## Other biomarkers

As discussed above, inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein, may be elevated in both inflammatory and infected aortic aneurysms. Procalcitonin, a polypeptide comprising 113 amino acids, is gathering increasing attention because of strong correlation between procalcitonin concentration and extent and severity of bacterial infections [90]. In the case of infected aortic aneurysm we had experienced (Fig. 1), serum procalcitonin level at admission was 1.05 ng/mL, a level that was suggestive of bacterial infection. Procalcitonin is produced ubiquitously by endotoxin or mediators released in response to bacterial infections; thus, utility of inflammatory cytokines [92] and procalcitonin for discriminating inflammatory IgG4-related, or non-IgG4-related, aortic aneurysm from infected aortic aneurysm should be assessed in future studies.

We recently reported that the serum sIL-2R level was elevated in 6 (75%) of 8 patients with chronic periaortitis [91], suggesting that sIL-2R may be another candidate biomarker for discriminating inflammatory from infected aortic aneurysm; again, however, little is known about sIL-2R levels in infected aneurysm. New biomarkers that specifically identify the inflammatory (or infected) aortic aneurysm are now under surveillance.

## Conclusions

Here we have briefly summarized the current understanding of both infected and inflammatory aortic aneurysm, and discussed the potential uncertainty for a differential diagnosis. These two clinical entities possess various similarities in clinical manifestation, biomarkers, CT, MRI, and radionucleotide imaging. It is considered that incorrect administration of immunosuppressing agents in infected aortic aneurysm would be hazardous [93] and delayed diagnosis may lead to uncontrolled growth of microorganisms. Caution should be taken to avoid the easy usage of corticosteroid or immunosuppressing drugs before the full diagnosis is established.

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Review

# Multifocal fibrosclerosis and IgG4-related disease involving the cardiovascular system

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**Summary** The cardiovascular system may be involved as a target organ of multifocal fibrosclerosis, which may manifest as idiopathic retroperitoneal fibrosis, inflammatory aortic aneurysm, inflammatory periarteritis, and inflammatory pericarditis. These pathological conditions can sometimes occur concomitantly. Idiopathic retroperitoneal fibrosis and inflammatory abdominal aortic aneurysm are both characterized by the presence of fibro-inflammatory tissue around the abdominal aorta expanding into the surrounding retroperitoneal structures, and together they may be termed 'chronic periaortitis'. Cardiovascular fibrosclerosis has become non-uncommonly encountered condition since imaging modalities have made its diagnosis more feasible. In addition, recent studies have demonstrated that a certain fraction, but not all, of cardiovascular fibrosclerosis may have a link with immunoglobulin-G4 (IgG4)-related sclerosing disease (IgG4-SD). IgG4-SD is histologically characterized by dense fibrosclerosis and infiltration of lymphocytes and IgG4-positive plasma cells, and these histopathologic findings seem to be essentially similar regardless of the organs involved. In this mini review, we summarize what is known so far about multifocal fibrosclerosis of the cardiovascular system and its association with IgG4-SD, and what remains to be clarified in future investigations.


## Contents



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## Introduction

Inflammatory and immune-mediated fibrosclerosis may involve various organs, including the cardiovascular system [1,2]. Immunoglobulin G4 (IgG4), which comprises about 4% of total immunoglobulin G (IgG), is unable to bind Clq complement and cannot activate the classic complement pathway [3]. Since Hamano et al. discovered the elevation of serum IgG4 levels and tissue infiltration of IgG4-positive plasma cells in autoimmune pancreatitis in 2001 [4,5], the relationship between IgG4-related immuno-inflammation and fibrosclerotic tissue degeneration has been gathering increasing attention [6,7], which is termed IgG4-related sclerosing disease (IgG4-SD) [8] or other synonyms [9]. IgG4-SD is now considered to encompass various organs including the lung [10], kidney [11], liver [12], and exocrinogical and endocrinological organs [13—15]. Regardless of the type of organs involved [16,17], the histopathologic findings of IgG4-SD seem to be essentially similar, which are characterized by dense fibrosclerosis, intense inflammatory cell infiltration with lymphocytes, IgG4-positive plasma cells, and scattered neutrophils and eosinophilic aggregates can also be observed [18]. In addition, IgG4-SD may appear as a mass-forming inflammatory pseudotumor [19,20].

A growing body of evidence suggests that the cardiovascular system may become a target of IgG4-related multifocal fibrosclerosis; it may be manifested as idiopathic retroperitoneal fibrosis, inflammatory aortic aneurysm, coronary periarteritis [21—23], and pericarditis [24]. In this mini review, we discuss briefly what is known about the cardiovascular manifestation of multifocal fibrosclerosis and its relationship with IgG4-related immuno-inflammatory conditions.

## Chronic periaortitis

Inflammatory aortic aneurysm and idiopathic retroperitoneal fibrosis may be grouped together under the umbrella of chronic periaortitis according to their common histopathological features [22,25]. Although chronic periaortitis had been considered to be a relatively rare disorder, its presence has been increasingly recognized with the advent of non-invasive imaging modalities such as computed tomography (CT) scanning.

### Clinical pictures of chronic periaortitis

Chronic periaortitis is commonly symptomatic at presentation, with the most frequent symptom being back and/or abdominal pain [26,27]. Abnormalities in inflammatory markers, such as elevated C-reactive protein and enhanced erythrocyte sedimentation rate, are common laboratory findings [28], and antinuclear antigen may be detected in about half of all cases [26,29]. Macroscopically, chronic periaortitis appears as a thick glistening retroperitoneal mass around the abdominal aorta or ileac arteries with a whitish surface [30]. Chronic periaortitis may be treated either medically or surgically. Corticosteroid and immunosuppressive drugs may be effective in the amelioration of radiological findings and in the reduction of inflammatory markers over a relatively short period [31].

Idiopathic retroperitoneal fibrosis, which is also called Ormond's disease [32], was first described by Albarran et al. in 1905 [33]. Retroperitoneal fibrosis may be caused by certain drugs, infections, radiotherapy, surgery, and malignancies [34]; however, more than two-thirds of cases are idiopathic in nature. Idiopathic retroperitoneal fibrosis has been considered to be an uncommon condition with an estimated incidence of 1.38 per 100,000 inhabitants [35]. Diagnosis of this disease relies primarily on imaging studies, most frequently CT scanning [26]; the disease is characterized by a fibroinflammatory soft tissue mass surrounding the aorta and/or adjacent tissues. Biopsy of the retroperitoneal mass is currently less frequently performed due to the potential risks; in some cases, however, the possibility of an alternative condition, such as malignancy or infection, should be ruled out histopathologically [36,37].

Inflammatory abdominal aortic aneurysm is a pathological condition that is estimated to account for less than 10% of all cases of abdominal aortic aneurysm [38,39]. Inflammatory abdominal aortic aneurysm may be termed the 'aneurysmal form of chronic periaortitis' and, when accompanied by ureteric blockade, 'perianeurysmal retroperitoneal fibrosis' [40], although these names have not been frequently used to date.

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## Relationship between chronic periaortitis and IgG4-SD

Neild et al. reported 12 patients with idiopathic retroperitoneal fibrosis which was diagnosed to be IgG4-related histologically and immunohistochemically [18]. In addition, Zen et al. reported 13 cases of idiopathic retroperitoneal fibrosis among 114 patients with histopathologically diagnosed IgG4-SD in a cross-sectional study [7]. Furthermore, Ito et al. reported a 77-year-old male patient who presented with malaise and intermittent lower abdominal pain and was diagnosed to have inflammatory aortic aneurysm which was shown to be IgG4-related immunohistochemically [41]. These findings indicate that chronic periaortitis may, at least in part, be IgG4-related.

Kasashima et al. identified 23 cases of inflammatory aneurysm whose diagnosis had been made on the basis of pathological findings from a total of 252 cases of surgically treated abdominal aortic aneurysm, and found that 13 cases (57%) were IgG4-related [42]. No clear differences were found between IgG4-related and non-IgG4-related inflammatory abdominal aortic aneurysms in terms of macroscopic findings in Kasashima et al.'s series. In addition, Sakata et al. compared the clinicopathologic characteristics of cases of inflammatory abdominal aortic aneurysm with age- and sex-adjusted cases of atherosclerotic abdominal aortic aneurysm [43]. They found that infiltration of IgG4-positive cell can occur in *atherosclerotic* aortic aneurysm, and that, conversely, not all cases of inflammatory abdominal aortic aneurysm are IgG4-related. Furthermore, we experienced a patient with idiopathic retroperitoneal fibrosis who had normal serum IgG4 levels (Fig. 1A) [44], and found that the clinical picture and response to corticoid treatment seemed to be similar between IgG4-related and non-IgG4-related idiopathic retroperitoneal fibrosis [45]. These observations indicate that not all the chronic periaortitis may be IgG4-related [46].

