

Multi-level Genomic Convergence of Secondary Aquatic Adaptation in Marine Mammals

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REPORT



Multi-level genomic convergence of secondary aquatic adaptation in marine mammals

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Shixia Xu
徐士霞



Guang Yang
杨光

The team has long focused on the diversity, evolutionary origins, secondary aquatic adaptations, evolutionary medicine resources, and conservation of marine mammals.

Independent Returns to the Sea

Three Independent Marine Lineages

- **Cetacea** (鲸目): Whales and dolphins, fully aquatic
- **Pinnipedia** (鳍足目): Seals and sea lions, semi-aquatic
- **Sirenia** (海牛目): Manatees, fully aquatic herbivores

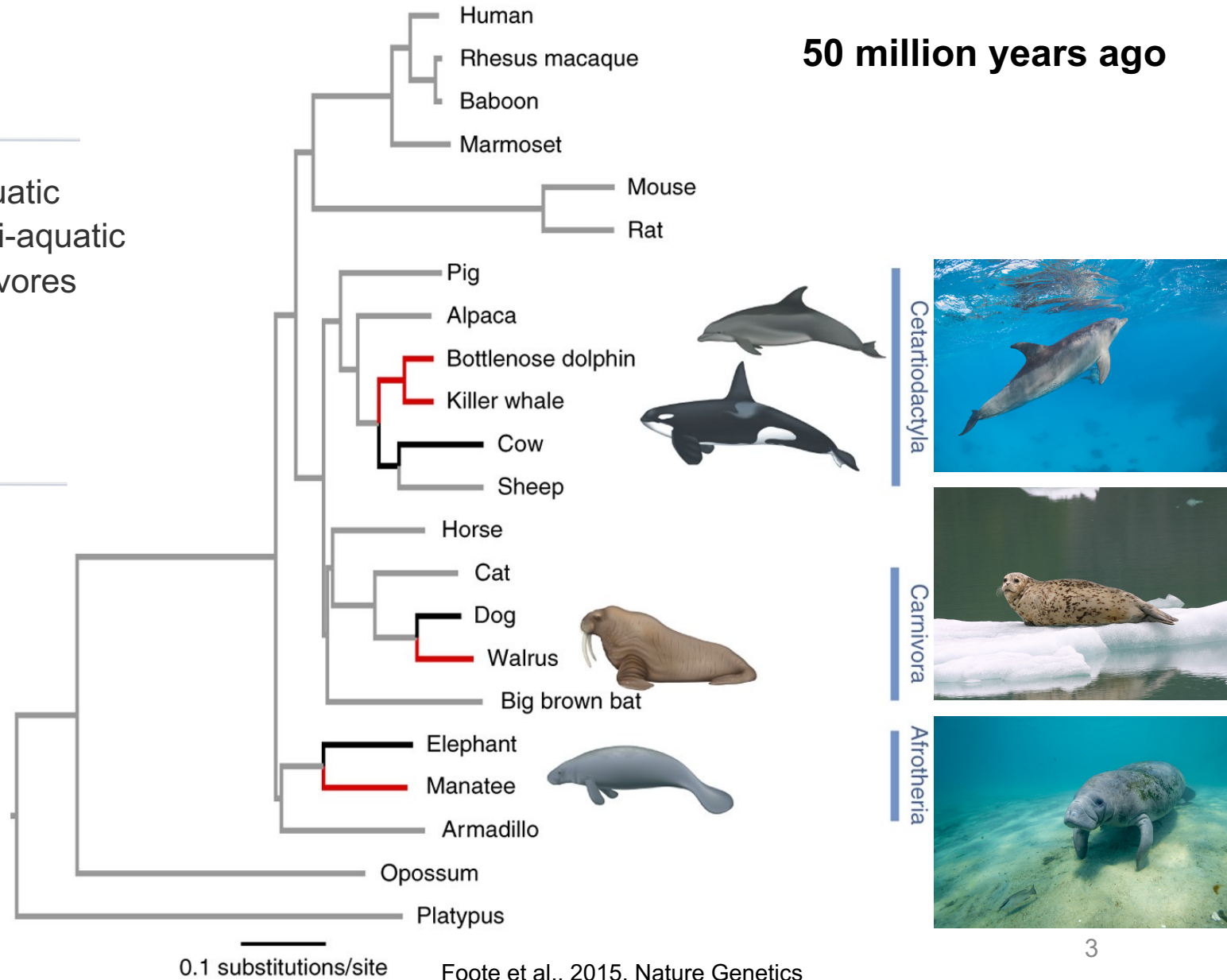
Convergent Phenotypes

- Streamlined body and flippers
- Thick blubber for thermoregulation
- Enhanced sensory systems

Scientific question:

Are these convergent phenotypes driven by molecular convergence?

Do identical morphological solutions rely on identical genomic modifications?



Knowledge Gap and Research Aim

Phenotypic Convergence (Body shape, Fins, Fat layers)

