

Figure S6.

| | | |
|------------------|--|----|
| MC2R-Human | -----MKHI----INSYE-NIN--NTARNNSDCPRVVLPEEIFF | 32 |
| MC2R-Mouse | -----MKHI----INSYE-HTN--DTARNNSDCPDVVLPEEIFF | 32 |
| MC2R-Rat | -----MKHI----INSYE-HTN--NTARNNSDCPDVVVPEEIFF | 32 |
| MC2R-Opossum | --ERASELIKILGHN----GNPPE-NIT--DNATNNTDCIQVVVPEEVFF | 41 |
| MC2R-Chicken | MSTEKPFNLILSAHAGQTSIPSLE-NIT--DFSLNITDCNQVVVPEEVFF | 47 |
| MC2R-Turkey | -----IKHAGQTSIPSLE-NIT--DFSLNITDCNQVVVPEEVFF | 36 |
| MC2R-Zebrafinch | MSTERPS--ILIKHPGQTSIPSLE-NIS--DFSLNITDCTQVVVPEEVFF | 45 |
| MC2R-AnoleLizard | -----VPEEIFF | 7 |
| MC2R-Takifugu | -----SSKLOVLKFTSLAMN-----ATTVNRSDCPEVNVPIHVFF | 35 |
| MC2R-Tetraodon | ----- | - |
| MC2R-Sickleback | -----MD-----TAAANRSDCPEVRVPVPLFF | 22 |
| MC2R-Medaka | -----SNFEVMN-----TNSVNRTDCPEVKVPFLIFF | 27 |
| MC2R-Zebrafish | -----MNPSAE-----SPSSIHTDCAEVQVPGQVFL | 26 |
| MC5R-Human | -----MNSSFHLHFLDLNLNATEGNLSGPNVKNKSSPCEDMGIAVEVFL | 44 |

| | TM1 | TM2 | |
|------------------|---|-----|----|
| MC2R-Human | TTISIVGVLENLIVLLAVFKNKNLQAPMYFFICSLAISDMLGSLYKILENI | | 82 |
| MC2R-Mouse | TTISVIGILENLIIVLLAVIKNKNLQSPMYFFICSLAISDMLGSLYKILENI | | 82 |
| MC2R-Rat | TTISIGVLENLIVLLAVIKNKNLQSPVYFFICSLAISDMLGSLYKILENI | | 82 |
| MC2R-Opossum | ATSIIGVLENLLVLLAVIKNRNLHSPMYFFICSLAVSDMLGSLYKILENI | | 91 |
| MC2R-Chicken | TVAAAGILENLLVAVIRNKNLHLPMYFFICSLAISDMLGSLYKTLENI | | 97 |
| MC2R-Turkey | TVAAAGILENLLVAVIRNKNLHLPMYFFICSLAISDMLGSLYKTLENI | | 86 |
| MC2R-Zebrafinch | TVAAAGILENLLILIAVVRNKNLHLPMYFFICSLAISDMLGSLYKTLENI | | 95 |
| MC2R-AnoleLizard | ITATLGLLENLLVLIIVGRNKNLHSPMYFFICSLAVSDMLGSLYKAVENI | | 57 |
| MC2R-Takifugu | TTIGFVSLLENLLVIGAIISWRNRLHSPMYCFIGSLAAFNTIVASVTKTWENL | | 85 |
| MC2R-Tetraodon | -----V | | 1 |
| MC2R-Sickleback | TTIGVVSIAENLLVVAVIRNRNLHSPMYCFICSLAAFNTIASLTKTWENL | | 72 |
| MC2R-Medaka | TVGIVSLAENLLVLLAVILNRNLHSPMYCFICSLAAFNTIASLTKTWENL | | 77 |
| MC2R-Zebrafish | VIAVASLSENLLVIVAVIKNKNLHSPMYCFICNLAVFNTISSFSKALENI | | 76 |
| MC5R-Human | TLGVISLLENLILVIGAVKKNLHSPMYFFVCSLAVADMLVSMSSAWETI | | 94 |

