INTRODUCTION

Novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) infection, named coronavirus disease 2019 (COVID-19), is spreading worldwide. According to the first extensive report from China on the clinical manifestations of COVID-19 patients, fever and cough were the main symptoms, while only two of 1099 patients (0.2%) presented with a skin rash. Therefore, skin symptoms in COVID-19 patients did not initially receive special attention. However, a report from Italy by Sachdeva et al. on skin manifestations in patients with COVID-19 changed this situation. Their analysis of 88 patients with COVID-19 reported that as many as 20% developed various skin symptoms. This study contributes to the controversy regarding the high incidence of skin symptoms in COVID-19 patients.

Since that report, there have been an increasing number of reports of COVID-19-associated skin manifestations worldwide. Analyzing the frequency and characteristics of the different skin manifestations is in progress. However, there is still no unified view, and one reason for this is that there may be regional and racial differences in COVID-19-associated skin manifestations. We believe it is necessary to evaluate COVID-19-associated skin rashes by race...
and country. We previously reported that 4.9% (3/69) of our patients had COVID-19-associated viral eruption. However, this was a small number of cases, but there have been few reports on COVID-19 skin manifestations in Japanese patients, and the analysis has not progressed.

Therefore, we collected data from COVID-19 patients treated at the authors’ hospital who presented with skin manifestations and analyzed the frequency and types of skin manifestations among a large cohort of 738 Japanese patients with COVID-19.

2 | METHODS

2.1 | Analysis of our hospital cases

This was a single-center, retrospective study. The hospital to which the authors belong started accepting COVID-19 patients in February 2020. We mainly admitted patients with mild to moderate severity who had symptoms such as cough and fever, shortness of breath, and oxygen demand but did not require mechanical ventilators. We provided further treatment, including ventilator management, when patients became critically ill in our hospital. From 22 February 2020 to 16 August 2021, we accepted 758 patients with laboratory-confirmed COVID-19 by polymerase chain reaction (PCR) or antigen tests. Of these, 738 were Japanese nationals. We enrolled these Japanese patients in this study and collected their data retrospectively from electronic medical records (MegaOak online imaging system, NEC). Among these patients, we analyzed COVID-19 patients who developed new skin manifestations during the disease period at our hospital. These do not include atopic dermatitis, chronic urticaria, and other skin conditions predating their COVID-19 infection. Our dermatologists, including the authors, diagnosed suspected COVID-19-associated viral eruption by referring to actual examinations, medical record descriptions, and photographs. It is difficult to distinguish between viral eruption and drug eruption since multiple drugs are used in the treatment of COVID-19. We ruled out the possibility of drug eruption if there was no recent new drug use and if the skin rash improved without drug changes during the disease. If the drug was changed or discontinued during the disease, the diagnosis was made based on a comprehensive judgment of the characteristics and the course of the skin rash and the type of drug used. We analyzed the frequency of COVID-19-associated viral eruptions, patient sex, age, timing and duration of skin manifestation, clinical types of skin manifestations, drugs used against COVID-19, drugs used against skin manifestations, and symptoms other than skin manifestations. In statistical analysis, the medians are reported for continuous variables. Categorical variables are summarized as frequencies (percentages).

We conducted this study based on the guidelines from the Declaration of Helsinki and obtained approval from the Institutional Review Board of Toyonaka Municipal Hospital (no. 2021-10-03). The requirement for informed consent was waived via the opt-out method on our hospital website.

2.2 | Review of literature

To analyze the occurrence of COVID-19-associated viral eruptions in Japan, we collected cases of viral eruptions in Japanese COVID-19 patients using PubMed, Google Scholar, and the Ichushi website (a Japanese article search site) to search for literature published between December 2020 and 31 August 2021. The following search terms were used: ([Coronavirus] or [COVID-19] or [SARS-CoV-2] and [skin] or [cutaneous] or [rash] or [maculopapular] or [exanthem]). We conducted the same search in Japanese. We determined the eligibility of each paper from the title and abstract. All observational studies, including case reports and case series, were included; review articles and commentaries were not included. We selected only the cases in Japan from among the papers. We also performed an extensive manual search of the reference lists of the relevant papers and reports. From the included studies, we extracted the following information: author, patient age, sex, clinical features of skin manifestations, symptoms other than skin symptoms, the term from the onset of other COVID-19 symptoms to the development of skin manifestations, duration of skin manifestations, drugs used against COVID-19, and drugs used against skin manifestations.

