

10

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CCRI      .....METPNTTEDYDVT. .... TEFDYGDATP.  QK
CCR2      ....MLSTSRSRFIRNTNE. .... SGEEVTTFFDYDYGAP.  HK
CCR3      ....MTTSLDVTETFGTT. .... SYDD. VGLL.  EK
CCR4      .....MNPTDIADTTLDESI. .... YSN... YYLYESIPKP.  TK
CCRS      .....MDYQVSSPIYDIN. .... YVTSEP.  QK
CCR6      .....MSGESMNPSSDVFDSS. .... EDYFVSVNTSYYSVDSEMLL  SL
CCR7      MDLGKPMKSVLVVALLVIFQVCLQDE. .... VTDDYIGDNTVDYTLFESL  SK
CCRS      .....MDYTLDLSTVTVD. .... YYPDIFSSP.  DA
CCR9      .....MTPTDFTSPIPN...MADDY. .... GSESTSSMEDYVNFNFTDFY  EK
CCR10     ....MGTEATEQVSWG. .... HYSGDEEDAYSAPLPPEL  YK
CXCR1     .....MSNIITDPQMWDFD. .... DLN... FTGMPAEDYSP  ML
CXCR2     .....MEDFNMESDSFEDFWKGE. .... DLSNYSYSTLPFPFLDAAP  EP
CXCR3     ....MVLEVSQDQVLNDAEVAALLENFSSSYDYGENESDSCTSP.  PQ
CXCR4     ....MEGISYTSNDNYTEEM. .... G..... SGDYDSMKEP.  FR
CXCR5     ....MNYPLTLEMDLEN. .... LEDLFWELDRLDNYNDTSLVENHLCPA  EG
CCR6      .....MAEH. .... DYHEDYGFSSFMDSSQEE.....  H
CXCR1     .....MESSGNP ..... ESTTFEYDLQSQP .....  CE
CX3CR1    ....MDQFPESVTEN..... FEYDDLAEA.  YI
ACKR1     ....MGNCLHRAELSPSTENSSQLDFEDVWN..... SSYGVNDSFPDGDYGANLEA  AP
ACKR2     ....MAATASPOPLATEDA..... DSENSSFYYDYLDVAFML  RK
ACKR3     .....MDLHLFDYSEFGNFS..... DISWPCNSSCIIVDTVM  FN
ACKR4     .....MALEQN...QSTDY..... YYEENE.MNGYDYYSQVELI  IK
ACKRS     ....MANYTLAPEDEYDVLI. .... EG.... ELESDEAEQ.  DK
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30

70

80

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CCRI      VNERAFGAQ ..... YERLKNMTSITLLNLATSLLFL
CCR2      FDKQIGAQ ..... CRKLKCLTDIYLLNLATSLLFL
CCR3      ADTRALMAQ ..... YERLRIMTNIYLLNLATSLLFL
CCR4      EGIKAFGEL ..... FV
CCRS      INVQIAAR ..... FL
CCR6      QEVRFQSRRL ..... FV
CCR7      KDVRFKAW ..... FV
CCRS      ELIQNKGL ..... FV
CCR9      NNVRQFASH ..... FL
CCR10     ADVQAFSRA ..... LA
CXCR1     .ETETLNKY ..... FA
CXCR2     .ESLEINKY ..... FA
CXCR3     DFLNEPORA ..... LW
CXCR4     EENANFNKI ..... FV
CXCR5     PLMASFKAV ..... V
CXCR6     QDFLQFSKV ..... FA
CXCR1     NQAWVFATL ..... FV
CX3CR1    GDVVVFGTV ..... FV
ACKR1     CHSCNLLDD ..... FS
ACKR2     DAVVSFGKV ..... FL
ACKR3     MPNKSULLYTLFSFY ..... AAKTTGYDTHCYILNLAIADLWVV
ACKR4     EDVREFAKV ..... YKKQRKTDVYILNLAVADLLL
ACKRS     YDAQALSAQ LNP SLCSAVFVIGVLDNLVLVLI LNK... YKGLKRVENIYLLNLAVSNLCFL
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90

