Surgical Outcome and Histological Differences between Individuals with TGFBR1 and TGFBR2 Mutations in Loeys-Dietz Syndrome

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Purpose: To identify differences in surgical outcomes between patients with transforming growth factor-beta receptor (TGFBR) 1 and TGFBR2 mutations in Loeys-Dietz syndrome (LDS).

Methods: In all, 22 LDS patients between 1998 and 2015 were divided into the two groups: TGFBR1 (n = 11) and TGFBR2 mutation (n = 11).

Results: The freedom from aortic reoperation was similar between the two groups (p = 0.19, log-rank). In the subanalysis, the freedom from aortic reoperation was lower in female patients with TGFBR2 mutations (n = 6) than in other patients (p = 0.08). The freedom from aortic dissection (AD) after the initial surgery was also lower in female patients with TGFBR2 mutation than in other patients (p = 0.025). All patients with TGFBR2 mutations revealed grade III cystic medial necrosis (CMN), whereas 67% of patients with TGFBR1 mutations showed CMN (p = 0.033) and only one patient had grade III (p <0.001).

Conclusion: LDS patients with TGFBR2 mutations had higher grade of CMN than those of TGFBR1 mutations. In particular, in female patients with TGFBR2 mutations, AD after the initial surgery and reoperation were more frequent than those of other LDS patients.

Keywords: Loeys-Dietz syndrome, transforming growth factor-beta receptor, cystic medial necrosis, surgical outcome

Introduction

Loeys-Dietz syndrome (LDS) is one of the hereditary aortic diseases (HAD), which is caused primarily by transforming growth factor-beta receptor (TGFBR) 1 and TGFBR2 mutations.1–3) Aortic lesions are considered to have great influences on the clinical prognosis. Our previous study reported a lower free rate from aortic events after the initial aortic surgery in patients with LDS and recommended earlier surgical interventions compared

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with Marfan syndrome.\textsuperscript{4} The current aortic management for LDS has been similar between patients with \textit{TGFBR1} and \textit{TGFBR2} mutations.\textsuperscript{1,4–6} However, the international LDS registry recently revealed that female patients with lower body surface area (BSA), \textit{TGFBR2} mutation, and severe extra-aortic features tended to have poorer prognosis.\textsuperscript{7} However, no reports have determined clearly any differences in the surgical outcomes according to the mutation differentiation.

This study is aimed to determine differences in surgical outcomes and histological differences between LDS patients with \textit{TGFBR1} and \textit{TGFBR2} mutations.

**Materials and Methods**

The flowchart of this study population based on the exclusion criteria and method is shown in Fig. 1. Medical records of 304 patients aged <50 years and underwent surgeries for thoracic aortic diseases between 1998 and 2015 were investigated. Depending on the different situations, genetic screening was conducted in 163 patients (54.0%) who underwent aortic surgeries at our center and were suspected of HADs due to their younger age (<50 years) at the onset of aortic dissection (AD), family history, and physical features. Patients with inflammatory aortic disease including Takayasu arteritis and Behçet’s disease, and the majority of patients with bicuspid aortic valve were excluded from the genetic screening. Among them, gene mutations were identified in 76.7% (n = 125/163) of patients: 94 (57.7%) with \textit{FBN1} mutations; 26 (15.9%) with \textit{TGFBR1}, \textit{TGFBR2}, \textit{SMAD3}, or \textit{TGFB2} mutations; 2 (1.2%) with \textit{COL3A1} mutations; and 9 (5.5%) with \textit{ACTA2} mutations. A total of 32 (19.7%) patients had no detectable mutations. All of them were determined at our research laboratory center. Patients with \textit{SMAD3} (n = 2) and \textit{TGFB2} (n = 2) mutations were excluded from the LDS category because the mechanisms of these four gene mutations causing aneurysm or dissection are still unknown. Finally, 22 patients (13.5%) with \textit{TGFBR1} (n = 11) and \textit{TGFBR2} mutations (n = 11) were enrolled in this study (Fig. 1).