## Thoracic periaortitis

Although the thoracic aorta has been considered relatively free from the inflammatory infiltration, several previous studies reported inflammatory aortic aneurysm or periaortitis at the thoracic aorta [47—50] (Fig. 1B).

### Clinical pictures of thoracic periaortitis

Bahler et al. presented a case with fibroinflammatory soft mass paralleling the aortic arch, occurrence of which had been preceded by the onset of idiopathic retroperitoneal fibrosis by six years [51]. In addition, Gluhovschi et al. reported a 45-year female who presented with idiopathic retroperitoneal fibrosis causing renal dysfunction and thoracic periaortitis, both of which were ameliorated by immunosuppressive therapy [52]. It is suggested that thoracic periaortitis can be a manifestation of systemic fibrosclerosis.

### Relationship between thoracic periaortitis and IgG4-SD

Some previous studies have investigated an association between thoracic aortic aneurysm/periaortitis and IgG4-related immuno-inflammation [16,53,54]. Kasashima et al. performed immunohistochemical analysis of the resected aorta from 125 patients of thoracic aortic aneurysm, and found five cases of IgG4-SD [55]; among them, one was diagnosed as *inflammatory* aneurysm and three were diagnosed as *atherosclerotic* aneurysm. Thus, the prevalence of IgG4-SD among thoracic aortic aneurysm/aortitis may be about 4% [55]. In Kasashima et al.'s series, mean age and sex-prevalence were similar between IgG4-related and non-IgG4-related thoracic aortic lesions; on the other hand, however, most of the IgG4-related thoracic lesions were located at the aortic arch, particularly in the distal arch, but only about one third of non-IgG4-related thoracic lesions were located at such regions. We recently reported a case of IgG4-related thoracic periaortitis at the aortic arch [54].

Stone et al. histologically analyzed 638 resected aortic samples obtained from thoracic aortitis cases, and reported that 33 (5.2%) were of a noninfectious nature [16]. In Stone et al.'s study, one of the cases of IgG4-related thoracic aortitis developed IgG4-SD involving liver, pancreas, and submandibular glands two years after aortic resection, suggesting that IgG4-related inflammatory thoracic aortitis may also represent a vascular manifestation of IgG4-related systemic fibrosclerosis. On the other hand, as in the case of abdominal aortic aneurysm [43], infiltration of IgG4-positive plasma cells or elevated serum IgG4 levels may not be a phenomenon exclusive to inflammatory aortic aneurysm/aortitis and, conversely, inflammatory aortic aneurysm/aortitis may not be always associated with these phenomena [56].

## Inflammatory periarteritis — vasculitis of smaller size arteries

Development of fibrosclerosis and infiltration of inflammatory cell in the perivascular tissue may occur, albeit less frequently, in smaller-sized arteries [57,58], which may be termed inflammatory periarteritis [22].

### Clinical pictures of inflammatory periarteritis

Mitchinson et al. reported two patients with ischemic heart disease in whom chronic coronary periarteritis was demonstrated histologically in conjunction with chronic periaortitis [21]. Maturen et al. have recently reported two patients with idiopathic retroperitoneal fibrosis who had perivascular low-attenuation soft tissue surrounding the coronary arteries, illustrated by CT, although significant luminal stenosis of the coronary artery was not noted at the site of periarteritis. [59] (Fig. 2). These findings suggest that coronary periarteritis may develop by the same pathological mechanisms as idiopathic retroperitoneal fibrosis.

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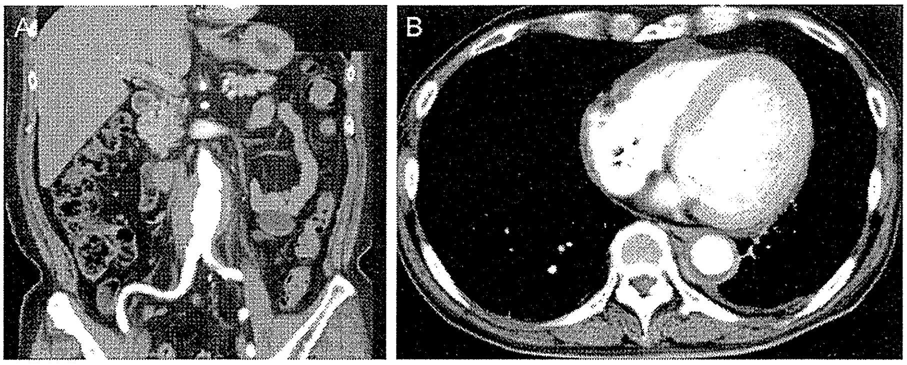


**Fig. 1** Contrast enhanced computed tomography of chronic periaortitis. (A) Retroperitoneal fibrosis in a reported case [44]. (B) Thoracic periaortitis in a reported case [69].

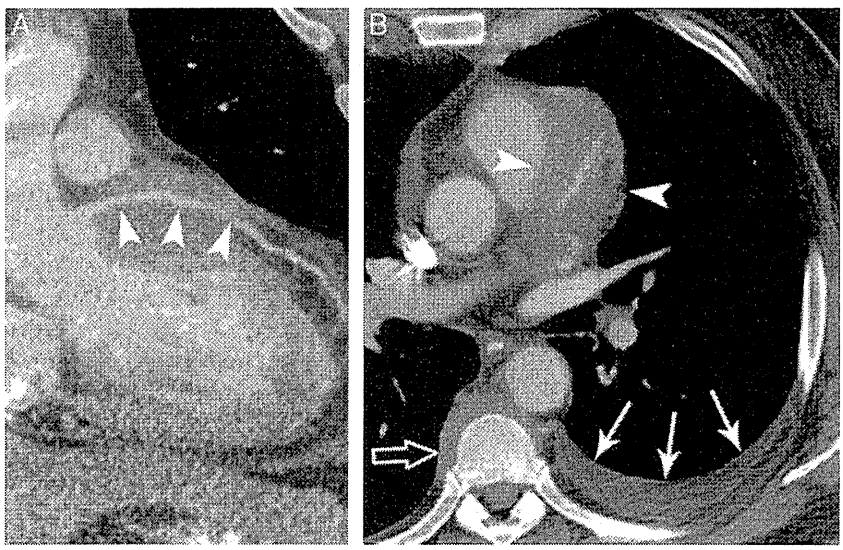


**Fig. 2** Contrast enhanced computed tomography of a case of idiopathic retroperitoneal fibrosis. (A) Abnormal soft tissue encasing normal diameter left main (white arrowheads) and proximal left anterior descending coronary arteries can be seen. (B) Axial image showing the abnormal soft tissue surrounding coronary arteries (white arrowheads), right paraspinal mass (open arrow), and left pleural effusion (white arrows). Reproduced from Maturen et al. [59].

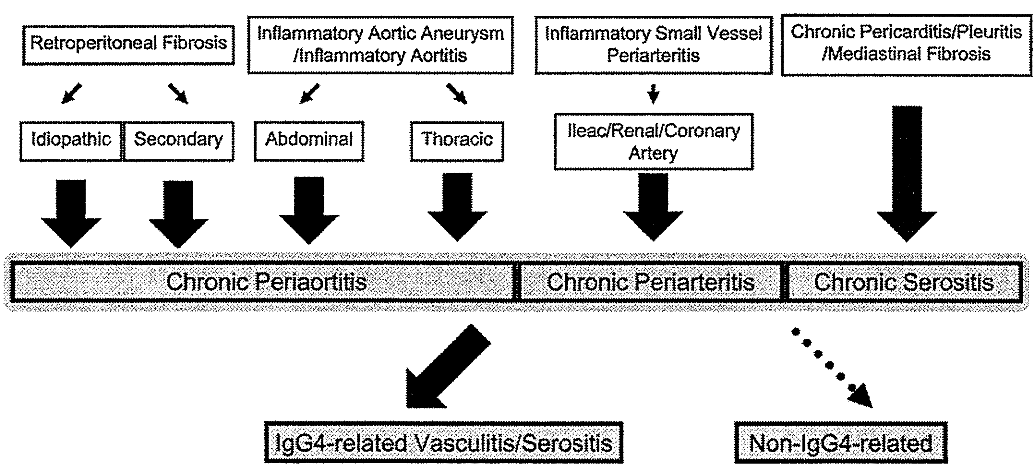


**Fig. 3** Proposed scheme of chronic vasculitis/serositis. This clinical entity may have to be reorganized according to the underlying immunopathological background.

