Current Thinking of Moyamoya Disease

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Department of Neurology & Neurotherapeutics
University of Texas Southwestern Medical Center
Disclosure

• None
Outline

• Epidemiology
• Pathology & Etiology
• Natural History
• Treatment
Epidemiology

• Regional difference
  – Incidence higher in Asia than North America
  – ICH in adults higher in Asia (21-50%) than North America (10%)

• Cases increasing world wide
Prevalence and Clinicoepidemiological Features of Moyamoya Disease in Japan
Findings From a Nationwide Epidemiological Survey

Shinichi Kuriyama, MD, PhD; Yasuko Kusaka, MD, PhD; Miki Fujimura, MD, PhD; Kenji Wakai, MD, PhD; Akiko Tamakoshi, MD, PhD; Shuji Hashimoto, PhD; Ichiro Tsuji, MD, PhD; Yutaka Inaba, MD, PhD; Takashi Yoshimoto, MD, PhD

(Stroke. 2008;39:42-47.)

- 3900 cases in 1994
- 7700 cases in 2003

An epidemiological survey of moyamoya disease, unilateral moyamoya disease and quasi-moyamoya disease in Japan

Kentaro Hayashi*, Nobutaka Horie, Kazuhiko Suyama, Izumi Nagata

Department of Neurosurgery, Nagasaki University School of Medicine, Japan


- 7511 cases in 2005
- Substantial increase within decade
Incidence, Prevalence, and Survival of Moyamoya Disease in Korea
A Nationwide, Population-Based Study

Il Min Ahn; Dong-Hyuk Park, MD, PhD; Hoo Jae Hann, MD, PhD; Kyoung Hoon Kim, MPH, PhD; Hyun Jung Kim, MPH, PhD; Hyeong Sik Ahn, MD, PhD

• Higher than previous studies
  – Total 8154 cases in 2011
  – Incidence: 1.7 to 2.3/10^5 from 2007 to 2011

(Stroke. 2014;45:1090-1095.)
Epidemiological and clinical features of moyamoya disease in the USA

Kainth D, Chaudhry SA, Kainth H, Suri FK, Qureshi AI
Zeenat Qureshi Stroke Research Center, Departments of Neurology, Neurosurgery, and Radiology, University of Minnesota, Minneapolis, MN, USA

- Nationwide inpatient sample between 2005 and 2008 in the USA, using ICD-9 codes for MMD
  - There were an estimated 7,473 patients admitted with a primary or secondary diagnosis of MMD.
  - The number has risen dramatically in the last decade.
Outline

• Epidemiology
• **Pathology** & Etiology
• Natural History
• Treatment
Pathology
Outline

• Epidemiology

• Pathology & Etiology
  – Genetics
  – Multifactorial and heterogeneity:
    • Autoimmune
    • Atherosclerotic disease
    • Others

• Natural History

• Treatment
Genetics

• Chromosomes regions:
  – 3p24.2-p26
  – 6q25
  – 8q23
  – 12p12
  – 17q25

• ACTA2: on 10q23.3

• RNF213: on 17q25
Mutations in Smooth Muscle Alpha-Actin (*ACTA2*) Cause Coronary Artery Disease, Stroke, and Moyamoya Disease, Along with Thoracic Aortic Disease

Dong-Chuan Guo,1,10 Christina L. Papke,1,10 Van Tran-Fadulu,1 Ellen S. Regalado,1 Nili Avidan,1 Ralph Jay Johnson,1 Dong H. Kim,1 Hariyadarshi Pannu,1 Marcia C. Willing,2 Elizabeth Sparks,3 Reed E. Pyeritz,4 Michael N. Singh,5 Ronald L. Dalman,6 James C. Grotta,1 Ali J. Marian,1,7 Eric A. Boerwinkle,1,7 Lorraine Q. Frazier,1 Scott A. LeMaire,7,8 Joseph S. Coselli,7,8 Anthony L. Estrera,1 Hazim J. Safi,1 Sudha Veeraraghavan,1 Donna M. Muzny,8 David A. Wheeler,8 James T. Willerson,7 Robert K. Yu,9 Sanjay S. Shete,9 Steven E. Scherer,8 C.S. Raman,1 L. Maximilian Buja,1 and Dianna M. Milewicz1.

