**Melanocortin Receptor Evolution**

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The melanocortin receptors are members of the G protein coupled receptors (GPCR) superfamily. In the human genome the GPCR superfamily is the fourth largest gene family (Rehman et al., 2023). Members of the family have seven transmembrane domains, and an intracellular carboxy terminus. As the name implies they are associated with the heterotrimeric large G protein family. Ligands bind to the GPCR outside the cell, and the GPCR then activates G proteins inside the cell that triggers a cascade of further signaling events. Most jawed vertebrates have five melanocortin receptor genes (MC1R, MC2R, MC3R, MC4R, and MC5R), but some lineages have lost members of the family and/or have further duplicated some of them. I have aligned the sequences of the chicken melanocortin receptor, and the *Lampetra fluviatilis* (lamprey, a jawless fish) melanocortin receptors a and b (MCa and MCb) amino acid sequences in Figure 1. They are paralogs of some ancestral GPCR. The proopiomelanocortin (*POMC*) mRNA is translated and the resulting protein is processed into various peptides that act as ligands for the melanocortin receptors (Dores and Baron, 2011). The common features of the melanocortin receptors are detailed in Figure 1. They share conserved regions for ligand binding, signaling, and have retained the ability to form heterodimers with each other during the evolution of the various functions of the 5 receptors.

Ancestral chordates did not have melanocortin receptors nor proopiomelanocortin (*POMC*) genes. An *MC1R*-like gene and *POMC* evolved in jawless fish after the R1 whole genome duplication event (Dores and Baron, 2011). *MC1R* evolved from some undetermined GPCR and *POMC* likely evolved from a gene that produced opioid ligands. Figure 2 has a phylogeny of how the 5 MCR paralogs may have evolved. The scenario came from Dores, 2013, but Ji et al., 2024 described the same scenario even though their phylogeny (Figure 3 below, based on sequence similarity) did not support Figure 2. Dores, 2013 and Ji et al., 2024 note that no melanocortin receptors have been found in extant nonvertebrate chordates. *MC1R*-like (*MCa*) and MC4R-like (*MCb*) melanocortin receptors that can bind melanocortin ligands have been found in jawless fish that also have a *POMC* gene (Ji et al., 2024). Ji et al., 2024 note that none of the protochordate *MC4R*-like GPCR genes (Figure 3) found in nonvertebrate chordates could bind melanocortin ligands. Ji et al., 2024 notes that the amino acids associated with orthosteric binding (**bold red** Figure 1) nor the CWXP motif in TM6 (sixth transmembrane region) associated with ligand activation of the receptor are not conserved among the *MC4R*-like GPCR genes. Ji et al., 2024 found that the protochordate MC4R-like receptors could not bind melanocortin ligands. Figure 3 clearly places MCa and MCb as being related to vertebrate MCR1-5 receptors. The R1 whole genome duplication event likely created the *MCa* and *MCb* genes. *MCa* would eventually become *MC1R* and *MCb* would become *MC4R*. The R2 whole genome duplication that occurred in the common ancestor of all jawed vertebrates produced *MC1R* and *MC2R* with *MC2R* duplicating to produce *MC5R* sometime after the R2 duplication event. The R2 whole genome duplication event would also create *MC4R* and *MC3R* (Figure 2).

As noted, the gene phylogeny of Figure 2 is not supported by the similarity phylogeny of Figure 3. The R2 whole genome duplication event occurred around half a billion years ago. All the melanocortin receptors have conserved sequences (Figure 1) that allow them to create heterodimers and bind melanocortin ligands, but outside of the functional sequence conserved regions any sequence similarity is likely due more to chance than to homology. If a position can change it has likely changed multiple times during the half billion years that the genes have been evolving. With paralogs you also have to deal with the possibility of gene conversion. In the case of gene conversion similar sequences can undergo something similar to genetic recombination where one gene sequence can convert a related duplicate of it’s sequence by strand invasion of one strand of DNA from one paralog invading the sequence of the related duplicate copy. This makes the duplicated copies more similar to each other than they should be if they had been evolving independently, so some gene sequences can have segments that come from another paralog.

