

대한뇌졸중학회 2017년 6월 보수교육

The Most Interesting Science Articles of 2017

Risk Factor and Prevention



박광열

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Introduction

AF Genetic Risk

SVD Genetic Risk

Genetic Risk of Recurrent Stroke

Summary

Risk factors for Stroke & Prevention

Non-modifiable factors

1. Age
2. Sex
3. Race
4. Family history
5. **Genetic variability**

Modifiable factors

1. Hypertension
2. Diabetes
3. Dyslipidemia
4. Smoking
5. Carotid disease
6. Cardiac disease such as **atrial fibrillation**
7. Obesity
8. Inactivity

We want something like this in genetics

 ORIGINAL CONTRIBUTION

Association of *BRCA1* and *BRCA2* Mutations With Survival, Chemotherapy Sensitivity, and Gene Mutator Phenotype in Patients With Ovarian Cancer

Da Yang, PhD

Sofia Khan, PhD

Yan Sun, MD, PhD

Kenneth Hess, PhD

Ilya Shmulevich, PhD

Anil K. Sood, MD

Wei Zhang, PhD

Context Attempts to determine the clinical significance of *BRCA1/2* mutations in ovarian cancer have produced conflicting results.

Objective To determine the relationships between *BRCA1/2* deficiency (ie, mutation and promoter hypermethylation) and overall survival (OS), progression-free survival (PFS), chemotherapy response, and whole-exome mutation rate in ovarian cancer.

Design, Setting, and Patients Observational study of multidimensional genomic and clinical data on 316 high-grade serous ovarian cancer cases that were made public between 2009 and 2010 via The Cancer Genome Atlas project.

Main Outcome Measures OS and PFS rates (primary outcomes) and chemotherapy response (secondary outcome).

 INCREASED SURVEILLANCE OF *BRCA1/2*
normal tissue mutation carriers is a norm.

Yang, D., et al. (2011). "Association of *BRCA1* and *BRCA2* mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer." *JAMA* 306(14): 1557-1565.

In the era of precision medicine,



The American College of
Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

patient education **Fact Sheet**

PFS007: BRCA1 and BRCA2 Mutations MARCH 2015

BRCA1 and BRCA2 Mutations

Cancer is a complex disease thought to be caused by several different factors. A few types of cancer run in families. These types, called "hereditary" or "familial" cancer, have been linked to changes in genes that can be passed from parents to children. Changes in genes are called mutations.

Hereditary breast and ovarian cancer syndrome is a type of familial cancer. It most commonly is linked to mutations in two genes called **BRCA1** and **BRCA2**. Inheriting one of these mutations increases the risk of getting breast cancer, ovarian cancer, and other types of cancer. About 10% of cases of ovarian cancer and 3–5% of cases of breast cancer are due to mutations in **BRCA1** and **BRCA2**.

Table 1. Breast Cancer and Ovarian Cancer Risk for Women With **BRCA** Mutations

Type of Cancer	Risk for the General Population	Risk With BRCA1 Mutation	Risk With BRCA2 Mutation
Breast	12%	55–65%	45%
Ovary	1.4%	39%	11–17%

In stroke,

Table 3. Selected Genetic Causes of Stroke

Disease	Mode of Inheritance	Gene/Protein	Mechanism of Stroke	Common Clinical Manifestations
Single gene disorders that primarily cause stroke				
Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy	Autosomal dominant	NOTCH3/GAD1013	Small vessel disease	Ischemic stroke, leukoencephalopathy, migraines, pectoral manifestations, and seizures
Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy	Autosomal dominant	HTSM1/-/HTSA serine peptidase-1	Small vessel disease	Ischemic stroke, leukoencephalopathy, premature baldness, and speech loss
Familial amyloid angiopathy	Autosomal dominant	APOE-amyloid precursor protein	Bursture of small cortical vessels	Lobar hemorrhage, intracysts, leukoencephalopathy, dementia, and aneurysm spills
Collagen 4 (COL4A1) mutations	Autosomal dominant	Col4A1/col4A1 chain of collagen type 4	Bursture of cortical and subcortical vessels	Superficial and deep hemorrhages, intracranial aneurysms, hematuria, and cystic kidney disease
Genetic disorders that include stroke as manifestations				
Ehlers-Danlos type 4	Autosomal dominant	Col3A1/type II procollagen	Arterial dissection	Arteric, mural, splanchnic, iliac dissections; ruptures; aneurysms; abdominal aortic; viscera and muscle dis ruptures; and uterine rupture during pregnancy
Fabry disease	X-linked	GAL- α -galactosidase A	Large and small artery disease	Ischemic stroke and neuroangiopathy, angiokeratomas, corneal opacities and cataracts, neuropathy (lesions in peripheral nerves), and renal failure
Marfan syndrome	Autosomal dominant	FBN1/fibrillin 1	Atrial dissection and cardiac embolism	Ischemic stroke, atrial fibrillation, ectopic, pericarditis, aortic dilatation, valvular dysfunction/heart failure, and ectopia lentis
Mitochondrial encephalopathy with lactic acid and stroke-like episodes	Maternal	Mitochondrial DNA (MT-III) 14484-mutant phenylalanine tRNA _{GAA} 2; others	Energy failure and metabolic stroke	Ischemic stroke that does not observe vascular boundaries, short stature, developmental delay, atrophy, vision loss, hypoglycemia, and diabetes mellitus.
Sickle cell disease	Autosomal recessive	HBB/HBZ-globin (hemoglobin subunit)	Large and small vessel disease and moyamoya syndrome	Ischemic stroke, painful crises, vascular crises, and bacterial infections
Smooth muscle α -actin mutation-associated disorders	Autosomal dominant	ACTA2/smooth muscle α -actin	Moyamoya syndrome	Ischemic stroke, coronary artery disease, thoracic aortic aneurysms, and moyamoya syndrome
Common genetic variants				
TPH2	Common variant	TPH2/tryptophan-2	Vascular development and arteriosclerosis	Large vessel ischemic stroke
PDK2	Common variant	PDK2/ortholog transcription factor	Small vessel disease; smooth muscle cell and pericyte coverage of central vessels	All strokes, small vessel stroke, and pneumonia and edema while water disease
ABO	Common and rare variants	ABO/blood group protein	Theoretical	Thrombosis and ischemic stroke
AGAT	Common and rare variants	AGAT/platelet desmosinase	Abnormalities	Large vessel ischemic stroke
PTG2	Common and rare variants	PTG2	Smooth muscle development and regulation of ion channels; modulation of surface receptors; and atrial fibrillation	Cardioembolic ischemic stroke and atrial fibrillation
ZFAT	Common and rare variants	ZFAT	Atrial fibrillation	Cardioembolic ischemic stroke and atrial fibrillation

