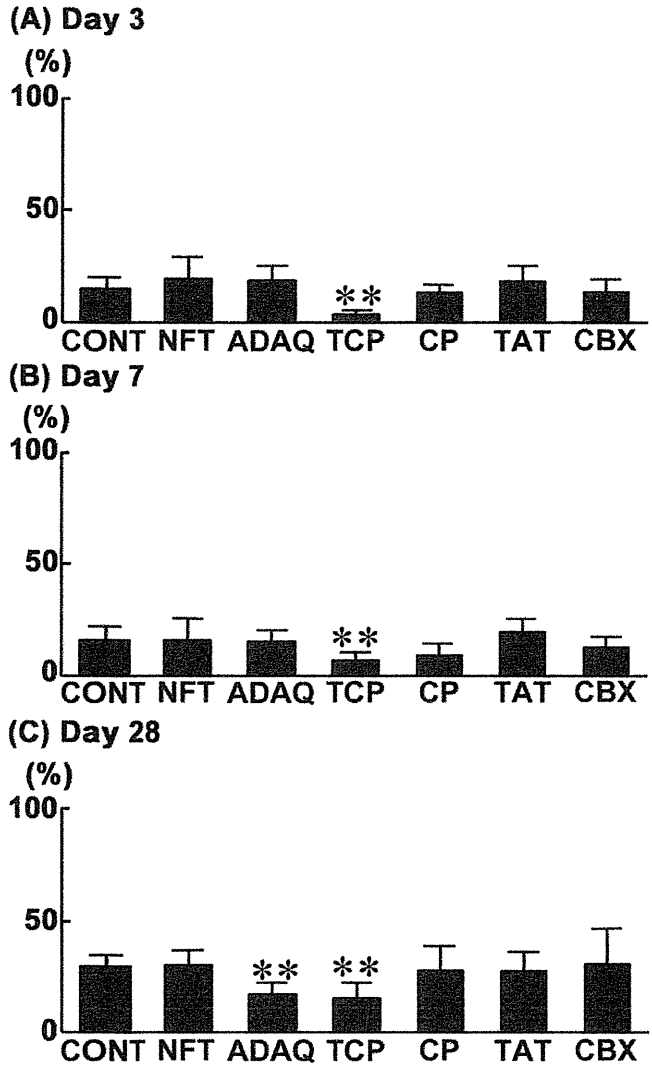

Fig. 15. p-Histone $H3^+$/Ki-67^+ cell ratio in the OSOM of rats at day 3, 7, and 28 after treatment with renal carcinogens or non-carcinogenic renal toxicants. The graphs show the p-Histone $H3^+$ cell ratio of renal tubular epithelial cells per number of Ki-67^+ cells counted in 10 animals of each group. Values represent mean + SD. (A) Day 3, (B) Day 7 and (C) Day 28. ** $P < 0.01$ vs. untreated controls (Steel's test).

