Supplementary Materials for

Developmental constraint shaped genome evolution and erythrocyte loss in Antarctic fishes following paleoclimate change

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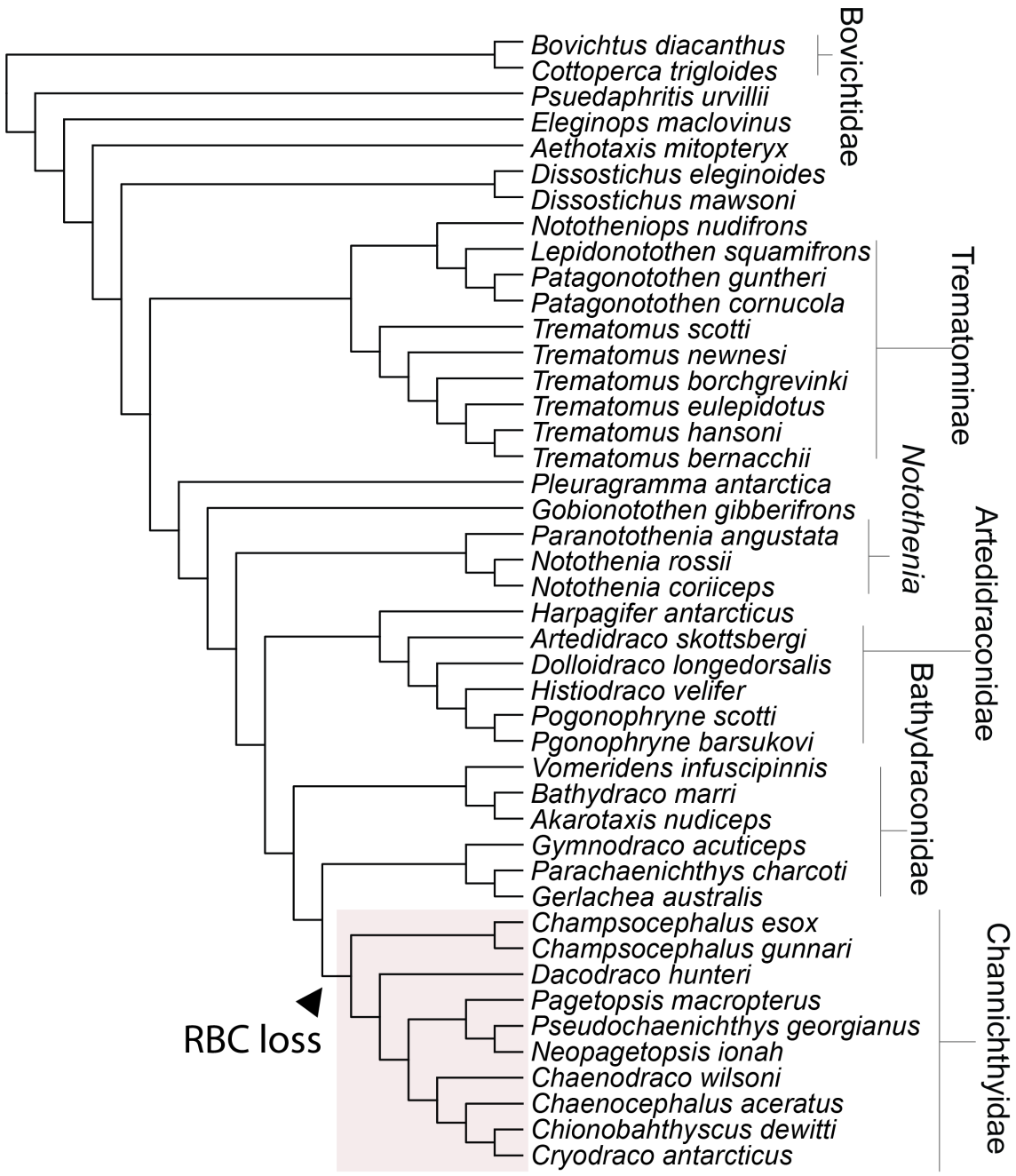
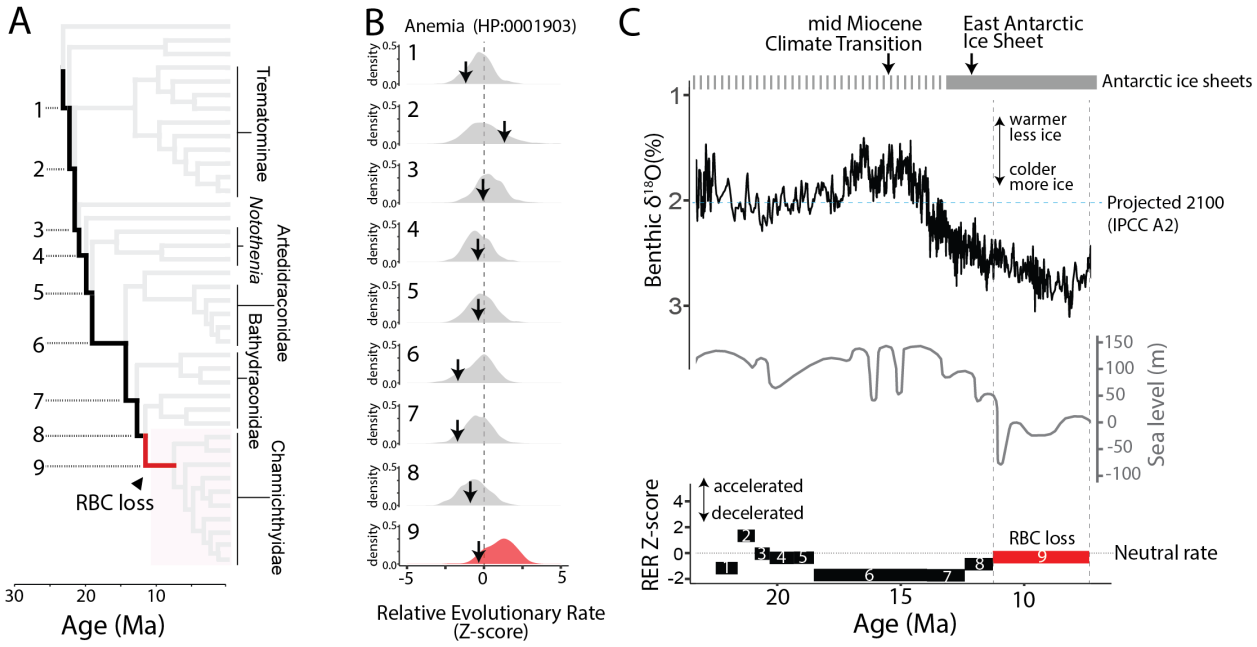
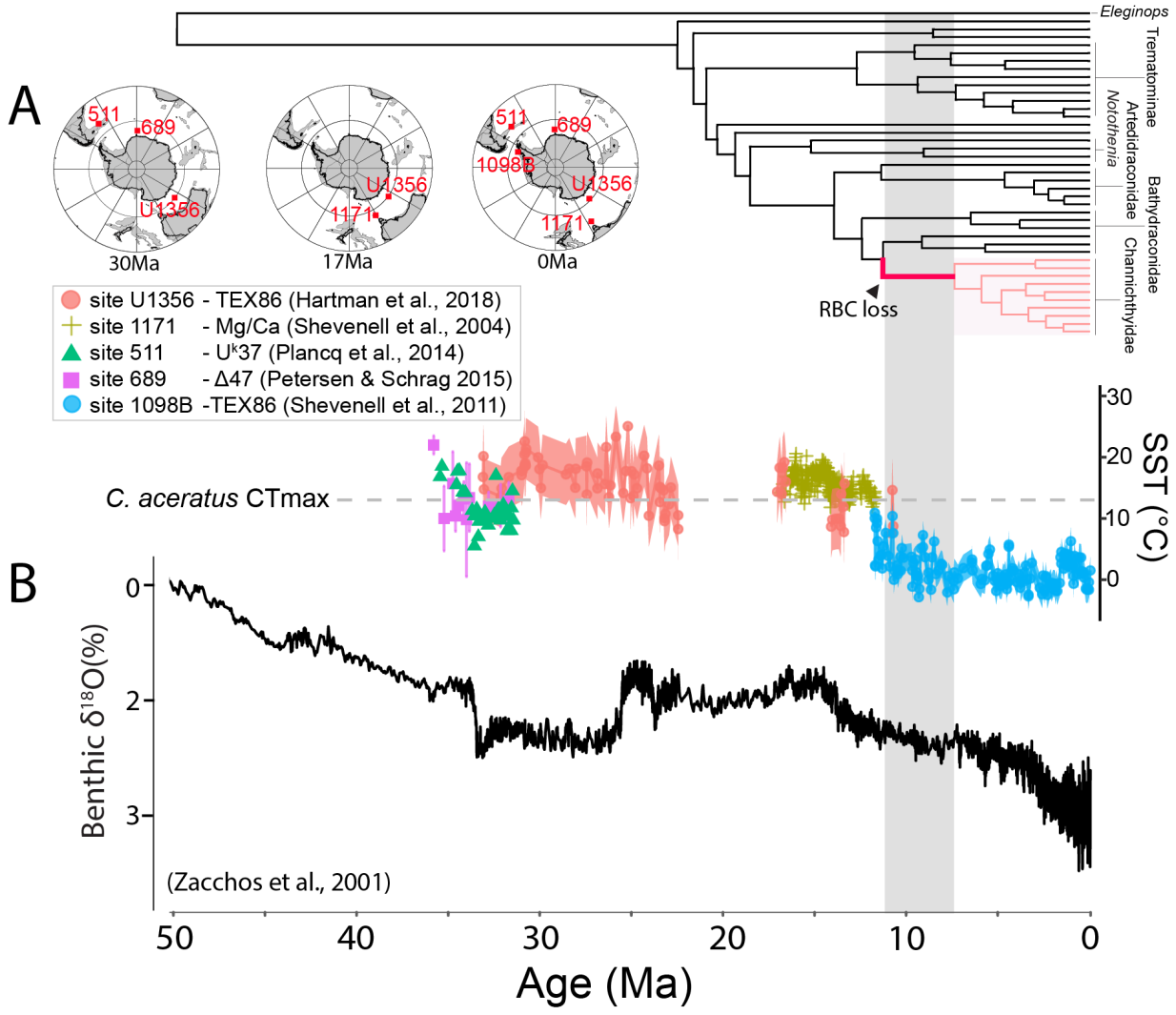


