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New Information on the Genetics of Stroke

James F. Meschia
Cerebrovascular Division, Department of Neurology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA

James F. Meschia: meschia.james@mayo.edu

Abstract

Ischemic stroke, white matter hyperintensities related to small vessel ischemia, and intracranial aneurysms all show heritability. This review focuses on recent progress in understanding the molecular genetics of these disorders. Also reviewed is recent progress in understanding single-gene disorders in which stroke is a major feature of the phenotype, including CADASIL, CARASIL, hereditary angiopathy with nephropathy, aneurysm and muscle cramps, and Fabry disease and progress in pharmacogenomics as it relates to response to antiplatelet therapy.

Keywords

Ischemic stroke; Genetics genomics; Cerebral aneurysm; Fabry disease; CADASIL; CARASIL; Leukoaraiosis; White matter hyperintensities; Family history; Cost effectiveness; Pharmacogenomics

Introduction

Given the fast pace of the field, I have chosen to focus on an overview of published discoveries in stroke genetics that have appeared in recent years. This review is not intended to be an exhaustive summary of every aspect of stroke genetics. For broad overviews, readers are encouraged to read a recent review [1].

Stroke

Family History of Stroke as a Risk Factor

Several studies over the years have supported a heritable component to stroke risk. Most of the earlier studies did not directly ascertain stroke status in multiple generations, but relied instead on survey data or record review, often failing to distinguish between ischemic and hemorrhagic stroke. The most robust study to date confirming the importance of family history of stroke as a risk factor for stroke was done by the Framingham investigators. Investigators documented 106 parental strokes by 65 years of age, of which 74 were ischemic; and 128 offspring strokes, of which 106 were ischemic [2]. Cox models were used adjusting for age, sex, sibship, and traditional vascular risk factors. When a parent had a history of stroke before 65 years of age, the risk of stroke in offspring was increased 2.79-fold (95% CI, 1.68–4.66). When a parent had a history of ischemic stroke before 65 years of age, the risk of ischemic stroke in offspring was 3.15 (95% CI, 1.69–5.88; $P<0.001$). Naturally, the relative contribution of shared environment and shared genes cannot be

Correspondence to: James F. Meschia, meschia.james@mayo.edu.

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established with this study design. Investigators further discovered an interaction between the Framingham Stroke Risk Profile score and verified parental history of stroke. The practical significance of this finding is that it might be justified to target for intense stroke prevention those individuals with a paternal history of stroke.

Rejection of *PDE4D* as a Risk Factor

A genome-wide linkage scan performed in an Icelandic population implicated phosphodiesterase 4D (*PDE4D*) as a risk factor for stroke [3]. Numerous attempts at independent replication ensued with varying results. A meta-analysis of 5200 cases and 6600 controls found no evidence of association between *PDE4D* and ischemic stroke [4]. Meta-analysis of genetic association studies is compromised when contributing studies have genotyped partially overlapping marker sets. Such was the case in the *PDE4D* meta-analysis. To overcome this limitation, a multi-locus Bayesian meta-analysis was performed [5]. It included 14 data sets from populations of European descent and a total of 12,929 subjects (5994 cases and 6935 controls). A total of 33 single nucleotide polymorphisms (SNPs) were genotyped in at least one study. The analysis was restricted to the 26 typed markers included in HapMap. It confirmed no association despite the increase in statistical power.

Genome-Wide Association Studies

Candidate gene studies have yielded mixed results [6,7]. This has led to a migration to hypothesis-neutral approaches such as the technique of genome-wide association using SNP-based polymorphisms. This technique has yielded important insights into the molecular genetics of ischemic stroke. Several investigative teams have confirmed an association between coronary artery disease and a locus on chromosome 9p21 [8–11]. Because ischemic stroke and myocardial infarction share many conventional risk factors, the International Stroke Genetics Consortium tested for an association between ischemic stroke and the 9p21 locus. Analysis of the full sample showed significant associations between six SNPs and atherosclerotic stroke even after controlling for demographic variables, coronary artery disease, myocardial infarction, and other vascular risk factors [12••]. The pooled odds ratio (OR) for the lead SNP (rs1537378-C) was 1.21 (95% CI, 1.07–1.37; P= 0.002). This supported the contention that the 9p21.3 locus is a risk factor for atherosclerotic stroke independent of the association with coronary artery disease.

