Acute Ischemic Stroke in Northeastern/Central Pennsylvania: Prediction Models and Genetic Associations

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Disclosures

- We have no financial relationships with any commercial entities producing health care related products.

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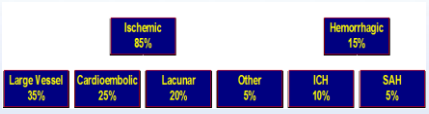
Types of stroke vary in etiology



TOAST classification of ischemic stroke[1]
1) Large-artery atherosclerosis
2) Cardioembolism
3) Small-vessel occlusion (lacunar)
4) Stroke of other determined etiology
5) Stroke of undetermined etiology

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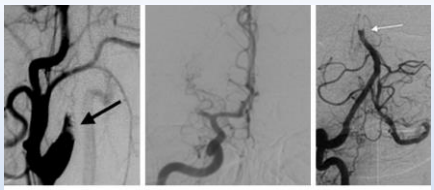
High mortality with Large Vessel Occlusion



ICA ~ 50% | MCA ~ 25% | Basilar artery ~ 90%

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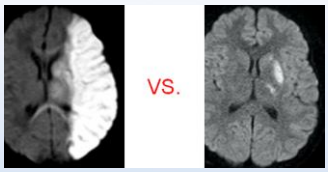
Despite stroke treatments like tPA and mechanical thrombectomy, why are there still bad outcomes in large vessel acute ischemic stroke?



Identical age, gender, co-morbidities, time from onset to revascularization, and success of revascularization

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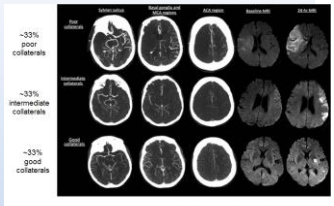
ARTERIAL COLLATERALS!

Liebeskind, Stroke. 2003;34:2279-2284



Liebeskind et al., Stroke 2014; Menon et al., Stroke 2015

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[1]> 20 mm size assoc. incomplete occlusion

[2]> 20 mm size and post. circ. assoc. with M&M

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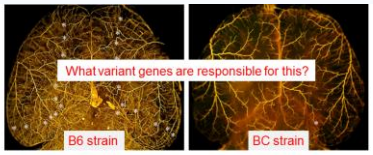
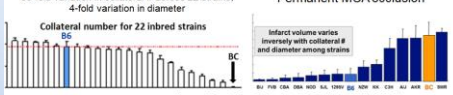
Extent of collaterogenesis varies greatly among mouse strains, and greatly influences infarct volume



30-fold variation in collateral # across 22 strains, 4-fold variation in diameter

Permanent MCA occlusion



Zhang, J Cereb Blood Flow Metab. 2010 May;30(5):923-34.
Wang, Circ Res. 2010 Aug 20;107(4):558-68.; Wang, PLoS One. 2012;7(3):e31910.

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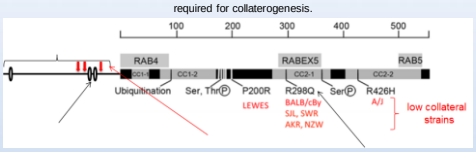
Rab GTPase–Effector Binding Protein-2 (RABEP-2)

Chromosome 7: Determinant of collateral extent-1 (Dce1) locus contains 28 protein-coding genes.
RABEP-2: highest priority candidate of those 28 genes; SNP (rs33080487) substitutes an adenine for a guanine resulting in arginine-to-glutamine (R298Q) substitution and poor collaterals.
Variants of Rabep2 alter collaterogenesis during embryogenesis, but have no effect on angiogenesis.
Rabep2 deficiency altered endosome trafficking known to be involved in VEGF-A→VEGFR2 signaling required for collaterogenesis.



2 consensus hormone response elements in proximal promoter (mouse, human)

3 SNPs linked to DWI-infarct volume and cardioembolic stroke (GASTROS, METASTROKE)

R298 in all high-collateral strains

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How can this impact clinical practice?

Geisinger MyCode is a voluntary, health system-wide exome sequencing program.