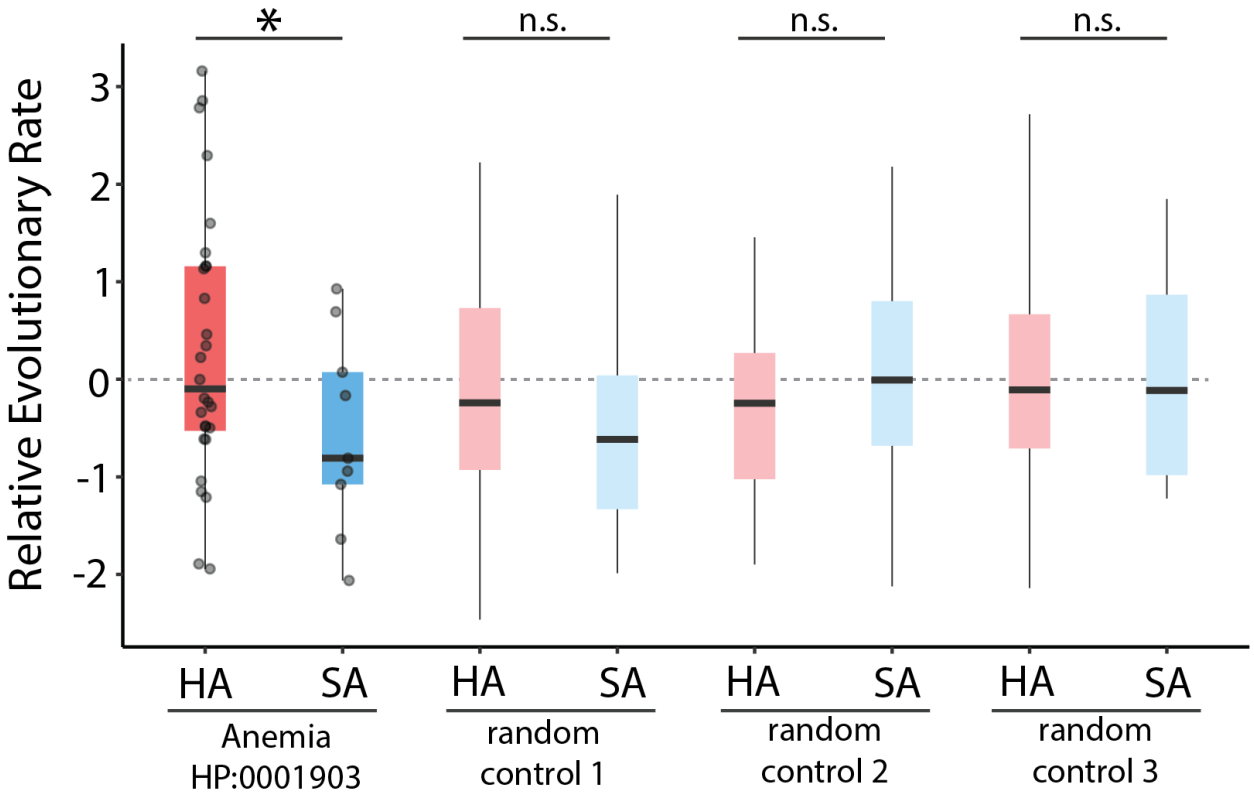
S1 Fig. Phylogeny of notothenioid species included in this study. Tree topology from Daane *et al*. (8). Phylogenetic relationships inferred from ASTRAL using 11,627 gene trees. All nodes in the phylogeny are supported by 100% quadpartition posterior probability. Asterisk (*) indicates position of red blood cell loss in the icefishes (Channichthyidae).



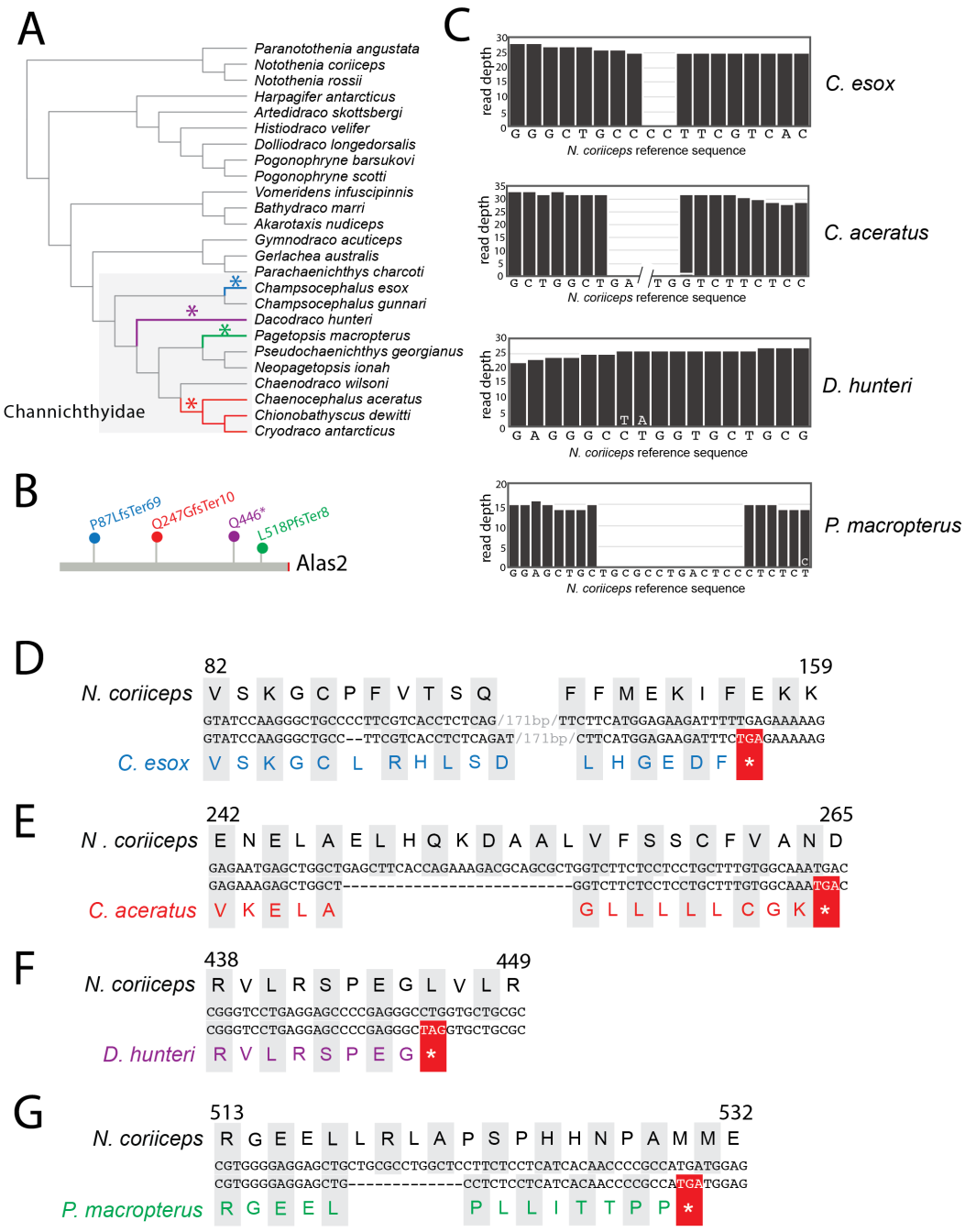
S2 Fig. Drift in coding sequences of anemia-associated genes did not follow erythrocyte loss or the decline in global temperatures. (**A**) Phylogeny of cryonotothenioids, highlighting the ancestral branches leading up to the loss of red blood cells (RBC) in icefishes (Channichthyidae). Numbers label branches in panels **B** and **C**. (**B**) Elevated relative evolutionary rate (RER) following loss of RBCs in icefishes. Distribution of Z-scores for average RER across groupings of genes. These genes were then clustered based on the Human Phenotype Ontology (HPO) (15). Arrow indicates position in histogram of the Anemia HPO term (HP:0001903). Z-scores > 0 are considered accelerated, while those < 0 have constrained evolution relative to the genome average. (**C**) Relative evolutionary rate across genes in icefishes following loss of RBCs and the fall of global temperatures remained steady. The five-point moving average of benthic δ18O ratios is adapted from Zachos et al. 2001 (17) and sea level estimations from Haq et al. 1987 (18).