| | TM3 | |
|------------------|---|-----|
| MC2R-Human | L-IILRNMGYLKPRGSFETTADDIIDSFLVLSLLGSIFSLSVIAADRYIT | 131 |
| MC2R-Mouse | L-IMFRNMGYLKPRGSFESTADDIIDCMFILSLLGSIFSLSVIAADRYIT | 131 |
| MC2R-Rat | L-IMFRNMGYLKPRGSLESTADDIIDCMFVLSLLGSIFSLSVIAADRYIT | 131 |
| MC2R-Opossum | L-IIFRNTGYLKPRGDFETTADDVVDSLFILSLLGSIFSLSVIAADRYIT | 140 |
| MC2R-Chicken | F-IILCKMGYLTRRGDFEKKLDDAMDSMFILSLLGSIFSLLAIAADRYIT | 146 |
| MC2R-Turkey | F-IILCKMGYLTRRGDFEKKLDDAMDSMFILSLLGSIFSLLAIAADRYIT | 135 |
| MC2R-Zebrafinch | F-IILCKMGYLTRRGDFEKKLDDAMDSMFILSLLGSIFSLLAIAADRYIT | 144 |
| MC2R-AnoleLizard | FYIIFCKMQYVKCRGKLAKTMDDILDFFMILSLLGSIFSLSAIAADRYIT | 107 |
| MC2R-Takifugu | M-ITFAEVGHLRKVGFSEKADDVDSLLCMSFLGSIFSLAIAVDRYIT | 134 |
| MC2R-Tetraodon | M-IMFADVGHLRKVGYLELKLDDVDSLLCMSFLGSIFSLAIAADRYIT | 50 |
| MC2R-Sickleback | M-IVFANIGLEKKGPSSETNVDDVDSLLCMSFVGSIFSLAIAADRYIS | 121 |
| MC2R-Medaka | M-IVFADVGOLEKRGPSSETKLDMDMSLLCMSFVGSIFSLAIAVDRYIT | 126 |
| MC2R-Zebrafish | L-LLFKDAGRNLNSRGPPELKIIDDIMDSLLCMCFLGSIFSLAIAVDRYIS | 125 |
| MC5R-Human | T-IYLLNKKHLVIADAFVRHIDNVFDSMICISVVASMSLLAIAVDRYIT | 143 |

140c

(Numbering according to human MC5R)

| | TM4 | |
|------------------|--|-----|
| MC2R-Human | IFHALRYHSIVTMRRTVVVLTVIWFCTGTGITMVI FSHHVPTVITFTSL | 181 |
| MC2R-Mouse | IFHALQYHSIVTMRRTIITLTI IWMFCTGSGITMVI FSHHIPTVLTFTSL | 181 |
| MC2R-Rat | IFHALQYHSIVTMRRTVITLTVIWMFCTGSGITMVI FSHHIPTVLTFTSL | 181 |
| MC2R-Opossum | IFHALQYHNIMTMRRRAISILAI IWFCTGSGITMVI FSHDVPVVISFTSL | 190 |
| MC2R-Chicken | IFYALRYHNIMTLQRALVILAI IWFCTAGSSIATALFSHEVATVIPFTIL | 196 |
| MC2R-Turkey | IFYALRYHNIMTVRRALVILAI IWFCTAGSSIATALFSHEIATVIPFTIL | 185 |
| MC2R-Zebrafinch | IFYALRYHNIMTLRRALVILAI IWFCTAGSSIATALFSYEAA TVIPFTIL | 194 |
| MC2R-AnoleLizard | IFYALRYHNIMTLKRALVMLGVIWAFCTGSGIAMVLSYEAVTVVSVTVL | 157 |
| MC2R-Takifugu | IFHALRYHNIMTMORTGAILGLI WTTTCGVSAMLMVRFDSNLMSCFVVF | 184 |
| MC2R-Tetraodon | IFHALRYHDIMTLORTGAILGVI WTTTCGVSAVLMVRFDSNLMGCFVVF | 100 |
| MC2R-Sickleback | IFHALRYHNIMTMRRTRAVLGV IWTTCGVSAVLMVRFDSNFIMICFVVF | 171 |
| MC2R-Medaka | IFNALRYHNIMTMORTGGILVVI WTTTCGVSAVLMVRFDFKFKIMICFVVF | 176 |
| MC2R-Zebrafish | IFHALRYHMLTMRRVLIILFTI WVLCTSGALMVGFFEAATVKIFFIVL | 175 |
| MC5R-Human | IFYALRYHIMTARRSGAIIAGI WAFCTGCGIVFILYSESTYVILCLISM | 193 |