3D Genome Architecture (TADs, loops)? Largely unexplored

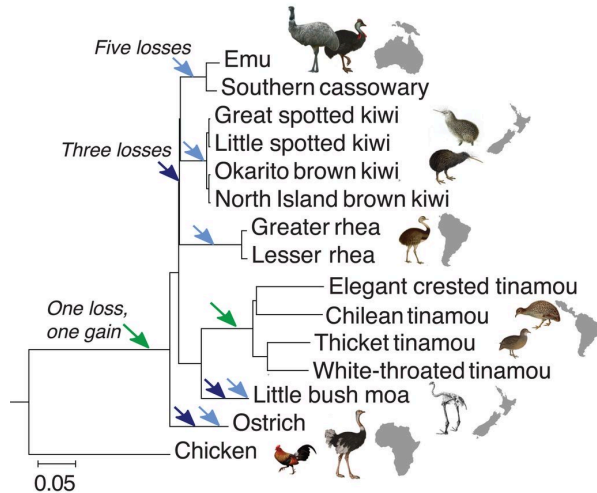
Coding genes
✓ Known, Rare

Non-coding (CNEs)
? Unknown

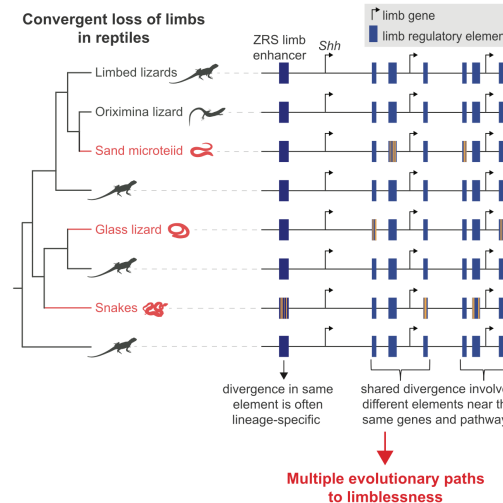
This Study's Aim

- Investigate multi-level genomic convergence
- From DNA sequence to 3D chromatin structure

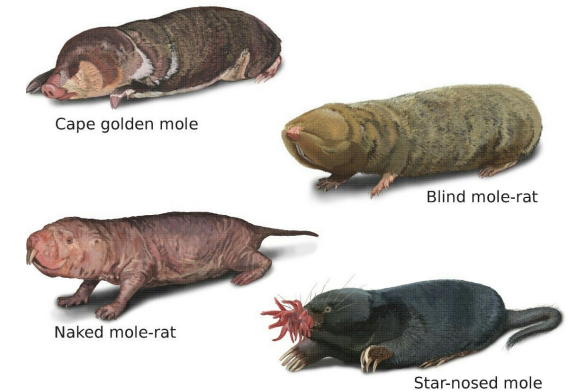
Evidence for CNE-Driven Convergent Evolution



Flight loss in palaeognathous birds
(Sackton et al., 2019, *Science*)



Limb loss in limbless reptiles
(Roscito et al., 2022, *Cell Reports*)



Eye regression in subterranean mammals
(Partha et al., 2017, *eLife*)

Study Design & Materials

A

Spotted seal



Phoca largha

Hog badger



Arctonyx collaris

Bottlenose dolphin



Tursiops truncatus

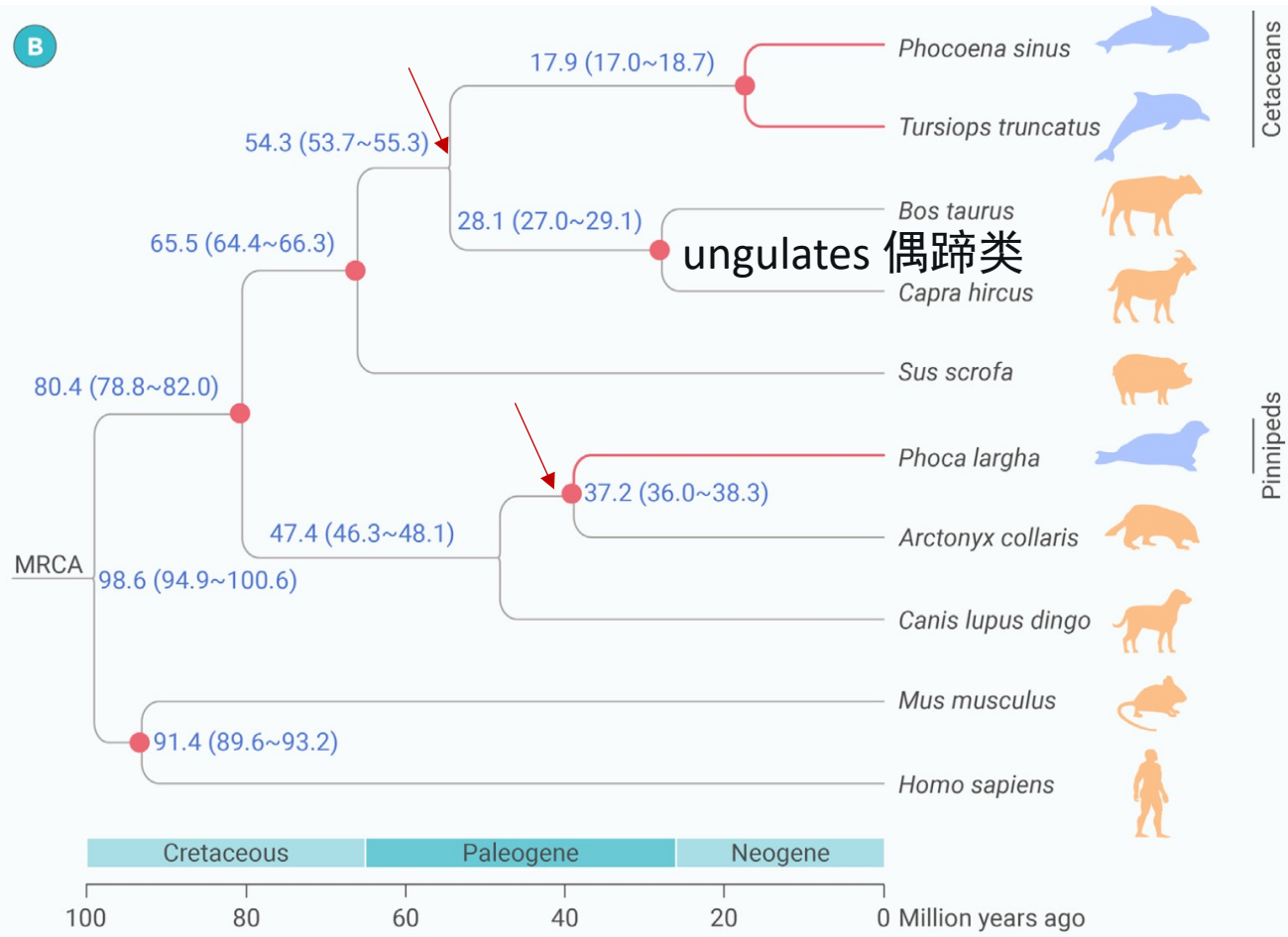
High-quality Genomes

Phoca largha (Spotted seal)
Tursiops truncatus (Bottlenose dolphin)
Arctonyx collaris (Hog badger)

Multi-Omics Data

PacBio long-read, Illumina short-read sequencing.
Hi-C data for 3D chromatin interaction maps.
RNA-seq, luciferase reporter assays, CRISPR-Cas9 mouse models.

