A MITOCHONDRIAL GENETICS AND DISEASE RISK: CURRENT EVIDENCE

Why can't we understand and cure the common diseases?

Neuropsychiatric Disorders: Autism, ADHD, Schizophrenia, Bipolar Disease, Stress Response, Alzheimer Disease, Parkinson Disease, ALS, Multiple Sclerosis, Blindness, Deafness…

Heart-Muscle: Cardiomyopathy, Myopathy, Chronic Fatigue…

Visceral: Renal, Hepatic, Immunological…

Metabolic: Diabetes, Obesity, Cardiovascular Disease…

Cancer & Aging

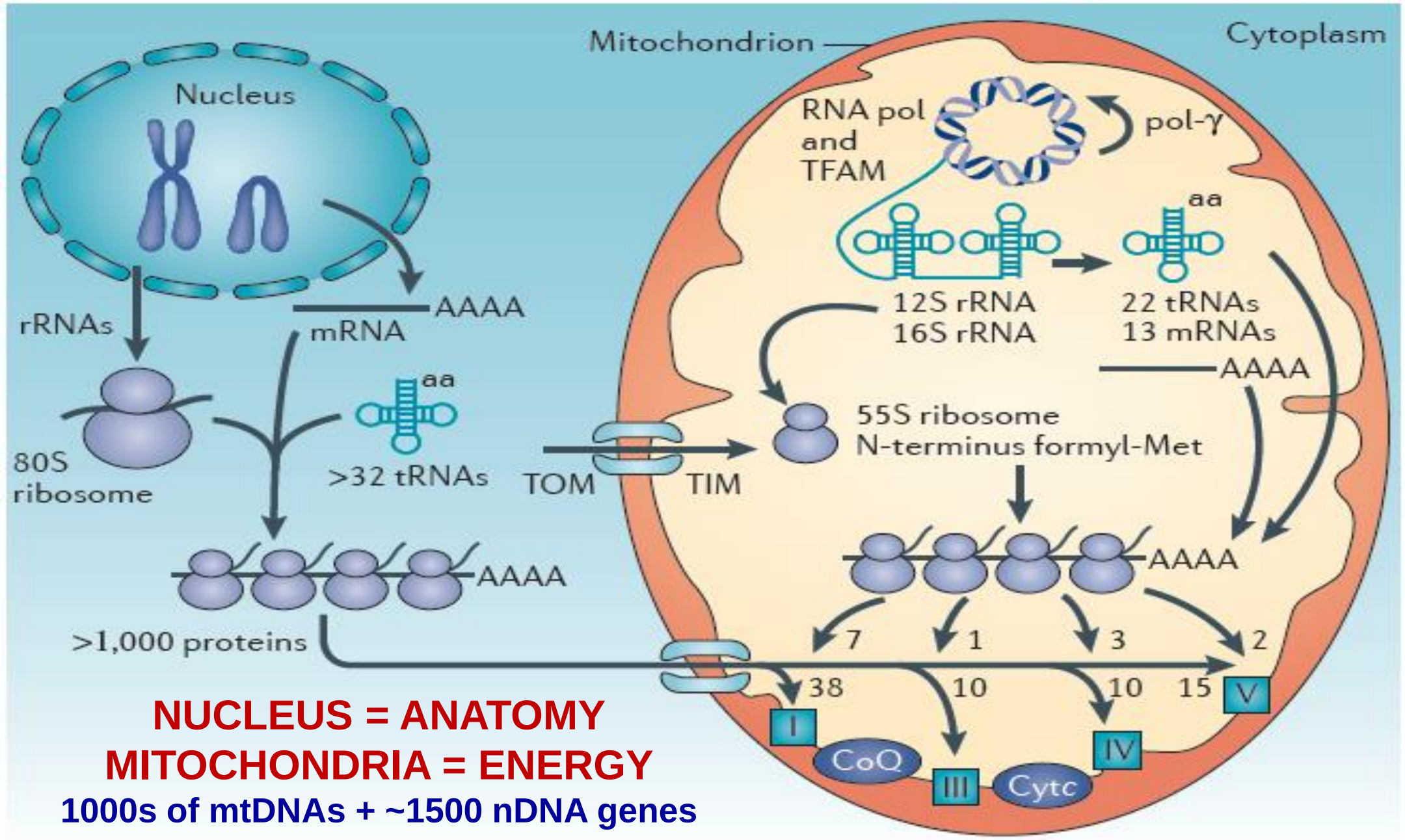
Western medicine has approached the common diseases primarily from an anatomical and Mendelian perspective, but

Life = Anatomy + Energetics + Information

Consequently, the role of bioenergetics and non-Mendelian bioenergetic inheritance has been largely ignored.