3 | RESULTS

3.1 | Analysis of our hospital cases

Seven hundred and thirty-eight Japanese patients with COVID-19 were treated in our hospital during the study period; 407 (55%) were male and 331 (45%) were female. The patients ranged in age from 0 to 99 years, with a median of 59 years. Seven hundred and thirteen patients (97%) had symptoms such as cough and fever due to COVID-19. A total of 342 patients (46%) took dexamethasone for COVID-19 treatment. Thirty-five (4.7%) of the COVID-19 patients treated at our hospital presented with some new skin manifestations. Of the 35 cases, we diagnosed 14 as seborrheic eczema or contact dermatitis and so forth after examination by dermatologists and after reviewing the photographs in the medical records. Thus, we suspected that the skin manifestations were viral eruptions caused by COVID-19 in the other 21 cases. Of the 21 cases, our dermatologists, including the authors, examined nine patients and referred them to the medical records or photographs for a diagnosis in the other 12 cases. Figure 1 shows the flow chart of patient enrollment to analyze COVID-19-associated skin manifestations.

Among 738 patients with COVID-19, 21 patients had skin manifestations suggestive of COVID-19-associated viral eruptions. This number represents 2.8% of all COVID-19 patients in our hospital. The 21 patients ranged from 0 to 81 years, with a median of 45 years, and there were 11 males and 10 females. In terms of skin manifestations, 19 cases were erythematous papules and two cases were the urticarial type. There were no pernio-like lesions, papulovesicular type, livedo reticularis, or necrotic lesions. The time from the onset of other COVID-19 symptoms to the development of skin
manifestations ranged from 0 to 21 days, with a median of 9 days. The duration of skin manifestations ranged from 3 to 14 days, with a median of 9 days. For the treatment of the skin manifestations, three (14%) patients received topical moisturizers, seven (33%) received topical steroids, one (5%) received topical crotamiton, three (14%) received oral antihistamines, three (14%) received topical steroids and antihistamines, one (5%) received an unspecified ointment that she initially had, and two (10%) had no specific treatment. A summary of patient characteristics, treatment for COVID-19, and skin manifestations is shown in Table 1. Information on these 21 patients is given in Table 2, and more detailed information is given in Table S1 and Appendix S1. We obtained informed consent from patients or their guardians for publication of the photographs of skin manifestations.

3.2 | Review of literature

In Japan, 12 cases of COVID-19–associated viral eruptions have been reported thus far.4,5,6–12 These reports are summarized in Table S2. The total number of cases of COVID-19–associated viral eruption in Japan was 33, including the 21 patients we saw. The patients ranged in age from 0 to 83 years. The median age was 48 years and the mean age was 42.8 years. There were 17 males and 16 females included in the review. The types of skin manifestations and their respective rates of occurrence were as follows: erythematous papules in 27 cases (82%), urticarial in three patients (9%), pernio-like lesions in two cases (one case combined with erythematous papules) (6%), papulovesicular type in zero patients (0%), livedo reticularis in one case (combined with erythematous papules) (3%), and others (erythema nodosum, toxic epidermal necrolysis[TEN]) in two patients (6%). Two patients with pernio-like lesions, known as COVID toes, have been reported in Japan, but one patient had systemic sclerosis as the primary disease.11 Pernio-like lesions in patients with no underlying disease are still rare, with only one case reported in Japan. There was one case each of TEN and erythema nodosum.4,10 The median time from the first symptom to the skin manifestations were 10.5 days, respectively, from 0 to 40 days. The duration of the skin manifestations ranged from 3 to 26 days, with a median of 9 days. A summary of age, sex, and skin manifestations of Japanese patients with COVID-19–associated viral eruption is shown in Table 3.