100

110

3

14

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CCRI      FTLPFWITDYKDKD.DWVFGDAMCRITLSGFYYTGL:: IFFIHLMLDML RMI vHA9FAL.
CCR2      ITLPFWAHSAN..EWFVGNAMCKLFTGLYHIGYFGGIFPIILLTIDRYLAI VHA9FAL.
CCR3      VTLPFWIHVVRGH.NWVFGHGMCKLLSGFYHTGLYSEIFFIILLTIDRYLAI VHA9FAL.
CCR4      FSLPFWGYYAAD..QWVFGGLGCMISWMYLVGYSGIFF ML SIDRYLAIVHA9FAL.
CCRS      LTPFWAHYAJA..QWDFGNIMCOLLTLGYFI GFSGIFFIILLTIDRYLAV VHA9FAL.
CCR6      LTLPFWAYSHAATG.AWVFSNATCKLLKGIYAINF CG LLLTCISMDRYAIAVQATKSEF.
CCR7      LTLPFWAYSAAKS..WVFGVHFCKLIFAIYKMSF SG LLLCISIDRYVAIVQAVSAHR.
CCRS      FSEPFQTYLLLD..QWVFGIVMCKVVSGFYYIGFYSS FEIT SVDRYLAVHVA9FAL.
CCR9      VTLPFWAIAAADQ..WKFTQPMCKVNSMYKMNYSYSC LLIM SVDRYIAIAQAMRAHT.
CCR10     LTLPFAAAGALQG..WSLGSATCRITISGLYASFPHAGFLFLA SADRYVAIARAIPAG.
CXCR1     LTLPFWAASKVNG..WIFGTFLCKRVVSLKEVNIFYSGILLLA SVDRYLAIVHA9FAL.
CXCR2     LTLPFWAASKVNG..WIFGTFLCKRVVSLKEVNIFYSGILLLA SVDRYLAIVHA9FAL.
CXCR3     LTLPFWAVDAAVQ..WVFGSGLCKRVAGALFNIFYAG LLLA SFDRYLNIVHA9FAL.
CXCR4     ITLPFWAVDAVA..NWYFGNFLCKAVHVIYTVNLVYS LLLA SLDRYLAIVHA9FAL.
CCRS      FTLPFAVAEGSVG..WVLGTFLCKRVVSLKEVNIFYSGILLLA AVDRYLAIVHA9FAL.
CXCR6     CTLPFWAYAGTHE..WVFGQVMCKSLGTYTINFYTS LILT TVDRFIVVKA9FAL.
CXCR1     CLLPFWMISPYHW..GWVLGDFLCKLLNMIFSIISLYSSIFFLT TIHRYLSVVSPLSTL.
CX3CR1    ATLPFWITHYLIN..EKGLHNAMCKFTTAPFFIGFFGSIFFIT SIDRYLAIVLA9FAL.
ACKR1     IVVPVLAPGLST..|.RSSALCKSLGYCWWYGSAFAQ LLLG ASLGHRLGAGVPGSL.
ACKR2     VTLPFWGLSVNAW..HWVFGSFLCKVWSTLYTINIFYSGIFFTS SLDRYLAIVHA9FAL.
ACKR3     LTLPFWVVSVOHNOVPMGELTCXVTHLTFISINLFGSIFFLT SVDRYLSITVNT.
ACKR4     FTLPFWAVNAVHG..WVLGKIMCKRITISALYTLNF SG QPLACISIDRYVAIVKVP SQSG.
ACKRS     LTLPFWAAR..|.AGSDPMCKRITIGLYFVGLYSETFF CLITV RYIVELHKG NFF.
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CCRI RAR.TVTFGVTSITIAADALLASMPGLVFSKTQWEFTHHTCS...LHFPHESLREWKLF
CCR2 RAR.TVTFGVTSITITWLVAVFASVFPGLIFTKCKEDSVYVCG...PYFPFG.....WNNF
CCR3 RAR.TVTFGVTSITITWLVAVFASVFPGLIFVETEELFEETLCS...ALYPEDTVYSWRHF
CCR4 RAR.TVTFGVTSITITWLVAVFASVFPGLISTCYTERNHTYCK...TKYSLNS.TTWKVL
CCRS RAR.TVTFGVTSITITWLVAVFASVFPGLISTCYTERNHTYCK...SH.FFY.SQIQFKNF
CCR6 LRSRTLPFSKHTICLVVIGLSTVITSSSTFVNQKYNTOGSDVCEPK.YQTVS.EPIRWKLL
CCR7 HRARVLLISKLSGVGHTILATVLSIPELL.SDLQSSSEQAMRCS.LIT.EHVEAFIT
CCRS KVR.TIRMGTTLCCLAVWLTAIMATIPLLVFYQVASEDGVLCQY...SFYNQOTLKWKIF
CCR9 WREKRLLYSKMVCFTITWLVAAALCIPELL.SQKEESG...IAICT.MVYPSDESTKLKSA
CCR10 PRPSTPGRARHLVSVITWLLSLLALPALLFS.QDQOREGQR.RCRLIFPEGLTQTVKGA
CCR1 QKRRLV...KFCVLCGCGLSMNLSPFLFLPQAYHP...NNSSPVC.YEVLGNDTAKWMV
CCR2 QKRRLV...KFCVLCGCGLSMNLSPFLFLPQAYHP...NNSSPVC.YEVLGNDTAKWMV
CCR3 RR.GFPARVTITCLAVWGLCLLFAIPDFITLSAHHDERLNAT.HCQYNFP.QVGRTA
CCR4 RPR...AEKVVYGVVWIPALLLTI.PDFIFANVSEADRYICDR,...FYPNDLWVVV
CCR5 RHRR...IHTTCGTITWLVGFLALP...
CCR6 QQAK.WGKVTSLITWISLVLSLFP...
XCRI RVP.TLRCR.VLVMTAAVVASILLSSILDTI.....COYS.ELTWYLT.FTKQKENE
CX3CR1 NNR.T.QHGVTISLGVAAAILVAAPOFM...CLG.....DYPEVLQEIWVPL
ACR1LGLTVGIVGVAALLLPLVTLASGASGG.....LCTLI
ACR2 RLR.T.AKS.LLLATIVWAVSLAVSIFDMVFOTHENPKGVWNCH...ADFGHGHTIWKLF
ACR3 .SSRKMRV.RVVCILWLLAFVSLPDTMY.LKTVTSASNNETVCR.SFVPESTIKEWLIG
ACR4 VEGP...CWICPCVMAAILLSIPQLVYVVDNAR...CI.PIFPRVLGTSMLK
ACKRS SARRR.PCG.I.TSMVLAWVTAJLLATLEEFVWKPMEDQKYKCAFSRTFFLPADETFWKHF

