

# GENETIC MARKERS ASSOCIATED WITH STROKE IN TWO PATIENT POPULATIONS

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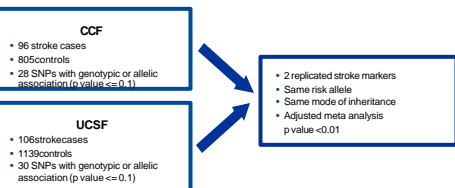
## Introduction

Genetics plays a role in an individual's risk for stroke  
 Few genetic markers for stroke have been replicated  
 The genotypes for 160 missense SNPs selected from 126 candidate genes were analyzed in two populations of patients who had undergone coronary angiography

- 901 patients from Cleveland Clinic Foundation (CCF)
- 1,245 patients from University of California San Francisco (UCSF)

About 10% of these patients had a history of stroke  
 Two SNPs were associated with stroke in both patient populations

## The CCF and the UCSF Studies



## Conclusions

160 missense SNPs from 126 candidate genes were tested for association with stroke in coronary angiography patients  
 Two SNPs were associated with stroke in two populations with the same risk allele and the same mode of inheritance  
 Missense SNPs in Apo A4 and GH1 were each associated with ~1.5 fold risk for stroke among minor allele carriers in two Caucasian angiography patient populations  
 These associations remained significant after adjusting for six major conventional risk factors  
 The high frequencies of the Apo A4 and GH1 SNPs (13% and 42%) and the at risk genotypes (25% and 66%) may account for a significant fraction of stroke risk in the Caucasian populations

### Apo A4 Asn147Ser Minor Allele Carriers vs. Major Allele Homozygotes Unadjusted

Study	OR (95%CI) <sup>1</sup>	p-Value <sup>2</sup>
CCF	1.5 (0.95-2.3)	0.09
UCSF	1.5 (0.96-2.3)	0.08
meta	1.5 (1.1-2.0)	0.01

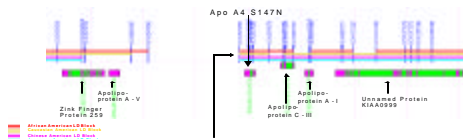
### Adjusted<sup>3</sup>

Study	OR (95%CI) <sup>1</sup>	p-Value <sup>2</sup>
CCF	1.5 (0.94-2.4)	0.09
UCSF	1.6 (1.0-2.5)	0.04
meta	1.5 (1.1-2.1)	0.009

Apo A4 minor allele (the S allele of N147S) is associated with s stroke risk

1. Odds ratio of the minor allele carriers vs major homozygotes
2. P value from logistic regression, not corrected for multiple SNPs tested
3. For sex, age, smoking, diabetes, hypertension, dyslipidemia

### Apo A4 Linkage Disequilibrium Block



Since the Caucasian LD Block with the SNP contains only the Apo A4 gene, Apo A4 may be the causative gene

### Apo A4 Asn147Ser

- Apo A4 is associated with chylomicron and the HDL particles involved in lipid transport and metabolism. It is a potent activator of lecithin-cholesterol acyltransferase in vitro
- May act as a satiety factor regulating food intake (Am J Physiol Gastrointest Liver Physiol. 2004 Jun;286(6):G885)
- The S allele of a different SNP (T347S) was associated with increased coronary disease risk and lower plasma Apo AIV levels in UK patients (Circ Res. 2003 May 16;92(9):969-75)
- Apo A4 polymorphisms associated with stroke have not been reported
- Carriers of the Ser allele had a 1.5 (CI 1.1-2.1) fold higher risk independent of major conventional risk factors (sex, age, smoking, hypertension, diabetes, and dyslipidemia)

### Growth Hormone 1 Ser182Arg Minor Allele Carriers vs. Major Allele Homozygotes Unadjusted

Study	OR (95%CI) <sup>1</sup>	p-Value <sup>2</sup>
CCF	1.9 (1.1-3.1)	0.02
UCSF	1.4 (0.93-2.3)	0.1
meta	1.6 (1.2-2.3)	0.004

