Genetic Risk Assessment of Elastin Gene Polymorphisms with Intracranial Aneurysm in Koreans

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Abstract

Elastin encoded by elastin gene (ELN) is a crucial extracellular matrix protein responsible for arterial resilience. The objective of this study was to identify single nucleotide polymorphisms (SNPs) of ELN gene susceptible to intracranial aneurysm (IA) in Korean population. Two SNPs of ELN gene, rs2071307 (Gly422Ser) and rs2856728 (intron), were genotyped in 90 patients with IA and 90 age and frequency matched controls. Fisher’s exact test was conducted to evaluate allelic association with IA. Of the two SNPs in ELN gene, T allele of rs2856728 (intron) showed statistically significant association with increased development of IA (odds ratio [OR]: 2.34, 95% confidence interval [CI]: 1.44–3.81, P = 7.6 × 10−4). However, G allele of rs2071307 (Gly422Ser) had no significant association with the development of IA (OR: 1.27, 95% CI: 1.44–3.81, P = 0.607). Interestingly, the odds of having rs2856728 variant was approximately 2-fold higher in males than that in females (OR: 3.46 vs. 1.88, P < 0.05). However, none of SNPs showed difference between single and multiple IA in this study. This preliminary study implies that the rs2856728 variant in ELN gene polymorphisms might play crucial roles in the development and pathogenesis of IA in Korean population.

Key words: intracranial aneurysm, subarachnoid hemorrhage, elastin, genetic variants

Introduction

Subarachnoid hemorrhage (SAH) has 30-day mortality rate ranging from 36% to 42%.1,2 Among SAH survivors, up to 50% of them have permanent disability.3,4 Intracranial aneurysm (IA) accounts for 85% of non-traumatic SAH.4,5 Hemodynamic studies have shown that elevated wall shear stress (WSS) may lead to IA formation by degenerative endothelial remodeling.6,7 Structural integrity of the arterial wall can be sustained by extracellular matrix (ECM).8 Bruno et al.8 have reported that focal degradation of ECM is related to the formation and growth of aneurysm.

Elastin encoded by elastin gene (ELN) is a crucial ECM protein responsible for resilience of arteries.9 Since arterial wall of IA has decreased level of ECM,10 ELN gene has been studied as a candidate for IA.11 Although two studies have shown a possible association between ELN gene in IA formation12,13 positive correlation between ELN gene and IA is not revealed in most studies. According to a meta-analysis by Paterakis et al.,14 ELN INT20 1315T > C variants is associated with IA formation (odds ratio [OR]: 0.66). However, its association is not shown in Caucasian population.13,15,16 Regarding ELN EX20 1264G > A, its association with IA formation is not significant in the three studies of Caucasian, although it is significant in one study on East Asians.10 In addition, higher incidence of IA in Asian compared to that in Caucasian has been reported.17 These results suggest that ELN variants could affect IA formation with ethnical difference. To the best of our knowledge,
genetic association study of ELN polymorphisms in Koreans has not been reported to date. Therefore, the objective of this study was to investigate the association between ELN gene polymorphisms and IA in a homogeneous Korean population to provide clue for the pathogenesis of IA in East Asians.

**Materials and Methods**

**Subjects**

This prospective study included radiologically confirmed 90 IA patients with saccular shape and 90 age- and gender-matched controls from April 2015 to December 2016. Aneurysms which showed non-saccular types such as fusiform, dissection, traumatic, or infectious aneurysms were excluded. The control group consisted of sex- and age-matched patients who underwent computed tomography or magnetic resonance angiography for headache evaluation or medical check-up. Those who had other neurological diseases including arteriovenous malformation, intracranial hemorrhage, and infarction were excluded. Medical records included sex, age, presentation (unruptured IA vs. SAH), multiplicity, hypertension (HTN), diabetes mellitus (DM), hyperlipidemia, smoking, and familial history of aneurysm (vs. sporadic). This study was approved by the Institutional Review Boards (No. 1504-087-665 and 2016-31).

