Lactate Dehydrogenase as a Candidate Genomic Marker of Climate Change in Mammals?

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Abstract:

Climate change imposes metabolic and thermal stress on mammals, yet genomic markers that track lineage-specific adaptation remain limited. Lactate dehydrogenase (LDH), a central enzyme in lactate metabolism and anaerobic stress response, has not previously been evaluated for its evolutionary association with climate change induced selection. Here, comparative genomics across 14 mammalian species and population-level reanalysis of American Pika and Bank Vole datasets were used to assess LDH gene family evolution under recent and historic climate change. LDHA, LDHB and LDHD exhibited lineage-specific signatures of selection, with pinnipeds showing consistent gene family expansion and elevated dN/dS across all paralogs. Bank Vole transcriptome screening revealed high polymorphism density in LDHB and LDHD, placing both genes within the top 80th percentile of evolving transcripts and consistent with historic and recent climate-driven genomic change. These findings identify LDH gene families as candidate genomic markers of mammalian climate adaptation. Functional validation is required to determine whether LDH polymorphisms causally contribute to climate-linked physiological resilience.

1. Introduction:

Climate change is a threat to ecosystems world-wide (1). Although climate change is a natural occurrence, the rate at which the climate is changing far exceeds the natural rate (2). Climate change can either be advantageous or deleterious for organisms (3, 4). Regardless of the direction of impact, climate change is bound to have a significant influence on the genetic makeup of wildlife species (5-7).

Mammals, or Mammalia, are characterised by high metabolic resting rate in comparison to ectothermic animals but are of a lower metabolic resting rate than the endothermic Aves (8). The intermediate metabolic status of mammals is suitable for the study of genotypic regulation of phenotypic adaptations in a changing climate. The tightly regulated homeothermy of most mammals means that behavioural adaptations to heat stress are less occurrent than ectothermic counterparts (9). The lower metabolic rate in comparison to Aves enables comparisons in the absence of the confounding extreme metabolic demands of flight – especially in the presence of migratory birds (10).

Lactate dehydrogenase (LDH) is the key governing mechanism for the metabolism of lactate, an anaerobic metabolite that results from metabolic stressors – such as strenuous exercise (11, 12). Although it is a well-established clinical and physiological marker, the genomic adaptations of lactate dehydrogenase under metabolic stress remains poorly understood in wildlife. The evolutionary dynamics of lactate will be examined both between and within species. The tissue and function specific gene families of the LDH genes are ideal for lineage specific evolution among mammals (ref).

The focus of the study is to (1) characterise the long-term patterns of selection and or gene expansion upon the LDH genes of fourteen mammals and to reanalyse genetic variants of (2) the American Pika and (3) the Bank Vole subject to ongoing and historic climate selection respectively.

2. Methods:

2.1 Data sourcing and preparation

Fourteen proteomes were collected from NCBI RefSeq for comparative genomics (Table 1). The translated coding DNA sequences (CDS) was imported into Galaxy Australia and was processed with default settings for OrthoFinder (13, 14). The OrthoFinder run terminated in the final stages but produced 13 levels of orthologous genes. The termination resulted from the job exceeding the resources available per job for Galaxy Australia. Before termination, all orthologs were identified, the termination occurred during the gene tree formation. The first two orthologous gene levels contained all platypus LDH genes – which was used as a basal root for the analyses.

Table 1: Data availability and sourcing: All data sources are acknowledged. Comparative genomics refers to the first component of the study whereby species are compared, the population reanalysis component of the study compared samples within the one species at a time.

