



Original Article

# Prevalence of unruptured intracranial aneurysms among first-degree relatives of Thai patients who had aneurysmal subarachnoid hemorrhage

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## ABSTRACT

**Background:** The prevalence of familial unruptured intracranial aneurysm (UIA) in Thai population was unknown.

**Methods:** Our study population comprised first-degree relatives of patients who were diagnosed with aneurysmal subarachnoid hemorrhage (aSAH) in two cerebrovascular neurosurgical centers from January 2018 to December 2018. The volunteers underwent three-dimensional time-of-flight magnetic resonance angiography for screening intracranial aneurysms (IA). Those who were reported positive or suspected of IA then underwent computed tomography angiography for confirmation.

**Results:** We identified 12 patients who had 12 unruptured IAs (UIAs) from among 93 first-degree relatives. The prevalence of UIA among our study population was 12.9%. An estimated prevalence of UIA among Thai population was 9.05% (95% confidence interval [CI] 7.32–10.78). Of the 93 relatives, 84 had only one first-degree relative who suffered aSAH. Siblings posed a higher risk for UIA than offspring (16% vs. 9.5%), but the difference was not statistically significant (odds ratio 1.810, 95% CI 0.50–6.50,  $P = 0.274$ ). The most common aneurysm location was the anterior cerebral artery territory (50%).

**Conclusion:** The prevalence of familial UIA in a Thai population was relatively high. There was no significant between-group difference in the occurrence of UIA between the siblings and offspring of the aSAH patients.

**Keywords:** First-degree relative, Prevalence, Screening magnetic resonance angiography, Unruptured intracranial aneurysm

## INTRODUCTION

The prevalence of intracranial aneurysms (IAs) has been reported to range from 1% to 3% according to autopsy and population-based studies in normal populations.<sup>[10,13,14,22,28]</sup> The prevalence of IA might be greater in patients with some inherited disorders, such as autosomal dominant polycystic kidney disease (ADPKD), Ehlers-Danlos syndrome type IV, and Marfan's syndrome. If an individual has one family member who harbors an IA, the likelihood of the individual

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having an unruptured IA (UIA) is increased from 2.3% to 4%. The relative risk for UIA is increased to 8% for individuals who have two or more first-degree relatives affected by IA, so-called familial IA.<sup>[23,28]</sup> Although the previous studies showed a very low incidence of aneurysmal subarachnoid hemorrhage (aSAH) in patients with UIA, aneurysm rupture might cause a high morbidity and mortality rate.<sup>[22,29,30]</sup> The identification of IA before its rupture is considered beneficial. In recent years, advances in the accessibility and quality of neuroimaging studies have improved the detection of IA. Magnetic resonance angiography (MRA) has been suggested to be a feasible screening tool for the detection of familial aneurysm.<sup>[18,21]</sup> Takahashi *et al.* revealed that mass screening of familial aneurysm using MRA is cost effective.<sup>[19,26]</sup>

The prevalence of familial aneurysm has been shown to vary among different races; Japanese,<sup>[8]</sup> Hong Kong Chinese,<sup>[4]</sup> and Singaporean patients have demonstrated a prevalence of 3.2%, 2.3%, and 3.5%, respectively.<sup>[27]</sup> However, the prevalence of familial aneurysm in Thai patients remains unknown. The objective of this study was to determine the prevalence of familial UIA in a Thai population.

## MATERIALS AND METHODS

We conducted a prospective study in two institutions located in the northern part of Thailand. These two cerebrovascular centers are the sole aneurysm centers for 4 million catchment residents. The study populations comprised all of the first-degree relatives of patients with aSAH from January 2018 to December 2018. Eligible volunteers who agreed to participate in this project were included consecutively. Exclusion criteria included patients with: a previous diagnosis of IA, at least one previous brain MRA or computed tomography angiography (CTA), first-degree relatives who had an unknown cause of stroke, and contraindications for magnetic resonance imaging, such as, pregnancy, metallic instrument implantation, pacemakers, and claustrophobia.

