

Threespine stickleback fish: a novel evolutionary mutant model for mitochondrial dysfunction.

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Attempt at self promotion
@Stickle_Beck

Learning Objectives:

Be able to explain what an evolutionary mutant model is

Understand how mitochondrial diseases arise and why they are so prevalent

Describe the threespine stickleback system and why it is a good model for studying mitochondria

Become super excited to help me

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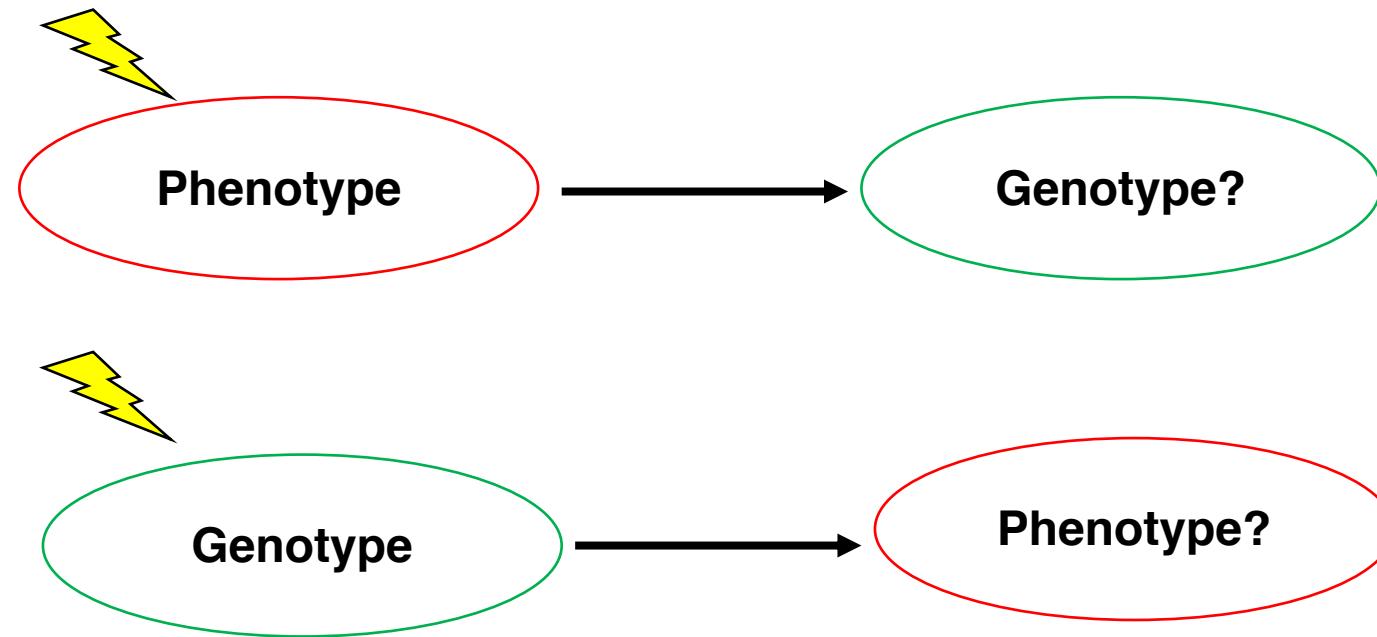
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Traditional laboratory mutant screens fall into two categories: Forward and Reverse

Forward Genetic
Mutant

Reverse Genetic
Mutant



Evolutionary Mutant Models (EMMs) are animals with adaptations that mimic maladaptive human disease

Trends in Genetics

Volume 38, Issue 1, January 2022, Pages 22-44

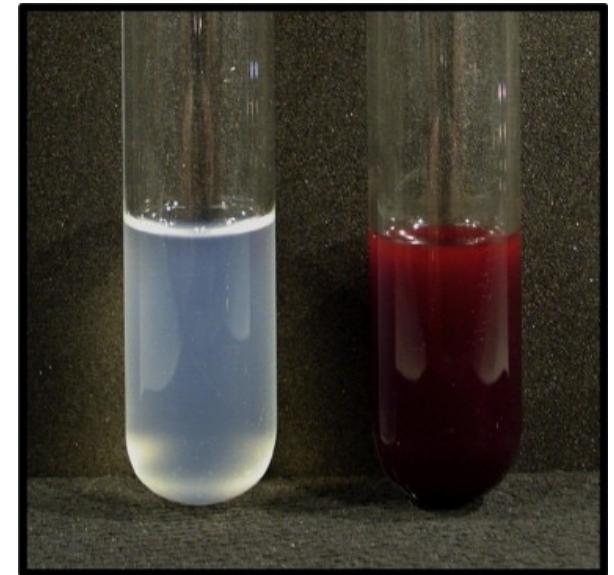
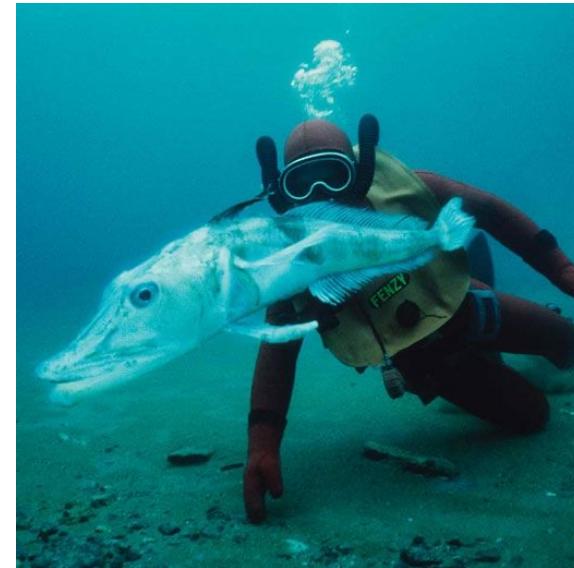


Feature Review

Focus issue: Studying genetic variation through an evolutionary lens

Advancing human disease research with fish
evolutionary mutant models

Emily A. Beck ^{1, 2}✉, Hope M. Healey ², Clayton M. Small ^{1, 2}, Mark C. Currey ², Thomas Desvignes ³,
William A. Cresko ^{1, 2}, John H. Postlethwait ³



Antarctic Ice Fish have evolved low bone density and white "antifreeze" blood making them excellent models for Anemia and Osteopenia

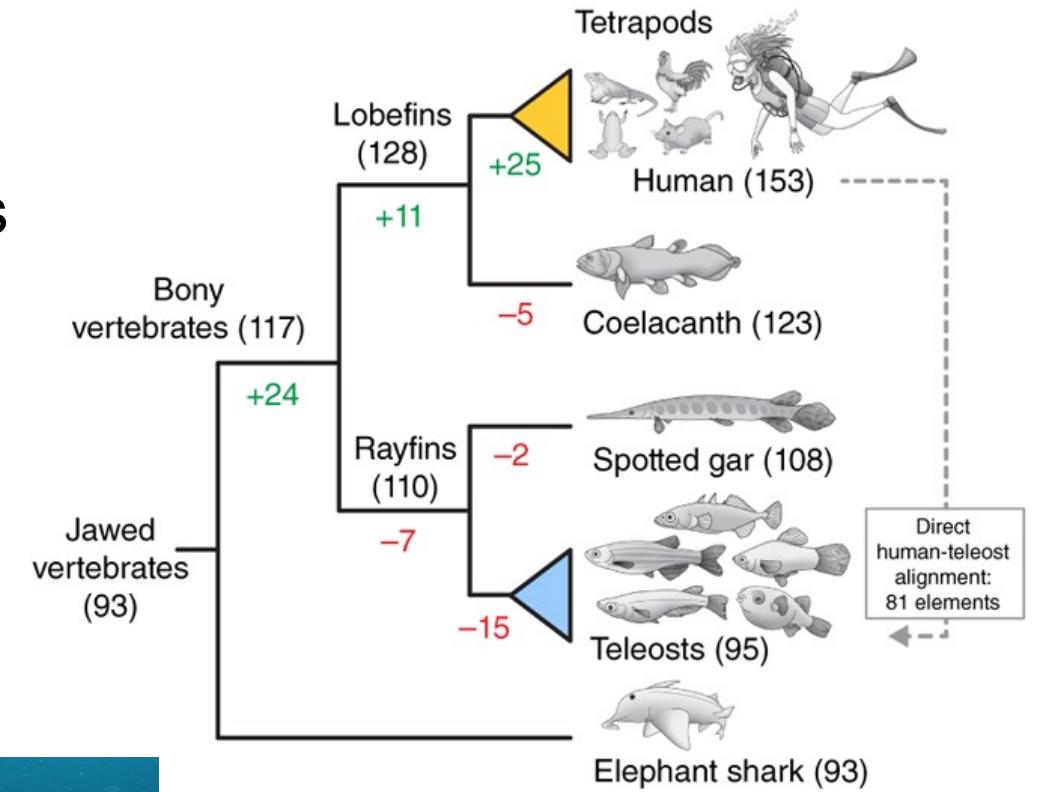
Fish are a rich source of EMMs

They are a very diverse group

There are long divergence times between groups

They have adapted to many environments

They have experienced genome duplications



Learning Objectives:

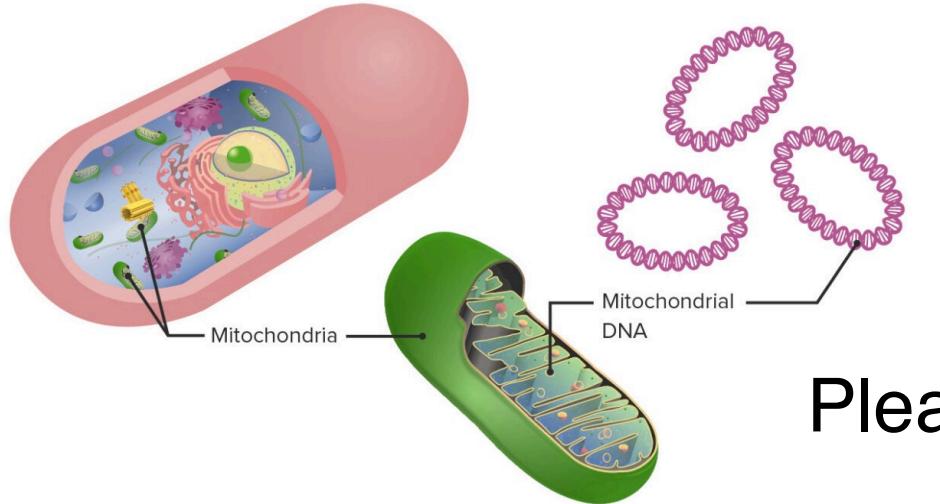
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Mitochondrial diseases are surprisingly prevalent and difficult to study



Mitochondrial diseases are those with symptoms caused by poorly functioning mitochondria

Please don't say "powerhouse of the cell"

Current Biology

Volume 16, Issue 14, 25 July 2006, Pages R551-R560

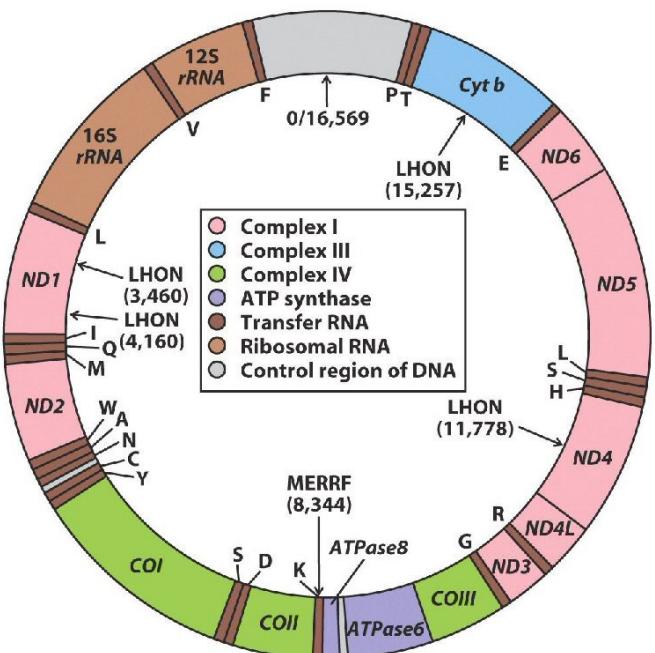
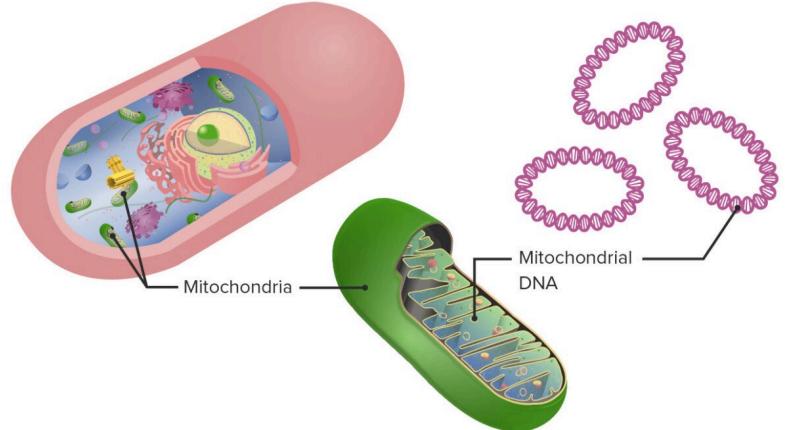


Review

Mitochondria: More Than Just a Powerhouse

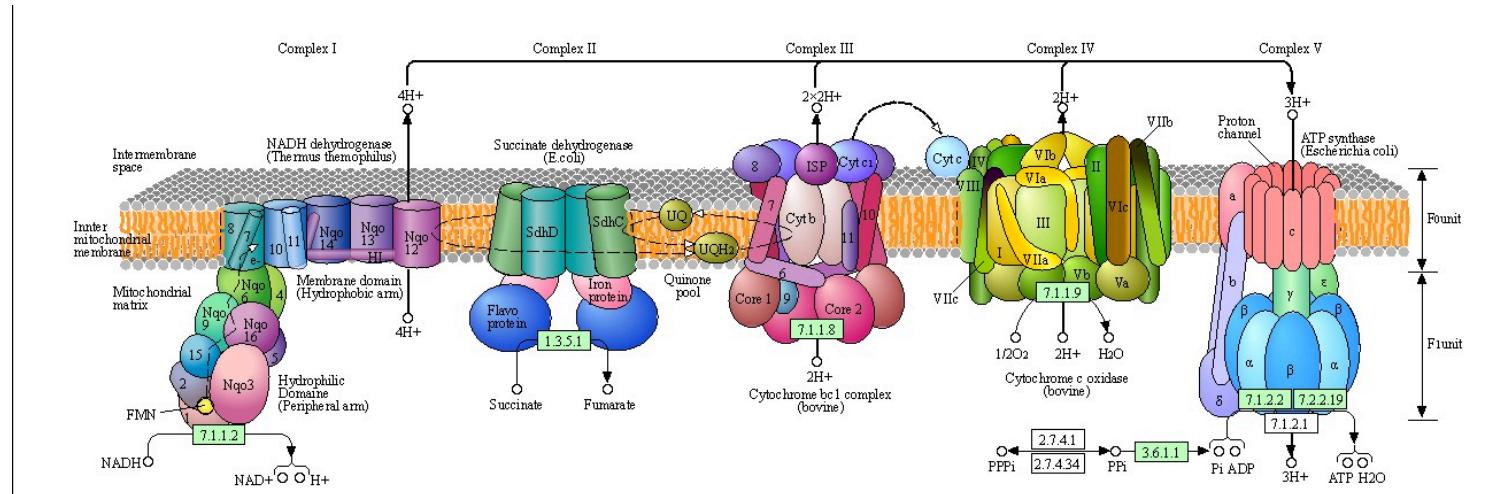
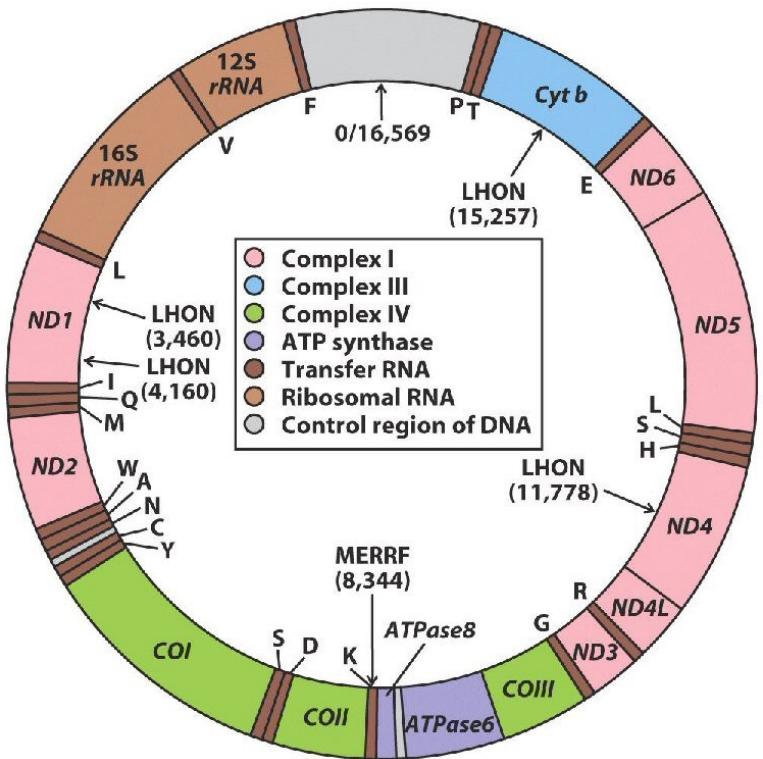
Heidi M. McBride ¹✉, Margaret Neuspiel ², Sylwia Wasiak ²