Patients enrolled in MyCode can be informed of genetic predisposition that may influence the prognosis of potential stroke/cardiovascular disease.

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Methods

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Geisinger Medical Center

Geisinger Community Medical Center

Geisinger Wyoming Valley Medical Center

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Data collection from Geisinger MyCode

- Reviewed acute ischemic stroke patients retrospectively from 10/2009 and 12/2016
  - All patients participated in the exome sequencing program (MyCode)
  - Initially had 1,728 patients from stroke registry and retained 94.2%.
- Used TOAST guidelines to classify the etiology of the ischemic event.
  - Used radiology studies, TEE, and hypercoagulable tests.
- Extracted risk factors from patient charts that could influence stroke.
- Determined the region of infarction through radiology reports and symptoms.
- Calculate NIH Stroke Scores, ASPECT scores and Modified Rankin Scale.

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Results

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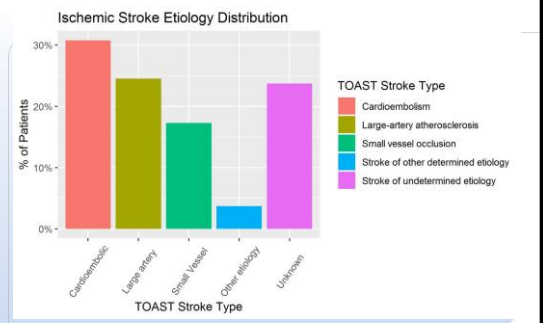

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Cardioembolic stroke is the most common etiology with greatest severity based on NIHSS

NIH Stroke Scale Score	Stroke Severity
0	No stroke symptoms
1-4	Minor stroke
5-15	Moderate stroke
16-20	Moderate to severe stroke
21-42	Severe stroke

TOAST STROKE TYPE	COUNT	PERCENT	NIHSS MEAN	SD NIHSS	MEAN AGE	SD AGE
CARDIOEMBOLISM	501	30.79	5.57	7.13	74.60	13.82
LARGE-ARTERY ATHEROSCLEROSIS	399	24.52	4.92	5.36	70.64	12.42
SMALL VESSEL OCCLUSION	281	17.27	2.93	3.05	70.47	11.63
STROKE OF OTHER DETERMINED ETIOLOGY	60	3.69	4.12	4.99	57.23	15.11
STROKE OF UNDETERMINED ETIOLOGY	386	23.72	4.20	5.39	71.24	13.90
TOTAL	1627					

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Part I: Large Vessel Occlusion (LVO) Prediction Scale

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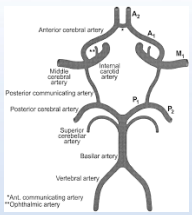
LVO Stroke

Table 1. Sites of large vessel occlusion (N = 362)

Anterior circulation	
Internal carotid artery	112 (30.9%)
Middle cerebral artery	
M1	77 (21.3%)
M2	59 (16.3%)
M3	4 (1.1%)
Anterior cerebral artery	
A1	4 (1.1%)
A2	3 (0.8%)
A3	1 (0.3%)
Posterior circulation	
Vertebral artery	54 (14.9%)
Basilar artery	10 (2.8%)
Posterior cerebral artery	
P1	23 (6.4%)
P2	15 (4.1%)



Patients with LVO stroke (cardioembolic, large-artery atherosclerosis, stroke of other/undetermined etiology) may meet criteria for mechanical thrombectomy.

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Earlier detection of LVO stroke with elements of PMH

- Early identification of LVO stroke is then critical for transferring patients to comprehensive stroke centers for appropriate care.
- Other prediction scales (PASS[3], VAN[4], LAMS[5], RACE[6]) have been produced to detect LVO stroke, but do not consider easily obtainable PMH information.
- Our study found that NIHSS, current smoking status, presence of intracranial atherosclerotic disease and extracranial atherosclerotic disease, as well as Type 2 Diabetes Mellitus (T2DM) are independently associated with anterior circulation LVO stroke.