**SNP selection and genotyping**

Two SNPs, rs2071307 and rs2856728, of ELN gene reported in previous studies were selected for this study. They accounted for linkage disequilibrium (LD, $r^2 < 0.8$) in Japanese and Chinese of Phase II HapMap data supported by LD TAG SNP Selection (TagSNP) of SNPinfo web server (http://snpinfo.niehs.nih.gov/guide.htm). For genotyping of the two SNPs, genomic DNA was extracted from peripheral blood of 90 patients and 90 controls using HiGene™ Genomic DNA Prep Kit (BIOFACT, Daejeon, Korea). Primers of the two SNPs (Table 1) were designed using Primer-3 v.0.4.0 program (http://bioinfo.ut.ee/primer3-0.4.0/). Polymerase chain reaction (PCR) was performed in 25 µl volume containing 100 ng genomic DNA, 1.5 µl of each primer (10 pmole/µl), and SolgTM 2X Taq PCR Pre-Mix (Solgent, Daejeon, Korea). Pre-denaturation was done at 95°C for 5 min, 34 cycles of denaturation at 95°C for 30 s, annealing at 63°C for 30 s, extension at 72°C for 1 min, and a final extension at 72°C for 5 min. Amplified fragments were confirmed by 1.5% agarose gel electrophoresis, purified with the SolgTM PCR purification kit (SolGent, Daejeon, Korea), and sequenced using an ABI PRISM 3730XL DNA Analyzer (Applied Biosystems, Foster City, CA, USA).

**Statistical analysis**

Baseline characteristics were described as mean ± standard deviation (SD) for age and the number of subjects. Percentage was used to describe other discrete variables. Chi-square and unpaired t-tests were used to evaluate difference of clinical variables between patients with IA and controls. Regarding allelic associations between IA and the two SNPs of ELN gene, Fisher’s exact test was performed to estimate OR with 95% confidence intervals (CIs). Descriptive and association analyses were conducted using STATA software v.11.2 (Stata Corp., College Station, TX, USA). Minor allele frequency (MAF) and Hardy–Weinberg equilibrium (HWE) were evaluated using Haploview v.4.2 (https://www.broadinstitute.org/haploview/haploview).

**Results**

**Demographic characteristics of the enrolled patients**

Baseline characteristics of the 90 patients with IA and 90 controls are summarized in Table 2. There were 61 (67.8%) female patients with IA and 54 (60.0%) female controls ($P = 0.368$). Mean ages of the 90 patients with IA and 90 controls were 57.8 years.

| Variables                  | IA ($n = 90$) | Controls ($n = 90$) | $P$-value |
|----------------------------|---------------|---------------------|-----------|
| Female                     | 61 (67.8%)    | 54 (60.0%)          | 0.368     |
| Age, years                 | 57.8 ± 10.2   | 56.6 ± 14.2         | 0.551     |
| Hypertension               | 30 (33.3%)    | 24 (26.7%)          | 0.331     |
| Diabetes mellitus          | 11 (12.2%)    | 9 (10.0%)           | 0.636     |
| Hyperlipidemia             | 18 (20.0%)    | 13 (14.4%)          | 0.325     |
| Smoking                    | 15 (16.7%)    | 10 (11.1%)          | 0.283     |
| Aneurysm rupture           | 7 (7.8%)      |                     |           |
| Multiple aneurysm          | 30 (33.3%)    |                     |           |

*P < 0.05 is significant.

Table 1 Primers designed for the two SNPs of elastin (ELN) gene

| SNP          | Primer      | Primer sequence           | Length |
|--------------|-------------|---------------------------|--------|
| rs2071307    | Forward     | 5’-AATCCATCAG-CATCCCTCAG-3’ | 395 bp |
| rs2856728    | Reverse     | 5’-CAACTTCTC-CCTGAGCACAT-3’ |        |

Neurol Med Chir (Tokyo) 58, January, 2018
and 56.6 years ($P = 0.551$), respectively. Seven (7.8%) patients with IA had aneurysm rupture. History of diseases and cigarette smoking showed no statistical difference between the two groups. Thirty (33.3%) patients with IA exhibited multiple aneurysms.