Demographic data, risk factors, genetic diseases, and compressive aneurysm symptoms were collected by interview and a review of the medical records. However, our routine institutional practice does not investigate genetic diseases; thus, genetic disease data may be underreported. Three-dimensional time-of-flight MR angiography was performed using two MR machines. The first hospital used a 1.5 T MR scanner (Ingenia 1.5T, Philips Medical Systems) using the following parameters: TR 23 msec, TE 6.9 msec, and FOV 200 × 200 × 176 mm<sup>3</sup>. The second hospital used a 1.5 T MR scanner (Magnetom Symphony 1.5 T, Siemen Medical Systems) using the following parameters: TR 24 msec, TE 6.0 msec, and FOV 190 × 166.3 × 117 mm<sup>3</sup>.

The MRA data of all patients were reviewed by two radiologists and confirmed independently by a neuroradiologist. Confirmatory CTA was performed for patients suspected

of a IA. This study was approved by Naresuan University Institutional Review Board (NU-IRB No. 180/57). Informed consent was acquired from all of the volunteers. We confirmed that all methods were carried out in accordance with the approval protocols and regulations.

We used IBM SPSS for Macintosh (IBM Inc., Armonk, New York) version 23.0.0 for the statistical analysis. For the quantitative variables, the mean, median, and percentages were measured. Fisher's exact test was used to identify between-group differences among the factors related to the presence of UIAs.  $P < 0.05$  was considered statistically significant. We calculated an estimated prevalence using calculating method for imperfect test (due to high false positives of CTA) described by Greenland to decrease biases.<sup>[7]</sup>

## RESULTS

During the study period, 96 patients suffered from aSAH. Ninety-three first-degree relatives of the patients who were included in this study were identified. Of the 93 relatives, 32 underwent MRA screening at the first hospital, and 61 underwent MRA screening at the second hospital. Patient demographic data are shown in [Table 1]. There were no between-group differences in age, sex, underlying diseases, smoking, or alcohol consumption.

Three-dimensional time-of-flight MRA detected a suspected aneurysm in 18 of the relatives. Confirmatory CTA revealed that 12 had UIA, whereas six did not. Thus, the prevalence of UIA among first-degree relatives in this population was 12.9%. The estimated prevalence of familial UIA among Thai populations was 9.05% (95% confidence interval [CI] 7.32–10.78). Siblings appeared to have a higher prevalence of IA than offspring (16.0% vs. 9.5%), but the difference was statistically insignificant (odds ratio [OR] 1.810, 95% CI 0.50–6.50,  $P = 0.274$ ), as shown in [Table 2]. Most of our study participants had only one first-degree relative who suffered SAH. UIAs were found only among the single affected group (17.6%), as shown in [Table 3].

Fourteen UIAs were identified among the 12 patients. Of these, 13 were located in the anterior circulations. The most common aneurysm location was the anterior cerebral artery territory [Table 4]. The mean aneurysm size was  $2 \pm 0.5$  mm. All of the UIAs found in this study were small (size <3 mm). None of our study participants had a history of genetic diseases, including ADPKD, Ehlers-Danlos syndrome type IV, and Marfan's syndrome.

## DISCUSSION

Screening MRA for UIA is recommended when two or more first-degree relatives have aneurysms or aSAH.<sup>[2,6,16,22,30]</sup> Bor *et al.* reported a cost-effective screening strategy. They recommended screening individuals with two or more first-

**Table 1:** Comparison of demographic data of the relatives of aSAH patients with and without unruptured intracranial aneurysms.

	Intracranial aneurysm		P-value
	Yes (n=12)	No (n=81)	
Age, Mean±SD	48.3±12.5	49.9±9.7	0.779
Sex (Male), %	25%	35.8%	0.535
Diabetes mellitus; n (%)	0 (0)	5 (6.2)	0.493
Hypertension; n (%)	3 (25.0)	22 (27.2)	0.591
Dyslipidemia; n (%)	3 (25.0)	18 (22.2)	0.540
Smoking; n (%)	1 (8.3)	7 (8.6)	0.726
Alcohol consumption; n (%)	3 (25)	18 (22.2)	0.498
Presence of compressive symptom (%)	0 (0)	0 (0)	-

aSAH: Aneurysmal subarachnoid hemorrhage

**Table 2:** Comparison of the type of first-degree relatives of a patient with subarachnoid hemorrhage and the prevalence of aneurysms (n=92; one relative who was the mother of a patient was excluded).