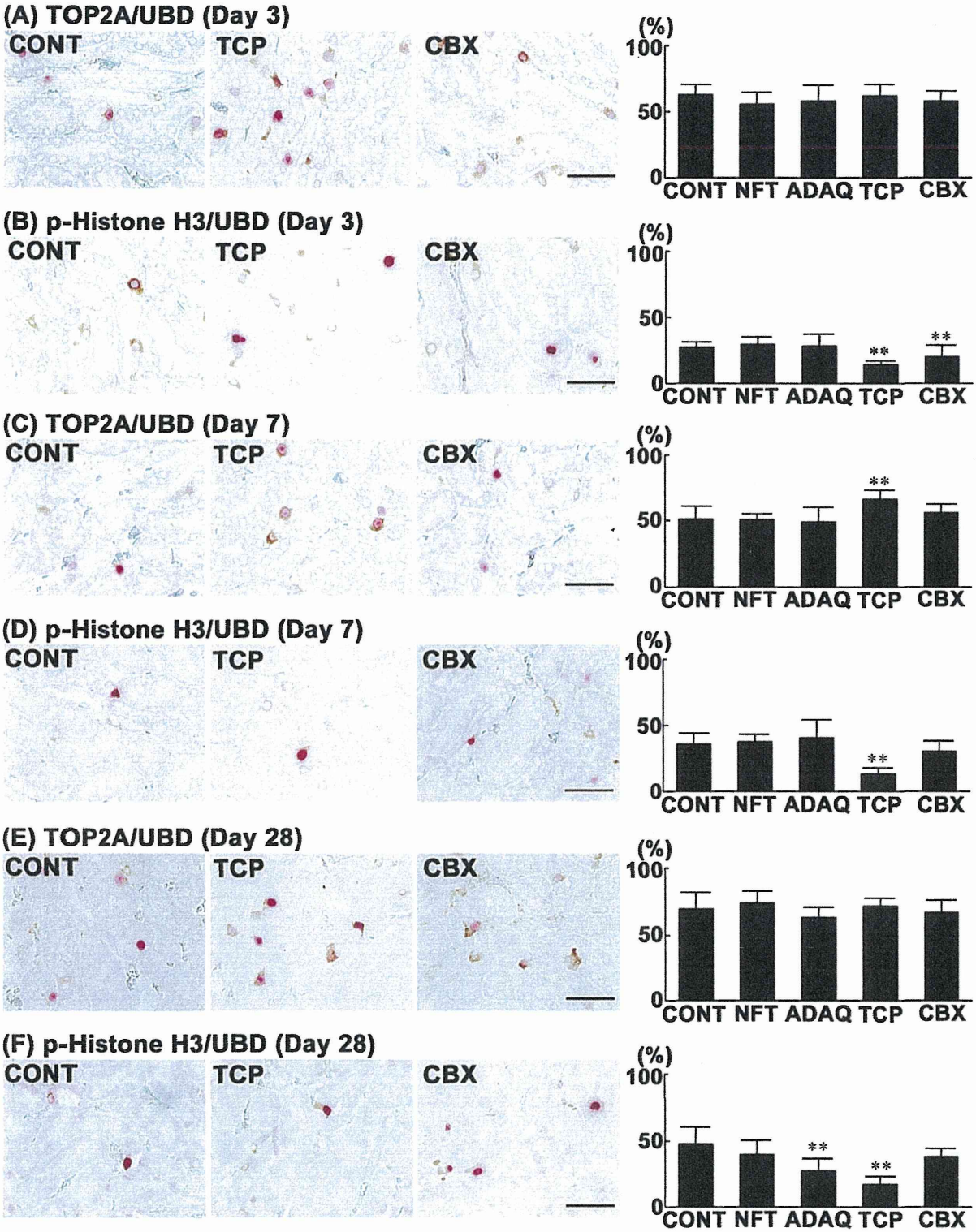

Fig. 16. Distribution of cell populations co-expressing UBD and TOP2A (TOP2A/UBD) or UBD and p-Histone H3 (p-Histone H3/UBD) in the OSOM of rats at days 3, 7, and 28. Photomicrographs show the distribution of TOP2A/UBD and p-Histone H3/UBD in the OSOM of representative cases from untreated controls and animals treated with TCP or CBX. The immunoreactivity of UBD (cytoplasm), and TOP2A (nucleus) or p-Histone H3 (nucleus) is visualized as brown and red, respectively. The graphs show the TOP2A or p-Histone H3-positive cell ratio (%) per total renal tubular epithelial cells immunoreactive to UBD counted in 10 animals of each group. Values represent mean + SD. (A) TOP2A/UBD (day 3), (B) p-Histone H3/UBD (day 3), (C) TOP2A/UBD (day 7), (D) p-Histone H3/UBD (day 7), (E) TOP2A/UBD (day 28), and (F) p-Histone H3/UBD (day 28). Bar = 50 μm. ** $P < 0.01$ vs. untreated controls (Dunnett's or Steel's test).

