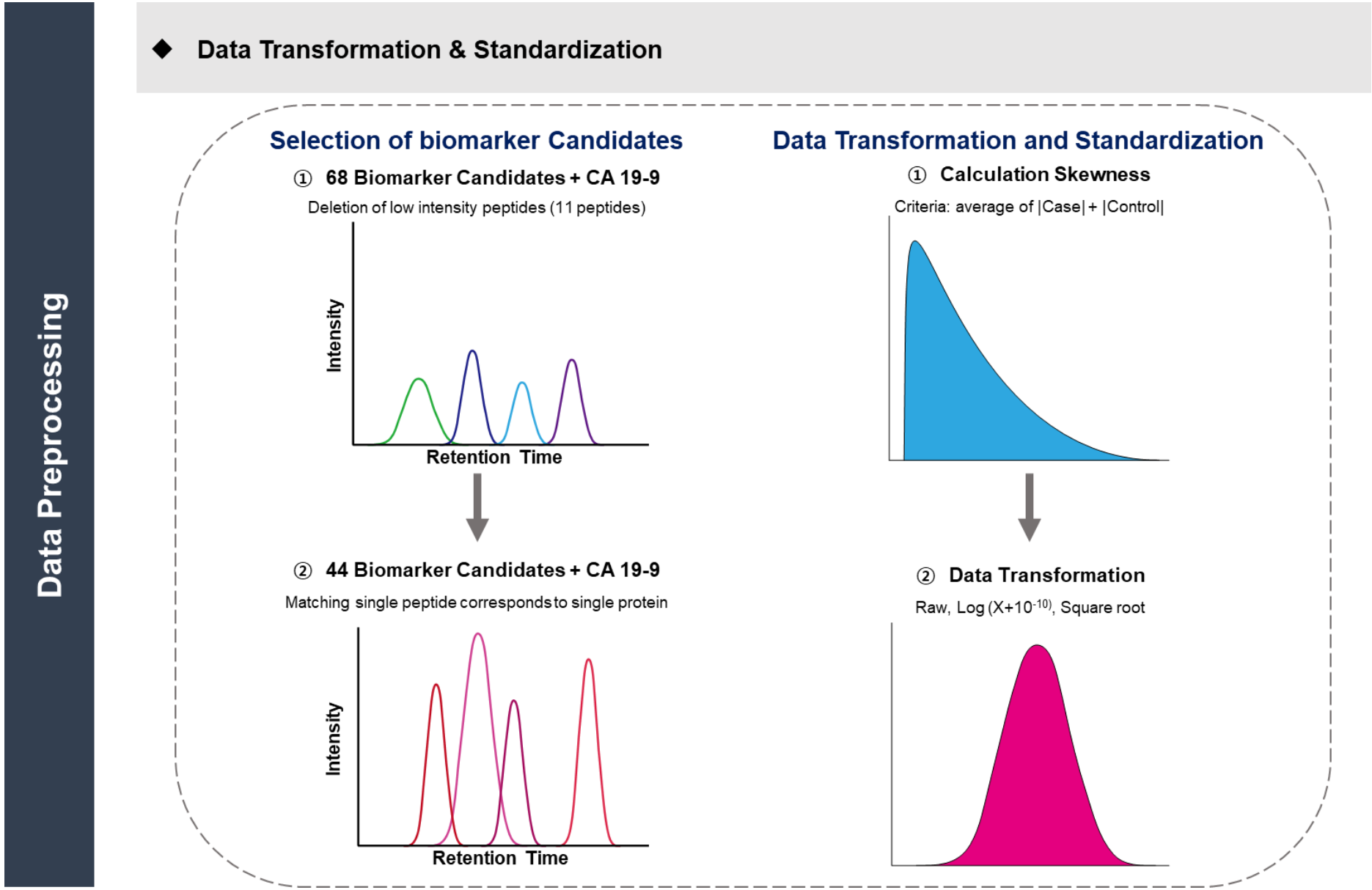
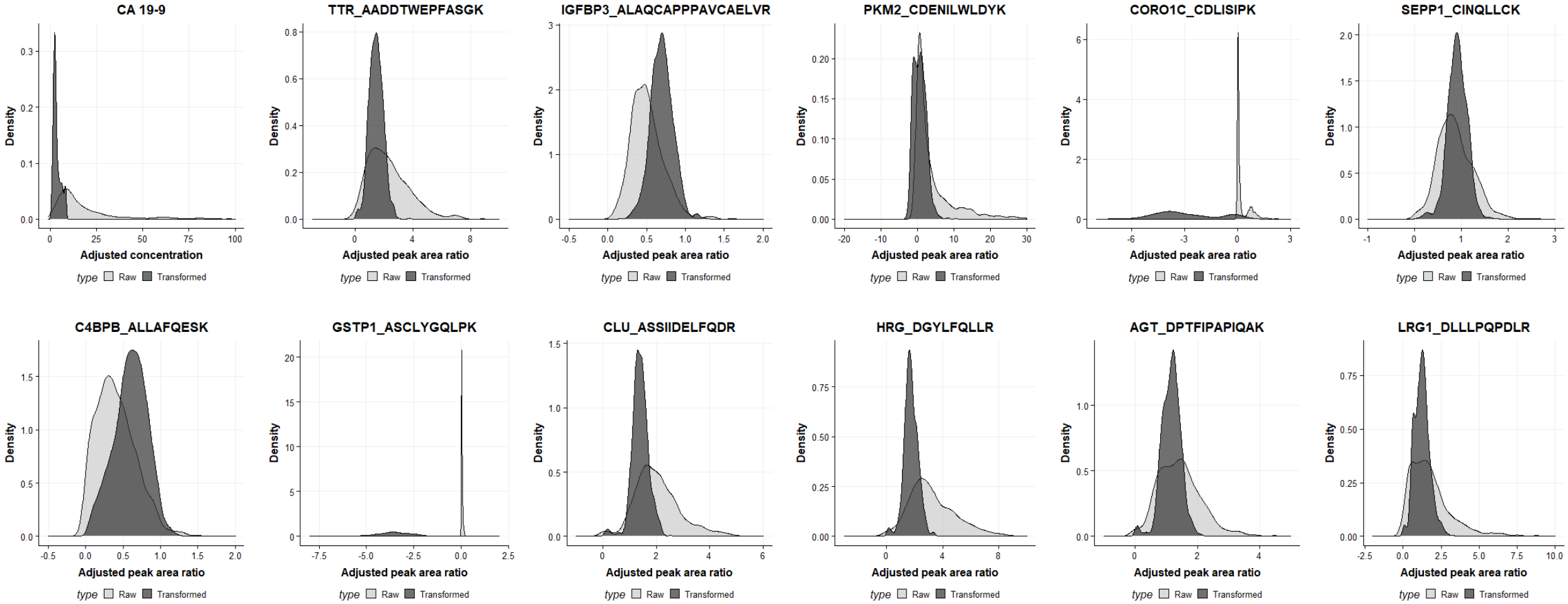


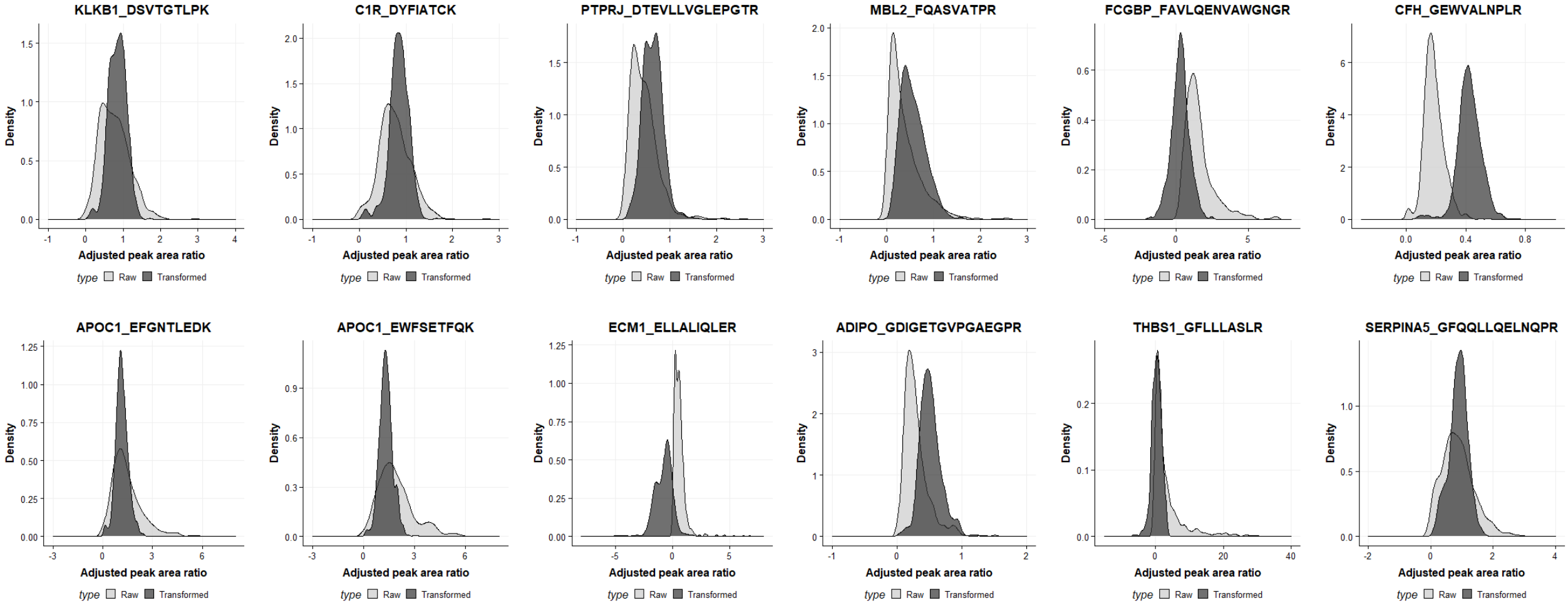
Supplementary Figure 1. Data preprocessing.
To obtain the robustness of the MRM-MS quantification, 11 targets with a detected intensity of less than 1000 were removed from among 68 biomarker candidates.
Next, skewness values were obtained after the data transformation into 3 types for 57 biomarker candidates and CA 19-9 ((1) raw, (2) log ($X+10^{-10}$), and (3) square root). The type of data transformation was selected, in which the average of the absolute values of the skewness was lowest between the case and control groups. After the data transformation, all biomarker candidates were standardized to have a mean of 0 and a standard deviation of 1. Prior to the development of the multi-marker panel, the proteins that were associated with multiple peptides were matched by selecting the best peptide, such that a single peptide corresponded to a single protein.

Supplementary Figure 2. Distribution of raw and transformed peak area ratios for 52 biomarker candidates and CA 19-9.
Three different types of data transformation were performed on 57 biomarker candidates and CA 19-9: (1) raw, (2) log ($x+10^{-10}$), and (3) square root. Skewness values were calculated for each case and control group. For 52 of the 57 biomarker candidates and CA19-9, the data transformation type with the smallest average of absolute values of skewness between the case and control groups was selected. The distributions before (grey) and after (black) the data transformation are shown by density plot.