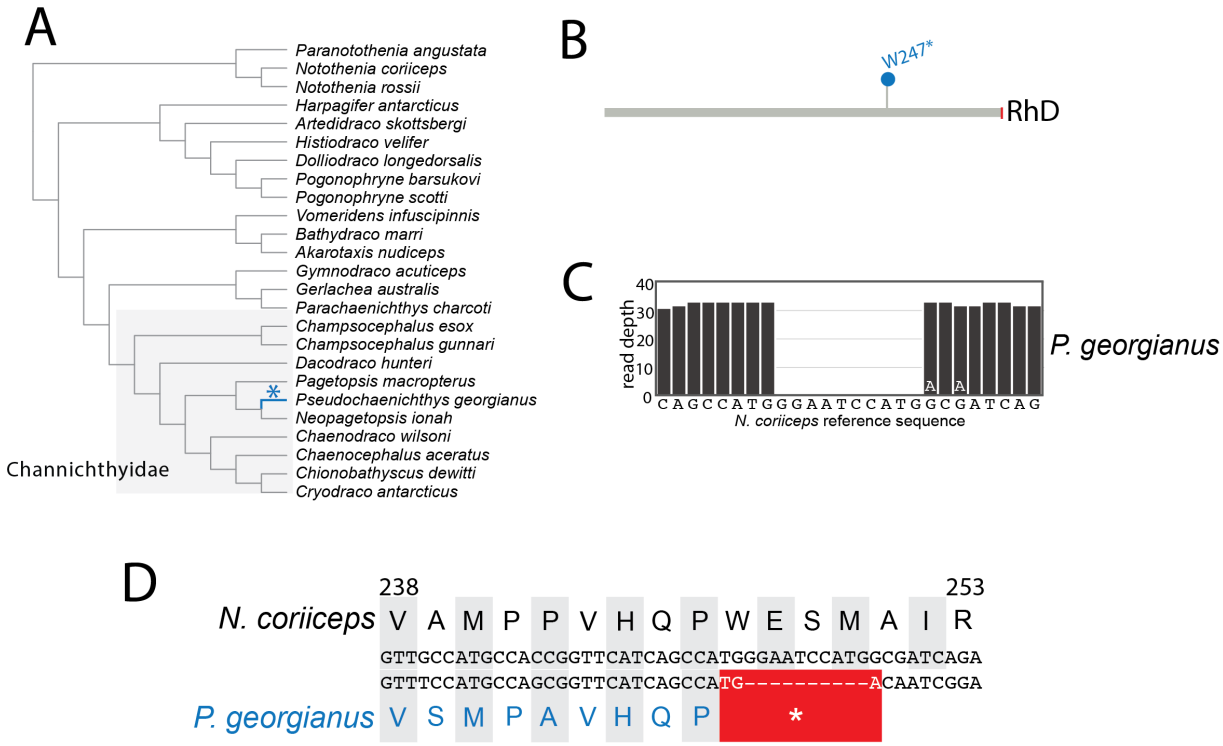
S3 Fig. Global and local paleo-temperature estimates and the loss of erythrocytes in icefishes. Overlay of time-calibrated phylogeny of cryonotothenioids and paleoclimate estimates shows loss of red blood cells (*, red branch) following decreases in global and local temperatures. (**A**) Sea surface temperature (SST) reconstructions from multiple Southern Ocean drill sites. Site location, SST method and citation are indicated in the inset. Modern and paleo drill site locations adapted from Hartman *et al.*, 2018 (ref), and mapped using the Ocean Drilling Stratigraphic Network Plate Tectonic Reconstruction Service (http://www.odsn.de/odsn/services/paleomap/paleomap.html). CT_{max} for the blackfin icefish, *Chaenocephalus aceratus*, is indicated by the dashed line. (**B**) The five-point moving average of global benthic $\delta^{18}O$ ratios is adapted from Zachos *et al.* 2001 (17). Higher $\delta^{18}O$ ratios indicate colder temperatures and more ice.



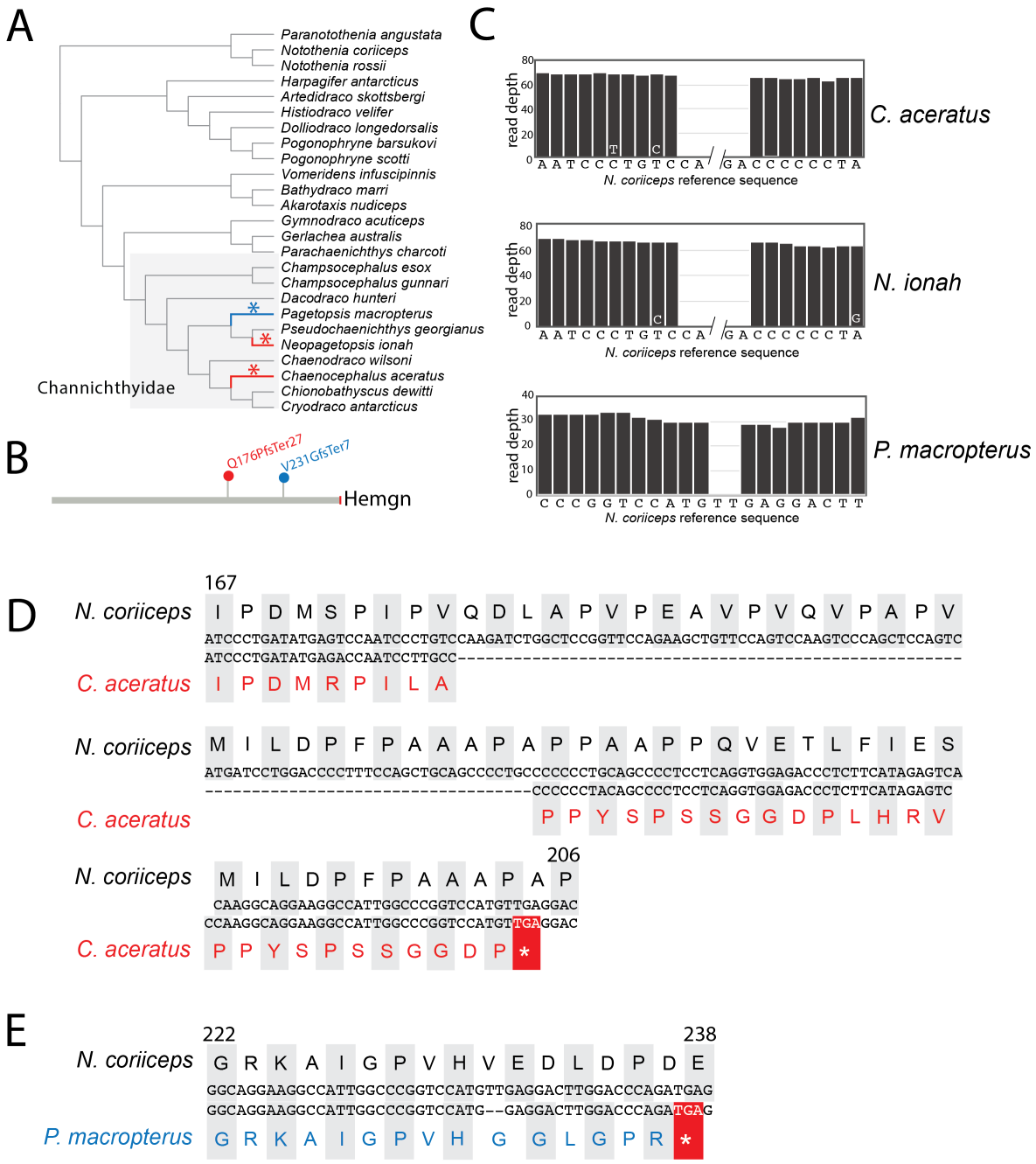
S4 Fig. Enrichment for elevated evolutionary rate in anemia-associated genetic regions compared to random gene sets. Three random sets of genes equal to the number of genes in HP:0001903 (n = 360) were created and the relative evolutionary rate between species distributed in the high-Antarctic (HA) and sub-Antarctic (SA) were compared. * indicates one-tailed t-test p-value < 0.05; n.s. is not significant.



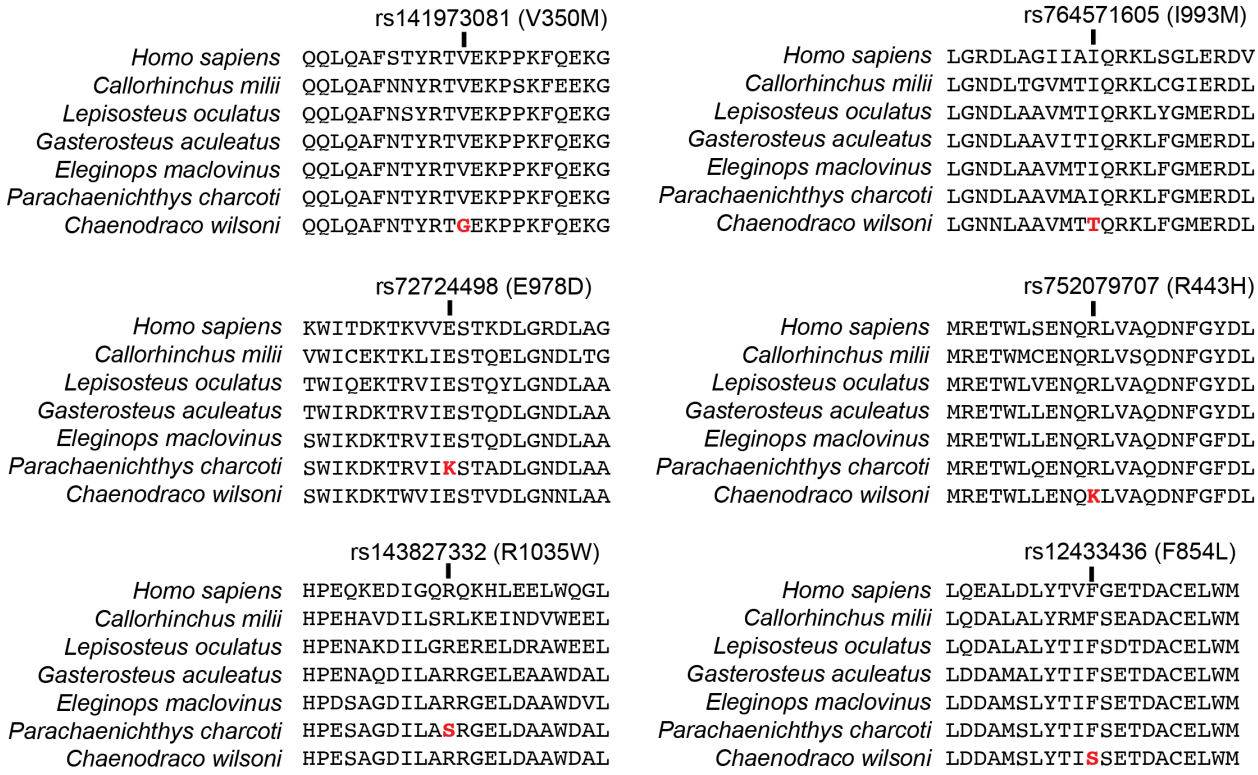
S5 Fig. Truncating mutations identified in icefish *erythroid-specific 5-aminolevulinate synthase* (*alas2*) gene. (**A**) Notothenioid phylogeny showing presence of truncating alleles (*) in four icefish species. (**B**) Mutant alleles; asterisk color corresponds to branches in **A**. (**C**) Sequencing read depth for each species aligned to the *Notothenia coriiceps* reference genome. Gaps in read depth correspond to deletions in each read relative to the reference genome. (**D-G**) The icefishes show distinct frameshifts and truncations in Alas2 compared to the *N. coriiceps* reference sequence. Alignment start/stop coordinates in D-G are based on position in the *N. coriiceps* genome assembly (XP_010782407.1).



