Abstract

Background: Hypertension and atherosclerosis are bidirectionally related, while platelet count could serve as an indicator of endothelial repair. Therefore, high platelet counts could be associated with hypertension by indicating more intense endothelial repair activity. Furthermore, short stature has been shown to constitute a risk of atherosclerosis. Since inflammation-related single-nucleotide polymorphism (SNP (rs3782886)) is reportedly associated with myocardial infarction and short stature, rs3782886 could be associated with a high platelet count and thus more intense endothelial repair activity.

Methods: We conducted a cross-sectional study of 988 elderly Japanese who participated in a general health check-up. Short stature was defined as a height of at or under the 25th percentile of the study population, and high platelet count as the highest tertiles of the platelet levels.

Results: High platelet counts were found to be independently and positively associated with hypertension while rs3782886 was independently associated with high platelet levels and short stature. The classical cardiovascular risk factor-adjusted odds ratio (OR) and 95% confidence interval (CI) of high platelet count for hypertension was 1.34 (1.02, 1.77). With non-minor homo of the rs3782886 as the reference group, the adjusted OR and 95% CI for high platelet count and short stature of minor home were 2.40 (1.30, 4.42) and 2.21 (1.16, 4.21), respectively.

Conclusion: SNP (rs3782886) was shown to be associated with high platelet count and short stature. This result partly explains how a genetic factor can influence the impact of height on endothelial repair.

Keywords: Height, Hypertension, Platelets, rs3782886, SNP

Background

Hypertension is known as a major risk factor of stroke for Japanese [1] while short stature is well known as a Japanese characteristic. Furthermore, short stature has been reported to have an independent association with hypertension [2], carotid atherosclerosis [3], and incidence of stroke [4]. However, previous studies of ours indicate that the presence of carotid atherosclerosis cannot explain the risk of stroke associated with short stature [3, 4].

Recently, hematopoietic activity has been revealed to be closely associated with vascular maintenance activity (endothelial repair activity [5–8]). Short stature has been shown to be associated with lower capacity for hematopoietic activity [9, 10] and with anemia [11] possibly due to the fact that height indicates the absolute volume of total bone marrow. Higher capacity for hematopoietic activity (high hemoglobin level) has been found to be positively associated with atherosclerosis [6, 7] and hypertension [8, 12].
Those studies raise issues emerging from paradoxical findings for short stature as a risk for anemia, hypertension, carotid atherosclerosis, and incidence of stroke.

Since atherosclerosis results from aggressive endothelial repair, the findings of these studies indicate that the risk of stroke in people with short stature might be associated with low endothelial repair activity (low hematopoietic activity).

Single-nucleotide polymorphism (SNP) (rs3782886) in breast cancer suppressor BRCA1-related associated protein (BRAP) is reportedly associated with risk of myocardial infarction [13], while SNP (rs3782886) is also found to be associated with short stature in a previous study by us [14]. Another study reported that BRAP activates inflammatory cascades and increases the risk of carotid atherosclerosis [15] but is not associated with risk of stroke [16]. Although an SNP (rs3782886) could be associated with carotid atherosclerosis, these studies indicate that it might also have a beneficial effect on stroke prevention by inducing endothelial repair in participants with short stature; otherwise, these participants would have high risks of hypertension [2], carotid atherosclerosis [3], and stroke [4].

Furthermore, platelet is known to contribute to endothelial repair [17]. We previously showed that platelet levels were positively associated with hypertension [18] and that platelet count could serve as an indicator of vascular repair (endothelial repair and developing atherosclerosis) [19]. Since the association between hypertension and atherosclerosis (increased arterial stiffness) is bidirectional [20–22], high platelet levels, which are associated with hypertension, can be expected to reflect a higher activity of endothelial repair.

Since height is inversely associated with platelet count in elderly men [23], clarification of the relationship of SNP (rs3782886) with short stature and high platelet counts, which are in turn associated with hypertension, should provide us with an efficient tool to clarify the underlying mechanism of the effect of height on endothelial repair.

We therefore hypothesized that hypertension is positively associated with a high platelet count, thus indicating active endothelial repair. Moreover, that SNP (rs3782886) is also associated with a high platelet count and short stature since it plays an important role in the activation of endothelial repair in participants with short stature.