Common Name	Species Name	Reference Source	Reference Name
		Comparative Genomics	
Human	*Homo sapians*	NCBI RefSeq	GCF_000001405.40_GRCh38.p14_translated_cds
Chimpanzee	*Pan troglodytes*	NCBI RefSeq	GCF_028858775.2_NHGRI_mPanTro3-v2.1_pri_translated_cds
Mouse	*Mus musculus*	NCBI RefSeq	GCF_000001635.27_GRCm39_translated_cds
Ryukyu Mouse	*Mus caroli*	NCBI RefSeq	GCF_900094665.2_CAROLI_EIJ_v1.1_translated_cds
Northern Fur Seal	*Callorhinus ursinus*	NCBI RefSeq	GCF_003265705.2_GSC_fseal_2.0_translated_cds
California Sea Lion	*Zalophus californianus*	NCBI RefSeq	GCF_009762305.2_mZalCal1.pri.v2_translated_cds
Echidna	*Tachyglossus aculeatus*	NCBI RefSeq	GCF_015852505.1_mTacAcu1.pri_translated_cds
Platypus	*Ornithorhynchus anatinus*	NCBI RefSeq	GCF_004115215.2_mOrnAna1.pri.v4_translated_cds
African Elephant	*Loxodonta africana*	NCBI RefSeq	GCF_030014295.1_mLoxAfr1.hap2_translated_cds
Asian Elephant	*Elephas maximus indicus*	NCBI RefSeq	GCF_024166365.1_mEleMax1_primary_haplotype_translated_cds

Two Toed Sloth	*Choloepus didactylus*	NCBI RefSeq	GCF_015220235.1_mChoDid1.pri_translated_cds
Tammar Wallaby	*Macropus eugenii*	NCBI RefSeq	GCF_028372415.1_mMacEug1.pri_v2_translated_cds
Fat Tailed Dunnart	*Sminthopsis crassicaudata*	NCBI RefSeq	GCF_048593235.1_ASM4859323v1_translated_cds
Tasmanian Devil	*Sarcophilus harrisii*	NCBI RefSeq	GCF_902635505.1_mSarHar1.11_translated_cds
		Population Reanalysis	
American Pika	*Ochotona princeps*	Dryad – Schmidt and Russello (15)	363_29709.vcf, indv_info_update.txt
American Pika	*Ochotona princeps*	NCBI RefSeq	GCF_014633375.1_OchPri4.0_genomic.gff
Bank Vole	*Clethrionomys glareolus*	Dryad – Kotlik, Markova (16)	var.flt.vcf.zip, reference_transcriptome.fa

68 **2.2 Phylogenetics and selective pressure metrics**

69 The LDH proteins of the platypus (NP_001121092.1, XP_028931082.1,
70 XP_028931083.1, XP_028914549.1 and XP_028914550.1) were queried against the
71 orthologous proteins to identify the paralogs to these genes among the thirteen other
72 species for comparative genomics. The gene families (LDHA, LDHB, LDHD) were aligned
73 within MAFFT under automatic settings and used for the generation of a phylogeny using
74 IQ-TREE 3 with 1,000 'ultrafast' bootstraps and a self-selecting phylogenetic model (17,
75 18). The alignments and phylogenies were not trimmed. Bootstraps of 1,000 were
76 chosen to balance computational burden with the minimal benefit from additional
77 bootstrap approximations given that the phylogeny is for inferencing relationships not
78 taxonomic origins. Gene expansion was visually assessed from the phylogenetic trees
79 for relative expansion compared to close ancestors and or neighbouring branches.

80 For the estimation of genetic selection, the proteins clustered by OrthoFinder
81 were queried against NCBI's nucleotide database to retrieve the CDS of the LDH genes.
82 The retrieved CDS was assembled into paralog gene families to be consistent with the
83 results of OrthoFinder and aligned in a codon-aware model by MACSE (19). The rate of
84 non-synonymous to synonymous mutations are assembled for comparisons of
85 selective pressure upon the LDH genes of each species and/or gene. This metric is
86 referred to as dN/dS.

87 The dN/dS metric was compared to the evolutionary age of the organisms for
88 which there was a phylogenetically reliable dated tree (20). To do so the dated tree tips
89 were compared to the dN/dS measurements through a Phylogenetic Generalised Least
90 Squares (PGLS) using the R package caper (21). Using the comparative.data() function a

phylogenetically aware covariance matrix of shared branch lengths were constructed. The PGLS models were fitted using pgls(), allowing estimation of Pagel's λ and correcting for non-independence among species when assessing the association between tip age and dN/dS (21).