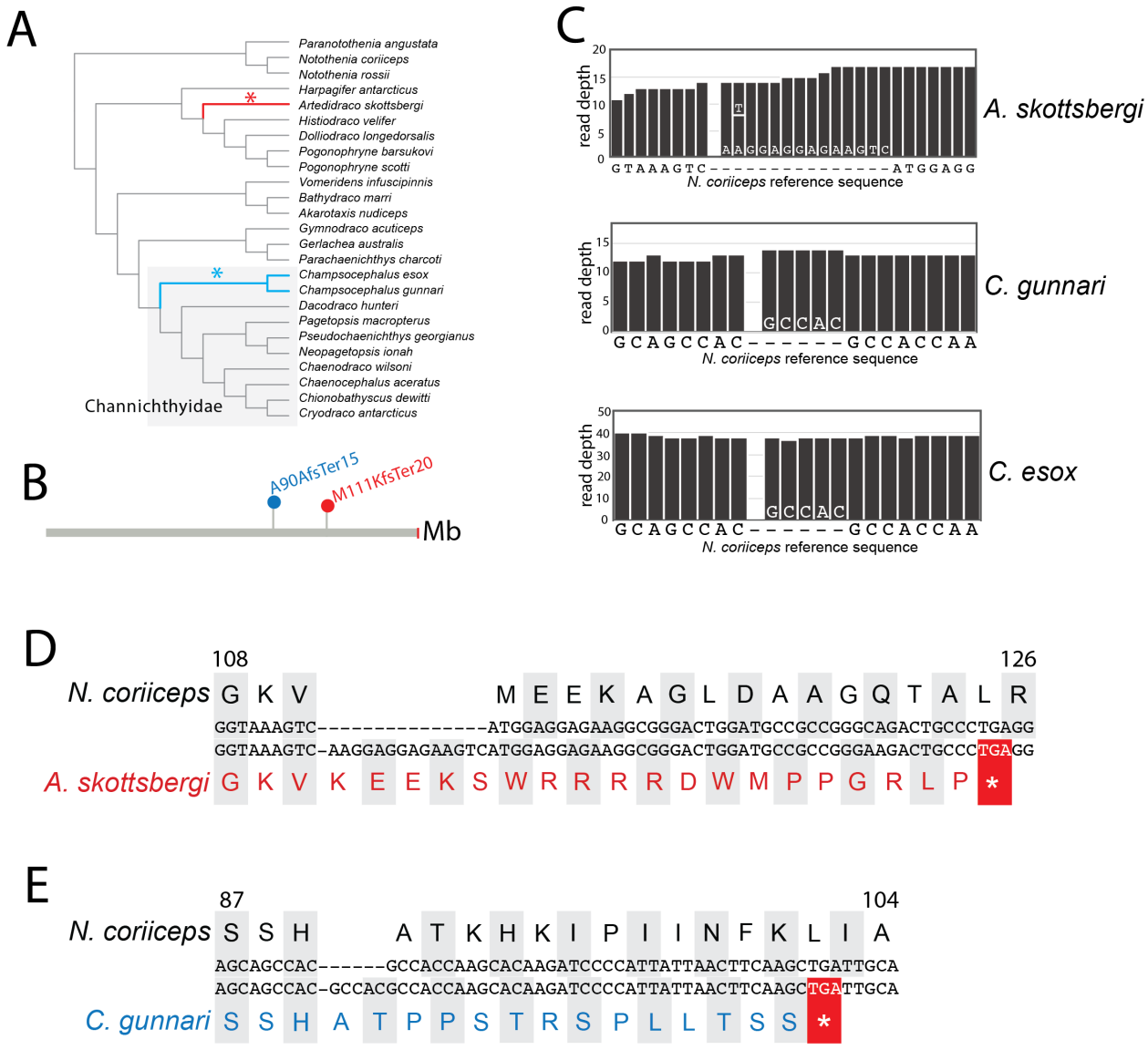
S6 Fig. Truncating mutation identified in *Pseudochaenichthys georgianus Rh blood group D antigen (rhd)* gene. (**A**) Notothenioid phylogeny showing presence of a truncating allele in *P. georgianus* (*). (**B**) The mutation encoded by the allele. (**C**) Sequencing read depth for *P. georgianus* as aligned to the *Notothenia coriiceps* reference genome. The gap in read depth corresponds to a deletion in each read relative to the reference genome. (**D**) *P. georgianus* shows a frameshift and truncation in Rhd compared to the *N. coriiceps* reference sequence. Alignment start/stop coordinates are based on position in the *N. coriiceps* genome assembly (XP_010782194.1).



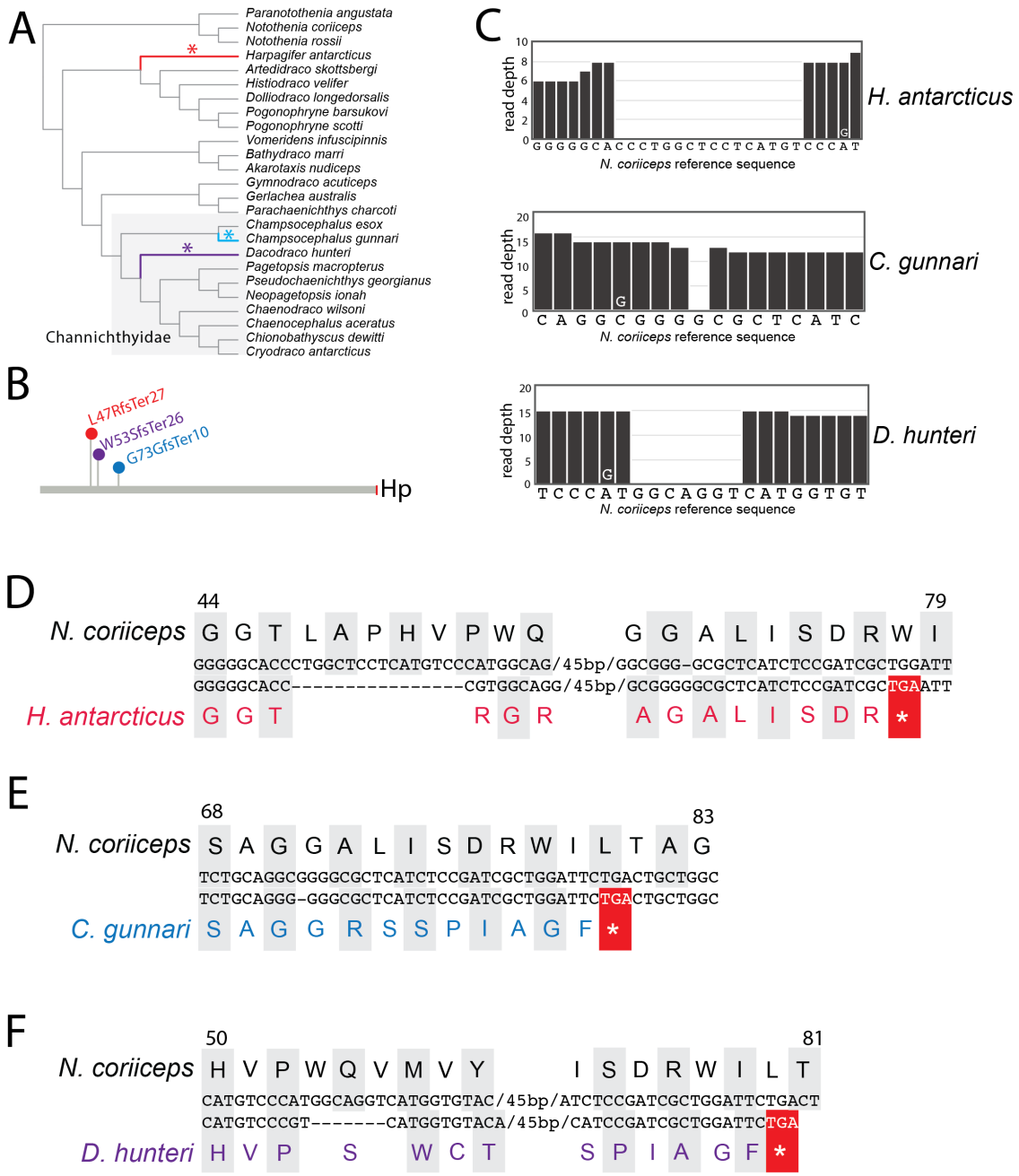
S7 Fig. Truncating mutations identified in icefish *hemogen* gene. (**A**) Phylogeny of the notothenioids showing the presence of truncating alleles (*) in three icefish species. (**B**) Mutant alleles; asterisk color corresponds to branches in **A**. (**C**) Sequencing read depth for each species aligned to the *Notothenia coriiceps* reference genome. Gaps in read depth correspond to deletions in each read relative to the reference genome. (**D**) *Chaenocephalus aceratus* and *Neopagetopsis ionah* show identical frameshifts and truncations in Hemgn compared to the *N. coriiceps* reference. (**E**) *Pageotopsis macropterus* shows a different frameshift and truncation. Alignment start/stop coordinates in **D** and **E** are based on position in the *N. coriiceps* genome assembly (XP_010773828.1).