Etiologies of stroke are diverse

Ischemic Stroke

- ▶ Atherosclerosis
- ▶ Small artery occlusion
- ▶ Cardiac disease causing embolism
- ▶ Other causes such as moyamoya disease

Hemorrhagic Stroke

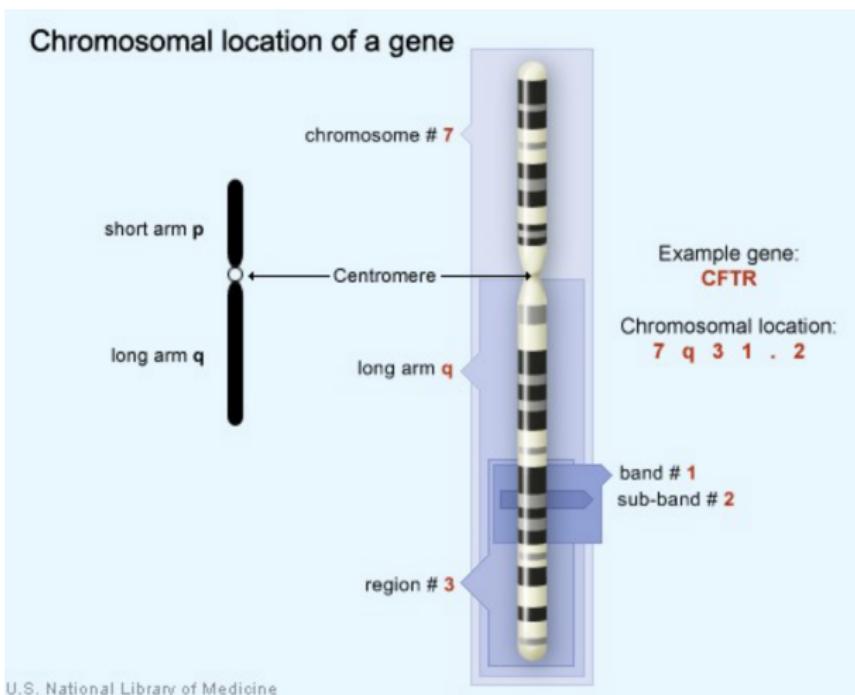
- ▶ Hypertensive hemorrhage
- ▶ Cerebral amyloid angiopathy
- ▶ Arteriovenous malformations
- ▶ Subarachnoid hemorrhage

Titles doesn't look friendly

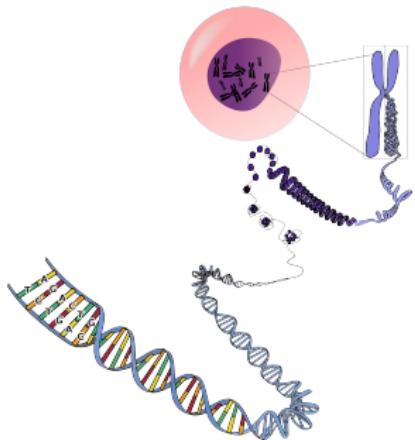
RESEARCH ARTICLE

Genetic Variation at 16q24.2 Is Associated With Small Vessel Stroke

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Location of DNA variation



- Whole chromosomal and whole genome changes: ~1-6 billion bp
 - Aneuploidy (abnormal number of chromosomes)
 - Aneusomy (fewer or more copies than 2 of a chromosome)
 - Interchromosomal translocations
 - Ring chromosomes
- Microscopic to submicroscopic
 - Segmental aneusomy
 - Chromosomal deletions
 - Chromosomal insertions
 - Chromosomal inversions
 - Intrachromosomal translocations
 - Chromosomal abnormality
 - Fragile sites
- 1 kb to submicroscopic
 - Copy number variants (CNVs)
 - Segmental duplications
 - Inversions, translocations
 - CNV regions
 - Microdeletions
 - Microduplications
- 2 bp to 1,000 bp
 - Microsatellites, minisatellites
 - Insertion-deletions (Indels)
 - Inversions
 - Di-, tri-, tetra-nucleotide repeats
 - Variable number tandem repeats e.g. microsatellites
- Single nucleotide 1 bp
 - Indels
 - SNPs

bp indicates base pairs; SNP single nucleotide polymorphisms.

