Identification of Quantitative Trait Loci for the Concentrations of Phenylpropanoid Glycosides in Brown Rice

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ABSTRACT: Rice (Oryza sativa L.) is a staple food for most of the world’s population, as it is eaten by nearly half of its inhabitants. Phenylpropanoid glycosides derived from plants have various biomedical effects. The comparison of the concentrations of the four major phenylpropanoid glycosides in brown rice, i.e., 6-O-feruloylsucrose (1), 3′,6-di-O-sinapoylsucrose (2), 3′-O-sinapoyl-6-O-feruloylsucrose (3), and 3′,6-di-O-feruloylsucrose (4), between a conventional japonica-type cultivar Koshihikari and a high-yielding indica-type cultivar Takanari revealed that they were 57–162% higher in Koshihikari than in Takanari. To identify quantitative trait loci (QTLs) for the concentrations of these compounds (1–4), reciprocal chromosome segment substitution lines derived from a cross between Koshihikari and Takanari were analyzed. We identified QTLs for the concentrations of compound 1 on chromosome 2 and of compound 2 on chromosome 4 in the reciprocal genetic background. The concentrations of these compounds were increased by the Koshihikari alleles and decreased by the Takanari alleles. Therefore, the favorable alleles of Koshihikari are available to ameliorate the lower concentrations of compounds 1 and 2 in Takanari. The combinations of QTLs identified in the present study together with those of other biologically active compounds make it possible to breed health beneficial cultivars.

1. INTRODUCTION

Rice (Oryza sativa L.) is a staple food eaten by nearly half the world’s inhabitants.1 According to physiological and morphological differences, rice cultivars are classified into indica and japonica types.2 Indica-type cultivars, which exhibit resistance to high temperatures,3 are adapted to the tropical regions,4 whereas japonica-type cultivars, which exhibit resistance to low temperatures,5 are adapted to the temperate regions.6 Although most of the rice that is consumed in the world is produced in japonica-type cultivars, the majority of the rice produced in Japan is from indica-type cultivars.

As brown rice has bioactive compounds that are beneficial to human health, such as γ-oryzanol, tocopherols, tocotrienols, phenylpropanoids, and γ-aminobutyric acid,7–9,9 eating brown rice has been focused on by many consumers.8 Phenylpropanoid glycosides exert several biomedical effects, such as antiviral,10 antibacterial,11 and antiinflammatory12 activities. Recently, we have isolated four phenylpropanoid glycosides, i.e., feruloyl and/or sinapoyl moieties and a sucrose moiety, 6-O-feruloylsucrose (1), 3′,6-di-O-sinapoylsucrose (2), 3′-O-sinapoyl-6-O-feruloylsucrose (3), and 3′,6-di-O-feruloylsucrose (4), together with γ-oryzanol containing a feruloyl moiety and a sterol moiety, from japonica-type cultivars of brown rice.10,11 The concentrations of γ-oryzanol, α-tocopherol, and α-tocotrienol are high in japonica-type cultivars compared to indica-type cultivars.12–14 In contrast, the concentration of γ-tocotrienol is high in indica-type cultivars relative to japonica-type cultivars.12,15 Recently, a gene involved in the biosynthesis of γ-tocotrienol showing strong biological activities has been identified.15 However, whether the concentrations of phenylpropanoid glycosides differ between indica- and japonica-type cultivars remains unknown. Furthermore, quantitative trait loci (QTLs) for the concentrations of phenylpropanoid glycosides have yet been identified.

Chromosome segment substitution lines (CSSLs) carrying a specific chromosome segment derived from a donor cultivar in the genetic background of a recurrent cultivar are a powerful tool for the more accurate identification of quantitative trait loci (QTLs) with even minor effects compared to primary mapping populations, such as recombinant inbred lines.16 Recently, Takai et al. have developed reciprocal CSSLs derived from a cross between a conventional japonica-type cultivar Koshihikari and a high-yielding indica-type cultivar Takanari.17 Moreover, several QTLs related to photosynthesis rate and lodging resistance were found using the CSSLs.18,19 More recently, we have identified QTLs for the concentration of γ-oryzanol using the CSSLs.14 This study aimed to identify QTLs responsible for the concentrations of phenylpropanoid glycosides using reciprocal CSSLs derived from a cross between Takanari and Koshihikari.

