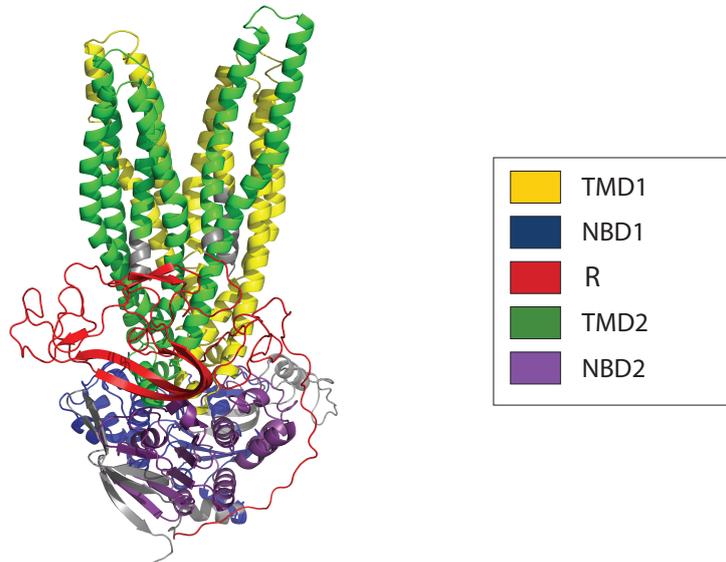
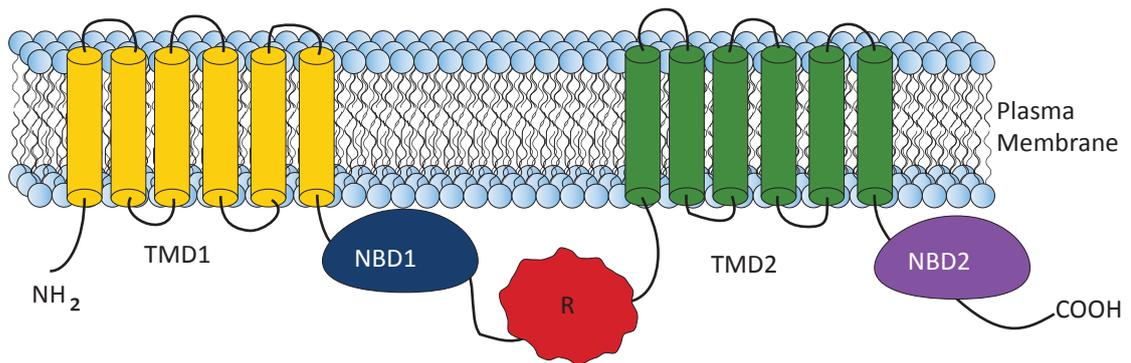
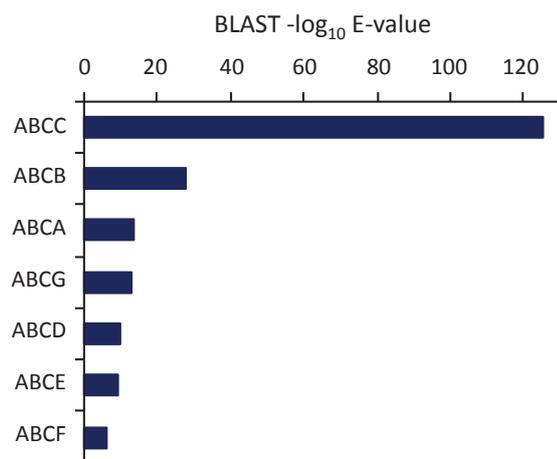