4 | DISCUSSION

In the present study we found that 2.8% (21 out of 738) of Japanese patients with COVID-19 had skin manifestations suspicious for COVID-19–associated viral eruption. There are few reports of COVID-19–associated viral eruptions in Japan. Only two reports mention skin manifestations in COVID-19 patients in Japan.
### TABLE 2  
Information on COVID-19 patients presenting skin manifestations in the authors’ hospital

| Case | Age (years) | Sex  | Features of skin manifestations | The time from the first symptom to the skin manifestations (days) | Duration of skin manifestations (days) | Drugs used against COVID-19 | Drugs used against skin manifestations |
|------|-------------|------|----------------------------------|------------------------------------------------------------------|---------------------------------------|----------------------------|----------------------------------------|
| 1    | 24          | Male | Multiple erythematous papules with mild infiltration of the extremities and trunk, edematous erythema of face | 8                                                                | 9                                    | Ciclesonide inhalation, Favipiravir, Hydroxychloroquine | Topical steroids, Oral antihistamines |
| 2    | 81          | Female | Multiple erythematous papules with mild infiltration of the upper limb. | 20                                                               | 7                                    | Ciclesonide inhalation | Topical crotamiton, Oral antihistamines |
| 3    | 54          | Male  | Multiple small erythematous papules with slight infiltrates on the abdomen | 9                                                                | 8                                    | Ciclesonide inhalation, Favipiravir, Hydroxychloroquine | Topical steroids, Oral antihistamines |
| 4    | 31          | Male  | Multiple erythematous papules of the anterior chest                      | 2                                                                | Unknown                              | None                        | Topical steroids                         |
| 5    | 38          | Female | Multiple erythemas of the brachium and thigh                            | 5                                                                | Unknown (Gradually improved)         | None                        | Topical crotamiton                        |
| 6    | 0           | Female | Multiple erythemas of the face and anterior chest                        | Unknown                                                          | Unknown (Gradually improved)         | None                        | External medicine unknown                |
| 7    | 4           | Male  | Multiple erythemas of the trunk                                          | 14                                                               | Unknown (Gradually improved)         | None                        | Topical moisturizer                       |
| 8    | 0           | Male  | Multiple erythemas with slight infiltrates on the right upper eyelid     | 9                                                                | Unknown (Gradually improved)         | None                        | none                                     |
| 9    | 32          | Female | Multiple erythematous papules of the axilla and groin                    | 9                                                                | Unknown                              | None                        | Topical steroids                         |
| 10   | 1           | Female | Multiple erythemas of the chest and abdomen                              | Unknown                                                          | Unknown                              | Dexamethasone, Tulobuterol patch, Expectorant | None                                     |
| 11   | 74          | Female | Multiple erythemas of the face and trunk                                 | 14                                                               | 9                                    | Favipiravir, Dexamethasone | Topical steroids                         |
| 12   | 78          | Female | Multiple small erythemas of the face and neck and trunk and brachium     | 17                                                               | Unknown                              | Favipiravir, Dexamethasone | Oral antihistamines                      |
| 13   | 49          | Male  | Erythemas of the neck and chest and limbs                                | 17                                                               | Unknown                              | Favipiravir, Dexamethasone | Topical steroids                         |
| 14   | 61          | Male  | Multiple erythematous papules of the chest and abdomen and limbs         | 13                                                               | 13                                   | Favipiravir                                | Topical steroids                         |
| 15   | 47          | Female | Multiple erythemas on the abdomen and joint part of limbs                | 0                                                                | Unknown                              | None                        | Topical steroids                         |
| 16   | 46          | Male  | Urticaria of the abdomen and limbs                                        | 7                                                                | 4                                    | Favipiravir, Dexamethasone, Antitussive | Topical steroids, Oral antihistamines    |

(Continues)
Matsunaga et al. reported that 0.6% (11/1850) and Nozaki et al. reported that 2.2% (4/181) of patients developed skin manifestations.\textsuperscript{13,5} Skin manifestations in patients with COVID-19 are often overlooked among other severe conditions, and minimum contact with COVID-19 patients to prevent infection or less involving dermatologists could be omitted from reports. In our hospital, 2.8% (21/738) of COVID-19 patients had skin manifestations, which is relatively close to the number reported by Nozaki et al. Our study involved dermatologists who examined the patients and analyzed their skin rashes as well as reported by Nozaki et al. Based on those reports, we speculated that the incidence of COVID-19-associated viral eruptions in our country was approximately 2–3%.