Mitochondria have their own genomes inherited independently from the nuclear genome



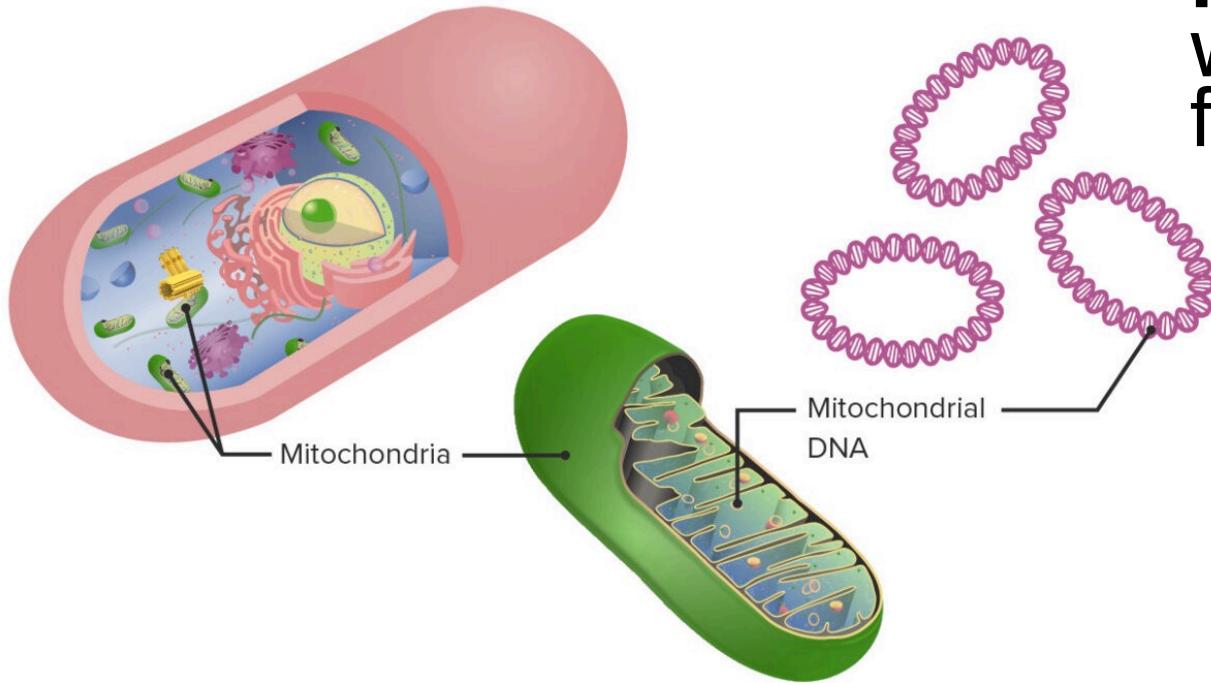
- Small Circular genome made of 13 protein coding genes, 2rRNAs, 22 tRNAs
- Maternally inherited instead of biparentally inherited like the nuclear genome
- Mutation rate that is 5-10 times greater than the nuclear genome

Mitochondrial encoded proteins make up parts of Oxidative Phosphorylation (OXPHOS)



Problem: You have mitochondrial proteins evolving 5-10 times faster AND independently than nuclear proteins but they have to work together

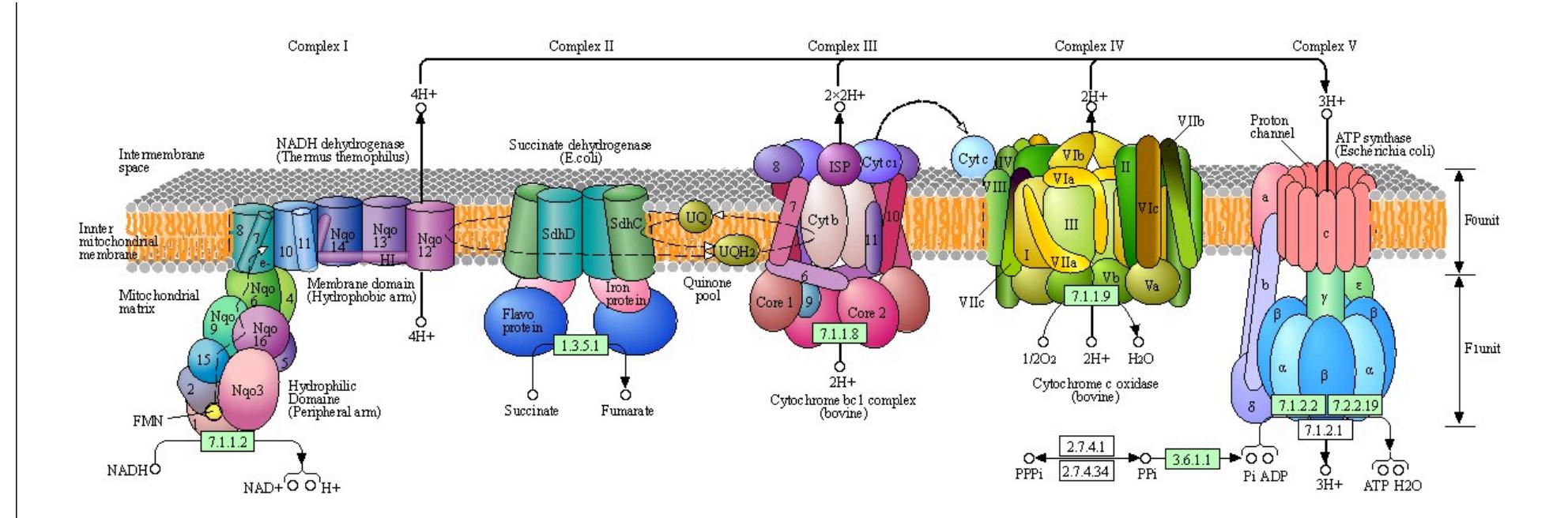
Mitochondrial diseases are **surprisingly prevalent** and difficult to study



Mitochondrial diseases are those with symptoms caused by poorly functioning mitochondria