Cytogenetic
changes

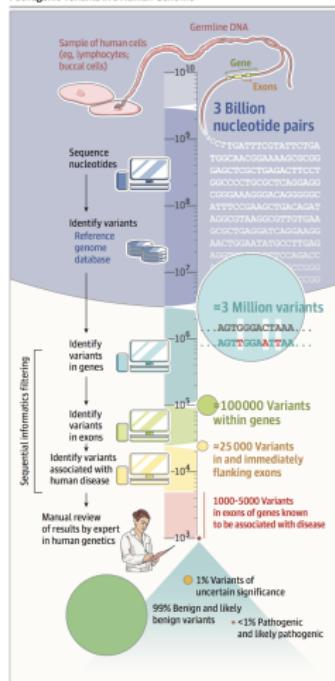


Molecular
genetic
changes



- ▶ Interpretation of information
 - ▶ 3,000,000,000 base pairs
 - ▶ 3,000,000 SNPs
 - ▶ 100,000 variants in exon
- ▶ significance level in GWAS:
 $5 * 10^{-8} = 0.05 * 10^{-6}$
- ▶ rs******(number):
 Reference SNP cluster ID

Figure. Informatic and Human Analysis Required for Finding Rare Pathogenic Variants in a Human Genome

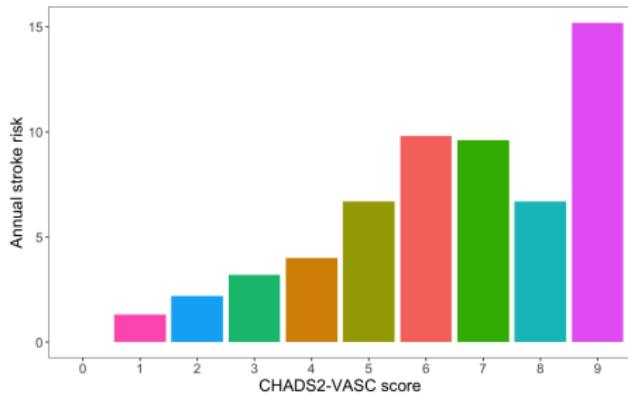


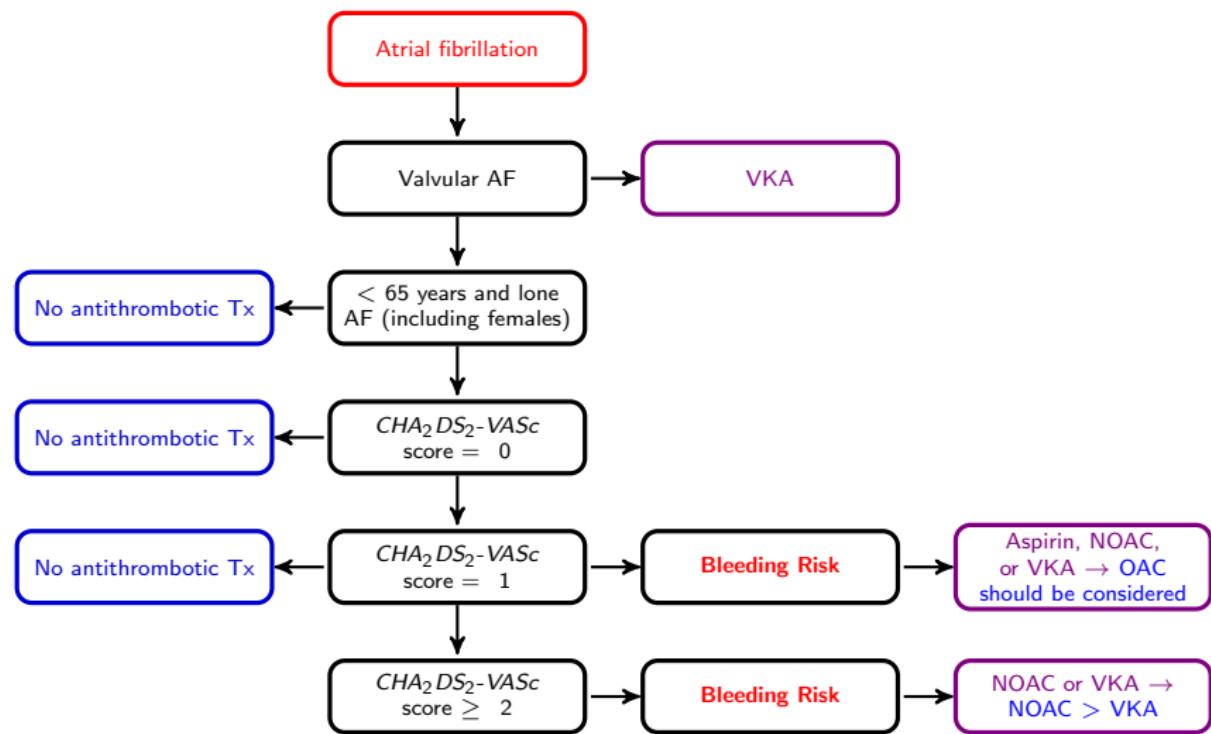
Genetic causes of stroke

- ▶ Specific rare single gene disorder:
 - CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)
 - Sickle cell anemia
- ▶ Common and rare variants of genetic polymorphism:
 - PITX2 (AF)
 - ABO (Thrombosis)

Thromboembolic risk of AF

<i>CHA₂DS₂-VASc</i> criteria	Score
CHF	1
Hypertension	1
Age \geq 75 years	2
Diabetes mellitus	1
Stroke or TIA	2
Vascular disease	1
Age 65-74 years	1
Sex category (female)	1





Frequently,

- ▶ AF is diagnosed after the development of large infarction.
- ▶ AF is asymptomatic.
- ▶ AF is paroxysmal.
- ▶ Stroke mechanism can not be determined in some patients.

Genetic marker of AF can be helpful in these situations.

ORIGINAL RESEARCH ARTICLE

Genetic Risk Prediction of Atrial Fibrillation

ORIGINAL RESEARCH
ARTICLE

Editorial, see p 1321

BACKGROUND: Atrial fibrillation (AF) has a substantial genetic basis. Identification of individuals at greatest AF risk could minimize the incidence of cardioembolic stroke.

METHODS: To determine whether genetic data can stratify risk for development of AF, we examined associations between AF genetic risk scores and incident AF in 5 prospective studies comprising 18 919 individuals of European ancestry. We examined associations between AF genetic risk scores and ischemic stroke in a separate study of 509

