points (early and late) via commonly-used, available metrics. Data collection should focus on mortality, recurrent events, physical impairment, and functional activity.

Outcome Measures (all preferred except where noted otherwise)

Date of death (minimum) and cause of death, neurologic improvement/deterioration (measured by NIHSS), recurrent stroke, quality of life, cognition, and post-stroke depression can be recorded. Functional status should be measured via standardized scales, such as the mRS (minimum), Barthel Index, Glasgow Outcome Scale, and Functional Independence Measurements.[24] HT after IS should be classified by subtype as hemorrhagic infarction (HI-1 or HI-2) or parenchymal hematoma (PH-1 or PH-2) since clinical outcomes vary substantially by HT subtype.[32]

Early outcomes (preferred)

Early outcomes data is collected at 24 hours and 7 days or at discharge. Pre-morbid mRS is the most important factor affecting early outcomes; additional contributing factors include: age, social support, cognitive function, depression, medication use, acute interventions, and post-stroke complications.[33]

Long-term outcomes

Ideally, data is collected at 3 (preferred) with additional timepoints of 6 and 12 months if possible. Additional factors affecting long-term outcomes include access to and amount/type of post-stroke rehabilitation therapy[34] and secondary prevention methods and adherence.

ETHICS OF GENETIC RESEARCH IN STROKE

Enrollment and Consent Methods

Despite its potential to advance medicine and benefit future individuals, most genetic research does not offer potential for direct benefit to participants. This can lead to refusal by research ethics committees to allow enrollment of adults lacking decisional capacity,[35] but excluding such patients may compromise the scientific validity of a study.[36] We encourage investigators to use ethically appropriate ways to include patients with stroke severe enough to impair their ability to consent. Typically, this means consenting via surrogate authorization by a legally authorized representative (LAR)[37] as other methods are uncommon (advanced research directives)[38] or impractical (awaiting return of decisional capacity). A data element denoting who provided consent (the patient, LAR, research advanced directive) will allow researchers to evaluate for potential bias introduced by various consent methodologies (preferred).

Additional Elements of Informed Consent (all minimal except where noted otherwise)

The consent should also address: 1) requirements to place genetic information into data repositories and/or data sharing, including sharing with international collaborators;[10] (2) the

storage and use of DNA samples for future studies; and 3) return of main or incidental findings to the subjects.

Future Studies—The informed consent should address whether participants request their samples to be destroyed after the primary analysis or whether biobanking for future research projects (in stroke and in additional, unforeseen diseases) is allowed. Participants should be informed if samples are mandated to be placed into a specific biorepository, such as dbGAP or European Genome-phenome Archive. Consent forms can offer an option to restrict sample use to certain investigator types (e.g. academia, industry) or a specific research focus, though ensuring adherence to these choices is not straight-forward, particularly when samples leave the control of the primary investigators. Investigators should consider their ability to adhere to participant choices prior to offering these options.

Return of Main or Incidental Findings to Research Subjects—The likelihood of unexpected findings in genetic studies is rising with new analytic techniques, necessitating formal plans for disclosure in the informed consent.[39] Study type affects the type of results expected: genome-wide association studies are likely to identify common variants with low-to-intermediate risk of disease and little actionable individual-level data, while approaches such as linkage analysis and whole genome sequencing are more likely to uncover mutations with a higher impact on disease risk.[32] There is not yet consensus on which results should be returned; returning no results is currently acceptable. If test results are returned, the test should be meaningful and predictive; the condition tested must be serious; follow-up healthcare interventions must be available; the patient must have consented to the return of individual-level data; and the analysis must meet legal requirements of test validity.[39]

CONCLUSIONS

This paper originates from experience of the ever-growing ISGC. We hope it will facilitate the ascertainment of tens of thousands of cases and controls for future genetic studies and help investigators across the globe develop and refine their ongoing ascertainment practices. The ISGC welcomes the participation of any investigator eager to join in the effort to leverage genetic investigation to reduce the burden of stroke for future generations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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