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History of current smoking, carotid stenosis, intracranial atherosclerosis, and T2DM associated with anterior circulation LVO stroke

	Derivation cohort (n=1026)			Validation cohort (=514)	
	Anterior circulation LVO (n=165)	Ø LVO (n = 861)	OR (95% CI) / p-value	Anterior circulation LVO (n=83)	Ø LVO (n= 431)
Age	67.7 ± 14.0	67.1 ± 13.3	0.582	66.7 ± 14.0	68.2 ± 12.6
Females	91 (55.2%)	441 (51.2%)	1.171 (0.838 – 1.637)	43 (51.8%)	190 (44.1%)
BMI ≥ 25	121 (73.3%)	688 (79.9%)	0.691 (0.471 – 1.014)	64 (77.1%)	342 (79.4%)
Current smoker[&]	50 (33.1%)	196 (22.9%)	1.667 (1.146 – 2.424)	27 (36.0%)	82 (19.2%)
Alcohol consumption[‡]	64 (45.1%)	311 (37.5%)	1.367 (0.954 – 1.957)	22 (29.7%)	138 (34.1%)
Carotid stenosis	100 (60.6%)	292 (33.9%)	2.998 (2.128 – 4.223)	50 (60.2%)	140 (32.5%)
Intracranial atherosclerotic stenosis	73 (44.2%)	222 (25.8%)	2.284 (1.621 – 3.219)	35 (42.2%)	114 (26.5%)
Atrial fibrillation	44 (26.7%)	184 (21.4%)	1.338 (0.914 – 1.960)	19 (22.9%)	98 (22.7%)
Diabetes mellitus type 2	43 (26.1%)	345 (40.1%)	0.527 (0.363 – 0.766)	28 (33.7%)	176 (40.8%)
NIHSS[§]	7.5 (10.0 ± 8.2)	2 (3.8 ± 4.5)	< 0.001	6 (9.0 ± 9.0)	2 (3.3 ± 4.0)
NIHSS[§] ≥ 6	94 (58.5%)	174 (21.2%)	5.288 (3.702 – 7.553)	41 (51.2%)	71 (17.3%)

NIHSS presented with median (mean ± SD). Data missing in derivation and validation cohort: & 19 and 11; ‡ 55 and 35; § 46 and 23 strokes

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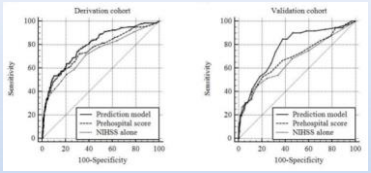
Prediction model more accurately predicts LVO stroke than NIHSS alone

Variable	OR (95% CI)	ß coefficients	Prediction model	Prehospital score
NIHSS (per point)	1.1552 (1.118 – 1.187)	0.141	+1	+1
Current smoker	1.599 (1.044 – 2.449)	0.469	+3	+3
Carotid stenosis	2.558 (1.699 – 3.852)	0.939	+7	N/A
Intracranial atherosclerotic stenosis	1.772 (1.167 – 2.692)	0.572	+4	N/A
Diabetes mellitus type 2	0.438 (0.282 – 0.681)	- 0.824	-6	-6



Prehospital score less accurately predicts LVO stroke than prediction model, but better than/similar to NIHSS alone

Derivation cohort AUC - 0.796 (95% CI 0.769-0.821)

Validation cohort AUC - 0.770 (95% CI 0.729-0.806)

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Example utilizations of the predictive model

The presence of T2DM, absence of extracranial carotid and intracranial atherosclerotic stenosis, and a low NIHSS score in non-smokers yielded a **prediction score of ≤ 5**, resulting in a **negative predictive value of > 95%.**

In contrast, a NIHSS of ≥ 10 in the smoking, non-diabetic stroke patients also suffering from extracranial carotid and intracranial atherosclerotic stenosis yielded a **score of ≥ 24**, resulting in a **positive predictive value of > 87%.**

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Conclusions/Next Steps

- While atherosclerotic disease may not be known until cerebrovascular imaging has been obtained, PMH elements like T2DM and smoking history can be easily obtained.
- T2DM and smoking history are components that can supplement the NIHSS as a pre-hospital score.
- Patients identified with these PHM can be triaged as having LVO stroke earlier, and subsequently assessed for mechanical thrombectomy.
- Further investigation needed to confirm efficacy of the above components in detecting LVO stroke