Result 1: Chromosome-Level Genomes & Evolutionary Timeline



Genome Assembly Quality Assessment

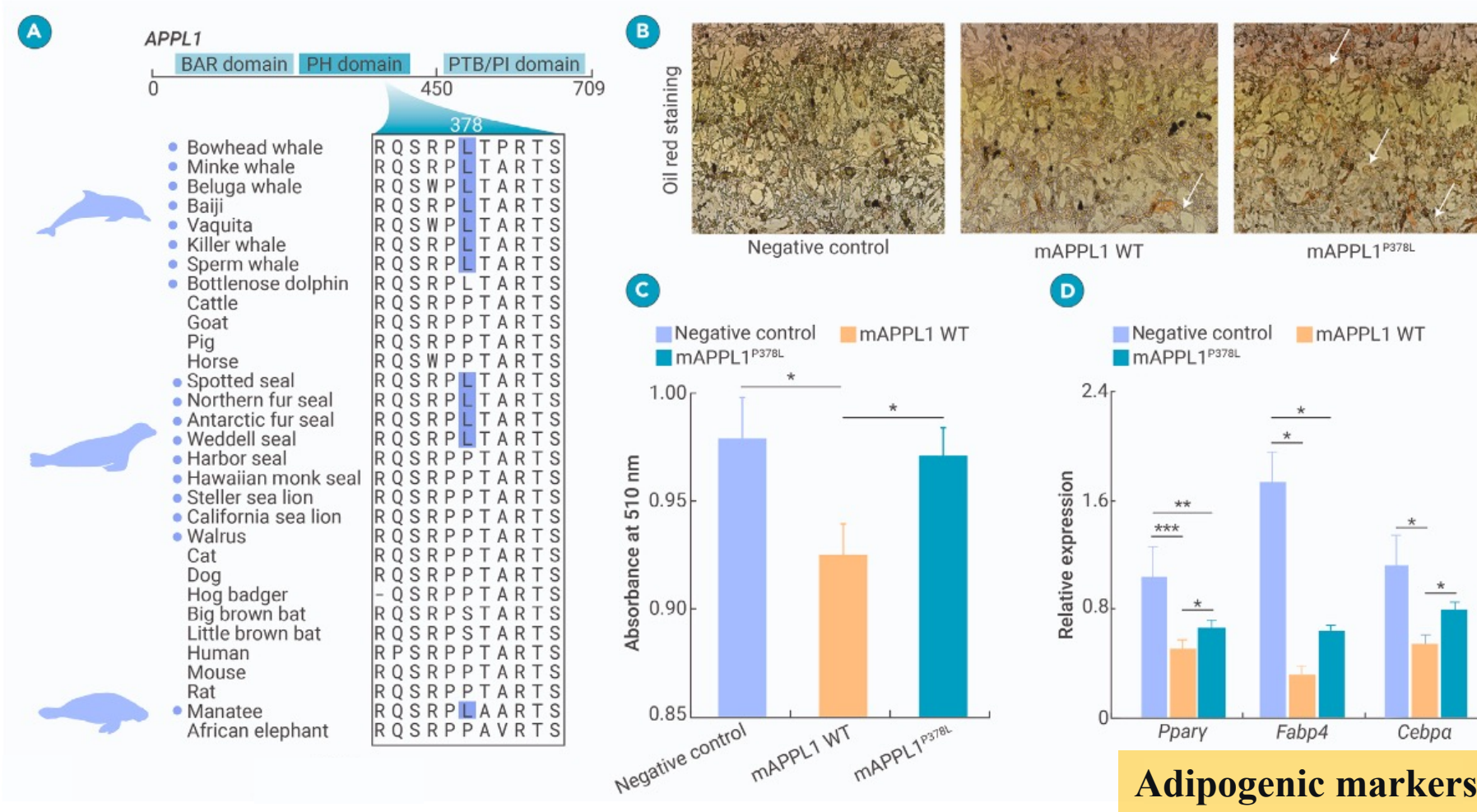
Contiguity (Scaffold N50): Achieved a range of **115.7 to 179.7 Mb**, representing chromosome-level continuity and minimal fragmentation in the assembled genomes.

	Bottlenose dolphin	Spotted seal	Hog badger
	(<i>Tursiops truncatus</i>)	(<i>Phoca largha</i>)	(<i>Arctonyx collaris</i>)
Assembly statistics			
Estimated depth	116×	75×	69×
Subread length N50 (kb)	26.16	25.55	28.36
Contig N50 (Mb)	18.4	6.3	8.7
Scaffold N50 (Mb)	115.7	179.7	133.2
Assembly size (Gb)	2.36	2.41	2.61
Gene number	24,118	21,069	21,567

Key Divergence Time Estimates

Cetacea diverged from even-toed ungulates at **54.3 Mya**;
Pinnipedia split from Mustelidae around **37.2 Mya**.

