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Advancing Stroke Genomic Research in the Age of Trans-Omics

Big Data Science: Emerging Priorities and Opportunities

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Advancing Stroke Genomic Research in the Age of Trans-Omics Big Data
Science: Emerging Priorities and Opportunities

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Advancing Stroke Genomic Research in the Age of Trans-Omics
Big Data Science: Emerging Priorities and Opportunities

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Abstract

Background—We systematically reviewed the genetic variants associated with stroke in genome-wide association studies (GWAS) and examined the emerging priorities and opportunities for rapidly advancing stroke research in the era of Trans-Omics science.

Methods—Using the PRISMA guideline, we searched PubMed and NHGRI-EBI GWAS catalog for stroke studies from 2007 till May 2017.

Results—We included 31 studies. The major challenge is that the few validated variants could not account for the full genetic risk of stroke and have not been translated for clinical use. None of the studies included continental Africans. Genomic study of stroke among Africans presents a unique opportunity for the discovery, validation, functional annotation, trans-omics study and
translation of genomic determinants of stroke with implications for global populations. This is because all humans originated from Africa, a continent with a unique genomic architecture and a distinctive epidemiology of stroke; as well as substantially higher heritability and resolution of fine mapping of stroke genes.

**Conclusion**—Understanding the genomic determinants of stroke and the corresponding molecular mechanisms will revolutionize the development of a new set of precise biomarkers for stroke prediction, diagnosis and prognostic estimates as well as personalized interventions for reducing the global burden of stroke.

**Keywords**

Stroke; Stroke Epidemiology; Genetic Research; Trans-omics; African Ancestry Population; GWAS; SNP; Genomics

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**1.0 INTRODUCTION**

Stroke is a leading cause of long-term disability, depression and dementia globally.\(^1\),\(^2\) For over 15 years, stroke remains the second most common cause of death worldwide with a higher burden among people of African ancestry compared to other populations.\(^2\)\(^–\)\(^5\) The lifetime risk of stroke has been estimated as one in five for middle-aged women and one in six for middle-aged men.\(^6\) Developing precise interventions to prevent and mitigate the devastating consequences of stroke requires a clear understanding of the environmental and genomic risk factors as well as the unique molecular pathways influencing its occurrence, type and outcome.\(^2\)

We systematically reviewed the literature on genetic variants associated with stroke in genome-wide association studies (GWAS) and examined the emerging priorities and opportunities for rapidly advancing stroke research in the era of Trans-Omics science by including African ancestry populations, especially those from the continent of Africa.

**2.0 METHODS**

**2.1 Search Strategy**

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline, we searched the National Human Genome Research Institute-European Bioinformatics Institute GWAS catalog up till May 7, 2017. In addition, we searched PubMed for relevant stroke GWAS studies from 2007 till May 7, 2017. Search terms included “GWAS” “stroke”, “ischemic stroke”, “hemorrhagic stroke”, “lacunar stroke”/”small vessel stroke”, and “large artery atherosclerosis”, and “cardioembolic stroke”/”cardiogenic stroke”.

**2.2 Eligibility Criteria**

We included individual GWAS studies and consortia studies with meta-analysis of GWAS focusing on stroke or stroke subtypes. We excluded Matsushita et al (2010)\(^7\) and Zhang et al (2012)\(^8\) which were large candidate gene studies, Zhang et al (2014)\(^9\) which was a whole exome sequencing (WES) study, Cole et al (2012)\(^10\) and Zhou et al (2014)\(^11\) which were

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small WES studies examining 10 and 9 subjects respectively; Opherk et al (2014)\textsuperscript{12} which described white matter hyperintensity (WMH) volume in cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); Keene et al (2014)\textsuperscript{13} which described SNPs significantly associated with Vitamins B6 and B12 in stroke patients (not as a risk of stroke); and Traylor et al (2017)\textsuperscript{14} which was not a GWAS study, but an heritability study which also applied genetic risk score.

\subsection*{3.0 RESULTS}

We included 31 studies (Figure 1) presented in Tables 1 and 2. Five studies were individual GWAS while 26 were meta-analyses. We provided information on year of publication, phenotype, sample size, sample ancestry, genetic loci, single nucleotide polymorphisms (SNPs), associated traits, odds ratio and p-values as well as replication status.