The fact that both MCa and MCb can bind melanocortin ligands is an indication that POMC and a melanocortin receptor would have evolved their ability to produce melanocortin ligands and bind those ligands before the R1 genome duplication event. Otherwise POMC would have evolved melanocortin ligands and two receptor genes (MCa and MCb) would have had to evolve the ability to recognize those ligands independently.

Protocordates do not develop a neural crest during their early embryonic development, but vertebrates do develop a neural crest. Melanocytes are derived from the neural crest. Chordates such as amphioxus do produce melanosomes in cells equivalent to retinal pigment epithelium (RPE) cells, but vertebrate RPE cells are not derived from the neural crest, and are not considered to be melanocytes. Jawless fish that have the *MC1R*-like (*MCa*) receptor gene have a *POMC* gene, produce melanocytes and develop a neural crest during their embryonic development. Melanocytes and the embryonic neural crest are features that may have evolved after the R1 whole genome duplication event. Melanocytes had evolved before the R2 whole genome duplication event that occurred in the common ancestor that all jawed vertebrates share. This means that the MCa of jawless fish may have evolved MC1R-like functions before the R2 whole genome duplication event. Braasch et al., 2009 note that nearly all the genes related to tetrapod vertebrate pigmentation had evolved by around the time of the R2 whole genome duplication event. This was a time when all jawed vertebrates were fish, and they all produced melanocytes and eumelanosomes. McNamara et al., 2021 note that MC1R may have been involved in the regulation of pigmentation in the fish ventral and dorsal regions (fish have more melanin on their backs than on their bellies). This likely means that MC1R regulated eumelanosome production and/or melanocyte distribution and activation in different regions of the animal. It would have been coopted to regulate the production of either eumelanosomes or pheomelanosomes in the common ancestor of tetrapod vertebrates (D’Alba and Shawkey, 2019) with the evolution of the production of pheomelanin in the ancestor of terrestrial tetrapods.

I should note that McNamara et al., 2021 cited a claim to have found pheomelanin in sea bass and jawless fish. Rogers et al., 2019 found evidence of pheomelanin in internal tissues of the fish. They found a ratio of around 50:1 (eumelanin to pheomelanin Sup Table S2). I can’t find any verification of anyone else finding pheomelanin in fish, but Rogers et al., 2019 found pheomelanin in Mollusca (squid) and fish. D’Alba and Shawkey, 2019 claim that fish do not produce pheomelanin. No one seems to have found any fish using pheomelanin as a pigment, but Rogers et al., 2019 claim to have found it expressed in the eyes of fish and squid. Since the MCa receptor of jawless fish may have evolved MC1R-like functions before the R2 duplication event and if jawless fish do produce pheomelanin as well as eumelanin, MCa may have also been involved in the repression of the production of pheomelanin. MC1R may be associated with pheomelanin production in jawed fish if sea bass really do make pheomelanin, but McNamara et al., 2021 continued to claim that the MC1R function of controlling the synthesis of eumelanin or pheomelanin began with the evolution of tetrapod terrestrial vertebrates.

**Conclusion:**

MC1R is involved in melanin pigmentation in vertebrates. It is possible that one of the first functions of newly evolved melancortin receptors was to regulate melanin biosynthesis in melanocytes. The initial MCa and MCb melanocortin receptors were created in the R1 whole genome duplication event along with POMC. The MCa receptor may have had MC1R-like functions, and MCa, MCb, and POMC exist in jawless fish that develop a neural crest in early embryo development and produce melanocytes. POMC produces the melanocortin ligands that bind to the melanocortin receptors and control signaling activity of those receptors. The Chordate ancestors of jawless fish did not develop a neural crest in their early embryos, and did not produce melanocytes, but they did produce melanosomes in their RPE cells. The system for regulating MC1R and producing melanocytes from the neural crest was established in jawless fish. MC1R, MC2R, MC3R and MC4R began diverging and establishing their current functions after the R2 whole genome duplication, that occurred in the ancestor of all jawed fish, with MC2R duplicating again to create the MC2R and MC5R paralogs.