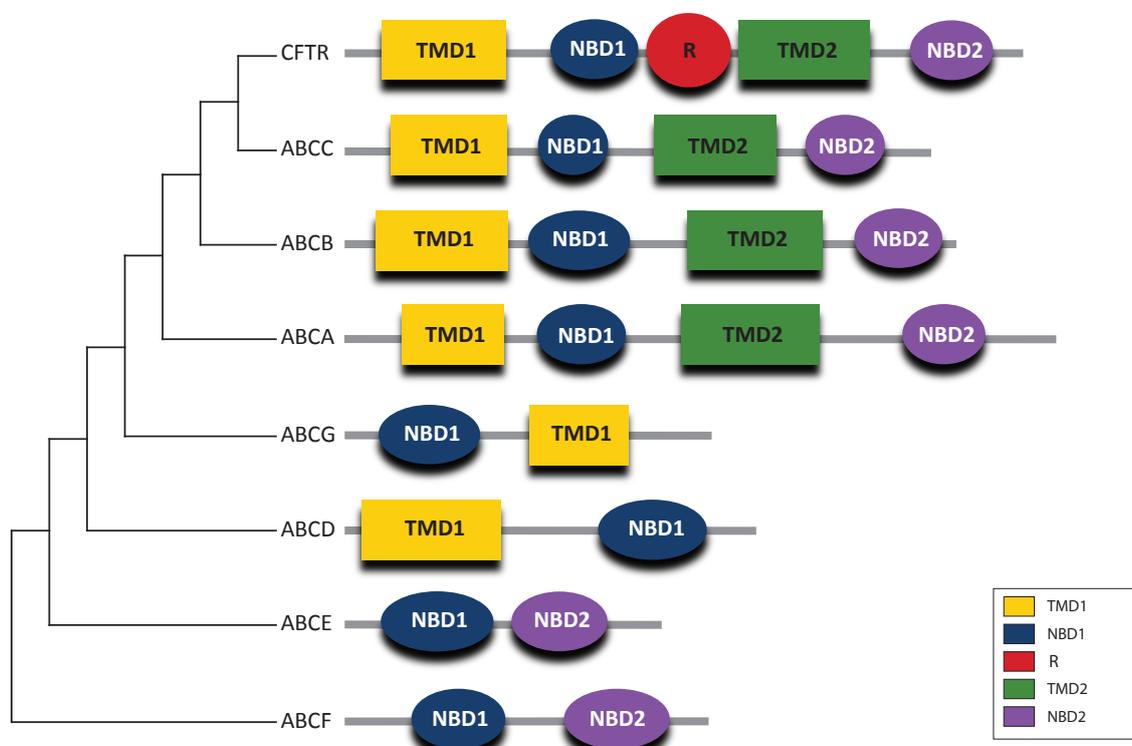
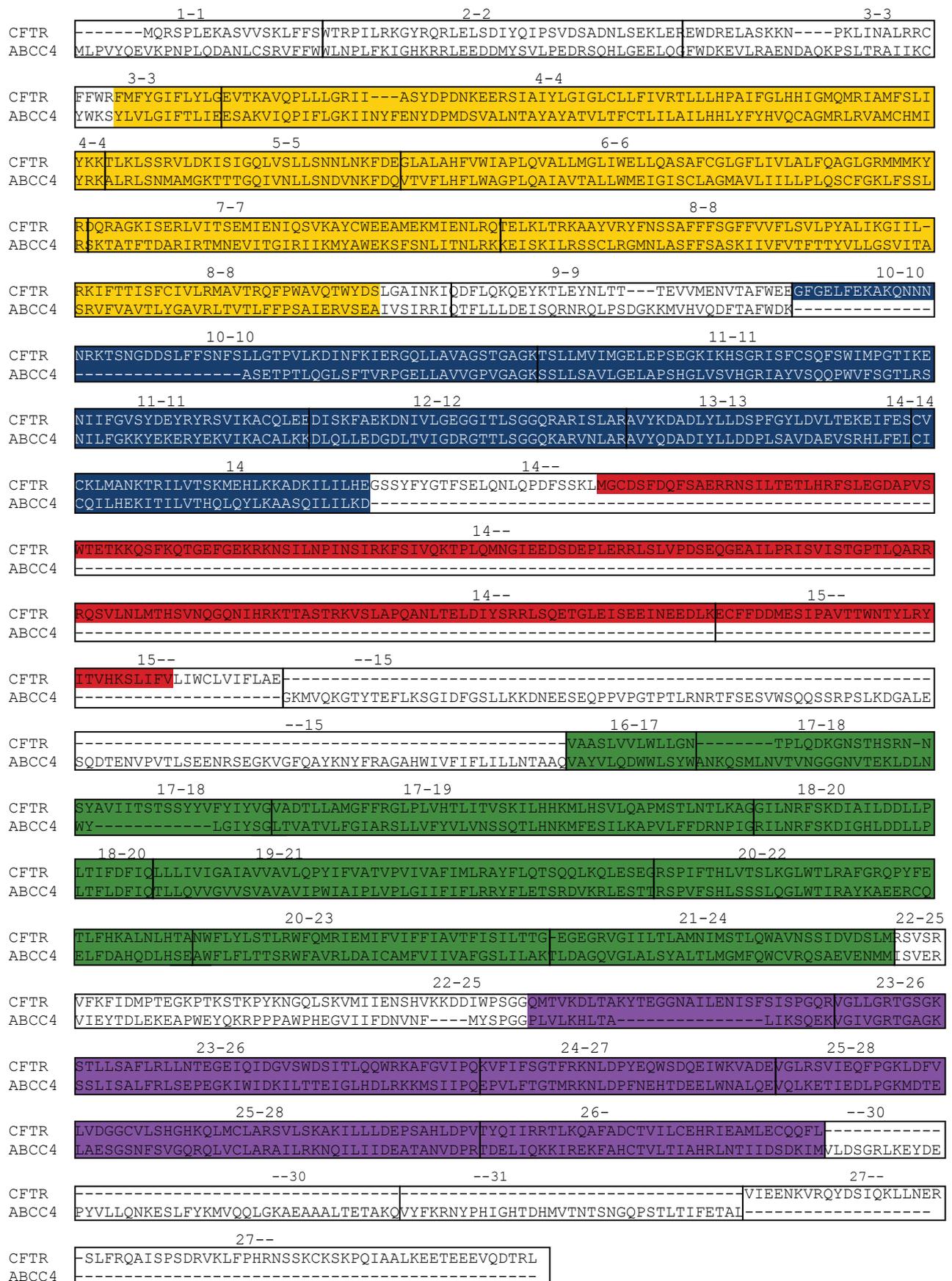