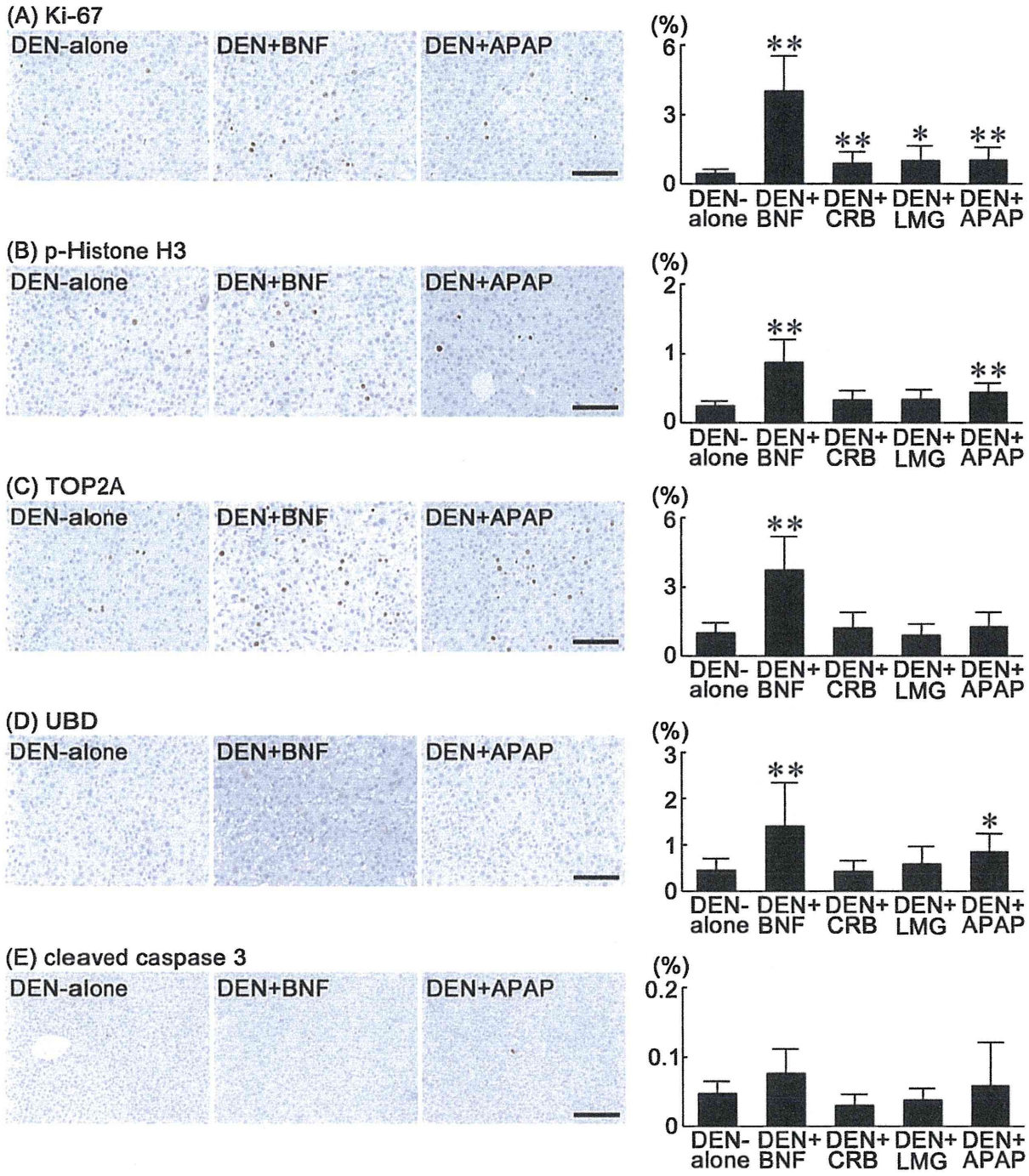

Fig. 17. Distribution of Ki-67$^+$, p-Histone H3$^+$, TOP2A$^+$, UBD$^+$ and cleaved caspase 3$^+$ hepatocytes in the liver of rats after 2 weeks of post-initiation treatment with hepatocarcinogens, hepatocarcinogenic tumor promoters or non-carcinogenic hepatotoxicants. Photomicrographs show the distribution of immunoreactive cells in the liver of representative cases from the DEN-alone, DEN+BNF or DEN+APAP. The graphs show mean positive cell ratios per total hepatocytes counted in each animal of DEN-alone (N=10), DEN+BNF (N=10), DEN+CRB (N=10), DEN+LMG (N=10) and DEN+APAP (N=9). Values represent mean + SD. (A) Ki-67, (B) p-Histone H3, (C) TOP2A, (D) UBD, (E) cleaved caspase 3. Bar = 100 μm (A–D) or 200 μm (E). * $P < 0.05$, ** $P < 0.01$ vs. the DEN-alone group (Steel's test).