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## Relationship between inflammatory periarteritis and IgG4-SD

Inoue et al. demonstrated 17 cases of inflammatory periaortitis or periarteritis that had occurred in the superior mesenteric, inferior mesenteric, and splenic arteries [60], and histologic examination of which, when available, revealed irregular fibrosis in the arterial walls and diffuse infiltration of IgG4-positive cells within the inflamed areas. In addition, Matsumoto et al. presented a case of IgG4-related abdominal periaortitis and inflammatory coronary periarteritis, manifested as a tumorous mass around the coronary artery [17]. Furthermore, we have recently experienced a patient with IgG4-related periarteritis of the coronary artery who was admitted to our hospital owing to the chest symptoms [23]. In this patient, serum IgG4 levels were elevated at 564 mg/dL, and a glittery white-yellowish elastic-hard periarterial mass surrounding the left circumflex artery could be seen after the incision of the pericardium. Whether IgG4-related coronary periarteritis plays a role in the development of coronary artery stenosis remains to be investigated, however, we may have to be, at least, aware that coronary periarteritis may increasingly be diagnosed in the era of multi-detector coronary-CT angiography.

## Inflammatory pericarditis and IgG4-SD

Several reports have demonstrated inflammatory pericardial fibrosis that occurred as a manifestation of systemic multifocal fibrosclerosis [2,24]. Sugimoto et al. reported a 68-year-old man who showed constrictive pericarditis as the initial manifestation, and staining of the excised pericardium with anti-IgG4 antibody revealed the infiltration of IgG4-positive plasma cell [61]. This patient developed pleural effusion and progressive pleural fibrosis six months after post-pericardiostomy. We have recently reported an 83-year-old man with pericardial fibrosis who died from cardio-respiratory failure due to massive pericardial effusion, and autopsy showed the infiltration of IgG4-positive plasma cells in the pericardium, as well as in the visceral and parietal pleura, pancreas, and retroperitoneal fibrous tissues [45]. This patient had a past history of autoimmune pancreatitis. These observations were consistent with the notion that inflammatory pericarditis may also develop as a feature of IgG4-related multifocal fibrosclerosis.

## Fibroinflammatory disorders of myocardium

Whether IgG4-related immuno-inflammation may underlie myocardial fibrosclerosis that would lead to cardiac failure seems to have been least extensively studied [62,63]. Cardiac sarcoidosis may be one of the disorders associated with the infiltration of lymphocytic cells and development of fibrosis in the heart [64]. We investigated the relationship between IgG4-SD and cardiac sarcoidosis; however, we could not find a meaningful relationship between these conditions [65]. Whether IgG4-related immuno-inflammation would underlie the pathogenesis of other myocardial disorders causing fibrosis and cardiac failure should be assessed in further studies.

## Hurdles to overcome for further investigations

As discussed above, IgG4-related autoimmunity may, although not always, underlie multifocal fibrosclerosis in the cardiovascular system. Toward achieving optimal therapeutic strategies and better understanding of the pathophysiology of IgG4-related fibrosclerosis in the cardiovascular system, there is an increasing need for research in this field; however, there are several hurdles to overcome before advances can be made.

First, the definition, as well as the nomenclature, of the disorder. Inflammatory aortic aneurysm is said to be present when periaortic fibrosis coexists with dilatation of the aorta; however, the cut-off value of aortic diameter that discriminates between idiopathic retroperitoneal fibrosis and inflammatory abdominal aortic aneurysm does not seem to be clear [34], or may sometimes be impractical. Likewise, retroperitoneal fibrosis may be subclassified as *IgG4-related* and *non-IgG4-related* forms; alternatively, however, it may also be subclassified as *idiopathic* and *secondary* forms. Furthermore, because IgG4-related fibrosclerosis can also occur in small-size vessels, pericardium, and possibly pleura, it might more suitably be termed 'IgG4-related (peri)vasculitis/serositis' (Fig. 3).

Second, differential diagnosis. In infected, or mycotic, aortic aneurysm, the bacterial culture may be negative in half of all cases [66] and serum IgG4 levels might be elevated [67]. Considering that about half of all cases of inflammatory aortic aneurysm may be IgG4-related [29], these situations may make differential diagnosis between inflammatory and infected aneurysm difficult. In addition, it should also be noted that diagnosis of IgG4-related or non-IgG4-related multifocal fibrosclerosis should not be made solely depending on the responsiveness to medical therapy, because some types of malignancy that might underlie or be misdiagnosed as fibrosclerotic disorders may also respond to corticosteroid therapy [68]. In patients with multiorgan fibrosis, we should not overlook the possibility of malignant disease.

Third, IgG4 positivity. Clinical pictures and therapeutic responsiveness of non-IgG4-related fibrosclerosis may be similar, sometimes almost identical, to IgG4-SD. It is possible that IgG4-positive cell infiltration may be a transient phenomenon during the development of fibrosclerotic tissue degeneration and that IgG4 may not play a central, but rather a bystander, role in the lesion formation.

## Conclusion

The cardiovascular system may be one of the target organs of IgG4-related, and non-IgG4-related, systemic multifocal fibrosclerosis. Cardiologists should be aware of this clinicopathological condition, not only because it can be potently managed by corticosteroid and/or immunosuppressive therapies, but also because it can take a rapid and fatal clinical course [45]. In addition, caution should be applied because cardiovascular fibrosclerosis may be accompanied by or misdiagnosed from other co-morbidities such as infection and malignancy. Further research is warranted in the field of IgG4-related cardiovascular fibrosclerosis.

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**Novel Insights from Clinical Experience**

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# Giant Tumorous Legions Surrounding the Right Coronary Artery Associated with Immunoglobulin-G4-Related Systemic Disease

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**Established Facts**

- A novel clinicopathological entity, immunoglobulin-G4-related systemic disease, can affect a wide variety of organs including the pancreas, bile duct, salivary glands and retroperitoneum.
- Further, immunoglobulin-G4-related systemic disease can be manifested as periarteritis, often as inflammatory abdominal aortic aneurysm.

**Novel Insights**

- Immunoglobulin-G4-related periarteritis can involve the coronary arteries.
- Immunoglobulin-G4-related systemic disease should be considered in any patient with abnormally increased wall thickness or ectatic lesions in the coronary arteries.

**Key Words**

Immunoglobulin-G4-related systemic disease · Coronary periarteritis · Autoimmune disease

**Abstract**

Immunoglobulin G4 (IgG4)-related systemic disease was first recognized as a clinicopathological entity about 10 years ago, and since then, it has attracted growing attention. It is an autoimmune disease which affects multiple organs including the pancreas, bile duct, salivary glands and retroperitoneum. Further, it was recently reported that it can be manifested as periarteritis, often as inflammatory abdominal aortic aneurysm. We describe the case of a 75-year-old man with autoimmune pancreatitis and parotitis who presented with angina. The serum concentration of IgG4 was significantly increased at 2,510 mg/dl. Coronary angiography showed multiple stenotic lesions and pronounced dilatation of the right coronary artery. Cardiac computed tomography disclosed increased wall thickness of the coronary arteries and focal tumorous lesions surrounding the right coronary artery. Treatment with steroids proved only marginally effective and he underwent surgical resection of the aneurysm and coronary artery bypass grafting. The diag-

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nosis of IgG4-related systemic disease was confirmed by histological examination of the resected mass, which showed a massive infiltration of IgG4-positive plasma cells. This case emphasizes the importance of considering the diagnosis in any patient with abnormally increased wall thickness or ectatic lesions in the coronary arteries.



## Introduction

Immunoglobulin G4 (IgG4)-related systemic disease is an autoimmune disorder in which IgG4-positive plasma cells infiltrate and expand in affected organs [1–6]. It was first recognized to involve the pancreas and is now known to involve diverse organs including not only the pancreas but also the bile duct, salivary glands, kidneys, lungs, retroperitoneum and aorta [7–10]. The spectrum of IgG4-related systemic disease is growing steadily, and it can be underdiagnosed simply due to a lack of awareness of this condition. We present a patient with IgG4-related coronary periarteritis in whom tumorous lesions surrounding the coronary arteries were demonstrated by cardiac computed tomography.

