A susceptibility locus in the *IL12B* but not *LILRA3* region is associated with vascular damage in Takayasu arteritis

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HLA-B*52 is an established genetic factor in Takayasu arteritis (TAK). Recently, single nucleotide polymorphisms (SNPs) in *IL12B* (rs6871626) and *LILRA3* (rs103294) were newly identified as non-HLA susceptibility loci in TAK. Here, we examined how these SNPs contribute to clinical characteristics and vascular damage in TAK. We retrospectively reviewed the medical records of 99 TAK patients enrolled in our previous genome-wide association study, and whose genotypes for *IL12B* rs6871626, *LILRA3* rs103294, and HLA-B*52 were available. Incidence of aortic regurgitation (AR) was significantly associated with the A allele (risk allele) of *IL12B* rs6871626 (CC 42%, AC 61%, AA 81%; p = 0.0052; odds ratio [OR] 2.45), as well as with the incidence of hypertension (p = 0.049; OR 1.82) and the proportion of patients who underwent aortic valve replacement (p = 0.023; OR 3.64). Regarding vascular damage, there was positive correlation between the Takayasu Arteritis Damage Score and the A allele of *IL12B* rs6871626 (CC 3.42 ± 2.71, AC 4.06 ± 3.25, AA 6.00 ± 2.81; p = 0.0035; β = 1.35) and between the Vasculitis Damage Index and the A allele (CC 3.47 ± 1.98, AC 4.33 ± 2.40, AA 5.37 ± 2.22; p = 0.0054; β = 0.96). Contrarily, no correlation was found between *LILRA3* rs103294 and vascular damage. In the present study, *IL12B* rs6871626 was associated with vascular damage in TAK, whereas *LILRA3* rs103294 was not. Genotyping of *IL12B* rs6871626 may help to identify patients at risk of disease progression.

Abbreviations

| AR       | Aortic regurgitation |
|---------|----------------------|
| CI      | Confidence interval  |
| GWAS    | Genome-wide association study |
| OR      | Odds ratio           |
| SNP     | Single nucleotide polymorphism |
| TADS    | Takayasu arteritis damage score |
| TAK     | Takayasu arteritis |
| UST     | Usutekinumab         |
| VDI     | Vasculitis Damage Index |

Takayasu arteritis (TAK) is an idiopathic, chronic, inflammatory disease, characterized by granulomatous panarteritis of the aorta and its major branches, and typically presents before the age of 40 years. TAK is a...
damage score (TADS) and Vasculitis Damage Index (VDI) have been developed. The former is a TAK-specific measure focusing mainly on disease-related damage in the cardiovascular system, whereas the latter is a validated damage score for use in all types of systemic vasculitides, which also captures treatment-related effects.

Treatment profiles. Treatment profiles stratified by genotypes of IL12B rs6871626 and LILRA3 rs103294 are summarized in Table 2. No association was found between IL12B rs6871626 or LILRA3 rs103294 and the use of glucocorticoids, oral immunosuppressants, or biologics, although the proportion of biologic users tended to be higher in the risk genotypes of IL12B rs6871626.

Regarding surgery or catheter intervention, the proportion of patients who had undergone aortic valve replacement was associated with the A allele of IL12B rs6871626 (CC 1/19 [5%], AC 2/53 [4%], AA 6/27 [22%];
p = 0.023; OR 3.64, 95% CI 1.08–12.24), whereas no association was found with genotypes of LILRA3 rs103294.

The overall proportion of surgery or catheter interventions and the proportion of patients who had undergone other specific vascular interventions, such as coronary artery bypass graft and percutaneous coronary intervention, were not associated with either IL12B rs6871626 or LILRA3 rs103294.