CCRI QALKLNDLGLVFLVMTICVGTGIRILDRPNEKR.SKAVRLIFVIMIIFLFWITDYNL
CCR2 HTLMR.LRCRNEKKRHRAVRVIFTIMVVFLEWTPYNI
CCR3 HTLMR.LL.M.ICYTGIKTLRLCPSK.YKAILIFVIMAVFFIFWITDYNV
CCR4KMIFAVVVFLGFWITDYNL
CCRS ::::IVYFLEWA
CCR6 MLGLELLFGFFIPLMFICYTFIVKTLVQAQNS.HKAI.LVFL.C.II-HNM
CCR7 IOVQCM.TGFL.VII.TLQARNF.NKAI.VVFT.FQL'YNG
CCR8 TNFKMNLGLL.RCQNH.TKAI.TASLLFIWV.FNV
CCR9 VLTCLKVILIGFF.QAKKS.HKAL.TVEVLSQF.YNC
CCR10 SAVAQV.LG.A.AA.RG.RRAL.AAF.LQL.YSL
CCR1 LRLPHTFIFGI.KAHMG.HRAM.LIFL.C.L.YNL
CCR2 ::::!
CCR3 ::::!
CCR4 ::::!
CCR5 ::::!
CCR6 VLATOMTIGFF.HAGGF.HRSV.OVFLFG.FNF
XCRI SVIQHNEFI.FL.RSRSK.HRTV.OVFLFG.FNF
CX3CR1 ::::!
ACR1 ::::!
ACR2 ::::!
ACR3 ::::!
ACR4 ::::!
ACKRS ::::!

260 270 280 290
CCRI TILTSVFDQFLFTH...EQSRHDLAVQVTE
CCR2 VILLNTFQEFFGLSN...CEST.S
CCR3 AILLSSYQSILFGND...CERS.K
CCR4 VLPSTILVEVLQD...CTFER
CCRS VILLNTFQEFFGLNN...CSS.SN
CCR6 VLLVTAAN.LGKMNR.S.CQSEK
CCR7 VVLAQIVANFNITSST.CELSK
CCR8 VLFITSLHSMHILDG...CSISQ
CCR9 I.L.O.IDAYAMFISN.CAVST
CCR10 ALLDTADLLAARERS.CEASK
CCR1 ::::!
CCR2 ::::!
CCR3 V.L.DILMDLGALARN.CGRES
CCR4 GISIDSPILLEIKQ.CEEN
CCR5 VIFLD.LARLKAVDNT.CKNG
CCR6 F!IRSTHWEYYAMT.....
XCRI T!FLQTLFRTQI.I.RS.,.CEAKQ
CX3CR1 MIFLETILKLYDFFPS...CDMRK
ACR1 VLGLDFLVRSL.LL.LSTCLAQO
ACR2 TPLTHHLLDQVGN...CEVSQ
ACR3 A.LLDIFSILHYIPT.CRLEH
ACR4 V.FCIR.IDIYSLITS.CNMSK
ACR5 AFFLSTFKEHFSLSL...CKSSY