| | TM5 | |
|------------------|--|-----|
| MC2R-Human | FPIMLVFIFILCLYVHMFL LARSHTRKISTLP-----RANMKGAI | 219 |
| MC2R-Mouse | FPIMLVFIFILCLYIHMFL LARSHARKISTLP-----RTNMKGAM | 219 |
| MC2R-Rat | FPIMLVFIFILCLYIHMFL LARSHARKISTLP-----RANMKGAM | 219 |
| MC2R-Opossum | FPIMLVFIFILCLYVHMFL LARSHAKKIISLPSS-RVQP-----RANMKGAI | 234 |
| MC2R-Chicken | FPIMLVFIFILCLYIHMFL LARSHAKKIASLPTS-AVHQ-----RTNMKGAI | 240 |
| MC2R-Turkey | FPIMLVFIFILCLYIHMFL LARSHAKKIASLPTG-AVHQ-----RTNMKGAI | 229 |
| MC2R-Zebrafinch | FPIMLVFIFILCLYIHMFL LARTHAKKIASLPS--TIHH-----RTNMKGAI | 237 |
| MC2R-AnoleLizard | FCFMLVIFILCLYIHMFL LARSHAKKIALMTTS-SVHQ-----GANMKGAI | 201 |
| MC2R-Takifugu | FVHSLAIVYILYVVMF ILARVHARKIAALPNGSGKHQHQR ^{230c} RWGHGMRGIL | 234 |
| MC2R-Tetraodon | FVHSLVIVYILYVVMF ILSRVHARRIAALPGGSGKHQHLLRRWNGMRGIM | 150 |
| MC2R-Sickleback | FVHSLAIVICFLYVVMFLAR ITHAKSIALPAS-----NGMRGAL | 210 |
| MC2R-Medaka | FIVSLAIVICFLYVVMFLAR ITHAKSIALP----- | 206 |
| MC2R-Zebrafish | FFTALLIILLYVHMFL LARHARRIASMPGAQAQHRK-----SGLRGAL | 220 |
| MC5R-Human | BFAMFLVLSLYIHMFL LARTHVKRIAALPGASSARQ-----RTSMQGA V ^{236a} | 238 |