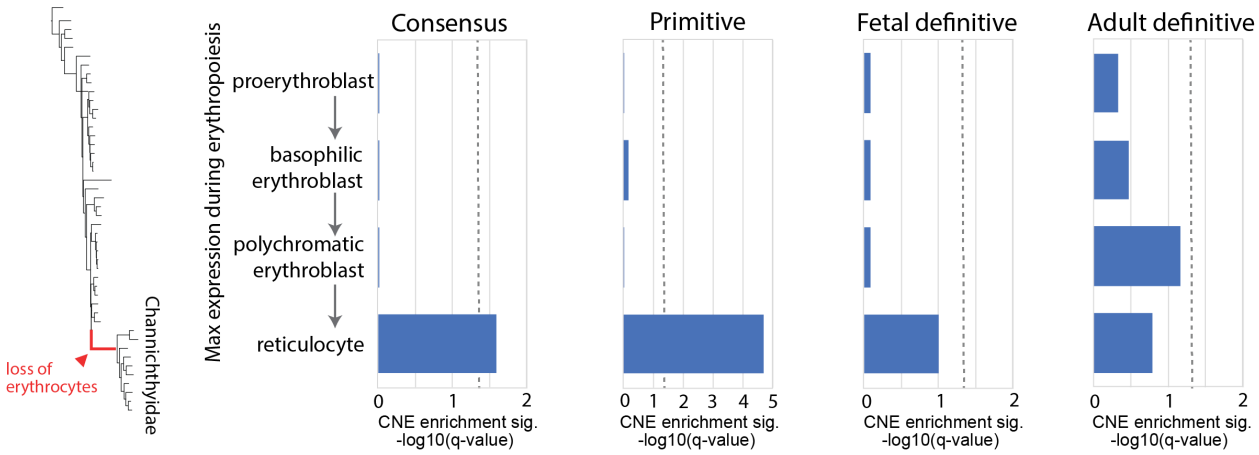
S8 Fig. Dragonfish and icefish mutations at highly-conserved and clinically-relevant sites in Beta-spectrin. Variant amino acid substitutions in Beta-spectrin of the dragonfish *Parachaenichthys charcoti* and a representative icefish *Chaenodraco wilsoni* highlighted in red. Beta-spectrin sequences for three-spined stickleback (*Gasterosteus aculeatus*), spotted gar (*Lepisosteus oculatus*), elephant shark (*Gallorhinchus milii*) and human (*Homo sapiens*) are provided for comparison. The dbSNP identifier (ClinVar) for deleterious variants found in human patients with spherocytic anemia/elliptocytosis are shown above each alignment.



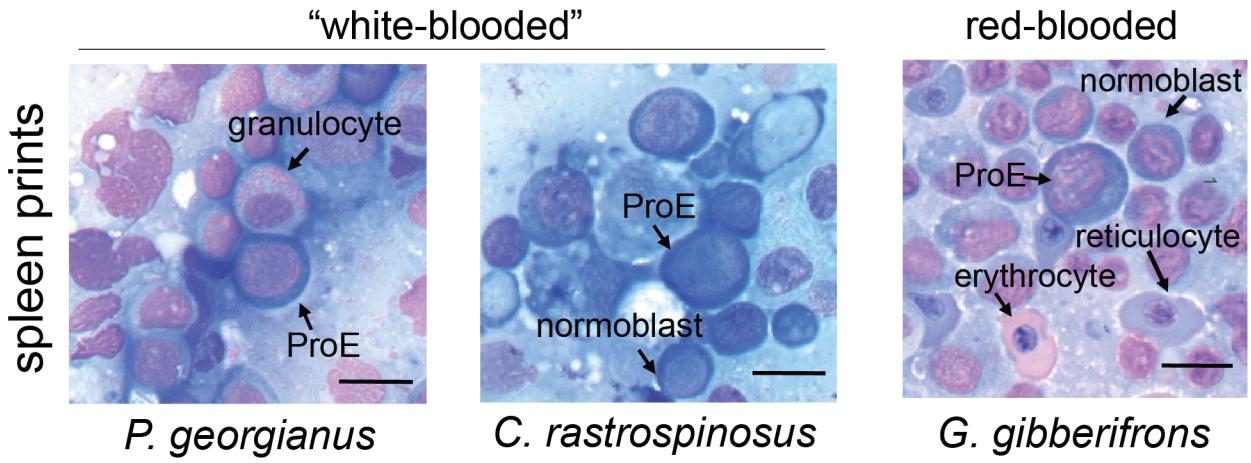
S9 Fig. Truncating mutations identified in notothenioid *myoglobin* gene. (**A**) Phylogeny of the notothenioids showing the presence of truncating alleles (*) in three species. (**B**) Mutant alleles; asterisk color corresponds to branches in **A**. (**C**) Sequencing read depth for each species aligned to the *Notothenia coriiceps* reference genome. Gaps in read depth correspond to deletions in each read relative to the reference genome. (**D**) Red-blooded species *Artedidraco skottsbergi* Mb compared to the *N. coriiceps* reference. (**E**) *Champsocephalus gunnari* and *C. esox* shows identical frameshifts in Mb. Alignment start/stop coordinates in **D** and **E** are based on position in the *N. coriiceps* genome assembly (NP_001290223.1).



S10 Fig. Truncating mutations identified in notothenioid *haptoglobin* gene. (**A**) Phylogeny of the notothenioids showing the presence of truncating alleles (*) in three species. (**B**) Mutant alleles; asterisk color corresponds to branches in **A**. (**C**) Sequencing read depth for each species aligned to the *Notothenia coriiceps* reference genome. Gaps in read depth correspond to deletions in each read relative to the reference genome. (**D**) Red-blooded species *Harpagifer antarcticus* Hp compared to the *N. coriiceps* reference. The icefish species (**E**) *Champsocephalus gunnari* and (**F**) *Dacodraco hunteri* have different frameshifts and truncations in Hp. Alignment start/stop coordinates in **D-F** are based on position in the *N. coriiceps* genome assembly (XP_010770321.1).



S11 Fig. Enrichment for accelerated sequence evolution in conserved non-coding elements (CNEs) near genes that are maximally expressed at distinct stages of erythropoiesis. Three waves of mammalian erythropoiesis are defined by distinct patterns of gene expression and (locations): primitive (yolk sac blood island), fetal definitive (liver) and adult definitive (bone marrow). For each erythropoietic wave, accelerated evolution of CNEs near maximally expressed genes is shown for four cellular stages of erythroid differentiation/maturation: proerythroblast, basophilic erythroblast/normoblast, polychromatic erythroblast/normoblast, reticulocyte. The Consensus is the intersection of maximally expressed genes across each the three erythropoietic waves. Dashed line corresponds to q-value of 0.05. Gene expression data from ErythronDB [*42*].



S12 Fig. Spleen prints from three notothenioid species: Wright/Giemsa-stained. Two "white-blooded" icefishes, *Pseudochaenichthys georgianus* and *Chionodraco rastrospinosus*, show the presence of erythroid progenitors [proerythroblasts (ProEs) and normoblasts] but lack later stages of maturation (e.g., reticulocytes, erythrocytes). By contrast, the red-blooded notothen, *Gobionotothen gibberifrons*, displays the complete erythropoietic progression: ProE → normoblast → reticulocyte → erythrocyte. Scale bar = 10 μm.

S3 Table. Relative evolutionary rate and notothenioid biogeography

Distribution†	Species	Family	RER‡
HA	*Pogonophryne barsukovi*	Artedidraconidae	3.160
HA	*Pagetopsis macropterus*	Channichthyidae	2.856
HA	*Histiodraco velifer*	Artedidraconidae	2.783
HA	*Trematomus bernacchii*	Nototheniidae	2.293
HA	*Dacodraco hunteri*	Channichthyidae	1.599
HA	*Vomeridens infuscipinnis*	Bathydraconidae	1.297
HA	*Neopagetopsis ionah*	Channichthyidae	1.163
HA	*Trematomus newnesi*	Nototheniidae	1.155
HA	*Pleuragramma antarctica*	Nototheniidae	1.133
sub-Antarctic	*Cottoperca trigloides*	Bovichtidae	0.927
HA	*Trematomus eulepidotus*	Nototheniidae	0.829
sub-Antarctic	*Paranotothenia angustata*	Nototheniidae	0.692
HA	*Chaenodraco wilsoni*	Channichthyidae	0.460
HA	*Trematomus hansoni*	Nototheniidae	0.344
HA	*Akarotaxis nudiceps*	Nototheniidae	0.224
sub-Antarctic	*Bovichtus diacanthus*	Bovichtidae	0.073
HA	*Cryodraco antarcticus*	Channichthyidae	-0.002
sub-Antarctic	*Champsocephalus esox*	Channichthyidae	-0.167
HA	*Parachaenichthys charcoti*	Bathydraconidae	-0.195
HA	*Pogonophryne scotti*	Artedidraconidae	-0.234
HA	*Aethotaxis mitopteryx*	Nototheniidae	-0.280
HA	*Trematomus borchgrevinki*	Nototheniidae	-0.339
HA	*Notothenia coriiceps*	Nototheniidae	-0.477
HA	*Gerlachea australis*	Bathydraconidae	-0.487
HA	*Trematomus scotti*	Nototheniidae	-0.499
HA	*Dissostichus mawsoni*	Nototheniidae	-0.612
HA	*Lepidonotothen squamifrons*	Nototheniidae	-0.617
sub-Antarctic	*Patagonotothen guntheri*	Nototheniidae	-0.810
sub-Antarctic	*Patagonotothen cornucola*	Nototheniidae	-0.942
HA	*Bathydraco marri*	Bathydraconidae	-1.044
sub-Antarctic	*Dissostichus eleginoides*	Nototheniidae	-1.078
HA	*Chionobathyscus dewitti*	Channichthyidae	-1.152

Distribution†	Species	Family	RER‡
HA	*Gymnodraco acuticeps*	Bathydraconidae	-1.210
sub-Antarctic	*Eleginops maclovinus*	Eleginopsidae	-1.639
HA	*Dolloidraco longedorsalis*	Artedidraconidae	-1.893
HA	*Artedidraco skottsbergi*	Artedidraconidae	-1.943
sub-Antarctic	*Pseudaphritis urvillii*	Pseudaphritidae	-2.063

† HA - high latitude Antarctic

‡ Relative evolutionary rate across all conserved non-coding elements flanking human anemia-associated genes (HP:0001903)