Our hypothesis is that bioenergetic dysfunction lies at the nexus of the genetic and environmental "causes" of the "common-complex" diseases.

THE EUKARYTIC CELL IS COMPOSED OF TWO ORGANISMS



NUCLEUS = ANATOMY

MITOCHONDRIA = ENERGY

1000s of mtDNAs + ~1500 nDNA genes

MITOCHONDRIAL FUNCTION IS CENTRAL TO HEALTH

ENERGY: Fats + Sugars + Oxygen = Energy (heat + work) + CO_2 + H_2O

REDOX BALANCE: Thiol-Disulfide Regulation of Pathways and Transcription Factors.

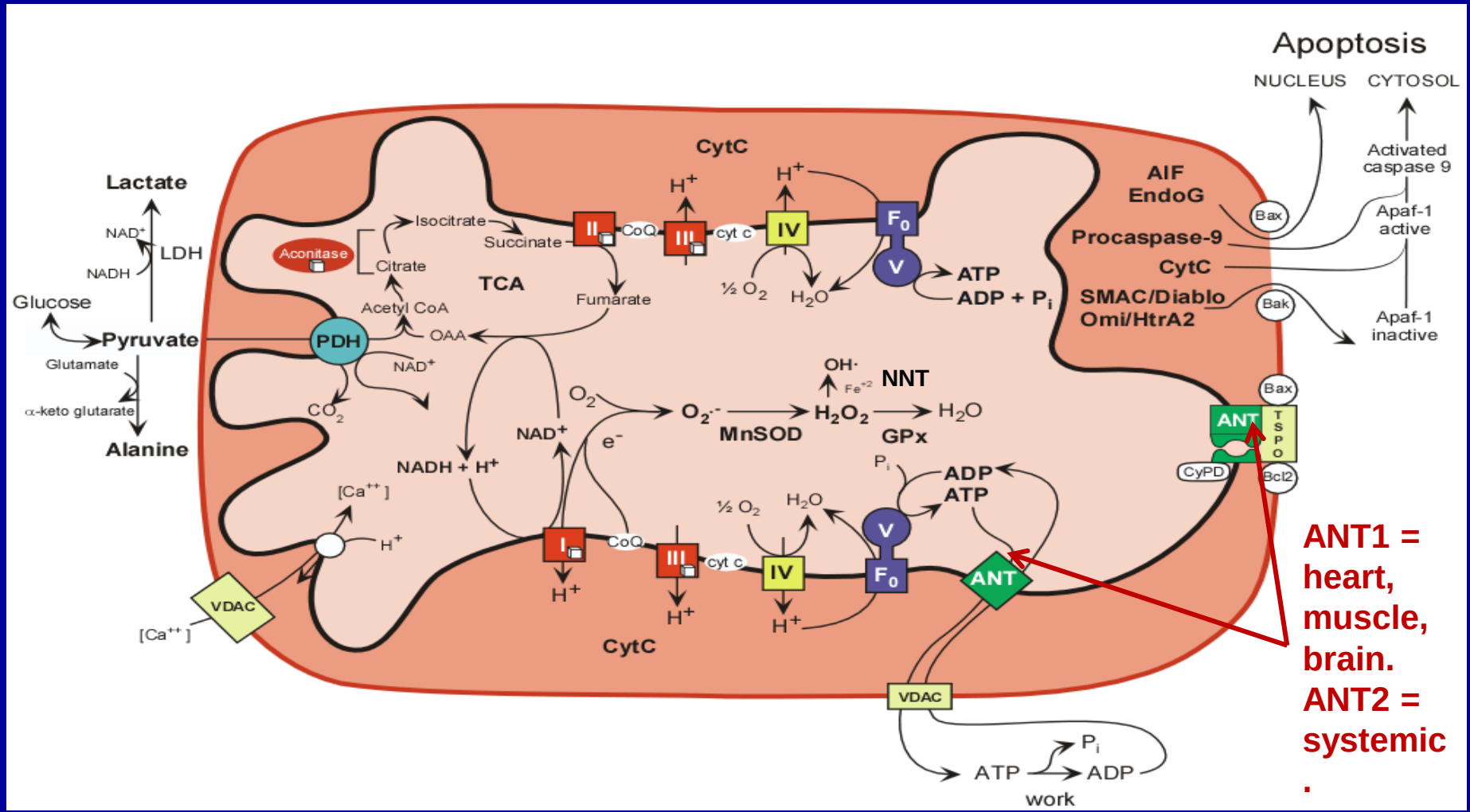
REACTIVE OXYGEN SPECIES (ROS): Oxygen Radicals + Signal Transduction.