**Genetic associations of 2 ELN polymorphisms with IA**

Results of genotype and allele frequencies with HWE $P$-value and associations of the two ELN polymorphisms, rs2071307 (Gly422Ser) and rs2856728 (intron), in 90 patients with IA and 90 healthy controls are shown in Table 3. ELN polymorphism rs2071307 with benign effect in the genome was not significantly associated with IA formation ($OR: 1.27; 95\% CI: 0.64–2.49, P = 0.607$). However, the major “T” allele of rs2856728 was strongly associated with the risk of developing IA ($OR: 2.34; 95\% CI: 1.44–3.81$). It was more frequent among IA patients compared to that in the control group in the current study ($P = 7.6 \times 10^{-4}$).

Genetic difference of the two ELN polymorphisms was compared between two gender groups. Results are shown in Table 4. The coding variant rs2071307 was not significantly different between the two gender groups. It showed no significant association with developing IA (in male group, $OR: 1.27, 95\% CI: 0.39–4.17$; in female group, $OR: 1.63, 95\% CI: 0.71–3.27$). On the other hand, the rs2856728 variant was significantly associated with developing IA in both gender groups ($P = 0.004$ in male and $P = 0.048$ in female). The T allele in this variant showed an approximately 2-fold high risk in males compared to that in females (male, $OR: 3.46$; female, $OR: 1.88$). However, no SNP showed an association with single or multiple aneurysms in the 90 IA patients ($P > 0.1$, data not shown).

**Discussion**

Due to absence of the external elastic lamina, internal elastic lamina (IEL) is a major contributor to the strength of the cerebral arterial wall. IEL has a longitudinal arrangement of elastin fiber. Defect of IEL or elastin degradation has been proposed to be related to IA formation. Associations between several ELN gene polymorphisms and sporadic IA in East-Asian and Caucasian populations have been studied. Compared to relative similar proportions of minor allele of rs2071307 in Japanese and Dutch populations ($55.2%$ in Japanese and $56.6%$ in Dutch), respectively. Seven (7.8%) patients with IA had aneurysm rupture. History of diseases and cigarette smoking showed no statistical difference between the two groups. Thirty (33.3%) patients with IA exhibited multiple aneurysms.

| SNP     | Group | N/R | NN/RR/RR | RAF | OR | 95% CI | P  |
|---------|-------|-----|----------|-----|----|--------|----|
| rs2071307 | Male | G/A | 23/6/0 | 31/4/1 | 0.10/0.08 | 1.27 | 0.39–4.17 | 0.766 |
|          | Female | A/G | 1/11/50 | 0/15/39 | 0.91/0.84 | 1.63 | 0.71–3.27 | 0.298 |
| rs2856728 | Male | C/T | 1/7/21 | 6/16/14 | 0.84/0.61 | 3.46 | 1.47–8.14 | 0.004 |
|          | Female | A/G | 2/20/39 | 7/20/27 | 0.80/0.69 | 1.88 | 1.03–3.43 | 0.048 |

$^a$N/R: non-risk/risk allele type, $^b$NN/RR/RR: non-risk homozygote/heterozygote/risk homozygote genotypes, $^c$RAF: risk allele frequency in patients and controls, $^d$odds ratio (OR), 95% confidence interval (CI). The $P$-value was estimated from allelic association analysis using Fisher’s exact test.

Elastin Gene Polymorphisms of Aneurysms

Neurol Med Chir (Tokyo) 58, January, 2018
population.\textsuperscript{12,13} Chinese Han population harboring sporadic IA has higher proportion of minor allele of rs2071307 (allele A).\textsuperscript{11} A recent meta-analysis on four studies,\textsuperscript{11,13,15,16} has shown that INT20 1315T > C variant has protective effect on IA formation (OR = 0.66).\textsuperscript{14} However, the protective effect of INT20 1315T > C variants is mainly found in East-Asian population. The other three studies did not yield an association between INT20 1315T > C and IA. Other variants such as EX20 1264G > A, INT23 1051 + 24 T > C, and INT4 196 + 71G > A are not associated with IA.\textsuperscript{14}