S4 Table. Coverage and mutations in candidate erythrocyte genes

Ensembl ID	Gene Name	Type	Avg Coverage†	Avg Coverage Icefish†	FE marrow	FE erythrocytes	Pleiotropy Score	Truncating variant (s) ‡
ENSGACG00000006807	Alas2	heme and hemoglobin biosynthesis	97.8%	100.0%	6.58	2.09	0	✓
ENSGACG00000001091	Dmtn	cytoskeleton	91.2%	94.1%	0.37	6.30	0	
ENSGACG00000017373	Hemgn	development/transcription factors	95.7%	100.0%	1.61	5.18	0	✓
ENSGACG00000013918	Hbb	heme and hemoglobin biosynthesis	78.9%	13.0%	8.59	2.70	0	✓
ENSGACG00000014492	Hba	heme and hemoglobin biosynthesis	81.0%	37.2%	4.99	2.56	0	✓
ENSGACG00000009865	Rhag	membrane proteins and solute transporters	71.9%	73.7%	23.77	6.82	0	
ENSGACG00000015628	Gypc	cytoskeleton	81.6%	100.0%	1.37	1.72	0	
ENSGACG00000007369	Rhd	membrane proteins and solute transporters	94.3%	98.4%	5.54	8.88	0	✓
ENSGACG00000007574	Slc25a28	membrane proteins and solute transporters	96.8%	99.8%	0.58	0.32	0	
ENSGACG00000001549	Tfcp2	development/transcription factors	96.1%	99.5%	0.16	0.69	0	
ENSGACG00000009512	Eif2ak1	heme and hemoglobin biosynthesis	73.6%	74.5%	0.49	1.69	1	
ENSGACG00000007530	Slc25a38	membrane proteins and solute transporters	96.1%	100.0%	0.54	3.16	1	
ENSGACG00000007468	Car6	carbonic anhydrases	97.8%	100.0%	0.00	0.25	1	
ENSGACG00000007890	Car3	carbonic anhydrases	74.8%	80.9%	0.00	0.18	1	
ENSGACG00000016482	Hmgb2	development/transcription factors	95.5%	100.0%	3.16	0.78	1	
ENSGACG00000002257	Kdm1b	development/transcription factors	97.8%	100.0%	0.40	0.13	1	
ENSGACG00000008971	Isg15	development/transcription factors	62.2%	63.1%	0.67	0.57	1	
ENSGACG00000012154	Aqp9	membrane proteins and solute transporters	97.5%	100.0%	0.11	0.57	2	
ENSGACG00000010765	Slc25a37	membrane proteins and solute transporters	91.2%	93.4%	1.64	0.94	2	
ENSGACG00000014377	Urod	heme and hemoglobin biosynthesis	97.7%	100.0%	0.91	3.53	2	
ENSGACG00000003213	Car5b	carbonic anhydrases	95.5%	99.9%	0.07	0.03	2	
ENSGACG00000015396	Car7	carbonic anhydrases	97.3%	100.0%	0.00	1.00	2	
ENSGACG00000018021	Alad	heme and hemoglobin biosynthesis	97.7%	100.0%	0.33	5.84	3	
ENSGACG00000001433	Epb41	cytoskeleton	95.0%	98.2%	0.80	0.56	3	
ENSGACG00000001495	Trf	heme and hemoglobin biosynthesis	96.2%	99.7%	0.00	0.01	3	
ENSGACG00000004180	Ppox	heme and hemoglobin biosynthesis	83.2%	87.7%	0.44	2.33	3	
ENSGACG00000018597	Tmod1	cytoskeleton	91.5%	94.5%	0.15	1.25	3	
ENSGACG00000012574	Slc2a1	membrane proteins and solute transporters	96.0%	99.9%	0.17	0.02	3	
ENSGACG00000011803	Car14	carbonic anhydrases	96.9%	99.9%	0.02	0.03	3	
ENSGACG00000018705	Chd4	development/transcription factors	96.5%	99.5%	0.33	0.35	3	
ENSGACG00000020462	Crebrf	development/transcription factors	96.8%	100.0%	1.12	0.14	4	
ENSGACG00000018134	Gfi1b	development/transcription factors	97.1%	100.0%	15.87	2.75	4	
ENSGACG00000009442	Nfe2	development/transcription factors	97.2%	100.0%	5.76	0.27	4	
ENSGACG00000013189	Add2	cytoskeleton	90.4%	91.2%	0.90	7.34	4	
ENSGACG00000008037	Ftl1	heme and hemoglobin biosynthesis	97.5%	100.0%	0.34	0.32	4	
ENSGACG00000003384	Xk	membrane proteins and solute transporters	97.8%	99.9%	0.70	2.18	4	
ENSGACG00000019222	Bcl11a	development/transcription factors	97.5%	100.0%	0.26	0.65	4	

Ensembl ID	Gene Name	Type	Avg Coverage†	Avg Coverage Icefish†	FE marrow	FE erythrocytes	Pleiotropy Score	Truncating variant (s) ‡
ENSGACG00000019143	Klf1	development/transcription factors	96.0%	100.0%	25.70	7.32	5	
ENSGACG00000009874	Lmo2	development/transcription factors	97.7%	100.0%	0.66	0.49	5	
ENSGACG00000016373	Tfrc	heme and hemoglobin biosynthesis	94.8%	100.0%	1.10	1.98	6	
ENSGACG00000010082	Cpox	heme and hemoglobin biosynthesis	97.6%	100.0%	1.04	6.33	6	
ENSGACG00000011054	Myb	development/transcription factors	96.3%	99.9%	0.77	0.20	6	
ENSGACG00000002554	Zfpm1	development/transcription factors	96.5%	98.7%	0.42	0.81	6	
ENSGACG00000005173	Hmbs	heme and hemoglobin biosynthesis	94.7%	97.3%	5.39	5.59	6	
ENSGACG00000012004	Flvcr1	heme and hemoglobin biosynthesis	55.7%	63.1%	0.19	0.58	6	
ENSGACG00000013741	Dntm1	development/transcription factors	97.2%	99.8%	0.54	0.50	6	
ENSGACG00000006591	Ets1	development/transcription factors	97.5%	100.0%	0.07	0.00	6	
ENSGACG00000013704	Jak2	development/transcription factors	97.5%	100.0%	0.51	0.43	6	
ENSGACG00000017365	Jak2	development/transcription factors	97.5%	100.0%	0.51	0.43	6	
ENSGACG00000009622	Slc4a1	membrane proteins and solute transporters	92.1%	94.8%	7.93	2.74	7	
ENSGACG00000015484	Fth1	heme and hemoglobin biosynthesis	96.5%	100.0%	1.18	0.60	7	
ENSGACG00000000651	Fech	heme and hemoglobin biosynthesis	94.1%	96.8%	2.25	4.07	8	
ENSGACG00000018336	Ldb1	development/transcription factors	96.8%	99.8%	0.44	0.60	8	
ENSGACG00000015635	Sox6	development/transcription factors	97.8%	100.0%	0.64	1.11	8	
ENSGACG00000010218	Gata1	development/transcription factors	96.7%	100.0%	19.53	2.31	8	
ENSGACG00000002608	Uros	heme and hemoglobin biosynthesis	95.4%	100.0%	0.51	5.32	8	
ENSGACG00000004999	Car2	carbonic anhydrases	96.9%	99.0%	0.14	4.73	8	
ENSGACG00000009013	Acvr1ba	development/transcription factors	97.7%	100.0%	0.15	0.01	8	
ENSGACG00000000719	Acvr1bb	development/transcription factors	97.8%	100.0%	0.15	0.01	8	
ENSGACG00000017383	Aqp1	membrane proteins and solute transporters	97.8%	100.0%	0.07	5.00	9	
ENSGACG00000009608	Gata2	development/transcription factors	96.9%	99.7%	0.04	0.05	9	
ENSGACG00000013846	Tal1	development/transcription factors	97.6%	100.0%	1.77	1.03	9	
ENSGACG00000011100	Sptb	cytoskeleton	95.1%	97.5%	0.89	5.58	10	
ENSGACG00000009679	Kdm1a	development/transcription factors	97.7%	100.0%	0.21	0.42	10	
ENSGACG00000008634	Stat5a	development/transcription factors	97.6%	100.0%	0.49	0.46	10	
ENSGACG00000015405	Stat5b	development/transcription factors	97.1%	99.8%	0.38	0.19	11	
ENSGACG00000009373	Kitl	development/transcription factors	95.7%	100.0%	0.01	0.01	12	
ENSGACG00000017699	Ank1	cytoskeleton	97.1%	100.0%	0.14	6.67	12	
ENSGACG00000015083	Acvr2a	development/transcription factors	97.7%	99.6%	0.09	0.11	13	
ENSGACG00000015589	Stat1	development/transcription factors	96.2%	99.6%	0.19	0.14	13	
ENSGACG00000008910	Foxo3	development/transcription factors	98.1%	100.0%	0.81	0.47	16	

† Average coverage across dataset at a minimum depth of 4x reads

‡ Whole gene deletion or truncating variant (nonsense, frameshift) in at least one icefish lineage