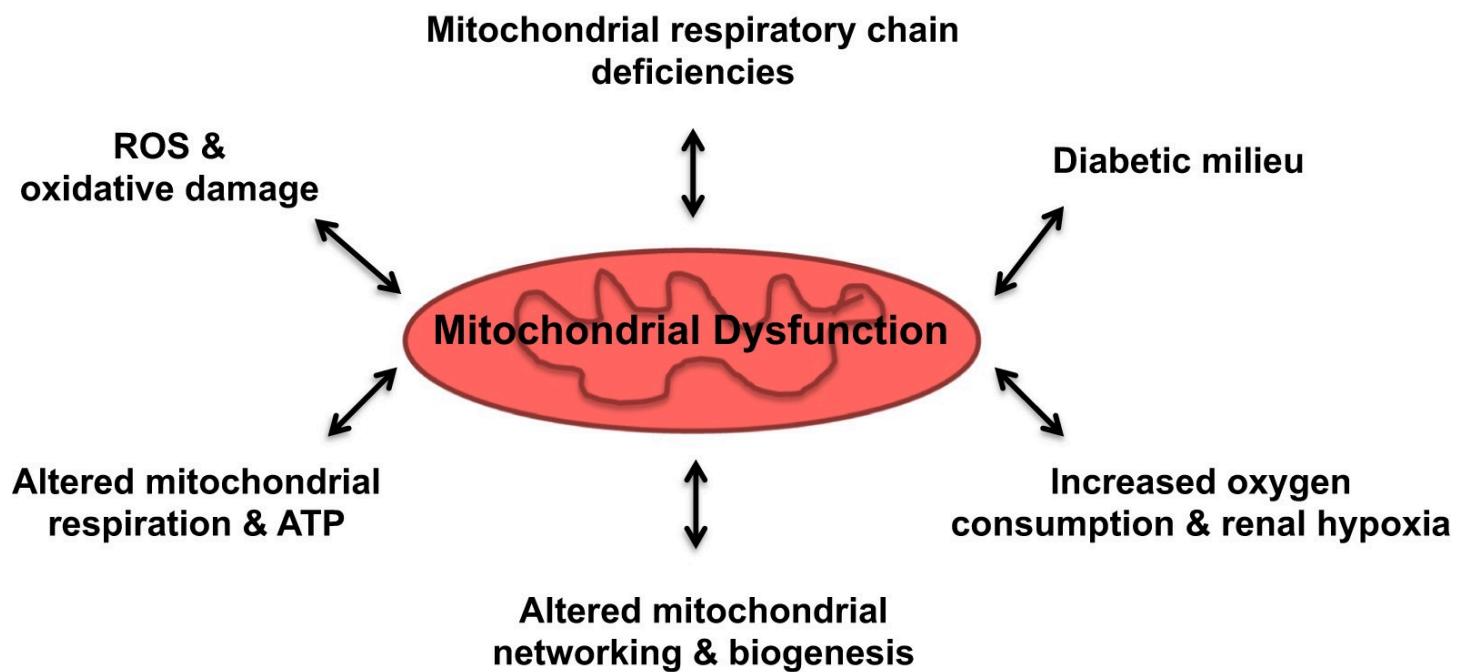
Who can name a mitochondrial disease?

Mutations in OXPHOS genes result in Primary Mitochondrial Disease



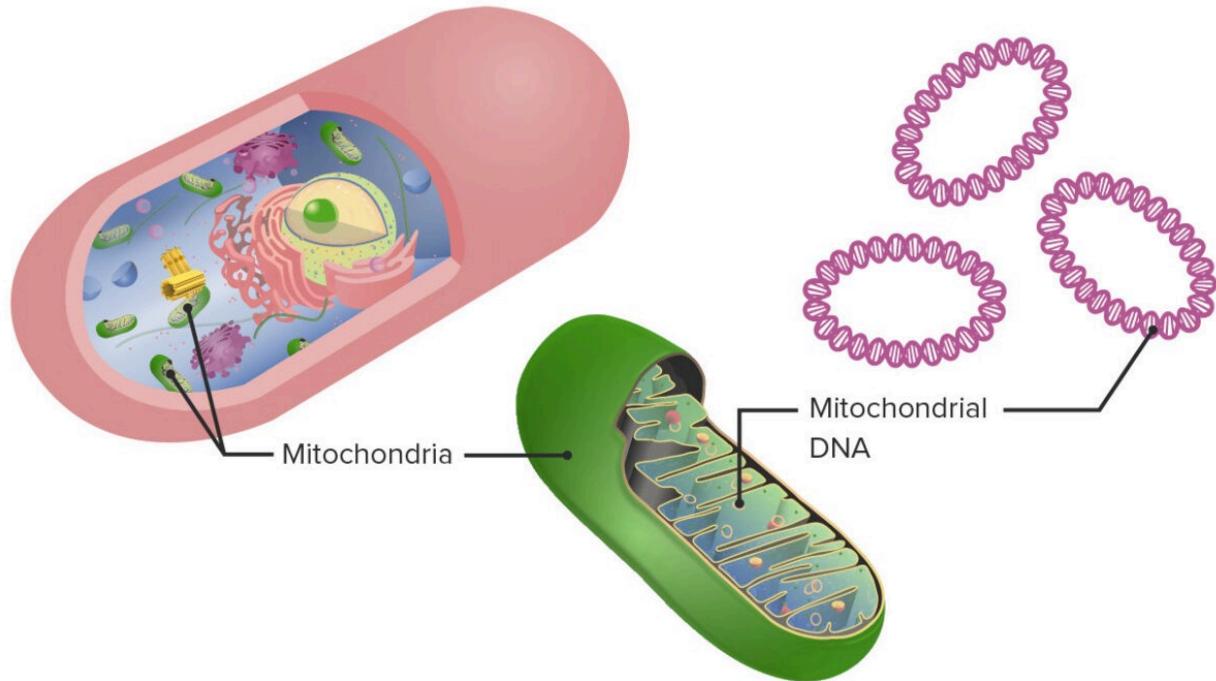
Leigh Syndrome
Kearns-Sayre Syndrome
Pearson Syndrome...etc

MANY mutations **outside** of OXPHOS can lead to mitochondrial dysfunction or Secondary Mitochondrial Diseases



Parkinson's Disease
ALS
Muscular Dystrophy
Diabetes
Cancer
Alzheimer's Disease

Mitochondrial diseases are surprisingly prevalent and **difficult to study**



Symptom severity, prognosis, and treatment efficacies are heavily influenced by the genetic background of the individual

Problem: Humans are genetically diverse while most laboratory organisms are inbred by design and almost all contain a single mitochondrial haplotype. Humans have over 5,000 mitochondrial haplotypes.

We need an organism with genetic variation and multiple mitochondrial haplotypes that is genetically amenable to high throughput studies.

We need an evolutionary mutant model of mitochondrial disease!

Learning Objectives:

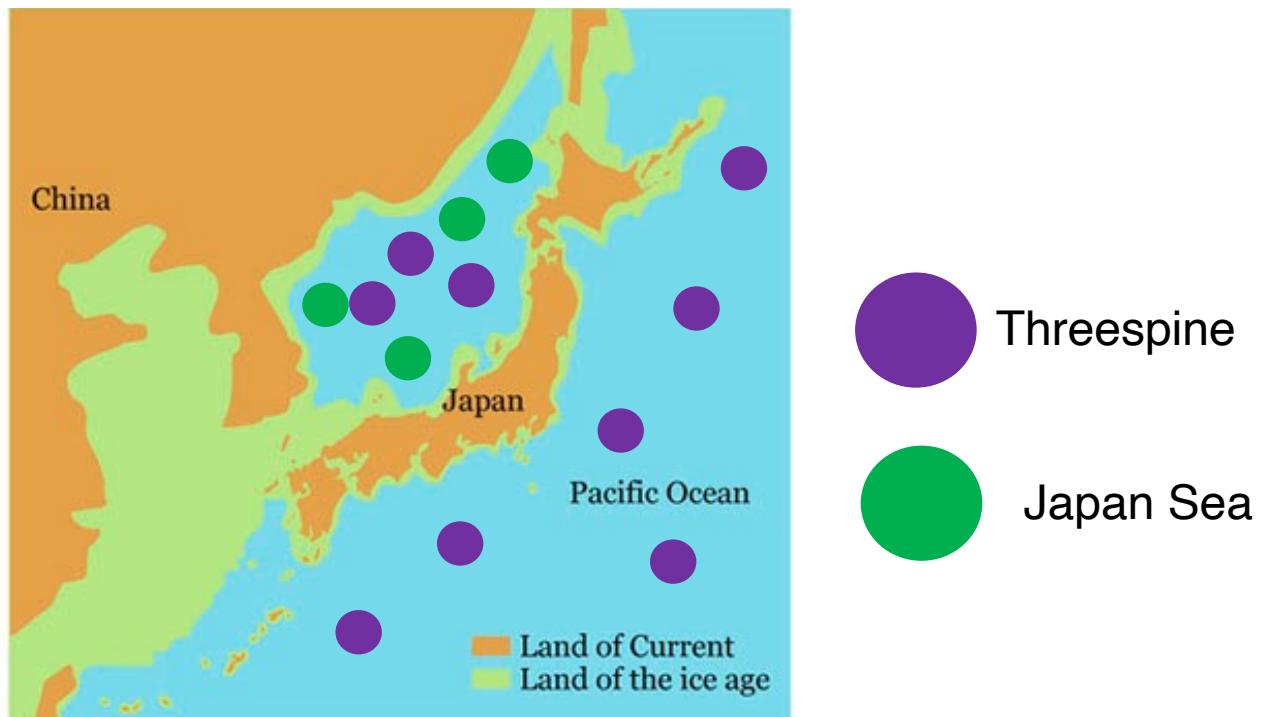
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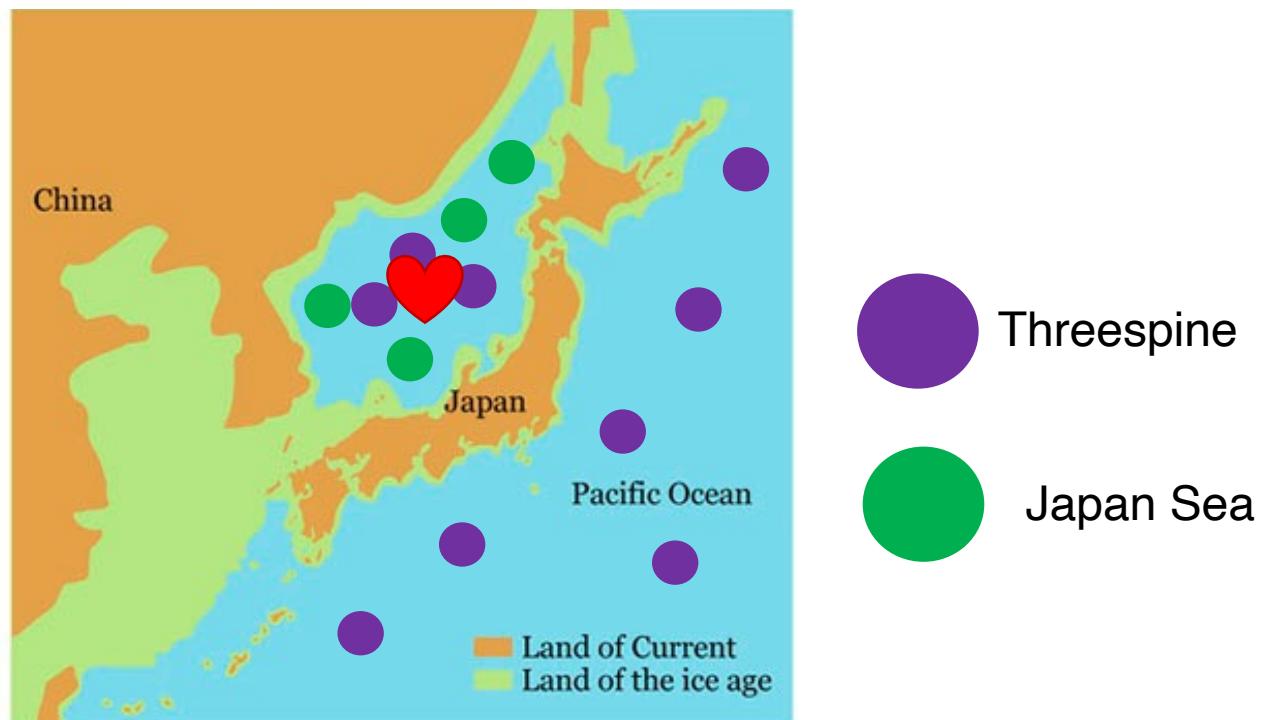
Subset of threespine stickleback were trapped in the Sea of Japan during last glacial maximum with Japan Sea stickleback



Hybridization occurred between threespine and Japan Sea stickleback

OII × OII

OII

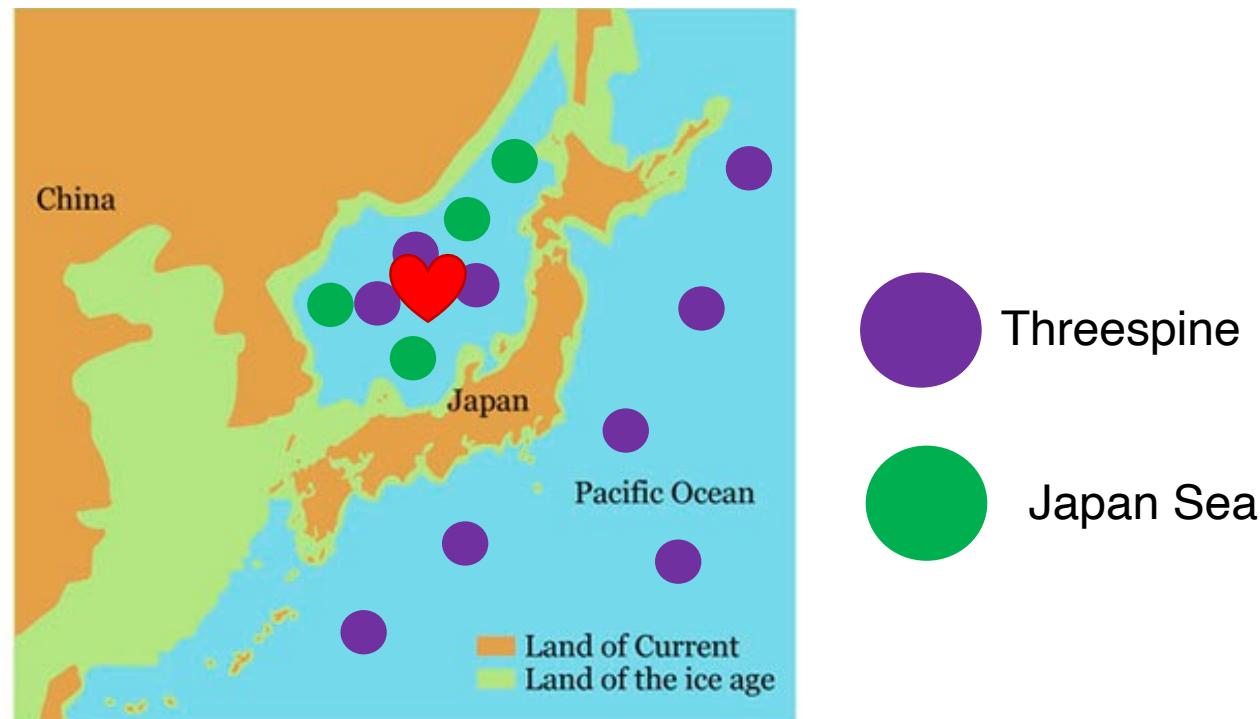


Through backcrossing the mitochondrial genome (and parts of the nuclear genome) introgressed from the Japan Sea stickleback to the threespine stickleback