To elucidate those associations, we conducted a cross-sectional study of 988 elderly Japanese participants aged 60–89 years who participated in a general health check-up in 2014 and 2015.

Methods

Study population

The total number of residents of Goto City aged 60–89 in 2015 was 16,176, based on an estimate by the National Institute of Population and Social Security Research in March 2013 [24].

The study population comprised 992 Japanese elderly residents aged 60–89 years from the rural communities of the Goto Islands in western Japan, who underwent annual medical check-ups in 2014 and 2015 as recommended by the Japanese government.

Participants without SNP data (n = 3) and without blood pressure data (n = 1) were excluded, leaving 988 participants with a mean age of 72.6 years (standard deviation (SD), 7.3; range, 60–89) enrolled in the study.

Data collection and laboratory measurements

Trained interviewers obtained information on medical history (lifestyle habit). Body weight and height were measured with an automatic body composition analyzer (BF-220; Tanita, Tokyo, Japan), and body mass index (BMI; kg/m²) was calculated. Systolic and diastolic blood pressure were recorded at rest. Blood samples were collected in an EDTA-2 K tube, a siliconized tube, and sodium fluoride tube. The number of platelets in samples from the EDTA-2 K tube was measured with an automated procedure at SRL, Inc. (Tokyo, Japan). Triglycerides (TG) and serum creatinine were measured enzymatically, while HDL cholesterol (HDLc) was measured with a direct method and hemoglobin A1c (HbA1c) with the latex coagulation method. Genomic DNA was extracted from 2 ml of whole peripheral blood by means of the Gene Prep Star NA-480 (Kurabo Industries Ltd., Osaka, Japan) and typed for SNP rs3782886 (BRAP on chromosome 12q24.12) by using the HybProbe method with LightCycler 480 (Roche Diagnostics, Basel, Switzerland). Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. A high platelet level was defined as the highest tertile (≥22.0 × 10⁴/μL for men and ≥24.2 × 10⁴/μL for women) and short stature as a height level at or under the 25th percentile of the study population (<158.4 cm for men and <146.4 cm for women) as in a previous study by us [3, 14].

Statistical analysis

Characteristics of the study population stratified by platelet level and SNP (rs3782886) genotype were expressed as mean ± standard deviation. A trend test was performed with analysis of variance (ANOVA) for continuous values, and chi-squared test was used for determining proportions.

Logistic regression models were also used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) in order to determine the influence of platelet level on hypertension. In addition, ORs and 95% CIs were calculated by using a logistic regression model to determine
the influence of SNP (rs3782886) on high platelet counts, hypertension, and short stature.

Adjustments for confounding factors were made by using two models. In the first model (model 1), adjustment was made only for age and sex. Alcohol consumption has been shown to be positively associated with height in previous studies [3, 4, 25], and white blood cell count to be a factor that is influenced by smoking status [26] while height is inversely associated with high white blood cell count [25]. BMI could be positively associated with endothelial repair (CD34-positive cell count) [8, 18, 27–29] while height is positively associated with CD34-positive cell count in participants with systolic hypertension [30]. Another study reported the identification of a primary association between a genetically determined short stature and an increased risk of cardiovascular disease which may be partly explained by the association between short stature and adverse lipid profile [31]. In one of our studies, we reported that the activity of endothelial repair (CD34-positive cells) might influence the association between blood pressure and TG [29] and HDLc [28]. HbA1c has also been found to be associated with atherosclerosis [32, 33]. All these factors are well-known classical cardiovascular risk factors. Furthermore, renal function is reportedly associated with SNP (rs3782886) [34], endothelial repair (CD34-positive cells) [35], anemia [36], and incidence of stroke [37]. We therefore added serum creatinine as a confounding factor to the aforementioned classical cardiovascular risk factors for the present analysis. Therefore, the second model (model 2) included other, possibly confounding, factors, namely, BMI (kg/m²), (systolic blood pressure (mmHg), which was not applicable to the analysis of the associations between platelet count and hypertension nor to the associations between SNP (rs3782886) and hypertension, alcohol consumption (never-drinker, former drinker, current drinker [<23 g/week, 23–46 g/week, 47–68 g/week, ≥69 g/week]), smoking status (never-smoker, former smoker, current smoker), HDLc (mg/dL), TG (mg/dL), HbA1C (%), and serum creatinine (mg/dL).