Based on this systematic review, only 24 genetic loci have been found to be associated with stroke. Many of them have neither been validated nor fine-mapped. Up to 61% have small to moderate effect sizes with odds ratios < 1.5. About 87\% of the study subjects were European Caucasian, while only 10\% were African Americans; however none was from the African continent."

\subsection*{4.0 DISCUSSION}

\subsubsection*{4.1 Genomic variants associated with stroke}

Stroke is a heterogenous trait which includes brain infarction (ischemic stroke with blockage of blood flow); spontaneous intracerebral hemorrhage (bleeding in the brain) or subarachnoid haemorrhage.\textsuperscript{15} It is defined based on pathological, imaging, or other objective evidence of vascular brain injury in a defined vascular distribution; or clinical evidence of focal vascular brain injury based on symptoms persisting beyond 24 hours or until death, with other etiologies excluded.\textsuperscript{15} The pathway to the occurrence of stroke involves the cardiovascular cascade including cardiovascular risk factors (e.g. hypertension, diabetes, dyslipidemia, obesity\textsuperscript{16}), and intermediate phenotypes such as atherosclerosis and microaneurysms.\textsuperscript{2,17} This makes unravelling the precise genomic determinants of its occurrence, type, severity and outcome and the delineation of its underlying mechanisms challenging.

Nevertheless, several genetic loci \textit{[PITX2, HDAC9, ZFHX3, 12q24.2 near ALDH2, 1p13.2 near TSPAN2, CDKN2A/CDKN2B, and others in Tables 1 and 2]} have been associated with ischemic stroke or its sub-types from genome-wide association studies (GWAS).\textsuperscript{5,18–23} Although some of these loci have been associated with specific subtypes, genetic overlaps have also been reported among them.\textsuperscript{20,22} For example, large artery atherosclerosis and small vessel disease, which were previously treated as genetically distinct, may share a substantial genetic component. Thus, combined analyses of both subtypes may increase power to identify small-effect alleles influencing shared pathophysiological processes.\textsuperscript{20,22} Furthermore, the novel locus 15q21.3 \textit{[AQP9-LIPC gene region]} was associated with both ischemic and hemorrhagic stroke in African Americans.\textsuperscript{24}
Genetic variation plays a substantial role in intracerebral hemorrhage (ICH) risk, hematoma volume and outcome. Promising candidates for risk alleles in ICH identified in populations (which had no continental Africans), include variants of the genes Apolipoprotein E (APOE), ACE, PMF1/SLC25A44, COL4A2, and MTHFR. Other genetic variants related to hemostasis, lipid metabolism, inflammation, and the central nervous system microenvironment as well as the locus 1q22 have also been linked to ICH in single candidate gene studies.

However, previously reported risk variants, many of which are yet to be validated or fine-mapped, account for only a portion of inherited genetic influence on ischemic stroke or ICH pathophysiology, pointing to additional loci yet to be identified.

4.2 Evidence Gaps

Although evidence for genetic contributions to stroke exist, the scientific community lacks the evidence required to translate the current knowledge to clinical and community settings for stroke prevention and interventions to improve the health of individuals and populations at risk. Translating current findings into causal variants and target genes, is a major challenge along this pathway. Additional validation and fine-mapping to improve functional annotation for variants, especially those in non-coding regions of the genome, is a necessary step to address this challenge. This would require a global effort to expand stroke research to include more diverse populations, particularly African ancestry population, to elucidate the genetics of stroke.

Furthermore, expanding the genetic study of stroke in African populations, a population that has significantly higher susceptibility to stroke, will help elucidate the global heritability of stroke; as well as assist in developing new, and broadening existing, potential therapeutic options. This is because novel variants (SNPs/copy number variants CNVs/insertion-deletions InDels) that contribute to the higher burden, earlier age of onset and poorer outcomes of stroke in people of African ancestry are yet to be characterized.

