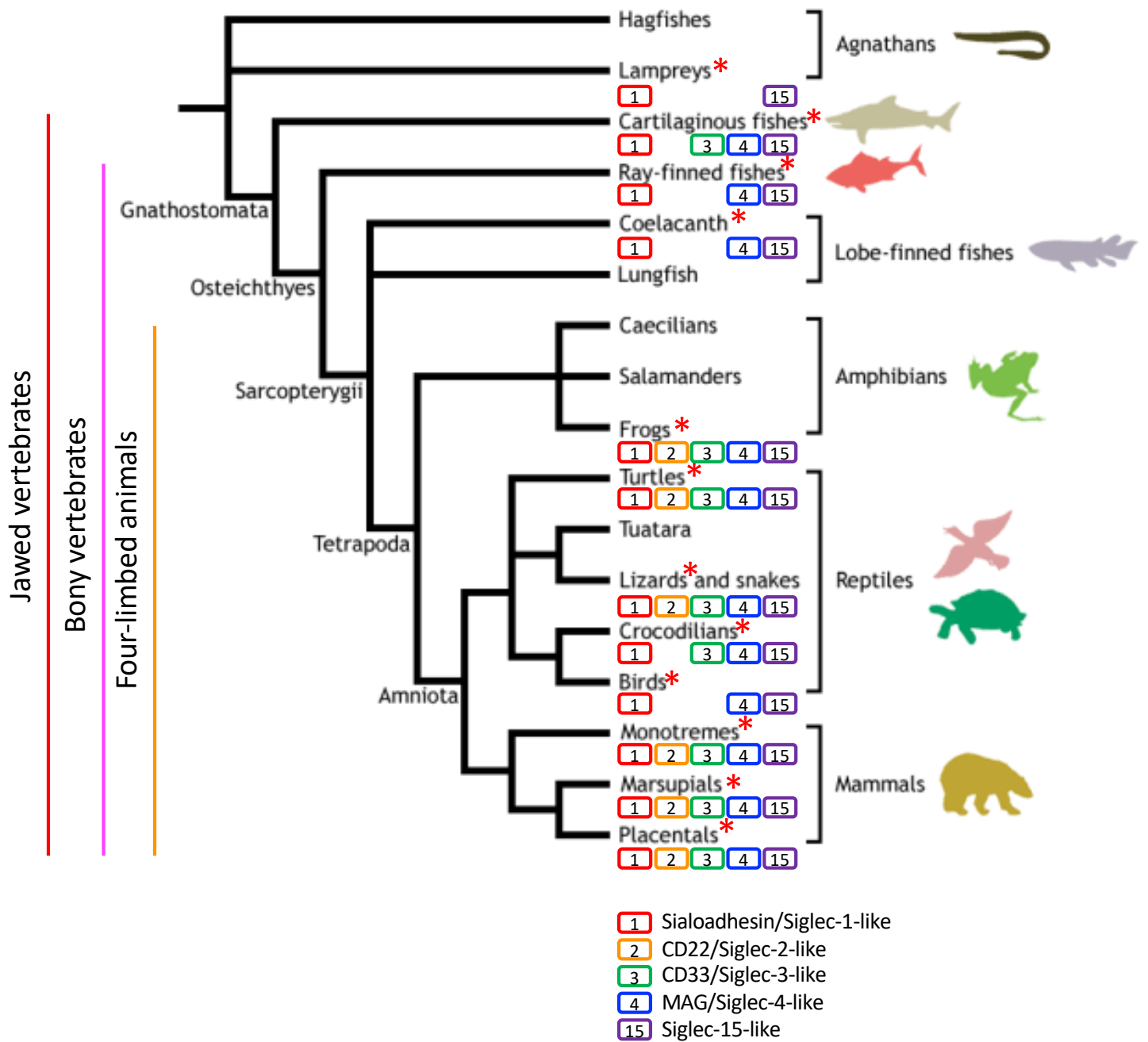


- Signal peptide
- Ig1
- Ig2
- * Essential Arg
- * Aromatic amino acid interacting with Sia
- ▽ Cys involved in inter-domain disulfide bond

Supplementary Figure 1. Alignment of human Siglecs.