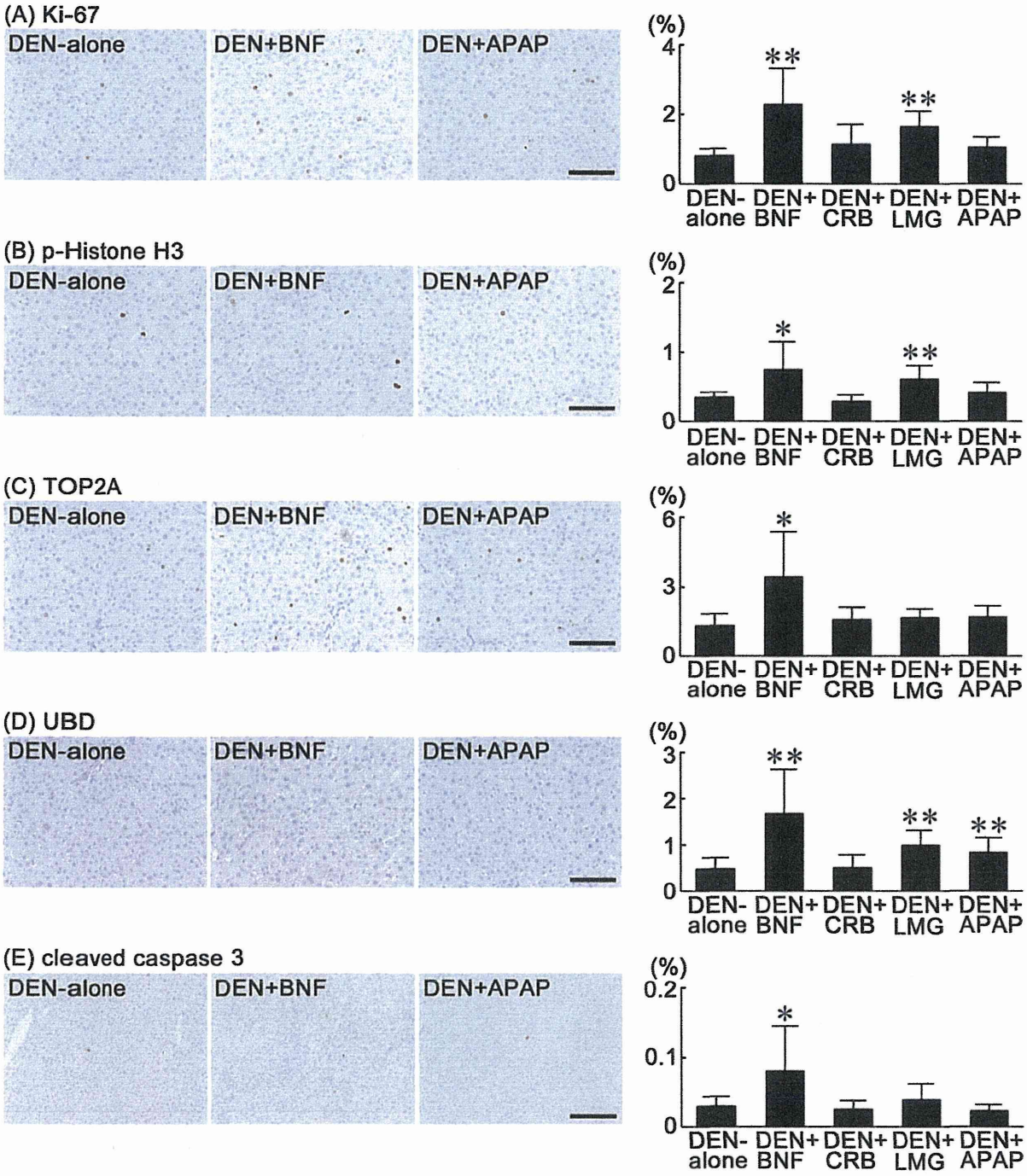

Fig. 18. Distribution of Ki-67$^+$, p-Histone H3$^+$, TOP2A$^+$, UBD$^+$ and cleaved caspase 3$^+$ hepatocytes in the liver of rats after 4 weeks of post-initiation treatment with hepatocarcinogens, hepatocarcinogenic tumor promoters or non-carcinogenic hepatotoxicants. Photomicrographs show the distribution of immunoreactive cells in the liver of representative cases from the DEN-alone, DEN+BNF or DEN+APAP. The graphs show mean positive cell ratios per total hepatocytes counted in 10 animals of each group. Values represent mean + SD. (A) Ki-67, (B) p-Histone H3, (C) TOP2A, (D) UBD, (E) cleaved caspase 3. Bar = 100 μm (A–D) or 200 μm (E). * $P < 0.05$, ** $P < 0.01$ vs. the DEN-alone group (Steel's test).

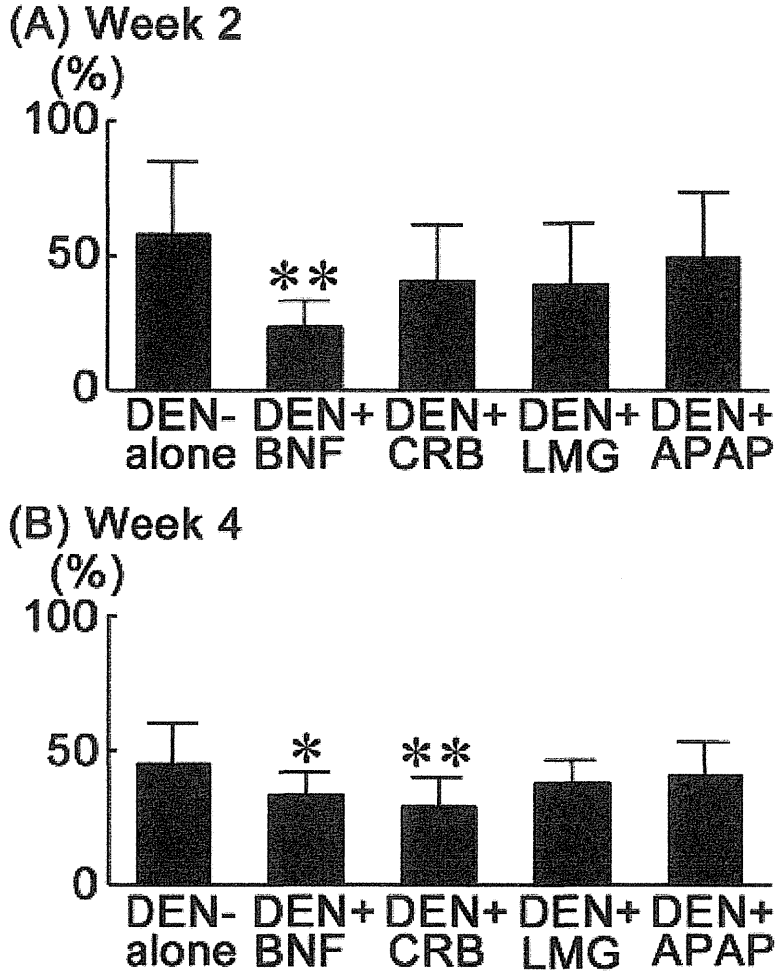

Fig. 19. Ratio of p-Histone $H3^+$ cell per total Ki-67^+ hepatocytes in the liver of rats after 2 or 4 weeks of post-initiation treatment with hepatocarcinogens, hepatocarcinogenic tumor promoters or non-carcinogenic hepatotoxicants. Number of animals examined was 10 for DEN-alone, DEN+BNF, DEN+CRB, DEN+LMG and 9 for DEN+APAP at week 2 and 10 for all groups at week 4. Values represent mean + SD. (A) p-Histone $H3^+$/Ki-67^+ cell ratio at week 2, (B) p-Histone $H3^+$/Ki-67^+ cell ratio at week 4. ** $P < 0.01$ vs. the DEN-alone group (Dunnett's test).