The erythematous papule type is the most common Japanese COVID-19-associated skin manifestation. Shams et al. conducted a systematic review of erythematous papules in COVID-19-associated viral eruption worldwide.\textsuperscript{14} They reported that the duration of erythematous papules ranged from 2 to 14 days with a mean of 8 days, and in 97% of cases (242/249), the skin symptoms appeared simultaneously as or after COVID-19 symptoms. The characteristics of erythematous papule manifestations in Japanese COVID-19 patients are similar to those reported by Shams et al. On the other hand, the erythematous papule-type is difficult to distinguish between viral eruption, drug eruptions, and other diseases.\textsuperscript{15} We ruled out the possibility of other diseases, such as contact dermatitis or seborrheic dermatitis, through examination or evaluation of photographs in the medical record by a dermatologist. In 13 of the 21 cases we experienced, the possibility of drug eruption or another skin rash was very low, so we diagnosed these patients with definite viral eruptions. One case was difficult to differentiate from a sweat rash for the remaining eight cases. For the other seven cases, the possibility of drug eruption was suspected. Therefore, some drugs (especially those started after hospitalization for COVID-19 and drugs to relieve various symptoms caused by COVID-19) were discontinued, making it challenging to differentiate drug eruptions from viral eruptions. It has been reported that favipiravir may cause drug eruptions, but the skin manifestation improves quickly with discontinuation of the drug, averaging 1.75 days.\textsuperscript{16} In five out of the seven cases, favipiravir was used to treat COVID-19, but all patients continued to have skin symptoms for a certain period of time after discontinuation, and their skin symptoms improved along with improvement of other symptoms of COVID-19, leading to the diagnosis of COVID-19-associated viral eruptions. The other two cases were also diagnosed as viral eruptions based on comprehensive judgment of the course of the skin manifestation and other factors.

There are regional differences in the frequency and type of skin manifestations in COVID-19 patients. Sameni et al.\textsuperscript{17} reported in a meta-analysis of skin manifestations in COVID-19 patients who the frequency of skin manifestations tended to be lower in Asian countries than in European countries. Few papers by dermatologists have described the frequency of skin manifestations in COVID-19 patients in Asia. The frequency of COVID-19-associated viral eruption was 2.5% (5/204) in Thailand,\textsuperscript{18} and 2.8% in our Japanese cohort. In Japan and Asia, erythematous papules are the most common skin manifestations.
TABLE 3 Summary of age, sex, and skin manifestations of Japanese patients with COVID-19-associated viral eruption

| Characteristics                              | Patients suspected COVID-19-related eruption in Japan |
|----------------------------------------------|-------------------------------------------------------|
| Age, median (average)                        | 48 (42.8)                                             |
| Male sex, n (%)                              | 17 (52)                                               |
| Type of skin manifestations                  |                                                       |
| Erythematous papules, n (%)                  | 27 (82)                                               |
| Urticaria, n (%)                             | 3 (9)                                                 |
| Pernio-like lesions, n (%)                   | 2 (6)                                                 |
| Papulovesicular type, n (%)                  | 0 (0)                                                 |
| Livedo reticularis, or necrotic lesions, n (%)| 1 (3)                                                 |
| Others, n (%)                                | 2 (6)                                                 |
| The time from the first symptom to the skin manifestations, median (days) | 10.5                                                   |
| Duration of the skin manifestations, median (days) | 9                                                      |

In conclusion, this study suggests that COVID-19-associated viral eruption occurs in approximately 2–3% of Japanese patients and that the type of erythematous papules is the majority. Now that there are racial differences in the frequency and types of skin manifestations in COVID-19 patients, it is necessary to strictly discuss the skin manifestations of COVID-19 by race and country. However, even within the same country, the prevalent variant of the virus has changed. It has also been pointed out that viruses acquire the ability to evade HLA by mutation. There is a possibility that the frequency of skin manifestations in COVID-19 patients and the proportion of each type of skin manifestation will change. We hope that more cases will be collected in Japan and worldwide.