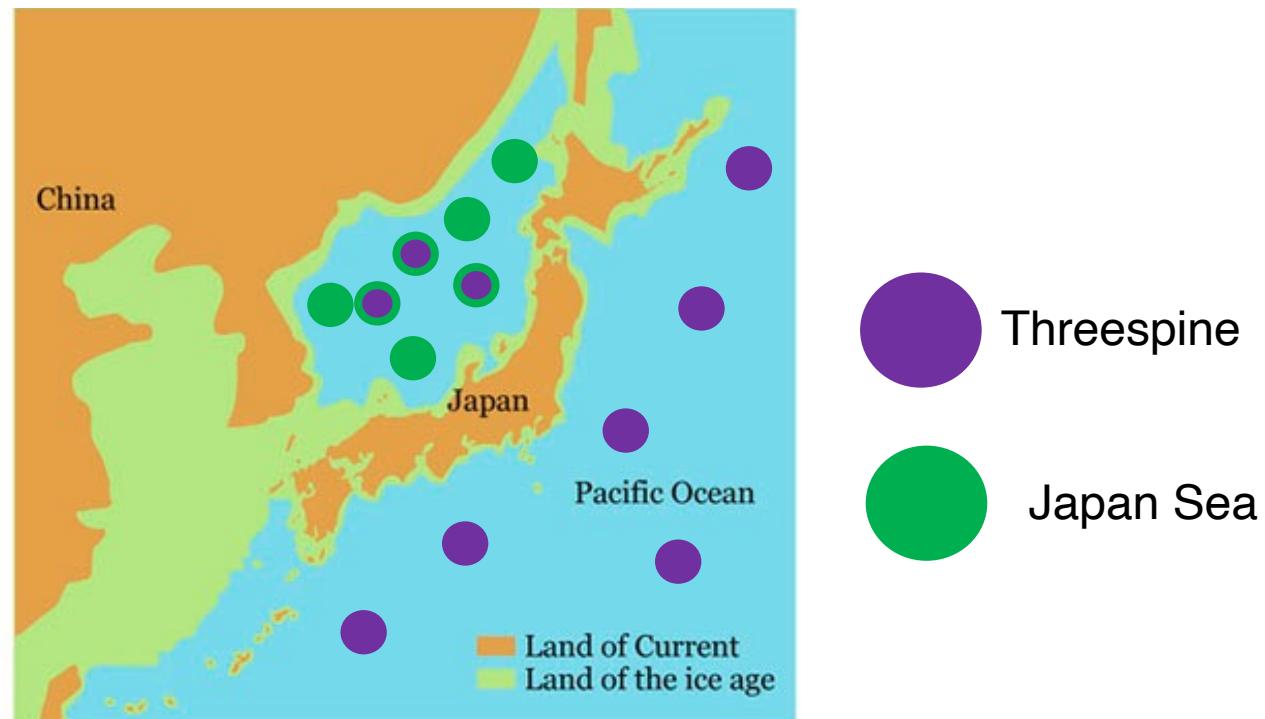
OII × OII

OII × OII

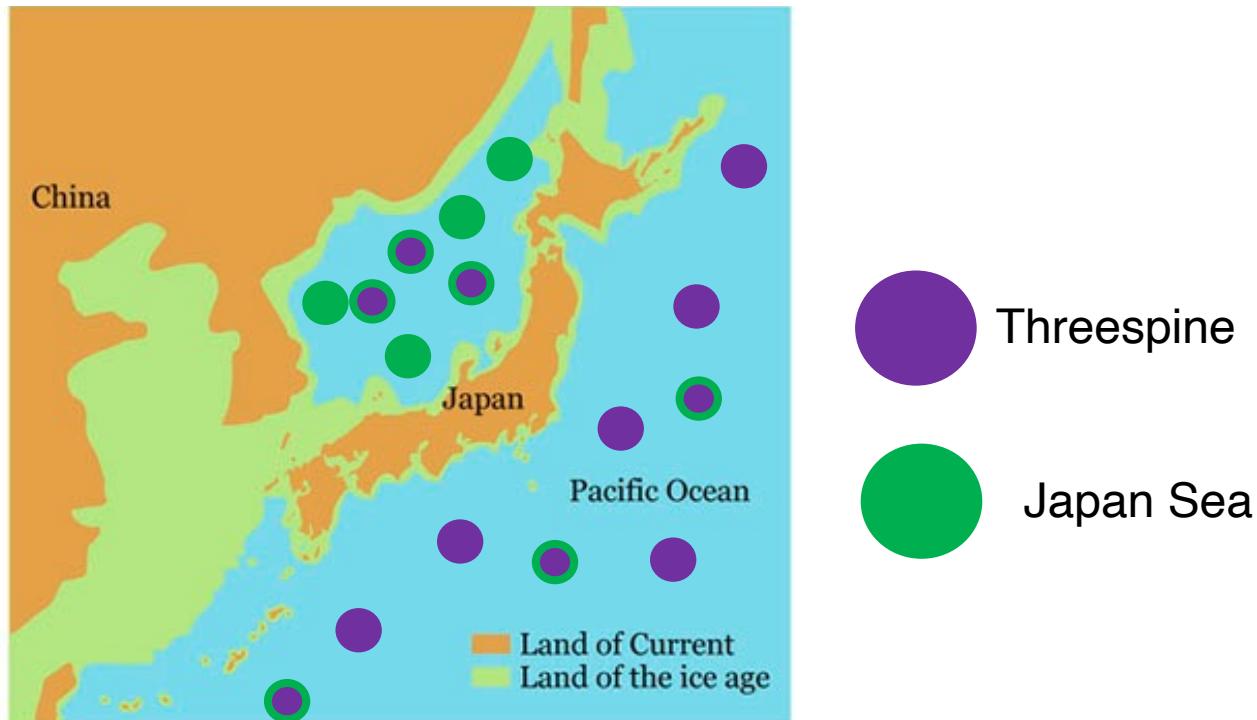
OII



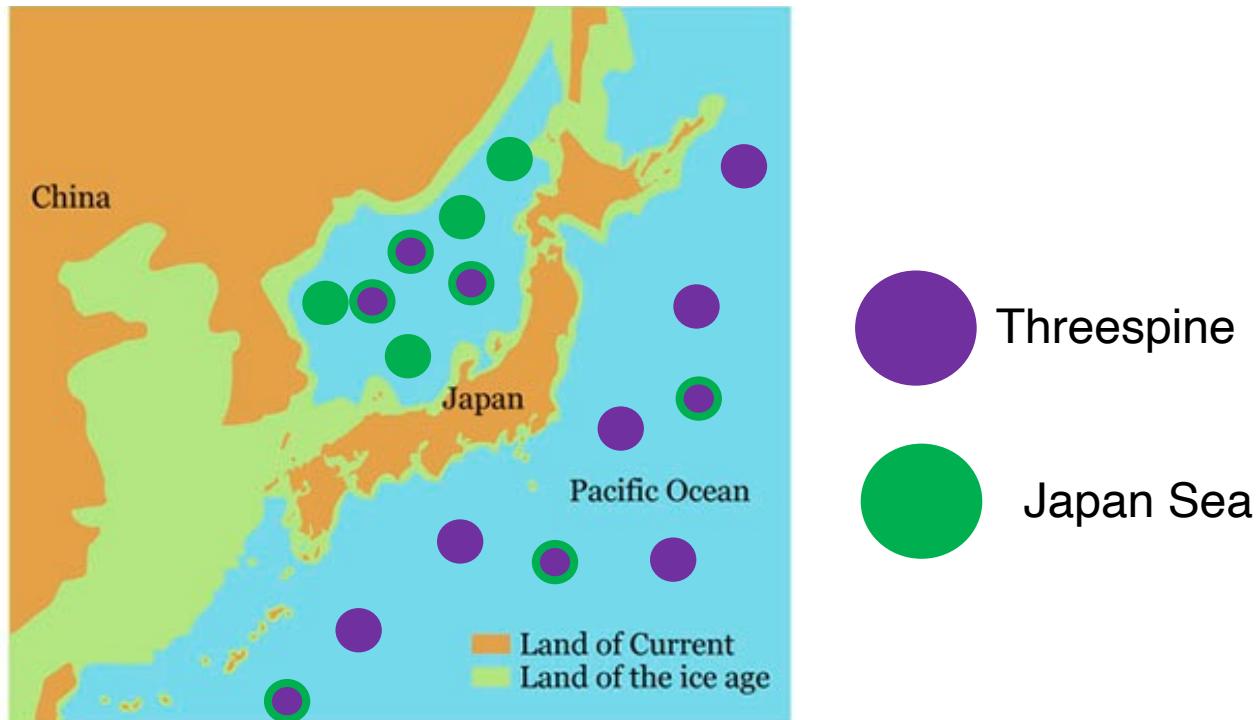
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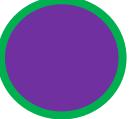
Ice melted and threespines with the Japan Sea mitochondria rejoined threespines with their original mitochondria



Ice melted and threespines with the Japan Sea mitochondria rejoined threespines with their original mitochondria



Now there are three groups of stickleback

-  Japan Sea
-  Threespine with Japan Sea mitochondria – Trans-North Pacific (TNP) mitotype
-  Threespine with Original mitochondria – Euro-North American (ENA) mitotype

There are two distinct mitochondrial haplotypes segregating in some threespine populations.

- Threespine with Japan Sea mitochondria – Trans-North Pacific (TNP) mitotype
- Threespine with Original mitochondria – Euro-North American (ENA) mitotype

How different are these “mitotypes”?

Are there physiological differences in fish with the differing mitotypes?

Currently in preparation

Extreme divergence in mitochondrial haplotypes makes the threespine stickleback fish a novel evolutionary mutant model for mitochondrial dysfunction.