Arterial involvement. Figure 2A,B summarizes the distribution of arterial involvement. No association was found between arterial involvement and genotypes of IL12B rs6871626 or LILRA3 rs103294, except for a lower incidence of right subclavian artery involvement in patients with the T allele (risk allele) of LILRA3 rs103294 (CC 1/1 [100%], CT 22/34 [65%], TT 22/56 [39%]; p = 0.010; OR 0.36, 95% CI 0.14–0.79) (Fig. 2A,B).

To quantify systemic vascular damage on imaging, we calculated ASS, ADS, and ACS. We did not observe the association between these scores and genotypes of IL12B rs6871626 or LILRA3 rs103294 (Fig. 2C, Supplementary Figure).

Vasculitis-associated damage measures. Then, we evaluated vasculitis-associated damage measures using TADS and VDI. There was a positive correlation between TADS and the A allele of IL12B rs6871626 in the additive model (CC 3.42 ± 2.71, AC 4.06 ± 3.25, AA 6.00 ± 2.81; p = 0.0035; β = 1.35) (Fig. 3A). In addition, VDI was positively correlated with the A allele in the additive model (CC 3.47 ± 1.98, AC 4.33 ± 2.40, AA 5.37 ± 2.22; p = 0.0054; β = 0.96) (Fig. 3A). When adjusted for disease duration, the correlation of TADS and VDI with the A
The allele of \( IL12B \) rs6871626 remained statistically significant (\( p = 0.013, \beta = 1.11 \) for TADS; \( p = 0.025, \beta = 0.72 \) for VDI). No correlation was found between \( LILRA3 \) rs103294 and TADS or VDI (Fig. 3B).

Figure 2. Association of genotypes with arterial involvement. (A,B) The association of \( IL12B \) rs6871626 and \( LILRA3 \) rs103294 with the distribution of arterial involvement. (C) The association of \( IL12B \) rs6871626 and \( LILRA3 \) rs103294 with Arteritis Composite Score. Rt right, Lt left, As ascending, Des thoracic descending, Abd abdominal descending, NS not significant. *\( P < 0.05 \).
In the dominant model, we did not observe significant associations between \( \text{IL12B} \text{rs6871626} \) and TADS or VDI, although their scores tended to be higher in risk genotypes of \( \text{IL12B} \text{rs6871626} \) (Supplementary Table).

**Association between clinical characteristics and \( \text{LILRA3} \text{rs103294} \) genotypes in HLA-B*52-positive patients.** We previously reported a significant epistasis effect between HLA-B*52 and \( \text{LILRA3} \text{rs103294} \). The TT genotype with HLA-B*52 was associated with TAK susceptibility, whereas the TT genotype without HLA-B*52 was not. In other words, \( \text{LILRA3} \text{rs103294} \) functions as a TAK susceptibility gene only in the presence of HLA-B*52. Therefore, we hypothesized that the association between clinical characteristics and \( \text{LILRA3} \text{rs103294} \) is found only in HLA-B*52-positive patients. However, as summarized in Table 3, there was no significant association between clinical characteristics and \( \text{LILRA3} \text{rs103294} \) even in HLA-B*52-positive patients. In addition, the association between clinical characteristics and \( \text{LILRA3} \text{rs103294} \) was not observed in HLA-B*52-negative patients (data not shown).

**Discussion**

In the present study, we examined for the first time the impact of \( \text{IL12B} \text{rs6871626} \) and \( \text{LILRA3} \text{rs103294} \), which were newly identified susceptibility loci, on clinical characteristics and vascular damage in TAK patients. Our study demonstrated that \( \text{IL12B} \text{rs6871626} \), but not \( \text{LILRA3} \text{rs103294} \), was associated with organ involvement and vascular damage assessed by TADS and VDI. Our study results suggest that patients harboring risk alleles of \( \text{IL12B} \text{rs6871626} \) may be at risk of disease progression, requiring close monitoring. In addition, we detected for the first time an association between \( \text{IL12B} \text{rs6871626} \) and hypertension in TAK, which was not attributed to renal artery involvement. Low compliance of arterial walls in patients with risk alleles may lead to systemic hypertension.