Ca^{++} REGULATION: Regulates Cytosol Ca^{++}, Metabolism, & mtPTP.

APOPTOSIS: Energy ↓ + ROS ↑ = mtPTP Activated → Cell Death (Apoptosis).

EPIGENOMIC REGULATION: Mito. (ATP, acetyl CoA, SAM, α-ketoglutarate) modify epigenome.

BIOENERGETIC HIERARCHY: Brain > Heart > Muscle > Kidney > Endocrine > Liver.



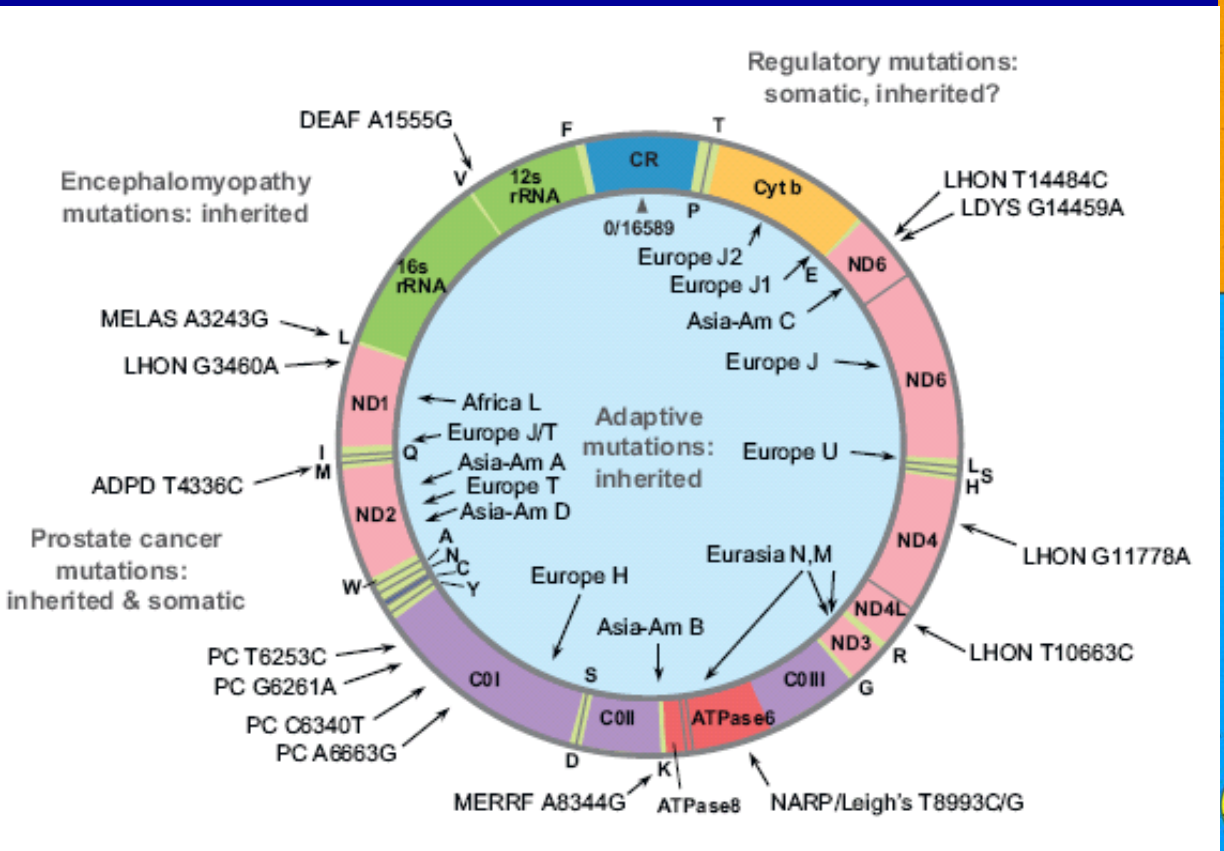
THE MITOCHONDRIAL GENOME IS DISTRIBUTED ACROSS THE nDNA & mtDNA

THE MITOCHONDRIAL GENOME:

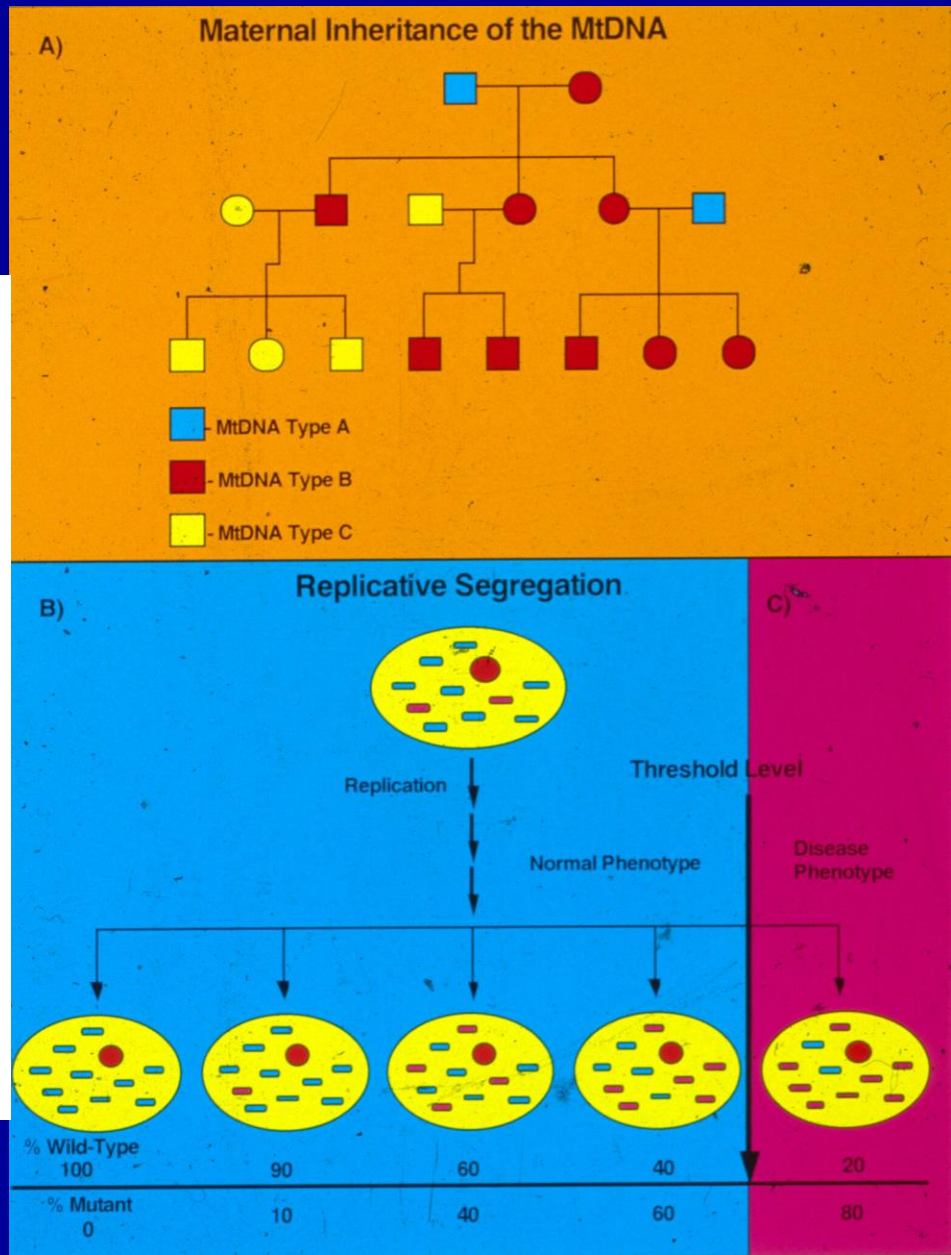
~ 1500 nDNA Genes

Dispersed Across the Chromosomes

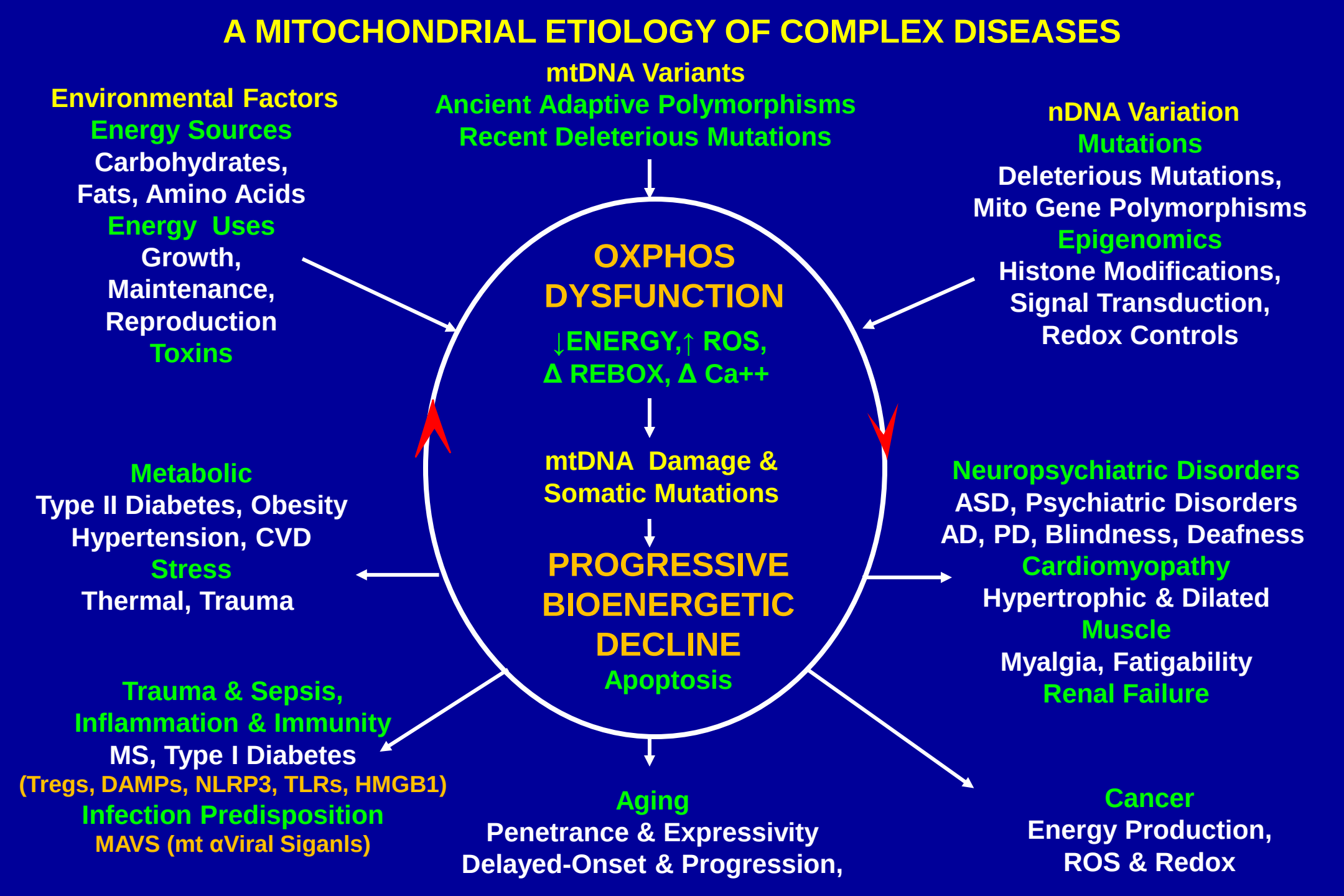