In all, 11 LDS patients with \textit{TGFBR1} mutation were assigned to the \textit{TGFBR1} group (8 males, 3 females; mean age at the first operation, 30 \pm 9.7 years) and the other 11 patients with \textit{TGFBR2} mutation were assigned to the \textit{TGFBR2} group (5 males, 6 females; 25 \pm 10 years). Preoperative hypertension (HT) was defined as the presence of systolic blood pressure of >140 mmHg or diastolic blood pressure of >90 mmHg or daily use of an antihypertensive medication. Preoperative HT was determined before diagnosing an aortic disease. Aortic root dilatation was defined as a Z-score of \geq 2, a tool that correlates aortic sizes with patients’ BSA scores.\textsuperscript{1}

**Patient characteristics**

Prevalent characteristics and clinical features of both groups are listed in Table 1. At the initial surgery, the prevalence of type A AD was similar between the two groups (45.4% vs. 9.1%; p = 0.15), whereas the number of type B AD significantly smaller in the \textit{TGFBR1} (9.1%) than in the \textit{TGFBR2} group (54.5%) (p = 0.034). The incidence of annulo-aortic ectasia was similar between the two groups (45.4% vs. 36.4%; p = 1.00). The proportion of patients with a family history of thoracic aortic diseases tended to be more frequent in the \textit{TGFBR1} (90.9%) than in the \textit{TGFBR2} group (54.5%) (p = 0.081). No differences were observed in other variables (Table 1).

**Operative techniques**

Valve-sparing root replacement (VSRR) was performed through a standard median sternotomy or lower...
mini-sternotomy with cardiopulmonary bypass (CPB) established with ascending aorta/femoral arterial cannulation in conjunction with bicaval venous drainage. In the aortic arch surgery, arterial cannulation to the right axillary artery in the axilla was usually performed with the ascending aorta and/or femoral artery cannulation for CPB. Patients were cooled to 25–28°C. Antegrade selective cerebral perfusion was employed for cerebral safety.\(^8\) A stepwise distal aortic anastomosis was frequently used to perform a secure and easy anastomosis.\(^9\) Patients who had thoracoabdominal aortic and descending aortic grafting were treated with 4th to 7th intercostal space thoracotomy. CPB was established with venous drainage from the femoral vein and the main pulmonary artery in conjunction with arterial return via the left axillary and femoral artery. Patients were cooled to a core temperature 18–20°C and an open proximal and/or distal aortic anastomosis was most frequently performed.

**Endpoint analysis**

The primary endpoint of this study was long-term aortic events, including a new AD, aortic reoperation, and aortic rupture. As the secondary endpoint, the long-term survival rate was determined, and pathohistological findings of surgical aortic specimens were also compared between the two groups. The international LDS registry showed an extremely poor prognosis in female patients and/or patients with TGFBR2 mutations compared with other LDS patients.\(^7\) To investigate these specific clinical courses, the patients were divided into two groups (Fig. 1). The follow-up rate was 100% among the survivors.

**Pathohistological examination**

Surgical specimens for the histopathological examination were obtained from the ascending aorta (including the Valsalva sinus and aortic arch) and/or the descending aorta to the Th10 level (excluding the infrarenal abdominal aorta). Regarding the histopathological results, including specimens sampled at the previous operations, cystic medial necrosis (CMN; defined as pooling of mucoid material), and elastin fragmentation (EF; characterized by elastin lamellae disruption) were determined. The two features were then classified into three grades (grade III, the severest), that is, according to the degree of cystic areas in patients with CMN and the amount of foci with EF in patients with EF.\(^10\) The specimens with a small amount of media was excluded from this study because performing an accurate evaluation might be difficult. The aortic wall having a large amount of media was included in this study, although a simple

| Variable                                      | TGFBR1 (n = 11) No. (%) | TGFBR2 (n = 11) No. (%) | p value |
|-----------------------------------------------|-------------------------|-------------------------|---------|
| Male/female                                   | 8/3                     | 5/6                     | 0.39    |
| Age (mean ± standard deviation)               | 30 ± 10                 | 25 ± 10                 | 0.32    |
| Diagnosis at initial surgery                  |                         |                         |         |
| AD (STA) (acute/chronic)                      | 5 (3/2) (45.5%)         | 1 (1/0) (9.1%)          | 0.15    |
| AD (STB) (acute/chronic)                      | 1 (0/1) (9.1%)          | 6 (0/6) (54.5%)         | 0.034   |
| Annulo-aortic ectasia                         | 5 (45.5%)               | 4 (36.4%)               | 0.66    |
| Other conditions                              |                         |                         |         |
| Hypertension                                  | 3 (27.3%)               | 5 (45.5%)               | 0.42    |
| Dissection during pregnancy in females        | 1 (33.3%)               | 1 (16.7%)               | 0.58    |
| Root dilatation (>Z2)                         | 7 (63.6%)               | 8 (72.7%)               | 0.68    |
| Family history of aortic disease              | 10 (90.9%)              | 6 (54.5%)               | 0.081   |
| Ectopia lentis                                | 0                       | 0                       | –       |
| Operative procedures                          |                         |                         |         |
| Root repair (valve sparing root repair/Bentall)| 7 (5/2) (63.3%)         | 4 (4/0) (36.4%)         | 0.39    |
| Hemiarch repair                               | 0                       | 1 (9.1%)                | 1.0     |
| Total arch repair                             | 3 (27.3%)               | 0                       | 0.21    |
| Descending repair                             | 0                       | 4 (36.4%)               | 0.045   |
| Thoracoabdominal repair                       | 1 (9.1%)                | 2 (18.2%)               | 0.61    |
| Emergency surgery                             | 3 (27.3%)               | 1 (9.1%)                | 0.59    |