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          320          330          340          350
CCR1  FRRVA.....VHLVKWLPFLSV...DRLRVSSSTS.PSTGEHELASAGF....
CCR2  LGCRIAPLQKPVCGGPGVRPGKNVKVTTQGLDGRGKGSIGRAPEASLQDKEGA....
CCR3  FRRHLL.....MHLGRYIPFLPS...EKLETTSSVS.PSTAEPELSIVF....
CCR4  FRTCRG.....LFVLCQYCGLLQIY...SADTFSSSYTQSTMDHDLHDAL....
CCR5  FQRHTA...KRFC.....KCCSIFQQ...EAPERASSSYTRSTGEQELSVGL....
CCR6  LKDLWCVRKKY.....KSSGFSACAGRYSENISRQTSSETADNDNASSFTM....
CCR7  FKDLGCLSQE.....QLRQWS...SCR.HIRRSSMSVEAETTTTFSP....
CCR8  FQKSCS.....QIFNYLGRQMPR...ESCEKSSSCQQHSSRSSSVVDYIL....
CCR9  LKNLGCISQA.....QWVSFT...RREGSLKLSSMLLETTSG.ALSL....
CCR10  LRGGSCFSGGQ.....PRRGCPRRPRLSS.CSAFTETHSLSDWN....
CXCR1  LAMHGLVSKKF.....LAR.....HRVTSYT.SSSVNVSSML....
CXCR2  LAIHGLISKDS.....LPK.....DSRPSFVGSSSGHTSTTL....
CXCR3  LLRLGCPN.....QRLQRPSSSRDRDSSWSESEASYSGL....
CXCR4  LTVSR.....GSSLKILSKGKRGHSSSVSTESESSSFHSS....
CXCR5  LTLGCTG.....PASLCQLFPWRSSLSSENAISLTTF....
CXCR6  VKDIGCLPYLG.....VSHQWK...SSEDNSKTPSASHNVEATSMFQL....
XCR1   LRQFWF.....CRLOAPSPASIPHSPGAFAYEGASY....
CX3CR1 YGKCLAVLCG.....RSVHVDSSSESQSRHGSVLSNFTYHTSDGDALLLL....
ACKR1  LP.....LPEGWSSSHLDTLGSKS....
ACKR2  LAAVLG.....WHLAPGTAQASLSSCSESSILTAQEEMTGMNDLGERQ
ACKR3  FIPKYS.....AKTGLTKLIDASRVSETEYSALEQSTK....
ACKR4  AKKYGSWR.....RQRO...SVEEFPFDSEGPTEPTSTFSI....
ACKR5  FHLSRN.....TPLQP.....RGQSAQGSTREEPDHSTEV....

CCR1  .....
CCR2  .....
CCR3  .....
CCR4  .....
CCR5  .....
CCR6  .....
CCR7  .....
CCR8  .....
CCR9  .....
CCR10 .....
CXCR1 .....
CXCR2 .....
CXCR3 .....
CXCR4 .....
CXCR5 .....
CXCR6 .....
XCR1  .....
CX3CR1 .....
ACKR1 .....
ACKR2  SENYPNKEDVGKSA
ACKR3  .....
ACKR4  .....
ACKR5  .....

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Figure S1. Sequence alignment of human chemokine receptors reveals conserved structural motifs and selectivity-determining regions. This figure presents a multiple sequence alignment of human CCR, CXCR, XCR, CX3CR, and ACKR family members. Conserved GPCR motifs—such as DRY, CWxP, and NPxxY—are retained across transmembrane domains, indicating their essential roles in signaling. In contrast, notable sequence divergence is observed in the N-terminal and ECL2 regions, which likely contribute to ligand specificity and offer potential targets for selective drug design.