There are also overlapping risk factors for atrial fibrillation and cardioembolic stroke. A multistage study using the Infinium HumanHap300 chip in 1661 ischemic stroke cases and 10,815 controls in the discovery phase found rs2200733 associated with ischemic stroke (OR, 1.26; $P=2.18\times10^{-10}$) and both rs2200733 and a nearby SNP, rs10033464, associated with cardioembolic stroke [13]. These SNPs had already been associated with atrial fibrillation. An association was also found with non-cardioembolic stroke, suggesting that a subset of patients diagnosed with noncardioembolic stroke have cryptogenic cardioembolism due to intermittent atrial fibrillation. However, a separate association study involving 4199 cases of ischemic stroke and 3750 controls found an association between the 4q25 locus and cardioembolic stroke, but no association with noncardioembolic subtypes of ischemic stroke, suggesting that gene testing might not be a useful way of characterizing patients who might have cryptogenic cardioembolism [14].

Overlapping genetic risk for atrial fibrillation and ischemic stroke was further observed for a sequence variant in zinc finger homeobox 3 (*ZFHX3*) gene on 16q22 [15]. Using the genome-wide scan approach on samples from Iceland, Norway, and the United States, investigators found that rs7193343-T associated significantly with atrial fibrillation (OR, 1.21; $P=1.4\times10^{-10}$), and associated nominally with ischemic stroke (OR, 1.11; P=0.00054)

and cardioembolic stroke (OR, 1.22; *P*=0.00021). The *ZFHX3* gene is thought to be involved in growth and differentiation of several tissues.

In the first genome-wide association study in ischemic stroke, our group used the Illumina Infinium Human-1 HumanHap300 on 278 cases and 275 neurologically normal controls and found no locus that reached genome-wide significance after adjusting for conventional risk factors [16]. Despite the lack of definitive discovery of a genetic association in our study, a separate investigative team chose to test for association of the top 25 associated SNPs in a Han Chinese population and found that 3 of the 25 SNPs replicated [17].

Using over 52,000 gene-based tag SNPs in a case–control study, a nonsynonymous SNP in the protein kinase C eta gene (*PRKCH*) was found to be associated with lacunar infarction in two independent Japanese samples [18]. A study that included Chinese patients with stroke (*n*= 1209) and controls (*n*=1174) replicated the finding of an association between *PRKCH* and stroke and further observed an association of variants in the gene with cerebral hemorrhage [19]. The same group used a panel of 52,608 gene-based SNPs on 1112 cases of brain infarction and age- and sex-matched controls and found a SNP in the 5′-flanking region of angiotensin receptor-like-1 (*AGTRL1*) gene to have a significant association (OR, 1.30; 95% CI, 1.14–1.47; *P*=0.000066) [20].

The CHARGE consortium analyzed genome-wide association data from four large cohorts, including 19,602 white persons in whom 1544 incident strokes developed over an average follow-up of 11 years [21]. Additional replication testing was done in black and white cohorts. There appeared to be an association between a locus on chromosome 12p13 and stroke. However, this finding did not replicate when tested in a series of case–control studies that involved nearly 9000 cases of ischemic stroke [22]. The failed replication showed no heterogeneity among studies, whereas the original CHARGE consortium results did show heterogeneity among studies.

A multistage study that used genome-wide association for the first stage found *CELSR1* (cadherin, epidermal growth factor laminin A G-type repeats seven-pass G-type receptor 1) to be a susceptibility gene for ischemic stroke in Japanese [23]. The finding has yet to be replicated.

Despite the apparent series of discoveries that have often been reported with genome-wide association studies of ischemic stroke, it is worth noting that no genome-wide association study finding has been replicated across studies [24]. The implication is that larger studies are required if we are to succeed in deciphering true from false-positive associations.

White Matter Hyperintensities

Heritability of white matter hyperintensities, a marker of small vessel ischemic diseases, is estimated at about 70%. The genetic basis for this endophenotype remains to be fully elucidated. Suggestive loci have been identified in the Framingham [25] and GENOA studies [26]. A meta-analysis of 19 candidate genes in about 19,000 subjects was performed, with the most studied genes being apolipoprotein E, methylenetetrahydrofolate reductase, and angiotensin [27]. No reliable association was identified. One would expect that large genome-wide association studies would be able to reliably identify risk loci for white matter hyperintensities.