## Case Report

A 75-year-old man was referred to our department for chest pain on exertion. He had a long history of diabetes mellitus, hyperlipidemia and hypertension, which had been adequately controlled with medications. At the age of 70 years, autoimmune pancreatitis was diagnosed by elevated serum IgG4 concentration and the findings on abdominal computed tomography and magnetic resonance imaging. It had been followed up without steroid therapy due to the lack of clinical symptoms. Also recently, he had bilateral parotitis with painful swelling of the parotid glands. On admission, he had severe xanthomas of the Achilles tendons and on the dorsum of the hands. Thus, a possible diagnosis of familial hypercholesterolemia was made, which was further supported by his family history of early atherosclerotic disease. Laboratory data showed an increase in erythrocyte sedimentation rate (112 mm/h). In addition, the serum concentration of total IgG was increased substantially (3,566 mg/dl, normal range 800–1,600), and the serum IgG4 level was dramatically elevated at 2,510 mg/dl (normal range 4.8–105).

Coronary angiography showed diffuse severe stenosis of the left anterior descending artery and focal stenosis in the proximal left circumflex artery (fig. 1a), and the right coronary artery was generally ectatic with pronounced dilatation of the distal segment (fig. 1b). Cardiac computed tomography disclosed increased wall thickness of the coronary arteries and, of note, two focal tumorous lesions surrounding the middle and distal portion of the right coronary artery were revealed (fig. 2a). The wall thickness of the aortic arch and the abdominal aorta was also increased (fig. 3). $^{18}$F-fluorodeoxyglucose positron-emission tomography demonstrated intense uptake not only in the pancreas and the parotid glands, but also in the wall of the coronary arteries, suggesting active inflammation in these lesions (fig. 4).

The patient was clinically diagnosed with IgG4-related systemic disease and treated with prednisone 30 mg daily, followed by a taper of the daily dose by 5 mg per 2-week period. The swelling of the parotid glands resolved soon. The serum levels of total IgG and IgG4 decreased significantly to 1,266 and 676 mg/dl, respectively, and the diffuse pancreatic mass was reduced in size in 4 weeks. On the other hand, the thickened walls and tumorous tissues around the coronary arteries and the ectatic lesion of the right coronary artery were only marginally improved. The stenosis of the left cor-

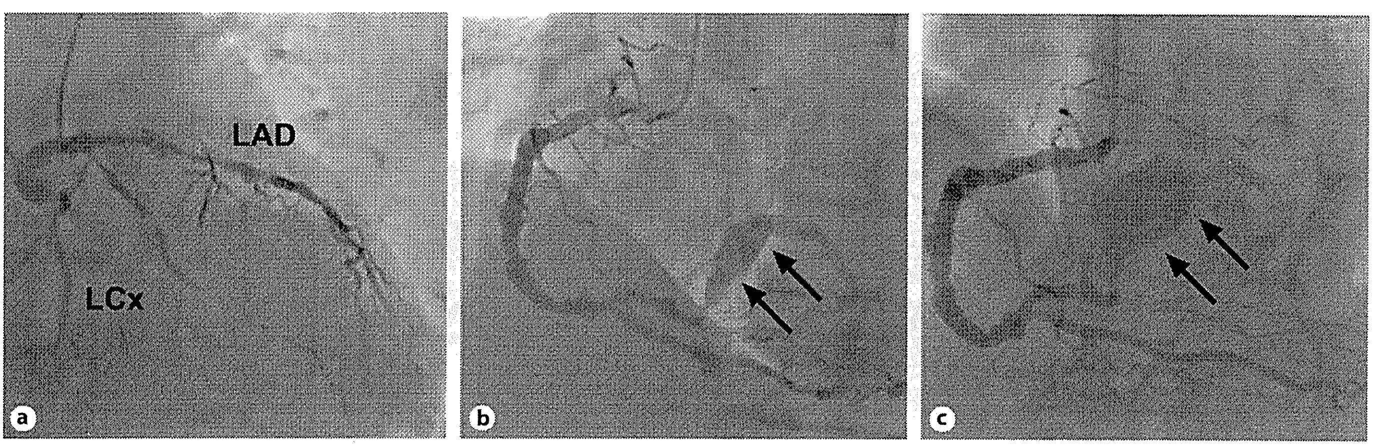


**Fig. 1.** Coronary angiography on first admission (**a**, **b**) and 4 months later (**c**). **a** Coronary angiography on first admission showing diffuse severe stenosis of the left anterior descending artery (LAD) and focal stenosis in the proximal left circumflex artery (LCx). **b** The right coronary artery was generally ectatic with pronounced dilatation of the distal segment (arrows). **c** Four months later, the ectatic lesion of the right coronary artery was further dilated (arrows).

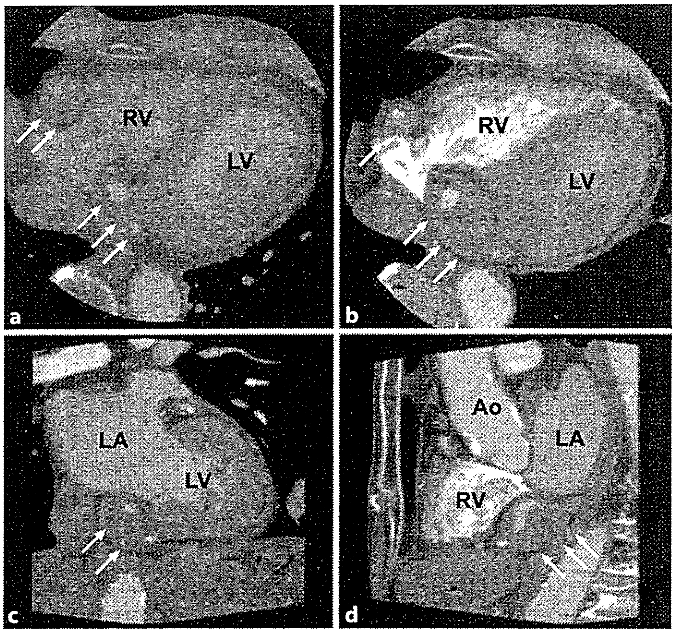


**Fig. 2.** Cardiac computed tomography on first admission (**a**) and 4 months later (**b–d**). RV = Right ventricle; LV = left ventricle; LA = left atrium; Ao = aorta. **a** Horizontal view of cardiac computed tomography on first admission demonstrating focal tumorous lesions surrounding the right coronary artery (arrows). **b–d** Four months later, the tumorous tissue in the distal portion (arrows) enlarged, as shown by horizontal (**b**), coronal (**c**) and sagittal view (**d**).