AAA: abdominal aortic aneurysm; AAE: annuloaortic ectasia; AD: aortic dissection; STA: Stanford type A; STB: Stanford type B; TGFBR: transforming growth factor-beta receptor
dissection flap excluded for the examination. The specimen with the severest grade from multiple samples was selected in each patient.

Data collection and statistical analysis
Data were collected from the hospital admission and outpatient medical records. All patients were followed up as outpatients either at our center or local hospitals. This retrospective observational study was approved by the institutional review board (M30-057), and individual oral and written informed consent was waived due to its retrospective design. Statistical analyses were conducted using STATA software (Stata Corp LLC, College Station, TX, USA). Categorical data were compared using the Fisher’s exact test. Continuous variables were expressed as the mean ± standard deviation and compared using t-test; p <0.05 was considered statistically significant. Survival rate, freedom from reoperation, and freedom from aortic operation after the initial operation were assessed using a Kaplan–Meier life-table analysis, and the log-rank test was used when comparing the subgroups.

Results

Operative findings, early morbidity, and mortality
Surgical procedures were compared between the two groups (Table 1). Descending thoracic aortic repair was more frequently performed in the TGFBR2 (36.4%) than in the TGFBR1 group (0%) (p = 0.045). Neither in-hospital deaths nor cerebral events occurred in both groups. VSRR was performed in five patients of the TGFBR1 group and four patients of the TGFBR2 group; complete atroventricular block requiring pacemaker implantation occurred in one patient from each group. No other postoperative complications were observed (Table 1). Staged operation was conducted in one patient of the TGFBR2 group, a 9-year-old boy with history of acute type A AD on chronic type B AD. He underwent VSRR and total arch replacement (TAR), followed by secondary thoracoabdominal repair within 1 year. Four emergent surgeries, including a Bentall procedure in two patients, hemiarch repair in one patient, and TAR in one patient, were performed for acute type A AD.

Late mortality
The long-term follow-up was available in 100% of survivors, and the mean follow-up time was comparable between the two groups: 95 ± 98 and 135 ± 61 months (p = 0.63). In the TGFBR1 group, one patient with hyperthyroidism suddenly died, presumably from ventricular arrhythmia at 1 month postoperatively. No other deaths occurred in both groups. The freedom from all-cause mortality was similar between the two groups (p = 0.32, log-rank).

Aortic reoperation
During the follow-up periods, eight aortic reoperations were performed for five patients in the TGFBR1 and 25 aortic reoperations for 10 patients in the TGFBR2 group. The freedom from aortic reoperation was similar between the two groups (p = 0.17, log-rank) (Fig. 2A). The details of surgical history in each group are presented in Table 2. In the TGFBR1 group, two redo emergency surgeries which included TAR for acute type A AD in one patient and descending thoracic aortic repair for rupture of acute type B AD in one patient were performed. In the TGFBR2 group, six redo emergency/urgent surgeries including isolated TAR in four patients, TAR with a Bentall procedure in one patient, and TAR with VSRR in one patient were performed for acute type A AD (Table 2). Among these eight redo surgeries due to AD, although the AD extended to the previous anastomosis in five patients, no new entries obviously arisen from the suture line of the initial surgery were detected. In the other three patients, AD did not extend to the previous anastomotic site.