+ 37 mtDNA Genes



High Mutation Rate: ROS



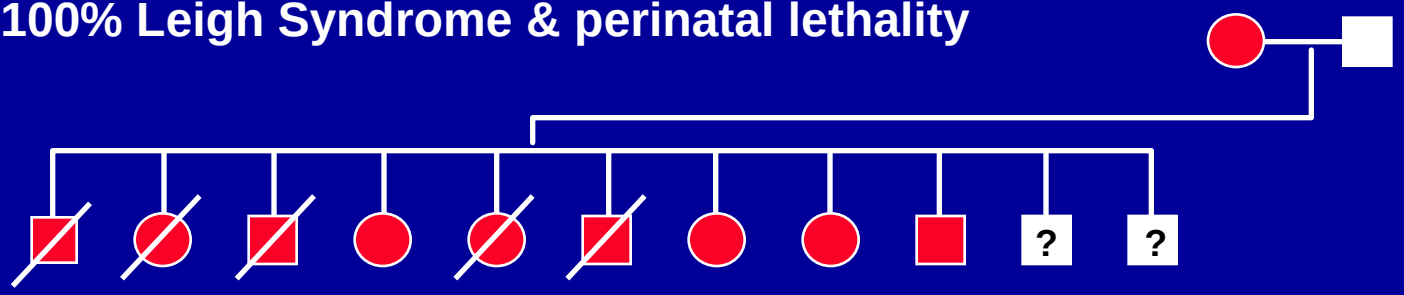
A MITOCHONDRIAL ETIOLOGY OF COMPLEX DISEASES