Result 2: Convergent Evolution of Coding Genes



Lipid Metabolism: *APPL1* (P378L)

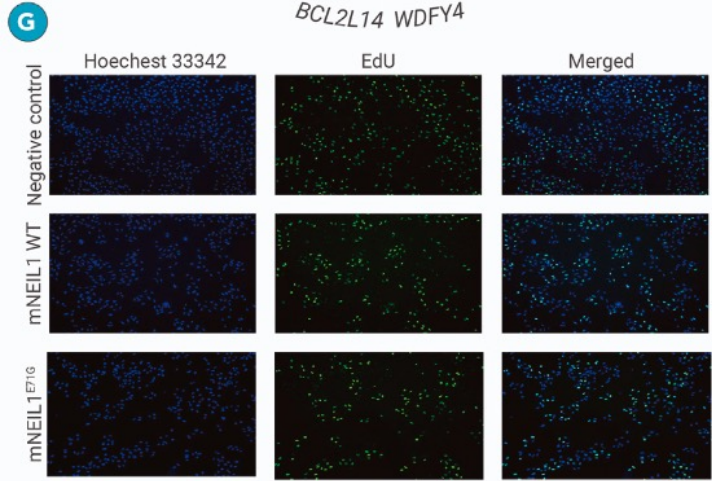
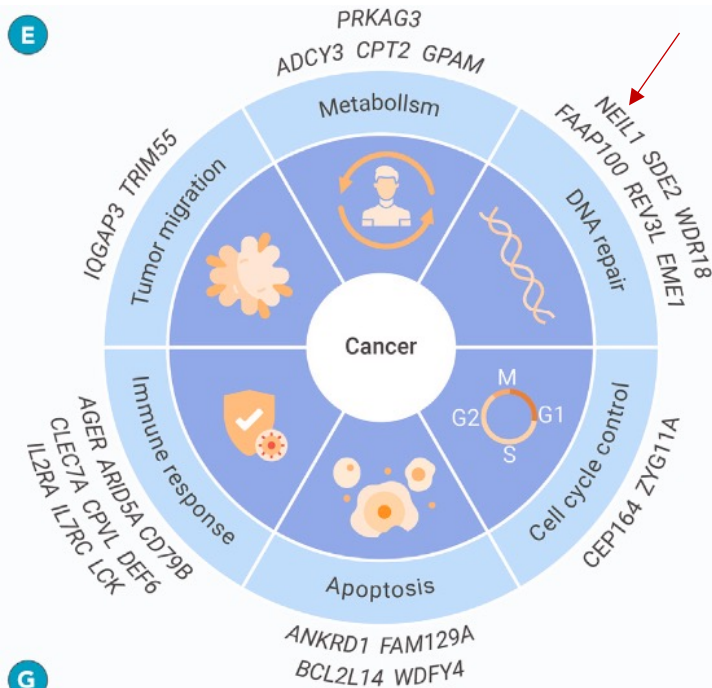
Function: Lipid metabolism
& adipogenesis

Finding: P378L mutation enhances lipid accumulation in 3T3-L1 cells

Conclusion: Drives blubber formation in marine mammals

- All three marine mammal groups share a specific change, P378L.
- The cells accumulated significantly more fat, as shown by the Oil Red O staining.

Result 2: Convergent Evolution of Coding Genes

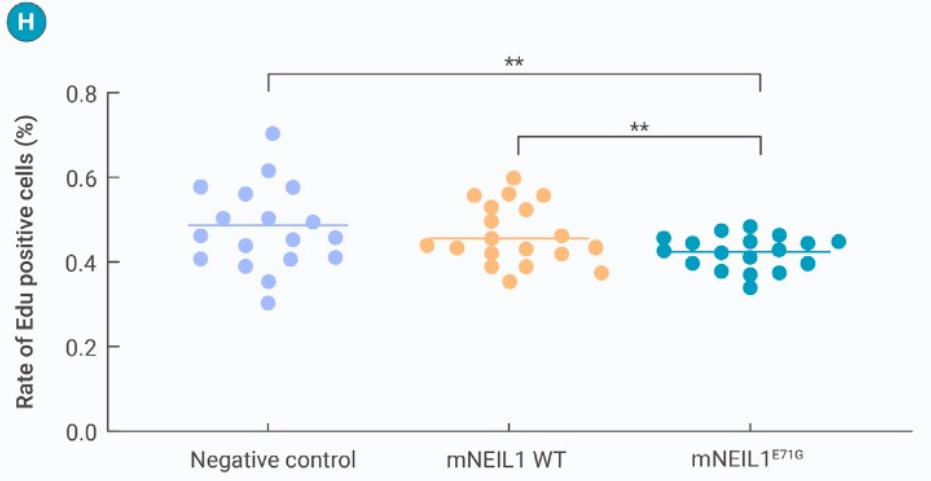


F

Formamidopyrimidine-DNA glycosylase N-terminal domain

71

	Primates	Human	Q	P	V	R	E	P	L	A	L	
		Macaque	Q	P	P	Q	E	P	L	A	L	
	Rodentia	Mouse	Q	P	P	Q	K	P	L	S	L	
		Naked mole-rat	Q	P	V	R	E	P	L	A	L	
	Cetartiodactyla	Bottlenose dolphin	●	Q	P	P	R	G	P	L	A	L
		Minke whale	●	Q	P	P	R	G	P	L	A	L
		Cattle		Q	P	H	R	E	P	L	A	L
		Goat		Q	P	P	R	E	P	L	A	L
	Chiroptera	Big brown bat		Q	P	P	R	E	P	L	A	L
		Little brown bat		Q	P	P	Q	E	P	L	A	L
	Carnivora	Dog		L	P	A	R	E	P	L	A	L
		Hog badger		Q	P	P	Q	E	P	L	A	L
		Spotted seal	●	E	P	P	R	G	P	L	A	L
		California sea lion	●	E	P	P	R	G	P	L	A	L
	Afrotheria	Manatee		Q	P	P	Q	E	P	L	A	L
		African elephant		Q	P	P	Q	E	P	L	A	L