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Table 1. Characteristics of Participants Included in Analyses of Incident Atrial Fibrillation

	MDCS	MESA	PREVEND	PROSPER*	BioVU
Total, n	8226	2451	1624	5212	1388
Incident AF, n	190	76	34	503	229
Age, y	59±7	63±10	58±8	75±3	60±11
Women, n (%)	4275 (52)	1321 (52)	770 (47)	2716 (52)	678 (49)
Height, cm	169±9	169±10	172±9	165±9	171±11
Weight, kg	75±14	79±16	80±14	73±13	86±22
Systolic blood pressure, mm Hg	145±20	124±20	135±21	155±22	131±20
Diastolic blood pressure, mm Hg	87±10	75±10	77±10	84±11	75±30
History of smoking, n (%)	2513 (31)	1401 (55)	671 (41)	1388 (27)	619 (45)
Antihypertensive medication, n (%)	1799 (22)	840 (33)	362 (22)	3854 (74)	1339 (96)
History of diabetes mellitus, n (%)	542 (7)	151 (6)	98 (6)	540 (10)	359 (26)
History of heart failure, n (%)	39 (0.5)	NA	4 (0.2)	NA	161 (12)
History of myocardial infarction, n (%)	487 (9)	NA	71 (4)	697 (13)	284 (20)

Data are presented as mean±SD when appropriate. AF indicates atrial fibrillation; BioVU, Vanderbilt University Deidentified DNA Biobank; MDCS, Malmö Diet and Cancer Study; MESA, Multi-Ethnic Study of Atherosclerosis; PREVEND, Prevention of Renal and Vascular Endstage Disease; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk.

*Maximum follow-up in PROSPER was 4 years.

Table 2. Characteristics of Participants of European Ancestry Included in Analyses of Ischemic Stroke From MGH-GASROS (Massachusetts General Hospital Genes Associated With Stroke Risk and Outcomes Study) and Referents

	Cases	Referents
Total, n	509	3028
Age, y	66.9±14.4	42.3±7.8
Women, n (%)	214 (24.2)	732 (42.0)
AF	87 (17)	...

Data are presented as mean±SD when appropriate. AF indicates atrial fibrillation.

Stroke etiologic subtype: cardioembolic (n=202, 39%), large artery (n=114, 22%), small vessel/lacunar (n=62, 12%), other (n=124, 24%), and undetermined (n=7, 1%).

P for comparison of age and sex between cases and referents <0.001.