2.3 Population reanalysis for the American Pika

The .vcf file of the American Pika study performed by Schmidt and Russello (15) was cross checked with the .gff file from NCBI's RefSeq for the genomic coordinates (Table 1) for the LDH genes. Any SNPs were also checked for intron or exon location and annotated for their geographical lineage using the .txt file from Table 1 and the lineages described within Schmidt and Russello (15). The lineages were scored for SNP burden through a presence/absence of SNPs for each lineage – with any alternative genotypes assigned a score of one.

2.4 Population reanalysis for the Bank Vole

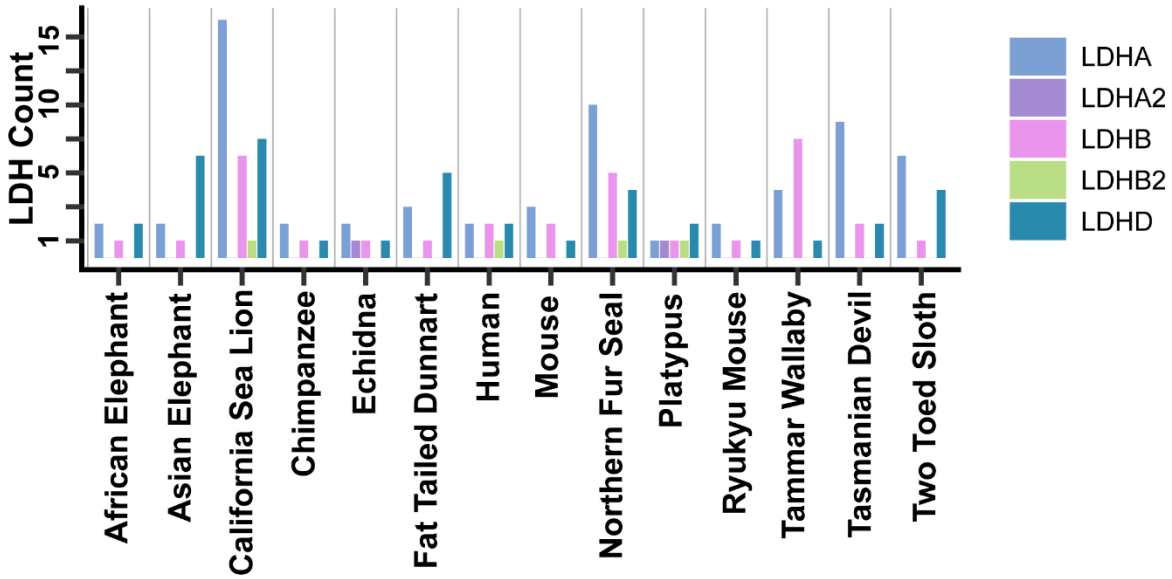
The Bank Vole transcriptome (Table 1) was annotated within Galaxy Australia using eggNOG functional sequence annotation by orthology (22, 23). LDH genes were manually searched using the search term "Lactate Dehydrogenase" and the LDH genes queried against the .vcf file. All polymorphisms were ranked by the density of the polymorphisms within the transcripts was ranked for every transcript. Density was determined as a function of polymorphism count divided by length. Transcript ranking occurred via percentile – for which the absolute density ranking was converted into a proportion of the most polymorphism-dense transcript of the whole transcriptome.