- **ACTA2**: encodes vascular SMC-specific isoform of alpha-actin
- **Diffuse and diverse vascular disease**
A novel distinctive cerebrovascular phenotype is associated with heterozygous Arg179 ACTA2 mutations

- Global SMC dysfunction
- Widespread arteriopathy
- Absence of typical moyamoya collateral vessels
**ACTA2 is not a major disease-causing gene for moyamoya disease**

Keiko Shimojima and Toshiyuki Yamamoto

International Research and Educational Institute for Integrated Medical Sciences (IREIIMS), Tokyo Women’s Medical University, Tokyo, Japan

- In 53 Japanese MMD patients (7 had familial MMD), no mutations were found in all coding ACTA2 exons.
55 patients with MMD, genomic sequencing did not find any mutation in all nine exons and exon-intron boundaries of ACTA2 gene.
Analysis of ACTA2 in European Moyamoya disease patients

Constantin Roder\textsuperscript{a}, Vera Peters\textsuperscript{a}, Hidetoshi Kasuya\textsuperscript{b}, Tsutomu Nishizawa\textsuperscript{c}, Sho Wakita\textsuperscript{c}, Daniela Berg\textsuperscript{d,e}, Claudia Schulte\textsuperscript{e}, Nadia Khan\textsuperscript{f}, Marcos Tatagiba\textsuperscript{a}, Boris Krischek\textsuperscript{a,*}

\textsuperscript{a}Department of Neurosurgery, University of Tübingen, Hoppe-Seyler-Str. 3. 72076 Tübingen, Germany
\textsuperscript{b}Division of Neurosurgery, Medical Center East, Tokyo Women’s Medical University, Tokyo, Japan
\textsuperscript{c}International Research and Educational Institute for Integrated Medical Sciences, Tokyo Women’s Medical University, Tokyo, Japan
\textsuperscript{d}Center of Neurology, Department of Neurodegeneration, University of Tübingen, Tübingen, Germany
\textsuperscript{e}The Hertie-Institute for Clinical Brain Research, Department of Neurodegeneration and German Center for Neurodegenerative Diseases, University of Tübingen, Tübingen, Germany
\textsuperscript{f}Department of Neurosurgery and Stanford Stroke Center, Stanford University School of Medicine, Stanford, CA, USA

- 39 patients with non-familial MMD
- One new mutation (R179H, heterozygous) in exon 6 of ACTA2 in MMD.
- No previously described mutations or significant sequence variations were identified.
Linkage of Familial Moyamoya Disease (Spontaneous Occlusion of the Circle of Willis) to Chromosome 17q25

Tohru Yamauchi, MD; Mitsuhiro Tada, MD; Kiyohiro Houkin, MD; Toshihiro Tanaka, MD; Yusuke Nakamura, MD; Satoshi Kuroda, MD; Hiroshi Abe, MD; Takuya Inoue, MD; Kiyonobu Ikezaki, MD; Toshio Matsushima, MD; Masashi Fukui, MD

(Stroke. 2000;31:930-935.)

Autosomal dominant moyamoya disease maps to chromosome 17q25.3


Neurology® 2008;70:2357-2363
A genome-wide association study identifies **RNF213** as the first Moyamoya disease gene

Fumiaki Kamada¹, Yoko Aoki¹, Ayumi Narisawa¹-², Yu Abe¹, Shoko Komatsuzaki¹, Atsuo Kikuchi³, Junko Kanno¹, Tetsuya Niihori¹, Masao Ono⁴, Naoto Ishii⁵, Yuji Owada⁶, Miki Fujimura², Yoichi Mashimo⁷, Yoichi Suzuki⁷, Akira Hata⁷, Shigeru Tsuchiya³, Teiji Tominaga², Yoichi Matsubara¹ and Shigeo Kure¹,³

- RNF213 on 17q25: Ring finger protein with AAA ATPase domain.
- Mutation: c.14576G>A (p.R4859K)
  - 19 of the 20 familial MMD (95%)
  - 46 of 63 non-familial MMD cases (73%)
- Greatly increases the risk of MMD
  - OD 190.8, 95% CI 71.7–507.9

Etiology: RNF213
Homozygous c.14576G>A variant of \textit{RNF213} predicts early-onset and severe form of moyamoya disease.