Received: July 4, 2019
Accepted: September 26, 2019
Published: October 7, 2019
In future breeding programs, our findings should help enhance the health benefits of brown rice.

2. RESULTS

2.1. 6-O-Feruloylsucrose (1) Concentrations in Reciprocal CSSLs. We examined the concentrations of compound 1 in Koshihikari and Takanari (Figures 1 and 2). Koshihikari exhibited a concentration (22.2 mg/kg) that was 57% higher than that of Takanari (14.2 mg/kg) (Figure 3). To identify QTLs for the concentration of this compound (1), we assessed the reciprocal CSSLs derived from a cross between Takanari and Koshihikari. Among the 40 lines of the Koshihikari genetic background, the concentrations varied from 15.9 to 31.6 mg/kg (Figure 3a). SL1206, SL1212, and SL1218 exhibited lower concentrations, whereas SL1201, SL1202, SL1208, SL1210, SL1213, and SL1235 had higher concentrations than Koshihikari. Among the 37 lines with the Takanari genetic background, the concentrations varied from 10.2 to 16.6 mg/kg (Figure 3b). SL1302, SL1303, and SL1305 accumulated higher concentrations, whereas SL1324, SL1327, and SL1330 had lower concentrations than Takanari. In addition, we confirmed that SL1206 had significantly ($P < 0.001$) lower concentration (17.8 ± 1.2 mg/kg) than Koshihikari (24.0 ± 0.3 mg/kg) in the samples obtained in 2011.

2.2. 3′,6-Di-O-Sinapoylsucrose (2) Concentrations in Reciprocal CSSLs. The examination of the concentrations of compound 2 in Koshihikari and Takanari (Figures 1 and 2) revealed that they were 162% higher in the former (9.6 mg/kg) compared to the latter (3.7 mg/kg) (Figure 4). In the Koshihikari genetic background, the concentrations varied from 6.0 to 13.9 mg/kg (Figure 4a). SL1217 was the only line with a lower concentration than Koshihikari. In the Takanari genetic background, the concentration varied from 0.4 to 6.6 mg/kg (Figure 4b). SL1315 was the only line that accumulated a higher concentration, whereas SL1324, SL1327, and SL1336 exhibited lower concentrations than Takanari. In addition, we confirmed that SL1217 had a significantly ($P < 0.05$) lower concentration (4.4 ± 0.4 mg/kg) compared to Koshihikari (5.7 ± 0.1 mg/kg) in the sample obtained in 2011.

2.3. 3′-O-Sinapoyl-6-O-Feruloylsucrose (3) Concentrations in Reciprocal CSSLs. The quantification of the concentrations of compound 3 in Koshihikari and Takanari...
Figures 1 and 2) showed that they were 84% higher in the former (18.0 mg/kg) compared to the latter (9.8 mg/kg) (Figure 5). In the Koshihikari genetic background, the concentrations varied from 12.5 to 22.6 mg/kg (Figure 5a). SL1212, SL1215, SL1218, and SL1224 had lower concentrations than Koshihikari; in contrast, no lines exhibited higher concentrations than this cultivar. In the Takanari genetic background, the concentrations varied from 4.4 to 12.4 mg/kg (Figure 5b). SL1324, SL1335, and SL1336 had lower concentrations compared to Takanari, whereas no lines exhibited higher concentrations than this cultivar.

