

## Cerebrovascular Disease Knowledge Portal An Open-Access Data Resource to Accelerate Genomic Discoveries in Stroke

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on behalf of the International Stroke Genetics Consortium

Stroke is a leading cause of death and disability across the globe, affecting 15 million people each year.<sup>1</sup> Stroke represents an archetypical common complex disease with both genetic and environmental determinants<sup>2,3</sup> playing a role in its occurrence. The proportion of stroke risk that can be attributed to genetic variation has been estimated to be 30%.<sup>4-6</sup> Although this estimate provides an indication of the overall importance of genetic variation in stroke, the key to developing new treatment strategies is to identify the specific genetic variants (mutations) that modify an individual's risk of stroke. Genetic association studies (GWAS) seek to identify these variants and link them to specific genes, which, in turn, point to specific cellular processes to become therapeutic targets for drug development. In addition, newly discovered genetic risk loci can be used to improve existing phenotyping systems, enhance prediction tools aimed to identify high-risk patients, and aid in establishing causality for associations involving nongenetic exposures.

Successfully identifying the range of genetic variants that cause stroke and leveraging these discoveries to reduce the suffering caused by this condition requires overcoming several key challenges. First, stroke is the final result of multiple different pathological processes and must, therefore, be accurately subtyped to identify underlying biology. Second, because large number of cases and controls are required to identify the culprit genetic variants, tens (even hundreds) of thousands of cases must be studied, requiring the collaboration of multiple centers, many of which use different ascertainment methods and criteria. Third, because genetic variation differs across the globe, representative

populations from all ethnicities must be studied. Finally, all these data must be shared rapidly and widely to ensure the most expedited progress in research and enable investigators with the brightest ideas to utilize these data provided by patients to facilitate stroke research. The Cerebrovascular Disease Knowledge Portal (CDKP) has been created by the International Stroke Genetics Consortium (ISGC) to overcome these challenges and enable data sharing as freely and rapidly as possible.

### Evolution of the Revolution: Open Access to Data From High Throughput Technologies

In the past decade, the introduction of high throughput genotyping technologies revolutionized the way we think about, and work with, genomic data. Genome-wide genotyping arrays, whole exome sequencing, and whole genome sequencing allow us collect massive amounts of common and rare genetic data from the entire genome and agnostically test these variants for association with human disease. These new technologies have been potentiated by the creation of large collaboration networks that allow the assembly of sample sizes unimaginable not long ago. Importantly, the experience accumulated with other complex diseases indicates that the field of stroke genomics is now approaching a breakthrough point. Concretely, because the overall sample size for stroke approximates the order of 100 000 cases, and sequencing technologies are applied to existing samples, it is expected that the discovery pace for new susceptibility loci will accelerate exponentially (Figure 1).<sup>7-11</sup> This discovery power will be especially helpful in successfully identifying

Received August 3, 2017; final revision received November 16, 2017; accepted December 6, 2017.

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(*Stroke*. 2018;49:470-475. DOI: 10.1161/STROKEAHA.117.018922.)

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*Stroke* is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.117.018922

low frequency and rare mutations, as well as hard-to-detect risk alleles for specific stroke subtypes and ethnic groups.<sup>12</sup> Formed in 2007, the ISGC was created to bring together clinicians, investigators, geneticists, and statisticians to assemble the sample sizes and expertise necessary to understand the genetic underpinnings of cerebrovascular disease and leverage these discoveries to help patients.<sup>13</sup> Through its launch of collaborative studies, including METASTROKE, the NINDS-SiGN Consortium (National Institute of Neurological Disorders and Stroke–Stroke Genetics Network), and MEGASTROKE and its partnership with the CHARGE consortium (Cohorts for Heart and Aging Research in Genomic Epidemiology),<sup>14,15</sup> the ISGC has been responsible for most of the confirmed stroke risk loci discovered in the era of GWAS.<sup>16</sup>