4.3 Advantages of conducting stroke genomics research in African populations

Significant advantages exist to conduct stroke research in African ancestry populations. Below we outline the reasons for conducting said research:

4.3.1. Universal implications—All modern humans originated in Africa before migrating to populate the rest of the world in the last 100,000 years, hence the expression ‘we are all Africans beneath our skin’. Therefore combining phenotype and genomic information from continental Africans (old genes in same environment) and the African Diaspora (interactions of old genes with modern environments) could lend novel insights into human evolution and adaptation, health disparities research, disease etiology, pathophysiology, and ancestry-based disease gene mapping. This could have significant universal implications for global populations.

4.3.2. Unique genomic architecture—Genetic adaptations that took place across Africa, particularly against fatal pathogens and ecological forces, have resulted in elevated
frequencies of alleles conferring survival advantages detectable in present-day continental Africans and those in the Diaspora. Unfortunately, some of these alleles are maladaptive contributing to the disproportionately high burden of some chronic diseases in these groups. The power to detect pathogenic genomic variants associated with such alleles is therefore substantially higher among people of African ancestry.

One important example is the 2 missense haplotype variants G1 and G2 in the apolipoprotein L1 (APOL1) gene, which have been found to be associated with end-stage renal disease in people of African ancestry. These haplotypes are common in African ancestry populations but absent in European Caucasians and Asians, presumably due to evolutionary positive selection because these APOL1 variants confer resistance to lethal Trypanosoma brucei infections, which cause African sleeping sickness. Only by studying people of African ancestry, were the associations of the G1 and G2 APOL1 variants identified, and these variants turned out to account for the large amount of the ethnic disparity in end-stage renal disease that had long been recognized between African and European ancestry populations.

Novel insights into disease etiology have also been gained by comparing diasporan populations to their ancestral populations in sub-Saharan Africa and by characterizing local admixture at disease risk loci. A study found that the association between the LPL SNP rs328 and lipid levels was stronger and the levels of HDL-cholesterol were higher among African Americans with predominantly European ancestry than among those with predominantly African ancestry at this locus. Lipid levels and their association with the LPL variant in African Americans with two African ancestry alleles at this locus were similar to those of West Africans despite widely different lifestyles and diets. This mutation possibly occurred centuries ago and was then transported to America through the trans-Atlantic slave trade.

4.3.3. Greater understanding of stroke epidemiology—Substantial disparities in stroke epidemiology exist between people of African ancestry compared to other populations. The burden of stroke in Africa is higher and increasing, with stroke being among the leading causes of morbidity and mortality throughout continental Africa while the burden is less and appears to be declining in many high-income countries. Globally, Africa has the highest burden of stroke with age standardized incidence of up to 316/100,000; age-adjusted prevalence of as high as 1,460/100,000; one month fatality of up to 43% (compared to 4% North America), and 3 year fatality of 84%. Furthermore, stroke afflicts the younger population (up to 15 years younger), and presents with a higher proportion of the hemorrhagic type (34% in Africans, vs 9% in high income countries). Similarly, African Americans experience a higher burden, more hemorrhagic type, younger age of onset and worse outcome compared to European Americans.

Some of the racial disparity and higher burden of stroke in people of African ancestry can be attributed to lifestyle and cardio-metabolic factors (eg diabetes mellitus, and hypertension) as well as socioeconomic factors such as inadequate access to health
care. \(^5\) However, even after adjustment for these factors, substantial risk remains, suggesting a strong genetic influence.\(^5\), \(^32\), \(^33\), \(^45\), \(^46\)

Studying the genetics of stroke in African ancestry populations may elucidate genetic mechanisms that could not be otherwise revealed in studies of non-African populations (e.g. European ancestry populations). However, most large stroke genomic consortia are based on subjects of predominantly European ancestry. As of May 7, 2017, the National Human Genome Research Institute-European Bioinformatics Institute GWAS catalog included 12 GWAS of stroke; in aggregate, these included 40,801 European Caucasian subjects but only 4,566 African American subjects. No subjects in these studies were from Africa despite the higher heritability of stroke in Africans.\(^5\), \(^14\)

4.3.4. Substantially higher heritability and greater potential for discovery of novel genes—It has been demonstrated that there is higher stroke genetic heritability among UK African ancestry sample (\(h^2 = 0.35\) [SE = 0.19], \(p = 0.043\)) compared to European populations (\(h^2 = 0.16\)).\(^14\) Thus the sample size requirement for detecting significant SNPs/CNVs/InDels associations may not be as large as what is often required among European populations. Therefore the potential and statistical power for discovery and functional investigation of genomic variants associated with stroke appears to be best among people of African ancestry.