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Part II

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Matrix Gla protein polymorphism rs1800801 is associated with recurrence of ischemic stroke

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Matrix Gla Protein

- Expressed in a variety of tissues: Heart, lungs, kidneys, skin and arterial vessel walls
- Chondrocytes, vascular smooth muscle cells, endothelial cells, and fibroblasts secrete these cells.
- Function is to inhibit calcification of vascular endothelium and bone.
- In mice, -/- Vitamin K dependent Matrix- Gla protein (GMP) leads to vascular calcifications and ultimately vascular rupture.

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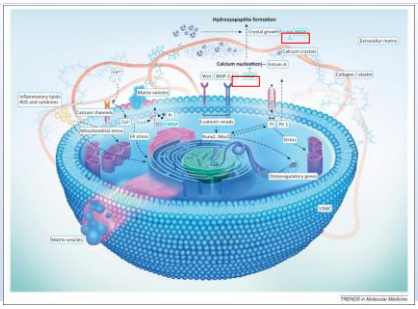
Matrix Gla Protein



Leon J. Schurgers , Jouni Uitto , and Chris P. Reutelingsperger, 2013

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GRECOS Project (Genotyping Recurrence Risk of Stroke): The Use of Genetics to Predict the Vascular Recurrence After Stroke.

Fernández-Cadenas I[1], Mendióroz M[2], Giralt D[2], Nafría C[2], García E[2], Carrera C[2], Gallego-Fabrega C[2], Domingues-Montanari S[2], Delgado P[2], Ribó M[2], Castellanos M[2], Martínez-Sí[2], Freijo M[2], Jiménez-Conde J[2], Rubiera M[2], Alvarez-Sabín J[2], Molina CA[2], Font MA[2], Grau Olivares M[2], Palomeras E[2], Perez de la Ossa N[2], Martínez-Zabaleta M[2], Maisterra O[2], Monicke F[2], Canovas D[2], Piñana C[2], Purroy F[2], Cocho D[2], Navas P[2], Tejero C[2], Aymerich N[2], Quílez N[2], Muiño E[2], Serena J[2], Rubio F[2], Davalos A[2], Roquer J[2], Arenillas JF[2], Martí-Fàbregas J[2], Keene K[2], Chen WM[2], Worrall B[2], Sale M[2], Arboix A[2], Krupinski J[2], Montaner J[2]; GRECOS Study Group.

- MGP SNP rs1800801 is associated with recurrent ischemic stroke within 1 year in a Spanish cohort, not North American.
- “G” allele was the high risk for recurrent ischemic stroke, not the “A” allele.
- GRECOS Score= (1.85 x Age >71) + (2x inclusion TIA) + (3.6 x AMI/ANGINA) + (2.26 x rs1800801(G allele))

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What about the Northeast/Central Pennsylvania region?

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Variables included in the predictive model

