



**Fig. S18: Intracellular loop two (IL2) amino acids in various class A GPCRs.** The structural dimension of the MC4R IL2 is indicated above respective sequence, as well as the in the main text discussed specific residues T150<sup>3,53</sup> (TM3) and L155<sup>IL2</sup>. The alignment was visualized using the software BioEdit (4). Background colors indicating conservation (Blossum62 matrix) among different receptors and reflecting chemical properties of the amino acid side chains: black - proline; blue - positively charged; cyan/green - aromatic and hydrophobic; green - hydrophobic; red - negatively charged; gray - hydrophilic; dark red - cysteines; and magenta - histidine.