Open data access is an opportunity to accelerate scientific discoveries in stroke. The CDKP is a comprehensive web-based resource that enables access and exploration of genetic and phenotypic data related to cerebrovascular diseases (available at [www.cerebrovascularportal.org](http://www.cerebrovascularportal.org)). The mission of the CDKP is to potentiate stroke research by democratizing access to high-quality genetic, phenotypic, and imaging data on large number of stroke patients. To accomplish this mission, the CDKP collects, securely stores, harmonizes, displays, and shares stroke genomic data with investigators from around the world. The CDKP houses 2 substantially different types of data: summary-level data and individual-level data. Summary-level data (summary statistics) consist of full sets of association results by single-nucleotide polymorphisms that form the basis of published genetic association studies; they generally cannot be used to identify individual subjects. Individual-level data consist of complete datasets containing phenotypic and genotypic information by subject. Subjects must give broad consent to allow for the sharing of their individual-level data, in part, because of the risk of identifiability.

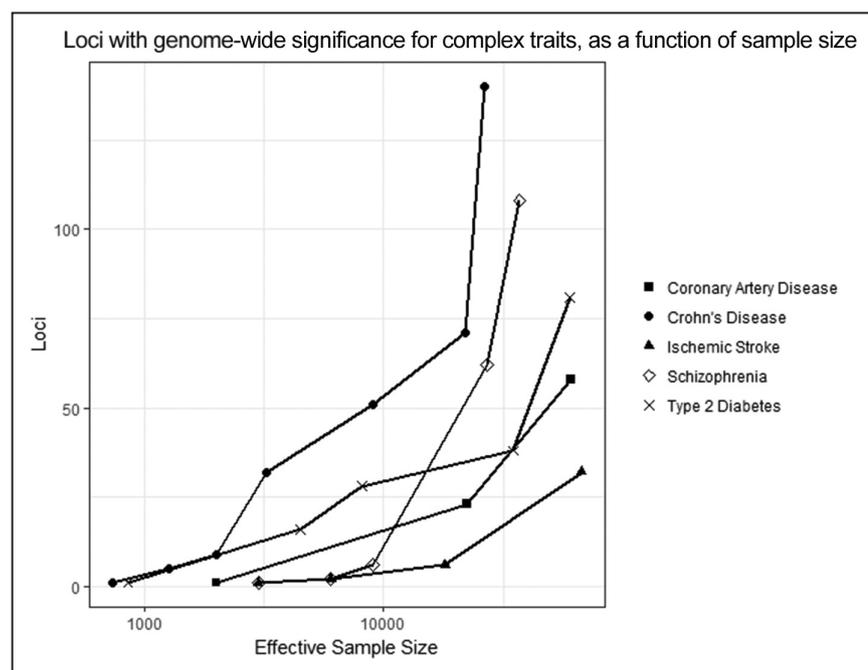
These 2 types of data are accessed through different paths (Figure 2). Summary-level data are accessed through the