2.4. 3’,6-Di-O-Feruloylsucrose Concentrations (4) in Reciprocal CSSLs. We also examined the concentrations of compound 4 in Koshihikari and Takanari (Figures 1 and 2). Koshihikari exhibited a concentration (5.3 mg/kg) that was 116% higher than that of Takanari (2.5 mg/kg) (Figure 6). However, in both the Koshihikari and Takanari genetic backgrounds, no lines exhibited significantly different levels of compound 4 compared to Koshihikari and Takanari, respectively.

2.5. QTL Mapping for the Concentrations of 6-O-Feruloylsucrose (1), 3’,6-Di-O-Sinapoylsucrose (2), and 3’,6-Di-O-Feruloylsucrose (3). According to the differences in the concentrations of compounds 1−3 in the reciprocal CSSLs derived from a cross between Takanari and Koshihikari, we mapped the QTLs for the concentrations of these three compounds (1−3). In the Koshihikari background, 13 QTLs for the compounds 1−3 were identified (Figure 7a). Eight QTLs for the concentration of compound 1 were identified on chromosomes 1, 2, 3, 5, and 10. The Takanari allele decreased this variable for three but increased it for five of these QTLs. Furthermore, one QTL for the concentration of compound 2 was identified on chromosome 4, and the Takanari allele decreased this variable. For the concentration of compound 3, four QTLs were identified on chromosomes 3, 4, 5, and 6, and the Takanari alleles showed negative effects on this variable.

In the Takanari background, 10 QTLs were identified for the concentrations of compounds 1−3 (Figure 7b). Five QTLs for the concentration of compound 1 were identified on chromosomes 1, 2, 7, 8, and 9. The Koshihikari allele increased this variable for two but decreased it for three of these QTLs. Furthermore, three QTLs for the concentration of compound 2 were identified on chromosomes 4, 8, and 11. The Koshihikari allele increased this variable for one but decreased it for two of these QTLs. For compound 3 concentration, two QTLs were identified on chromosomes 7 and 11 and the Koshihikari alleles showed negative effects on this variable.

2.6. Relationships between the Daily Mean Air Temperatures during Ripening and the Concentrations of 6-O-Feruloylsucrose (1), 3’,6-Di-O-Sinapoylsucrose (2), and 3’,6-Di-O-Feruloylsucrose (3). According to the differences in the concentrations of compounds 1−3 in the reciprocal CSSLs derived from a cross between Takanari and Koshihikari, we mapped the QTLs for the concentrations of these three compounds (1−3). In the Koshihikari background, 13 QTLs for the compounds 1−3 were identified (Figure 7a). Eight QTLs for the concentration of compound 1 were identified on chromosomes 1, 2, 3, 5, and 10. The Takanari allele decreased this variable for three but increased it for five of these QTLs. Furthermore, one QTL for the concentration of compound 2 was identified on chromosome 4, and the Takanari allele decreased this variable. For the concentration of compound 3, four QTLs were identified on chromosomes 3, 4, 5, and 6, and the Takanari alleles showed negative effects on this variable.

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(2), 3′-O-Sinapoyl-6-O-Feruloylsucrose (3), and 3′,6-Di-O-Feruloylsucrose (4). Correlation coefficient analyses were conducted to determine the effects of the daily mean air temperatures during ripening on the concentrations of compounds 1−4 (Figure 8). No positive or negative correlations were observed between the temperatures and the concentrations of compounds 1−4 in the Koshihikari genetic background and those of compounds 1 and 4 in the Takanari genetic background (Figure 8a−e,h). The temperatures exhibited positive correlations with the concentrations of compounds 2 (r = 0.394**) and 3 (r = 0.509***) (Figure 8f,g). However, the exclusion of the values obtained for SL1335 and SL1336 canceled these correlations.