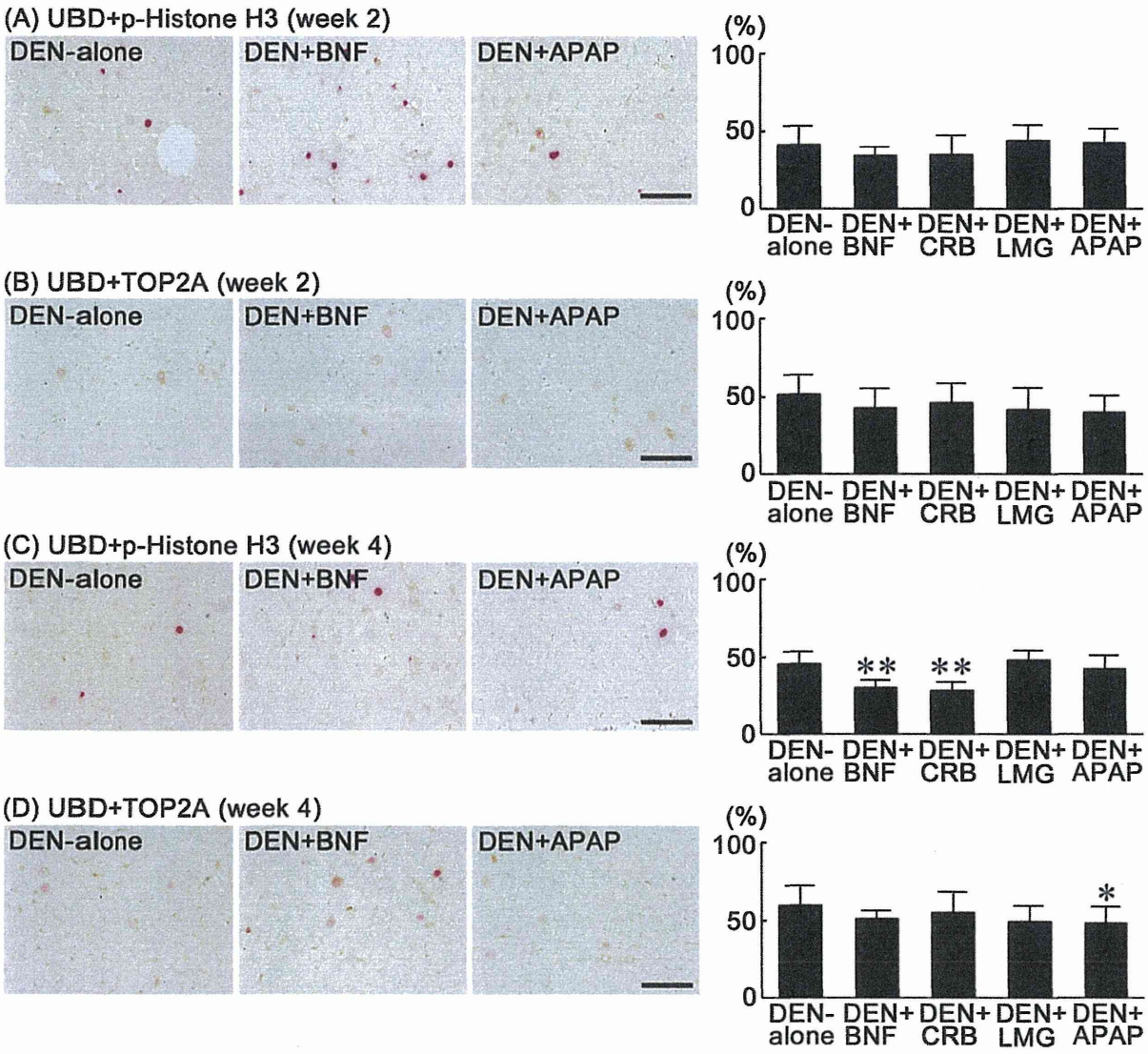

Fig. 20. Incidence of hepatocytes expressing p-Histone H3 or TOP2A in UBD$^+$ populations in the liver of rats after 2 or 4 weeks of post-initiation treatment with hepatocarcinogens, hepatocarcinogenic tumor promoters or non-carcinogenic hepatotoxicants. Photomicrographs show the distribution of immunoreactive cells in the liver of representative cases from the DEN-alone, DEN+BNF or DEN+APAP. The immunoreactivity of UBD (cytoplasm) is visualized as brown, and that of p-Histone H3 (nucleus) or TOP2A (nucleus) as red. The graphs show the incidence ratio of p-Histone H3- or TOP2A-positive cells (%) per total hepatocytes immunoreactive to UBD. Number of animals examined was 10 for DEN-alone, DEN+BNF, DEN+CRB, DEN+LMG and 9 for DEN+APAP at week 2 and 10 for all groups at week 4. Values represent mean + SD. (A) p-Histone H3$^+$/UBD$^+$ cell ratio at week 2, (B) TOP2A$^+$/UBD$^+$ cell ratio at week 2, (C) p-Histone H3$^+$/UBD$^+$ cell ratio at week 4, (D) TOP2A$^+$/UBD$^+$ cell ratio at week 4. Bar = 100 μm. * $P < 0.05$, ** $P < 0.01$ vs. the DEN-alone group (Dunnett's test).