A**B**

Supplementary Figure 1. CFTR protein structure and domain architecture. (A) Open state CFTR homology model, ribbon representation from Serohijos et al. 2008 PNAS 105:3256. CFTR domains are color coded as shown in the legend. (B) Schematic representation of CFTR domain organization in and around the plasma membrane.

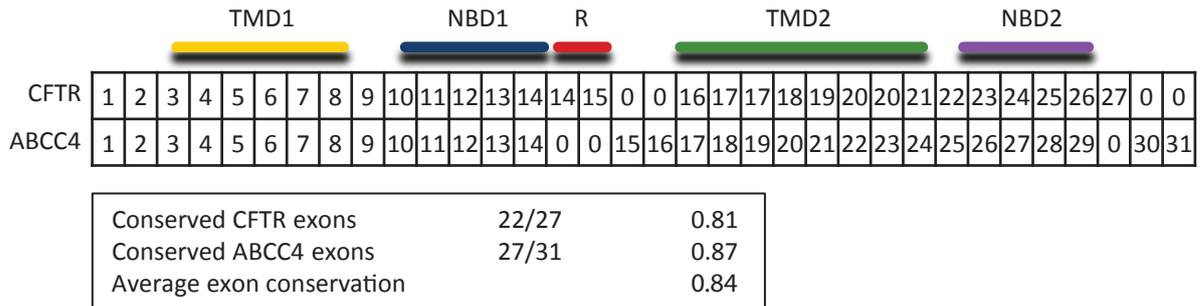
A**B**

Supplementary Figure 2. Sequence similarity and domain architecture of CFTR and related ABC transporters. (A) Statistical significance of BLASTP hits of the human CFTR protein sequence against representative human ABC family members. (B) Dendrogram showing the relationship between CFTR and representative ABC family members along with their domain architectures.

