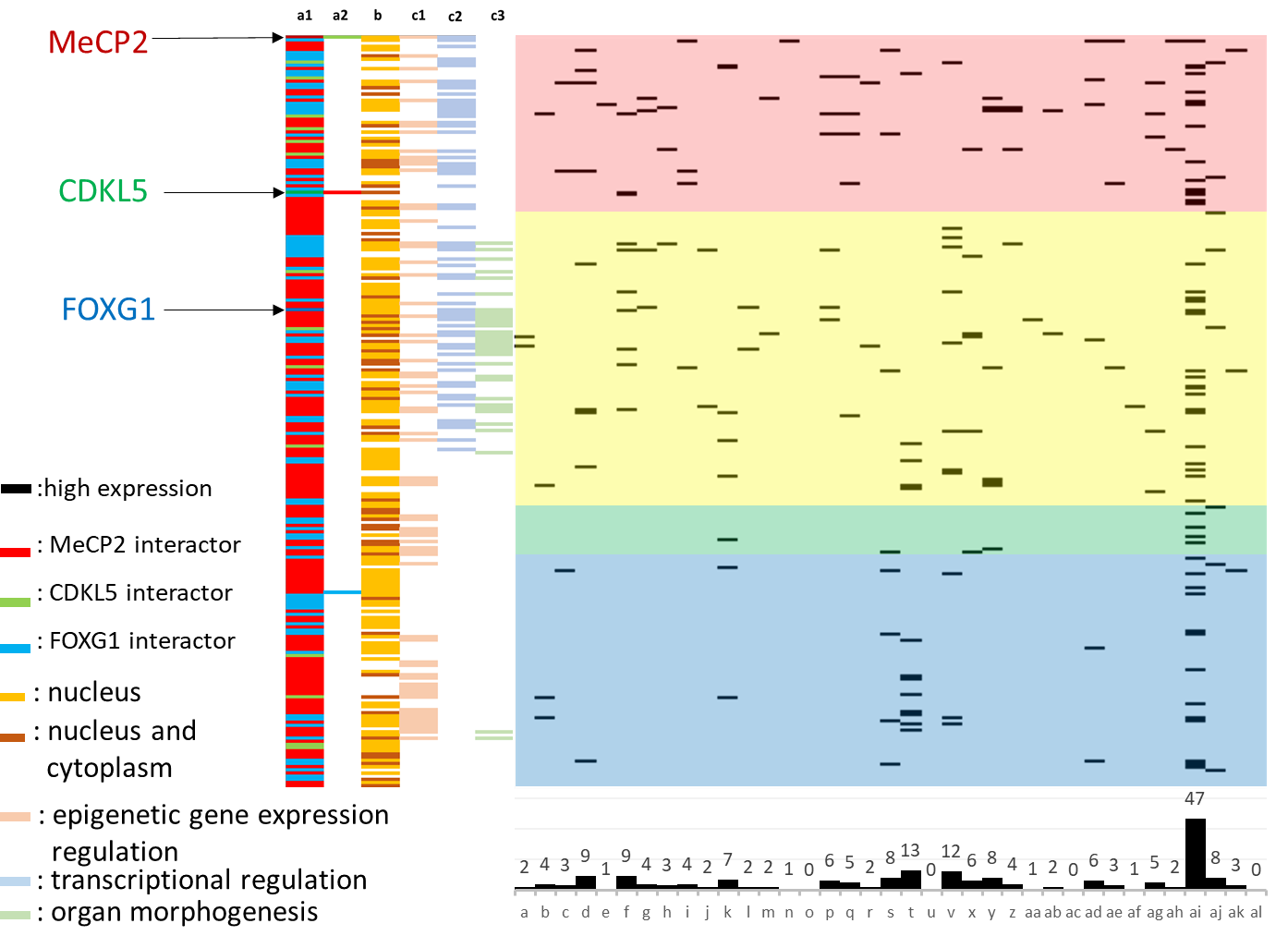
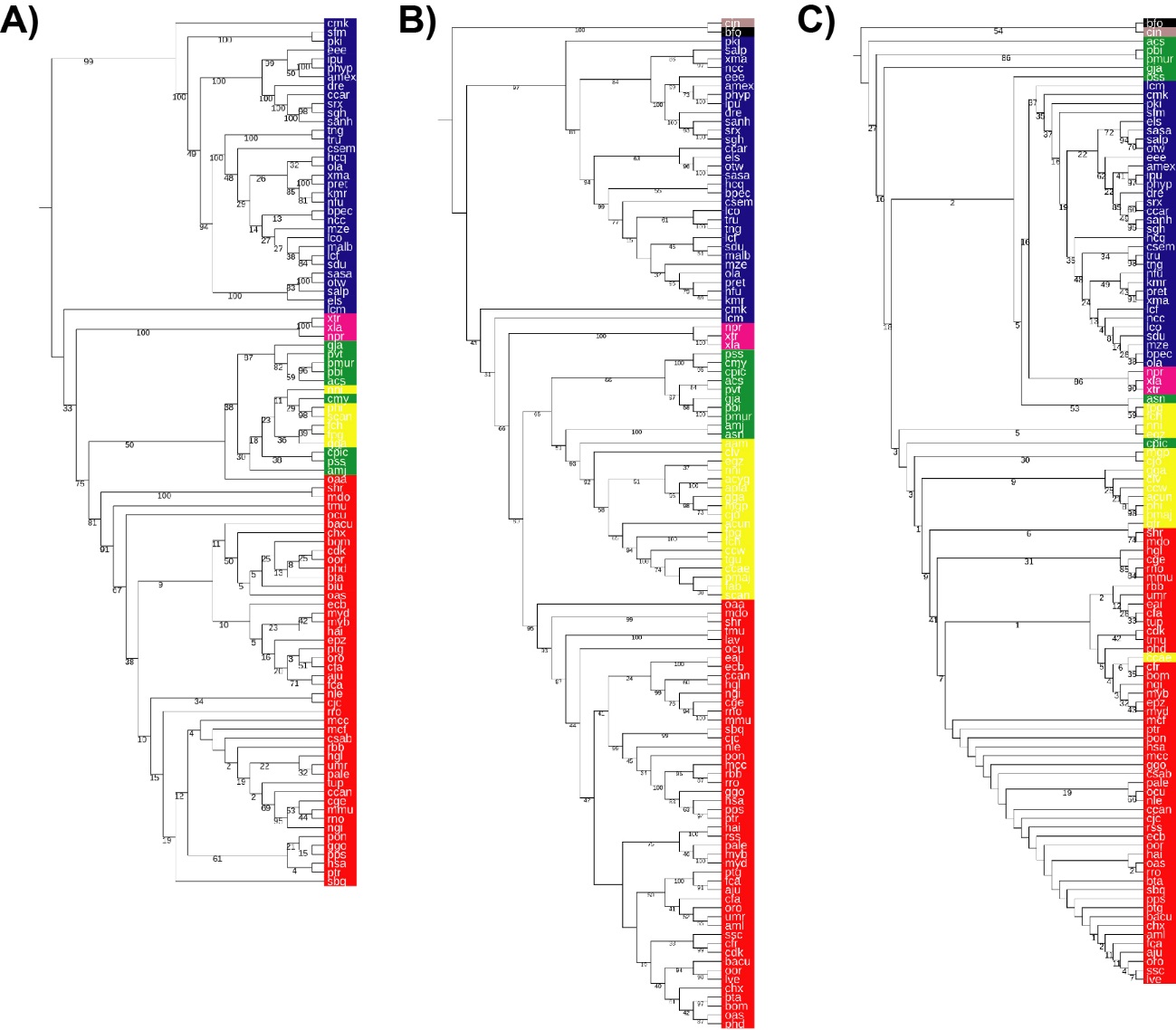