Amino acid sequences of the N-terminal part (signal peptide – Ig1 – Ig2) of human Siglecs were aligned with ClustalO, and conserved residues (>70% consensus) are highlighted. Black shade: same amino acid; Gray shade: similar amino acids.



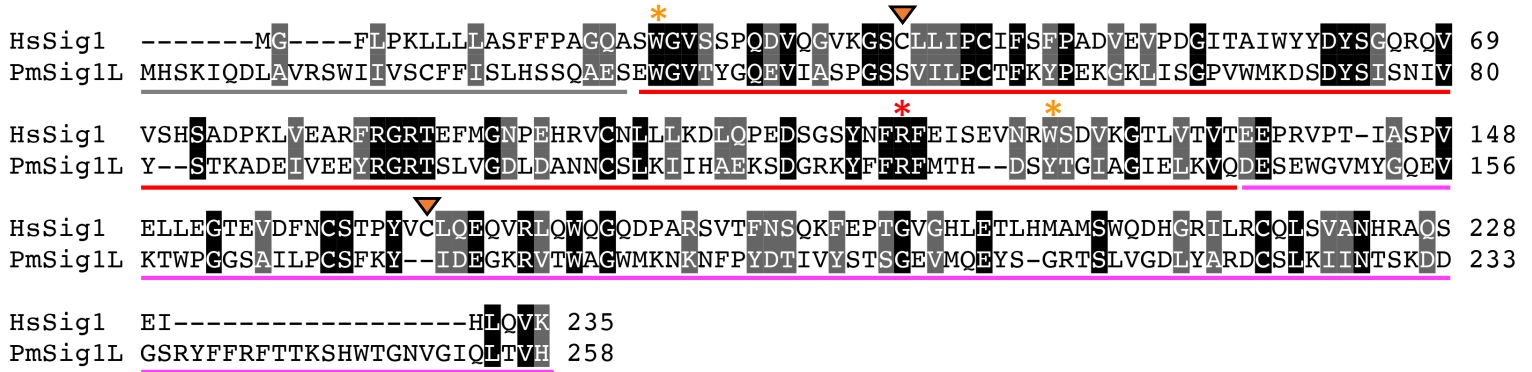
Supplementary Figure 2. Tree of vertebrate life and presence of Siglecs.

The phylogenetic tree of vertebrates is based on Meyer and Zardoya (2003) *Annu. Rev. Ecol. Evol. Syst.* 34:311–338, and was downloaded from University College London website (<https://www.ucl.ac.uk/museums-static/obl4he/vertebratediversity/index.html>).

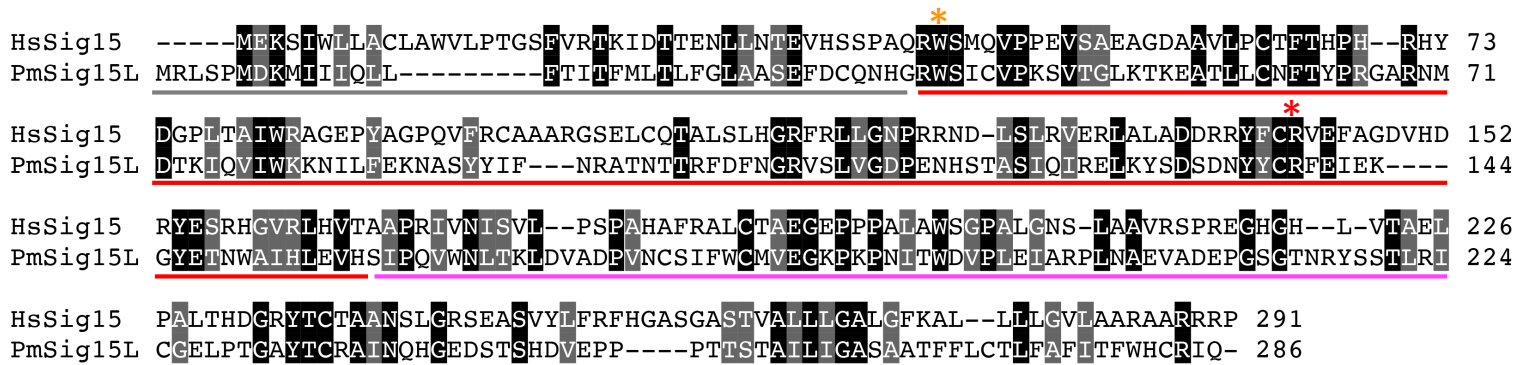
One or more of the species belonging to the clade indicated with red asterisk (*) were subjected to genomic DNA sequence survey for Siglec V-set (Ig1) domain-like sequence and mentioned in the main text.