Melanocytes were likely fully functional in the production of eumelanosomes by the R2 whole genome duplication. McNamara et al., 2021 note that the R2 whole genome duplication occurred in a common ancestor of all jawed vertebrates, and that this ancestor had evolved nearly all the genes associated with melanocyte pigmentation. This likely means that the melanocyte functions of MC1R could have evolved before the R2 duplication event that produced the MC1R and MC2R paralogs. The MC2R paralog would have had to diverge and take on the current neurological functions of MC2R. The early evolution of MC1R could mean that it was coopted from MC1R’s original melanocyte stimulating activity to regulating eumelanosome or pheomelanosome production because pheomelanin production evolved in the common ancestor of tetrapod vertebrates a couple hundred million years after the R2 genome duplication event. If pheomelanin is produced in jawless fish and sea bass it could mean an earlier involvement of MC1R with pheomelanin synthesis.

 3

 3

 **G**

MC1R MSMLAPLRLL ---------R EPW**NAS**EG**NQ SNAT**AGAGGA W**C**QGL 36

MC2R MSTEKPFNLI LSAHA----- -GQTSIPSLE **NIT**DFSL**NIT** D**C**NQV 39

MC5R M**NTS**SQLYV- --------SE L**NLS**AFGS**NF T**VPTVKSKSS P**C**EQV 36

MC3R M**NST**HFTFSF QPVLL----- --**NVT**EDISD SILN**NRS**SDG F**C**EQV 38

MC4R M**NFT**QHRGTL QPLHFW--**NQ S**NGLHRGASE PSAKGHSSGG **C**YEQL 43

lMCa M**NLS**EALFPN PFV------G TSGPDD**NGT**A SASA**NRT**RFS P**C**HNF 39

lMCb MTFSAGGVGG VVNNHHHGAN HQGGG**NHS**GH G**NAT**GGGHGR P**C**EQV 45

 5 6 7 8 9

 8 9 1 2 2

 **L** **L** **T** **E** **K**

MC1R DIPNEL**F**LTL GLVSLV**E**NLL V**V**AAILKNRN LH**S**P**M**YY**F**IC CLAVS**D**MLVS VSNLA**E**TLFM 96

MC2R VVPEEV**F**FTV AAAGIL**E**NLL VLVAVIRNKN LHLPMYF**F**IC SLAIS**D**MLGS LYKTL**E**NIFI 99

MC5R VIAAEV**F**LTL GIVSLL**E**NIL VICAIVKNKN LHSPMYF**F**VC SLAVA**D**MLVS VSNAW**E**TITI 96

MC3R FIKAEV**F**LTL GIISLM**E**NIL VILAVLKNGN LHSPMYF**F**LC SLAVA**D**MLVS TSNAL**E**TIMI 98

MC4R FVSPEV**F**VTL GIISLL**E**NVL VIVAIAKNKN LHSPMYF**F**IC SLAVA**D**MLVS VSNGS**E**TIVI 103

lMCa SIPTEV**F**LAL GIVSLV**E**NAL VIAAIARNRN MHSPMYC**F**IC SLAVA**D**LLVC LSNAW**E**TIAI 99

lMCb LIPIEV**F**LIL GVISLL**E**NIL VITAILKNKN LHSPMYY**F**IC SLAVA**D**MLVS VSNAW**E**TIIM 105

 TM1 TM2

 1

 3 1 1 1 1 1 1

 9 3 3 4 4 4 5 5

 8 **P** 7 0 3 9 3 5

 **P** **Q** **T** **H** **A** **C** **T** **A**

MC1R L**L**MEHGVLVI RASIVRHM**D**N VI**D**MLICSSV VSSLSF**L**GVI **A**V**DR**YI**T**IFY AL**R**YHS**I**M**T**L 156

MC2R ILCKMGYLTR RGDFEKKL**D**D AM**D**SMFILSL LGSIFSLLAI AA**DR**YITIFY ALRYHNIMTL 159

MC5R YLINNRHIIM EDAFVRHI**D**N VF**D**SLICISV VASMCSLLAI AV**DR**YITIFY ALRYHNIMTV 156

MC3R AILSSGYLII DDHFIQHM**D**N VF**D**SMICISL VASICNLLVI AI**DR**YITIFY ALLYHSIMTV 158

MC4R TLLNN-TDTD AQSFTINI**D**N VI**D**SVICSSL LASICSLLSI AV**DR**YFTIFY ALQYHNIMTV 162

lMCa ALVHGRHVHI PARILQHV**D**N VF**D**SFICISV VASMCNLLAI AV**DR**YVTIFY ALQYHSIVTM 159

lMCb ALLQNGSLAM QEDTLKQM**D**N IM**D**SMICTSV VASMCSLLAI AV**DR**YVTIFY ALRYHNIMTV 165