**Figure S1.** Boxplots of evolutionary rates for predicted structural order–disorder residues of human RTT-causing proteins. (a–c) Boxes representing predicted ordered (blue) and disordered (red) structure residues in MECP2 (A), CDKL5 (B), and FOXG1 (C). The x and y axes represent predicted conformation and Z score of evolutionary rates, respectively.



**Figure S2.** Tissue and organ expression analysis of human RTT-related proteins. The vertical axis shows 237 RTT-related proteins, and each bar shows MeCP2-interacter (red), CDKL5-interacter (green), and FOXG1-interactor (blue) (a1 and a2); cellular localization (b); epigenetic regulation of gene expression (c1); transcriptional regulation (c2); and organogenesis (c3). The horizontal axis shows 37 tissue types classified according to the Human Protein Atlas [37]. The tissue expressing each protein satisfying the range determined with Equation 3 is shown in black. The lower part of the figure shows the number of specifically expressed proteins. a, adipose tissue; b, adrenal gland; c, appendix; d, bone marrow; e, breast; f, cerebral cortex; g, cervix; uterine; h, colon; i, duodenum; j, endometrium; k, epididymis; l, esophagus; m, fallopian tube; n, gallbladder; o, heart muscle; p, kidney; q, liver; r, lung; s, lymph node; t, ovary; u, pancreas; v, parathyroid gland; x, placenta; y, prostate; z, rectum; aa, salivary gland; ab, seminal vesicle; ac, skeletal muscle; ad, skin; ae, small intestine; af, smooth muscle; ag, spleen; ah, stomach; ai, testis; aj, thyroid gland; ak, tonsil; al, urinary bladder.



**Figure S3.** Phylogenetic trees of MECP2, CDKL5, and FOXG1 with maximum likelihood bootstrap. Color bars in the tips of trees indicate the taxa of species following to figure 1.