

Diving mammals lose *Paraoxonase 1* function in multiple different ways

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Main conclusions

The ancestors of extant semi-aquatic mammals lost PON1 protein function at least 4 times.
At least one functional loss was due to changes in regulatory sequence, and some conserved non-coding regions represent strong candidates for site(s) of the causal change(s).
PON1 functional loss may have been driven by changes in selective pressure due to diving and likely was not due to changes in diet.

Background

Paraoxonase 1 (PON1) shows the strongest signature of convergent functional loss among aquatic mammals genome-wide.
PON1 encodes a bloodstream enzyme involved in oxidation of lipoprotein fatty acids that incidentally protects humans and other mammals from organophosphate toxicity.
Whereas PON1 function was lost >50 MYA in cetaceans and sirenians, it appears to have been lost more recently in pinnipeds, which display functional variability (Figure 1) (1).

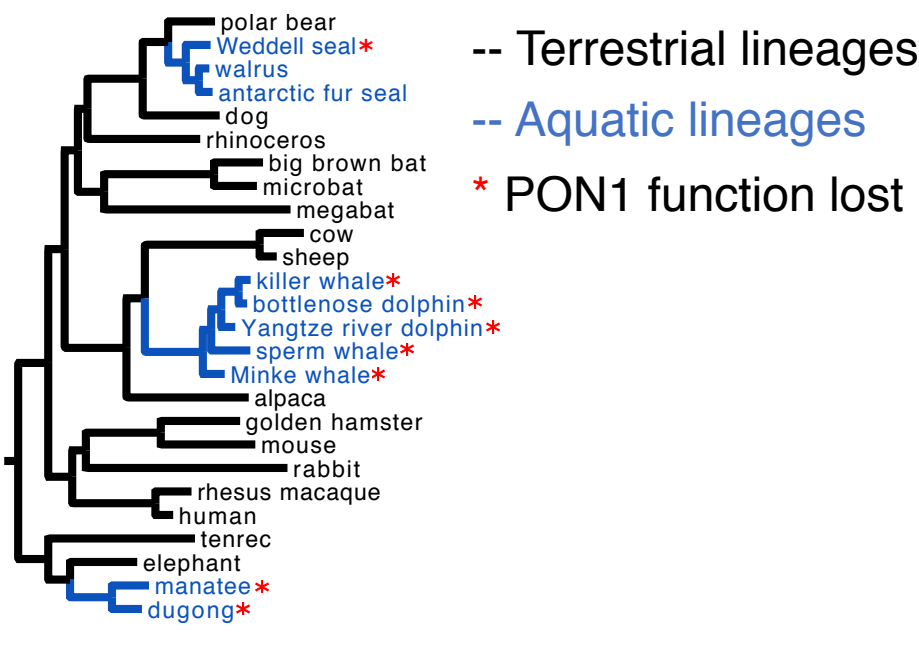


Figure 1. PON1 function is lost in all cetaceans and sirenians but only some pinnipeds.

Motivating question: How and why did diving mammals lose PON1 function?

Results

Semi-aquatic mammals lost PON1 function at least 4 distinct times.

