THE JOURNAL OF GENERAL PHYSIOLOGY

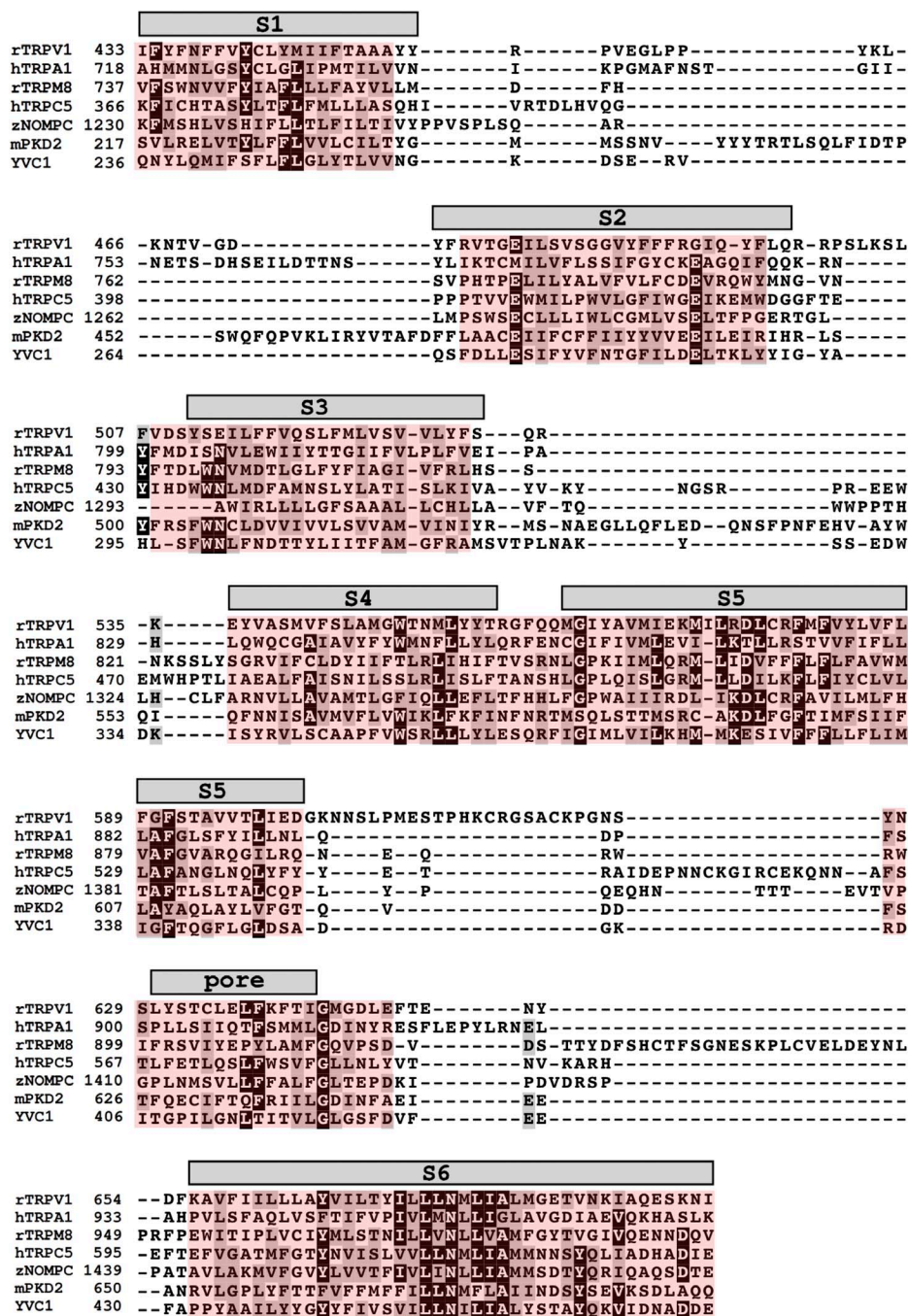**Figure S1.** MSA of representative TRP channel sequences aligned in the TM region. Selected members from each of the seven TRP subfamilies, aligned throughout their TM score. UniProt accession numbers for each sequence: rTRPV1, O35433; hTRPA1, O75762; rTRPM8, Q8R455; hTRPC5, Q9UL62; zNOMPC (zebrafish no-mechanosensor potential C, a TRPN channel), Q7T1G6; mPKD2 (mouse polycystic kidney disease protein 2, a TRPP channel), O35245; YVC1 (yeast vacuolar conductance protein 1, a TRPY channel), Q12324. Alignments in nonhelical loop regions (outside the regions highlighted in red) should be disregarded. A large, putatively extracellular domain between S1–S2 in mPKD2 was removed for clarity.
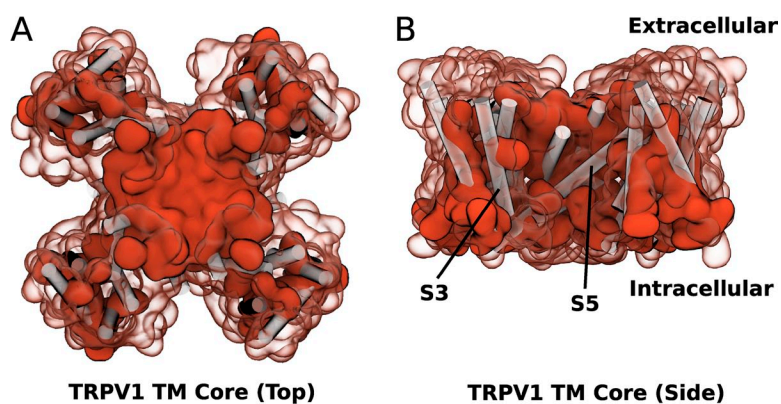
Figure S2. Relative entropy of the TRP channel TM region with respect to Kv channels. TM region of TRPV1 from above (A) and from the side (B), with positions diverging from Kv channels ($H_{\text{rel}}(\text{TRP}(i)\|\text{Kv}(i)) > 3.0$ nats) shown as a red surface and nondivergent positions shown as a transparent surface. Positions with low relative entropy primarily putatively face the lipids, whereas the core-facing regions of the two channel families have distinct distributions of residues, except for the indicated lower portions of S3 and S5.