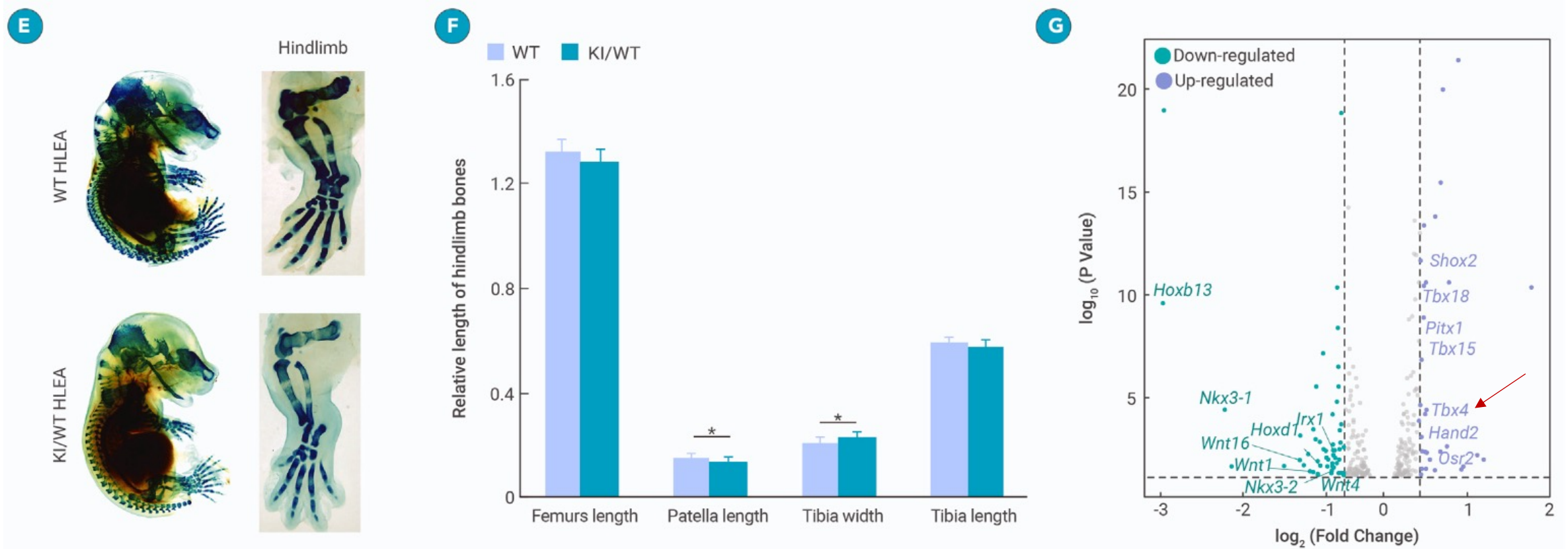
Tumor Suppression:
NEIL1(E71G)

Function: DNA repair & tumor suppression

Finding: E71G mutation suppresses HeLa cell proliferation

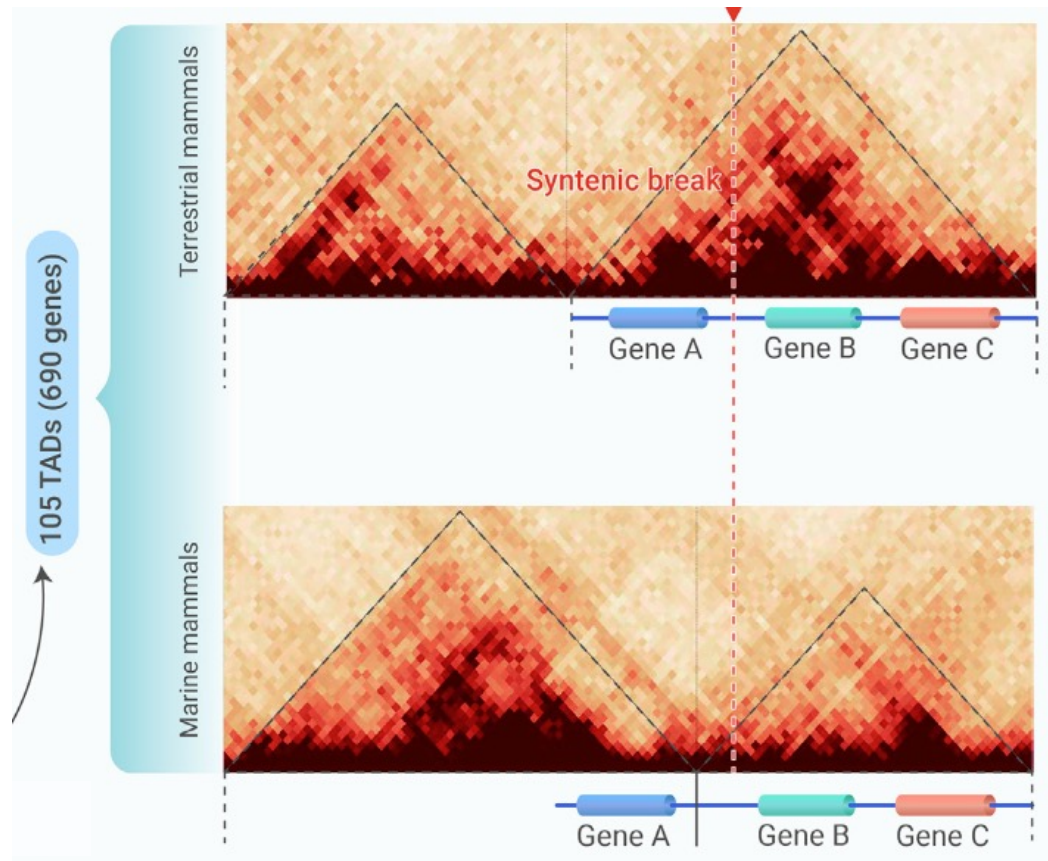
Conclusion:Contributes to cancer resistance (Peto's paradox)

Result 3: Regulatory CNEs Drive Limb Evolution



- **Concept:** CNEs act as enhancers to regulate gene expression.
- **Finding:** Marine-specific CNEs are enriched in limb development genes.
- **Key Example:** HLEA (**h**ind**l**imb-specific **e**nhancer) (**Tbx4 Enhancer**) - 4 cetacean-specific deletions identified.
 - CRISPR knock-in (KI) mice show altered hindlimb bones (wider tibia, shorter patella).
- **Conclusion:** HLEA mutations likely drove hindlimb regression in cetaceans.