3. Results:

3.1 Five Isotypes of Lactate Dehydrogenase Within the Platypus genome

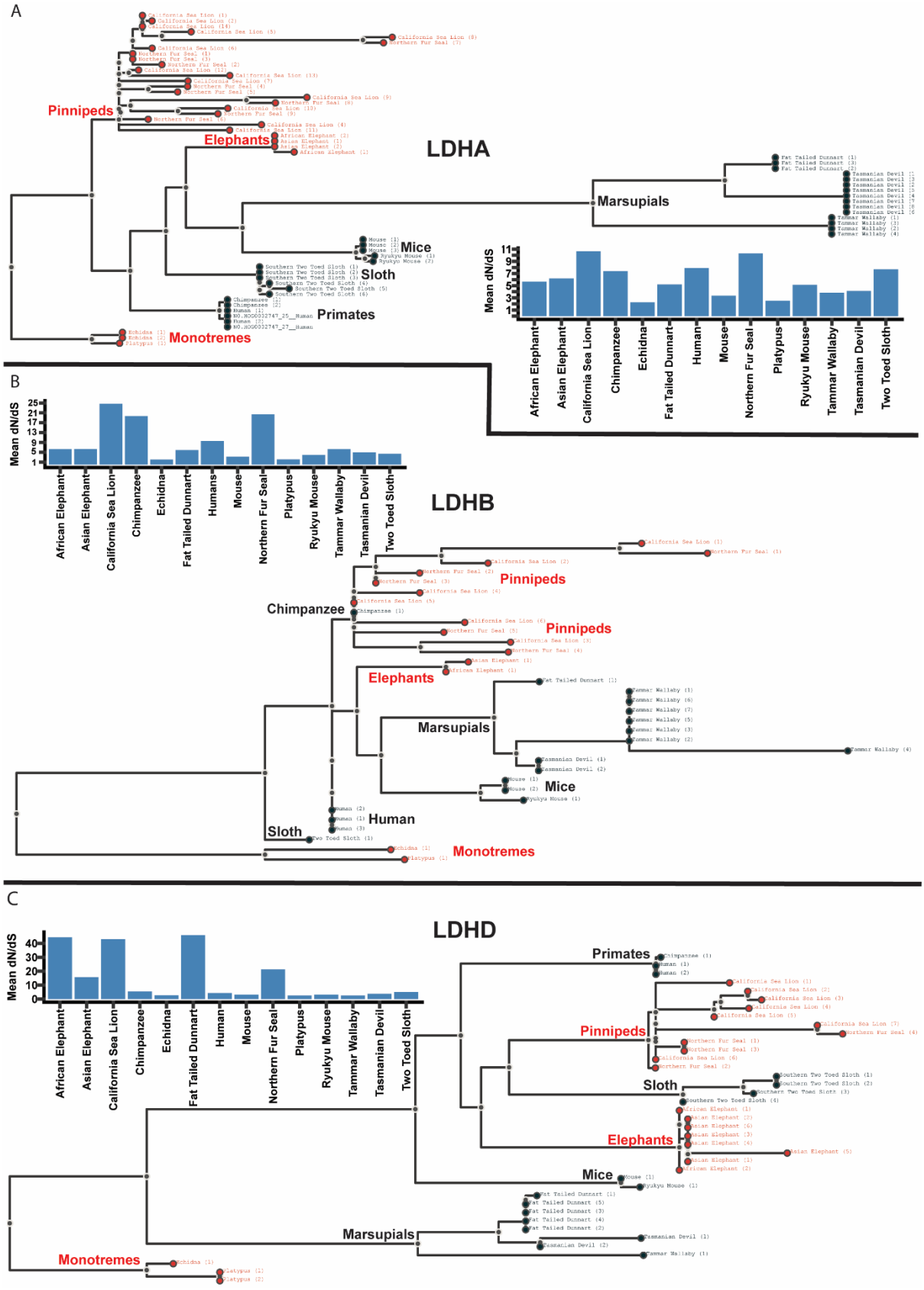
The three main identified isotypes (LDHA, LDHB and LDHD) were present in all 14 genomes. Two additional isotypes of the platypus were discovered LDHA2 and LDHB2. The alternative platypus isotype LDHA2 was detected in the genome of the California Sea Lion, Human, Northern Fur Seal and Platypus. LDHB2 was only present in the Echidna and Platypus (Figure 1).

Figure 1: Lactate Dehydrogenase copy number dependent on physiology. The LDH counts as determined by OrthoFinder's matches for the platypus genome. LDHA is primarily for rapid metabolism within muscle, LDHB is primarily within the brain and heart for recovery from hyperlactatemia and LDHD metabolises D-lactate to support the methylglyoxal pathway of glucose metabolism. Pinnipeds were disproportionate for the three main isotypes of LDH: LDHA, LDHB and LDHD.



The three main LDH families differed in overall patterns of selection and gene expansion and/or contraction events; however, for all three LDH families (LDHA, LDHB and LDHD) the two pinniped species (California Sea Lion and Northern Fur Seal) were under both positive selection and experienced expanded gene families (Figure 2A, B, C). Two toed sloths were under positive selection and experienced gene expansion in the fast-twitch LDHA gene family (Figure 2A). The only other species non-pinniped with both gene family expansion and positive selection was the Fat Tailed Dunnart for the LDHD gene family. All other species had either positive selection, gene expansion or neither. Gene expansion was not a significant predictor for selective pressure (Figure 2A, B, C).