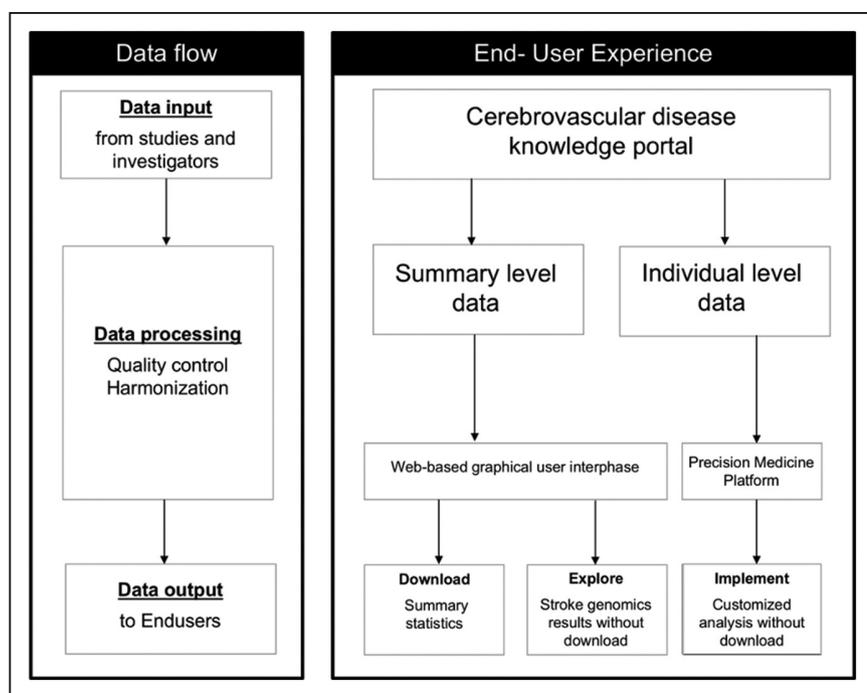
CDKP web-based platform itself, whereas the CDKP will direct the user to the American Heart Association Precision Medicine Platform (PMP; [www.precision.heart.org](http://www.precision.heart.org)) to access individual-level data. Within the PMP, individual-level data are hosted in a secure environment that allows investigators to implement complex genetic analyses without downloading the data. These analyses are run in a cloud computing-based workspace powered by Amazon Web Services. This workspace is simple to use and was specifically designed to guide and teach first-time users on how to migrate to a cloud-based ecosystem. New data and tools are constantly being incorporated to both the CDKP and the PMP.

Here, we describe the design and available features of this new resource, emphasizing opportunities and challenges that may arise in the near future.

### Design and Development of the CDKP

The creation of the CDKP, funded by the National Institute of Neurological Disorders and Stroke, has been a joint effort of the ISGC, the Broad Institute, and the American Heart Association Institute for Precision Cardiovascular Medicine. Given its extensive experience with similar projects, the Broad Institute hosts the data available through the platform and developed the informatic framework and analytic tools used by the CDKP. A dedicated steering committee, consisting of ISGC members who have contributed data to the portal, oversees the CDKP. An operations committee, consisting of ISGC members and Broad Institute staff, is responsible for the everyday operations of the CDKP. In addition, the ISGC has created a Data Access Committee that is responsible for ensuring access to all data. Any investigator wishing to contribute data to the CDKP can contact the Operations Committee at [cerebrovascular.disease.portal@gmail.com](mailto:cerebrovascular.disease.portal@gmail.com). Several different types of data can be deposited in the CDKP, including summary statistics, raw individual-level genetic data, and postprocessing





**Figure 2.** Data access through the Cerebrovascular Disease Knowledge Portal (CDKP). Data flow describes the generalized path that all data take through the CDKP. The end-user experience details how a user interacts with the resources. Summary-level data can be accessed through the CDKP web-based graphical user interphase designed to run queries and allow for download of data, whereas individual-level data can be accessed through the PMP to run custom analysis.

(eg, post-quality control and imputation) individual-level genetic data. Furthermore, as the CDKP evolves, there will be opportunities to deposit a broad range of phenotypic data, including imaging. Before transfer to the CDKP, proper institutional review board and legal approval for each data set is required, including assurance from the originating institution that all subjects are consented for this type of data sharing. Datasets transferred to the portal are harmonized following a standardized pipeline that evaluates the presence of important data points (such as a unique identifier for each subject) and identifies systematic errors. Phenotype–genotype harmonization takes place at the Broad Institute, which serves as the Data Coordinating Center. Individual-level data are subsequently transferred to the secure working space of the PMP.

### Specific Tools Available Through the CDKP

Within the CDKP and PMP, genomic data can be accessed through 3 main tools: (1) a graphical user interphase that allows quick and easy exploration of both individual- and summary-level data contained in the portal, (2) a repository of full sets of summary-level data produced by landmark-published studies in the field, and (3) a repository of individual-level data that investigators can analyze directly in a secure workspace (Figure 2).