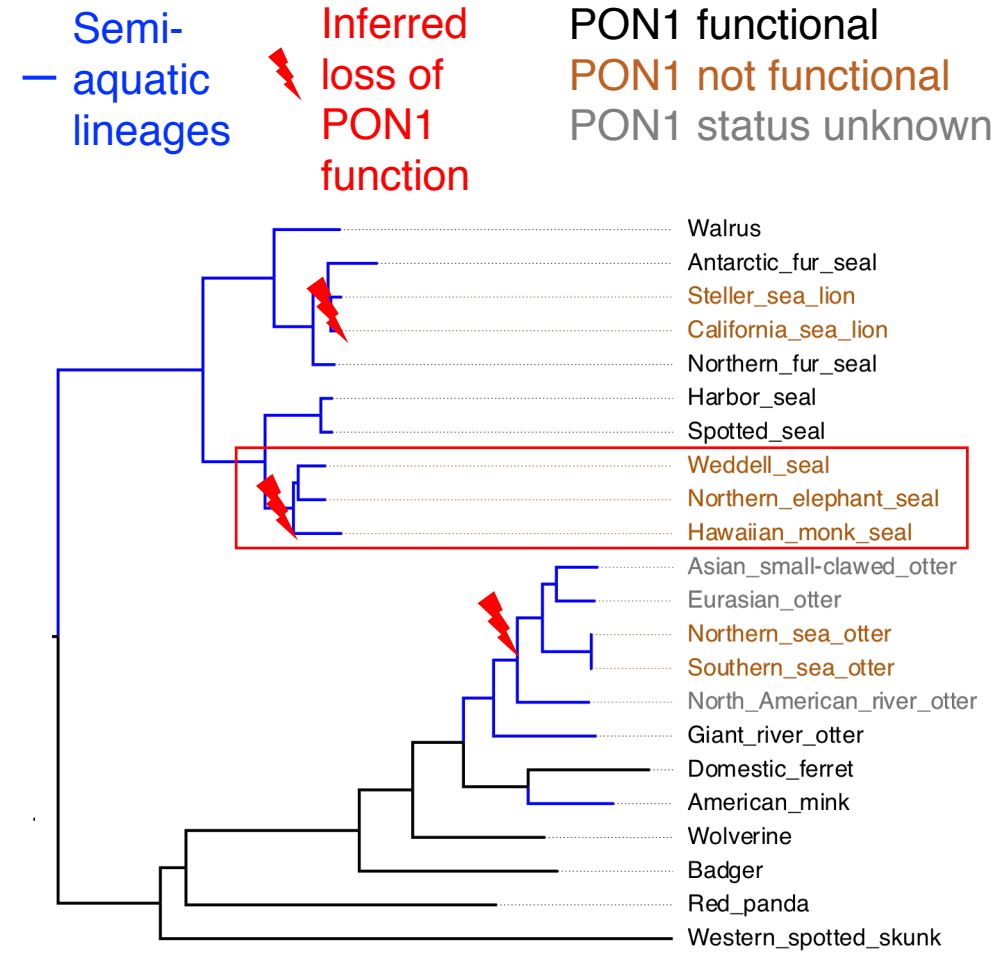


Figure 2. Patterns of PON1 function and lack of function in extant species enable inference of three independent losses in Carnivora. Not pictured: fourth functional loss in Rodentia (beaver, genus Castor).

Regulatory changes in candidate regions may have driven PON1 functional loss.