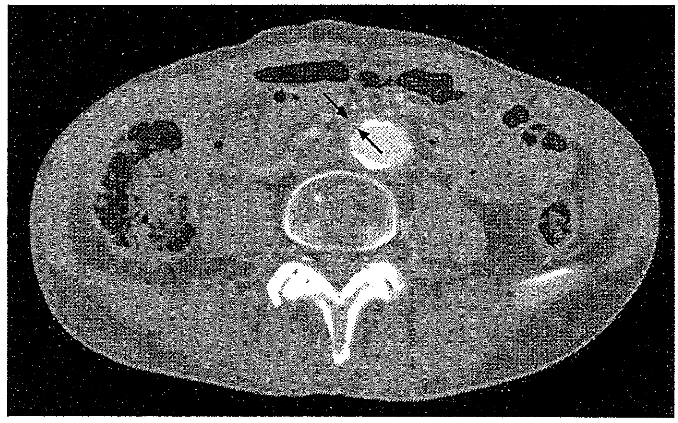

**Fig. 3.** Abdominal computed tomography showing the increased wall thickness of the abdominal aorta (arrows).

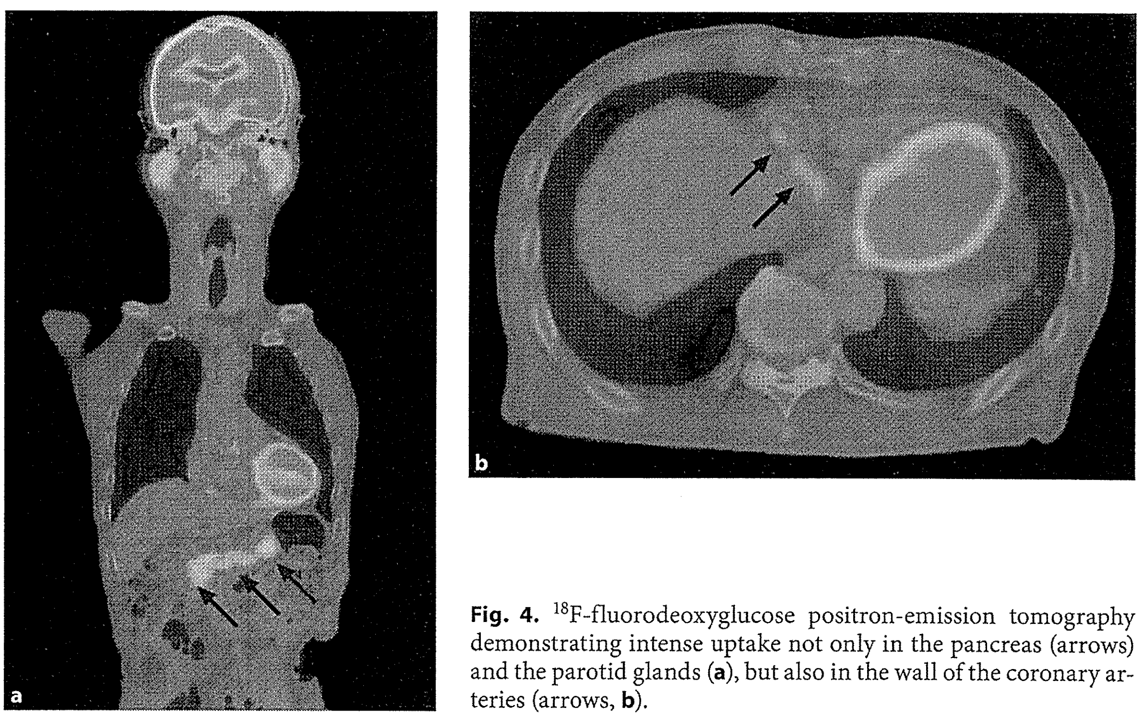


**Fig. 4.** $^{18}$F-fluorodeoxyglucose positron-emission tomography demonstrating intense uptake not only in the pancreas (arrows) and the parotid glands (**a**), but also in the wall of the coronary arteries (arrows, **b**).

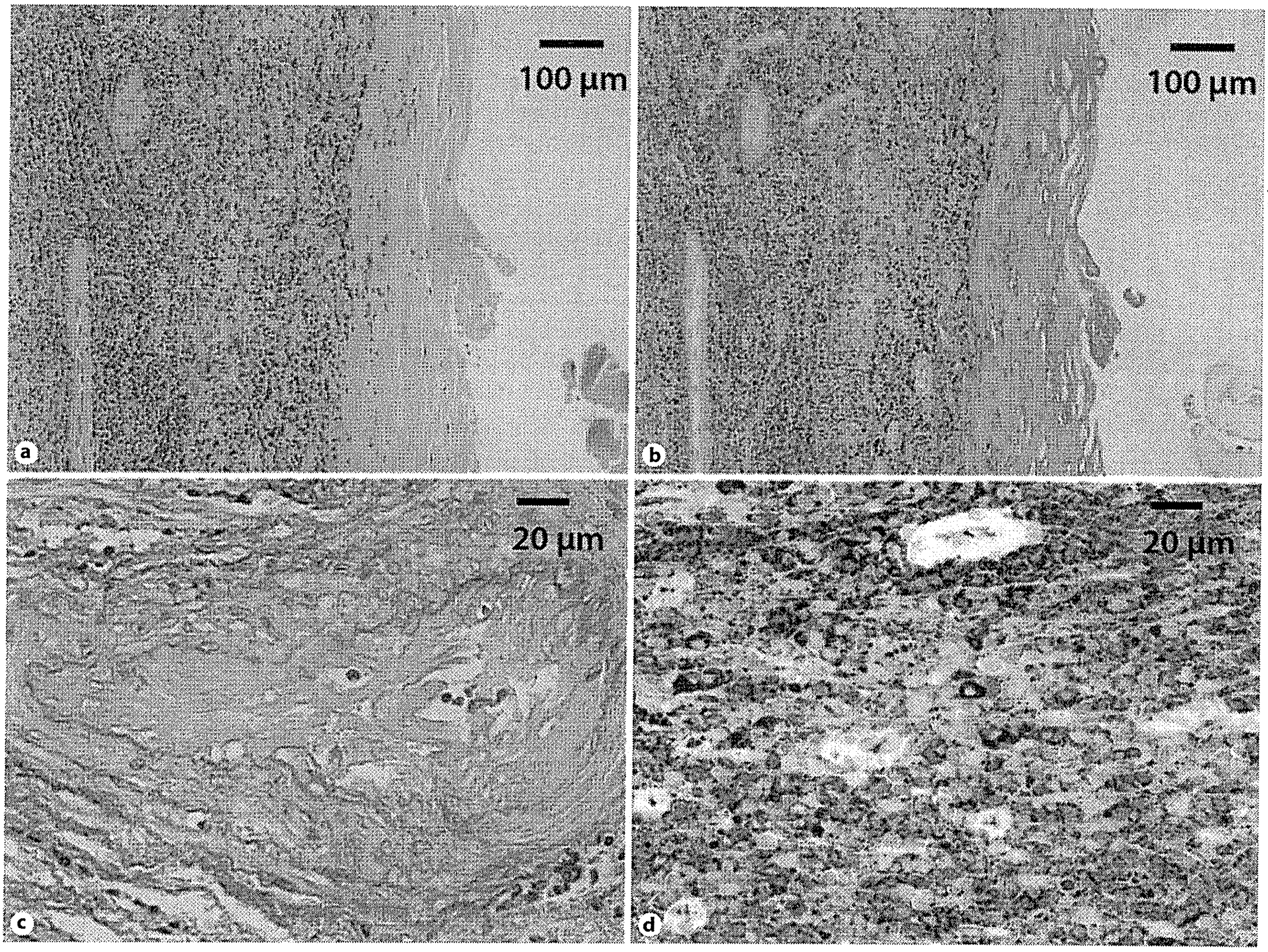


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**Fig. 5.** Histological examination of the resected mass. **a**, **b** Massive lymphoplasmacytic infiltrate and fibrosis were shown mainly in the adventitia as demonstrated by hematoxylin-eosin staining (**a**) and elastin van Gieson staining (**b**). **c** The small vessels in the adventitia were hypertrophied and some of them were occluded by the thrombus. **d** Immunohistological analysis using an anti-IgG4 antibody revealing that a majority of infiltrated cells were IgG4-positive plasma cells.

onary artery still remained. We performed percutaneous coronary intervention with placement of two drug-eluting stents in the left anterior descending artery. He was discharged without symptoms, taking prednisone at a dose of 15 mg per day.

Four months later, follow-up angiography demonstrated that the ectatic lesion of the right coronary artery was further dilated (fig. 1c) and the surrounding tumorous tissue enlarged from 40 × 24 to 48 × 29 mm (fig. 2b–d). Considering the risk of rupture, the patient underwent surgical resection of the aneurysm and coronary artery bypass grafting by attaching a saphenous vein graft sequentially to the left circumflex artery and the distal portion of the right coronary artery. He was angina free with prednisone at a dose of 7.5 mg per day at the last follow-up visit 4 months after surgery.

Histological examination of the resected mass showed a prominent lymphoplasmacytic infiltrate and fibrosis predominantly in the adventitia, with destruction of normal structures of the intima and the media (fig. 5a, b). The small vessels in the adventitia were severely hypertrophied, and some of them were occluded by the thrombus (fig. 5c). Immunohistological analysis revealed that a majority of infiltrated cells were IgG4-positive plasma cells, thus confirming the diagnosis (fig. 5d).

## Discussion

Since elevated serum IgG4 levels in patients with autoimmune pancreatitis were first reported in 2001 [3], there are rapidly emerging evidences that a novel clinicopathological entity, IgG4-related systemic disease, can affect multiple organs including the pancreas, bile duct, salivary glands and retroperitoneum [1–6]. Further, it is a recent topic of interest that IgG4-related systemic disease can be manifested as periarteritis, often as inflammatory abdominal aortic aneurysm [7–10]. A recent report described the first reported case of IgG4-related periarteritis presenting with a tumorous lesion of the right coronary artery [11]. The surgically resected mass showed the pathological features of diffuse lymphoplasmacytic infiltration and numerous IgG4-positive plasma cells. The radiological and histological findings are similar to those of our case. Thus, our case is considered to be the second reported case of IgG4-related periarteritis of the coronary arteries with severer manifestations. It is tempting to envision the possibility that concomitant familial hypercholesterolemia influenced these quite unusual radiological findings. Our patient was treated with steroids, and autoimmune pancreatitis and parotitis were ameliorated. However, on the other hand, the effect on periarteritis seemed to be limited, and surgical resection was required. While IgG4-related systemic disease often responds dramatically to corticosteroid therapy, there is no consensus on the optimal treatment of IgG4-related periarteritis, and further studies are needed.