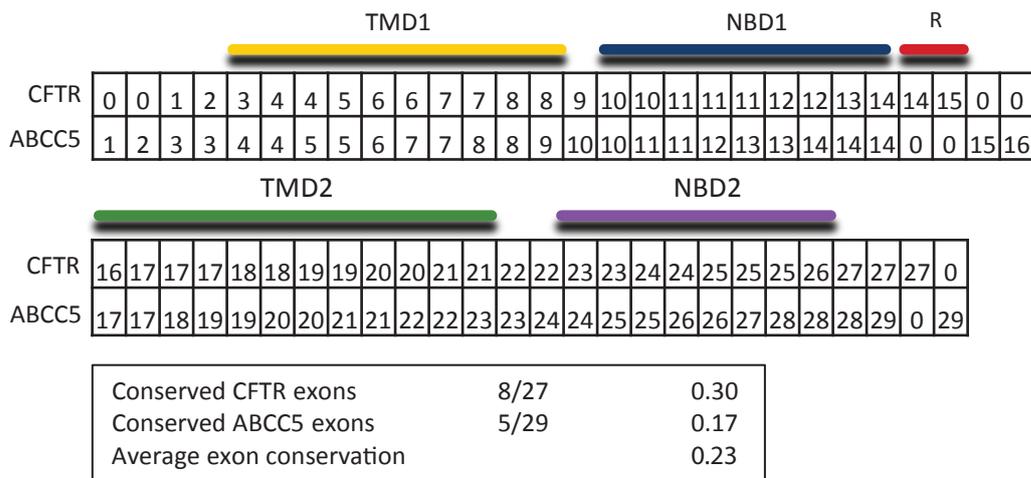


Supplementary Figure 3. Pairwise alignment of human CFTR and ABCC4 proteins shown along with locations of the protein coding sequence exons. The CFTR exon number is shown first followed by the corresponding ABCC4 exon. The locations of CFTR domains are indicated with colors as in Supplementary Figure 1.