Conflicting results on the association between \textit{ELN} and IA have been published. Genome-wide linkage analysis of IA in 104 Japanese with affected sib pairs has revealed possible associations of chromosome 5q, 7q, and 14q with IA formation.\textsuperscript{12} In particular, chromosome 7q11 near \textit{D7S2472} in the vicinity of \textit{ELN} gene is found to be closely related to IA.\textsuperscript{12}

Although no association between IA and 14 SNPs in \textit{ELN} has been noted, haplotype at INT20/INT23 has been significantly observed in IA than that in controls (\(P = 3.81 \times 10^{-6}\)). Exon 22 of the \textit{ELN} (minor allele frequency 0% in SAH and 2.8% in control) has been found to be associated with SAH presentation in Dutch sporadic aneurysms.\textsuperscript{13} Haplotypes of INT5/EX22 and INT4/EX22 are found to be significantly associated with SAH presentation. In both cases, major allele (G-G haplotypes) is more evident in SAH patients than that in controls.\textsuperscript{13}

On the contrary, Hofer et al.\textsuperscript{15} have reported that there is no significant relationship between the two SNPs (INT 20 and INT23) of \textit{ELN} and IA in Central Europe. Haplotype frequencies of INT20/INT23 was not associated with IA either (\(P = 0.45\)).

For Caucasian population, 10 SNPs of \textit{ELN} are not associated with SAH at allele or haplotype level.\textsuperscript{22} Mineharu et al.\textsuperscript{23} have also reported that there is no association between alleles or haplotypes of \textit{ELN} and IA in a Japanese population.

In this study, we identified two polymorphisms, rs2071307 (Gly422Ser) and rs2856728 (intron), in \textit{ELN} gene susceptibility to develop IA in a Korean population. Among these variants, Yang et al.\textsuperscript{11} have reported that minor A allele of rs2071307 is significantly associated with increased risk of IA in a Chinese population. However, this variant showed an insignificant association with IA formation (\(P = 0.607\)) in the present study. However, the T allele of rs2856728 intron variant showed a constant association with IA in both Chinese and Korean populations (OR: 2.12 and 2.34, respectively; \(P < 0.001\)). Interestingly, the risk of developing IA was found to be influenced by rs2856728 variant in the current study. This risk was significantly higher (\(P < 0.05\)) in males than that in females in the current study of a Korean population. Previous studies have revealed that female gender was a risk factor for IA formation, in particular postmenopausal age. The incidence of SAH was also higher in female patients. Such data imply that estrogen may contribute to the biological process of IA.\textsuperscript{24} On the contrary, protective aspirin (≥3 times/week) effect on SAH development was more noted in male than female IA patients.\textsuperscript{25,26}

Therefore, genetic factors and gender difference should be further evaluated in IA formation in the future work.

Results such as familial IA (vs. sporadic IA), SAH presentation (vs. unruptured IA), and allele frequencies in enrolled patients might have conflicting results.\textsuperscript{11} Most comparisons have been done between ruptured cases and controls without including unruptured cases.\textsuperscript{13} Accordingly, such results could not accurately reflect SAH-specific genetic loci due to the absence of unruptured cases. Yang et al.\textsuperscript{11} have analyzed \textit{ELN} gene allele between ruptured and unruptured aneurysms. In their study, minor allele of rs2071307 was found to be significantly associated with ruptured aneurysms (31.3% vs. 23.2% in ruptured cases; OR: 1.51, \(P = 0.013\)), while rs2856728 was not significantly associated with aneurysm rupture (OR: 0.88, \(P = 0.48\)). Khurana et al.\textsuperscript{27} also reported that three tandem endothelial nitric oxide (\textit{eNOS}) gene variations such as promoter SNP (T-786C), intron-4 27-base pair variable number of tandem repeats, and exon-7 SNP (G894T) were more prone to aneurysm rupture in Caucasian. However, these data was not replicated in Japanese patient sample.\textsuperscript{28}