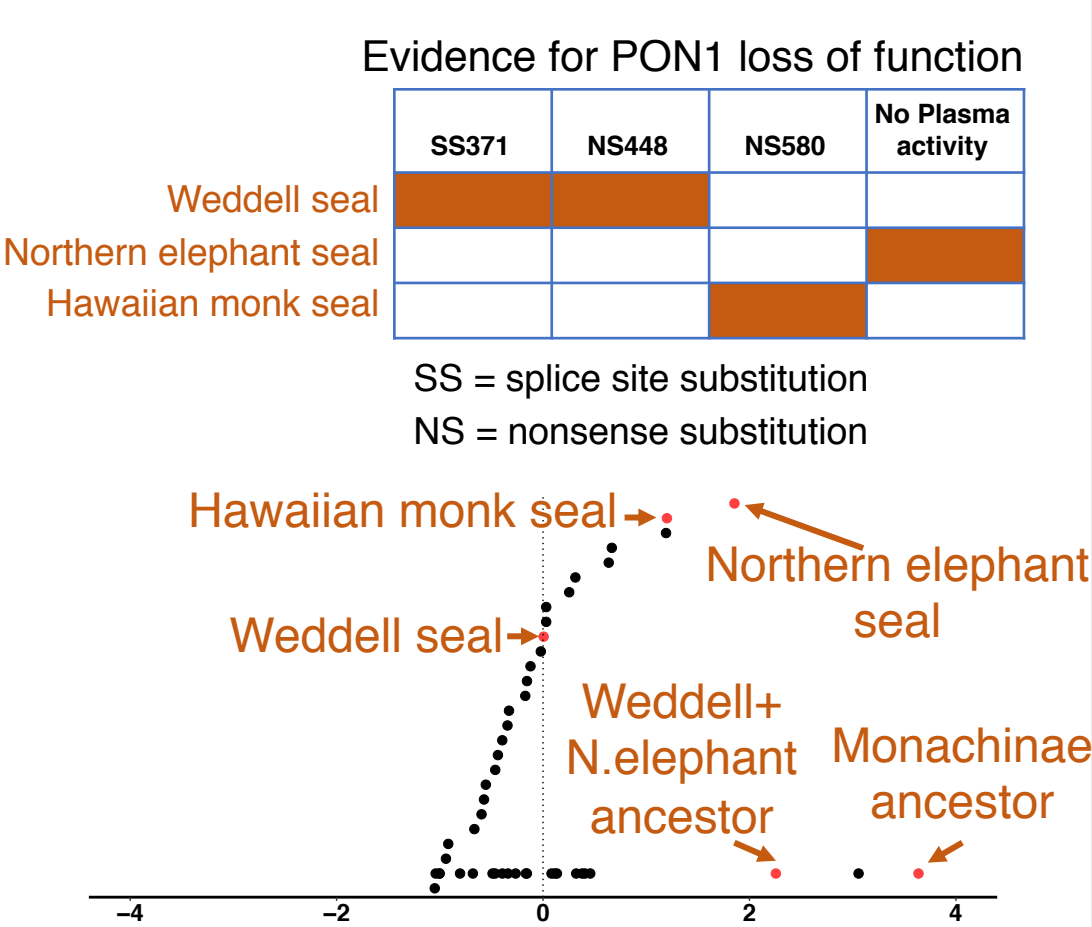


Figure 3. Top: Each species in the clade Monachinae shows different evidence for PON1 loss of function. Bottom: A putative carnivoran enhancer (overlapping an ATAC-seq peak in dog liver) evolves rapidly in Monachinae relative to other carnivorans.

Diving depth shows a weak association with PON1 functional loss.

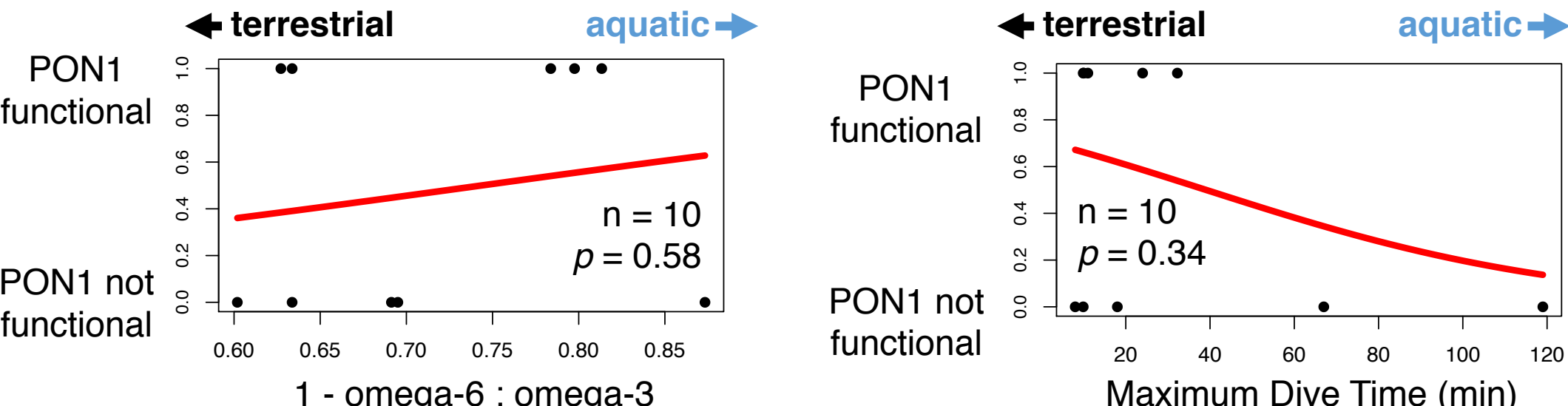


Figure 4. Dietary ω -6/ ω -3 ratio is not associated with PON1 function in the expected direction, but maximum dive time shows a weak trend in the expected direction, with longer divers more likely to have lost PON1 function.

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PON1 functional loss may have been driven by changes in selective pressure due to diving and likely was not due to changes in diet.