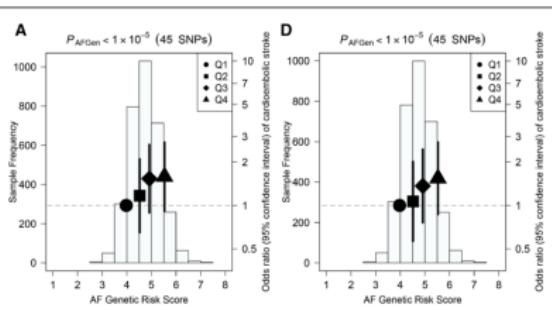


Figure 2. Risk of cardioembolic stroke in MGH-GASROS (Massachusetts General Hospital Genes Associated With Stroke Risk and Outcomes Study) according to atrial fibrillation (AF) genetic risk. Odds ratios for cardioembolic stroke in relation to AF genetic

AF genetic risk was strongly associated with cardioembolic stroke, suggesting that elevated AF genetic risk might serve as a surrogate for thromboembolism from AF.

Atrial Fibrillation Genetic Risk and Ischemic Stroke Mechanisms

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Peter M. Rothwell, MD, PhD; Jonathan Rosand, MD, MSc; Patrick T. Ellinor, MD, PhD;
Hugh S. Markus, DM; Matthew Traylor, PhD;
on behalf of the WTCCC2, International Stroke Genetics Consortium, and AFGen Consortia

Background and Purpose—Atrial fibrillation (AF) is a leading cause of cardioembolic stroke, but the relationship between AF and noncardioembolic stroke subtypes are unclear. Because AF may be unrecognized, and because AF has a substantial genetic basis, we assessed for predisposition to AF across ischemic stroke subtypes.

Methods—We examined associations between AF genetic risk and Trial of Org 10172 in Acute Stroke Treatment stroke subtypes in 2374 ambulatory individuals with ischemic stroke and 5175 without from the Wellcome Trust Case-Control Consortium 2 using logistic regression. We calculated AF genetic risk scores using single-nucleotide polymorphisms associated with AF in a previous independent analysis across a range of preselected significance thresholds.

Results—There were 460 (19.4%) individuals with cardioembolic stroke, 498 (21.0%) with large vessel, 474 (20.0%) with small vessel, and 814 (32.3%) individuals with strokes of undetermined cause. Most AF genetic risk scores were associated with stroke, with the strongest association ($P=6\times 10^{-4}$) attributed to scores of 944 single-nucleotide polymorphisms (each associated with AF at $P<1\times 10^{-3}$ in a previous analysis). Associations between AF genetic risk and stroke were enriched in the cardioembolic stroke subset (strongest $P=1.2\times 10^{-9}$, 944 single-nucleotide polymorphism score). In contrast, AF genetic risk was not significantly associated with noncardioembolic stroke subtypes.

Conclusions—Comprehensive AF genetic risk scores were specific for cardioembolic stroke. Incomplete workups and subtype misclassification may have limited the power to detect associations with strokes of undetermined pathogenesis. Future studies are warranted to determine whether AF genetic risk is a useful biomarker to enhance clinical discrimination of stroke pathogeneses. (*Stroke*. 2017;48:1451-1456. DOI: 10.1161/STROKEAHA.116.016198.)

Table 1. Characteristics of Wellcome Trust Case-Control Consortium 2 Participants Included in the Analysis

	n (%)	Age, y	Men, %	History of AF, n (%)	History of IHD, n (%)	MRI, n (%)	Echocardiogram, n (%)	Extracranial Imaging, n (%)
All ischemic stroke	2374	72.2±12.5	53.8	479 (20.1)	552 (23.3)	881 (37.1)	847 (35.7)	2176 (91.7)
Cardioembolic	460 (19.4)	75.4±12.5	62.1	362 (78.7)	141 (30.7)	113 (24.6)	259 (56.3)	393 (85.4)
Large vessel disease	498 (20.1)	68.2±10.8	66.2	2 (0.4)	136 (27.3)	196 (39.4)	133 (26.7)	487 (98.2)
Small vessel disease	474 (20.0%)	69.6±11.7	52.3	10 (2.1)	76 (16.0)	285 (60.1)	139 (29.1)	455 (96.0)
Unknown	814 (34.3)	70.8±13.8	45.7	26 (3.2)	153 (18.8)	248 (30.5)	248 (30.5)	726 (89.2)
Referents	5175	...	49.5

Data presented as mean±SD or n (%) unless otherwise specified. A further 128 (5.4%) individuals had stroke of tandem pathogenesis and were not included in any subgroup analyses. All patients underwent computed tomographic imaging and an ECG. Extracranial cerebral arterial imaging includes carotid and vertebral artery ultrasound, or computed tomographic angiography, or MRI. AF indicates atrial fibrillation; IHD, ischemic heart disease; and MRI, magnetic resonance imaging.