Our results are compatible with previous reports showing the association of \( \text{IL12B} \text{rs6871626} \) with AR, inflammatory marker levels, and disease severity\(^{14,6} \). \( \text{IL12B} \) encodes IL-12p40, a common subunit of IL-12 and IL-23\(^{14} \). More specifically, IL-12p40-dependent cytokines include IL-12p70, IL-12p80, and IL-23\(^{15} \). IL-12p70 is composed of IL-12p40 and IL-12p35 subunits, while IL-12p80 is a homodimer of IL-12p40 and considered as an antagonist of IL-12p70 function\(^{15} \). Although there have been conflicting results regarding whether IL-12p70\(^{16-19} \) and IL-23\(^{19-22} \) participate in the pathogenesis of TAK, our recent work has demonstrated that both IL-12p40 and IL-12p70 were enriched in the plasma of TAK patients, and was more pronounced in patients with the risk allele of \( \text{IL12B} \text{rs6871626} \). Taken together, the risk genotype of \( \text{IL12B} \text{rs6871626} \) may contribute to the severe phenotype of TAK through subsequent overproduction of IL-12p40 and IL-12p70.
This hypothesis is supported by our pilot study using ustekinumab (UST), a monoclonal antibody targeting IL-12p40, for treating TAK. We confirmed the improvement of symptoms, inflammatory marker levels, and safety in the first three months of treatment with UST. We have also conducted an observational study evaluating long-term outcomes of refractory TAK patients treated with biologics, and found that UST has effects on reducing inflammatory marker levels and glucocorticoid dose. IL-12B rs6871626 has also been reported as a susceptibility locus in inflammatory bowel disease and ankylosing spondylitis. Co-occurrence of TAK and ulcerative colitis is not uncommon, and the two diseases are reported to share a significant proportion of genetic overlap. IL-12p40 blockade is an approved treatment of choice for inflammatory bowel disease. In light of this, further studies are warranted to assess the clinical efficacy of IL-12p40 blockade in TAK.

In this study, we did not identify any influence of LILRA3 rs103294 on clinical phenotypes of TAK, except for a lower incidence of right subclavian artery involvement in the risk genotype. In our study population, the genotype of LILRA3 rs103294 was strongly biased towards risk genotypes, with only one patient having the CC genotype. This may have limited the power of this study to identify the association of LILRA3 rs103294 with vascular damage, and is irrelevant to disease progression, thus contributing differently to TAK pathogenesis from IL12B rs6871626. It is unclear why patients with the non-risk allele showed a significantly higher frequency of right subclavian artery lesions (Fig. 2), but this may have been confounded by the systemically advanced vascular lesions of only patients with the CC genotype.

LILRA3 is the only soluble form of LILR and is not detected on the cell surface. It is speculated that LILRA3 functions as an antagonist or a negative regulator of other LILRs, but its detailed functions and mechanisms are still not known. The risk allele of LILRA3 rs103294 is associated with decreased expression of LILRA3. Therefore, decreased levels of LILRA3 may contribute to the pathogenesis of TAK. To date, associations between LILRA3 and various autoimmune diseases have been reported. LILRA3 deficiency is a risk factor for multiple sclerosis in German and Spanish populations. Homozygous LILRA3 deletion is associated with Sjögren's syndrome in a German population, while functional LILRA3 is a susceptibility factor for Sjögren's syndrome in a Chinese population. In addition, functional (non-deleted) LILRA3 is a susceptibility factor for systemic lupus erythematosus and rheumatoid arthritis, especially for anti-citrullinated protein antibody-positive cases. Considering these previous reports, it can be speculated that LILRA3 contributes differently to the pathogenesis of different autoimmune diseases. Further study is necessary to elucidate the pathogenic role of LILRA3 in various autoimmune diseases and the function of LILRA3 per se.