CADASIL

CADASIL, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy, causes the clinical phenotype of migraine headaches, lacunar strokes,

and ultimately, vascular dementia. Classically, the syndrome is the result of mutations in the Notch3 that result in an unpaired cysteine residue. However, not every individual with the CADASIL phenotype has a notch3 mutation. A multi-year retrospective case series from a tertiary cerebrovascular clinic in Italy performed notch3 sequencing on 81 probands and found that only 20% had a pathogenic mutation [28]. Features that were significantly more common among notch3 mutation–positive patients were history of migraine, stroke before 60 years of age in a relative, severe leukoencephalopathy, white matter changes extending to the anterior temporal lobes, external capsule involvement, and lacunar infarcts. However, none of these features was pathognomonic.

Skin biopsy remains a practical way to obtain a diagnosis of CADASIL. A retrospective investigation of 131 Finnish, Swedish, and French CADASIL patients showed that 100% had accumulation of granular osmio-philic material [29]. Collectively, patients had 34 different pathogenic mutations, showing the genetic diversity of the disease. Because of the retrospective design of the study, it is possible that selection bias may have inflated the sensitivity of skin biopsy. Diagnostic skin biopsy should include the border zone between the deep dermis and upper subcutis.

There has been more progress in genotype-phenotype correlation in patients with *NOTCH3* mutations. *NOTCH3* is expressed in vascular smooth muscle cells. Notch3 is a heterodimer with a large extracellular domain containing 34 epidermal growth factor receptor (EGFR)—like repeats noncovalently attached to a membrane-spanning domain. The gene for Notch3 has 33 exons. Most mutations occur in exons 2 to 24, resulting in an odd number of cysteine residues. Most mutations do not appear to alter Notch3 receptor function. However, a new study suggests that mutations in the Delta/Serrate/LAG-2 (DSL) ligand-binding domain, EGFR 10–11, may disrupt Notch3 receptor function [30]. Patients with mutations in the DSL-binding domain appear to differ phenotypically from patients with mutations outside of the DSL-binding domain. Patients with mutations in the DSL-binding domain have higher Mini-Mental State Scores despite higher volume of white matter hyperintensities.

There continues to be refinement in our understanding of the CADASIL phenotype. A 7-year longitudinal study of 25 *NOTCH3* mutation carriers showed that on MRI, increase in lacunar infarcts, microbleeds, and ventricular volume but not white matter lesions or atrophy correlate with cognitive decline in CADASIL [31]. Apathy appears to be a common symptom. In one prospective series, apathy was evident in 41% (54/132) of patients with CADASIL, and adversely affected disability [32]. Monozygotic twins with CADASIL due to mutation Cys251Tyr demonstrated significant phenotypic differences in disease severity [33]. The twin who was sedentary and smoked suffered a stroke 14 years earlier than the twin who exercised regularly and did not smoke. The implication is that environmental factors can modify disease severity.

CARASIL

Cerebral autosomal-recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) patients are typically normotensive and have alopecia with onset in their teen years, spondylosis with onset in their 20 s and 30 s, stroke beginning in their 30 s, and dementia with onset in their 30 s to 50 s. Linkage analysis has shown mutations in the HtrA serine protease 1 (*HTRA1*) gene have been shown to cause CARASIL [34• •]. Patients with mutations tend to have protein products with low protease activity that is not able to repress signaling by the transforming growth factor-β family.

Intracranial Aneurysms

Unruptured intracranial aneurysms (IAs) are tempting targets for prevention of subarachnoid hemorrhage. The difficulty is in predicting which patients with IAs are at greatest risk of rupture. The FIA study screened for aneurysms in first-degree relatives of those with a family history of IAs who had a history of smoking or hypertension [35•]. A total of 113 subjects had 148 IAs by magnetic resonance angiograms. The rupture rate of IAs detected in the FIA study was 1.2% per year. This represents a 17-fold increase in risk of rupture of IAs in the ISUIA study.