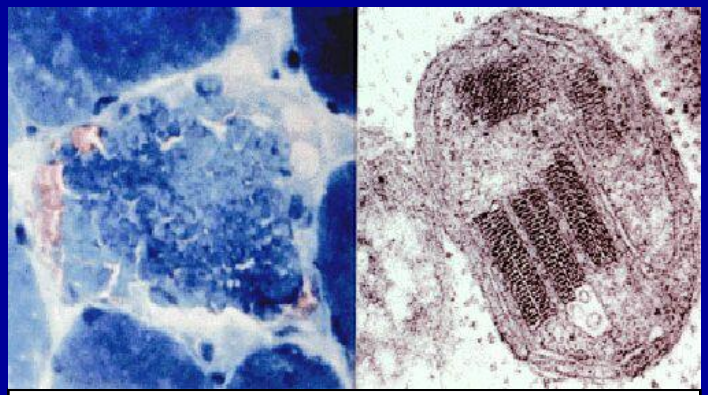
mtDNA GENE MUTATIONS GIVE VARIABLE PHENOTYPES

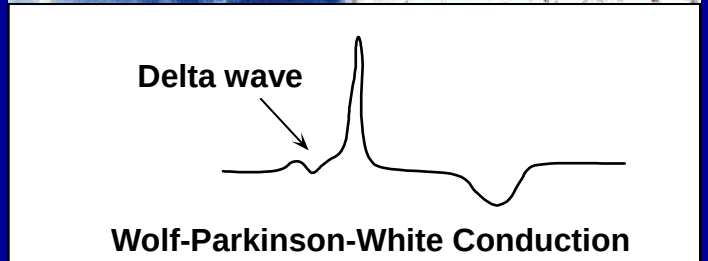
THE SAME mtDNA $tRNA^{Leu(UUR)}$ np A3243G MUTATION CAUSES DIFFERENT DISEASES

10-30% Autism & Type I & II diabetes;
> 70% mutation myopathy, cardiomyopathy & MELAS;
~100% Leigh Syndrome & perinatal lethality



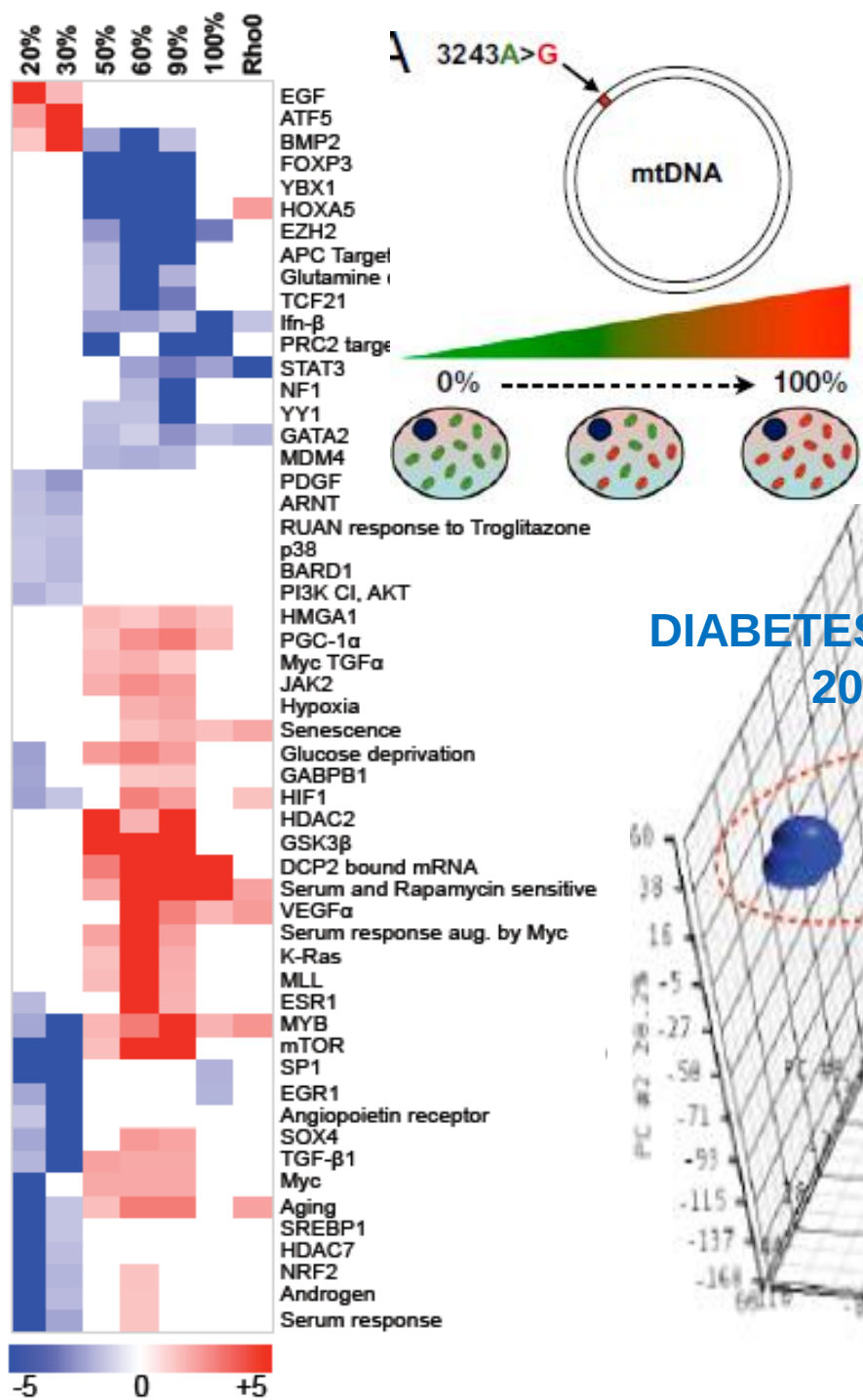
Lactic Acidosis	+	+	+	+	+	+	+	+	+	?	?	+	-
Growth Retardation	+	+	+	+	+	+	+	+	+	?	?	+	-
Dementia	+	+	+	+	+	+							
Stroke-Like Episodes	+	+	+	+	-								
Hypertrophic Cardiomyopathy	+	+	+	+	+	+							
Conduction Abnormalities	+	+		+	+	+							