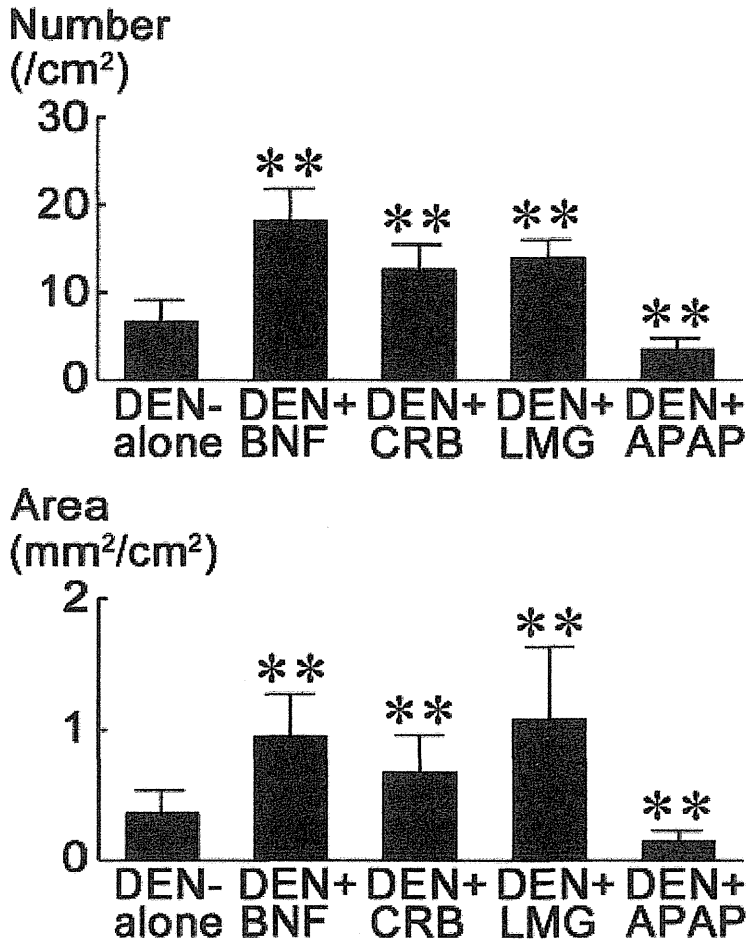

Fig. 21. Number and area of GST-P$^+$ liver cell foci in the liver of rats after 6 weeks of post-initiation treatment with hepatocarcinogens, hepatocarcinogenic tumor promoters or non-carcinogenic hepatotoxicants. Number of animals examined was 14 for DEN-alone, 15 for DEN+BNF, 16 for DEN+CRB, 16 for DEN+LMG and 15 for DEN+APAP. ** P <0.01 vs. the DEN-alone group (Steel's test).