Future directions

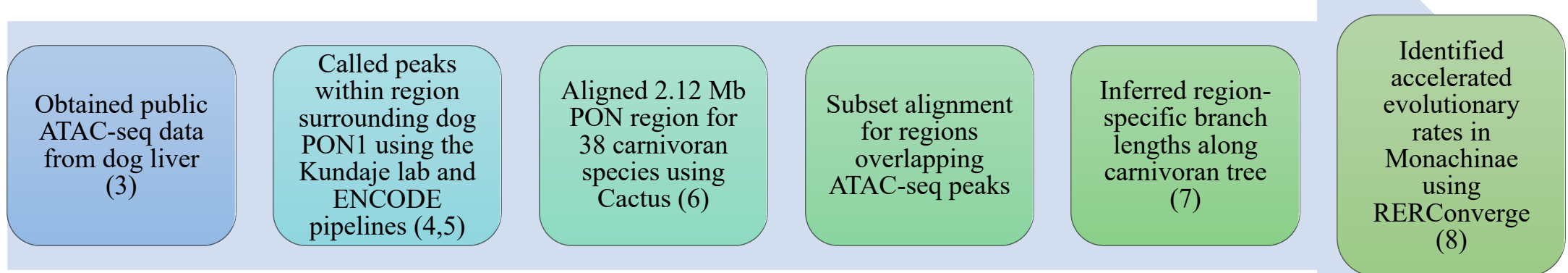
- Continued investigation of regulatory regions that are candidates for underlying PON1 functional loss in pinniped sub-clades
PON1 region sequencing and enzymatic testing of blood plasma PON1 activity for additional pinnipeds to:
- 1) Improve power to test association of diving ability with PON1 functional loss
 - 2) Further refine estimates of timing of PON1 functional loss
 - 3) Identify species that should be monitored for signs of organophosphate toxicity if exposed to agricultural runoff
- Characterization of PON1 activity in additional lutrid (otter) species

Methods

Determining PON1 status (functional/not functional)

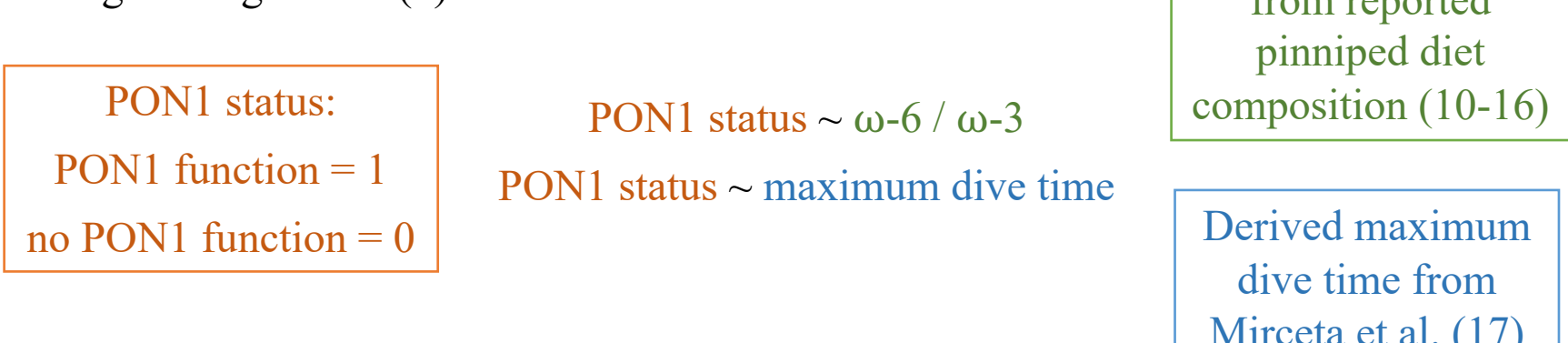
	Known from previous study (1)	Annotated public genome sequence	Sequenced PON1 exons via PCR	Assessed blood plasma activity against organophosphate substrates (2)
Walrus				
Antarctic fur seal				
Steller sea lion				
California sea lion				
Northern fur seal				
Harbor seal				
Spotted seal				
Weddell seal				
Northern elephant seal				
Hawaiian monk seal				
Northern sea otter				
Southern sea otter				
Giant river otter				
American mink				
Canadian beaver				

Identifying candidate regulatory substitutions associated with PON1 functional loss



Testing for association between PON1 functional loss and dietary and diving phenotypes

Phylogenetic logistic regression (9):



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