The spectrum of IgG4-related systemic disease in the cardiovasculature is not fully understood, and IgG4-related periarteritis involving the coronary arteries may be underdiagnosed. IgG4-related systemic disease should be considered in any patient with abnormally increased wall thickness or ectatic lesions in the coronary arteries.

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# Evaluating Japanese Patients With the Marfan Syndrome Using High-Throughput Microarray-Based Mutational Analysis of Fibrillin-1 Gene

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**Marfan syndrome (MS) is an inherited connective tissue disorder, and detailed evaluations of multiple organ systems are required for its diagnosis. Genetic testing of the disease-causing fibrillin-1 gene (FBN1) is also important in this diagnostic scheme. The aim of this study was to define the clinical characteristics of Japanese patients with MS and enable the efficient and accurate diagnosis of MS with mutational analysis using a high-throughput microarray-based resequencing system. Fifty-three Japanese probands were recruited, and their clinical characteristics were evaluated using the Ghent criteria. For mutational analysis, an oligonucleotide microarray was designed to interrogate FBN1, and the entire exon and exon-intron boundaries of FBN1 were sequenced. Clinical evaluation revealed more pulmonary phenotypes and fewer skeletal phenotypes in Japanese patients with MS compared to Caucasians. The microarray-based resequencing system detected 35 kinds of mutations, including 23 new mutations. The mutation detection rate for patients who fulfilled the Ghent criteria reached 71%. Of note, splicing mutations accounted for 19% of all mutations, which is more than previously reported. In conclusion, this comprehensive approach successfully detected clinical phenotypes of Japanese patients with MS and demonstrated the usefulness and feasibility of this microarray-based high-throughput resequencing system for mutational analysis of MS.**  **(Am J Cardiol 2011;108:1801–1807)**

The Marfan syndrome (MS) is an inherited connective tissue disorder with an autosomal dominant inheritance, primarily involving the skeletal, ocular, and cardiovascular systems, caused by mutations in fibrillin-1 gene (FBN1).[1] Diagnosis of the MS has been made using the Ghent criteria[2] on the basis of data from European and American populations, but the Ghent criteria may not be completely suitable for the Japanese population.[3] Therefore, epidemiologic and genetic surveys in the Japanese population are mandatory to establish more Japanese-specific (or Asian-specific) diagnostic criteria for the MS. The Ghent criteria were recently further revised.[4] More weight is now given to FBN1 testing, and a diagnosis can be made if a patient has the FBN1 mutation plus either an aortic phenotype or ectopia lentis. These new criteria are much simpler than the original criteria. Thus, genetic testing of MS is becoming more important. FBN1 spans a 230-kb genomic region and contains 65 exons. More than 1,000 reported mutations are spread throughout the gene and are mostly unique in each affected family.[5,6] Classic genetic analysis methods such as direct sequencing are very time consuming. Thus, the introduction of a more efficient genetic analysis tool is needed. Custom-designed resequencing microarrays enable the analysis of multiple genes spanning 30 to 300 kb on a single array. The microarray identifies individual nucleotides by comparative, high-fidelity hybridization using oligonucleotide probes[7–9] (Figure 1). In the present study, we comprehensively evaluated the clinical characteristics of Japanese patients with suspected MS and also conducted mutational analysis of these patients by adopting a high-throughput genetic diagnosing system to achieve more efficient and accurate diagnoses.

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## Methods

Fifty-three consecutive probands suspected of having MS who visited the MS clinic at our hospital were enrolled. All patients were assessed using the original Ghent criteria.[2,10] This study was conducted according to the Declara-

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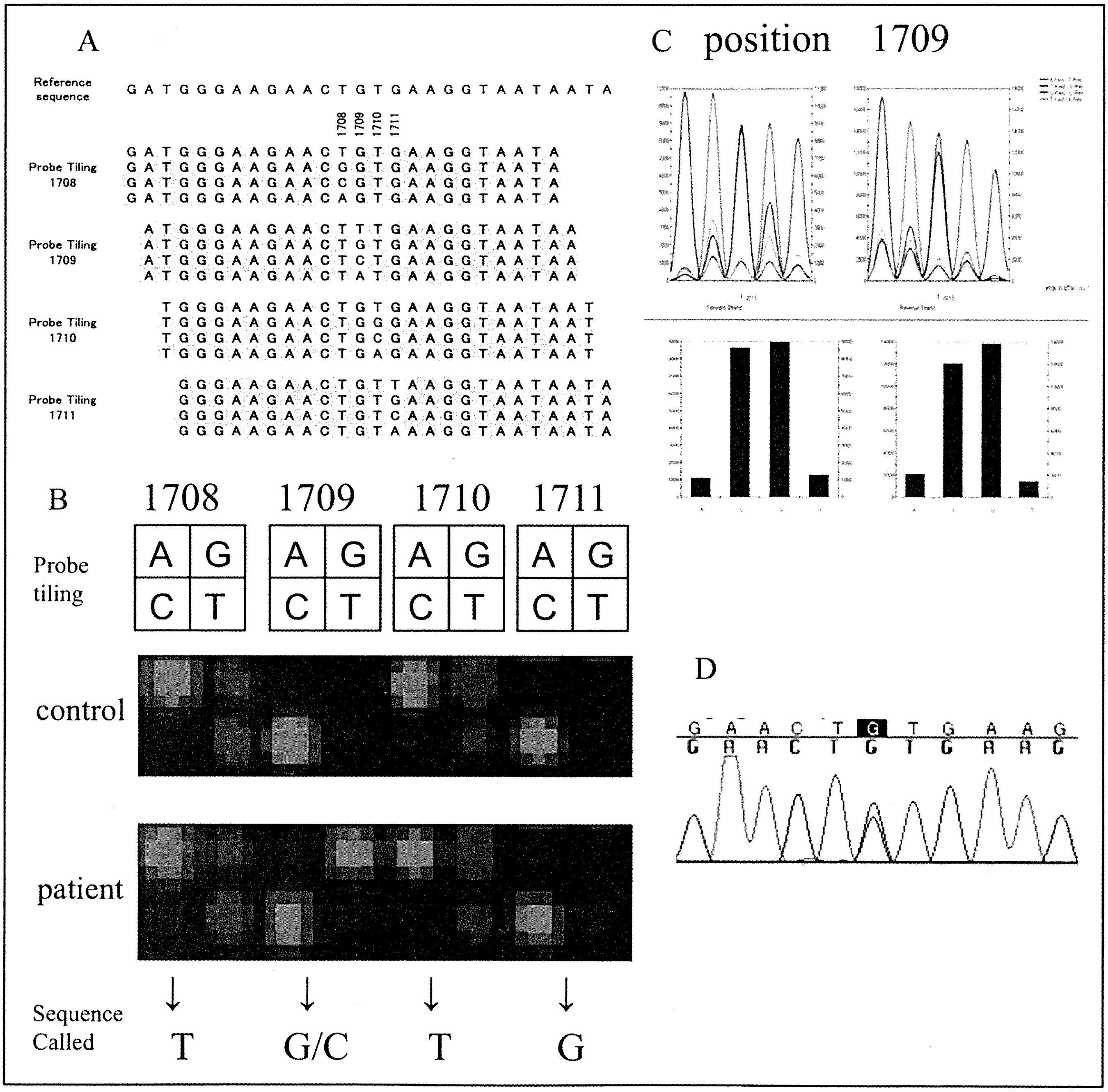


Figure 1. Representative example of mutational analysis using the present microarray-based resequencing system. *(A)* The microarray identifies individual nucleotides by comparative, high-fidelity hybridization using oligonucleotide probes that are synthesized in situ by photolithography and solid-phase DNA synthesis. For each base position, 8 unique 25-mer probes (4 oligonucleotide probes for each strand) are tiled on the array, and each 25-mer probe is varied at the central position to incorporate each possible nucleotide (A, G, C, or T), allowing the detection of all possible nucleotide substitutions. *(B)* Scan images of the probes around the nucleotide position 1709. In patients with the FBN1 c.1709G>C mutation, high signal intensities can be observed in probe G and C at nucleotide 1709 compared to control. *(C,D)* Signal intensity data at nucleotide position 1709. The intensity data for each base position can be also displayed as traces and bar graphs. The missense mutation (c.1709G>C) was successfully detected *(C)* and was verified by direct sequencing *(D)*.

tion of Helsinki and was approved by the institutional ethics committee. Written informed consent was obtained after providing a detailed explanation of the study. Genomic deoxyribonucleic acid (DNA) was extracted from buffy coat using a Genomix DNA extraction kit (Talent, Trieste, Italy). For amplification of the 65 exons of FBN1, polymerase chain reaction (PCR) primers were designed by referring to previous reports.[11–13] After performing the PCRs according to the standard protocol, the PCR products were subjected to hybridization on the microarray.