Figure 2: LDHA, LDHB and LDHD all under selective pressure for pinnipeds. The elephants, pinniped and monotremes were highlighted in red as extreme physiology and or basal root species which are expected to undergo phylogenetic and or ancestral gene expansion or contraction. A. LDHA is displayed for all protein variants among the fourteen species along side the mean dN/dS per species as a metric of selection. The three of the four species (California Sea Lion, Northern Fur Seal and Two Toed Sloth) with high rate of dN/dS experienced significant gene expansion. Two labels (N0.HOG0002747_25_Human and N0.HOG0002474_27_Human) were duplicate proteins of identical accession numbers which were artefacts from the processing steps. B. LDHB is plotted for the dN/dS and phylogenetic representation of the gene family's proteins. The two pinniped species both experienced gene expansion and the only other high dN/dS species (chimpanzee), despite only having one gene copy was subject to a high level of gene selection and situated among the pinnipeds on the phylogenetic tree rather than with the human copy. C. LDHD was displayed for protein phylogeny and nucleotide dN/dS. The African Elephant was subject to high selective pressure as evident in the dN/dS plot but did not experience gene expansion – unlike the Asian Elephant. The California Sea Lion, Fat Tailed Dunnart and Northern Fur Seal all experienced gene expansion.


A
LDHA
Pinnipeds
Elephants
Mice
Sloth
Primates
Monotremes
Marsupials
Mean dN/dS
African Elephant
Asian Elephant
California Sea Lion
Chimpanzee
Echidna
Fat Tailed Dunnart
Human
Mouse
Northern Fur Seal
Platypus
Ryukyu Mouse
Tammar Wallaby
Tasmanian Devil
Two Toed Sloth
B
LDHB
Mean dN/dS
Pinnipeds
Chimpanzee
Elephants
Marsupials
Mice
Human
Sloth
Monotremes
C
LDHD
Mean dN/dS
Primates
Pinnipeds
Sloth
Elephants
Mice
Marsupials
Monotremes