### Web-Based Graphical User Interphase

The graphical user interphase offers users a wide menu of integrated tools for data visualization and analysis, as well as the possibility to implement on-the-fly descriptive and association analyses focused on specific items of interest: base-pair positions, genomic regions, genes, or single-nucleotide polymorphisms, to name a few possibilities. Users can also explore descriptive and association results from GWAS of other related (hypercholesterolemia, hypertension, diabetes mellitus, and coronary artery disease) and unrelated traits

(psychiatric conditions). Figures, tables, and results generated with this tool can be easily exported and downloaded. This functionality does not require a formal request, although users are required to register to use the portal.

### Summary-Level Data (Summary Statistics)

The CDKP contains full sets of summary statistics from landmark-published studies. Because all association results are provided without filtering for specific *P* value thresholds, several million results are available for each specific study. These summary-level data can be accessed through a single mouse click, without submitting a formal application. The rationale for this strategy is to encourage and accelerate preliminary analyses to evaluate different working hypotheses. By providing summary-level results from published studies only, users can easily identify the methods and study populations that were used to generate the summary statistics. Although the majority of currently available stroke data comes from subjects of European descent, data from populations of African-American, African, and Asian descent are scheduled to be added in the coming year. Each set of summary statistics has an accompanying document that describes the rules and limitations of use, including (1) data are provided as-is, meaning each user is responsible for the design, implementation, and interpretation of any analyses based on this summary-level data; (2) commercial use of these data is prohibited (including deposition of these data into commercial databases); (3) cohorts of stroke cases and matched controls are usually used by >1 study; consequently, it is the user's responsibility to check for possible overlaps when using summary statistics from different studies; and (4) scientific communications based on CDKP data must acknowledge the use of the portal. Currently, the CDKP contains full sets of results from 4 landmark papers (Table 1), and this list will rapidly grow in coming months.

**Table 1. Summary-Level Data (Summary Statistics) Contained in the International Stroke Genetics Consortium Cerebrovascular Disease Knowledge Portal**

Reference Number	Author	Year	Phenotype	Discovered Loci	Title
PMC3980413	Woo et al	2014	Intracerebral hemorrhage (ICH)	<i>TRHDE, PMF1/SLC25A44</i>	Meta-Analysis of Genome-Wide Association Studies Identifies 1q22 as a Susceptibility Locus for Intracerebral Hemorrhage
PMC4818561	Malik et al	2016	Ischemic stroke	<i>ABO, HDAC9, PITX2, ZFH3</i>	Low-Frequency and Common Genetic Variation in Ischemic Stroke: The METASTROKE Collaboration
PMC3490334	Traylor et al	2012	Ischemic stroke	<i>HDAC9, PITX2, ZFH3</i>	Genetic Risk Factors for Ischemic Stroke and Its Subtypes (the METASTROKE Collaboration): A Meta-Analysis of Genome-Wide Association Studies
PMC4912948	SiGN et al	2015	Ischemic stroke	<i>TSPAN2, HDAC9, PITX2, ZFH3, ALDH2</i>	Loci Associated With Ischemic Stroke and Its Subtypes (SiGN): A Genome-Wide Association Study.

### Individual-Level Data

Through the PMP, the CDKP also allows users to search, discover, and analyze individual-level data directly (Table 2). For administrative, legal, and security reasons, this option requires submission of a research plan and approval by the CDKP Data Access Committee. Once access to the data is granted, users are able to analyze data in the secure cloud-based computational workspace provided by the PMP. This secure workspace provides users with access to data set(s) for which authorization has been granted; although results can be easily downloaded, the individual-level data never leaves the PMP (eg, cannot be downloaded). The PMP workspace offers powerful cloud-based cluster computing capabilities through a script-driven environment that uses Jupyter Notebooks ([www.jupyter.org](http://www.jupyter.org))—an open-source web application that allows users to create and share script documents to run different kernels, or computer languages, in the cloud ([https://precision.heart.org/ICH\\_GWAS\\_2014\\_notebook.html](https://precision.heart.org/ICH_GWAS_2014_notebook.html)). Commands contained in these scripts are submitted to the cloud computing system, where they are executed in parallel using the appropriate kernels.