Emily A. Beck^{1,2}, Byron Hetrick³, Carrie E. McCurdy³, Susan Bassham¹, & William A. Cresko^{1,2}

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1. Institute of Ecology and Evolution, University of Oregon, Eugene, OR, USA

2. Presidential Initiative in Data Science, University of Oregon, Eugene, OR, USA

3. Department of Human Physiology, University of Oregon, Eugene, OR, USA

Q: How different are these “mitotypes”?

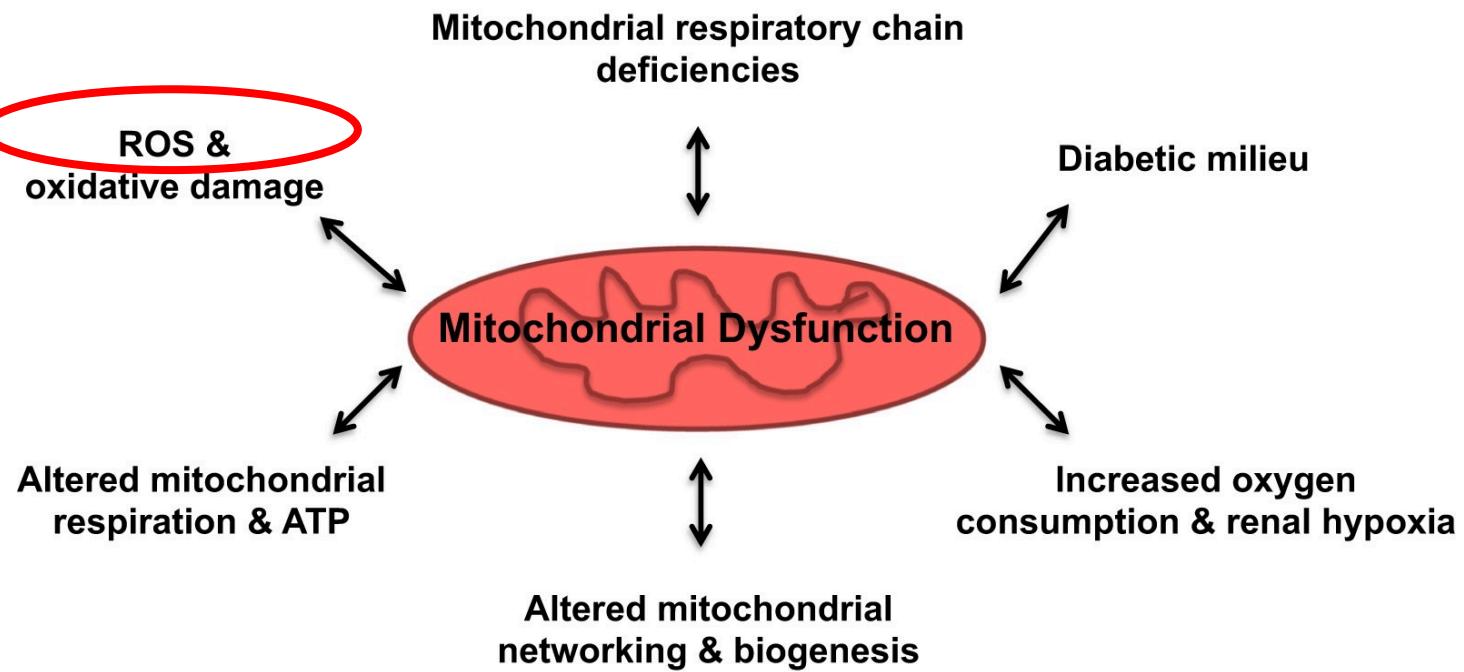
A: VERY

We assessed divergence across the TNP and ENA mitogenomes

Species	Nucleotide Divergence
Threespine stickleback (<i>G. aculeatus</i>) TNP vs ENA	0.032-0.034
Mouse (<i>Mus musculus musculus</i> vs <i>M.m.domesticus</i>)	0.023
Human (<i>Homo sapien sapiens</i> vs <i>H.s. neanderthalensis</i>)	0.011
Human (<i>Homo sapien sapiens</i> vs <i>H.s. denisova</i>)	0.02
Human (<i>Homo sapien sapiens</i> vs <i>H.s. heidelbergensis</i>)	0.026

Q: Are there physiological differences in fish with the differing mitotypes?

A: YES

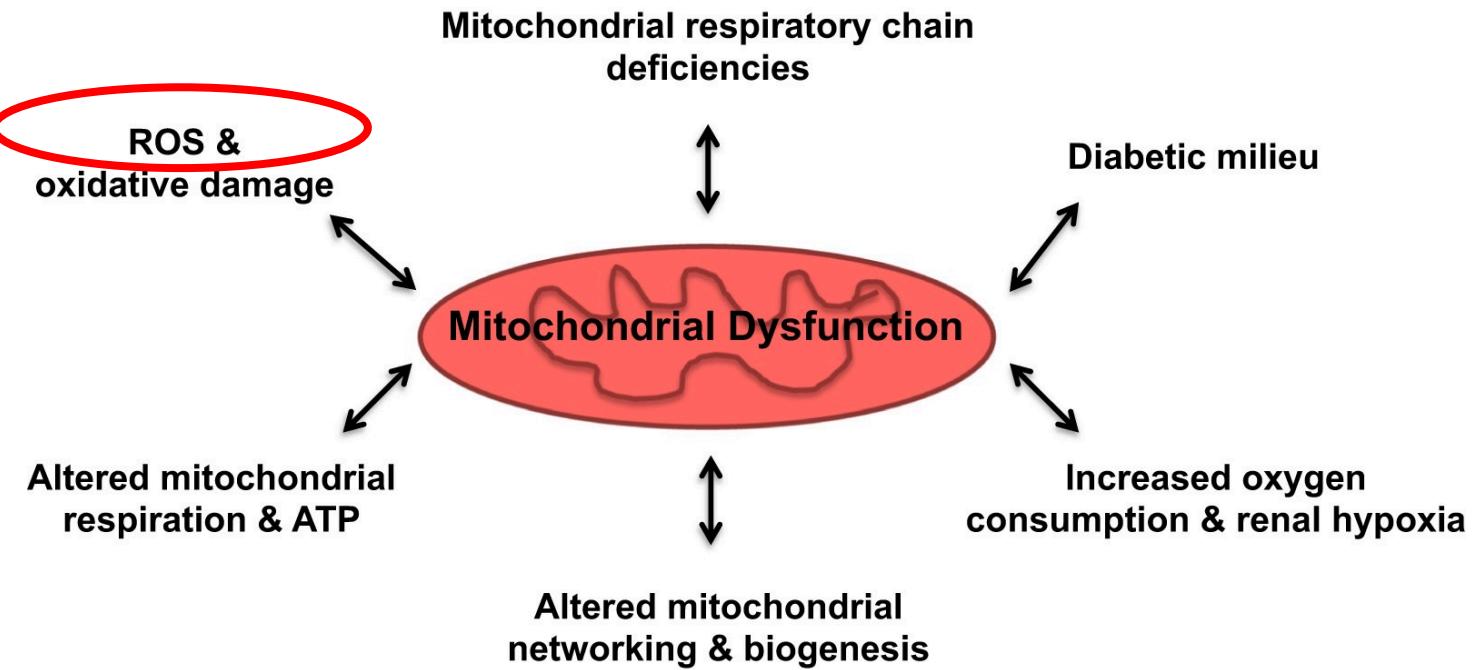


Remember:

Mitochondria naturally produce ROS during OXPHOS, but they also function to clear ROS to prevent damage and apoptosis

Q: Are there physiological differences in fish with the differing mitotypes?