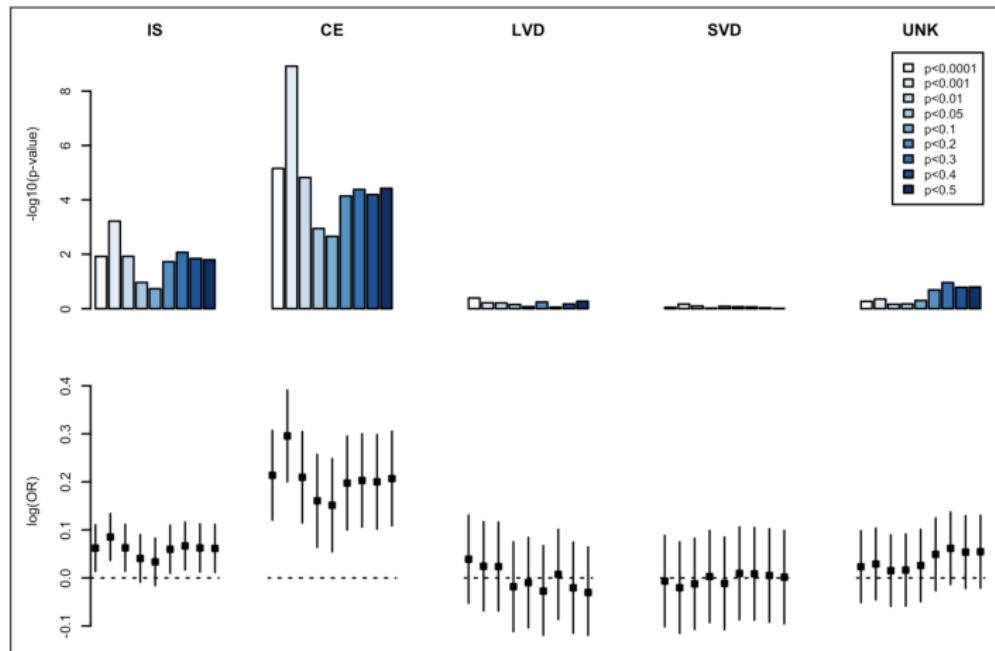
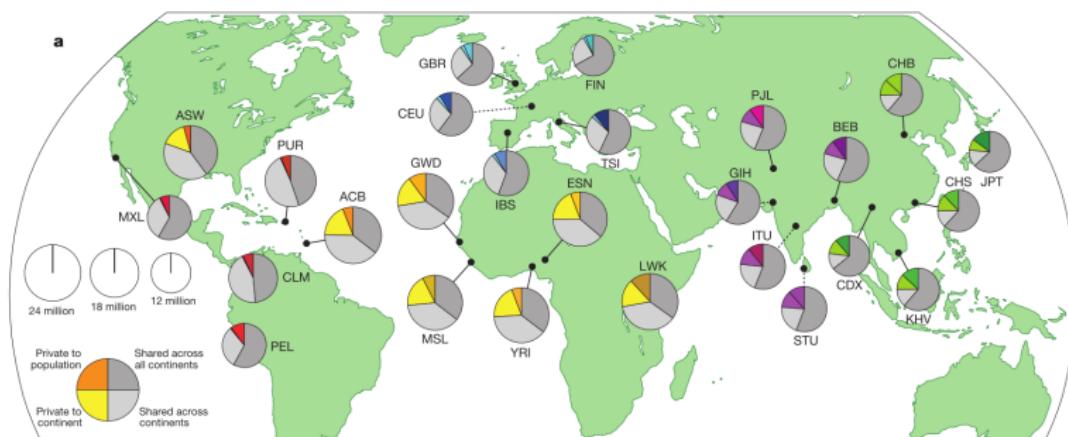


Figure. Association between atrial fibrillation genetic risk and ischemic stroke subtypes. **Top,** The strength of association between genetic risk scores comprised atrial fibrillation genetic markers and ischemic stroke subtypes are displayed. Separate scores were calculated corresponding to differences in the strength of association between each variant and atrial fibrillation in a prior independent analysis.³² **Bottom,** The magnitude of association per 1-U change in each genetic risk score is displayed. CE indicates cardioembolic stroke; IS, all ischemic stroke; LVD, large vessel disease stroke; OR, odds ratio; SVD, small vessel disease stroke; and UNK, stroke of unknown pathogenesis.

A global reference for human genetic variation



RESEARCH ARTICLE

Genetic Variation at 16q24.2 Is Associated With Small Vessel Stroke

Matthew Taylor,¹ Rainer Malik,² Mike A. Nalls,³ Ioana Cotlarciuc,⁴
Farid Radmanesh,^{5,6,7} Gudmar Thorleifsson,⁸ Ken B. Hanscombe,¹
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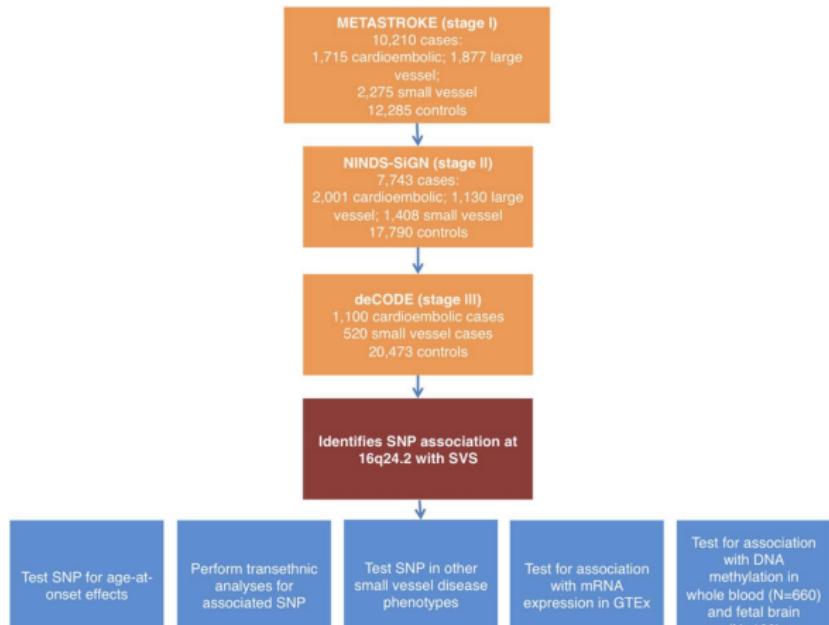