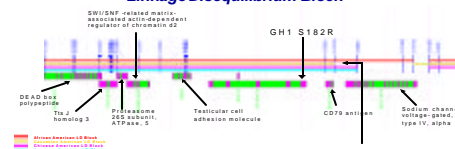
### Adjusted<sup>3</sup>

Study	OR (95%CI) <sup>1</sup>	p-Value <sup>2</sup>
CCF	1.8 (1.1-2.9)	0.03
UCSF	1.5 (0.94-2.3)	0.09
meta	1.6 (1.1-2.2)	0.007

GH1 minor allele (the R allele of S182R) is associated with stroke risk

1. Odds ratio of the minor allele carriers vs major homozygotes
2. P value from logistic regression, not corrected for multiple SNPs tested
3. For sex, age, smoking, diabetes, hypertension, dyslipidemia

### Growth Hormone 1 Linkage Disequilibrium Block



The Caucasian LD Block containing the SNP extends beyond GH1. GH1 may or may not be the causative gene

### Growth Hormone 1 Ser182Arg

- GH regulates growth by stimulating IGF-1 secretion
- Deficiency or excess can result in heart disease (Mayo Clin Proc. 2003 Dec;78(12):1521)
- May be neuronal (Neurosci Lett. 2004 Jan 2;354(1):64) or cardio-protective post-ischemia (J Cardiovasc Pharmacol. 1998 Aug;32(2):260)
- GH polymorphisms associated with stroke have not been reported
- This Ser182Arg SNP has a 42% allele frequency in these populations. The Apptera database suggests that this is a missense SNP.
- Carriers of the Arg allele had a 1.6 (CI 1.1-2.2) fold higher risk independent of conventional risk factors (sex, age, smoking, hypertension, diabetes, and dyslipidemia)

## CCF Patient Characteristics

	Case <sup>1</sup>	Control <sup>1</sup>	P value <sup>2</sup>
Number	96	805	
Age <sup>4</sup>	61.6 (+/-8.7)	61.1 (+/-9.4)	0.62*
Sex (% male)	50 (52.1%)	485 (60.2%)	0.12
Smoking <sup>5</sup>	70 (72.9%)	537 (66.7%)	0.22
Diabetes <sup>5</sup>	32 (33.3%)	234 (29.1%)	0.39
Hypertension <sup>5</sup>	90 (93.8%)	739 (91.9%)	0.53
Hyperlipidemia <sup>5</sup>	76 (81.7%)	613 (77.4%)	0.34
Severe CAD <sup>6</sup>	67.7%	59.4%	0.11
History of MI	60.0%	48.7%	0.82

1. Cases: Caucasian angiography patient, clinically diagnosed stroke
2. Controls: Caucasian angiography patient, reported no stroke history
3. Chi-square test or t-test (\*)
4. Age(+SD) at enrollment
5. Self reported and/or history of medication
6. Severe CAD by angiography

## UCSF Patient Characteristics

	Case <sup>1</sup>	Control <sup>1</sup>	P value <sup>2</sup>
Number	106	1139	
Age <sup>4</sup>	59.7 (+/-9.7)	58.0 (+/-10.2)	0.11*
Sex (% male)	64 (60.4%)	685 (60.1%)	0.96
Smoking <sup>5</sup>	72 (67.9%)	673 (59.1%)	0.08
Diabetes <sup>5</sup>	33 (31.1%)	155 (13.6%)	<0.0001
Hypertension <sup>5</sup>	83 (78.3%)	646 (56.7%)	<0.0001
Hyperlipidemia <sup>5</sup>	85 (80.0%)	904 (79.4%)	0.85
Severe CAD <sup>6</sup>	59.8%	47.6%	0.08*
History of MI	56.8%	41.3%	0.002

1. Cases: Caucasian angiography patient, self reported stroke
2. Controls: Caucasian angiography patient, reported no stroke history
3. Chi-square test, t-test (\*), or Wilcoxon rank sum test (\*\*)
4. Age(+SD) at enrollment
5. Self reported and/or history of medication
6. Percent with CAD severity in top quartile by angiography

## Limitations and Strengths

- Limitations:
  - Cases include all stroke subtypes
  - The numbers of cases were small
  - The p values were not corrected for multiple testing
- Strengths:
  - These genetic associations with stroke were replicated
  - These associations were independent of conventional risk factors