 TM3

 1 2 2

 5 1 1

 8 3 5

 **W** **C** **P**

MC1R Q**R**AVVTMASV WLASTVSSTV LITYYRNNAI LLCLIGF**F**LF MLVLMLVLYI **H**MFALA**R**H**H**V 216

MC2R QRALVILAII WTFCAGSSIA IALFSHEVAT VIPFTIL**F**PL MMIFILCLYI **H**MFLLARSHA 219

MC5R KRSGLIIACI WTFCTGCGII FILYYESTYV IICLITM**F**FT MLFLMVSLYI **H**MFLLARTHV 216

MC3R KKALTLIVLI WISCIICGII FIAYSESKTV IVCLITM**F**FT MLFLMASLYV **H**MFLFARLHV 218

MC4R KRVGVIITCI WAACTVSGIL FIIYSDSSVV IICLISM**F**FT MLILMASLYV **H**MFMMARMHI 222

lMCa RRAAVVIACV WAACVVSGTL FITYWDHRTV IVCLIAL**F**VT MLVLMASLYA **H**MFALARSHA 219

lMCb RRAASIIGAI WGTCTLCGVI FIVYSDSTAV IICLITM**F**FT MLVLMASLYV **H**MFMLARLHA 225

 TM4 TM5

 2 2 2

 6 6 7

 4 8 2

 **G** **H** **G**

MC1R RSISSQQKQP ---TIYRTSS LKGAVTLTIL LGV**F**FIC**W**GP **F**FF**H**LILIVT **C**PTN**P**F**C**T**C**F 273

MC2R KKIASLPTS- ---AVHQRTN MKGAITLTIF LGV**F**LCC**W**AP **F**VL**H**ILLARF **C**PHNPY**C**A**C**Y 276

MC5R KKIAALPGYN ---SVHQRTS MKGAITLTML LGI**F**IVC**W**AP **F**FL**H**LILMIS **C**PQNLY**C**V**C**F 273

MC3R KRIAALPVDG ---VPSQRTC MKGAITITIL LGV**F**IVC**W**AP **F**FL**H**LILIIS **C**PMNPY**C**V**C**Y 275

MC4R KKIAVLPGTG ---PIRQGAN MKGAITLTIL IGV**F**VVC**W**AP **F**FL**H**LIFYIS **C**PYNPY**C**V**C**F 279

lMCa QRISAQPRSS RQGQQNGAAS LKGAVTLSIL LGV**F**VFC**W**AP **F**FL**H**LTFIIS **C**PANPY**CC**AY 279

lMCb KRIAALPASG ---IIQHKTS MRGAITLTIL LGV**F**IVC**W**AP **F**FL**H**LILIVS **C**PRSPY**C**V**C**Y 282

 TM6

 2 3

 9 1

 1 2

 **H** **A**

MC1R FSY**F**NLFLIL IICNSVV**D**PL IYAFRSQELR RTLREVVL**C**S W 314

MC2R MSI**F**HVNGTL IMCNAII**D**PM IFAFRSPELR STFKKMFCCA RYNWNWWKLN EGEY 330

MC5R MSH**F**NMYLIL IMCNSVI**D**PL IYAFRSQEMR KTFKEIICCY SVRMV--CGL SNKY 325

MC3R TSH**F**NTYLVL IMCNSVI**D**PL IYAFRSLEMR KTFKEIVCCC YGVSV--GQC ML 325

MC4R MSH**F**NFYLIL IMCNSII**D**PL IYAFRSQELR KTFKEIICCC NLRGL--CDL PGKY 331

lMCa IAY**F**PLYLLL IMINSVI**D**PL IYAFRSPELR VIIRDTLRKC GRGRGRGANG TRGSSCCCVQ VR 341

lMCb MSH**F**NLYLVL IMLSSVI**D**PI IYAFRSHEMR HTFKEIVCCY SGSLYCALPA TWKY 336

 TM7

MC2R ---------- ---------- ---YRSTPMQ HHFAELKILT QNDTT--LAG NCR 357

Figure 1. Chicken melanocortin receptor protein sequence comparison of MCR1 to MC2R, MC5R MC3R, MC4R and lamprey lMCa and lMCb. The polymorphisms have the chicken MC1R amino acid sequence position numbers. The transmembrane regions are underlined (from Yang et al., 2007 (the transmembrane designations do differ a little from other publications in the amino acid residues associated with some of them)). The transmembrane residues involved in ligand orthosteric binding are in **bold Red** and the conserved transmembrane residues identified by Yang, 2011 are in **bold black**. The conserved CWXP sequence associated with ligand binding is highlighted in green. The position numbers of the functional polymorphisms are for the chicken MC1R polypeptide. The Cysteine residues in **bold blue** are believed to be involved in dimerization (Zanna et al., 2008). Known MC1R polymorphisms found in chickens are noted in **bold purple**. Change