

# Polymorphisms in Matrix Metalloproteinase-3 and -9 Genes and Risk of Stroke in Young Women

Helen Kim, M.P.H.

University of Washington



*CHRU*

Cardiovascular Health Research Unit

# Matrix Metalloproteinases (MMPs)

- Family of  $Zn^{2+}$ -dependent enzymes
- Extracellular matrix (ECM) remodeling
- Activity regulated through transcription, activation, and inhibition
- Associated with atherothrombotic diseases
- Instability of blood vessel wall

# Polymorphisms in Promoter Region of MMP genes

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Gene	Polymorphism
MMP-3 (Stromelysin)	-1612 del/ins (5A/6A)
MMP-9 (Gelatinase B)	-90 microsatellite (CA) <sub>n</sub>

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# Purpose of Study

- To obtain estimates of the association of MMP-3 and MMP-9 gene polymorphisms with ischemic and hemorrhagic stroke in young women

# Study Methods

- Population-based case-control study
- Women aged 18-44 years
- Residents of King, Snohomish, Pierce Counties between 1991-1995
- No prior history of cerebrovascular or cardiovascular disease

# Study Subjects

- Cases were women discharged from hospitals with diagnosis of first nonfatal ischemic or hemorrhagic stroke
  - 42 ischemic, 55 hemorrhagic
- Controls were women identified from the community using RDD
  - frequency matched on age distribution
  - 248 controls

## MMP-3 5A/6A Genotype and Allele Frequencies in Young Caucasian Women

MMP-3 5A/6A Polymorphism	Ischemic n=37	Hemorrhagic n=43	Controls n=224
<b>Genotype</b>			
5A/5A	0.27	0.26	0.24
5A/6A	0.51	0.37	0.58
6A/6A	0.22	0.37	0.18
<b>Allele</b>			
5A	0.53	0.44	0.53
6A	0.47	0.56	0.47