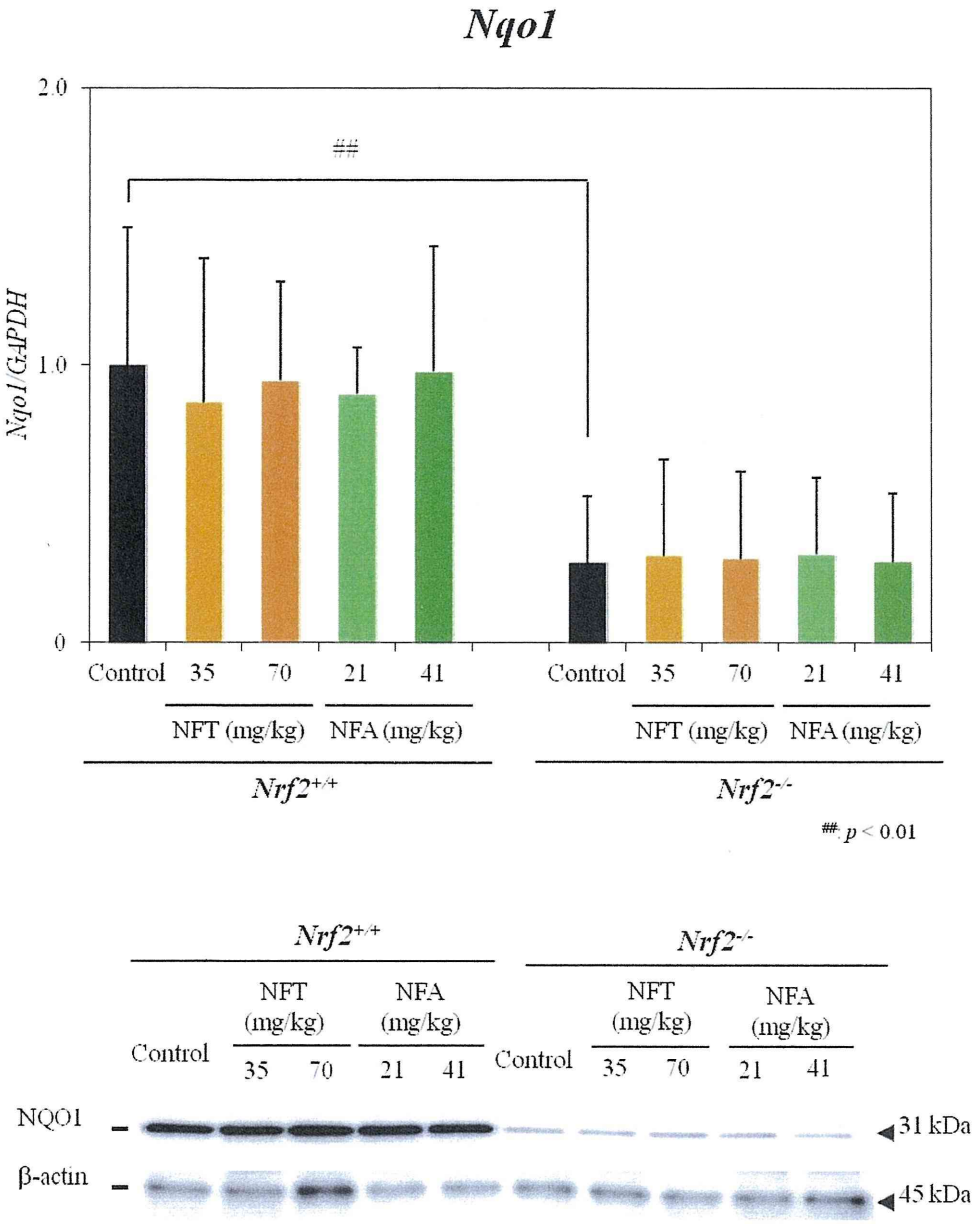

Fig. 22. (A) Change in the mRNA levels of *Nqo1* gene in the kidneys of *Nrf2* $^{+/+}$ *or Nrf2* $^{-/-}$ *gpt* delta mice treated with NFT or NFA for 13 weeks. Data were normalized to GAPDH mRNA levels. (B) Western blotting analysis of NQO1 in the kidneys of *Nrf2* $^{+/+}$ *or Nrf2* $^{-/-}$ *gpt* delta mice treated with NFT or NFA for 13 weeks.