S5 Table. Coverage and mutations in erythroid-biased genes

Ensembl ID	Gene Name	Avg Coverage†	Avg Coverage Icefish†	FE marrow	FE erythrocytes	Pleiotropy Score	Truncating variant (s) ‡
ENSGACG00000000027	Mcm2	93.3%	96.4%	1.27	1.18	11	
ENSGACG00000004199	Hdgf	97.9%	100.0%	1.06	1.46	1	
ENSGACG00000006776	Mcm5	72.1%	69.9%	1.05	1.41	1	
ENSGACG00000009622	Slc4a1	92.1%	94.8%	7.93	2.74	7	
ENSGACG00000007018	Slc4a1	96.7%	98.4%	7.93	2.74	7	
ENSGACG00000002407	Cdt1	94.1%	98.8%	4.34	1.45	0	
ENSGACG00000003179	Timm23	97.8%	100.0%	1.34	1.02	4	
ENSGACG00000018996	Usp15	97.5%	99.9%	1.81	1.83	5	
ENSGACG00000004862	Josd1	83.2%	86.6%	1.04	1.62	1	
ENSGACG00000010082	Cpox	97.6%	100.0%	1.04	6.33	6	
ENSGACG00000016373	Tfrc	94.8%	100.0%	1.10	1.98	6	
ENSGACG00000005398	Tfrc	95.4%	100.0%	1.10	1.98	6	
ENSGACG00000009865	Rhag	71.9%	73.7%	23.77	6.82	0	
ENSGACG00000000651	Fech	94.1%	96.8%	2.25	4.07	8	
ENSGACG00000006807	Alas2	97.8%	100.0%	6.58	2.09	0	✓
ENSGACG00000020793	Rabgef1	68.1%	71.0%	1.14	2.15	4	
ENSGACG00000013350	Pecam1	95.5%	99.9%	6.11	5.67	0	
ENSGACG00000019062	Tk1	97.0%	100.0%	1.19	1.70	10	
ENSGACG00000014938	Pigq	96.9%	99.8%	1.37	3.27	1	
ENSGACG00000019155	Mcm10	96.3%	100.0%	1.02	1.33	2	
ENSGACG00000018134	Gfi1b	97.1%	100.0%	15.87	2.75	4	
ENSGACG00000017832	Clp1	97.9%	100.0%	1.17	1.21	8	
ENSGACG00000005726	Pcna	97.8%	100.0%	1.20	1.06	5	
ENSGACG00000017373	Hemgn	95.7%	100.0%	1.61	5.18	0	✓
ENSGACG00000005437	Orc1	81.5%	86.2%	2.27	2.43	1	
ENSGACG00000013846	Tal1	97.6%	100.0%	1.77	1.03	9	
ENSGACG00000007369	Rhd	94.3%	98.4%	5.54	8.88	0	✓
ENSGACG00000010218	Gata1	96.7%	100.0%	19.53	2.31	8	
ENSGACG00000016176	Abcb10	89.8%	92.4%	1.97	3.94	3	
ENSGACG00000005173	Hmbs	94.7%	97.3%	5.39	5.59	6	
ENSGACG00000012552	Blvrb	97.1%	100.0%	2.17	2.85	2	
ENSGACG00000004430	Rpia	97.3%	100.0%	1.14	1.63	2	
ENSGACG00000019143	Klf1	96.0%	100.0%	25.70	7.32	5	
ENSGACG00000014492	Hba-a1	79.9%	37.2%	4.99	2.56	0	✓
ENSGACG00000004078	Fastkd5	97.4%	100.0%	1.20	1.27	4	
ENSGACG00000015628	Gypc	81.6%	100.0%	1.37	1.72	0	
ENSGACG00000013918	Hbb	79.9%	13.6%	8.59	2.70	0	✓

† Average coverage across dataset at a minimum depth of 4x reads

‡ Whole gene deletion or truncating variant (nonsense, frameshift) in at least one icefish lineage

S6 Table. Excluded terms from Mammalian Phenotype Ontology (MP) in pleiotropy analysis

MP Term	Name
MP:0000202	abnormal circulating alkaline phosphatase level
MP:0000208	decreased hematocrit
MP:0000215	absent erythrocytes
MP:0000226	abnormal mean corpuscular volume
MP:0000233	abnormal blood flow velocity
MP:0000237	obsolete decreased blood cell number
MP:0000245	abnormal erythropoiesis
MP:0000248	macrocytosis
MP:0000256	echinocytosis
MP:0000314	schistocytosis
MP:0000315	hemoglobinuria
MP:0000332	hemoglobinemia
MP:0000348	abnormal aerobic fitness
MP:0000603	pale liver
MP:0000689	abnormal spleen morphology
MP:0000734	muscle hypoplasia
MP:0000748	progressive muscle weakness
MP:0000752	dystrophic muscle
MP:0000759	abnormal skeletal muscle morphology
MP:0001189	absent skin pigmentation
MP:0001190	reddish skin
MP:0001191	abnormal skin condition
MP:0001201	translucent skin
MP:0001264	increased body size
MP:0001265	decreased body size
MP:0001569	abnormal circulating bilirubin level
MP:0001574	abnormal oxygen level
MP:0001577	anemia
MP:0001585	hemolytic anemia
MP:0001586	abnormal erythrocyte cell number
MP:0001588	abnormal hemoglobin
MP:0001589	abnormal mean corpuscular hemoglobin
MP:0001598	abnormal blood viscosity
MP:0001599	abnormal blood volume
MP:0001697	abnormal embryo size
MP:0001698	decreased embryo size

MP:0001699 increased embryo size
MP:0001721 absent visceral yolk sac blood islands
MP:0001722 pale yolk sac
MP:0001730 embryonic growth arrest
MP:0001731 abnormal postnatal growth
MP:0001732 postnatal growth retardation
MP:0001770 abnormal iron level
MP:0001786 skin edema
MP:0001933 abnormal litter size
MP:0001934 increased litter size
MP:0001935 decreased litter size
MP:0002088 abnormal embryonic growth/weight/body size
MP:0002089 abnormal postnatal growth/weight/body size
MP:0002095 abnormal skin pigmentation
MP:0002106 abnormal muscle physiology
MP:0002108 abnormal muscle morphology
MP:0002224 abnormal spleen size
MP:0002225 obsolete abnormal spleen cellularity
MP:0002227 abnormal spleen capsule morphology
MP:0002228 abnormal spleen trabecular vein morphology
MP:0002288 obsolete litter size
MP:0002319 hyperoxia
MP:0002329 abnormal blood gas level
MP:0002354 abnormal spleen trabecular artery morphology
MP:0002355 obsolete abnormal spleen venous sinus
MP:0002356 abnormal spleen red pulp morphology
MP:0002357 abnormal spleen white pulp morphology
MP:0002358 abnormal spleen periarteriolar lymphoid sheath morphology
MP:0002359 abnormal spleen germinal center morphology
MP:0002361 abnormal spleen central arteriole morphology
MP:0002362 abnormal spleen marginal zone morphology
MP:0002363 abnormal spleen marginal sinus morphology
MP:0002424 abnormal reticulocyte morphology
MP:0002447 abnormal erythrocyte morphology
MP:0002591 decreased mean corpuscular volume
MP:0002592 obsolete mean erythrocyte count traits
MP:0002593 high mean erythrocyte cell number
MP:0002594 low mean erythrocyte cell number
MP:0002596 abnormal hematocrit
MP:0002608 increased hematocrit

MP:0002640 reticulocytosis
MP:0002641 anisopoikilocytosis
MP:0002642 anisocytosis
MP:0002643 poikilocytosis
MP:0002810 microcytic anemia
MP:0002811 macrocytic anemia
MP:0002812 spherocytosis
MP:0002813 microcytosis
MP:0002814 hyperchromasia
MP:0002874 decreased hemoglobin content
MP:0002875 decreased erythrocyte cell number
MP:0002897 blotchy skin
MP:0002954 obsolete abnormal aerobic energy metabolism
MP:0002966 decreased circulating alkaline phosphatase level
MP:0002968 increased circulating alkaline phosphatase level
MP:0003015 abnormal circulating bicarbonate level
MP:0003016 increased circulating bicarbonate level
MP:0003017 decreased circulating bicarbonate level
MP:0003060 increased aerobic running capacity
MP:0003131 increased erythrocyte cell number
MP:0003342 accessory spleen
MP:0003396 abnormal embryonic hematopoiesis
MP:0003656 abnormal erythrocyte physiology
MP:0003657 abnormal erythrocyte osmotic lysis
MP:0003717 pallor
MP:0003852 skeletal muscle necrosis
MP:0003956 abnormal body size
MP:0003984 embryonic growth retardation
MP:0004142 abnormal muscle tone
MP:0004143 muscle hypertonia
MP:0004151 decreased circulating iron level
MP:0004152 abnormal circulating iron level
MP:0004196 abnormal prenatal growth/weight/body size
MP:0004197 abnormal fetal growth/weight/body size
MP:0004198 abnormal fetal size
MP:0004199 increased fetal size
MP:0004200 decreased fetal size
MP:0004201 fetal growth retardation
MP:0004229 abnormal embryonic erythropoiesis
MP:0004230 abnormal embryonic erythrocyte morphology

MP:0004232 decreased muscle weight
MP:0004233 abnormal muscle weight
MP:0004797 increased anti-erythrocyte antigen antibody level
MP:0004817 abnormal skeletal muscle mass
MP:0004818 increased skeletal muscle mass
MP:0004819 decreased skeletal muscle mass
MP:0004827 increased susceptibility to autoimmune hemolytic anemia
MP:0004828 decreased susceptibility to autoimmune hemolytic anemia
MP:0004846 absent skeletal muscle
MP:0004951 abnormal spleen weight
MP:0004952 increased spleen weight
MP:0004953 decreased spleen weight
MP:0004969 pale kidney
MP:0005028 abnormal trophectoderm morphology
MP:0005097 polychromatophilia
MP:0005152 pancytopenia
MP:0005288 abnormal oxygen consumption
MP:0005289 increased oxygen consumption
MP:0005290 decreased oxygen consumption
MP:0005344 increased circulating bilirubin level
MP:0005369 muscle phenotype
MP:0005406 abnormal heart size
MP:0005505 thrombocytosis
MP:0005561 increased mean corpuscular hemoglobin
MP:0005562 decreased mean corpuscular hemoglobin
MP:0005563 abnormal hemoglobin content
MP:0005564 increased hemoglobin content
MP:0005635 decreased circulating bilirubin level
MP:0005637 abnormal iron homeostasis
MP:0005640 abnormal mean corpuscular hemoglobin concentration
MP:0005641 increased mean corpuscular hemoglobin concentration
MP:0005642 decreased mean corpuscular hemoglobin concentration
MP:0005649 increased spleen neoplasm incidence
MP:0006034 myoglobinuria
MP:0006208 lethality throughout fetal growth and development
MP:0006351 abnormal glycosylated hemoglobin level
MP:0006352 decreased glycosylated hemoglobin level
MP:0006353 increased glycosylated hemoglobin level
MP:0008234 absent spleen marginal zone
MP:0008387 hypochromic anemia