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A



B



- Signal peptide
- Ig1
- Ig2
- * Essential Arg
- * Aromatic amino acid interacting with Sia
- ▼ Cys involved in inter-domain disulfide bond

Supplementary Figure 3. Alignment of putative lamprey Siglecs with human homologs.

Amino acid sequences of the N-terminal part (signal peptide – Ig1 – Ig2) of (A) human Siglec-1 (HsSig1) and lamprey homolog (PmSig1L), and (B) human Siglec-15 (HsSig15) and lamprey homolog (PmSig15L) were aligned with ClustalO, and conserved residues are highlighted.

Black shade: same amino acid; Gray shade: similar amino acids. GenBank accession number for Lamprey Siglec-1-like sequence: XM_032693083; Siglec-15-like sequence: XM_032963052.

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HsSiglec15 ----MEKSIWLLACLAWLPTGSFVRTKIDTTENLLNTEVHSSPAQRWSSMQVPPPEVSAEAGDAAVLPCTFTHPHRHYDGP 76
HsHAVCR2  MFSHLPFDCVLL---LLLLLL-----TRSEVEYRAEVGQNAYLPCFYTPAAPGNLVP 50
HsHAVCR1  -MHPQVVIIISLII---HLAD-----SVAGSVKVGGEAGPSVTLPCHYSG----AVTS 44
HsTIMD4   -MSKEPLILWLMIEFWWLYLT-----PVTSETVVTEVLGHRVTLPLCLYSSWS-HSNS 51

HsSiglec15 LTAIWRAGEPYAGPQVFRCAAARG-SELQOTALSLHGREFRLLGNPRRNDLSLRVERLALADDRRYFCRVEFAGDVHDRYE 155
HsHAVCR2  --VCWKGKA---CPVFECGNVVLRTDERDVNYWT-SRYWLNQDFRKGDVSLTIENVTLADSGIYCCRIQIIPGIMNDEK- 122
HsHAVCR1  --MCWNRGS---CSLFTCONGIWVINGTHVYRKDTRYKLLCDLSRRDVSLTIENTAVSDSGVYCCRVEHRCWFNDMK- 117
HsTIMD4   --MCWKGKQ---CPYSGCKEALIRTDGMRVTSRKSAKYRLQCTIPRGDVSLTIENPSESDSGVYCCRIEVPWFNDVK- 124

HsSiglec15 SRHGVRHVT- 165
HsHAVCR2  --FNLKLVIKP 131
HsHAVCR1  --ITVSLIIVP 126
HsTIMD4   --INVRLNLQR 133

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Supplementary Figure 4. Alignment of human Siglec-15 and related IgSF proteins.

Amino acid sequences of the signal peptide – Ig1 of human Siglec-15, TIM-1 (*HAVCR1*), TIM-3 (*HAVCR2*), TIM-4 (*TIMD4*) were aligned with ClustalO, and conserved residues (>70% consensus) are highlighted.

Black shade: same amino acid; Gray shade: similar amino acids.