- In 204 MMD, c.14576G>A mutation was identified in 95.1% of familial MMD, 79.2% of sporadic MMD
- OD 259, \( p < 0.001 \)
- Homozygous c.14576GA in 15 patients
**RNF213 Rare Variants in an Ethnically Diverse Population With Moyamoya Disease**

Alana C. Cecchi, MS, CGC; Dongchuan Guo, PhD; Zhao Ren, BS; Kelly Flynn, BS; Regie Lyn P. Santos-Cortez, MD, PhD; Suzanne M. Leal, PhD; Gao T. Wang, BS; Ellen S. Regalado, MS, CGC; Gary K. Steinberg, MD, PhD; Jay Shendure, MD, PhD; Michael J. Bamshad, MD; University of Washington Center for Mendelian Genomics; James C. Grotta, MD; Deborah A. Nickerson, PhD; Hariyadarshi Pannu, PhD; Dianna M. Milewicz, MD, PhD

- **RNF213 p.R4810K was sequenced in 110 MMD**
  - 56% (9/16) of MMD of Asian descent
  - Not in 94 non-Asian decent (82 European American)
- **Whole exome was sequenced in 24 MMD**
  - 7 additional variants were identified in 7 (29%) MMD
  - 2 variants were associated with MMD

*Stroke. 2014;45:3200-3207.*
# Brief Report

**Moyamoya Disease in a Primarily White, Midwestern US Population**

**Increased Prevalence of Autoimmune Disease**

Regina S. Bower, MD; Grant W. Mallory, MD; Macaulay Nwojo, BS; Yogish C. Kudva, MD; Kelly D. Flemming, MD; Fredric B. Meyer, MD

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Number of Patients (%)</th>
<th>Prevalence in general US population, %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia</td>
<td>26 (27.7)</td>
<td>16.3&lt;sup&gt;12&lt;/sup&gt;</td>
<td>0.003</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (20.2)</td>
<td>24.7&lt;sup&gt;13&lt;/sup&gt;</td>
<td>0.38</td>
</tr>
<tr>
<td>Current or previous tobacco use</td>
<td>12 (12.8)</td>
<td>19.3&lt;sup&gt;13&lt;/sup&gt;</td>
<td>0.13</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>6 (6.4)</td>
<td>7.9&lt;sup&gt;11&lt;/sup&gt;</td>
<td>0.74</td>
</tr>
<tr>
<td>Autoimmune disease of any kind</td>
<td>21 (22.3)</td>
<td>3.2&lt;sup&gt;14&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>8 (8.5)</td>
<td>0.4&lt;sup&gt;11&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graves disease (hyperthyroid)</td>
<td>2 (2.1)</td>
<td>0.43*</td>
<td>0.01</td>
</tr>
<tr>
<td>Hashimoto thyroiditis (hypothyroid)</td>
<td>14 (14.9)</td>
<td>7.6*</td>
<td>0.007</td>
</tr>
</tbody>
</table>

94 MMD, 85% white

Etiology: Intracranial atherosclerotic disease
Etiology: Intracranial atherosclerotic disease
Etiology: Intracranial atherosclerotic disease

Intracranial atherosclerotic disease associated with moyamoya collateral formation: histopathological findings

Case report

Thomas Jiang, M.D.,¹ Arie Perry, M.D.,² Ralph G. Dacey Jr., M.D.,³ Gregory J. Zipfel, M.D.,³,⁴ and Colin P. Derdeyn, M.D.¹,³,⁴

Outline

• Epidemiology
• Pathology & Etiology
  – Genetics
  – Multifactorial and heterogeneity:
    • Autoimmune
    • Atherosclerotic disease
    • Others
• Natural History
• Treatment
21 white patients, all had ischemic infarct

- Risk of recurrent stroke
  - Highest in first 2 years
  - Medical treatment: 80% in the first year
  - Surgical treatment: 45% in the first year

*(Stroke. 2008;39:3193-3200.)*
Clinical Features and Outcome in North American Adults With Moyamoya Phenomenon