For the sensitivity analysis, we repeated our investigations with sex-specific models.

All statistical analyses were performed with the SAS system for Windows (version 9.4; SAS Inc., Cary, NC). Values of <0.05 were regarded as being statistically significant.

Results

Characteristics of study population in relation to platelet levels

Table 2 shows ORs and 95% CIs for hypertension in relation to platelet count. Independent of known cardiovascular risk factors, the high platelet level group showed significantly higher OR for hypertension compared with the reference group of non-high platelet levels (T1 and T2); the adjusted OR and 95% CI for hypertension was 1.34 (1.02, 1.77).

Table 1: Characteristics of the study population in relation to platelet levels

| Platelet levels | No. of participants | Age, years | Gender of men, % | Body mass index (BMI), kg/m² | Systolic blood pressure, mmHg | Diastolic blood pressure, mmHg | Current drinker, % | Current smoker, % | Serum triglycerides (TG), mg/dL | Serum HDL cholesterol (HDLc), mg/dL | Hemoglobin A1c (HbA1c), % | Serum creatinine, mg/dL | Platelets, × 10⁴/μL |
|----------------|---------------------|-----------|-----------------|-----------------------------|-----------------------------|-----------------------------|---------------------|-----------------|--------------------------|-----------------------------|--------------------------|------------------------|----------------------|
| T1 (low)       | 332                 | 73.6 ± 7.1| 37.0            | 23.1 ± 3.6                  | 139 ± 18                    | 80 ± 11                    | 22.6                | 3.3             | 93 ± 54                   | 59 ± 16                     | 5.7 ± 0.5                | 0.78 ± 0.22             | 16.6 ± 2.7 |
| T2             | 327                 | 72.4 ± 7.3| 37.6            | 23.3 ± 3.1                  | 139 ± 17                    | 81 ± 11                    | 23.5                | 6.4             | 108 ± 63                  | 60 ± 18                     | 5.6 ± 0.4                | 0.75 ± 0.19             | 21.5 ± 1.4 |
| T3 (high)      | 329                 | 71.6 ± 7.4| 37.4            | 23.2 ± 3.2                  | 141 ± 19                    | 82 ± 11                    | 27.4                | 8.8             | 106 ± 53                  | 60 ± 15                     | 5.8 ± 0.6                | 0.73 ± 0.18             | 27.7 ± 5.1 |

Values: mean ± standard deviation. Platelet levels for men are <18.7 × 10⁴/μL for T1, 18.7–21.9 × 10⁴/μL for T2, and ≥22.0 × 10⁴/μL for T3, for women are <20.3 × 10⁴/μL for T1, 20.3–24.1 × 10⁴/μL for T2, and ≥24.2 × 10⁴/μL for T3.
Characteristics of the study population by genotype of SNPs (rs3782886)

Characteristics of the study population by genotype of SNPs (rs3782886) are shown in Table 3. Of the 988 elderly Japanese participants, 609 were major homogeneous (A/A), 332 were heterogeneous (A/G), and 47 were minor homogeneous (G/G). This SNP was in Hardy-Weinberg equilibrium. Current drinker was inversely significantly associated with minor allele frequency (G) while platelet level showed a significantly positive association.

Associations between rs3782886 genotype and high platelet levels

Table 4 shows the associations between genotype and high platelet levels. For model 1 with major homogeneity (A/A) as the reference group, no significant association was observed for heterogeneity (A/G), while a significant association was observed for minor homogeneity (G/G). When we made further adjustment for other known cardiovascular risk factors, those associations with the reference group became slightly stronger and the statistical value became significant for heterogeneity.

Associations between rs3782886 genotype and short stature

Table 5 shows the associations between genotype and short stature. With major homogeneity (A/A) as the reference group, no significant association was observed for heterogeneity (A/G), while a significant association was observed for minor homogeneity (G/G). However, a comparison of the two categories non-minor heterogeneity and minor homogeneity showed a significant association.

Associations between rs3782886 genotype and hypertension

No significant associations between genotype and hypertension were observed (Table 6).