Table 1. Patient characteristics

	Recurrent stroke within first year	No recurrent stroke	Statistics OR (95% CI) / p-value
Patients (N)	79/1068 (7.4%)	989/1068 (92.6%)	
Age in years [mean ± SD]	66.9 ± 14.5	68.2 ± 13.2	0.387
Sex			
Female	44/79 (55.7%)	483/989 (48.8%)	1.317 (0.830 – 2.089)
Male	35/79 (44.3%)	506/989 (51.2%)	
TOAST subtypes of stroke			≤ 0.001
Cardioembolism[]	24/79 (30.4%)	313/989 (31.6%)	
Large-artery atherosclerosis	25/79 (31.6%)	222/989 (22.4%)	
Small vessel occlusion	5/79 (6.3%)	168/989 (17.0%)	
Stroke of undetermined etiology	17/79 (21.5%)	263/989 (26.6%)	
Stroke of other determined etiology	8/79 (10.1%)	23/989 (2.3%)	
History of hypertension	67/79 (84.8%)	784/989 (79.3%)	1.460 (0.775 – 2.750)
Diabetes mellitus II	35/79 (44.3%)	392/989 (39.6%)	1.211 (0.783 – 1.923)
Dyslipidemia	64/79 (81.0%)	704/989 (71.2%)	1.727 (0.968 – 3.081)
Smoking status[]			
Current	20/79 (25.3%)	205/967 (21.2%)	1.260 (0.742 – 2.141)
Former	25/79 (31.6%)	390/967 (40.3%)	
Never	34/79 (43.0%)	372/967 (38.5%)	
Alcohol consumption[]	25/79 (31.6%)	344/936 (36.8%)	0.797 (0.487 – 1.304)
BMI ≥ 25	63/79 (79.7%)	786/989 (79.5%)	1.017 (0.575 – 1.798)
Peripheral vascular disease	13/79 (16.5%)	107/989 (10.8%)	1.624 (0.867 – 3.043)
Coronary artery disease	33/79 (41.8%)	301/989 (30.4%)	1.640 (1.028 – 2.616)
Atrial fibrillation	18/79 (22.8%)	223/989 (22.5%)	1.014 (0.587 – 1.751)
Prior stroke	35/79 (44.3%)	75/989 (7.6%)	9.694 (5.865 – 16.022)
Carotid stenosis	28/79 (35.4%)	384/989 (38.8%)	0.865 (0.536 – 1.396)
Intracranial arteriosclerosis	32/79 (40.5%)	333/989 (33.7%)	1.341 (0.840 – 2.142)
Anemia	13/79 (16.5%)	145/989 (14.7%)	1.146 (0.617 – 2.132)
Pro-coagulant coagulation disorder	9/79 (11.4%)	31/989 (3.1%)	3.973 (1.820 – 8.674)
Family history	24/79 (30.4%)	207/989 (20.9%)	1.648 (0.996 – 2.727)

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AA genotype has the highest risk

Table 2. Genotype frequencies of SNP rs1800801

Polymorphism	Genotype	Recurrent stroke	No recurrent stroke	P value
rs1800801	GG (N = 422)	22/422 (5.2%)	400/422 (94.8%)	0.011
	GA (N = 506)	39/506 (7.7%)	467/506 (92.3%)	
	AA (N = 140)	18/140 (12.9%)	122/140 (87.1%)	
	HWE	0.928	0.424	

Linear-by-linear association p = 0.004. HWE = Hardy-Weinberg equilibrium

Subgroup analysis between AA Vs. GA genotypes suggests the AA genotype is at higher risk for recurrent ischemic stroke within 1 year (OR = 2.062, 95% CI 1.013 – 3.937, p = 0.029).

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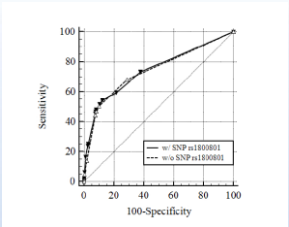
Improved model with Gla SNP, but not significant



With SNP rs1800801: AUC of 0.744 (95% CI 0.717 – 0.770)

Without SNP rs1800801: AUC of 0.740 (95% CI 0.712 – 0.766)

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How do our results compare to others?

- The “A”allele is high risk for recurrence Vs. “G” allele in GRECOS
- GRECOS did not find an association between the Gla SNP and recurrence of ischemic stroke in a North American population.[7]
- AA genotype was associated with increased ischemic atherothrombotic stroke in Ukranian females.[8,9]
- In a meta-analysis by Sheng et al., the A allele in the rs1800801 SNP is associated with vascular calcification and atherosclerotic disease in Caucasians, but not Asians.

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Take home message/Next Steps

- “A” allele in rs1800801 SNP is significantly associated with recurrence of ischemic stroke within 1 year.
- Inclusion of rs1800801 SNP into predictive models for recurrent ischemic stroke within 1 year is marginally beneficial.
- We will need to expand our participant racial demographics to see if the “A” allele is high risk in non-caucasian populations.
- Conduct larger association studies with 100,000+ patients in order to compare multiple SNPs.
  - Our study with 1,700 patients is not large enough to conduct multiple comparisons.

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