Christopher L. Hallemeier, BA; Keith M. Rich, MD; Robert L. Grubb, Jr, MD; Michael R. Chicoine, MD; Christopher J. Moran, MD; DeWitte T. Cross III, MD; Gregory J. Zipfel, MD; Ralph G. Dacey, Jr, MD; Colin P. Derdeyn, MD

- 34 patients
  - 24 ischemic
  - 7 hemorrhagic
  - 3 asymptomatic
- 14 patients had surgery
- 5-year risk of recurrent stroke
  - 65% (82% if bilateral involvement) in medical treatment
  - 17% in surgical treatment

(Stroke. 2006;37:1490-1496.)
Natural History: Asymptomatic MMD

Radiological Findings, Clinical Course, and Outcome in Asymptomatic Moyamoya Disease
Results of Multicenter Survey in Japan

Satoshi Kuroda, MD; Nobuo Hashimoto, MD, PhD; Takashi Yoshimoto, MD, PhD; Yoshinobu Iwasaki, MD, PhD; for the Research Committee on Moyamoya Disease in Japan

- 34 medical treatment: annual stroke risk 3.2%
  - 3 TIA
  - 1 ischemic stroke
  - 3 hemorrhagic stroke
- 6 surgical treatment: none
- Outcome: good
  - mRS of 0 (n38)
  - mRS of 1 (n1, ischemic stroke)
  - mRS of 4 (n1, intracranial bleeding)

(Stroke. 2007;38:1430-1435.)
Asymptomatic MMD may progress, annual risk of stroke 0-3.4%
Disturbed hemodynamics was linked to ischemic episodes.

*TABLE 2. Relationship Between Cerebral Hemodynamics at Initial Diagnosis and Cerebrovascular Events During Follow-Up Periods in Patients Who Were Medically Treated*

<table>
<thead>
<tr>
<th>Cerebrovascular Event</th>
<th>None</th>
<th>TIA/Infarct</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>36</td>
<td>2*</td>
<td>1</td>
</tr>
<tr>
<td>Moderate ischemia</td>
<td>15</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Severe ischemia</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Not examined</td>
<td>6</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*Cerebrovascular events were closely related to disease progression during follow-up periods.*
Asymptomatic microbleeds in moyamoya disease: $T_2^*$-weighted gradient-echo magnetic resonance imaging study

**Ken-ichiro Kikuta, M.D., Ph.D., Yasushi Takagi, M.D., Ph.D., Kazuhiko Nozaki, M.D., Ph.D., Takashi Hanakawa, M.D., Ph.D., Tsutomu Okada, M.D., Nobuhro Mikuni, M.D., Ph.D., Yukio Miki, M.D., Ph.D., Yasutaka Fushimi, M.D., Akira Yamamoto, M.D., Keisuke Yamada, M.D., Ph.D., Hidenao Fukuyama, M.D., Ph.D., and Nobuo Hashimoto, M.D., Ph.D.**

- 25 patients
- MMD with ischemia (18): 8 (44%)
- MMD with Hemorrhage (7): 3 (43%)
Natural History: Asymptomatic microbleeds

Incidence, Locations, and Longitudinal Course of Silent Microbleeds in Moyamoya Disease
A Prospective T2*-Weighted MRI Study

Satoshi Kuroda, MD, PhD; Daina Kashiwazaki, MD; Tatsuya Ishikawa, MD, PhD;
Naoki Nakayama, MD, PhD; Kiyohiro Houkin, MD, PhD

- Annual risk of hemorrhagic stroke in adult MMD
  - 1.7%
  - 6.6% with silent MB

(Stroke. 2013;44:516-518.)
Outline

• Epidemiology
• Pathology & Etiology
  – Genetics
  – Multifactorial and heterogeneity:
    • Autoimmune
    • Atherosclerotic disease
    • Others
• Natural History
• Treatment
No treatment may halt progression of the disease or even reverse the intracranial arteriopathy

- Surgery
- Endovascular treatment
- Medical treatment

There are strong indications that neurosurgical intervention can reduce the risk of ischemic stroke, although randomized clinical trials have not been performed.