Wolf-Parkinson-White Conduction

MULTIPHASIC NUCLER RESPONSES TO CHANGING mtDNA 3243A>G HETEROPLASMY EXPLAINS PHENOTYPIC VARIAITON



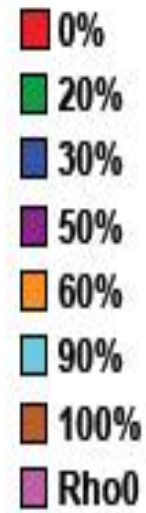
LEIGH SYNDROME & PERINATAL LETHALITY
100%

NEUODEGENERATION
50-90%

DIABETES & AUTISM
20-30%

NORMAL
0%

ρ^o

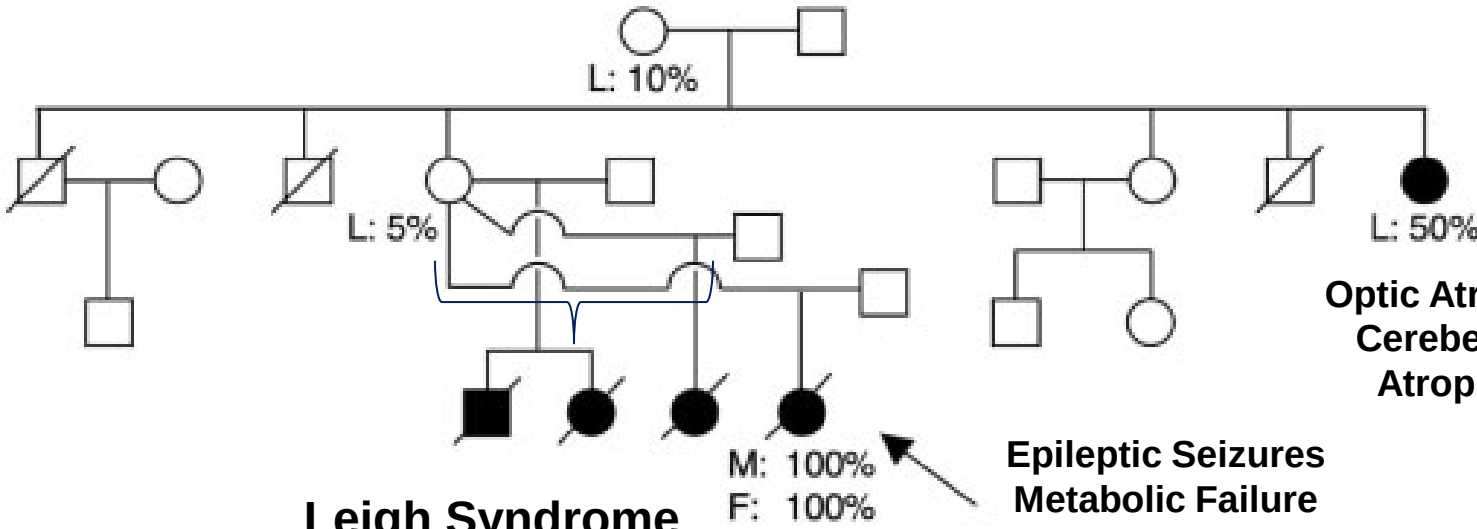


mtDNA MUTATIONS AND DISEASE

HETEROPLASMIC mtDNA MUTATIONS SEGREGATE RAPIDLY

A HETEROPLASMIC mtDNA *ND6* G14600A P25L MUTATION SEGREGATES TO GIVE VARIOUS PHENOTYPES

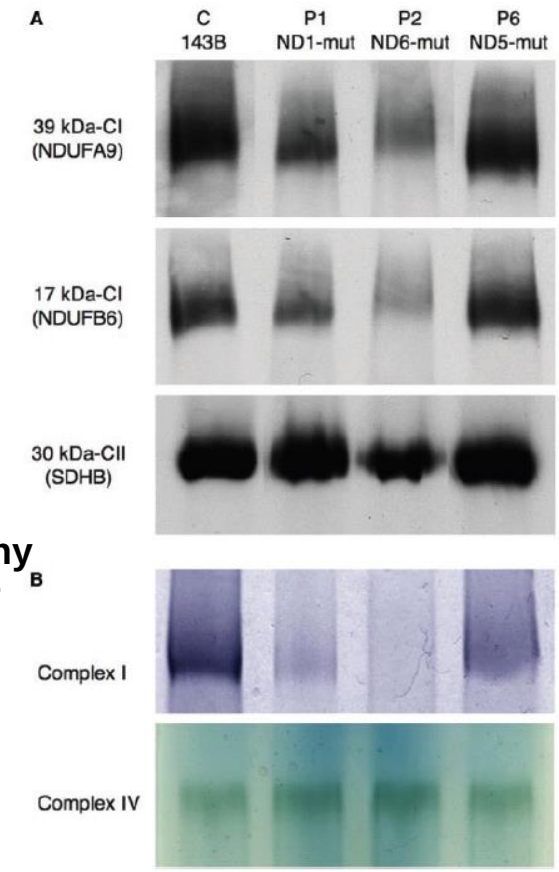