3. DISCUSSION

Brown rice has bioactive compounds, for instance, γ-oryzanol and phenylpropanoid glycosides.5,7,14 To breed rice cultivars containing abundant bioactive compounds, first it is necessary to determine the difference in their concentrations among cultivars (e.g., between indica- and japonica-type cultivars) and identify the corresponding QTLs using plant materials for genetic analysis. The concentration of γ-oryzanol is higher in japonica-type cultivars compared to indica-type cultivars.12−14 In our previous study, a japonica-type cultivar Koshihikari accumulated a 37% higher concentration of total γ-oryzanol than an indica-type cultivar Takanari.14 In the present study, we compared the concentrations of compounds 1−4 between Koshihikari and Takanari and found that they were 57−162% higher in the former than in the latter (Figures 3−6). γ-Oryzanol consists of one phenylpropanoid moiety (i.e., the feruloyl moiety) and one of sterol moiety, and compounds 1−4 consist of one or two phenylpropanoid moieties (feruloyl and/or sinapoyl moieties) and one sucrose moiety, suggesting that Koshihikari might accumulate higher concentrations of compounds with phenylpropanoid moieties.

To identify the QTLs for the concentrations of compounds 1−4, the concentrations of the reciprocal CSSLs derived from a cross between Koshihikari and Takanari were analyzed. We identified QTLs for the concentration of compound 1 at RM6842−RM17836 on chromosome 2 in the reciprocal genetic backgrounds (Figure 7). These concentrations were enhanced by the Koshihikari allele but diminished by the Takanari allele. Moreover, we confirmed that SL1305, which carries the Takanari allele on chromosome 2 in the Koshihikari genetic background, exhibited a concentration of compound 1 that was 19% higher than Takanari (Figure 3b). In the same region of chromosome 2, a QTL for the concentration (w/w) of cycloartenyl ferulate, one of the major components of γ-oryzanol, was identified previously only in the...
Takanari genetic background and the concentration was increased by the Koshihikari allele. We also found QTLs for the concentrations of compound at RM3916−RM5608 on chromosome 4 in the reciprocal genetic backgrounds (Figure 7). These concentrations were increased by the Koshihikari allele but decreased by the Takanari allele. Furthermore, we confirmed that SL1217, which carries the Takanari allele on chromosome 4 in the Koshihikari genetic background, showed a lower concentration of compound than Koshihikari in the samples obtained in 2011. SL1315, which carries the Koshihikari allele in the Takanari genetic background, exhibited a concentration of compound that was 63% higher than Takanari (Figure 3b). In the same region of chromosome 4, a QTL for the concentration of cycloartenyl ferulate (weight/grain) was identified previously in the reciprocal genetic backgrounds and the concentration was increased by the Koshihikari allele but decreased by the Takanari allele. Compound inhibits activity of soluble epoxide hydrolase, which catalyzes the hydrolysis of epoxyeicosatrienoic acids, thus exhibiting biologically beneficial properties. In addition to the above-mentioned QTLs identified in the reciprocal genetic backgrounds, many QTLs were identified in only one of the two genetic backgrounds (Figure 7). In our previous study, we identified QTLs for the concentrations of total γ-oryzanol and 24-methylenecycloartanyl ferulate, which is one of the major components of γ-oryzanol, at RM6034−RM3838-1 on chromosome 5 in the reciprocal genetic backgrounds. In the present study, QTLs for the concentrations of compounds 1 and 3 were identified in this vicinity of chromosome 5 only in the Koshihikari genetic background and the concentrations of these compounds (1 and 3) were decreased by the Takanari allele (Figure 7). SL1218 and SL1219 exhibited lower concentrations (weight/weight) of total γ-oryzanol and 24-methylenecycloartanyl ferulate than Koshihikari in a previous study. However, SL1218 exhibited concentrations of compounds 1 and 3 that were 31% and 35% lower, respectively, than those of Koshihikari, whereas SL1219 had similar concentrations of compounds 1 and 3 compared to Koshihikari in the present study (Figures 3 and 5). This result suggests that QTLs for the
concentrations of compounds 1 and 3 and γ-oryzanol exist separately on chromosome 5 and that the QTL for the concentrations of compounds 1 and 3 may undergo epistatic interactions with other loci. Koshihikari is the most representative leading cultivar in Japan with a planted area of approximately 490,000 ha (i.e., 35% of the food rice grown in Japan) in 2018. QTLs for the concentrations of compound 1 were identified at RM3688−RM3515−1 on chromosome 2 and RM7332−3−RM5442 and RM6970−RM7389 on chromosome 3 only in the Koshihikari genetic background (Figure 7). Interestingly, unlike the QTLs identified at RM6842−RM5897 on chromosome 2, RM3513 on chromosome 3, and RM1248−RM17836 on chromosome 5, the concentrations were greatly enhanced by the Takanari allele. SL1208, SL1210, and SL1213, which carry the Takanari alleles in the Koshihikari genetic background, exhibited concentrations of compound 1 that were 33−36% higher than those of Koshihikari (Figure 3). Thus, the favorable alleles of Takanari can be used to increase further the elevated concentration of compound 1 in Koshihikari.