Aortic dissection
AD during the follow-up is defined as performance of any types of AD developed after the initial aortic surgeries, including recurrent AD. AD after the initial surgery was detected in three patients in the TGFBR1 and six patients of the TGFBR2 group during the follow-up. The freedom from AD after the initial surgery was similar between the two groups (p = 0.55, log-rank) (Fig. 2B).

Subgroup analysis of female patients with TGFBR2
The freedom from aortic reoperation tended to be lower in female patients of the TGFBR2 group than that in other patients (p = 0.08, log-rank) (Fig. 2C). The freedom from AD was significantly lower in female patients of the TGFBR2 group than that in others (p = 0.025, log-rank) (Fig. 2D).

Details of pathohistological examination
The specimen was examined in nine patients (82%) of the TGFBR1 group and 10 (91%) of the TGFBR2 group. Grading of specimens in both groups is listed in Table 2. All patients of the TGFBR2 group revealed grade III CMN, whereas it was found in 67% (6/9) of patients of
the TGFBR1 group (p = 0.033). Of these, only one patient revealed grade III (p < 0.001) (Fig. 3A). Aortic specimens in patients with both TGFBR1 and TGFBR2 mutations demonstrated more than Grade II EF in all patients (p = 1.0). In terms of the grade III EF, it was more frequent in the TGFBR2 (10/10: 100%) than that in the TGFBR1 group (5/9: 55.6%) (p = 0.033) (Fig. 3A). The most common specimen with grade II CMN in the TGFBR1 group and grade III CMN in the TGFBR2 group are presented in Fig. 3B and 3C, respectively.

Discussion

LDS is a HAD caused by TGFBR1 or TGFBR2 mutation and no differences in phenotypes are observed between individuals with TGFBR1 and TGFBR2 mutations.1) However, Tran-Fadulu et al.11) reported on some clinical differences between them, demonstrating that male patients died at younger age than females in families with TGFBR1 mutations, and that more patients with TGFBR2 mutations develop AD even at the aortic diameters <5.0 cm than ones with TGFBR1 mutations. However, no causes of death were described, and the causes of such clinical differences remain unclear. Recently, the international registry of 441 LDS patients revealed some differences between patients with these mutations.7) Jondeau et al. demonstrated that patients with TGFBR1 or TGFBR2 mutation had the same prevalence of systemic features and survival, and recommended earlier preventive aortic surgery at the size of 40 mm in female patients with TGFBR2 mutation and lower BSA.
Table 2  Details of surgical history and grading of the specimens in both TGFBR1 and TGFBR2 groups

| Variable | Age | Gen | Initial surgery | Second | Third | Fourth | Fifth | CMN Ascending | EF Ascending | CMN Descending | EF Descending |
|----------|-----|-----|----------------|--------|-------|--------|-------|---------------|--------------|----------------|---------------|
| **TGFBR1** |     |     |                |        |       |        |       |               |              |                |               |
| 1        | 32  | M   | VSRR           |        |       |        |       | III           | III          | N/A            | N/A           |
| 2        | 46  | M   | TAR*           |        |       |        |       | II            | II           | N/A            | N/A           |
| 3        | 26  | M   | VSRR           |        |       |        |       | II            | II           | N/A            | N/A           |
| 4        | 25  | M   | VSRR           |        |       |        |       | I             | II           | N/A            | N/A           |
| 5        | 27  | M   | VSRR           |        |       |        |       | No CMN        | III          | N/A            | N/A           |
| 6        | 32  | M   | Bentall + TAR* | TAAAR  |       |        |       | No CMN        | III          | N/A            | N/A           |
| 7        | 38  | F   | TAR            | TAAAR**|       |        |       | N/A           | N/A          | II             | II            |
| 8        | 36  | F   | TAAAR          |        |       |        |       | N/A           | N/A          | II             | III           |
| 9        | 40  | F   | TAR            | DTAAR  |       |        |       | N/A           | N/A          | No CMN         | III           |
| 10       | 15  | M   | VSRR           | TAR**  | TAAAR | Re TAAAR|       | N/A           | N/A          | N/A            | N/A           |
| 11       | 16  | M   | Bentall*       | TAR    | Re-Bentall |       |       | N/A           | N/A          | N/A            | N/A           |
| **TGFBR2** |     |     |                |        |       |        |       |               |              |                |               |
| 1        | 19  | M   | VSRR           | Bentall|       |        |       | III           | III          | N/A            | N/A           |
| 2        | 36  | M   | TAAAR          | Bentall +TAR**| TAAAR|       |       | III           | III          | N/A            | N/A           |
| 3        | 22  | M   | VSRR           |        |       |        |       | III           | III          | N/A            | N/A           |
| 4        | 39  | F   | DTAAR          | TAR**  | TAAAR | VSRR  |       | III           | III          | N/A            | N/A           |
| 5        | 19  | F   | VSRR           | TAR**  |       |        |       | III           | III          | N/A            | N/A           |
| 6        | 39  | M   | DTAAR          | Re DTAAR| TEVAR| TAAAR |       | III           | III          | III            | III           |
| 7        | 15  | M   | VSRR           | TAR**  | DTAAR | TAAAR |       | III           | III          | III            | III           |
| 8        | 20  | F   | HAR*           | VSRR  | TAR   | TAAAR |       | III           | III          | No CMN         | III           |
| 9        | 9   | M   | TAAAR          | VSRR +TAR|       |       |       | III           | III          | No CMN         | III           |
| 10       | 30  | F   | DTAAR          | VSRR +TAR| Re DTAAR| Bentall | TAAAR | N/A           | N/A          | III            | III           |
| 11       | 30  | F   | DTAAR          | TAR**  | TAAAR | Bentall | TEVAR | N/A           | N/A          | N/A            | N/A           |