A: YES



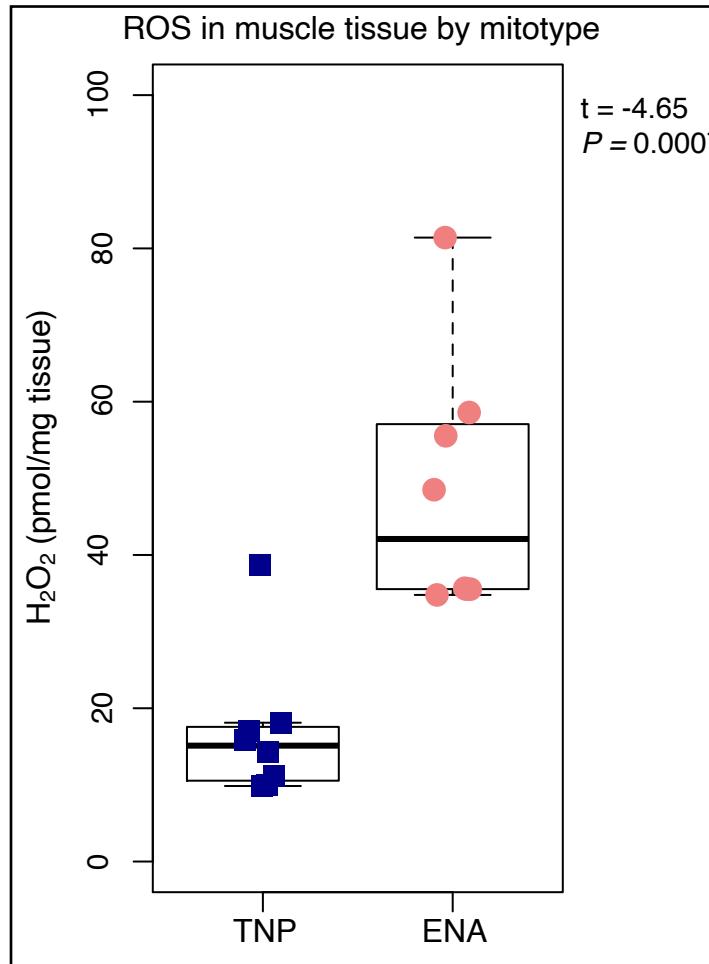
Remember:

Mitochondria naturally produce ROS during OXPHOS, but they also function to clear ROS to prevent damage and apoptosis

Which mitotype do you think produced more ROS? The original mitogenome or the new/introgressed mitogenome?

Q: Are there physiological differences in fish with the differing mitotypes?

A: YES



This work only focuses on the mitochondrial genome.

Burning question: How has the nuclear genome responded to having two mitochondrial haplotypes?

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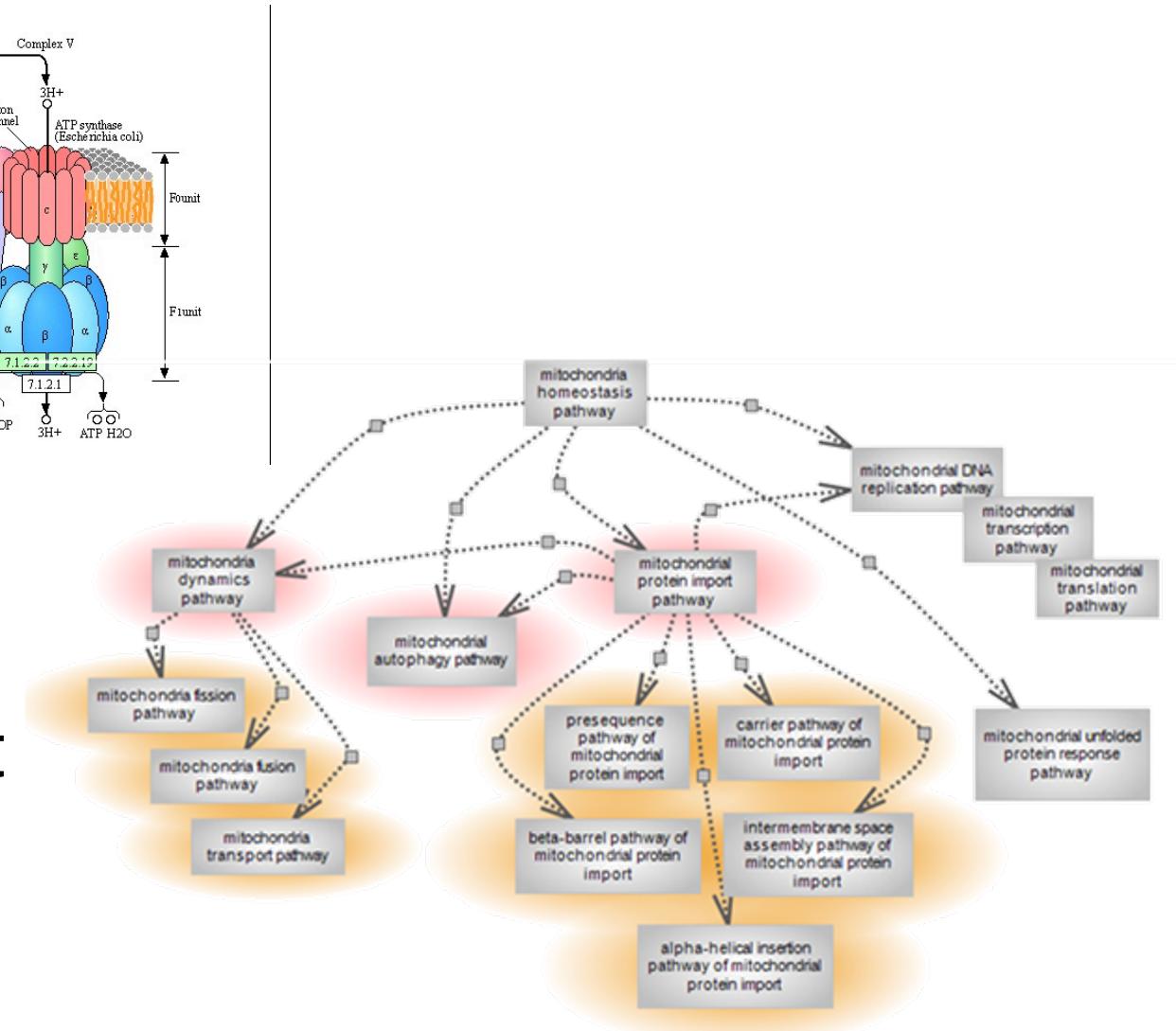
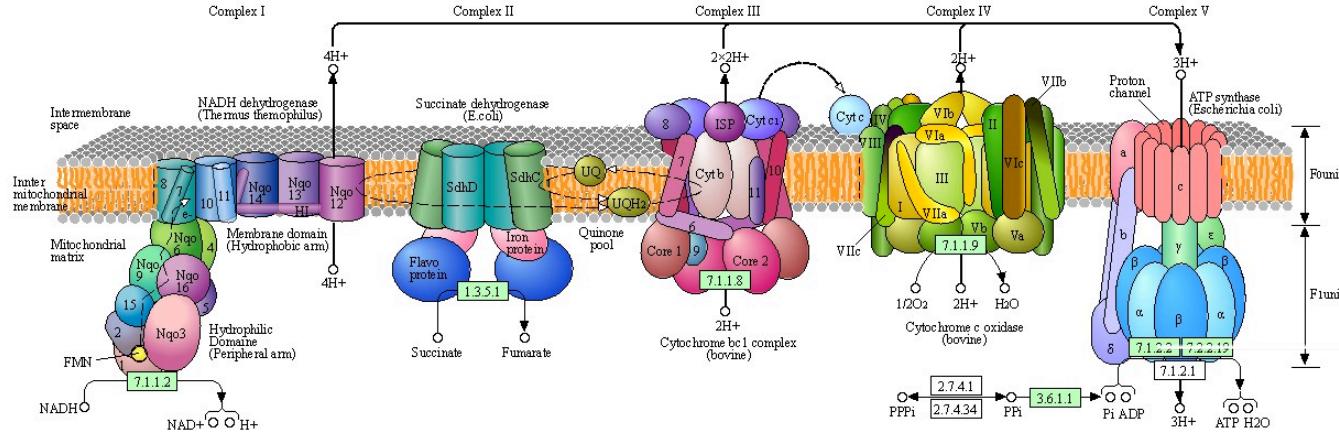
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More than just a powerhouse



There are many well described pathways of nuclear genes that impact mitochondrial function

Together we can identify how nuclear pathways are impacted by the presence of different mitogenomes

We have:

- (1) A curated database of nuclear encoded proteins and pathways that are essential to mitochondria (MitoCarta)
- (2) Whole genome sequences from stickleback around the world with each mitotype

Acknowledgements:

Cresko Laboratory at UO Institute of Ecology and Evolution

Bill Cresko

Susan Bassham

McCurdy Laboratory at UO Department of Human Physiology

Carrie McCurdy

Byron Hetrick

Funding:

- National Institutes of Health
- UO Office of the Vice President for Research and Innovation
- Presidential Initiative in Data Science