Result 4: Convergent 3D Genome Architecture (TADs & Syntenic Breaks)

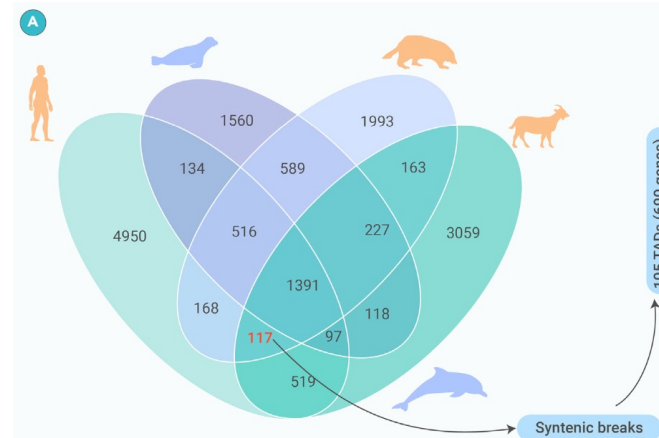


Signature 1: Conserved TADs

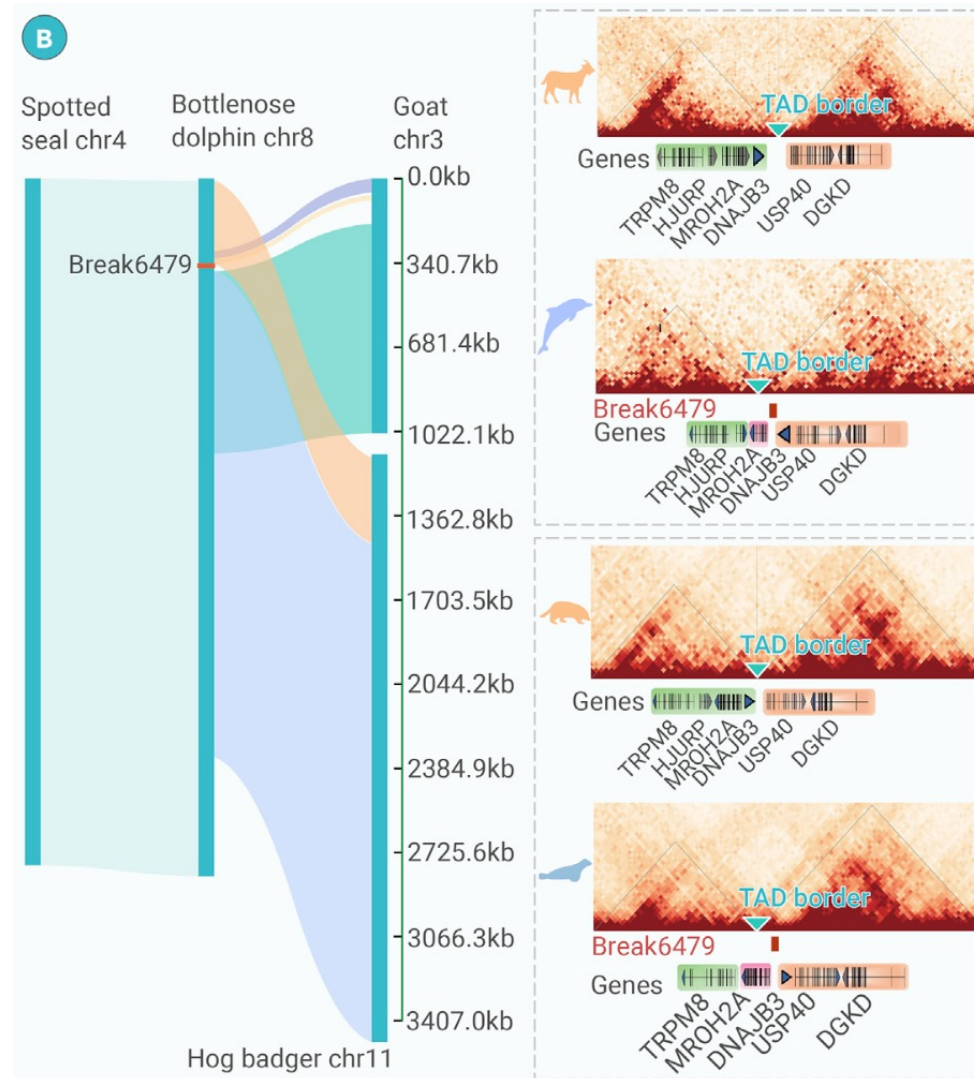
205 TADs uniquely conserved between dolphin and seal lineages, suggesting critical structural constraints for aquatic adaptation.

Signature 2: Recurrent Syntenic Rearrangements

117 shared syntenic breaks across independent marine mammal branches, indicating non-random genome architectural evolution.