This study has some limitations. First, although the number of TAK patients included is relatively large for a single institution, this study is still limited by the sample size. The small sample size of our study made it difficult to draw a firm conclusion especially on the association of LILRA3 rs103294 with vascular damage, because our study included only one patient with CC genotype of LILRA3 rs103294. Further study with a larger sample size is awaited. Second, this study was based on a retrospective review of patients. Further prospective studies are required to confirm the findings of this study. Third, there might be a bias in the assessment and treatment of TAK, because this study was conducted in a single institution. Fourth, we did not assess disease activity measures such as Birmingham Vasculitis Activity Score and Indian Takayasu Clinical Activity Score. Fifth, since all the patients included in this study were Asian, mostly Japanese, our findings may not be applicable to patients with other ethnic backgrounds. Finally, vasculitis-associated damage measures (i.e. TADS and VDI) and angiographic scores (i.e. ASS, ADS, and ACS) were evaluated at different time points in each patient, making it difficult to draw a firm conclusion especially on the association of LILRA3 rs103294 with these outcomes.

### Table 3. Clinical characteristics of HLA-B52-positive patients stratified by LILRA3 genotypes. TADS Takayasu arteritis damage score, VDI vasculitis damage index. Data are n (%) or mean ± standard deviation.

| Medication           | Total      | CC     | CT     | TT     | p value |
|----------------------|------------|--------|--------|--------|---------|
| Number               | 1          | 16     | 39     |        |         |
| Age at onset (years) | 32 ± 13    | 45     | 34 ± 12| 31 ± 13| 0.27    |
| Female               | 53 (95%)   | 1 (100%)| 16 (100%)| 36 (92%)| 0.13    |
| Visual loss          | 1 (2%)     | 0 (0%) | 0 (0%) | 1 (3%) | 0.4     |
| Hypertension         | 31 (56%)   | 1 (100%)| 8 (53%)| 22 (56%)| 0.82    |
| Aortic regurgitation | 39 (71%)   | 1 (100%)| 11 (73%)| 27 (69%)| 0.57    |
| Ischemic heart disease | 3 (5%) | 0 (0%) | 0 (0%) | 5 (8%) | 0.14    |
| Cerebrovascular accident | 5 (9%) | 0 (0%) | 1 (7%) | 4 (10%)| 0.59    |
| Pulmonary artery involvement | 14 (25%) | 0 (0%) | 6 (40%)| 8 (21%)| 0.31    |
| Renal artery involvement | 12 (22%) | 1 (100%)| 4 (27%)| 7 (18%)| 0.15    |
| TADS                 | 4.3 ± 3.0  | 7      | 3.7 ± 3.3| 4.5 ± 3.0| 0.78    |
| VDI                  | 4.2 ± 2.4  | 3      | 4.6 ± 2.9| 4.1 ± 2.2| 0.71    |
because a recent whole-body contrast-enhanced angiography was not available in a substantial proportion of patients. This might have led to the discrepancy between the results on vasculitis-associated damage measures and angiographic scores.

In conclusion, our study showed for the first time that IL12B rs6871626 is associated with vascular damage in TAK, whereas LILRA3 rs103294 was not. IL12B rs6871626 cannot be only a susceptibility marker, but also a marker for disease progression in TAK. Better understanding of the pathogenesis with the aid of genetic studies may enable physicians to fine-tune the treatment strategy for TAK based on the genotype of individual patients.

Methods

Patients. We enrolled 99 TAK patients who were enrolled in our previous genome-wide association study (GWAS) and whose genotypes for rs6871626, rs103294, and HLA-B*52 were available. The patients fulfilled either the 1990 American College of Rheumatology classification criteria or the diagnostic criteria for the Japan Circulation Society 2008. This was a retrospective cohort study, and patient information in the electronic patient chart was retrospectively reviewed. We obtained approval from the Ethics Committee of Kyoto University Graduate School and the Faculty of Medicine for the study (No. G1006-9). Written informed consent was obtained from all patients. All study procedures were performed in accordance with the principles of the Declaration of Helsinki.