	Type of relative		P-value
	Sibling (n=50)	Offspring (n=42)	
Presence of aneurysm (%)	8 (16.0)	4 (9.5)	0.274
Age, Mean±SD	52.8±9.6	45.9±9.3	0.001*
Diabetes mellitus; n (%)	3 (6.0)	2 (4.8)	0.583
Hypertension; n (%)	16 (32.0)	9 (21.4)	0.184
Dyslipidemia; n (%)	13 (26)	8 (19.0)	0.295
Smoking; n (%)	5 (10.0)	3 (7.1)	0.723

**Table 3:** Comparison of single and multiple affected first-degree relatives.

	Number of affected relatives		P-value
	One (n=84)	Two or more (n=9)	
Presence of aneurysm (%)	12 (17.6)	0 (0)	0.271
Age, Mean±SD	49±10.0	56.3±7.43	0.021*
Diabetes mellitus; n (%)	5 (6.0)	0 (0)	0.594
Hypertension; n (%)	21 (25.0)	4 (44.4)	0.184
Dyslipidemia; n (%)	19 (22.6)	2 (22.2)	0.671
Smoking; n (%)	7 (8.3)	1 (11.1)	0.572

**Table 4:** Characteristics and locations of unruptured aneurysms.

Patients (sex, age)	Location	Size (mm)
F, 64	Cavernous part of internal carotid artery	3
F, 56	A1 part of anterior cerebral artery	1.5
F, 56	A1 part of anterior cerebral artery	2
	Anterior communicating artery	1.6
F, 61	P1-P2 junction of posterior cerebral artery	2
F, 63	Anterior communicating artery	1.5
	Posterior communicating artery	1.6
M, 24	Anterior communicating artery	1.5
F, 51	Anterior communicating artery	2
F, 34	Internal carotid artery bifurcation	2
F, 45	Internal carotid artery bifurcation	2
M, 39	M2 part of middle cerebral artery	3
M, 40	A2 part of anterior cerebral artery	2
F, 53	Posterior communicating artery	3

degree relatives with subarachnoid hemorrhage every 7 years from age 20 to 80.<sup>[2]</sup> We considered that this suggestion was proper for neurosurgical practice in our country. Thus, our study population included only first-degree relatives of patients with aSAH instead of all patients with IA regardless of rupture status. According to a systematic review, the prevalence of UIA among individuals who have two or more first-degree relatives affected by IA is 8%.<sup>[28]</sup> Although most of our study population had only one first-degree relative who suffered aSAH, the prevalence of familial UIA among study populations was 12.9%. However, this prevalence might be biased due to high false positive of CTA in small aneurysm. Rustemi *et al.* reported that the false positives of CTA for small aneurysm are 18%.<sup>[25]</sup> From meta-analysis study, estimated sensitivity and specificity of CTA are 84% and 85%, respectively.<sup>[5]</sup> Thus, we adjusted the prevalence using Greenland's method to decrease biases.<sup>[7]</sup> The estimated prevalence of familial UIA among Thai populations was 9.05% which appeared to be higher than that in other Asian countries.<sup>[4,8,27]</sup> We have no information regarding the prevalence of IA in the normal Thai population. Jiranukool *et al.* reported that the prevalence of IA among Thai acute ischemic stroke patients was approximately 7%.<sup>[15]</sup> Their findings was relatively higher than the prevalence of IA reported among Japanese and Korean acute ischemic stroke patients.<sup>[12,20]</sup> These findings indicate that the Thai population slightly have a higher risk of harboring UIAs. To date, no specific gene of IAs was demonstrated but genetic risks for smoking and hypertension play substantial roles for IA.<sup>[1,9]</sup> Korja *et al.* revealed that smoking and hypertension are clustered in some families as the major risk factors for IA.<sup>[17]</sup> Thus, we remained the recommendation to screen for UIA when two or more first-degree relatives have aneurysms or aSAH. However, we suggest that the criteria for screening MRA among each race could be adjusted according to its prevalence of IA.