| | TM6 | TM7 | |
|------------------|--|-----|-----|
| MC2R-Human | TLTILLGVFIFCWAPFVLH VLLMTFCPSNPYCACYMSLFOVNGMLIMCNA | | 269 |
| MC2R-Mouse | TLTILLGVFIFCWAPFVLH VLLMTFCPNNPYCVCYMSLFOVNGMLIMCNA | | 269 |
| MC2R-Rat | TLTILLGVFIFCWAPFVLH VLLMTFCPNNPYCVCYMSLFOVNGMLIMCNA | | 269 |
| MC2R-Opossum | TLTILLGVFLCCWAPFVLH ILLVTFCPNNPYCACYLSIFOVNGMLIMCNA | | 284 |
| MC2R-Chicken | TLTIFLGVFLCCWAPFVLH ILLARFCPHNPYCACYMSIFHVNGTLIMCNA | | 290 |
| MC2R-Turkey | TLTIFLGVFLCCWAPFVLH ILLARFCPHNPYCACYMSIFHVNGTLIMCNA | | 279 |
| MC2R-Zebrafinch | TLTIFLGVFLCCWAPFVLH ILLARFCPHNPYCACYMSIFHVNGTLIMCNA | | 287 |
| MC2R-AnoleLizard | TLTVLVAVFLFCWSPFVLH MLLMTFCPONPYCICYGSIFHVHGMLIMCNA | | 251 |
| MC2R-Takifugu | TLTILFGAFMVCWAPFVLH LILFLMACPMNPYCECYRSMFOLHLVLLMSHA | | 284 |
| MC2R-Tetraodon | TLTILFGAFMVCWAPFVLH LILFLMVCPMNPYCECYRSLFELHVLLMSHA | | 200 |
| MC2R-Sickleback | TLTILFGAFVVCWAPFVLH LILFLMVCPTNPYCECYRSLFOLHVLLMSHA | | 260 |
| MC2R-Medaka | ----- | | - |
| MC2R-Zebrafish | TLTILIGVFAVCWAPFSLH LLLIMICPENPYCECYRSLFOLHVLLVSHA | | 270 |
| MC5R-Human | TVTMLLGVFTVCWAPFVLH LTLMLSCPONLYCSRFSHFNMYLILIMCNS | | 288 |

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|------------------|--|-----|
| | | |
| MC2R-Human | VIDPFIYAFRSPELRDAFKKMFCSRYW----- | 297 |
| MC2R-Mouse | VIDPFIYAFRSPELRDAFKRMLFCNRY----- | 296 |
| MC2R-Rat | VIDPFIYAFRSPELRDAFKRMLFCNRY----- | 296 |
| MC2R-Opossum | IIDPMIYAFRSPELRSTFKKMFCCSGYK----- | 312 |
| MC2R-Chicken | IIDPMIFAFRSPELRSTFKKMFCCARYNWNWWKLNEGEYYRSTPMQHFFA | 340 |
| MC2R-Turkey | IIDPMIFAFRSPELRSTFKKMFCCARHNW----- | 308 |
| MC2R-Zebrafinch | IINPMIFAFRSPELRSTFKKMFYCSRSNCSW----- | 318 |
| MC2R-AnoleLizard | VIDPMIYAFRSPELRSTFRRFISCSY----- | 277 |
| MC2R-Takifugu | LIDPVIYAFRIPELRHTFRMLPCLNWR----- | 312 |
| MC2R-Tetraodon | LIDPGIYAFRIPELRHTFRMLLCLNWRLSLT----- | 232 |
| MC2R-Sickleback | FIDPAIYAFRSVELRHTFRKMLLCSDWKRCS----- | 291 |
| MC2R-Medaka | ----- | - |
| MC2R-Zebrafish | VIDPAIYAFRSVELRNTYKMLLSASRICKRCA----- | 304 |
| MC5R-Human | VMDPLIYAFRSQEMRKTFKEIICRGFRIACSFPRRD----- | 325 |

| | | |
|------------------|-------------------|-----|
| MC2R-Human | ----- | - |
| MC2R-Mouse | ----- | - |
| MC2R-Rat | ----- | - |
| MC2R-Opossum | ----- | - |
| MC2R-Chicken | ELKILTQNDTTLAGNCQ | 357 |
| MC2R-Turkey | ----- | - |
| MC2R-Zebrafinch | ----- | - |
| MC2R-AnoleLizard | ----- | - |
| MC2R-Takifugu | ----- | - |
| MC2R-Tetraodon | ----- | - |
| MC2R-Sickleback | ----- | - |
| MC2R-Medaka | ----- | - |
| MC2R-Zebrafish | ----- | - |
| MC5R-Human | ----- | - |