### Interaction With Existing Data Resources

The CDKP seeks to complement other related platforms, like the Database of Genotypes and Phenotypes and the European Genome-Phenome Archive. In contrast to these repositories,

the CDKP specializes in capturing genomic data related to cerebrovascular diseases and is not limited to a specific country or continent. In addition, the CDKP has been specifically designed to provide fast and easy access to stroke genomic information, without specific requirements (other than registering a name and e-mail address) to browse results and download summary statistics and with a brief and efficient application process to access individual-level data. The primary advantage in using the CDKP is that data have already been harmonized and cerebrovascular disease specific phenotypes have been gathered. This allows the CDKP data to be immediately ready for analysis on access. Further, cerebrovascular disease is not one single condition, but a collection of unique subtypes, each with a distinct biology and genetic risk. Therefore, to properly study cerebrovascular disease, more samples than usual and special attention to phenotyping are needed to account for aforementioned biological heterogeneity observed across the different cerebrovascular disease subtypes.

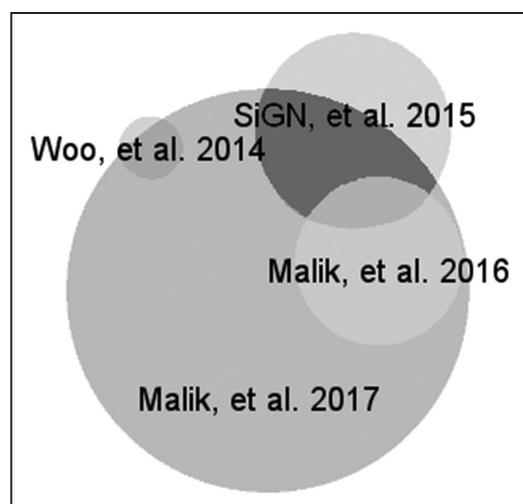
### Problems and Solutions

The creation of international collaborative data platforms is not straightforward. Several challenges arose during the design, development, and deployment of the CDKP. One important barrier encountered was the variability in approval processes and required assurances, especially when comparing

**Table 2. Individual-Level Data Available Through the Cerebrovascular Disease Knowledge Portal**

Cohort	Site	Principal Investigator	Upload Date	Cases	Controls	Phenotypes	Platform Used for Genotyping
ICH GWAS I	Boston, MA	Jonathan Rosand	2016	316	457	All (lobar+nonlobar ICH)	Illumina HumanHap610-Quad
						Lobar ICH	
						Nonlobar ICH	
ICH GWAS I	Cincinnati, OH	Daniel Woo	2016	797	539	All (lobar+nonlobar ICH)	Affymetrix 6.0
						Lobar ICH	
						Nonlobar ICH	
GERFHS III	Cincinnati, OH	Daniel Woo	2016	628	856	ICH	Affymetrix 6.0
VISP	Winston-Salem, NC	Bradford Worrall	2017	2100	0	Ischemic stroke	Illumina HumanOmni1-Quad_v1-0_B BeadChip

GERFHS III indicates Genetic and Environmental Risk Factors for Hemorrhagic Stroke; ICH, intracerebral hemorrhage; and VISP, Vitamin Intervention for Stroke Prevention Trial.



**Figure 3.** Subject overlap across the datasets within the Cerebrovascular Disease Knowledge Portal.

institutions located in different countries. The differences in governance structure and institutional review boards that exist internationally are something that must be dealt with on a case-by-case and country-by-country basis.