The resequencing microarray was designed on the basis of the reference sequences from the Ensembl database. Because highly homologous sequences lead to cross-hybridization, FBN1 was checked for possible repetitive sequences using RepeatMasker software (http://repeatmasker.org/chi-bin/webrepeatmasker). No repetitive elements were

Table 1
Background of participants who underwent genetic analysis (n = 53)

| Variable | Total (n = 53) | Ghent-Positive Patients (n = 45) |
|---|---|---|
| Age (years) | 33.1 ± 9.8 | 33.1 ± 10.4 |
| Men | 35/53 (66%) | 30/45 (67%) |
| Ghent positive | 45/53 (85%) | 45/45 (100%) |
| Skeletal major criteria | 12/49 (25%) | 12/41 (29%) |
| Skeletal minor criteria | 19/49 (39%) | 17/41 (42%) |
| Ectopia lentis | 25/53 (47%) | 25/45 (56%) |
| Cardiovascular major criteria | 48/53 (91%) | 44/45 (98%) |
| Cardiovascular minor criteria | 36/48 (75%) | 32/41 (78%) |
| Pulmonary | 22/49 (45%) | 19/42 (45%) |
| Skin | 26/49 (53%) | 23/42 (55%) |
| Dural ectasia | 34/47 (72%) | 33/40 (83%) |
| Family history of MS | 31/55 (56%) | 28/45 (62%) |

Data are expressed as mean ± SD or as number (percentage).

observed. The microarray contained sense and antisense sequences for the 65 exons of FBN1 and ≥12 flanking base pairs of the splice junctions. The PCR product was fragmented, end-labeled with biotin, and hybridized to the array. Washing and staining with streptavidin-phycoerythrin were performed on automated fluidic stations according to the manufacturer's protocol (Affymetrix, Santa Clara, California). Hybridization signals were read by a high-resolution laser scanner, and the data collection and interpretation were carried out using GeneChip Operating Software and GeneChip Sequence Analysis Software (Affymetrix), respectively.

Candidate nucleotide substitutions detected by the microarray-based resequencing system were subsequently validated by fluorescent dideoxy DNA sequencing using BigDye terminator version 3.1 on an ABI PRISM 3100xl genetic analyzer (Applied Biosystems, Foster City, California).

Some patients underwent cardiovascular surgery, and written informed consent for research use of surgical specimens was obtained from each patient. Total ribonucleic acid (RNA) was extracted using an RNeasy Fibrous Tissue Mini Kit (Qiagen, Venlo, The Netherlands). For patients whose aortic tissues were not available, total RNA was extracted from blood using a QIAamp RNA Blood Mini Kit (Qiagen). The RNA was converted to complementary DNA using SuperScript III First-Strand Synthesis SuperMix (Invitrogen, Carlsbad, California). PCR analyses were performed with specific primers designed for the target regions. PCR samples or subcloned plasmids after TA cloning of PCR products using a TOPO-TA vector (Invitrogen) were subjected to fluorescent dideoxy DNA sequencing.

DNA from patients whose mutations were not found by the aforementioned methods was screened by multiplex ligation-dependent probe amplification using a SALSA MLPA kit P065/P066 (MRC-Holland, Amsterdam, The Netherlands)[14] for large deletions and duplications.

All quantitative data are expressed as mean ± SD. Statistical comparisons of distributions between groups were made using the chi-square test. Significance was taken as $p < 0.05$.

Table 2
Detailed clinical findings of Ghent-positive patients (n = 45)

| Criterion | n (%) |
|---|---|
| Skeletal major criteria | |
| Pectus carinatum | 9/42 (21%) |
| Pectus excavatum, requiring surgery | 7/44 (16%) |
| Arm span/height ratio >1.05 | 8/41 (20%) |
| Wrist and thumb signs | 32/43 (74%) |
| Scoliosis of >20% or spondylolisthesis | 21/44 (48%) |
| Reduced extension at the elbows (<170°) | 2/41 (5%) |
| Medial displacement of medial malleolus, causing pes planus | 16/41 (39%) |
| Protrusio acetabuli | 8/39 (21%) |
| Skeletal minor criteria | |
| Pectus excavatum of moderate severity | 10/44 (23%) |
| Joint hypermobility | 7/41 (17%) |
| Highly arched palate with crowding of teeth | 31/40 (78%) |
| Facial appearance | 15/40 (38%) |
| Cardiovascular major criteria | |
| Dilatation/dissection of the ascending aorta | 44/45 (98%) |
| Cardiovascular minor criteria | |
| Mitral valve prolapse | 23/42 (55%) |
| Dilatation of main pulmonary artery | 9/20 (45%) |
| Calcification of mitral annulus | 0/34 (0%) |
| Dilatation/dissection of descending thoracic/abdominal aorta | 12/43 (28%) |
| Pulmonary minor criteria | |
| Spontaneous pneumothorax | 13/43 (30%) |
| Apical blebs | 15/44 (34%) |
| Skin minor criteria | |
| Striae atrophicae | 24/42 (57%) |
| Recurrent or incisional herniae | 0/41 (0%) |

## Results

Of the 53 probands enrolled, 45 were diagnosed with MS according to the original Ghent criteria. Because our Marfan clinic offers cardiac surgery and some patients were referred for aortic surgery from other hospitals, most of the patients had aortic phenotypes (Table 1). Dural ectasia and ectopia lentis were common findings, and positive family histories were seen in about half of the probands. We confirmed a lower frequency for some of the skeletal manifestations in Japanese patients with MS compared to that reported in a Western database, such as an arm span/height ratio >1.05 (20% in our study vs 55% in Western populations) and reduced extension at the elbows (<170°) (5% vs 15%), findings that were similar to the report of Akutsu et al[3,6] (Table 2). However, the frequency of major skeletal criteria (29%) was higher than a previous Japanese report (15%), which is partially due to a lack of evaluation of protrusio acetabuli in the earlier study. We found a higher frequency of spontaneous pneumothorax (30% vs 7%) in our Japanese population compared to a previous study conducted in Western patients. Calcification of the mitral annulus and frequency of dilatation of the main pulmonary artery were rarely reported. Actually, mitral annular calcification was not detected at all. However, pulmonary artery dilatation was relatively frequent (45% [9 of 20]) in our study, after excluding those patients whose main pulmonary artery diameters were difficult to evaluate.