FIGURE 1: Flow chart of analyses performed. GTEx = Genotype-Tissue Expression; mRNA = messenger RNA; SNP = single-nucleotide polymorphism; SVS = small vessel stroke; [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1. Ischemic Stroke Study Participants

Population	IS	CE	LAS	SVS	Controls	% Cases With MRI	Age of Cases (mean (SD))
Stage I populations							
ASGC	1,162	240	421	310	1,244	43.0	72.9 (13.2)
WTCCC2-Germany	1,174	330	346	106	797	83.0	66.7 (12.9)
WTCCC2-UK	2,374	474	498	460	5,175	37.2	72.2 (12.5)
Milano	366	64	73	25	407	86.7	57.4 (15.6)
DNA-lacunar/GENESIS	1,287	80	64	1,012	970	100.0	59.6 (12.0)
LSS	455	157	70	55	455	89.0	67.7 (14.5)
ISGS/SWISS	1,014	235	217	187	1,370	83.0	66.5 (13.6)
BRAINS	361	29	120	97	444	30.8	74.4 (14.2)
MGH-GASROS	294	106	68	23	376	60.0	66.7 (14.5)
VISP	1,723	—	—	—	1,047	47.0	68.0 (10.7)
Total (discovery)	10,210	1,715	1,877	2,275	12,285		
Stage II populations							
NINDS Stroke Genetics Network	7,743	2,001	1,130	1,408	17,970	62.0	66.3 (14.8)
Stage III populations							
deCODE	—	1,100	—	520	20,473	NA	72.7 (11.6)
Total	17,953	4,816	3,007	4,203	50,728		

IS = all ischemic stroke; CE = cardioembolic stroke; LAS = large artery stroke; SVS = small vessel stroke; ASGC = Australian Stroke Genetics Collaborative; WTCCC2 = Wellcome Trust Case Control Consortium 2; LSS = Leuven Stroke Study; BRAINS = Bio-repository of DNA in stroke; MGH-GASROS = The MGH Genes Affecting Stroke Risk and Outcome Study; VISP = The Vitamin Intervention for Stroke Prevention Trial; NA = information not available.

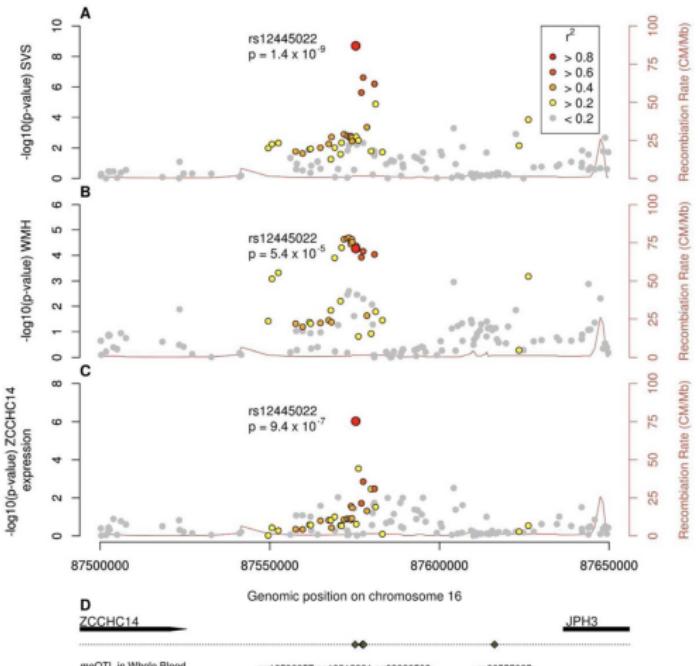


FIGURE 2: Associations at 16q24.2 with (A) small vessel stroke, (B) cerebral white matter hyperintensities, (C) mRNA expression of ZCCHC14, and (D) gene locations and associations of the locus with DNA methylation. mRNA = messenger RNA; SVS = small vessel stroke; WMH = white matter hyperintensities; ZCCHC14 = zinc finger CCHC domain-containing 14; JPH3 = junctophilin 3; meQTL = methylation quantitative trait locus. [Color figure can be viewed at wileyonlinelibrary.com]