We previously found that the concentrations of compounds 2 and 3 were lower in plants that ripened at low air temperatures than in those that ripened at high air temperatures. In all tested reciprocal CSSLs and their parent cultivars, heading dates were much later in SL1335 and SL1336 than in other lines and cultivars, showing that SL1335 and SL1336 ripened under low air temperature conditions (Figure 8f,g). SL1335 and SL1336 had very low concentrations of compounds 2 and 3 compared to other reciprocal CSSLs and their parent cultivars (Figures 4b, 5b, and 8f,g). Therefore, the lower concentrations of compounds 2 and 3 observed in SL1335 and SL1336 and the QTLs located on chromosome 11 may be attributed to the lower air temperatures experienced during ripening. However, the concentrations of compounds 1−4 in the other lines did not vary significantly according to temperature (Figure 8a−e,h).

In conclusion, the comparison of the concentrations of compounds 1−4 between Koshihikari and Takanari revealed that these levels were much higher in Koshihikari than in Takanari. We identified QTLs for the concentrations of compound 1 on chromosome 2 and compound 2 on chromosome 4 in the reciprocal CSSLs derived from a cross between Koshihikari and Takanari. These concentrations were increased by the Koshihikari allele but decreased by the Takanari allele. We also found that QTLs for compound 1 were identified on chromosomes 2 and 3 only in the Koshihikari genetic background. Interestingly, the concentrations of this compound (1) were enhanced by the Takanari allele. The combinations of QTLs identified in the present study, together with those for the concentrations of γ-oryzanol and γ-tocotrienol, will allow the breeding of cultivars that are beneficial to human health.

4. EXPERIMENTAL METHODS

4.1. Plant Materials. This study was conducted in 2012 in the experimental paddy field of the Institute of Crop Science,
We used reciprocal CSSLs (40 and 39 lines in the Koshihikari and Takanari genetic backgrounds, respectively) and their parent cultivars (Koshihikari and Takanari). Two paddy fields were used and each CSSL grown in each paddy field was arranged in a randomized complete block design with three replicates.

Geminated seeds were sown in nursery boxes in late April. Plant seedlings were transplanted by hand into the paddy field in mid-May at a density of 22.2 hills/m² (one seedling per hill) with a spacing of 15 cm between hills and 30 cm between rows. Seven days before transplanting, the field was applied 6 g N m⁻² in the form of controlled-release fertilizer with the same proportion of LP40, LPS100, and LP140, and also applied 5.2 g P m⁻² and 7.5 g K m⁻² in the form of synthetic fertilizer. Eighty percent of the total N content in LP40 and LP140 is released at a uniform rate up to 40 and 140 days after application, respectively, and that in LPS100 is released at a sigmoid rate up to 100 days after application at 20–30 °C. After trimming, the area of each plot was 5.7 m².

At maturity (mid- to late September), plants from 1.8 m² (40 hills) were harvested and the air-dried plants were threshed. The rough rice grains were dehusked and used for the determination of compounds.