Administrative and legal barriers exist for both summary- and individual-level data. For summary-level data, the main barrier is that some studies explicitly prohibit the use of results by commercial users. This limitation is clearly explained in the README document that accompanies each downloadable data set that describes the conditions of use for each set of summary statistics available on the portal. For individual-level data, the main barriers are (1) the possibility that users may try to use genetic data to identify study subjects and (2) that users may use the data for different purposes than those described in their application for access. The CDKP addresses both risks by providing access to individual-level data through the PMP—a dedicated cloud-based workspace that allows the implementation of sophisticated analyses without downloading data (eg, individual-level data never leaves the workspace) and offers the possibility to fully monitor the work undertaken by each user.

Another identified challenge is how to integrate datasets with overlapping individuals—an issue with which the field continues to struggle.<sup>17,18</sup> This challenge is faced when working with multiple consortia, which often contain overlapping subsets of participating subjects. Several analytic tools have been developed to handle this problem when individual-level data are available.<sup>18</sup> In the cases of summary statistics, when overlap between 2 datasets is unknown, linkage disequilibrium score regression can be implemented to estimate the redundancy across multiple groups, although this approach can be inaccurate when working with small sample sizes. We envision that the widespread availability of summary- and individual-level data related to stroke genomics will propel research on this and other technical and analytic problems. Figure 3 displays the overlap across summary-level data currently available in the CDKP.

### Future of the CDKP

Two windows exist for individuals interested in search and discoverability, as well as analysis of stroke data: the CDKP

([www.cerebrovascularportal.org](http://www.cerebrovascularportal.org)) and the PMP ([www.precision.heart.org](http://www.precision.heart.org)). Each window provides complementary services that will accelerate stroke research. We anticipate the addition of multiple new analytic and data resources. Ten additional landmark papers have already been identified by the CDKP steering committee, and conversations are ongoing to deposit their summary results in the portal. In addition, as the ISGC official data sharing portal, the CDKP will contain summary- and individual-level data from new studies conducted by the consortium. As an important example, the ISGC will share, immediately after publication, the full set of association results of the MEGASTROKE Collaboration—the largest genetic study of stroke conducted to date, including >65 000 cases and 450 000 controls.

An important priority in coming months will be to expand the CDKP and PMP to include new types of phenotypic data. Most of the summary- and individual-level genetic data currently contained by the portal pertain to stroke risk: either summary statistics from case/control analyses or full datasets of matched cases and controls. Plans are underway to move beyond risk analyses to incorporate information related to clinical status during admission, neuroimaging biomarkers, and functional outcome, extending the range of scientific questions to be tackled within the CDKP framework. In addition to clinical and radiological data points, we will also endeavor to enrich the portal with other omics data, including transcriptomics, metabolomics, and proteomics.

The guiding principle for the future development of the CDKP and PMP is to meet the needs and interests of the portal's users. For this reason, we will deploy several tools aimed at establishing a fluent communication with those utilizing the resource and will strive to integrate the users' feedback to make decisions on future steps.

### Acknowledgments

We would like to recognize all members of the technical teams at the Broad Institute and American Heart Association Institute for Cardiovascular Precision Medicine.

### Sources of Funding

The Cerebrovascular Disease Knowledge Portal (CDKP) was launched with funding from the National Institute of Neurological Disorders and Stroke (R24 NS092983) to Dr Rosand. Dr Rosand is supported by the National Institute of Neurological Disorders and Stroke (NS073344 and NS093870). Dr Falcone is supported by a Yale Pepper Scholar Award (P30AG021342) and the Neurocritical Care Society Research Fellowship. Dr Malik is supported by the European Union Horizon 2020 project CoSTREAM (grant agreement No. 667375).

### Disclosures

None.

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KEY WORDS: cause of death ■ cerebral hemorrhage ■ humans ■ research ■ stroke

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*Stroke*. 2018;49:470-475; originally published online January 15, 2018;  
doi: 10.1161/STROKEAHA.117.018922

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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