Neurosurgical intervention (direct bypass) may reduce the risk of hemorrhagic stroke
Surgical revasculization

- Direct revascularization
  - Superficial temporal to middle cerebral artery bypass (STA-MCA)
- Indirect bypass
  - Encephaloduroarteriosynangiosis (EDAS)
  - Encephalo-duro-arterio-myo-synangiosis (EDAMS)
  - Pial synangiosis
- Combined procedures (combination of direct and indirect procedures)
Effects of Extracranial–Intracranial Bypass for Patients With Hemorrhagic Moyamoya Disease
Results of the Japan Adult Moyamoya Trial

Susumu Miyamoto, MD, PhD; Takashi Yoshimoto, MD, PhD; Nobuo Hashimoto, MD, PhD; Yasushi Okada, MD, PhD; Ichiro Tsuji, MD, PhD; Teiji Tominaga, MD, PhD; Jyoji Nakagawara, MD; Jun C. Takahashi, MD, PhD; on behalf of the JAM Trial Investigators

Table 4. Details of Outcomes and Cox Regression Analysis

<table>
<thead>
<tr>
<th></th>
<th>Surgical Group (n=42)</th>
<th>Nonsurgical Group (n=38)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Rate, %</td>
<td>n</td>
<td>Rate, %</td>
</tr>
<tr>
<td>Primary end point</td>
<td>6</td>
<td>14.3</td>
<td>13</td>
<td>34.2</td>
</tr>
<tr>
<td>Recurrent bleeding</td>
<td>5</td>
<td>11.9</td>
<td>12</td>
<td>31.6</td>
</tr>
<tr>
<td>Completed stroke</td>
<td>1</td>
<td>2.4</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Crescendo TIA (bypass required)</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>2.6</td>
</tr>
<tr>
<td>Secondary end point (recurrent bleeding or related death/severe disability)</td>
<td>5</td>
<td>11.9</td>
<td>12</td>
<td>31.6</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and TIA transient ischemic attack.

(Stroke. 2014;45:1415-1421.)
Endovascular treatment of symptomatic moyamoya

Bradley A. Gross • Ajith J. Thomas • Kai U. Frerichs

- 17 patients (6 MMD, 11 MMS)
- 28 procedures (11 stenting, 17 angioplasty)
- High complication and recurrence rates
  - Peri-procedure complications
    - Devastating ICH: 2 (7%)
    - Unsuccessful: 3 (11%)
  - Follow up 7 months
    - Angiographic recurrence: 16 (70%)
    - Clinical symptoms recurrence: 13 (57%)
    - Surgical revascularization needed: 8/15 (53%)
Intracranial Stenting Using a Drug-Eluting Stent for Moyamoya Disease Involving Supraclinoid Internal Carotid Artery: A Case Report

Tackeun KIM,¹ O-Ki KWON,¹ Chang Wan OH,¹ Jae Seung BANG,¹ Gyojun HWANG,¹ and Young-Jin LEE¹
Endovascular Treatment: rule out MMD from true ICAD
Endovascular Treatment: rule out MMD from true ICAD

High-Resolution Magnetic Resonance Wall Imaging Findings of Moyamoya Disease

Sookyung Ryoo, MD; Jihoon Cha, MD; Suk Jae Kim, MD; Jin Wook Choi, MD; Chang-Seok Ki, MD; Keon Ha Kim, MD; Pyoung Jeon, MD; Jong-Soo Kim, MD; Seung-Chyul Hong, MD; Oh Young Bang, MD, PhD

(Stroke. 2014;45:2457-2460.)
Moyamoya Disease Biomarker in Patients With Intracranial Atherosclerotic Stroke

- To investigate the proportion of patients with Moyamoya disease among the patients who were diagnosed as having intracranial atherosclerotic stroke
- Biomarker
  - Gene (RNF213)
  - HR-MRI to image vessel wall pathology

Endovascular Treatment: rule out MMD from true ICAD
Medical Therapy

• No approved pharmacotherapy at present
  – Antiplatelet
  – Risk factors control

• New targets for medical therapy
  – Reduced cerebrovascular reserve &
  – Cognitive impairment
What is the expert’s option on antiplatelet therapy in moyamoya disease? Results of a worldwide Survey