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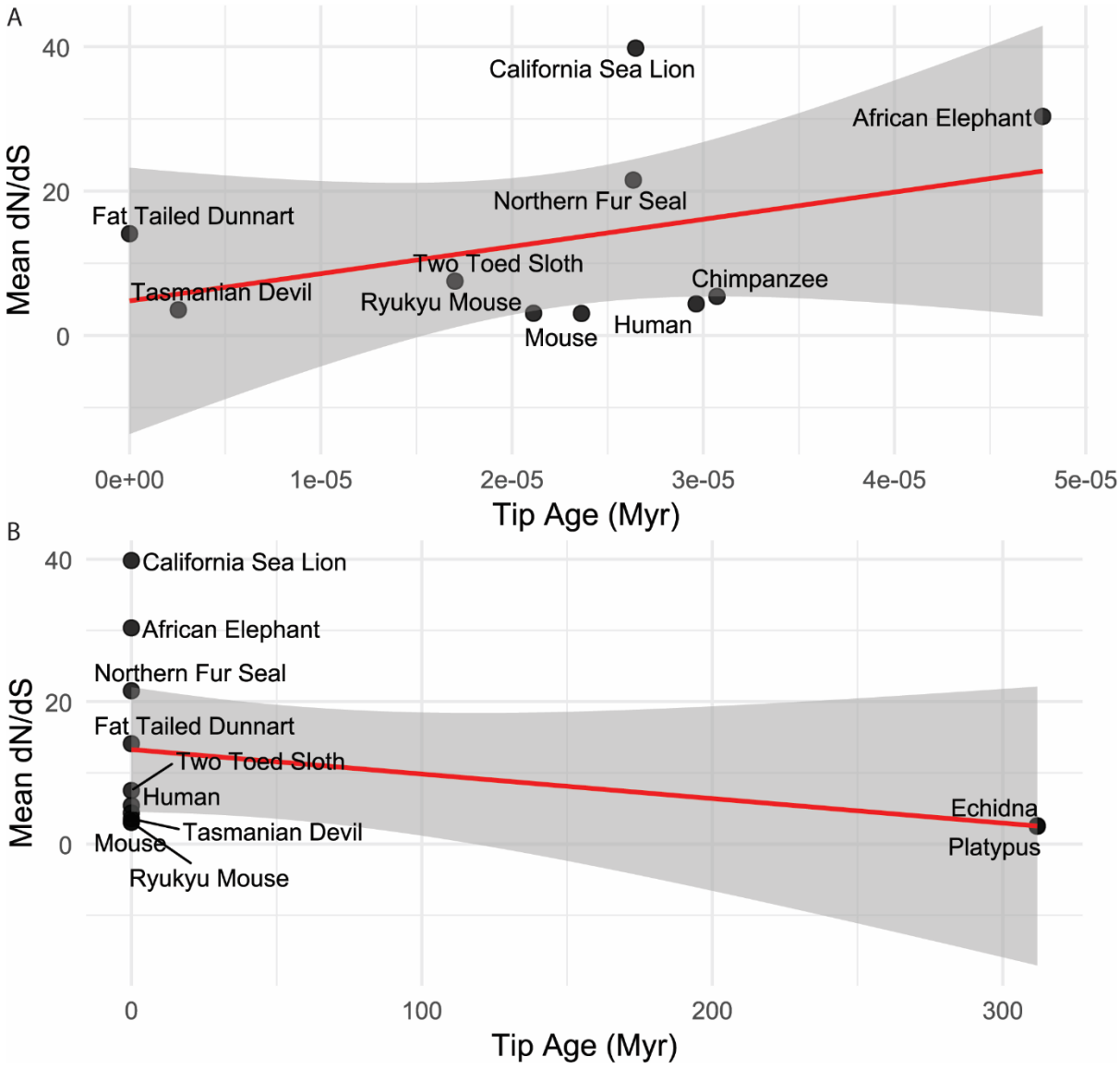
3.2 Evolutionary age not associated with Lactate Dehydrogenase selective pressure

Evolutionary age was not a feature of Lactate Dehydrogenase selective pressure (Figure 3A, B), when considering the phylogenetic tip distance of the mammalian phylogenetic tree produced by Upham, Esselstyn (20).

Figure 3: Evolutionary age was independent of lactate dehydrogenase selective pressure. The average dN/dS of all three main LDH gene families was shown for all matching data to a reference mammalian phylogeny by Upham, Esselstyn (20). A. The excluded Platypus and Echidna samples – the distance between the monotremes and other mammals distorted the visual – had an average dN/dS of 2.49-2.58. The Tammar Wallaby and Asian Elephant were not featured in the phylogeny and were excluded. B. The Platypus and Echidna samples were included.



3.3 Lactate dehydrogenase evolution in the American Pika:

Lactate dehydrogenase was assessed as a site for climate change adaptation by screening for SNPs in 363 individual American Pika RADseq data performed by Schmidt and Russello (15). Only the LDHB gene presented with a polymorphism. Two geographical regions were present for an intronic G2T SNP within the LDHB gene – 1/35 of the polymorphic samples was from the CU lineage (one of 28 individuals sampled). The remaining 34 individuals were from the 48 sampled individuals from the SRM lineage. The SRM lineage was disproportionally affected by warmer temperatures and low precipitation conditions (15). No other LDH polymorphisms were present in the data. The CU lineage had the lowest SNP burden followed by the SRM lineage.

3.4 Bank Vole experiences significant selective pressure in the LDHB and LDHD genes during a changing climate

The Bank Vole transcriptome polymorphisms sequenced by Kotlik, Markova (16) was reanalysed for the selective pressures of a historically changing climate upon the LDH genes. The LDHB gene was ranked as the 87.56 percentile top evolving transcript of the Bank Vole for polymorphisms, while the LDHD gene was in the top 80.27 percentile for most polymorphsims.