in function variants from other species are noted in **bold green** (Garcia-Borron et al., 2005, Garcia-Borron et al., 2014 and Herraisz et al., 2012). Possible N terminal glycosylation sites (NXS and NXT) are noted in **bold orange** (Garcia-Borron et al., 2014). Phosphorylation sites Thr305 and Ser 313 are highlighted in blue (Garcia-Borron et al., 2014). The MC1R sequence (Ellett, 2000) is the *e+* allele from the Richardson strain of Red Junglefowl (*Gallus gallus murghi*). The *Gallus* *gallus* MC2R (NP\_001026686.1), MC3R (XP\_004947293.2), MC4R (NP\_001026685.2), and MC5R (NP\_001026186.2) were used. *Lampetra fluviatilis* lMCa (ABB36647.1) and lMCb (ABB36648.1) were used. The chicken MC1R polymorphisms come from Ellett, 2000 and Davila et al., 2014. I aligned the sequences by eye, and where there was a lack of similarity I used amino acid size and hydrophobicity and minimized in/del events to align sequences in regions with insertion/deletions between genes, so parts of the alignment are best-guess-fiction. I aligned the C terminal additional sequence of MC2R as shown because it seemed to have a similar size and hydrophobicity pattern as the C terminal sequences of MC3R, 4R, and 5R.

**Functional polymorphisms of MC1R (Chicken sequence amino acid position numbers):**

Cys33Gly: Gly or Ala at this position inactivates the receptor (Garcia-Borron et al., 2005) both cAMP and ERK pathways are inactivated (Herraiz et al., 2012).

Val58Leu: Leu58 may be associated with red hair (Garcia-Borron et al., 2005) and results in 50% loss of function for cAMP pathway, but the ERK pathway showed normal function (Herraiz et al., 2012).

Ser69Leu: Leu69 leads to receptor hyperactivity in tobacco mice, and it is a potential phosphorylation site. (Garcia-Borron et al., 2005).

Met71Thr: Thr71 was found in the presumptive *E* allele (extended black) (Ellett, 2000) and in black feathered breeds (Davila et al., 2014).

Asp82Glu: Glu82 nearly a complete loss of the receptor’s ability to couple with cAMP stimulation and associated with red hair (Garcia-Borron et al., 2005).

Glu92Lys: Lys92 was found in the presumptive *E* and *ER* alleles (extended black and birchen black) (Ellet, 2000) and black feathered breeds (Davila et al., 2014), and causes constituative activity in the Sombre mouse (Garcia-Borron et al., 2005).

Leu98Pro: Pro98 may be associated with receptor activation (Garcia-Borron et al., 2005).

Leu133Gln: Gln133 was found in the Fayoumi birchen allele (Ellet, 2000) and in black feathered breeds (Davila et al., 2014).

Leu133Pro: Pro133 was found in Buff Prat and Red-barred Vasca (Davila et al., 2014).

Ala137Thr: Thr137 was found in Red Villafranquina (Davila et al., 2014).

Arg140His: His140 inhibits cAMP stimulation (Garcia-Borron et al., 2005).

Thr143Ala: Ala143 was found in breeds likely having dominant wheaten (Ellet, 2000). It is also a potential phosphorylation site and phosphorylation of this loop is associated with trafficking MC1R to the cell surface Garcia-Borron et al., 2014.