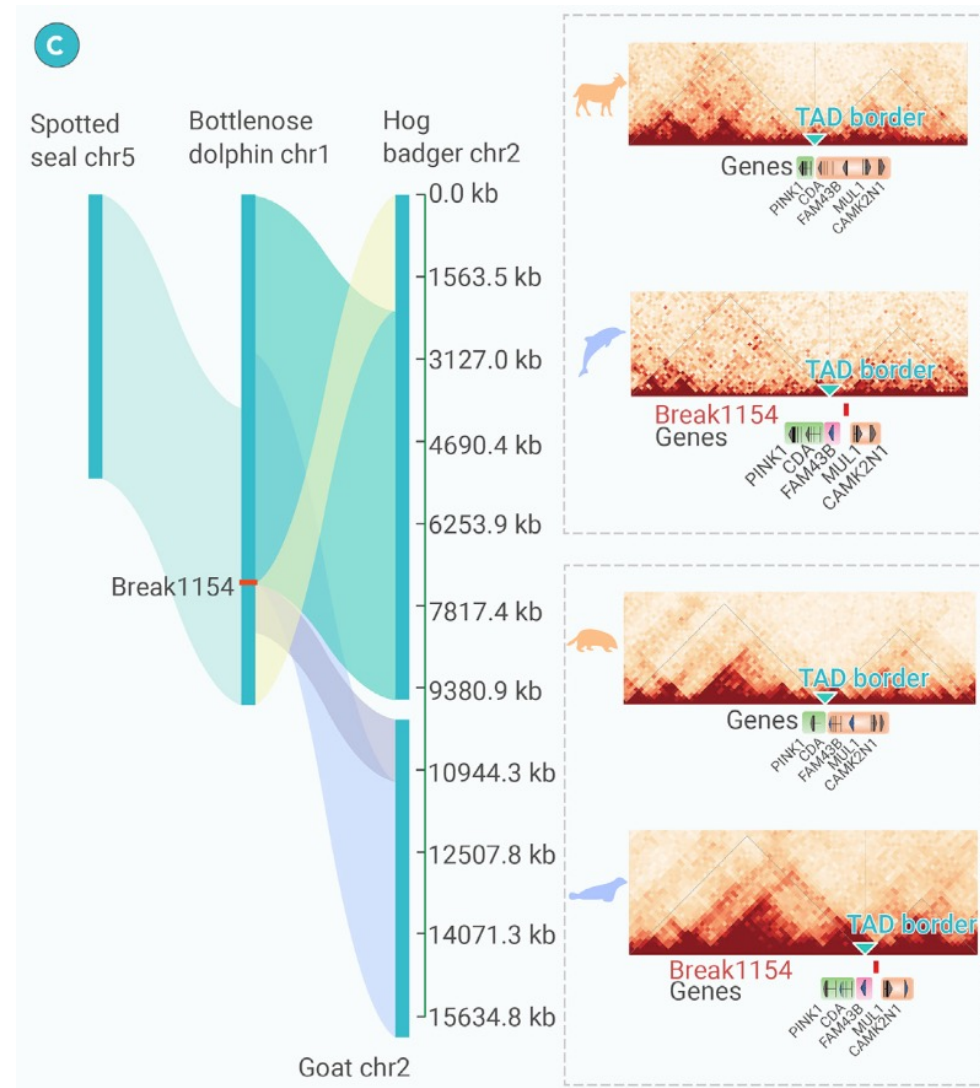
Result 4: Convergent 3D Genome Architecture (TADs & Syntenic Breaks)



Functional Implication: Blubber Development

Rearrangements near *DNAJB3* disrupt TADs, rewiring regulation to enhance **adipogenesis and fat storage**.

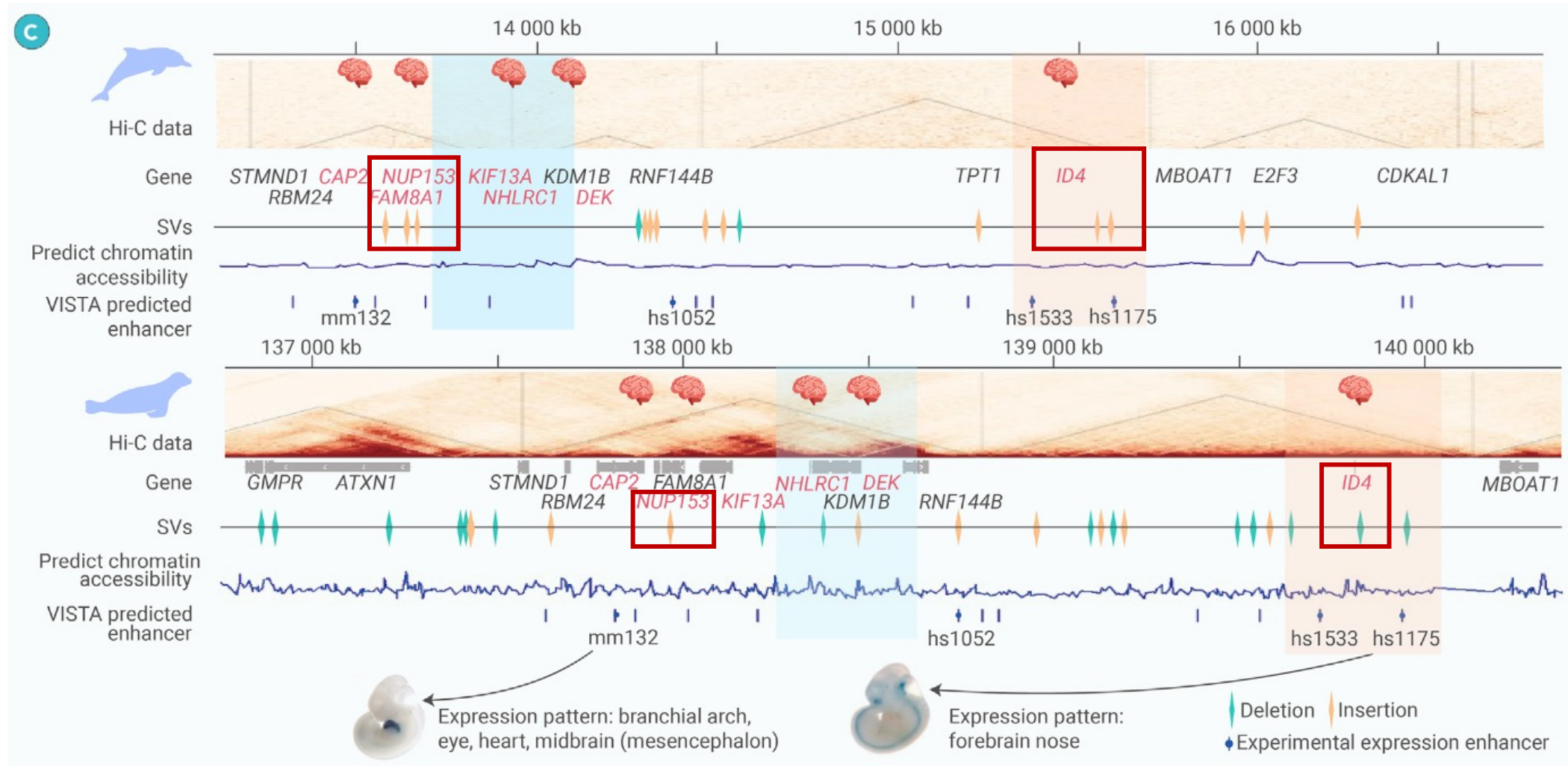
Result 4: Convergent 3D Genome Architecture (TADs & Syntenic Breaks)



Functional Implication: Cancer Resistance

Break 1154 relocates *FAM43B* to a TAD boundary, modulating interactions and potentially **conferring tumor suppression**.