M. Kraemer\textsuperscript{a}, P. Berlit\textsuperscript{a}, F. Diesner\textsuperscript{b} and N. Khan\textsuperscript{c}

\textsuperscript{a}Department of Neurology, Alfried-Krupp-Hospital, Essen, Germany; \textsuperscript{b}Department of Neurosurgery, Alfried-Krupp-Hospital, Essen, Germany; and \textsuperscript{c}Neurosurgical Moyamoya Clinic, Children’s University Hospital Zurich, Zurich, Switzerland

Table 2 Answers of the question ‘In your opinion, the medical treatment of moyamoya disease consists of…?’ (*P < 0.05)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Asian experts</th>
<th>Non-Asian experts</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longterm antiplatelet drugs e.g. acetylsalicylic acid 100 mg/day (*)</td>
<td>3 (3/21 = 14%)</td>
<td>7 (7/11 = 64%)</td>
<td>10 (10/32 = 31%)</td>
</tr>
</tbody>
</table>

Table 4 Answers of the question ‘If you do not prescribe antiplatelet treatment, why?’ (*P < 0.05)

<table>
<thead>
<tr>
<th>Reasons</th>
<th>Asian experts</th>
<th>Non-Asian experts</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>It does not have benefits on hemodynamic insufficiency</td>
<td>10 (10/15 = 67%)</td>
<td>1 (1/2 = 50%)</td>
<td>11 (11/17 = 65%)</td>
</tr>
<tr>
<td>Afraid on cerebral hemorrhage under antiplatelet drugs</td>
<td>9 (9/15 = 60%)</td>
<td>1 (1/2 = 50%)</td>
<td>10 (10/17 = 59%)</td>
</tr>
<tr>
<td>Not applicable/no opinion (*)</td>
<td>6 (6/21 = 29%)</td>
<td>9 (9/11 = 82%)</td>
<td>15 (15/32 = 47%)</td>
</tr>
</tbody>
</table>
New Treatment targets: CVR and cognition

Cognitive Function of Patients with Adult Moyamoya Disease

Yoshio Araki, MD, PhD,* Yasushi Takagi, MD, PhD,* Keita Ueda, MD, PhD,† Shiho Ubukata, MHS, † Junko Ishida, OTR, ‡ Takeshi Funaki, MD,* Takayuki Kikuchi, MD, PhD,* Jun C. Takahashi, MD, PhD,* Toshiya Murai, MD, PhD, † and Susumu Miyamoto, MD, PhD *

Table 2. Summary of radiological features of each patient group

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Group</th>
<th>Minor stroke</th>
<th>Bleeding</th>
<th>Lesions on MR imaging</th>
<th>SPECT findings</th>
<th>CVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>lt basal ganglia</td>
<td>Impaired in lt MCA territory</td>
<td>Impaired in bil ACA and MCA territory</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>-</td>
<td>lt. paraventricular region</td>
<td>Preserved</td>
<td>Preserved</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>lt basal ganglia</td>
<td>-</td>
<td>Impaired in lt MCA territory</td>
<td>Impaired in bil ACA and MCA territory</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>Preserved</td>
<td>Impaired in bil ACA and MCA territory</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>Preserved</td>
<td>Impaired in bil ACA territory</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>rt frontal lobe CoI.</td>
<td>-</td>
<td>Impaired in rt ACA territory</td>
<td>Impaired in rt ACA territory</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>Preserved</td>
<td>Impaired in bil ACA and MCA territory</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>bil occipital and temporal lobe CoI.</td>
<td>-</td>
<td>Impaired in bil PCA territory</td>
<td>Impaired in bil ACA, MCA and PCA territory</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>Impaired in rt ACA and MCA territory</td>
<td>Impaired in rt ACA and MCA territory</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>Preserved</td>
<td>Impaired in bil ACA and MCA territory</td>
<td></td>
</tr>
</tbody>
</table>
In Summary

• MMD is a complex disease
• Genetics (RNF213 and others, but unlikely ACTA2) plays important role
• Surgical revascularization decreases risk of ischemic stroke, and maybe hemorrhage as well
• Endovascular treatment should be avoided but distinguishing MMD from ICAD maybe crucial
• MMD is also a medical disease
Thank you!