4.3.5. Substantially better resolution for fine mapping—African ancestry populations have been shown to substantially increase the resolution of fine-mapping\(^5\), \(^47\) due to its low linkage disequilibrium and high genetic heterogeneity.\(^18\), \(^19\), \(^35\) This is the reason African ancestry data is critically needed (in independent and trans-ethnic analyses) to fine-map loci previously identified in GWAS studies of European populations so as to pinpoint specific causal variant(s) and gene(s) for various complex diseases including stroke.\(^5\), \(^47\)

Genomic data for unravelling causative variants can take the form of dense-GWAS\(^29\) or whole exome sequencing (WES) or whole genome sequencing (WGS). Dense-GWAS using novel chips such as the 2.5 million SNPs array H3Africa chip\(^48\), \(^49\) with 850K custom African content combined with imputation based on 5,500 WGS reference genomes can facilitate functional association analysis.\(^50\) (The reference genomes comprise the Genome Diversity in Africa Project (GDAP)\(^51\), Uganda 2000 Genomes\(^52\), African Genome Variation Project\(^53\), 1000 Genomes\(^54\), \(^55\), TrypanoGEN,\(^48\), \(^49\) Baylor College\(^48\), \(^49\), and South African Human Genome Programme SAHGP\(^48\), \(^49\), \(^56\)) The advantage of GWAS is that it is cost-efficient and can cover common variations of small to moderate effects (minor allelic frequency MAF>1 %) in large populations. Performing GWAS in people of African ancestry will substantially increase the diversity within the GWAS catalogue.\(^50\)

Whole genome sequencing (WGS) has several advantages over GWAS. WGS covers the entire genome and can detect rare variants (with MAF<1 %), as well as other types of functionally important variations (copy number variations, insertions/deletions).\(^57\), \(^58\) Importantly, WGS gives single base resolution of the entire genome which is ~100–300-fold finer resolution than that provided by GWAS chips. Also, WGS is not biased by, or restricted
to, the SNPs that have been placed on commercially available SNP chips (assumes commonly used chip-based methods).\textsuperscript{57, 58} It provides the best possible resource for linkage disequilibrium (LD) mapping due to the maximal marker density and lack of ascertainment bias.

Nevertheless WGS is at least 10 times more expensive than GWAS, and produces massive amounts of data for analysis (100 to 300 fold more than GWAS data), some of which are of uncertain significance.\textsuperscript{59} With future costs to generate WGS data reducing, WGS in large populations of continental Africans with stroke for discovery\textsuperscript{39}; followed by validation in African Americans, is the most plausible approach to discover and pinpoint causal variants for stroke with implications for the entire human race. This is due to the African origin of all humans and the substantially higher heritability of stroke among African ancestry populations. Meanwhile, dense GWAS with novel chips and imputation using WGS data can also produce useful results, while samples can be stored for future WGS as prices reduce.

4.4 Understanding Complex traits in the era of Trans-Omics science

Although GWAS approach is a very powerful tool to tag genetic loci related to stroke etiology, it may not pinpoint the exact causal genetic variation or delineate the mechanistic path from DNA variation to regulation of gene transcription, translation and post-translation modification, all the way to the pathogenesis of stroke. It is necessary to combine the emerging tools of genomics (including genome wide genotyping with novel high throughput chips, and next generation whole exome sequencing and whole genome sequencing) with functional omics including transcriptomics, epigenomics, proteomics, and metabolomics in various integrative manners. Functional omics can further GWAS findings in two ways. First, functional omics can offer insight into which and how the static DNA variation leads to dynamic functional changes at RNA and protein level. One common application of Trans-Omics approach is to annotate the expression and methylation quantitative trait loci (eQTL and mQTL) for fine-mapping GWAS causal signals. For example, schizophrenia risk-associated SNPs in the Disrupted In Schizophrenia 1 (DISC1) gene has been shown to regulate RNA splicing and thus lead to expression changes of certain isoforms of DISC1 transcripts\textsuperscript{60}. Prostate cancer risk allele rs11986220 found by GWAS locates in an enhancer region and can result in stronger FoxA1 binding and stronger androgen responsiveness.\textsuperscript{61}