A population-based case–control study showed an interaction between smoking and family history in terms of risk of aneurysmal subarachnoid hemorrhage (aSAH) [36]. Compared to current nonsmokers with no first-degree relatives with an aSAH, the OR for aSAH for nonsmokers with a positive family history of aSAH was 2.5. The OR for current smokers with a negative family history was 3.1 and the OR for current smokers with a positive family history was 6.4. The implication is that it is particularly important to council against smoking in individuals with a family history of aSAH.

The FIA investigator found no evidence for anticipation. Although the first filial (F1) generation had a rupture at younger age than the parental (F0) generation, this could be explained by the shorter duration of follow-up in the F1 generation [37]. This implied to investigators that all types of mutations, including single base changes, deletions, and insertions, need to be investigated as possible causes for the heritability of intracranial aneurysms.

Family history of subarachnoid hemorrhage is a sufficient risk factor to aid in decisions regarding screening for IAs. Modeling shows that it appears to be cost effective to screen for IAs in patients with a family history of two or more first-degree relatives with SAH [38• •].

A European and Japanese collaboration reported a second genome-wide association study with discovery and replication cohorts comprising 5891 cases and 14,181 controls [39• •]. The study confirmed prior associations near *SOX17* (8q11.23–q12.1; OR, 1.28; $P=1.3\times10^{-12}$) and *CDKN2A-CDKN2B* (9p21.3; OR, 1.31; $P=1.5\times10^{-22}$). Three new loci were also identified: 18q11.2 (OR, 1.22; $P=1.1\times 10^{-12}$), *STARD13-KL* on 13q13.1 (OR, 1.20; $P=2.5\times10^{-9}$), and a gene-rich region on 10q24.32 (OR, 1.29; 1.2×10^{-9}) (Table 1). It is not clear whether these same loci associate with aSAH. As family history studies have demonstrated, not every IA poses comparable risk of rupture.

Hereditary Angiopathy with Nephropathy, Aneurysm, and Muscle Cramps (HANAC)

Mutations in the *COL4A1* gene affecting glycine residues that are in close proximity in exons 24 and 25 within the triple helix domain of the protein can cause a syndrome known as HANAC (hereditary angiopathy with nephropathy, aneurysm, and muscle cramps). The *COL4A1* gene encodes for the alpha1(IV) chain of type 4 collagen. HANAC patients have disruption of the basement membrane systemically. The nephropathy causes hematuria and renal cysts. The muscle cramps can occur with or without elevations in serum creatine kinase. Patients have a characteristic retinal arteriopathy. There has been further characterization of the neurovascular phenotype in a series of families [40]. Infarcts not related to cardiac or large vessel pathology can occur at an early age. Patients may be predisposed to posttraumatic hemorrhage. IAs are common within pedigrees. These aneurysms are characteristically localized to various levels of the carotid siphon. White matter changes seen on MRI typically spare temporal and occipital lobes and U fibers.

Moyamoya Disease

Moyamoya disease is defined by progressive nonathero-sclerotic occlusion of the terminal intracranial segments of the internal carotid arteries. Moyamoya is associated with sickle cell disease, neurofibromatosis type 1, cranial therapeutic irradiation, especially in children, and Down's syndrome. Linkage and association studies in 20 families showed that heterozygous mutations in the alfa-actin (*ACTA2*) gene can cause the syndrome of thoracic aortic aneurysms and dissections (TAAD), premature coronary artery disease, ischemic stroke, and moyamoya disease [41]. Very early onset strokes and moyamoya disease occurred in patients harboring mutations altering R258. Mutations in *ACTA2* cause inappropriate proliferation of vascular smooth muscle cells.

Fabry Disease

Fabry disease is associated with premature stroke, cerebrovascular dolichoectasia, and white matter hyperintensities [42]. Further progress has been made in characterizing the long-term effects of enzyme replacement therapy for Fabry disease. Five-year data were reported on patients in the prospective multicenter observational Fabry Outcome Survey [43]. Treatment resulted in sustained favorable changes in cardiac parameters, including reduction in left ventricular mass and an increase in midwall fractional shortening. There was significant reduction in pain and significant improvement in quality of life. It remains to be seen how effective enzyme replacement is in preventing stroke and other cerebrovascular abnormalities.