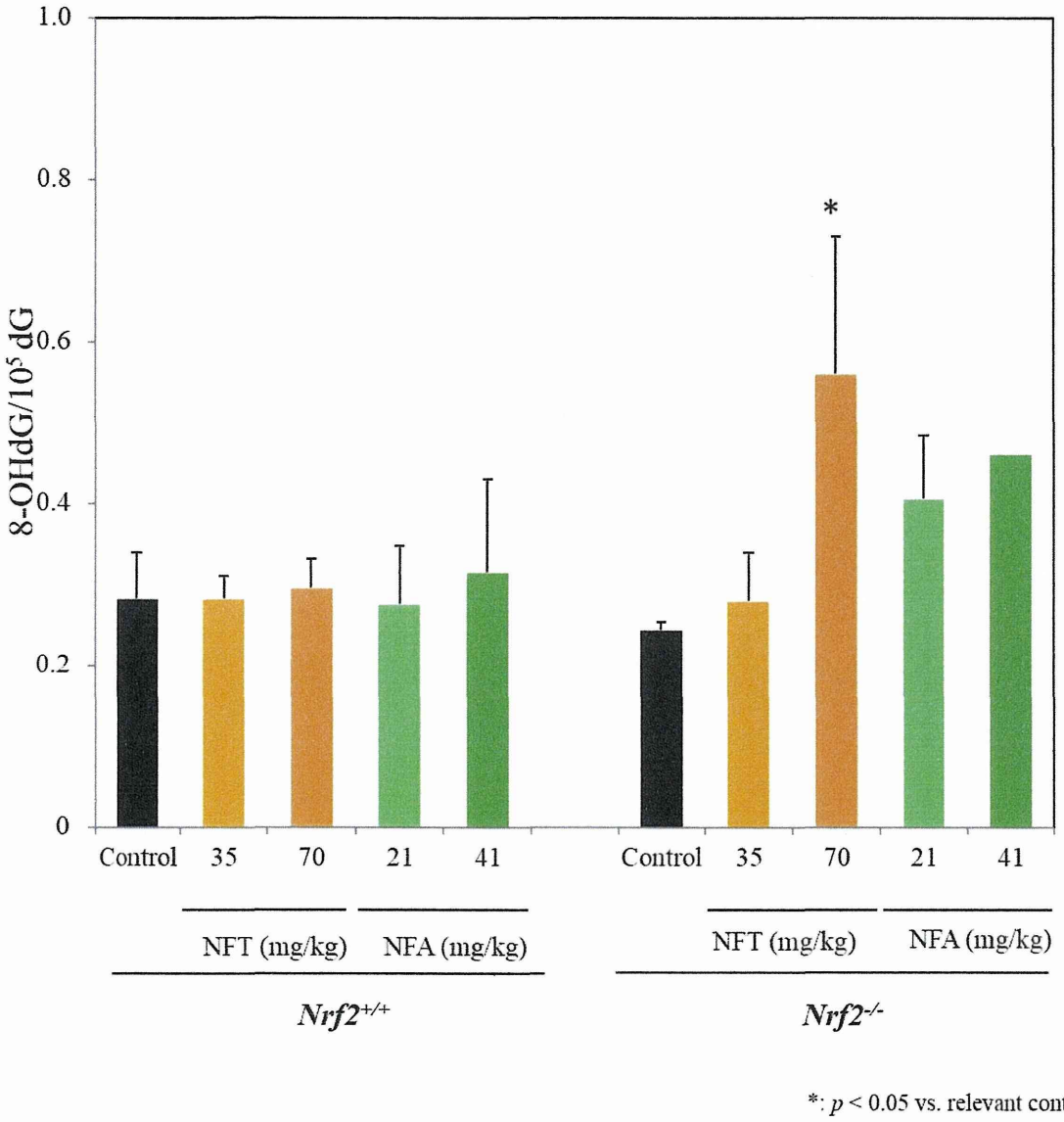

Fig. 23. 8-OHdG levels in the kidneys of *Nrf2* $^{+/+}$ *or Nrf2* $^{-/-}$ *gpt* delta mice treated with NFT or NFA for 13 weeks.

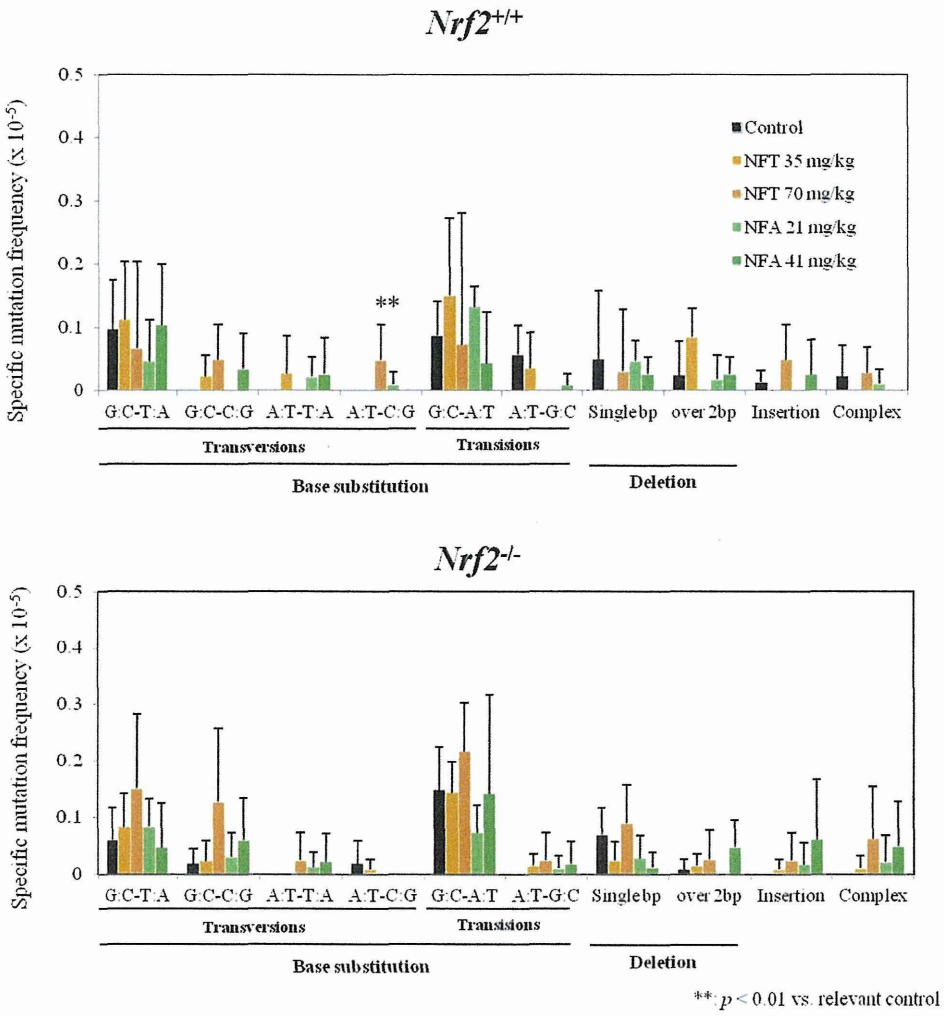

Fig. 24. Mutation spectra of *Nrf2* $^{+/+}$ *or Nrf2* $^{-/-}$ *gpt* delta mice treated with NFT or NFA for 13 weeks.