Table 3
Mutations found in this study

| Exon | Complementary DNA | Protein |
|---|---|---|
| Missense mutations | | |
| 4 | c.386G>A | p.Cys 129 Tyr |
| 13 | c.1709G>C* | p.Cys 570 Ser |
| 14 | c.1786T>G* | p.Cys 596 Gly |
| 15 | c.1911T>G* | p.Cys 637 Trp |
| 18 | c.2171T>G* | p.Ile 724 Arg |
| 18 | c.2201G>T | p.Cys 734 Phe |
| 21 | c.2638G>A | p.Gly 880 Ser |
| 24 | c.3043G>A | p.Ala 1015 Thr |
| 26 | c.3263A>G* | p.Asn 1088 Ser |
| 28 | c.3503A>G | p.Asn 1168 Ser |
| 34 | c.4280A>G* | p.Tyr 1427 Cys |
| 43 | c.5371T>C* | p.Cys 1791 Arg |
| 47 | c.5873G>A* | p.Cys 1958 Tyr |
| 50 | c.6296G>T | p.Cys 2099 Phe |
| 53 | c.6518G>A* | p.Gly 2173 Ser |
| 57 | c.7015T>G* | p.Cys 2339 Gly |
| 60 | c.7466G>A* | p.Cys 2489 Tyr |
| 62 | c.7754T>C | p.Ile 2585 Thr (2 probands) |
| Nonsense mutations | | |
| 8 | c.945T>A* | p.Cys 315 X |
| 12 | c.1585C>T | p.Arg 529 X |
| 29 | c.3603C>A* | p.Cys 1201 X |
| 37 | c.4709G>A* | p.Trp 1570 X |
| 38 | c.4777G>T* | p.Glu 1593 X |
| 38 | c.4786C>T | p.Arg 1596 X |
| 54 | c.6658C>T | p.Arg 2220 X |
| 58 | c.7240C>T | p.Arg 2414 X |
| 65 | c.8521G>T* | p.Glu 2841 X |
| Splicing mutations | | |
| 11–12 | c.IVS11+5G>A | p.Cys474Tyr Glu475_Asp490del |
| 15–16 | c.IVS15-3T>G* | |
| 16–17 | c.IVS16+3A>C* | |
| 18–19 | c.IVS18+1G>C* | |
| 34–35 | c.IVS34-1G>A* | p.Asp1446ValfsX21 |
| 40–41 | c.IVS40+1G>A* | |
| 52–53 | c.6453C>T* | p.Cys2151Tyr, Glu2152_Asp2166del |
| 56–57 | c.IVS56+5G>A* | |
| Deletion mutations | | |
| 54 | c.6665delT* | p.Val2222GlyFsX69 |
| 54 | c.6703-6704delGG* | p.Gly2235IlefsX7 |
| 55 | c.6837delG* | p.Tyr2280IlefsX10 |
| 57 | c. 7071_7079delCGTCACCAA* | p.Val2358SerfsX511 |
| 65 | c. 8532_8delTACAACT* | p.Thr2785X |
| 3 | Exon 3 deletion* | |

* Newly found mutation.

In our mutational analysis, the base call rate of this system for FBN1 was >96% when examining 5 representative cases, and resequencing as many as 12,688 bp per patient was easily accomplished in 3 working days, demonstrating the high fidelity and high throughput of this system.

In the 53 probands, 35 kinds of FBN1 mutations were found in 36 probands using this system (Table 3). There were 18 missense and 9 nonsense mutations. Eight other mutations located near the exon-intron boundaries were thought to alter the splicing patterns. Supplemental direct sequencing in probands with no mutation detected by the microarray-based method revealed 5 deletion mutations in FBN1 (Table 3). Furthermore, multiplex ligation-dependent probe amplification assay revealed a large deletion mutation (exon 3) in 1 proband. Finally, novel mutations were found in 23 probands using microarray and in 29 probands in total. All possible mutations found by the microarray-based resequencing system were verified by direct sequencing, and thus the microarray detected point mutations with 100% accuracy. A representative example of genetic analysis using the microarray-based resequencing system is shown in Figure 1. Of 18 missense mutations, 11 were either affecting or creating cysteine residues. For other novel missense mutations, none of the mutations were found in ≥200 ethnically matched control subjects. The mutation detection rate

Table 4
Number of mutations detected

| Mutation Detection Method | Total (n = 53) | Ghent Positive (n = 45) | Other (n = 8) |
|---|---|---|---|
| Microarray | 36 (68%) | 32 (71%) | 4 (50%) |
| Direct sequencing | 5 (9%) | 5 (11%) | 0 |
| Multiplex ligation-dependent probe amplification | 1 (2%) | 1 (2%) | 0 |
| Total of all 3 modalities | 42 (79%) | 38 (84%) | 4 (50%) |

of the microarray-based resequencing system for the Ghent-positive patients was 71%. The overall mutation detection rate after additional analysis by fluorescent dideoxy DNA sequencing and multiplex ligation-dependent probe amplification reached 84% (Table 4).

Eight possible splicing mutations were identified, and these mutations constituted 19% of all mutations, which was more than the 11% currently reported in the UMD-FBN1 mutation database.[5] One patient and his 2 relatives with MS had the same silent mutation in FBN1 exon 52 (c.6453C>T, p.Cys2151Cys; Figure 2). Therefore, we resequenced complementary DNA from his aortic tissue and verified an alternation of the splicing pattern between FBN1 exon 52 and 53. The C at nucleotide position 6453 of FBN1 complementary DNA was substituted with a T, which resulted in the creation of a new splicing donor site, causing abnormal shorter messenger RNA. Another patient had a mutation at the fifth nucleotide of the beginning of intron 11 (c.IVS11+5G>A), although it is well known that the first 2 nucleotides at the beginning of the intron are very important as a splice donor site. We found by sequencing the complementary DNA that the latent splice donor site within exon 11 was activated and created the frame-shift mutation (Figure 2).

Six additional mutations possibly causing a splicing aberration were also found (Table 3). Although aortic tissue was unavailable for these patients, splicing aberrations were successfully confirmed in 2 whose complementary DNA was clinically available by resequencing FBN1 complementary DNA obtained from peripheral blood (Figure 2).

In published research, it has been suggested that mutations causing the in-frame loss or gain of the central coding sequence through deletions, insertions, or splicing errors are thought to be associated with more severe disease phenotypes. In contrast, nonsense mutations that result in rapid degradation of mutant transcripts are reported to be potentially associated with milder conditions. However, we could not find any associations between mutation types and clinical severity in our study subjects. A higher incidence of ectopia lentis in patients who carried a missense mutation involving a cysteine substitution or splicing mutation has been reported.[15] However, these correlations were not observed in our study. Among 4 patients who had mutations located between FBN1 exons 24 and 32, the so-called "neonatal region," none had the neonatal or early-onset form of MS.

## Discussion

The Ghent criteria for MS diagnosis are based on data obtained mainly from European and American populations. Our clinical evaluations revealed that there were more pulmonary phenotypes and fewer skeletal phenotypes in Japanese patients with MS compared to Western patients. Therefore, the criteria for systemic and orthopedic features in the Ghent nosology may not be entirely suitable for application to Japanese and perhaps other Asian populations. Further epidemiologic and genetic studies in the Japanese population should be conducted to establish Asian- or Japanese-specific diagnostic criteria for MS.

The present microarray-based resequencing system is an efficient method for rapid and affordable mutation analysis of heterogenous disorders such as MS. The mutation detection rate is influenced by the accuracy of the clinical diagnosis of MS, the type of mutation, and the ability of the testing method. It ranged from 55% to 91% in previous reports.[11,16–18] The mutation detection rate of our system was concordant with previous reports. Its greatest advantages are high throughput and digitalized sequencing data. The digitally retrieved sequencing data are easily computable and can be displayed in various ways. In most of the cases, we could identify the mutations within a few minutes of data collection. Several other causative genes, such as transforming growth factor receptor types 1 and 2 (TGFBR1 and TGFBR2),[19] smooth muscle $\alpha$-actin (ACTA2),[20] myosin heavy chain 11 (MYH11),[21] and SMAD3,[22] have been identified for syndromic or nonsyndromic aortic aneurysms and dissection. Such additional candidate genes can also be included on the same array because 1 array can resequence up to 300 kb.

Our system can detect point mutations with 100% accuracy and thus is a reliable first screening method for detecting single nucleotide substitutions. In contrast, it is difficult to detect heterozygous deletion or insertion mutations, because an abnormal allele containing a deletion or an insertion mutation is difficult to hybridize to probes. For patients with MS with no mutation detected by the microarray system, conventional direct sequencing and multiplex ligation-dependent probe amplification was helpful for searching for possible deletion or insertion mutations. Because there is a certain number of patients with MS without mutations in FBN1,[12,19] the 7 probands without any mutations may have possessed mutations in undiscovered disease-causing genes.

Eight splicing mutations that accounted for 19% of all the mutations were found. Because this type of mutation represented a greater proportion than that of previous reports, every exon-intron boundary should be resequenced. It is also advisable to obtain messenger RNA in addition to DNA for analyzing the splicing pattern. We successfully demonstrated altered splicing patterns using FBN1 messenger RNA extracted from peripheral leukocytes. Thus, we also recommend the extraction of RNA as well as genomic DNA from peripheral blood, if a surgically retrieved specimen is not available.

We also assessed patients using the recently published revised Ghent criteria. Forty-two of the 45 original Ghent-positive patients were also diagnosed with MS using the revised criteria. One patient, who was positive according to the original Ghent criteria, did not satisfy the revised criteria and was diagnosed with ectopia lentis syndrome. Two patients (aged 20 and 30 years) failed to meet the revised Ghent criteria because their z scores of aortic diameter were not