Climate conditions and the heading dates of reciprocal CSSLs, Koshihikari, and Takanari were as described by Takai et al. Chromosome numbers are shown above each physical map. The colored arrows show putative QTLs for the concentrations of 6-O-feruloylsucrose (1), 3′,6-di-O-sinapoylsucrose (2), and 3′-O-sinapoyl-6-O-feruloylsucrose (3), and the upward and downward arrowheads indicate where a concentration was increased by the Koshihikari or Takanari allele, respectively.

Figure 7. Substitution mapping of quantitative trait loci (QTLs) for the concentrations of 6-O-feruloylsucrose (1), 3′,6-di-O-sinapoylsucrose (2), and 3′-O-sinapoyl-6-O-feruloylsucrose (3) by comparing overlapping segments among chromosome segment substitution lines (CSSLs) in the Koshihikari (a) and Takanari (b) genetic backgrounds grown in 2012. Chromosome numbers are shown above each physical map. Marker names are indicated at the left of each chromosome. The colored arrows show putative QTLs for the concentrations of 6-O-feruloylsucrose (1), 3′,6-di-O-sinapoylsucrose (2), and 3′-O-sinapoyl-6-O-feruloylsucrose (3), and the upward and downward arrowheads indicate where a concentration was increased by the Koshihikari or Takanari allele, respectively.

To confirm the results obtained from the plants grown in 2012, grains of two lines SL1206 and SL1217, which carry the Takanari alleles on chromosomes 2 and 4, respectively, and of Koshihikari grown in 2011 were used.

4.2. Determination of Compounds. Powdered grains (50 grains) were extracted with aqueous acetone (acetone/H₂O, 1:1 (v/v), 20 mL) at 25 °C for 1 day in the dark. The aqueous acetone extracts were subjected to C₁₈ HPLC (TStack ODS-80Ts, Tosoh, 4.6 × 250 mm²; eluent, CH₃CN/H₂O/TFA, 5:95:0.05 to 35:65:0.05 (v/v) for 60 min by linear gradient; flow rate, 0.8 mL/min; UV detection at 280 nm. The HPLC-Chip system consisted of a pump (LC-20AT, Shimadzu) and a column (Silica 300, 5 μm, 4.6 × 200 mm, Thermo Scientific) and was connected to a UV detector (SPD-M10AVP, Shimadzu). The detection wavelength was 280 nm. The concentrations of 6-O-feruloylsucrose (1), 3′,6-di-O-sinapoylsucrose (2), and 3′-O-sinapoyl-6-O-feruloylsucrose (3) were determined by comparing the retention times and UV spectra of the samples with those of authentic standards.
320 nm) to determine 1 (tR 28.8 min), 2 (tR 44.1 min), 3 (tR 45.2 min), and 4 (tR 46.2 min). The identity of peaks 1–4 was confirmed with previously isolated 6-O-feruloylsucrose (1), 3′,6-di-O-sinapoylsucrose (2), 3′-O-sinapoyl-6-O-feruloylsucrose (3), and 3′,6-di-O-feruloylsucrose (4). The amounts of 1–4 were calculated using standard curves according to peak areas.

### 4.3. Statistical Analysis

Statistical analyses were performed using a general linear model in SPSS (version 17.0, SPSS Inc., Chicago, IL). Analysis of variance was used to examine the response of the concentrations of compounds 1–4 to CSSL. CSSL and replication were considered as a fixed effect and a random effect, respectively. Significant treatment effects (P < 0.10) were determined using Dunnett’s test. To delineate candidate QTL regions, substitution mapping was conducted by comparing overlapping segments among the CSSLs according to a previous study.

### ACKNOWLEDGMENTS

Financial support in part by JSPS KAKENHI Grant Numbers 17K07629 and 25712003 is greatly appreciated. The authors thank Chiemi Nagamatsu and Mika Kikutsugi from Kyushu Okinawa Agricultural Research Center, NARO, and Rie Sawabe from the Institute of Crop Science, NARO, for their technical assistance.

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