4. Discussion:

The aim of the study was to examine if LDH genes are reliable markers of lineage specific adaptations to climate change in mammals. Through an examination of the LDH paralogs both between and within species the aim was addressed. The results are species dependent; however, this was a strength of the study, supporting the

hypothesis of lineage specific adaptations shaped by a changing climate. Species context must be considered to avoid confounding analyses. The study was constructed to feature numerous and diverse mammal species to provide a diverse array of physiological and ecological contexts. Three contrasting physiological phenotypes were sloths with remarkably low metabolic rates, the extreme size and fermentative digestion of Elephants and extreme anaerobic demands of pinnipeds mid-dive (24-26).

The Two Toed Sloth genome featured within the study experienced both gene expansion and selective pressure upon the LDHA gene family, which is incongruent with physiological context. With limited metabolism, sloths have limited capacity to adapt to rising temperatures and the associated metabolic costs (24). With rising metabolic rates lactate production is expected to follow to meet metabolic demands.

African Elephants and Asian Elephants had either high selective pressures or gene expansion respectively for the LDHD gene. The LDHD gene is primarily a metaboliser of D-Lactate – rather than the vertebrate dominant L-Lactate metabolites (27, 28). D-Lactate is also the primary metabolite of microbes and can cause acidosis for fermentative animals, such as ruminants (29). Heat stress in ruminants is associated with increased ruminal lactate production as a result of the fermentative digestion of these animals (30). The Elephant LDHD evolutionary dynamics is best explained by the fermentative digestion of the Elephant, by which a combination of historic fermentative life history and rising temperatures have predisposed elephants to rising D-Lactate levels (26).

Although the selective metrics of the study were causal to evolutionary change, the results are still inferential. Until physiological studies are performed LDH genes are

candidate genomic markers for climate change and not causal markers. However, inferencing was attempted by the inclusion of two pinniped species was intentional as a control for the analyses, by which diving physiology is expected to result in anaerobic associated adaptations (31). Thus, pinnipeds serve as control for phenotype extremes rather than climatic extremes. Australian pinnipeds are sensitive to changes in water temperature due to metabolic stress and minimal capacity to regulate metabolic demands under rising temperatures (32). The role of climate change in LDH evolution for pinnipeds must also be interpreted with caution.

Both the American Pika and Bank Vole were also chosen for the recent and historic selection respectively (15, 16). The Bank Vole dataset had limited metadata – restricting the inferencing capabilities for dating of the lineages as performed for the American Pika. The use of the American Pika as a recent experimental exposure group to climate change was examined as a mechanism of recent genetic drift, whereas the Bank Vole served the opposite purpose. The American Pika was subject to population contractions due to climate change (33). The Bank Vole recently experienced colonisation and population expansion (16, 34). The Bank Vole's genomic changes coincide with recent climatic change as well as historic change (35). Together the two datasets complemented each other by reflecting a genetic bottle neck and a genetic expansion event.

The within species, population genomic approach furthers the study of lineage dependent climate change adaptation. Although the American Pika did not experience a noticeable response to climate change via LDH selection the species is undergoing recent population contractions due to climate change and so the timescale for

evolution may be premature (33). However, the extreme rate of transcriptomic polymorphisms within the Bank Vole's LDHB and LDHD gene families was evident of historic shifts in climate and possibly ongoing climate change (35).

LDH biology throughout ectothermic animals has been extensively studied as a biochemical model for thermal adaptations (36-38). However, mammalian LDH biology has not explored the impacts of changing climate – further research is needed to ascertain the relationship between long term thermal regulation and LDH genetics. Unlike the physiological studies of ectotherms, this study lacks any physiological measurements and is purely inferenced. Ideally future studies would add physiological context to the LDH biology in mammals to evaluate the role of this ubiquitous genetic marker for climate change adaptation tracking.

5. Conclusions:

The study examined the lineage specific adaptations of mammals to climate change for the lactate dehydrogenase gene families, both between and within species. Although the study was limited to inferencing, there was circumstantial evidence of the lactate dehydrogenase gene family representing a potential candidate marker for climate change adaptations. Further physiological integration is needed to elaborate on the genomic changes in the lactate dehydrogenase gene family with global warming.

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7. Data Availability:

All code is available in the GitHub repository: tsto3616/LDH-evo: Evolutionary dynamics of LDH genes in mammals. The generated data is available in the GitHub repository.

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