A previous study revealed an increasing trend for UIA with an increasing number of affected first-degree relatives.<sup>[23,24]</sup> Our findings appear to contradict this finding. We demonstrated that single affected and multiple affected relatives had no between-group difference in the prevalence of aneurysms. However, our multiple affected first-degree relatives cohort had a small sample size ( $n = 9$ ) that might limit the assumption. A review by Brown *et al.* indicated that siblings of SAH patients had a higher relative risk for IA than offspring.<sup>[3]</sup> Our findings showed the same predilection, but the difference was not statistically significant. The prevalence of UIA shows an increasing relative risk with increasing age.<sup>[27]</sup> The significantly higher age in the sibling group might have confounded the prevalence of aneurysms. Of 93 volunteers, only one parent participates in this study. The other eligible parents disagreed to participate. Their main reasons were fear of knowing and a far distance from the studying hospitals.

Thein *et al.* reported that the most common aneurysm location in Singaporeans was the cavernous part of the internal carotid arteries, whereas that of our patients was the anterior cerebral artery territories.<sup>[27]</sup> This finding supports the notion that different races might have differences in the prevalence and characteristics of IA. A case series of aSAH from the authors' institutions showed that ruptured aneurysms were mostly located at the internal carotid-posterior communicating artery (50%), whereas ruptured anterior communicating arteries accounted for 25% of the locations.<sup>[11]</sup> These findings appear to indicate that the common location of IA might be different among different study populations even of the same race.

From our study, the positive predictive value (PPV) of three-dimensional time-of-flight MR angiography was 66.6%. Raaymaker *et al.* revealed a PPV of 58% when a possible aneurysm was interpreted from MRA, which is comparable to our study.<sup>[21]</sup>

The major limitation of this study was the small sample size. Thus, the statistical power might not be adequate to detect the true prevalence of IA. In addition, only patients who were suspected of having aneurysms proceeded to undergo confirmatory CTA. Thus, the sensitivity and negative predictive value could not be evaluated. Finally, we did not perform digital subtraction angiography. Our mean aneurysm size was  $2 \pm 0.5$  mm that might be within the limits of CTA. Thus, the effective prevalence could not be reported.

## CONCLUSION

The estimated prevalence of familial aneurysm among a Thai population was approximately 9.05%.

### Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Bakker MK, van der Spek RA, van Rheenen W, Morel S, Bourcier R, Hostettler IC, *et al.* Genome-wide association study of intracranial aneurysms identifies 17 risk loci and genetic overlap with clinical risk factors. *Nat Genet* 2020;52:1303-13.
2. Bor AS, Koffijberg H, Wermer MJ, Rinkel GJ. Optimal