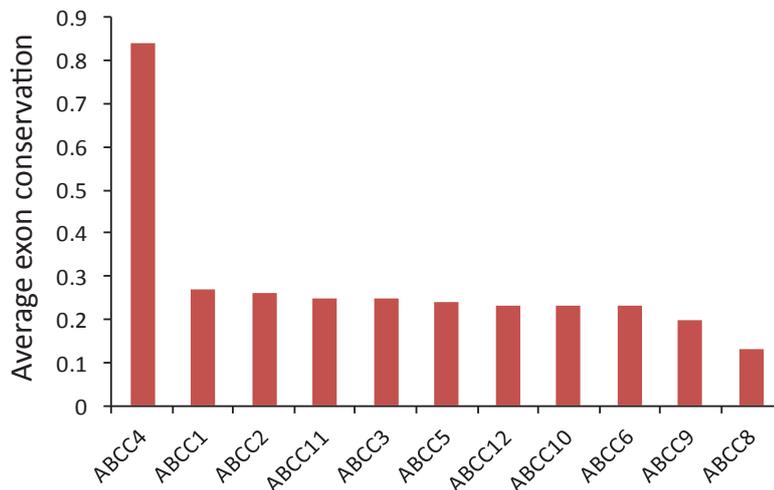
A



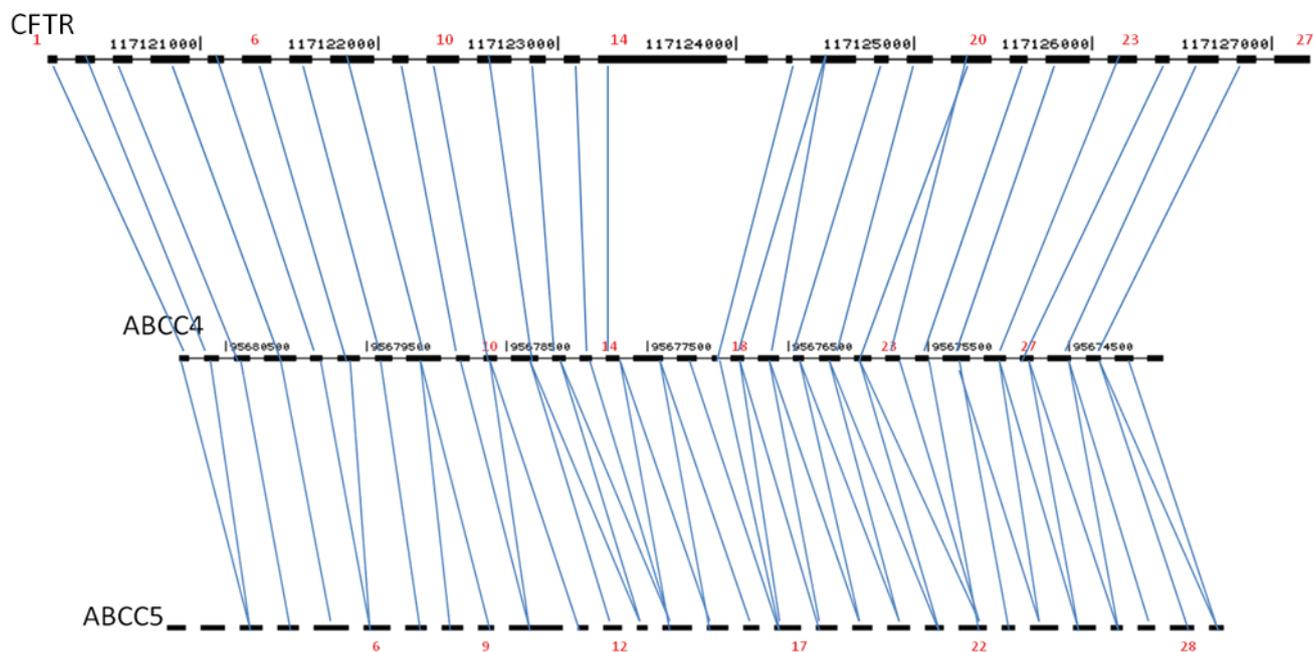
B



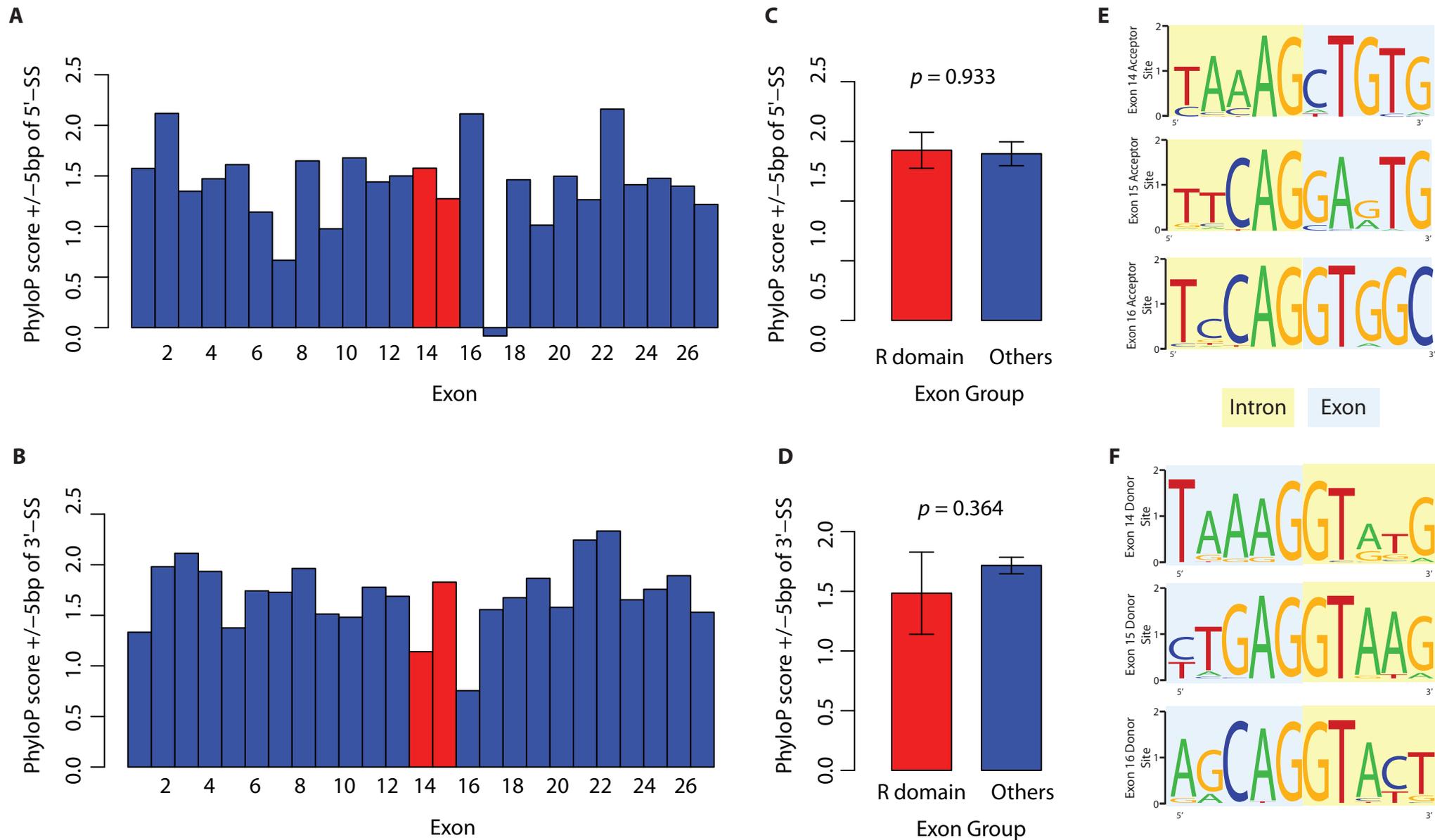
C



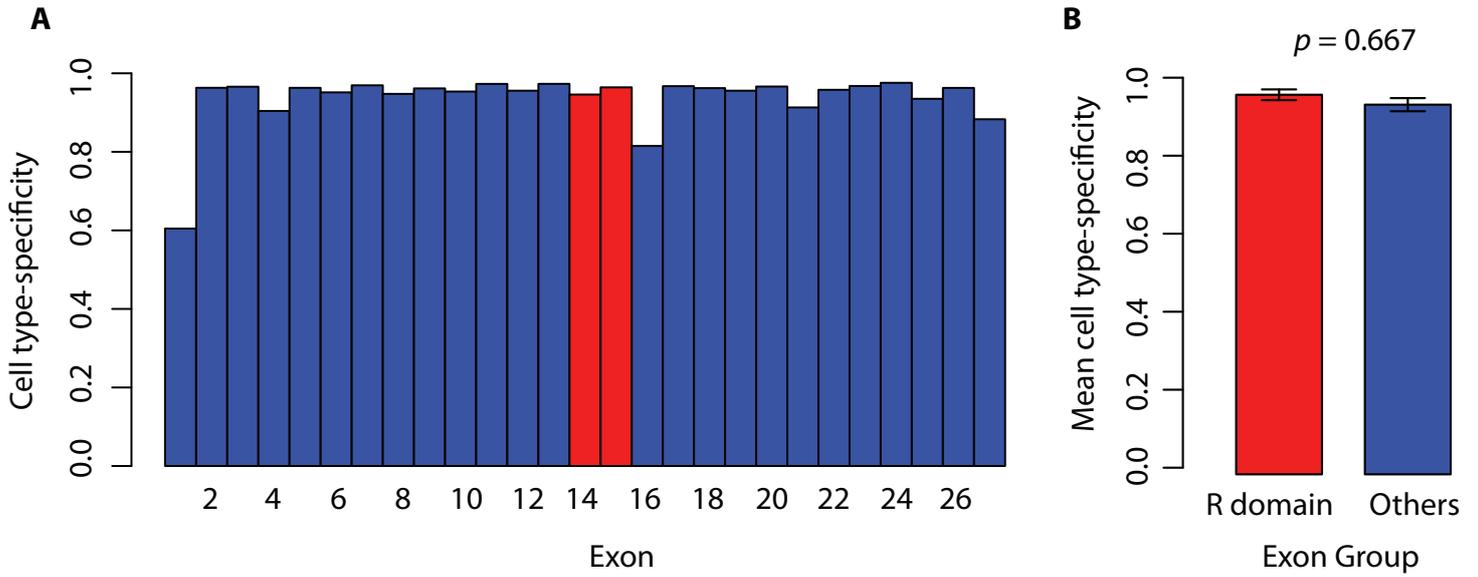
Supplementary Figure 4. Comparison of exon-intron structure between CFTR and ABCC subfamily members. Correspondence of exons between CFTR-ABCC4 (A) and CFTR-ABCC5 (B). Corresponding exonic regions are placed in the same column, and exons (or exonic regions) that do not have corresponding sequences are marked with 0. Locations of CFTR domains are indicated above. Fractions of conserved exons are shown below. (C) Average exon conservation (i.e. fractions of conserved exons) are shown between CFTR and members of the ABCC subfamily.