Although, ruptured aneurysms showed significantly increased lymphocytes and natural killer cells, similar histological findings of atherosclerotic lesions with cellular infiltration of macrophage and proliferating smooth muscle cells were noted in both ruptured and unruptured aneurysms.\textsuperscript{29,30} Accordingly, we have included both ruptured and unruptured aneurysms. In our study, both SNPs showed no difference between rupture and non-rupture groups among the 90 IA patients. Four loci (1p34.3-p36.13, 7q11, 19q13.3, and Xp22) have been replicated in other studies of familial IA.\textsuperscript{31} SNPs of chromosome 4 near endothelin receptor A gene at chromosome 9 within cyclin-dependent kinase inhibitor 2B antisense inhibitor gene and at chromosome 8 near \textit{SOX} 17 transcription regulator gene have been found to be significantly related to sporadic IA.\textsuperscript{32} Compared to relative similar proportion of minor allele of rs2071307 in Japanese\textsuperscript{32} and Dutch population,\textsuperscript{13} Chinese Han population harboring sporadic IA has higher proportion of minor allele of rs2071307 (allele A).\textsuperscript{11} In our study,
7 (7.8%) patients presented with SAH and one (1.1%) patient had family history of SAH. Accordingly, differences in ethnicity and aneurysm status should be carefully considered when interpreting study results.

Conclusions

Despite a small sample size, rs2856728 variant in ELN gene polymorphisms was found to be significantly associated with IA in this study. This might imply a sufficient statistical power due to its large effect size. Furthermore, we found that ELN polymorphism might play crucial roles in the development and pathogenesis of IA in Koreans. The major “T” allele of rs2856728 highly increased the risk of IA formation. When determining the effect of this variant on the development of IA, genetic difference between gender groups needs to be considered. Further studies using large-scale independent population are needed to validate our novel findings.

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Conflicts of Interest Disclosure

The authors report no conflicts of interest.

References

1) Ingall T, Asplund K, Mähönen M, Bonita R: A multinational comparison of subarachnoid hemorrhage epidemiology in the WHO MONICA stroke study. Stroke 31: 1054–1061, 2000
2) Sandvei MS, Mathiesen EB, Vatten LJ, et al.: Incidence and mortality of aneurysmal subarachnoid hemorrhage in two Norwegian cohorts, 1984–2007. Neurology 77: 1833–1839, 2011
3) Rose MJ: Aneurysmal subarachnoid hemorrhage: an update on the medical complications and treatments strategies seen in these patients. Curr Opin Anaesthesiol 24: 500–507, 2011
4) D’Souza S: Aneurysmal Subarachnoid Hemorrhage. J Neurosurg Anesthesiol 27: 222–240, 2015
5) Priebe HJ: Aneurysmal subarachnoid haemorrhage and the anaesthetist. Br J Anaesth 99: 102–118, 2007
6) Jeong W, Rhee K: Hemodynamics of cerebral aneurysms: computational analyses of aneurysm progress and treatment. Comput Math Methods Med 2012: 782801, 2012
7) Hoi Y, Meng H, Woodward SH, et al.: Effects of arterial geometry on aneurysm growth: three-dimensional computational fluid dynamics study. J Neurosurg 101: 676–681, 2004
8) Bruno G, Todor R, Lewis I, Chyatte D: Vascular extracellular matrix remodeling in cerebral aneurysms. J Neurosurg 89: 431–440, 1998
9) Debelle L, Alix AJ: The structures of elastins and their function. Biochimie 81: 981–994, 1999
10) Chyatte D, Reilly J, Tilson MD: Morphometric analysis of reticular and elastin fibers in the cerebral arteries of patients with intracranial aneurysms. Neurosurgery 26: 939–943, 1990
11) Yang S, Wang T, You C, et al.: Association of polymorphisms in the elastic gene with sporadic ruptured intracranial aneurysms and unruptured intracranial aneurysms in Chinese patients. Int J Neurosci 123: 454–458, 2013
12) Onda H, Kasuya H, Yoneyama T, et al.: Genomewide-linkage and haplotype-association studies map intracranial aneurysm to chromosome 7q11. Am J Hum Genet 69: 804–819, 2001
13) Ruigrok YM, Seitz U, Wolterink S, Rinkel GJ, Wijmenga C, Urbjn Z: Association of polymorphisms and haplotypes in the elastin gene in Dutch patients with sporadic aneurysmal subarachnoid hemorrhage. Stroke 35: 2064–2068, 2004
14) Paterakis K, Koutsias S, Doxani C, et al.: Variants of the elastin (ELN) gene and susceptibility to intracranial aneurysm: a synthesis of genetic association studies using a genetic model-free approach. Int J Neurosci 127: 567–572, 2017
15) Hofer A, Hermans M, Kubassek N, et al.: Elastin polymorphism haplotype and intracranial aneurysms are not associated in Central Europe. Stroke 34: 1207–1211, 2003
16) Krex D, König IR, Ziegler A, Schackert HK, Schackert G: Extended single nucleotide polymorphism and haplotype analysis of the elastin gene in Caucasians with intracranial aneurysms provides evidence for racially/ethnically based differences. Cerebrovasc Dis 18: 104–110, 2004
17) Ohaegbulam SC, Dujovny M, Ausman JJ, Diaz FG, Malik GM: Ethnic distribution of intracranial aneurysms. Acta Neurochir (Wien) 106: 132–135, 1990
18) Jeon JP, Cho YD, Rhim JK, et al.: Extended monitoring of coiled aneurysms completely occluded at 6-month follow-up: late recanalization rate and related risk factors. Eur Radiol 26: 3319–3326, 2016
19) Barrett JC, Fry B, Maller J, Daly MJ: Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 21: 263–265, 2005
20) Mimata C, Kitaoka M, Nagahiro S, et al.: Differential distribution and expressions of collagens in the cerebral aneurysmal wall. Acta Neuropathol 94: 197–206, 1997
21) Miskolczi L, Guterman LR, Flaherty JD, Hopkins LN: Saccular aneurysm induction by elastase digestion of the arterial wall: a new animal model. *Neurosurgery* 43: 595–600; discussion 600–601, 1998