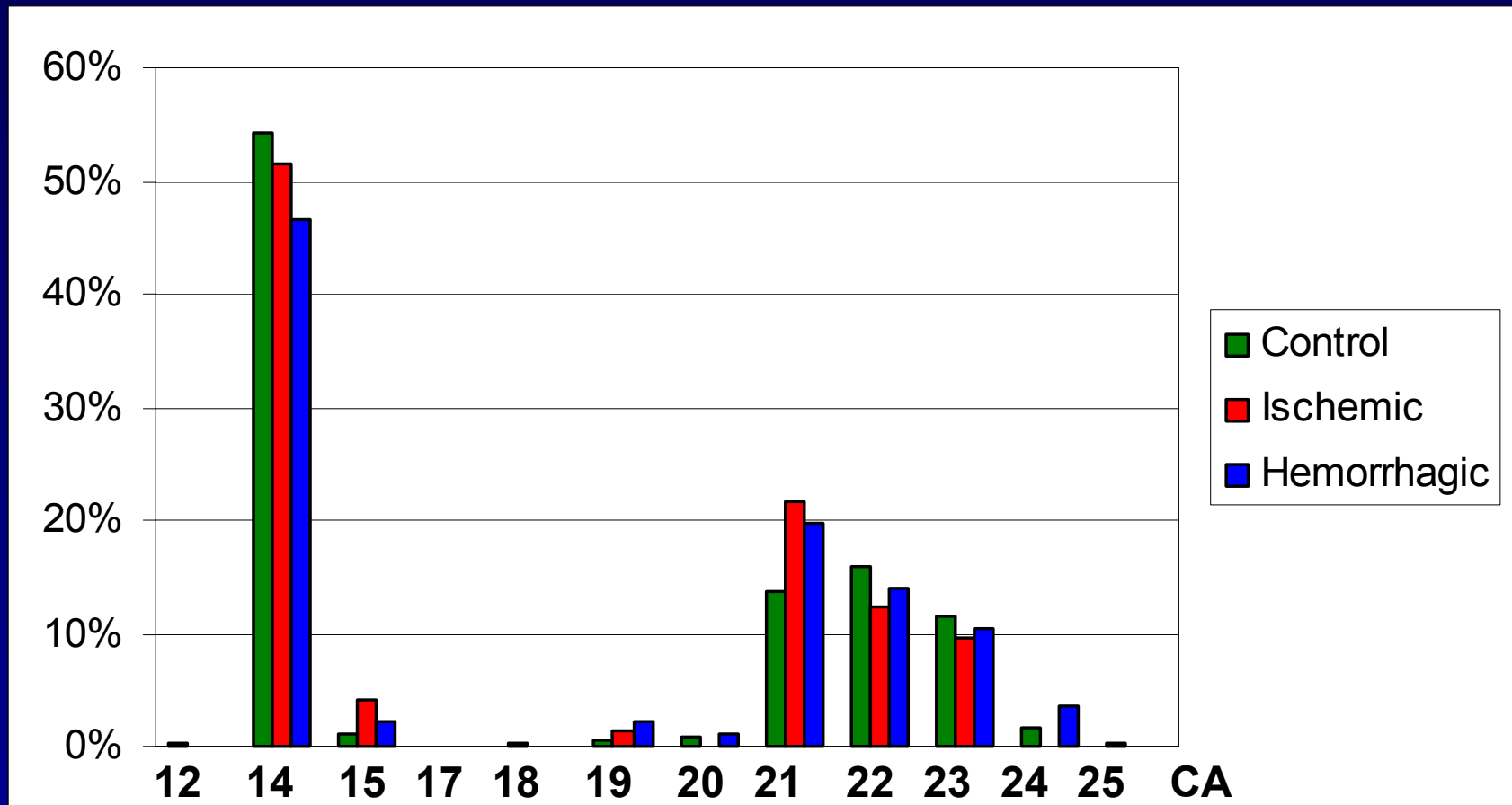
HWE Test (controls): Exact  $p = 0.0232$

## MMP-3 5A/6A Polymorphism and Risk of Ischemic and Hemorrhagic Stroke in Young Caucasian Women

Model	MMP-3 Genotype	Odds Ratio <sup>†</sup> (95% C.I.)	
		Ischemic Stroke	Hemorrhagic Stroke
Codominant	6A/6A	1.0	1.0
	6A/5A	0.75 (0.3 - 1.9)	0.31 (0.1 - 0.7)
	5A/5A	0.93 (0.3 - 2.6)	0.55 (0.2 - 1.3)
Dominant	Any 5A	0.80 (0.3 - 1.9)	0.38 (0.2 - 0.8)
Recessive	5A/5A	1.15 (0.5 - 2.5)	1.16 (0.5 - 2.5)

<sup>†</sup> Adjusted for age

# Frequency distribution of MMP-9 CA repeat polymorphism



HWE Test (controls): Exact  $p = 0.034$

## MMP-9 CA repeat and Risk of Ischemic and Hemorrhagic Stroke in Young Caucasian Women

CA repeat	Ischemic	Hemorrhagic
	OR <sup>†</sup> (95% CI)	OR <sup>†</sup> (95% CI)
14	0.68 (0.30-1.56)	0.61 (0.29-1.31)
21	1.95 (0.93-4.06)	1.62 (0.80-3.28)
22	0.81 (0.36-1.81)	0.82 (0.38-1.73)
23	0.70 (0.27-1.76)	0.64 (0.26-1.54)

<sup>†</sup>Adjusted for age

# Limitations

- Small sample size
- H-W disequilibrium in controls
- Inadequate power to evaluate interactions

# Conclusions

- MMP-3 and MMP-9 appear to be associated with stroke type in young Caucasian women
  - MMP-3 5A allele may be associated with reduced risk of stroke
  - MMP-9 CA(21) allele may be associated with increased risk of stroke

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