Arg149Cys: Cys149 inhibits cAMP stimulation may be associated with red hair and impairs MC1R trafficking, but is capable of activating ERK (Garcia-Borron et al., 2014).

Ser152: is a potential phosphorylation site (Garcia-Borron et al., 2014).

Ile153Thr: Thr153 is found in humans and results in 50% loss of function for cAMP pathway, but the ERK pathway showed normal function (Herraiz et al., 2012).

Thr155Ala: Ala155 blocks phosphorylation at this site and MC1R is misrouted and is retained in an intercellular compartment and does not get to the cell surface (Garcia-Borron et al., 2014) and results in loss of function for cAMP and ERK pathways (Herraiz et al., 2012).

Arg158Trp: Trp158 inhibits cAMP stimulation may be associated with red hair and impairs MC1R trafficking due to inhibiting phosphorylation of Thr155, but remains capable of activating ERK (Garcia-Borron et al., 2014).

Arg213Cys: Cys213 was found in *e+* Welsummers and San Diego zoo red junglefowl (Ellet 2000) but was found in *ey* (recessive wheaten) breeds (Davila et. al., 2014). I also found this polymorphism in Speckled Sussex that were supposed to be *ey* (unpublished sequence).

His215Pro: Pro215 was found in the *eb* brown allele of the Smyth Brown line (Ellet, 2000).

Cys264Gly: Gly or Ala at this position inactivates the receptor (Garcia-Borron et al., 2005).

Pro268His: His268 was found in green junglefowl (more eumelanic plumage) unpublished sequence.

Cys272Gly: Gly or Ala at this position inactivates the receptor (Garcia-Borron et al., 2005).

Asp291His: His291 inhibits cAMP stimulation and associated with red hair, but remains capable of activating ERK (Garcia-Borron et al., 2014).

Ser299: is a potential phosphorylation site (Garcia-Borron et al., 2014).

Thr305: is a potential phosphorylation site and may be involved in internalization and desensitization (Garcia-Borron et al., 2014).

Cys312Ala: Ala312 greatly impairs melanocortin binding sites and Gly312 completely inhibits receptor signalling (Garcia-Borron et al., 2014).

Ser313: is a potential phosphorylation site and may be involved in internalization and desensitization

(Garcia-Borron et al., 2014).

R1

MC1R/2R/MCa

Jawless Fish

MC4R/MCb

MC1R

MC2R/5R

MC3R

MC4R

MC2R

MC5R

R2

Figure 2. Phylogeny of the melanocortin receptors derived from Dores, 2013 and described in Ji et al., 2024. The R1 whole genome duplication event may have created two melanocortin receptor genes that had ACTH ligands (MCa and MCb found in Lamprey). The R2 whole genome duplication event produced the MCa duplication that became MC1R and MC2R/5R (later duplicated into MC2R and MC5R) and the MCb duplication that became MC3R, and MC4R.

hMC1R

MCa Lampetra

MCb Lampetra

hMC4R

hMC5R

hMC3R

hMC2R

bbMc4r like1

flMc4r like1

bbMc4r like2

scMc4r like

ciMc4r like

S1PR1

LPA1

CB2R

CB1R

Figure 3 is derived from Ji et al., 2024 Figure 1. The branch lengths are to scale, but the sequences are so short and so divergent that the branch points are not well supported. It just gives a basic idea of the relationships of the melanocortins with other G protein coupled receptors (GPCR) with 7 transmembrane domains. The Lamprey CMa and CMb receptors nest within the other melanocortins and this phylogeny does not support Figure 2, likely due to the half billion years of divergence between melanocortin receptors and evolution of new functions among the paralogs after the R2 whole genome duplication event. Even though the receptors took on new functions they had to retain ligand binding ability and the ability to form heterodimers with the other paralogs. Ji et al., found that the Mc4r like genes found in early chordate lineages could not bind ACTH ligands (derived from POMC), and likely were not melanocortin receptors. S1PR1, LPA1, CB2R, and CB1R are human GPCR genes that seem to be most closely related to the human melanocortin receptors (hMC1R, hMC2R, hMC3R, hMC4R, hMC5R). This phylogeny does indicate that the Mc4r like genes found in chordates may have had a more recent common ancestor with the melanocortin receptors than the other human GPCR genes used in the analysis, but these receptors did not bind melanocortin ligands.

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