A report from Germany had suggested that Fabry disease is a relatively common cause of cryptogenic ischemic stroke in young men, detected at a rate of 4.9% [44]. Recent data suggest that Fabry is not so common a cause of premature cryptogenic stroke in the multiracial US population. The Stroke Prevention in Young Men Study, an epidemiologic study with the Baltimore-Washington area being the catchment, observed Fabry disease in 0.18% of all strokes and 0.65% of cryptogenic strokes [45].

Pharmacogenomics

There have been advances in the understanding of the genetics behind clopidogrel resistance. Clopidogrel, a thienopyridine, is a prodrug that requires metabolism by the cytochrome P450 complex to act on its target, the platelet $P2Y_{12}$ receptor. Genetic studies nested within phase 3 cardiology trials have shown that a reduced-function allele of the *CYP2C19* gene reduces the clinical effectiveness of clopidogrel in preventing recurrent myocardial infarction and in-stent thrombosis [46]. A current challenge for clinicians is that there now is a warning by the US Food and Drug Administration that some patients may be poor responders to clopidogrel and that gene tests exist for screening for poor responsiveness. It is not known how cost effective screening would be in all patients in whom clopidogrel would otherwise be considered. However, it may be reasonable to test patients who have an ischemic stroke or transient ischemic attack on clopidogrel for the *CYP2C19* reduced-function allele. Some have argued that patients might benefit more from platelet function assays rather than gene testing, but direct comparison of various methods for trying to individualize stroke prevention with clopidogrel have yet to be done.

The third-generation thienopyridine, prasugrel, was tested against clopidogrel in the TRITON-TIMI 38 trial in a patient population undergoing percutaneous coronary intervention for acute coronary syndrome. Gene testing for *CYP2C19* poor responder variants was found to be a useful way of distinguishing patient populations with a differential efficacy response to clopidogrel versus prasugrel [47]. Because at present there

is no clear indication for prasugrel for stroke prevention, this finding is not helpful in guiding therapy after gene testing.

Conclusions

The first wave of ischemic stroke genome-wide association studies has been done. The second wave of studies is underway, including the Wellcome Trust Case Control Consortium-2 and the National Institute of Neurological Disorders and Stroke (NINDS) Stroke Genetics Network. The Network focuses on detailed phenotyping using the web-based algorithmic Causative Classification System (CCS) [48]. Using the CCS requires reclassification of most cases across participating study cohorts. Primary adjudicators are physicians who have been trained and certified online. Quality control in the use of the CCS is established through a process of centralized physician re-adjudication. As of September 15, 2010, more than 750 cases have been classified by certified physicians across seven US cohorts. The goal is to have genome-wide genotyping on at least 7000 ischemic stroke cases. Hopefully, this second wave of ischemic stroke genome-wide association studies will yield findings as compelling as have been made for IAs. Even as the second wave of genome-wide association studies nears completion, investigators have begun the search for rare variants using new technologies such as exome sequencing.

The stroke clinician can no longer ignore pharmacogenomics in practice. There are now tests approved for clinical use that can identify high from low responders to clopidogrel. Optimal use of genetic testing in this setting has yet to be established, although it may be reasonable to test patients for *CYP2C19* gene variants if they develop atherothrombotic events despite clopidogrel.

As the genetics of stroke risk and response to treatment become clearer, testing ought to be incorporated into phase 3 clinical trials so that they can be properly validated in terms of clinical utility.

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Clinical Trial Acronyms

CHARGE	Cohorts for Heart and Aging Research in Genomic Epidemiology
FIA	Familial Intracranial Aneurysm
GENOA	Genetic Epidemiology Network of Arteriopathy
ISUIA	International Study of Unruptured Aneurysm
TRITON-TIMI 38	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction 38

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Table 1

Loci associated with intracranial aneurysms discovered using genome-wide association

Locus	Proximate gene	Gene name
8q11.23-q12.1	*SOX17*	SRY (sex-determining region Y)-box 17
9p21.3	*CDKN2A-CDKN2B*	Cyclin-dependent kinase inhibitor 2A-2B
10q24.32	NA	NA
13q13.1	*STARD13-KL*	Rho-GAP and C-terminal STAR-related lipid transfer (START) domains
18q11.2	NA	NA

NA not applicable.