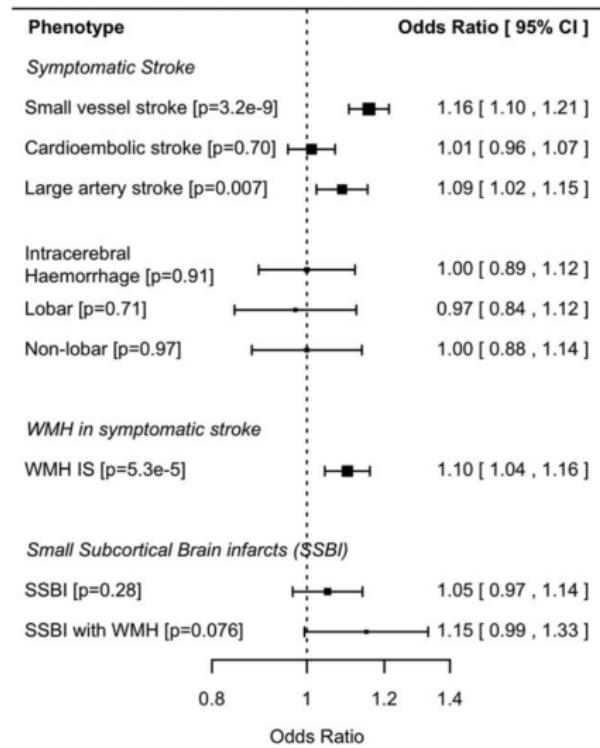


FIGURE 5: Associations with rs12445022 for stroke and

GRECOS Project (Genotyping Recurrence Risk of Stroke)

The Use of Genetics to Predict the Vascular Recurrence After Stroke

Background and Purpose—Vascular recurrence occurs in 11% of patients during the first year after ischemic stroke (IS) or transient ischemic attack. Clinical scores do not predict the whole vascular recurrence risk; therefore, we aimed to find genetic variants associated with recurrence that might improve the clinical predictive models in IS.

Methods—We analyzed 256 polymorphisms from 115 candidate genes in 3 patient cohorts comprising 4482 IS or transient ischemic attack patients. The discovery cohort was prospectively recruited and included 1494 patients, 6.2% of them developed a new IS during the first year of follow-up. Replication analysis was performed in 2988 patients using SN Plex or HumanOmni1-Quad technology. We generated a predictive model using Cox regression (GRECOS score [Genotyping Recurrence Risk of Stroke]) and generated risk groups using a classification tree method.

Results—The analyses revealed that rs1800801 in the *MGP* gene (hazard ratio, 1.33; $P=9\times10^{-03}$), a gene related to artery calcification, was associated with new IS during the first year of follow-up. This polymorphism was replicated in a

Spanish cohort ($n=1.305$); however, it was not significantly associated in a North American cohort ($n=1.683$). The GRECOS score predicted new IS ($P=3.2\times10^{-09}$) and could classify patients, from low risk of stroke recurrence (1.9%) to high risk (12.6%). Moreover, the addition of genetic risk factors to the GRECOS score improves the prediction compared with previous Stroke Prognosis Instrument-II score ($P=0.03$).

Conclusions—The use of genetics could be useful to estimate vascular recurrence risk after IS. Genetic variability in the *MGP* gene was associated with vascular recurrence in the Spanish population. (*Stroke*. 2017;48:1147-1153. DOI: 10.1161/STROKEAHA.116.014322.)

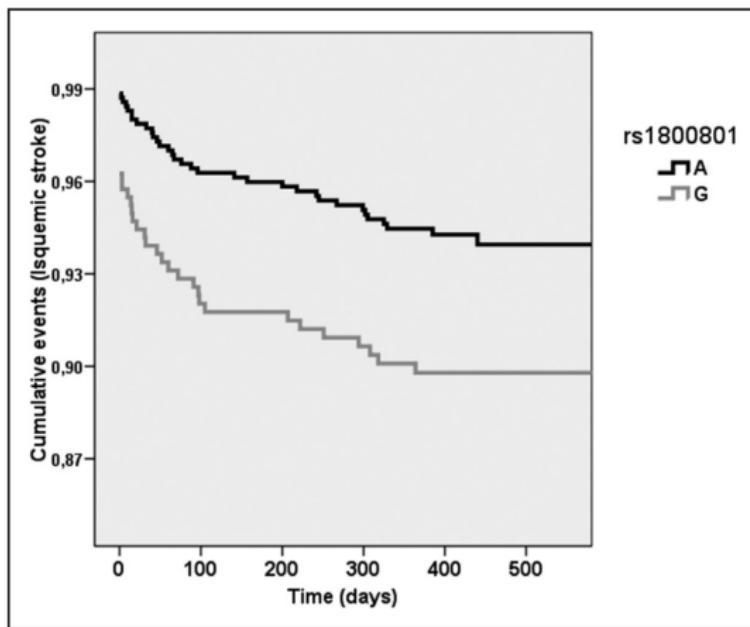


Figure 1. Kaplan-Meier curves of rs1800801 and time of recurrent ischemic stroke event. x axis: time (days) from first stroke or transient ischemic attack to recurrent ischemic stroke, P value=9×10⁻³. y axis: cumulative events (ischemic strokes). Data

Take-Home Message

- ▶ Precision medicine will be our future
- ▶ Genetic variation might be useful in differentiating stroke mechanism and predicting vascular recurrence
- ▶ Specific genetic variation associated with disease might be different among races