ACKNOWLEDGMENTS
We thank all staff of our hospital who made great efforts to treat COVID-19 patients.
CONFLICT OF INTEREST
None declared.

ORCID
Masakazu Tamai https://orcid.org/0000-0002-0120-4828

REFERENCES
1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–20.
2. Sachdeva M, Gianotti R, Shah M, Bradanini L, Tosi D, Veraldi S, et al. Cutaneous manifestations of COVID-19: report of three cases and a review of literature. J Dermatol Sci. 2020;98:75–81.
3. Tamai M, Maekawa A, Nishida T, Iwahashi H, et al. Three cases of COVID-19 patients presenting with erythema. J Dermatol. 2020;47:1175–8.
4. Kuriyama Y, Shimizu A, Oka H, Sato M, Makioka K, Ikota H, et al. Erythema nodosum-like eruption in coronavirus disease 2019: a case report and literature review of Asian countries. J Dermatol. 2021;48:1588–92.
5. Mizutani Y, Nagai M, Tsuzuku A. Late-onset cutaneous manifestations in a patient with severe COVID-19 infection. J Dermatol. 2020;47:e347–8.
6. Sachdeva M, Gianotti R, Shah M, Bradanini L, Tosi D, Veraldi S, et al. Development of maculopapular exanthem in a COVID-19 patient. J Dermatol. 2020;47:e426–7.
7. Eun Seon Lee SS, Fujihara J, Sakai N, Ito H, Saruta Y, Watanabe H, et al. A case of COVID-19 with initial diagnosis based on cutaneous manifestation. Jpn J Dermatol. 2020;131:1539–44.
8. Ishii T. “Pinboke syashin...sono wake ha? Hisin ga COVID-19 kansen kukanin no ichiho to natta 1 rei!”[Out of focus photos...why? A case of COVID-19 patients whose skin rash helped to suspect COVID-19 infection]. Vis Dermatol. 2020;19:1072–3.
9. Motohishi I, Takano T, Ie K, Hashimoto Y, Akino S, Okuse C. Development of maculopapular exanthem in a COVID-19 patient. J Dermatol. 2020;130:2385–9.
10. Tanaka A, Isei M, Kikuzawa C, Hinogami H, Nishida K, Gohma I, et al. Development of toxic epidermal necrolysis in a coronavirus disease 2019 patient with recurrence of positive SARS-CoV-2 viral RNA. J Dermatol. 2021;48:e144–5.
11. Maruyama A, Oshita A, Kato H. Severe skin ulcer in systemic scleroderma due to severe acute respiratory syndrome coronavirus 2 infection. J Dermatol. 2021;48:e343–4.
12. Sugawara-Mikami M, Ishii N, Yamazaki M, Kambara T, Sasaki H, Tachikawa N, et al. Skin manifestations of suspected COVID-19: complications of the disease or reactivation of latent viral infections? JAAD Case Rep. 2021;12:15–7.
13. Matsunaga N, Hayakawa K, Terada M, Ohtsu H, Asai Y, Tsuzuki S, et al. Clinical epidemiology of hospitalized patients with coronavirus disease 2019 (COVID-19) in Japan: report of the COVID-19 Registry Japan. Clin Infect Dis. 2021;73:e3677–89.
14. Shams S, Rathore SS, Anvekar P, Sundhi M, Kanherla N, Tousif S, et al. Maculopapular skin eruptions associated with Covid-19: a systematic review. Dermatol Ther. 2021;34:e14788.
15. Galván Casas C, Català A, Carretero Hernández G, Rodríguez-Jiménez P, Fernández-Nieto D, Rodríguez-Villa Lario A, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol. 2020;183:71–7.
16. Punyaratbandhup, Vanitchpongphan S. Favipiravir-induced cutaneous adverse reactions in patients infected with COVID-19. Clin Exp Dermatol. 2021;47:573–7.
17. Sameni F, Hajikhani B, Yaslanifard S, Goudarzi M, Owlia P, Nasiri MJ, et al. COVID-19 and skin manifestations: an overview of case reports/case series and meta-analysis of prevalence studies. Front Med. 2020;7:573188.