Second, functional omics reflect the results of both endogenous DNA genetic coding and exogenous dynamic environmental factors. Thus, it provides a unique opportunity to quantify complex gene-gene and gene-environment interactions for complex diseases, to which both genetics and environmental factors contribute substantially. Only through Trans-Omics approach can we draw a complete picture of the biological mechanisms of stroke and its various subtypes as well as its outcome. For example a recent publication conducted a GWAS of blood pressure in continental Africans and African Americans to identify genes conferring susceptibility to increased blood pressure. This research identified three novel genomic regions associated with blood pressure and utilized transomic techniques to unravel the associated pathways, which have not been previously reported in studies of other race/ethnicity.\textsuperscript{62} Likewise, stroke research utilizing Africans and African ancestry populations can produce significant dividends because of the association between high blood pressure and stroke in African ancestry populations.\textsuperscript{62}
Trans-Omics approach has been utilized successfully in immunology, oncology, cardiovascular diseases, and some neurological diseases such as Alzheimer’s diseases, schizophrenia, and autism. Although still rudimentary, this approach is also being employed in stroke research too, mostly using transcriptome and more recently epigenomics. For instance, transcriptome study observed that genes regulated in large-vessel atherosclerotic stroke are expressed in platelets and monocytes and modulate hemostasis while genes regulated in cardioembolic stroke are expressed in neutrophils and modulate immune responses to infectious-like stimuli. In the development of intracranial aneurysms, genomic DNA methylation has been found to play an important role in the genetic expression regulation involved in immune and inflammatory reactions, cell function, cell maintenance, and cell signal transduction. In ischemic stroke patients, CDKN2B methylation in peripheral blood leukocytes was found to be associated with carotid artery calcification. Epigenomic study discovered that DNA methylation level for TRAF3 gene is associated with vascular recurrence in ischemic stroke patients treated with clopidogrel.

4.5 Methodological Standards, Current Research Priorities and Opportunities in Stroke Genomics and Trans-Omics

Important methodological considerations for stroke genomic research include adequate sample size, the selection of appropriate controls, careful clinical phenotyping using standardized classification systems, and determining associations with stroke subtypes as well as stroke as a whole. It is essential that positive associations are replicated in independent (but similar) populations, and appropriate methodology is used in such studies. Top priorities identified for global stroke genomic research include greater sample size and research within subtypes of stroke to aid discoveries, translation of existing findings, and utilization of novel techniques. African ancestry populations are critically needed for discovery of novel loci associated with stroke and fine-mapping of known loci discovered in American and other populations to pinpoint the precise causal variant(s) and gene(s) and translate to clinical applications. The largest population of (continental) Africans with stroke in a single funded study are included in the Stroke Investigative Research and Education Network (SIREN) study, part of the H3Africa Project, which has >3000 case-control pairs, (with a targeted recruitment of 5000 case-control pairs) accurately phenotyped with the pictographic questionnaire for verification of stroke-free status (pQVSFS) and ACCESS tool (for standardized phenotyping of ischemic and hemorrhagic strokes). Cases and controls are comprehensively evaluated for stroke risk factors to ensure appropriate co-variate adjustment. Furthermore, the controls, who are recruited from the same catchment population that produced the cases are matched for age, sex and ethnicity to minimize confounding due to population structure.

Preliminary data (n=917) from candidate gene studies (24 SNPs) in SIREN show that the IL-6 rs1800796 was significantly associated with ischemic stroke in West African men (OR = 2.006, 95% CI = [1.065, 3.777]). In addition, rs2383207 in CDKN2A/CDKN2B was also associated with ischemic stroke in men (OR = 2.550, 95% CI = [1.027, 6.331]). However, these findings need to be explored further in the entire SIREN dataset.
4.6 Next Steps

To advance stroke genomics with existing opportunities and resources, the following steps are most likely to yield the best outcome.