*Emergent surgery at initial surgery, **Emergent surgery due to type A/B dissection at redo surgery. AVR: aortic valve replacement; CMN: cystic medial necrosis; DTAAR: descending aortic repair; EF: elastin fragmentation; F: female; Gen: gender; M: male; N/A: no available specimen; TAR: total arch repair; TAAAR: thoracoabdominal aortic repair; TGFBR: transforming growth factor-beta receptor; VSRR: valve-sparing root replacement
In this study, similar to the previous study, no significant differences in the survival rates were observed between the two mutations. Moreover, there were also no differences in the freedom from reoperation and AD after the initial surgery. However, female patients with TGFBR2 mutation, who were more notable compared with the other LDS patients, tended to have a lower freedom from aortic reoperation and AD after the initial surgery. These results suggest that aortic structures might differ in patients with both mutations. In other words, patients with TGFBR2 mutation, especially females, might potentially have severer aortic pathologies.

In terms of aortic pathology, type B AD was more frequent in patients with TGFBR2 mutation compared to those with TGFBR1 mutation in this study, which suggested that aortic structures might differ between the two mutations. Previously, similar consequences were demonstrated in a large cohort. Regarding the type A AD, as the first aortic event, the international registry of acute AD showed a smaller aortic diameter before the AD onset in patients with TGFBR2 mutation than those with TGFBR1 mutation (51.8 ± 13.4 mm vs. 68.3 ± 23.0 mm; p = 0.06), due to some structural differences in the aorta with both mutations.

In this study, the most prominent observation was on pathohistological differences in the degree of CMN between the two mutations. Initial recognition of tissue disorders underlying the aortic dilation in LDS is medial degeneration, which is characterized by findings of EF, loss of smooth muscle cell, and glycosaminoglycan replacement. The presence of medial degeneration from the extracellular pooling of glycosaminoglycan-rich basophilic solid and insufficient cells leads to CMN. In general, CMN is occasionally found in non-HAD patients. Becker et al. reported that CMN was found in approximately 60% of the normal aorta for all generations. More commonly, CMN is also observed in patients with HADs, which is related to a higher risk for aortic events. In addition, EF is characterized by damaged elastin lamella and is one of the categories indicating medium changes of the aorta and reflects intimal degeneration and CMN. Recently, Wanga et al. hypothesized that EF plays a
causal role in the aortic calcification in MFS and proposed microcalcification as a novel imaging marker to monitor local EF and thus predict aortic events in patients with MFS. Regarding the relationship between EF and LDS, Nakajima et al.\(^{17}\) reported the pathohistological findings of the aortic wall, showing EF in LDS with \(TGFBR1\) mutation. In this study population, fewer specimens of the aorta with \(TGFBR1\) mutations revealed CMN compared with aortic specimens with \(TGFBR2\) mutations. In addition, grade III CMN was observed in only 11% of patients with \(TGFBR1\) mutations and 100% of patients with \(TGFBR2\) mutations. This difference might be related to the dissimilarities of surgical outcomes between \(TGFBR1\) and \(TGFBR2\) mutations. Conversely, specimens with both \(TGFBR1\) and \(TGFBR2\) mutations demonstrated more than the average EF in all patients. This finding indicates that both tissue abnormalities are advanced similarly.\(^{10,16,17}\) However, when limited to grade III EF, grade III EF was more frequent in \(TGFBR2\) mutations than in \(TGFBR1\) mutations. Therefore, this difference might be related to differences in surgical outcomes between two mutations.