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### Table 2
Odds ratios (ORs) and 95% confidence intervals (CIs) for hypertension in relation to platelet levels

|                  | Platelet levels |         |         |         |
|------------------|-----------------|---------|---------|---------|
|                  | T1 (low) | T2     | T3 (high) | P for trend | 1 SD increment of platelet |
| No. at risk | 332     | 327     | 329     |         |         |
| No. of cases (percentage) | 160 (48.2) | 170 (52.0) | 185 (56.2) |         |         |
| Model 1          | 1.00     | 1.22 (0.89, 1.66) | 1.49 (1.09, 2.04) | 0.012 | 1.16 (1.02, 1.33) |
| Model 2          | 1.00     | 1.35 (1.03, 1.77) | 0.029 |         |         |

**Model 1 adjusted only for sex and age. Model 2 further adjusted for body mass index, alcohol consumption (never-drinker, former drinker, current drinker [< 23 g/week, 23–45 g/week, 46–68 g/week, ≥ 69 g/week]), smoking status (never-smoker, former smoker, current smoker), HDL cholesterol, triglycerides, HbA1C, and serum creatinine. Hypertension is defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg. Platelet levels for men are < 18.7 × 10^4/μL for T1, 18.7–21.9 × 10^4/μL for T2, and ≥ 22.0 × 10^4/μL for T3, for women are < 20.3 × 10^4/μL for T1, 20.3–24.1 × 10^4/μL for T2, and ≥ 24.2 × 10^4/μL for T3. 1 standard deviation (SD) increments of platelet are 6.23 × 10^4/μL for men and 5.26 × 10^4/μL for women.**

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### Table 3
Characteristics of the study population by genotype of rs3782886

| rs3782886 | Major homo (A/A) | Hetero type (A/G) | Minor homo (G/G) | P       |
|-----------|------------------|------------------|------------------|---------|
| No. of participants | 609 | 332 | 47 |         |         |
| Age, years | 72.1 ± 7.2 | 73.2 ± 7.4 | 72.8 ± 7.1 | 0.089 |         |
| Gender of men, % | 36.3 | 40.1 | 31.9 | 0.382 |         |
| Body mass index (BMI), kg/m^2 | 23.1 ± 3.2 | 23.4 ± 3.5 | 23.0 ± 3.3 | 0.274 |         |
| Systolic blood pressure, mmHg | 140 ± 18 | 140 ± 18 | 139 ± 19 | 0.990 |         |
| Diastolic blood pressure, mmHg | 82 ± 11 | 80 ± 11 | 81 ± 11 | 0.134 |         |
| Current smoker, % | 8.2 | 4.8 | 2.1 | 0.171 |         |
| Serum triglycerides (TG), mg/dL | 102 ± 60 | 103 ± 53 | 100 ± 39 | 0.941 |         |
| Serum HDL cholesterol (HDLc), mg/dL | 61 ± 17 | 58 ± 15 | 60 ± 18 | 0.066 |         |
| Hemoglobin A1c (HbA1c), % | 5.7 ± 0.5 | 5.7 ± 0.5 | 5.7 ± 0.6 | 0.722 |         |
| Serum creatinine, mg/dL | 0.75 ± 0.20 | 0.77 ± 0.19 | 0.75 ± 0.20 | 0.149 |         |
| Platelets, × 10^4/μL | 21.5 ± 4.9 | 22.4 ± 6.9 | 23.2 ± 4.9 | 0.019 |         |

Values: mean ± standard deviation
The sensitivity analysis showed similar associations to those obtained for the main results.

**Discussion**

The major findings of the present study with elderly Japanese participants are that a high platelet level is positively associated with hypertension for elderly Japanese participants and that inflammation-related SNP (rs3782886) is significantly associated with a high platelet level and short stature.