4.6.1 Discovery of novel variants in the continental African dataset—Increasing the sample size of the SIREN study with additional 2000 case-control pairs will make it the largest ever stroke genomic dataset from a single study (10,000 subjects, 5000 case-control pairs). This will give over 81% power to detect Genetic Relative Risk of at least 1.46 with minimum allele frequency of 0.05. Thus, the statistical power, the genomic diversity and unique allelic frequencies of certain variants in Africans\(^5\) as well as substantially higher heritability\(^{14}\) will maximize the opportunity for discovery of novel variants (SNPs/CNVs/InDels) for total stroke, and its predominant subtypes, severity and outcome of relevance to African Americans (71% of whom migrated from West Africa several centuries ago) and indeed the entire human species.\(^{32, 33, 35}\) Moreover, certain variants may be unique to populations of African Ancestry thus accounting for some of the observed racial disparities in stroke. The power for discovery will be further enhanced with pathway-based analyses.

4.6.2 Validation and Fine-mapping—Because African subjects are best suited for validation and fine-mapping,\(^5, 47\) the phenotype and genomic dataset of 5000 case-control pairs (WGS or dense GWAS data with imputation) should also be utilized for validation; and fine-mapping of variants previously associated with stroke in GWAS studies of Europeans and other populations.\(^{29, 47, 84, 85}\) Secondly, variants discovered in continental Africans can be validated among African Americans within the Consortium of Minority Population Genome-Wide Association Studies of Stroke (COMPASS)\(^{24}\), International Stroke Genetics Consortium (ISGC) and other consortia.

4.6.3 Trans-ancestry big data meta-analyses including large datasets from people of African ancestry—The data generated in 4.6.1 and 4.6.2 above can be utilized in trans-ancestry meta-analysis and fine-mapping within harmonized consortia including NINDS-funded Stroke Genetics Network (SiGN)\(^{86}\), METASTROKE,\(^{75}\) ISGC\(^{75}\) and SIREN-Reasons for Geographic and Racial Differences in Stroke (REGARDS) collaboration\(^{44}\) to discover, validate and fine-map additional novel variants associated with stroke across European, African and other ancestry populations. This could provide more statistical power for discovery, fine-mapping and validation of loci with novel causal variant(s) and gene(s) for stroke and stroke types especially when they include large-scale African ancestry data.\(^{29, 87}\) It is crucial to promote opportunities for generation of high quality data from the African continent and dialog to facilitate mutual data sharing among international consortia of stroke genomics studies and investigators from the African continent, especially those currently involved in the SIREN study, through conferences and funded research collaborations.

4.6.4 Functional Genomics—Identified variants and target genomic loci can be investigated further with functional genomics to unravel the molecular mechanisms mediating their action (expression) using a combination of transcriptomics, epigenomics and metabolomics studies. Epigenomics, transcriptomics, and metabolomics can be selected as...
priority compared to other Omics mainly due to their relative maturity and feasibility of implementing in large international consortium settings.

5.0 Conclusions

To revolutionize the understanding of genomic contributions to stroke occurrence, severity, type and outcome, the best potential is provided by expanding available high quality, comprehensive, accurate phenotype and genomic data in continental Africans for independent trans-omics analyses, and then combining this with big data from African Americans and other populations in trans-ethnic trans-Omics meta-analyses. Delineation of molecular mechanisms of validated genomic determinants of stroke can facilitate the development of a new array of precise biomarkers for stroke prediction, diagnosis and prognostic estimates as well as discovery of new therapeutic targets for personalized interventions. These developments could revolutionize stroke prevention, treatment and recovery globally.

Acknowledgments

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References


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Figure 1.
PRISMA Flow Chart of the Search Process for this Review Article
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IS-ischemic stroke; CE-Cardioembolic stroke;
#(pooled)
*replicated genes
### Table 2

Stoke GWAS Studies – Consortium-based Meta Analytic Studies

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<td>1.16</td>
<td>3.2 × 10⁻⁹</td>
</tr>
</tbody>
</table>

IA-intracranial aneurysm; IS-ischemic stroke; ICH-intracerebral hemorrhage; LAA-Large Artery Atherosclerosis; LVD-Large Vessel Disease; SVD-Small Vessel Disease; CE-Cardioembolic stroke; AA-African American; HA-Hispanic American UND-undetermined; Tables 1 and 2 are not limited to associations which attain genome wide significance alone (p < 5.0 × 10⁻⁸).

* indicates genetic associations which have been replicated; † Carty et al: Table reported findings from primary discovery analysis.