18. Punyaratbandhup, Chirachanakul P. Cutaneous eruption in COVID-19-infected patients in Thailand: an observational descriptive study. J Dermatol. 2021;48:14–20.
19. Jia JL, Kamceva M, Rao SA, Linos E. Cutaneous manifestations of COVID-19: a preliminary review. J Am Acad Dermatol. 2020;83:687–90.
20. Tan SW, Tam YC, Oh CC. Skin manifestations of COVID-19: a worldwide review. JAAD Int. 2021;2:119–33.
21. Daneshgaran G, Dubin DP, Gould DJ. Cutaneous manifestations of COVID-19: an evidence-based review. Am J Clin Dermatol. 2020;21:627–39.
22. Freeman EE, McMahon DE, Lipoff JB, et al. The spectrum of COVID-19-associated dermatologic manifestations: an international registry of 716 patients from 31 countries. J Am Acad Dermatol. 2020;83:1118–29.
23. Motozono C, Toyoda M, Zalradnik J, Saito A, Nasser H, Tan TS, et al. SARS-CoV-2 spike L452R variant evades cellular immunity and increases infectivity. Cell Host Microbe. 2021;29:1124–36.e11.
24. Hoffmann M, Kleine-Weber H, Schroder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181:271–80.e8.
25. Colmenero I, Santonja C, Alonso- Riaño M, Noguera- Morel L, Jiménez P, Fernández- Nieto D, Rodríguez- Villa Lario A, et al. Development of toxic epidermal necrolysis in a coronavirus COVID-19 patient. Clin Dermatol Ther. 2021;34:e14788.
26. Galván Casas C, Català A, Carretero Hernández G, Rodríguez-Jiménez P, Fernández-Nieto D, Rodríguez-Villa Lario A, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol. 2020;183:71–7.
27. Sameni F, Hajikhani B, Yaslanifard S, Goudarzi M, Owlia P, Nasiri MJ, et al. COVID-19 and skin manifestations: an overview of case reports/case series and meta-analysis of prevalence studies. Front Med. 2020;7:573188.
28. Punyaratbandhup, Chirachanakul P. Cutaneous eruption in COVID-19-infected patients in Thailand: an observational descriptive study. J Dermatol. 2021;48:14–20.
29. Jia JL, Kamceva M, Rao SA, Linos E. Cutaneous manifestations of COVID-19: a preliminary review. J Am Acad Dermatol. 2020;83:1118–29.
30. Tan SW, Tam YC, Oh CC. Skin manifestations of COVID-19: a worldwide review. JAAD Int. 2021;2:119–33.
31. Daneshgaran G, Dubin DP, Gould DJ. Cutaneous manifestations of COVID-19: an evidence-based review. Am J Clin Dermatol. 2020;21:627–39.
32. Freeman EE, McMahon DE, Lipoff JB, et al. The spectrum of COVID-19-associated dermatologic manifestations: an international registry of 716 patients from 31 countries. J Am Acad Dermatol. 2020;83:1118–29.
33. Motozono C, Toyoda M, Zalradnik J, Saito A, Nasser H, Tan TS, et al. SARS-CoV-2 spike L452R variant evades cellular immunity and increases infectivity. Cell Host Microbe. 2021;29:1124–36.e11.
34. Hoffmann M, Kleine-Weber H, Schroder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181:271–80.e8.
35. Colmenero I, Santonja C, Alonso- Riaño M, Noguera- Morel L, Jiménez P, Fernández- Nieto D, Rodríguez- Villa Lario A, et al. Development of toxic epidermal necrolysis in a coronavirus COVID-19 patient. Clin Dermatol Ther. 2021;34:e14788.

SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

How to cite this article: Tamai, M., Sakamoto, R., Goto, N., Morimura, O., Nishida, T. & Iwahashi, H. et al. (2022) Cutaneous manifestations of coronavirus disease 2019 patients in Japan. The Journal of Dermatology, 49, 872–878. Available from: https://doi.org/10.1111/1346-8138.16433