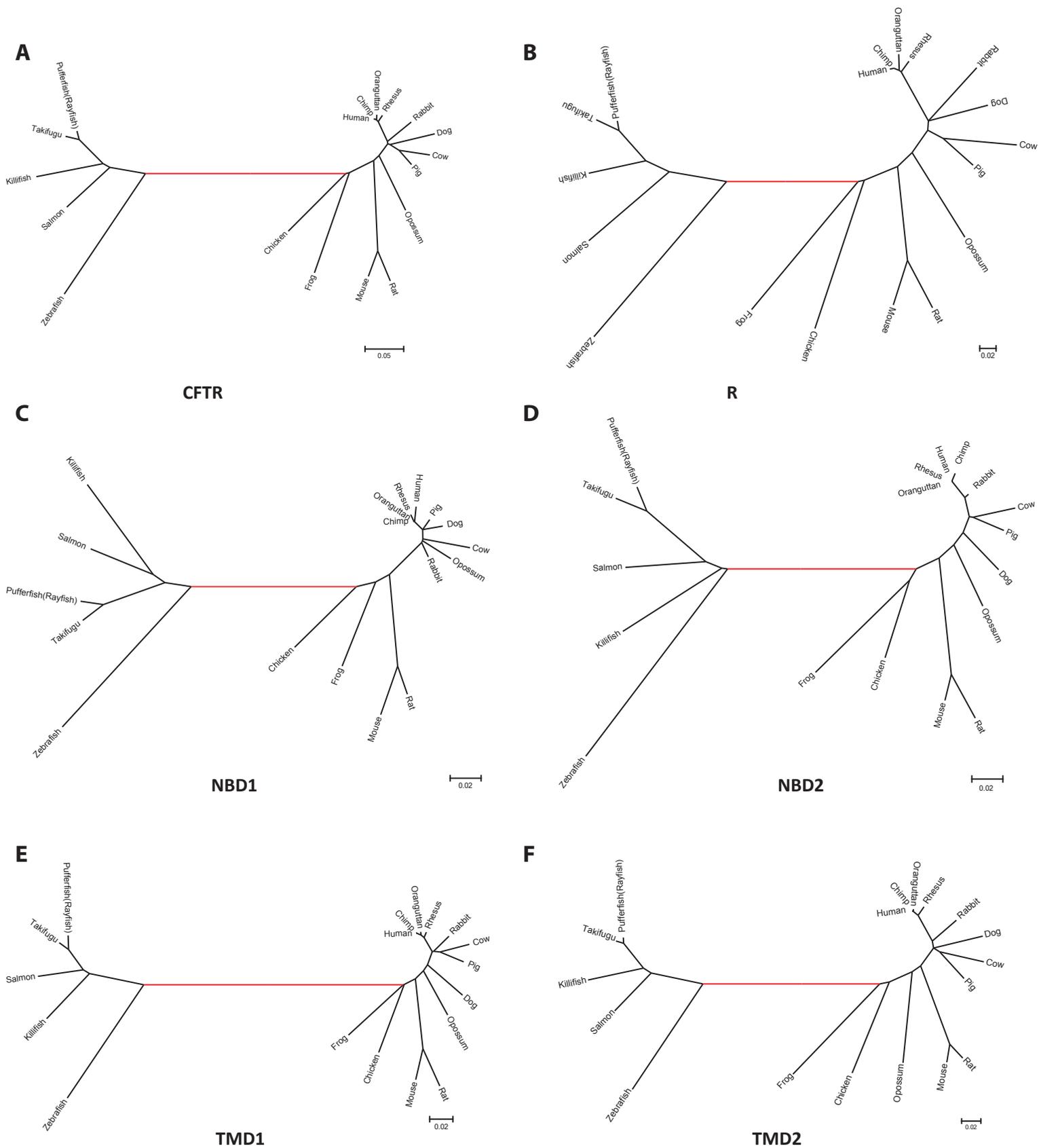
Supplementary Figure 5. Comparison of gene structures between CFTR and closely related ABCC subfamily members. The CFTR exon-intron structure is schematically represented in comparison to those of the most closely related ABCC subfamily members: ABCC4 & ABCC5. Exons are represented as black boxes and vertical blue lines between gene models connect corresponding (*i.e.* homologous) exons. For purposes of visual clarity, exons are drawn to scale, whereas introns are arbitrarily truncated.