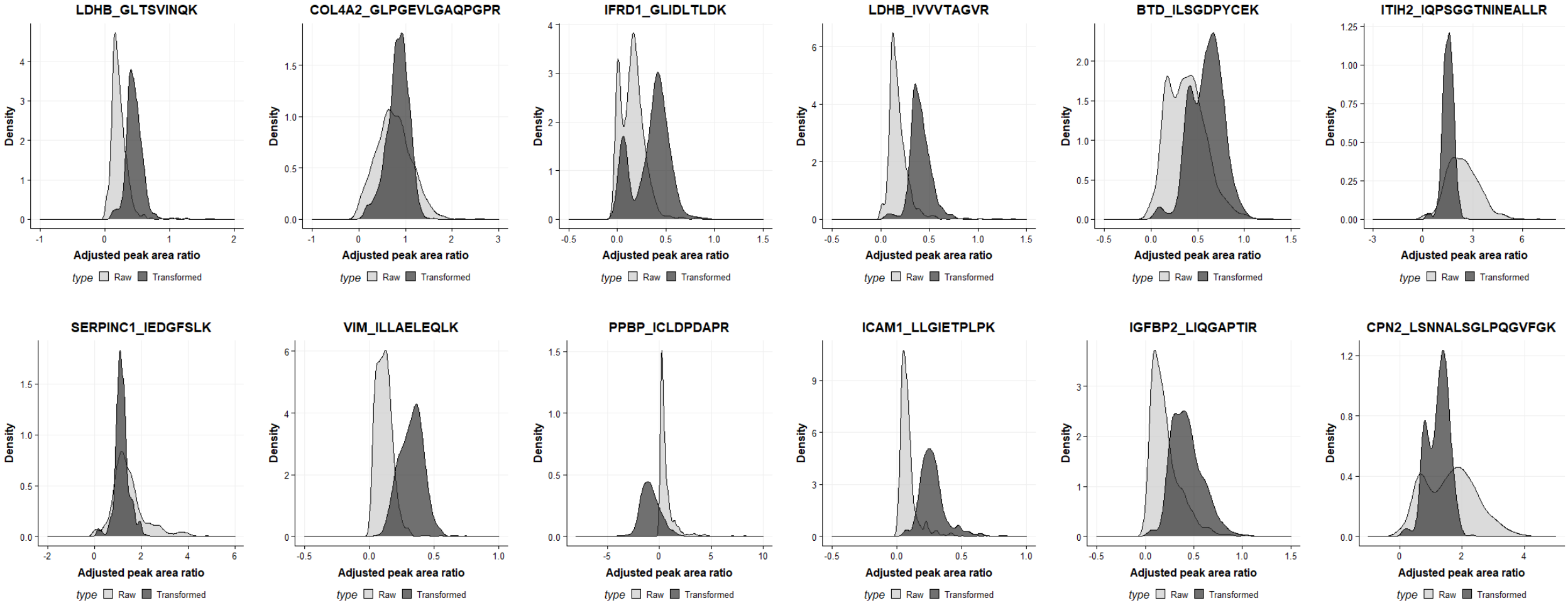
Supplementary Figure 2 (Continued)



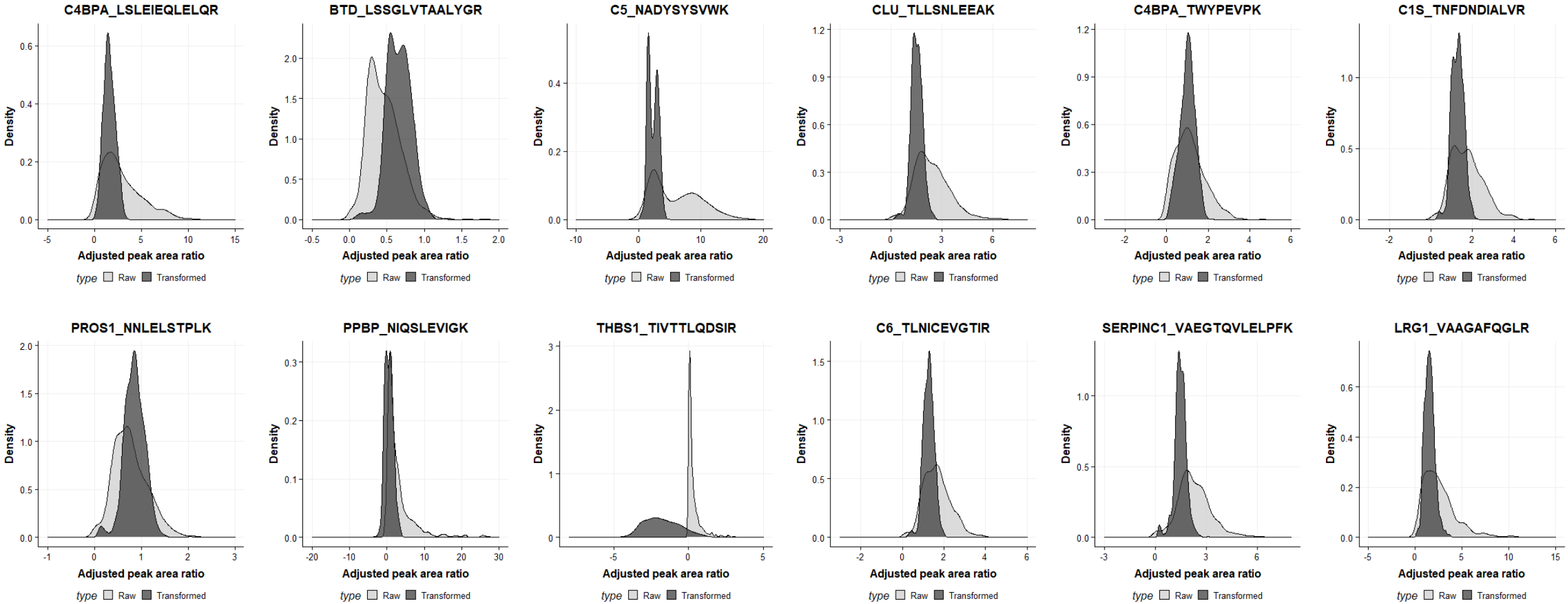
Supplementary Figure 2 (Continued)



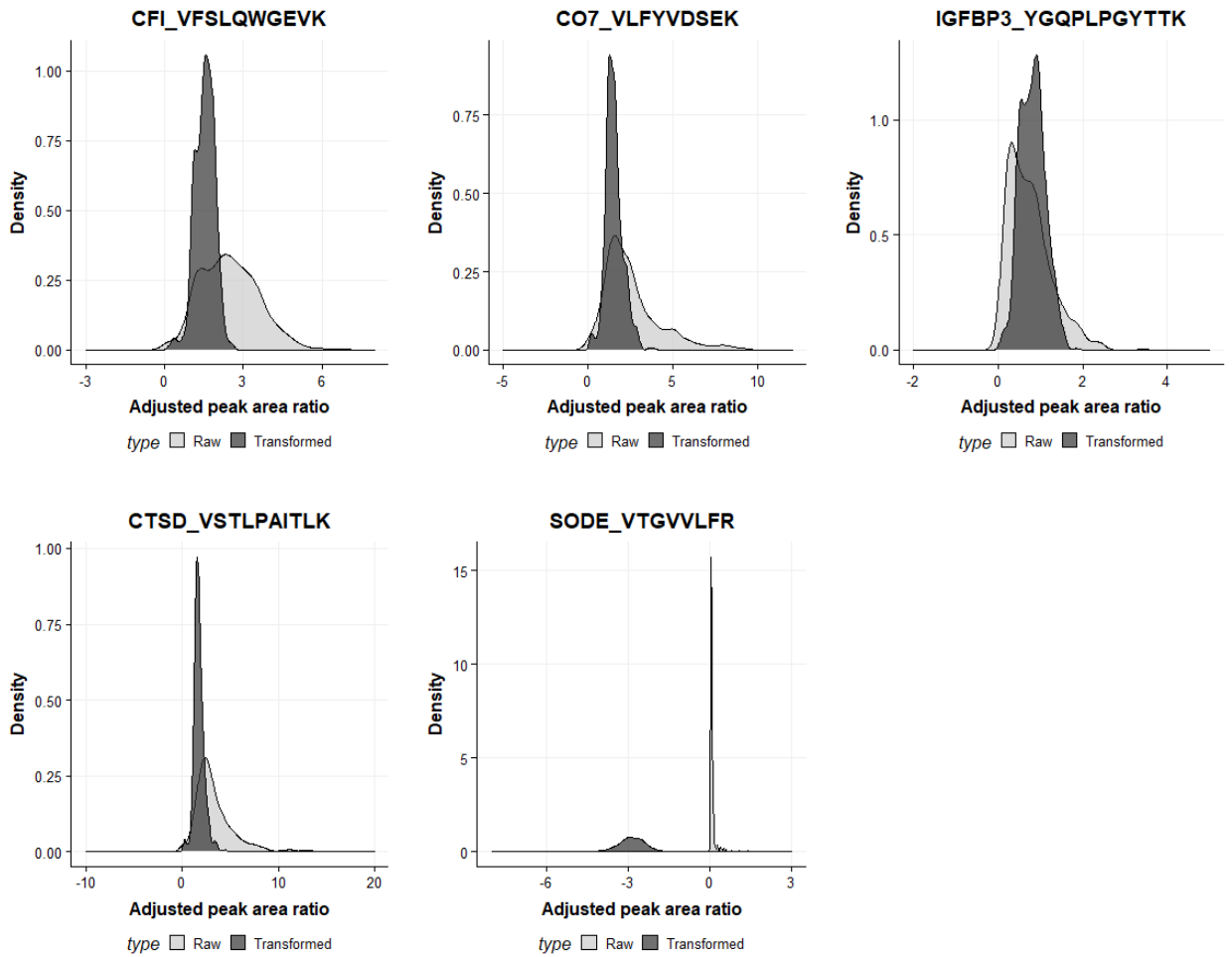
Supplementary Figure 2 (Continued)

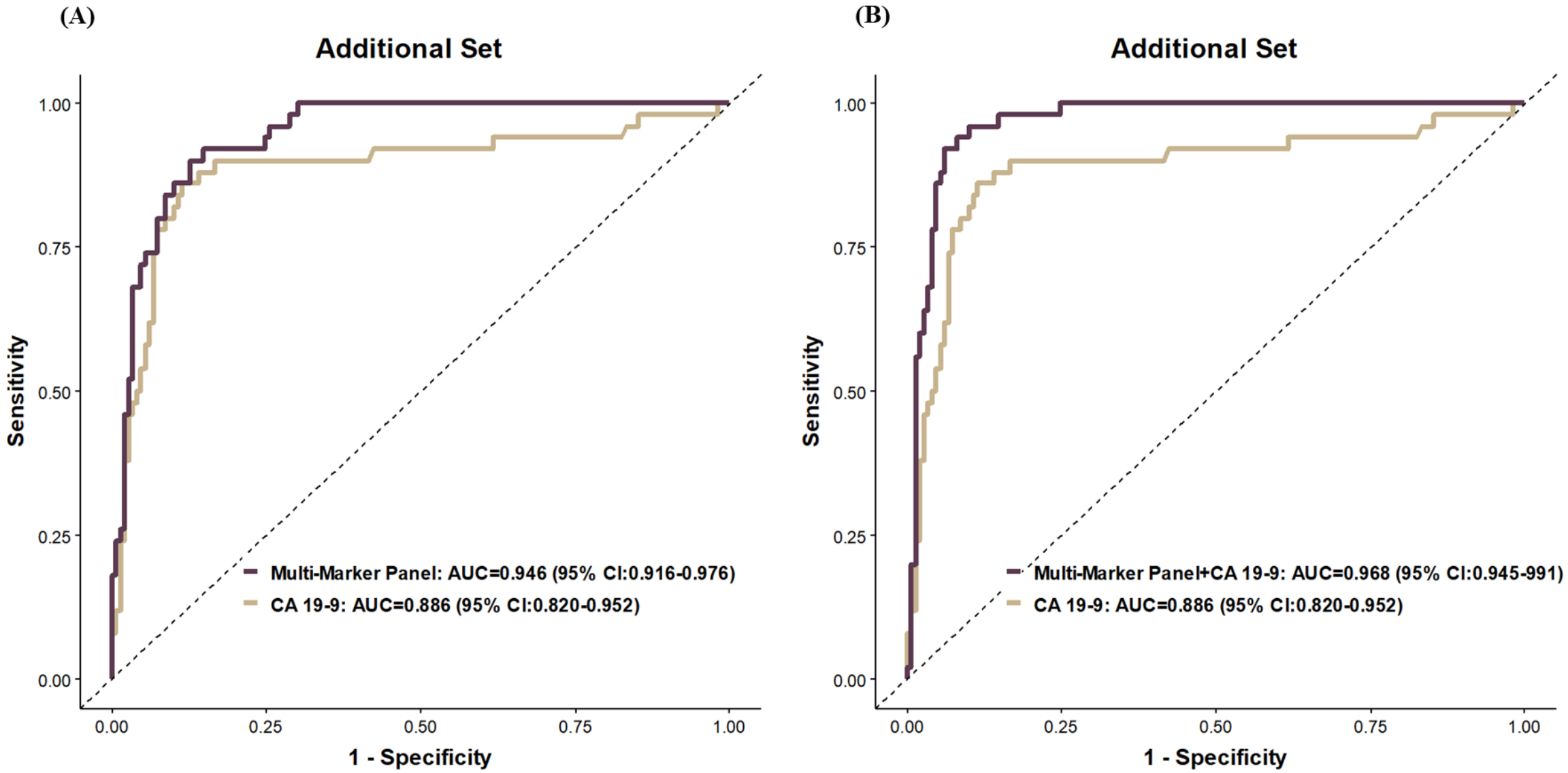


Supplementary Figure 2 (Continued)

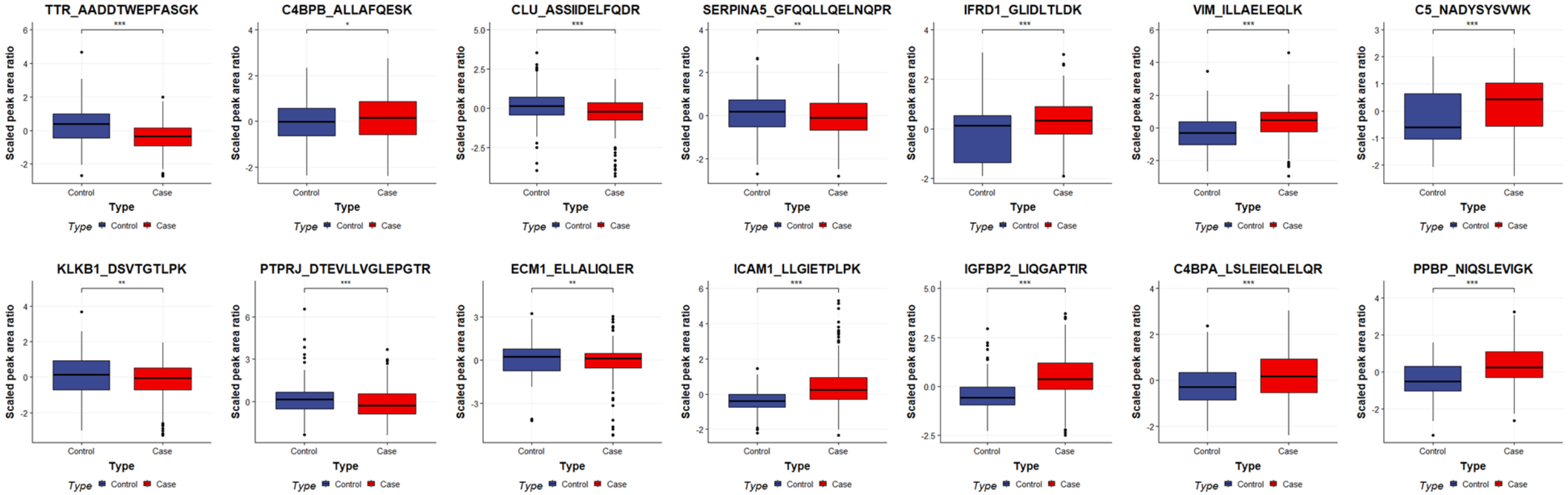


Supplementary Figure 2 (Continued)

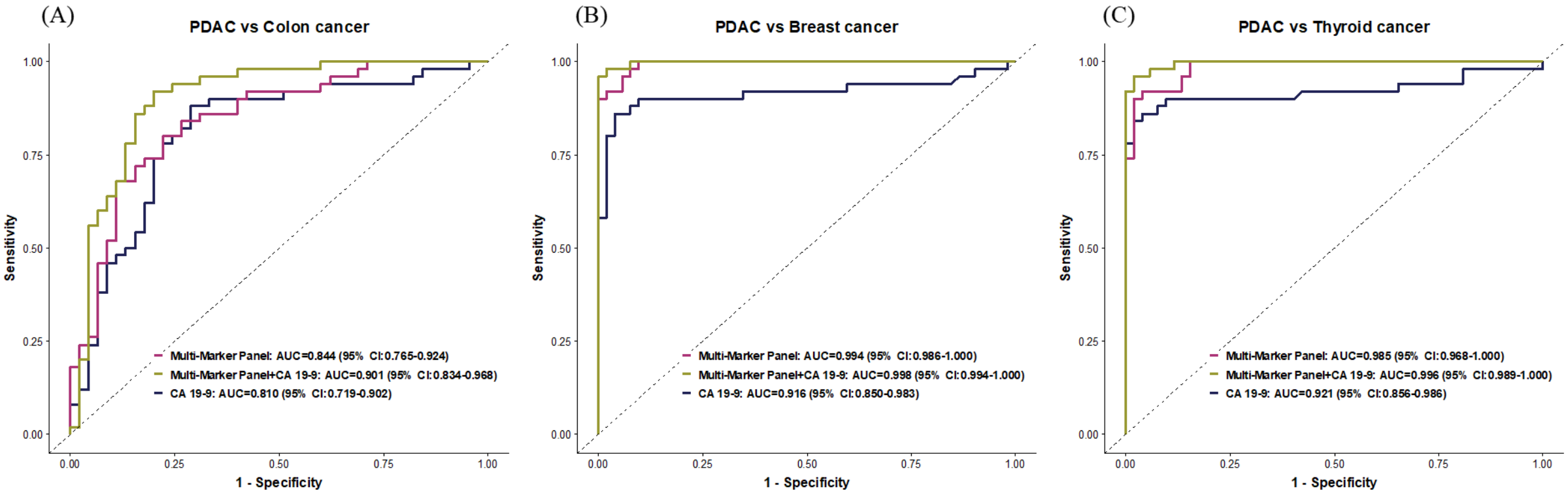




Supplementary Figure 3. Discriminatory ability of the multi-marker panel, combined panel, and CA 19-9 between pancreatic ductal adenocarcinoma (PDAC) and other cancers. Receiver operating characteristic (ROC) curves of the multi-marker panel, combined panel, and CA 19-9 in the additional set. The AUC value of the multi-marker panel is 0.946 (95% CI:0.916-0.976), and (B) the combined panel yielded an AUC value of 0.968 (95% CI:0.945-0.991) in the additional set. The combined panel showed a statistically significant increase in AUC compared with CA 19-9 (*P*-value: < 0.01; Delong's test). Abbreviations: AUC, area under the curve; CI, confidence interval.



Supplementary Figure 4. Expression levels of 14 biomarker candidate proteins in the case and control groups.
Quantitative MRM-MS results are shown for the 14 proteins (TTR, C4BPB, CLU, SERPINA5, IFRD1, VIM, C5, KLKB1, PTPRJ, ECM1, ICAM1, IGFBP2, C4BPA, PPBP) that constitute the multi-marker panel. Between case and control groups, all of the proteins showed significant differences in expression level. Statistical significance was determined by Wilcoxon rank-sum test (*: $P < 0.05$, ** $P < 0.01$, ***: $P < 0.001$).



Supplementary Figure 5. Discriminatory ability of the multi-marker panel, combined panel, and CA 19-9 between pancreatic ductal adenocarcinoma (PDAC) and each cancer group. Receiver operating characteristic (ROC) curves of the multi-marker panel, combined panel, and CA 19-9 in each cancer group. (A) The AUC value of the multi-marker panel was 0.844 (95% CI:0.765-0.924), and the AUC value of the combined panel was 0.901 (95% CI:0.834-0.968) between PDAC and colon cancer. (B) In the comparison between PDAC and breast cancer, the multi-marker panel had an AUC value of 0.994 (95% CI:0.986-1.000), and the combined panel had an AUC value of 0.998 (95% CI:0.994-1.000). (C) When discriminating between PDAC and thyroid cancer, the multi-marker panel had an AUC value of 0.985 (95% CI:0.968-1.000), and the combined panel had an AUC value of 0.996 (95% CI:0.989-1.000). The multi-marker panel showed a statistically significant increase in AUC compared with CA 19-9 between PDAC and breast cancer ($P < 0.05$; Delong's test), and the combined panel showed a statistically significant increase in AUC compared with CA 19-9 in all three groups ($P < 0.01$ in (A) and $P < 0.05$ in (B, C) Delong's test). Abbreviations: AUC, area under the curve; CI, confidence interval.