**Study Limitations**

This was a retrospective study on a specific patient cohort, and the sample size was limited. Proper assessment to obtain reproducible results of histopathological findings in these types of patients will require a larger cohort.

**Conclusion**

Patients with LDS with \(TGFBR2\) mutation had a higher grade of CMN than those with \(TGFBR1\) mutation. When limited to female patients with \(TGFBR2\) mutations, AD after the initial surgery occurred more frequently compared to other LDS patients.

**Disclosure Statement**

All authors have no conflict of interest.

**References**

1) Loeys BL, Chen J, Neptune ER, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive, and skeletal development caused by mutations in \(TGFBR1\) or \(TGFBR2\). Nat Genet 2005; 37: 275–81.
2) van de Laar IM, Oldenburg RA, Pals G, et al. Mutations in SMAD3 cause a syndromic form of aortic aneurysms and dissections with early-onset osteoarthritis. Nat Genet 2011; 43: 121–6.
3) Lindsay ME, Schepers D, Bolar NA, et al. Loss-of-function mutations in \(TGFBR2\) cause a syndromic presentation of thoracic aortic aneurysm. Nat Genet 2012; 44: 922–7.
4) Iba Y, Minatoya K, Matsuda H, et al. Surgical experience with aggressive aortic pathologic process in Loeys-Dietz syndrome. Ann Thorac Surg 2012; 94: 1413–7.
5) Van Laer L, Dietz H, Loeys B. Loeys-Dietz syndrome. Adv Exp Med Biol 2014; 802: 95–105.
6) Loeys BL, Schwarz U, Holm T, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med 2006; 355: 788–98.
7) Jondeau G, Ropers J, Regalado E, et al. International registry of patients carrying \(TGFBR1\) or \(TGFBR2\) mutations: results of the MAC (Montalcino Aortic Consortium). Circ Cardiovasc Genet 2016; 9: 548–58.
8) Minatoya K, Ogino H, Matsuda H, et al. Evolving selective cerebral perfusion for aortic arch replacement: high flow rate with moderate hypothermic circulatory arrest. Ann Thorac Surg 2008; 86: 1827–31.
9) Ogino H, Ando M, Sasaki H, et al. Total arch replacement using a stepwise distal anastomosis for arch aneurysms with distal extension. Eur J Cardiothorac Surg 2006; 29: 255–7.
10) Schlatmann TJ, Becker AE. Histologic changes in the normal aging aorta: implications for dissecting aortic aneurysm. Am J Cardiol 1977; 39: 13–20.
11) Tran-Fadulu V, Pannu H, Kim DH, et al. Analysis of multigenerational families with thoracic aortic aneurysms and dissections due to \(TGFBR1\) or \(TGFBR2\) mutations. J Med Genet 2009; 46: 607–13.
12) Romaniello F, Mazzaglia D, Pellegrino A, et al. Aortopathy in Marfan syndrome: an update. Cardiovasc Pathol 2014; 23: 261–6.
13) Girdauskas E, Kuntze T, Borger MA, et al. Long-term prognosis of type A aortic dissection in non-Marfan patients with histologic pattern of cystic medial necrosis. Ann Thorac Surg 2008; 85: 972–7.
14) Seike Y, Minatoya K, Sasaki H, et al. Clinical outcomes of aortic repair in young adult patients with \(ACTA2\) mutations. Gen Thorac Cardiovasc Surg 2017; 65: 686–91.
15) Fujiyoshi T, Minatoya K, Ikeda Y, et al. Impact of connective tissue disease on the surgical outcomes of aortic dissection in patients with cystic medial necrosis. J Cardiothorac Surg 2017; 12: 97.
16) Wanga S, Hibender S, Ridwan Y, et al. Aortic microcalcification is associated with elastin fragmentation in Marfan syndrome. J Pathol 2017; 243: 294–306.
17) Nakajima T, Tachibana K, Miyaki Y, et al. Acute dilatation of the ascending aorta and aortic valve regurgitation in Loeys-Dietz syndrome. Ann Thorac Surg 2014; 97: 2188–90.