Clinical evaluation. The presence or absence of AR, ischemic heart disease, cerebrovascular events, visual loss, renal replacement therapy, and inflammatory bowel disease were evaluated as organ involvement. The diagnosis of AR was based on transthoracic echocardiography and was used to detect AR. Ischemic heart disease was defined as angina pectoris or myocardial infarction requiring vascular interventions such as coronary artery bypass graft or percutaneous coronary intervention. Cerebrovascular events were included only if they had focal neurological signs such as paresis and weakness. Renal replacement therapy was defined as the condition requiring chronic hemodialysis. Inflammatory bowel disease was diagnosed after scrutiny by gastroenterologists, including endoscopic evaluation and cautious differential diagnosis, to exclude other causes such as drug-induced enterocolitis and infections.

Arterial involvement. Involvement of individual arteries was comprehensively determined using digital subtraction angiography, enhanced computed tomography (CT), magnetic resonance angiography (MRA), ultrasonography, or fluorodeoxyglucose positron emission tomography to differentiate other conditions such as atherosclerosis.

To perform a systemic evaluation of arterial involvement in a qualitative and quantitative manner, we assessed ASS, ADS, and ACS. These scores were calculated with the last whole-body contrast-enhanced CT angiography or MRA of each patient if available.

Evaluation of vascular damage. Vasculitis-associated damage was evaluated using TADS and VDI. TADS captures TAK-specific vascular damage, whereas VDI is applied to all types of systemic vasculitides. TADS and VDI were measured at the last visit before November 2020.

Treatments. We obtained clinical data regarding the administration of glucocorticoids, immunosuppressants, and biological disease-modifying anti-rheumatic drugs such as infliximab, tocilizumab, and ustekinumab.

Vascular surgery and catheter intervention. The medical history of coronary artery bypass grafting, percutaneous coronary intervention, aortic valve replacement, aortic aneurysm repair, and bypass surgery were retrospectively reviewed.

Genotyping. Illumina Infinium arrays were used for genome scanning, as previously described. Genotypes of the HLA-B allele were identified by the Luminex microbead method in the NPO HLA laboratory (Kyoto, Japan).

Statistical analysis. Data are presented as the mean ± standard deviation for continuous variables and numbers (%) for categorical variables.

We generally adopted the additive model to analyze the association between genotypes of SNPs and clinical characteristics. To determine the association between genotypes of SNPs and categorical variables, such as the frequency of organ involvement, arterial involvement, and treatment profiles, logistic regression analysis was performed to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) of the risk allele. To determine the correlation between genotypes of SNPs and continuous variables, such as age, TADS, and VDI, linear regression analysis was performed to calculate the effect size (β) of the risk allele.

In addition, we also analyzed the association of IL12B rs6871626 with clinical characteristics using the dominant model. The Mann–Whitney test was used to compare continuous variables, and Fisher's exact test was used to compare categorical variables. We did not use the dominant model in the analysis of LILRA3 rs103294, because there was only one patient with CC genotype of LILRA3 rs103294.

Statistical analyses were performed using JMP Pro 14.0.0 (SAS Institute, Cary, NC, USA), and p values < 0.05 were considered significant.
**Ethics approval and consent to participate.** We obtained the approvals of the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine for the study (No. G1006-9). Written informed consent was obtained from all patients. All study procedures were performed in accordance with the principles of the Declaration of Helsinki.

**Data availability** The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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**Author contributions**

K. Kadoba, R.W. and H.Y. designed the study, collected the clinical data, contributed to the data interpretation, and wrote the manuscript. T.I. contributed to the data interpretation, and validated the manuscript. T.N. collected the clinical data, and validated the manuscript. C.T. collected the genomic data, and validated the manuscript. K. Kitagori, S.A., K.M., R.N., M.H., M.T., K.O. and A.M. validated the manuscript. All authors approved the final manuscript.

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**Additional information**

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