Recently, platelets have been revealed to play a major role in inflammation, as well as to be important as an initial activator for the development of atherosclerotic lesions [38]. Even though development of atherosclerosis is only one aspect of endothelial repair, the association between hypertension and endothelial dysfunction (atherosclerosis) is bidirectional: hypertension induces increased arterial stiffness and vice versa [20–22]. Since our study presented here discovered a significant positive association between high platelet levels and hypertension, the former can be assumed to indicate a greater level of endothelial repair activity. In one of our previous studies, a high platelet count was found to be positively associated with hypertension in elderly men [18]. We also found that platelet levels are positively associated with carotid intima-media thickness (CIMT) in elderly hypertensive men [18, 19]. Those findings also support our hypothesis that a high platelet count is likely to indicate a higher level of endothelial repair activity. In addition, SNP (rs3782886) is known to be located in the BRAP gene on chromosome 12q24 and that a higher expression of the BRAP minor allele is associated with an increased risk of atherosclerosis by heightening the degree of inflammation through activation of the NF-κB protein [15, 39]. Since activation of the NF-κB pathway also could promote platelet activation protein [40], our finding that SNP (rs3782886) is significantly associated with high platelet levels is likely to indicate that the genetic factor might influence the level of endothelial repair activity.

Furthermore, short stature has been shown to constitute an inflammatory risk for elderly Japanese men as shown by a high white blood cell count [25]. Moreover, SNPs (rs3782886) were shown to be associated with short stature in a previous study by us [14]. SNPs (rs3782886) were also found to be significantly associated with hypertension in elderly men [18]. We also found that platelet levels are positively associated with carotid intima-media thickness (CIMT) in elderly hypertensive men [18, 19]. Those findings also support our hypothesis that a high platelet count is likely to indicate a higher level of endothelial repair activity. In addition, SNP (rs3782886) is known to be located in the BRAP gene on chromosome 12q24 and that a higher expression of the BRAP minor allele is associated with an increased risk of atherosclerosis by heightening the degree of inflammation through activation of the NF-κB protein [15, 39]. Since activation of the NF-κB pathway also could promote platelet activation protein [40], our finding that SNP (rs3782886) is significantly associated with high platelet levels is likely to indicate that the genetic factor might influence the level of endothelial repair activity.

### Table 4

| rs3782886                  | Non-minor homo | Hetero (A/G) | Minor homo (G/G) | P for trend |
|----------------------------|----------------|--------------|------------------|------------|
| No. at risk                |                |              |                  |            |
| No. of cases (percentage)  |                |              |                  |            |
| Model 1                    | 1.00           | 1.00         | 1.00             |            |
| Model 2                    | 1.00           | 1.00         | 1.00             |            |

*Model 1 adjusted only for sex and age. Model 2 further adjusted for body mass index, systolic blood pressure, alcohol consumption (never-drinker, former drinker, current drinker (< 23 g/week, 23–45 g/week, 46–68 g/week, ≥ 69 g/week)), smoking status (never-smoker, former smoker, current smoker), HDL cholesterol, triglycerides, HbA1C, and serum creatinine. The high platelet level is defined as the highest tertiles of platelets levels (≥ 22.0 × 10^4/μL for men and ≥ 24.2 × 10^4/μL for women)*

### Table 5

| rs3782886                  | Non-minor homo | Hetero (A/G) | Minor homo (G/G) | P for trend |
|----------------------------|----------------|--------------|------------------|------------|
| No. at risk                |                |              |                  |            |
| No. of cases (percentage)  |                |              |                  |            |
| Model 1                    | 1.00           | 1.00         | 1.00             |            |
| Model 2                    | 1.00           | 1.00         | 1.00             |            |

*Model 1 adjusted only for sex and age. Model 2 further adjusted for body mass index, systolic blood pressure, alcohol consumption (never-drinker, former drinker, current drinker (< 23 g/week, 23–45 g/week, 46–68 g/week, ≥ 69 g/week)), smoking status (never-smoker, former smoker, current smoker), HDL cholesterol, triglycerides, HbA1C, and serum creatinine. Short stature is defined as a height level at or under the 25th percentile of the study population (< 158.4 cm for men and < 146.4 cm for women)*
associated with a high platelet count and short stature in the current study, indicating that the genetic factor may at least partly influence the risk of inflammatory changes which induce endothelial repair in participants with short stature. Another study by us of elderly men also supports the notion of this mechanism. In this study, we showed that platelet level is positively associated with CIMT and circulating endothelial progenitor cells (CD34-positive cells) while height is inversely associated with platelet count for participants with high hemoglobin levels [23].