22) Kaushal R, Woo D, Pal P, et al.: Subarachnoid hemorrhage: tests of association with apolipoprotein E and elastin genes. *BMC Med Genet* 8: 49, 2007

23) Mineharu Y, Inoue K, Inoue S, et al.: Association analysis of common variants of ELN, NOS2A, APOE and ACE2 to intracranial aneurysm. *Stroke* 37: 1189–1194, 2006

24) Amenta PS, Medel R, Pascale CL, Dumont AS: Elucidating sex differences in cerebral aneurysm biology and therapy: the time is now. *Hypertension* 68: 312–314, 2016

25) Wiebers DO, Whisnant JP, Huston J, et al.; International Study of Unruptured Intracranial Aneurysms Investigators: Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet* 362: 103–110, 2003

26) Chalouhi N, Starke RM, Correa T, et al.: Differential sex response to aspirin in decreasing aneurysm rupture in humans and mice. *Hypertension* 68: 411–417, 2016

27) Khurana VG, Meissner I, Sohni YR, et al.: The presence of tandem endothelial nitric oxide synthase gene polymorphisms identifying brain aneurysms more prone to rupture. *J Neurosurg* 102: 526–531, 2005

28) Krischek B, Kasuya H, Akagawa H, et al.: Using endothelial nitric oxide synthase gene polymorphisms to identify intracranial aneurysms more prone to rupture in Japanese patients. *J Neurosurg* 105: 717–722, 2006

29) Kosierkiewicz TA, Factor SM, Dickson DW: Immunocytochemical studies of atherosclerotic lesions of cerebral berry aneurysms. *J Neuropathol Exp Neurol* 53: 399–406, 1994

30) Krischek B, Tatagiba M: The influence of genetics on intracranial aneurysm formation and rupture: current knowledge and its possible impact on future treatment. *Adv Tech Stand Neurosurg* 33: 131–147, 2008

31) Ruigrok YM, Rinkel GJ: Genetics of intracranial aneurysms. *Stroke* 39: 1049–1055, 2008

32) Alg VS, Sofat R, Houden H, Werring DJ: Genetic risk factors for intracranial aneurysms: a meta-analysis in more than 116,000 individuals. *Neurology* 80: 2154–2165, 2013

33) Hong EP, Park JW: Sample size and statistical power calculation in genetic association studies. *Genomics Inform* 10: 117–122, 2012

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