Supplementary Figure 6. Comparative splice site analysis for CFTR-specific R domain splice sites versus the splice sites of the remaining CFTR exons. (A-B) Rates of sequence conservation (PhyloP scores) are compared for 5' splice acceptor sites and 3' splice donor sites for CFTR R domain encoding exons (red) versus the remaining CFTR exons (blue). (C-D) Average \pm SE rates of splice site sequence conservation are shown along with the P -values for the differences. (E-F) Splice acceptor and donor sites are shown for CFTR R domain encoding (and proximal) exons 14, 15 & 16.



Supplementary Figure 7. Comparison of cell type-specificity for CFTR R domain encoding exons (red) versus the remaining CFTR exons (blue). Cell type-specificity values are shown for individual CFTR exons (A) along with average \pm SE values and (B) the P -values for the differences.



Supplementary Figure 8. Phylogenies of CFTR and individual CFTR domains. Phylogenies show two main groups: fish and other vertebrates. For each domain, the ratio B1/C shown in Figure 6 are calculated as the between group branch length (shown in red) divided by the average within group branch lengths (shown in black).

Supplementary Table 1. CFTR and ABC transporter sequences used in the analyses reported here.

Human CFTR and ABCC subfamily protein & gene sequences		
Sequence Name	RefSeq Accession	Gene ID
CFTR (ABCC7)	NP_000483	1080
ABCC1	NP_004987	4363
ABCC2	NP_000383	1244
ABCC3	NP_003777	8714
ABCC4	NP_005836	10257
ABCC5	NP_005679	10057
ABCC6	NP_001162	368
ABCC8	NP_000343	6833
ABCC9	NP_005682, NP_064693	10060
ABCC10	NP_001185863	89845
ABCC11	NP_115972	85320
ABCC12	NP_150229	94160
Vertebrate CFTR protein and coding nucleotide sequences		
Species	Protein Accession	Nucleotide Accession
Human (<i>Homo Sapiens</i>)	NP_000483	NM_000492
Chimp (<i>Pan troglodytes</i>)	NP_001073386	NM_001079917
Orangutan (<i>Pongo abelii</i>)	NP_001162017	NM_001168545
Rhesus (<i>Macaca mulatta</i>)	NP_001028110	NM_001032938
Rabbit (<i>Oryctolagus cuniculus</i>)	NP_001076185	NM_001082716
Dog (<i>Canis lupus familiaris</i>)	NP_001007144	NM_001007143
Cow (<i>Bos taurus</i>)	NP_776443	NM_174018
Pig (<i>Sus scrofa</i>)	NP_001098420	NM_001104950
Opossum (<i>Monodelphis domestica</i>)	XP_001368450	XM_001368413
Rat (<i>Rattus norvegicus</i>)	NP_113694	NM_031506
Mouse (<i>Mus musculus</i>)	NP_066388	NM_021050
Chicken (<i>Gallus gallus</i>)	NP_001099136	NM_001105666
Frog (<i>Xenopus laevis</i>)	AAC60023	U60209
Zebrafish (<i>Danio rerio</i>)	NP_001038348	NM_001044883
Salmon (<i>Salmo salar</i>)	NP_001117005	NM_001123533
Killifish (<i>Fundulus heteroclitus</i>)	AAC41271	AF000271
Takifugu (<i>Takifugu rubripes</i>)	NP_001041505	NM_001048040
Pufferfish (<i>Tetraodon nigroviridis</i>)	AAR16330	AE017192