The inverse association between height and hypertension which is reported in a Chinese study [2] is probably due to a reduced anti-oxidative stress capacity [20, 21, 41] since short stature is associated with lower hematopoiesis activity [9, 10] and higher risk of anemia [11]. Lower endothelial repair capacity which is a characteristic of short stature [23, 30] also might induce hypertension because of its reduced ability to compensate for blockage of the blood flow. Moreover, hypertension is a well-known major risk factor for stroke in Japanese [1] who are known to be characterized by short stature and low BMI. Since we reported in a previous study that platelet level is positively associated with CIMT and circulating endothelial progenitor cells (CD34-positive cells) while height is inversely associated with platelet count for participants with high hemoglobin levels [23].

"The present findings are efficient for clarifying the mechanism underlying the association between height and endothelial repair as they indicate that genetic factors could at least partly influence this association. In addition, the present findings also clarify the reason why the extent of inflammatory disadvantage-associated hypertension (rs3782886) is low [9, 10, 23]."

Table 6 Odds ratios (ORs) and 95% confidence intervals (CIs) for hypertension in relation to rs3782886 genotype

| rs3782886 | Non-minor homo | Hetero (A/G) | Minor homo (G/G) | P for trend |
|-----------|---------------|--------------|------------------|------------|
| No. at risk | 609 | 332 | 47 |
| No. of cases (percentage) | 320 (52.5) | 170 (51.2) | 25 (53.2) |
| Model 1 | 1.00 | 0.91 (0.70, 1.20) | 1.00 (0.55, 1.82) | 0.652 |
| Model 2 | 1.00 | 1.03 (0.57, 1.87) | 0.324 |
| Model 2 | 1.00 | 0.93 (0.70, 1.23) | 1.05 (0.57, 1.93) | 0.912 |

"Table 6 Odds ratios (ORs) and 95% confidence intervals (CIs) for hypertension in relation to rs3782886 genotype. Model 1 adjusted only for sex and age. Model 2 further adjusted for body mass index, alcohol consumption (never-drinker, former drinker, current drinker [< 23 g/week, 23–45 g/week, 46–68 g/week, ≥ 69 g/week]), smoking status (never-smoker, former smoker, current smoker), HDL cholesterol, triglycerides, HbA1C, and serum creatinine. Hypertension is defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg."
relationships were not able to be established. Furthermore, because our study used elderly Japanese who participated in a general health check-up, selection bias arising from this kind of study is unavoidable.

Conclusion
In conclusion, there is a significant and positive association between high platelet count and hypertension, and SNPs (rs3782886) were shown to be associated with high platelet count and short stature. These results partly explain how a genetic factor can influence the impact of height on endothelial repair.

Abbreviations
ANOVA: Analysis of variance; BMI: Body mass index; BRAP: BRCA1-related associated protein; CI: Confidence interval; CIMT: Carotid intima-media thickness; GFR: Glomerular filtration rate; HDLc: HDL cholesterol; OR: Odds ratio; SD: Standard deviation; SNP: Single-nucleotide polymorphism; TG: Triglycerides

Acknowledgements
We are grateful to staff from Goto City Hall for their outstanding support.

Funding
This study was supported by Grants-in-Aids for Scientific Research from the Japan Society for the Promotion of Sciences (No.18K08644, No.17K03740).

Availability of data and materials
The datasets generated during and/or analyzed during the current study are not publicly available due to ethical consideration but are available from the corresponding author on reasonable request.

Authors’ contributions
YS designed the study and performed the statistical analyses, interpreted the data, and drafted the manuscript or revised it. YS, HY, YN, JK, MN, SF, MT, S-YK, and KA assisted with the design of the study, were involved in the data collection, and checked the manuscript. HY, S-YK, and TM participated in the study concept and checked the manuscript. TM was the general coordinator and also designed the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution research committee and with the 1964 Helsinki declaration and its later amendments for comparable ethical standards. The Ethics Committee for Human Use of Nagasaki University obtained ethical approval. This study was approved by the Ethics Committee of Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan. This study was supported by Grants-in-Aids for Scientific Research from the Japan Society for the Promotion of Sciences (No.18K08644, No.17K03740).

Consent for publication
Not applicable

Competing interests
The authors declare that there are no competing interests.

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Received: 3 September 2018 Accepted: 9 April 2019
Published online: 01 May 2019

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