- screening strategy for familial intracranial aneurysms a cost-effectiveness analysis. *Neurology* 2010;74:1671-9.
3. Brown RD, Broderick JP. Unruptured intracranial aneurysms: Epidemiology, natural history, management options, and familial screening. *Lancet Neurol* 2014;13:393-404.
  4. Chan DY, Abrigo JM, Cheung TC, Siu DY, Poon WS, Ahuja AT, *et al.* Screening for intracranial aneurysms? Prevalence of unruptured intracranial aneurysms in Hong Kong Chinese. *J Neurosurg* 2016;124:1245-9.
  5. Chen X, Liu Y, Tong H, Dong Y, Ma D, Xu L, *et al.* Meta-analysis of computed tomography angiography versus magnetic resonance angiography for intracranial aneurysm. *Medicine (Baltimore)* 2018;97:e10771.
  6. Gorelick PB. Should we be screening relatives of patients with aneurysmal subarachnoid hemorrhage for asymptomatic intracranial aneurysm? *Curr Atheroscler Rep* 2000;2:89-91.
  7. Greenland S. Basic methods for sensitivity analysis of biases. *Int J Epidemiol* 1996;25:1107-16.
  8. Harada K, Fukuyama K, Shirouzu T, Ichinose M, Fujimura H, Kakumoto K, *et al.* Prevalence of unruptured intracranial aneurysms in healthy asymptomatic Japanese adults: Differences in gender and age. *Acta Neurochir (Wien)* 2013;155:2037-43.
  9. Helgadottir A, Thorleifsson G, Magnusson KP, Gretarsdottir S, Steinthorsdottir V, Manolescu A, *et al.* The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. *Nat Genet* 2008;40:217-24.
  10. Inagawa T, Hirano A. Ruptured intracranial aneurysms: An autopsy study of 133 patients. *Surg Neurol* 1990;33:117-123.
  11. Intarakhao P, Thiarawat P, Tewaritrueangsri A, Pojanasupawun S. Low-dose adenosine-induced transient asystole during intracranial aneurysm surgery. *Surg Neurol Int* 2020;11:235.
  12. Ishikawa Y, Hirayama T, Nakamura Y, Ikeda K. Incidental cerebral aneurysms in acute stroke patients: Comparison of asymptomatic healthy controls. *J Neurol Sci* 2010;298:42-5.
  13. Jakubowski J, Kendall B. Coincidental aneurysms with tumours of pituitary origin. *J Neurol Neurosurg Psychiatry* 1978;41:972-9.
  14. Jellinger K. Pathology of intracerebral hemorrhage. *Zentralbl Neurochir* 1977;38:29-42.
  15. Jiranukool J, Thiarawat P, Galassi W. Prevalence of intracranial aneurysms among acute ischemic stroke patients. *Surg Neurol Int* 2020;11:341.
  16. Kirkpatrick PJ, McConnell RS. Screening for familial intracranial aneurysms. *BMJ* 1999;319:1512-3.
  17. Korja M, Kaprio J. Controversies in epidemiology of intracranial aneurysms and SAH. *Nat Rev Neurol* 2016;12:50-5.
  18. Mackey J, Brown RD, Moomaw CJ, Sauerbeck L, Hornung R, Gandhi D, *et al.* Unruptured intracranial aneurysms in the familial intracranial aneurysm and international study of unruptured intracranial aneurysms cohorts: Differences in multiplicity and location clinical article. *J Neurosurg* 2012;117:60-4.
  19. Miller TD, White PM, Davenport RJ, Al-Shahi Salman R. Screening patients with a family history of subarachnoid haemorrhage for intracranial aneurysms: Screening uptake, patient characteristics and outcome. *J Neurol Neurosurg Psychiatry* 2012;83:86-8.
  20. Oh YS, Lee SJ, Shon YM, Yang DW, Kim BS, Cho AH. Incidental unruptured intracranial aneurysms in patients with acute ischemic stroke. *Cerebrovasc Dis* 2008;26:650-3.
  21. Raaymakers TW, Buys PC, Verbeeten B Jr., Ramos LM, Witkamp TD, Hulsmans FJ, *et al.* MR angiography as a screening tool for intracranial aneurysms: Feasibility, test characteristics, and interobserver agreement. *AJR Am J Roentgenol* 1999;173:1469-75.
  22. Rinkel GJ. Intracranial aneurysm screening: Indications and advice for practice. *Lancet Neurol* 2005;4:122-8.
  23. Ronkainen A, Hernesniemi J, Kuivaniemi H, Tromp G. Current implications for the efficacy of noninvasive screening for occult intracranial aneurysms in patients with a family history of aneurysms. *J Neurosurg* 1996;84:534-6.
  24. Ronkainen A, Puranen MI, Hernesniemi JA, Vanninen RL, Partanen PL, Saari JT, *et al.* Intracranial aneurysms: MR angiographic screening in 400 asymptomatic individuals with increased familial risk. *Radiology* 1995;195:35-40.
  25. Rustemi O, Alaraj A, Shakur SF, Orning JL, Du X, Aletich VA, *et al.* Detection of unruptured intracranial aneurysms on noninvasive imaging. Is there still a role for digital subtraction angiography? *Surg Neurol Int* 2015;6:175.
  26. Takahashi E, Haku M, Suzuki Y, Fukagawa K, Iida Y, Yoshida K, *et al.* Effectiveness of magnetic resonance angiography for mass screening of unruptured intracranial aneurysms. *Nihon Koshu Eisei Zasshi* 1997;44:509-17.
  27. Thien A, See AA, Ang SY, Primalani NK, Lim MJ, Ng YP, *et al.* Prevalence of asymptomatic unruptured intracranial aneurysms in a Southeast Asian population. *World Neurosurg* 2017;97:326-32.
  28. Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: A systematic review and meta-analysis. *Lancet Neurol* 2011;10:626-36.
  29. Wermer MJ, van der Schaaf IC, Algra A, Rinkel GJ. Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: An updated meta-analysis. *Stroke* 2007;38:1404-10.
  30. Wiebers DO, Whisnant JP, Huston J 3<sup>rd</sup>, Meissner I, Brown RD Jr., Piepgras DG, *et al.* Unruptured intracranial aneurysms: Natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet* 2003;362:103-10.

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