MP:0008388 hypochromic microcytic anemia
MP:0008389 hypochromic macrocytic anemia
MP:0008473 abnormal spleen follicular dendritic cell network
MP:0008474 absent spleen germinal center
MP:0008475 intermingled spleen red and white pulp
MP:0008476 increased spleen red pulp amount
MP:0008477 decreased spleen red pulp amount
MP:0008478 increased spleen white pulp amount
MP:0008479 decreased spleen white pulp amount
MP:0008481 increased spleen germinal center number
MP:0008482 decreased spleen germinal center number
MP:0008483 increased spleen germinal center size
MP:0008484 decreased spleen germinal center size
MP:0008737 abnormal spleen physiology
MP:0008738 abnormal liver iron level
MP:0008739 abnormal spleen iron level
MP:0008740 abnormal intestinal iron level
MP:0008741 abnormal heart iron level
MP:0008742 abnormal kidney iron level
MP:0008743 decreased liver iron level
MP:0008772 increased heart ventricle size
MP:0008807 increased liver iron level
MP:0008808 decreased spleen iron level
MP:0008809 increased spleen iron level
MP:0008810 increased circulating iron level
MP:0008849 abnormal hemoglobin concentration distribution width
MP:0008850 increased hemoglobin concentration distribution width
MP:0008851 decreased hemoglobin concentration distribution width
MP:0008941 reticulocytopenia
MP:0008945 hyperchromic macrocytic anemia
MP:0008954 abnormal cellular hemoglobin content
MP:0008955 increased cellular hemoglobin content
MP:0008956 decreased cellular hemoglobin content
MP:0008962 abnormal carbon dioxide production
MP:0008963 increased carbon dioxide production
MP:0008964 decreased carbon dioxide production
MP:0009246 pale spleen
MP:0009323 abnormal spleen development
MP:0009395 increased nucleated erythrocyte cell number
MP:0009398 abnormal skeletal muscle fiber size

MP:0009399 increased skeletal muscle fiber size
MP:0009403 increased variability of skeletal muscle fiber size
MP:0009405 increased skeletal muscle fiber number
MP:0009406 decreased skeletal muscle fiber number
MP:0009408 decreased skeletal muscle fiber density
MP:0009409 abnormal skeletal muscle fiber type ratio
MP:0009410 abnormal skeletal muscle satellite cell proliferation
MP:0009411 abnormal skeletal muscle fiber triad morphology
MP:0009412 skeletal muscle fiber degeneration
MP:0009413 skeletal muscle fiber atrophy
MP:0009414 skeletal muscle fiber necrosis
MP:0009415 skeletal muscle degeneration
MP:0009416 cardiac muscle degeneration
MP:0009417 skeletal muscle atrophy
MP:0009418 cardiac muscle atrophy
MP:0009458 abnormal skeletal muscle size
MP:0009459 skeletal muscle hyperplasia
MP:0009460 skeletal muscle hypoplasia
MP:0009461 skeletal muscle hypertrophy
MP:0009462 skeletal muscle hypotrophy
MP:0009547 elliptocytosis
MP:0009568 abnormal red blood cell deformability
MP:0009642 abnormal blood homeostasis
MP:0009701 abnormal birth body size
MP:0009702 increased birth body size
MP:0009703 decreased birth body size
MP:0009841 foam cell reticulosis
MP:0009931 abnormal skin appearance
MP:0010020 spleen vascular congestion
MP:0010034 abnormal erythrocyte clearance
MP:0010035 increased erythrocyte clearance
MP:0010036 decreased erythrocyte clearance
MP:0010067 increased red blood cell distribution width
MP:0010068 decreased red blood cell distribution width
MP:0010074 stomatocytosis
MP:0010175 leptocytosis
MP:0010176 dacryocytosis
MP:0010177 acanthocytosis
MP:0010178 increased number of Howell-Jolly bodies
MP:0010237 abnormal skeletal muscle weight

MP:0010238	increased skeletal muscle weight
MP:0010239	decreased skeletal muscle weight
MP:0010240	decreased skeletal muscle size
MP:0010245	abnormal spleen perifollicular zone morphology
MP:0010375	increased kidney iron level
MP:0010376	decreased kidney iron level
MP:0010399	decreased skeletal muscle glycogen level
MP:0010401	increased skeletal muscle glycogen level
MP:0010563	increased heart right ventricle size
MP:0010577	abnormal heart right ventricle size
MP:0010579	increased heart left ventricle size
MP:0010580	decreased heart left ventricle size
MP:0010630	abnormal cardiac muscle tissue morphology
MP:0010632	cardiac muscle necrosis
MP:0010696	increased siderocyte number
MP:0010832	lethality during fetal growth through weaning
MP:0010865	prenatal growth retardation
MP:0010866	abnormal prenatal body size
MP:0010957	abnormal aerobic respiration
MP:0011089	perinatal lethality, complete penetrance
MP:0011091	prenatal lethality
MP:0011098	embryonic lethality during organogenesis, complete penetrance
MP:0011099	lethality throughout fetal growth and development, complete penetrance
MP:0011101	prenatal lethality, incomplete penetrance
MP:0011109	lethality throughout fetal growth and development, incomplete penetrance
MP:0011111	lethality during fetal growth through weaning, complete penetrance
MP:0011112	lethality during fetal growth through weaning, incomplete penetrance
MP:0011171	increased number of Heinz bodies
MP:0011188	increased erythrocyte protoporphyrin level
MP:0011204	abnormal visceral yolk sac blood island morphology
MP:0011235	abnormal blood oxygen capacity
MP:0011236	increased blood oxygen capacity
MP:0011237	decreased blood oxygen capacity
MP:0011239	abnormal skin coloration
MP:0011240	abnormal fetal derived definitive erythrocyte morphology
MP:0011241	abnormal fetal derived definitive erythrocyte cell number
MP:0011242	increased fetal derived definitive erythrocyte cell number
MP:0011243	decreased fetal derived definitive erythrocyte cell number

MP:0011244 absent fetal derived definitive erythrocytes
MP:0011245 abnormal fetal derived definitive erythrocyte physiology
MP:0011263 abnormal spleen mesenchyme morphology
MP:0011514 skin hemorrhage
MP:0011519 abnormal placenta labyrinth size
MP:0011520 increased placental labyrinth size
MP:0011521 decreased placental labyrinth size
MP:0011526 abnormal placenta fetal blood space morphology
MP:0011630 increased mitochondria size
MP:0011631 decreased mitochondria size
MP:0011890 increased circulating ferritin level
MP:0011891 decreased circulating ferritin level
MP:0011892 abnormal circulating transferrin level
MP:0011893 increased circulating transferrin level
MP:0011894 decreased circulating transferrin level
MP:0011895 abnormal circulating unsaturated transferrin level
MP:0011896 increased circulating unsaturated transferrin level
MP:0011897 decreased circulating unsaturated transferrin level
MP:0011913 abnormal reticulocyte cell number
MP:0011992 increased erythrocyte catalase activity
MP:0012056 abnormal polar trophectoderm morphology
MP:0012057 abnormal mural trophectoderm morphology
MP:0012102 absent trophectoderm
MP:0012115 abnormal trophectoderm cell proliferation
MP:0012116 increased trophectoderm cell proliferation
MP:0012117 decreased trophectoderm cell proliferation
MP:0012118 absent trophectoderm cell proliferation
MP:0012119 increased trophectoderm apoptosis
MP:0012120 trophectoderm cell degeneration
MP:0012363 abnormal erythrocyte sodium level
MP:0012364 decreased erythrocyte sodium level
MP:0012365 increased erythrocyte sodium level
MP:0012366 abnormal erythrocyte magnesium level
MP:0012367 decreased erythrocyte magnesium level
MP:0012368 increased erythrocyte magnesium level
MP:0012369 abnormal erythrocyte potassium level
MP:0012370 decreased erythrocyte potassium level
MP:0012371 increased erythrocyte potassium level
MP:0012372 abnormal erythrocyte ion content
MP:0012373 abnormal erythrocyte magnesium ion content

MP:0012374 decreased erythrocyte magnesium ion content
MP:0012375 increased erythrocyte magnesium ion content
MP:0012376 abnormal erythrocyte potassium ion content
MP:0012377 decreased erythrocyte potassium ion content
MP:0012378 increased erythrocyte potassium ion content
MP:0012379 abnormal erythrocyte sodium ion content
MP:0012380 decreased erythrocyte sodium ion content
MP:0012381 increased erythrocyte sodium ion content
MP:0012384 abnormal erythrocyte ion transport
MP:0012385 abnormal erythrocyte potassium:chloride symporter activity
MP:0012386 decreased erythrocyte potassium:chloride symporter activity
MP:0012387 increased erythrocyte potassium:chloride symporter activity
MP:0012388 abnormal erythrocyte sodium:hydrogen antiporter activity
MP:0012389 decreased erythrocyte sodium:hydrogen antiporter activity
MP:0012390 increased erythrocyte sodium:hydrogen antiporter activity
MP:0012391 abnormal erythrocyte sodium:potassium-exchanging ATPase activity
MP:0012392 decreased erythrocyte sodium:potassium-exchanging ATPase activity
MP:0012393 increased erythrocyte sodium:potassium-exchanging ATPase activity
MP:0012394 abnormal erythrocyte calcium-activated potassium channel activity
MP:0012395 decreased erythrocyte calcium-activated potassium channel activity
MP:0012396 increased erythrocyte calcium-activated potassium channel activity
MP:0012397 abnormal nucleated erythrocyte cell number
MP:0012398 decreased nucleated erythrocyte cell number
MP:0012650 abnormal erythrocyte catalase level
MP:0012653 decreased erythrocyte catalase level
MP:0012656 increased erythrocyte catalase level
MP:0012663 decreased haptoglobin level
MP:0012664 decreased circulating haptoglobin level
MP:0012665 increased haptoglobin level
MP:0012666 increased circulating haptoglobin level
MP:0013215 abnormal haptoglobin level
MP:0013301 abnormal pancreas iron level
MP:0013302 increased pancreas iron level
MP:0013303 decreased pancreas iron level
MP:0013403 abnormal circulating lactate level
MP:0013404 decreased circulating lactate level
MP:0013405 increased circulating lactate level
MP:0013657 abnormal blood cell morphology
MP:0020240 increased skeletal muscle cell apoptosis
MP:0020241 decreased skeletal muscle cell apoptosis

MP:0020323	abnormal heart apex size
MP:0020365	increased brain iron level
MP:0020366	decreased brain iron level
MP:0020367	increased heart iron level
MP:0020368	decreased heart iron level
MP:0020369	increased intestinal iron level
MP:0020453	abnormal erythrocyte aggregation
MP:0020454	decreased erythrocyte aggregation
MP:0020455	increased erythrocyte aggregation
MP:0020825	ectopic spleen