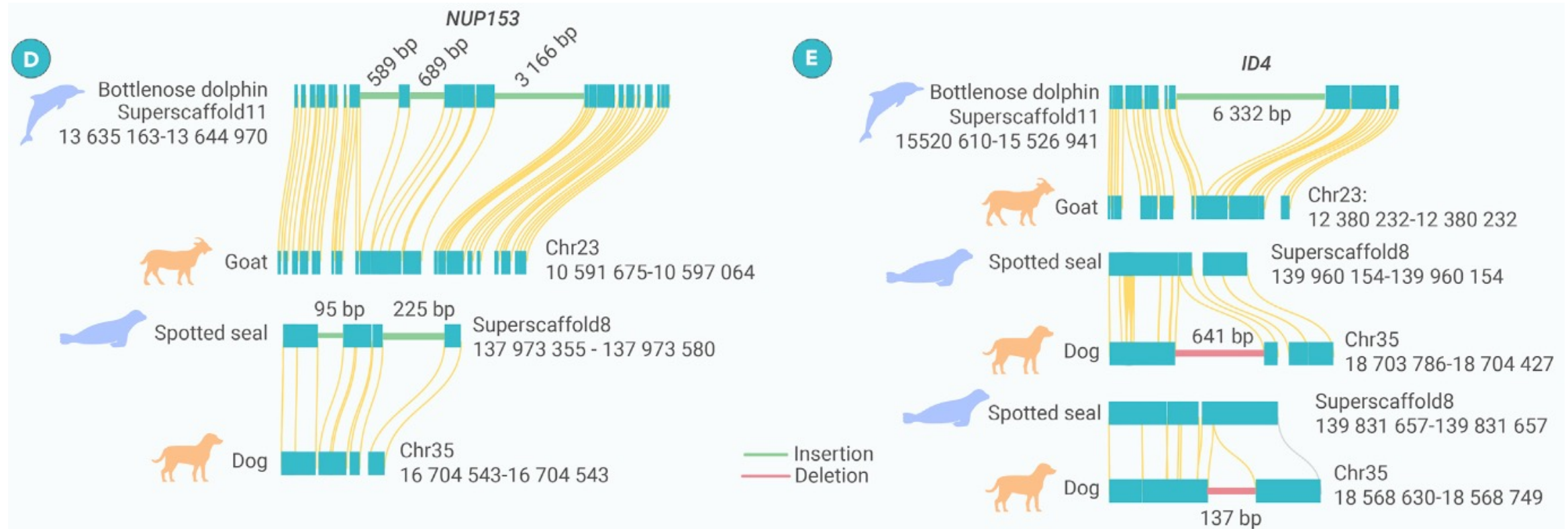
Result 5: Structural Variants & Neural Adaptation



SV Identification

- **Lineage-Specific SVs:** 339 cetacean-specific; 1054 pinniped-specific
- **Genomic Localization:** Located within conserved TADs near neuronal genes

Result 5: Structural Variants & Neural Adaptation



Functional Drivers & Conclusion

- **NUP153**: Maintains neural stem cell fate
- **ID4**: Regulates quiescence; linked to Alzheimer's
- **Conclusion**: SVs rewired regulatory networks for advanced cognition & social behavior

Convergent Evolution of Marine Mammals

Protein coding genes

	exon	exon	exon
Naked mole-rat	Q	P	V
Bottlenose dolphin	Q	P	R
Minke whale	Q	P	R
Cattle	Q	P	H
Dog	L	P	A
Hog badger	Q	P	P
Spotted seal	E	P	P
California sea lion	E	P	P
Manatee	Q	P	P
African elephant	Q	P	P

Conserved non-coding elements

3D genome structures

Structural variations

Key Genes:APPL1, NEIL1 | Drives adaptive phenotypes including blubber deposition and enhanced cancer resistance in marine mammals.

Elements:**HLEA, CNE300** | Modulates gene expression networks associated with hindlimb loss and aquatic adaptation.

Genes:**ASXL3, FAM43B** | Chromatin topological changes facilitate convergent traits in blubber development and cancer suppression.

Variants:**NUP153, ID4** | Structural rearrangements contribute to the evolution of enhanced cognitive functions.

Strengths & Highlights

Multi-Omics Integration

Combines genomics, 3D epigenomics, transcriptomics, and functional assays.

Rigorous Functional Validation

From in vitro to in vivo testing using CRISPR knock-in mice.

Novel Evolutionary Perspective

First systematic demonstration of 3D genome convergence in adaptive evolution.

High-Quality Data Resource

Chromosome-level assemblies provide a valuable community resource.

Limitations & Future Directions

Current Limitations

- Taxonomic Sampling Bias:**Over-reliance on cetaceans and pinnipeds.
- Functional Validation Gap:**Limited to a small subset of candidate loci.
- Causal Inference Challenges:**Correlation does not always equal causation. The direct, causal link between some of the observed TAD changes and gene expression still needs to be rigorously tested.

- 1.附件图的质量比较差，非矢量且看不清楚。
- 2.正文中，部分结果描述顺序比较混乱。

Strategic Future Directions

- Expanded Genomic Landscape:**Incorporate more sirenian (海牛目) genomes.
- High-throughput Functional Assays:**Test thousands of candidate elements.
- Universality of Convergence:**Test the model in other adaptive transitions.
- Single-Cell Epigenomic Profiling:**Dissect cell-type-specific changes.



REPORT

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Thank You

Questions are welcome!

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