Zeviani Group Brain (2007), **130**, 1894–1904

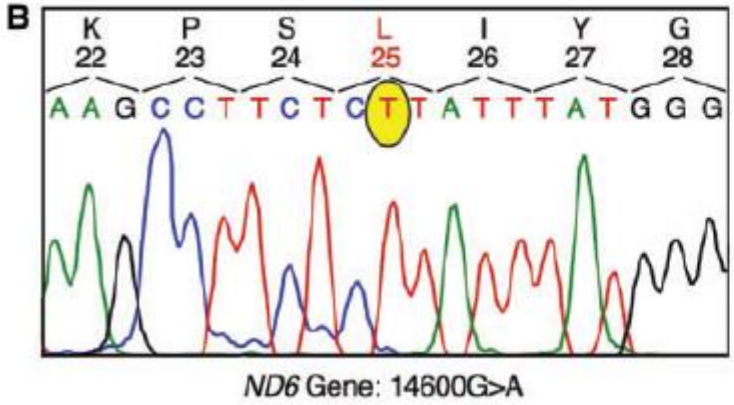


Leigh Syndrome

Optic Atrophy
Cerebellar Atrophy

Epileptic Seizures
Metabolic Failure
Muscle Myopathy
Cerebral atrophy
Death





ND6 Gene: 14600G>A

P25L

Human	15	GFVGFSSKPS P IYGGLVLIVS	35
Bovine	16	GFVGFSSKPS P IYGGLGLIVS	36
Pig	16	GFVGFSSKPS P IYGGLGLIVS	36
Rat	15	GCLGLALKPS P IYGGFGLIVS	35
Mouse	15	GCLGLALKPS P IYGGLGLIVS	35
Xenopus	15	GLVAVASNPS P FYAALGLVLA	35
Zebrafish	15	GMIA IASNPA P YFAAFGLVVV	35

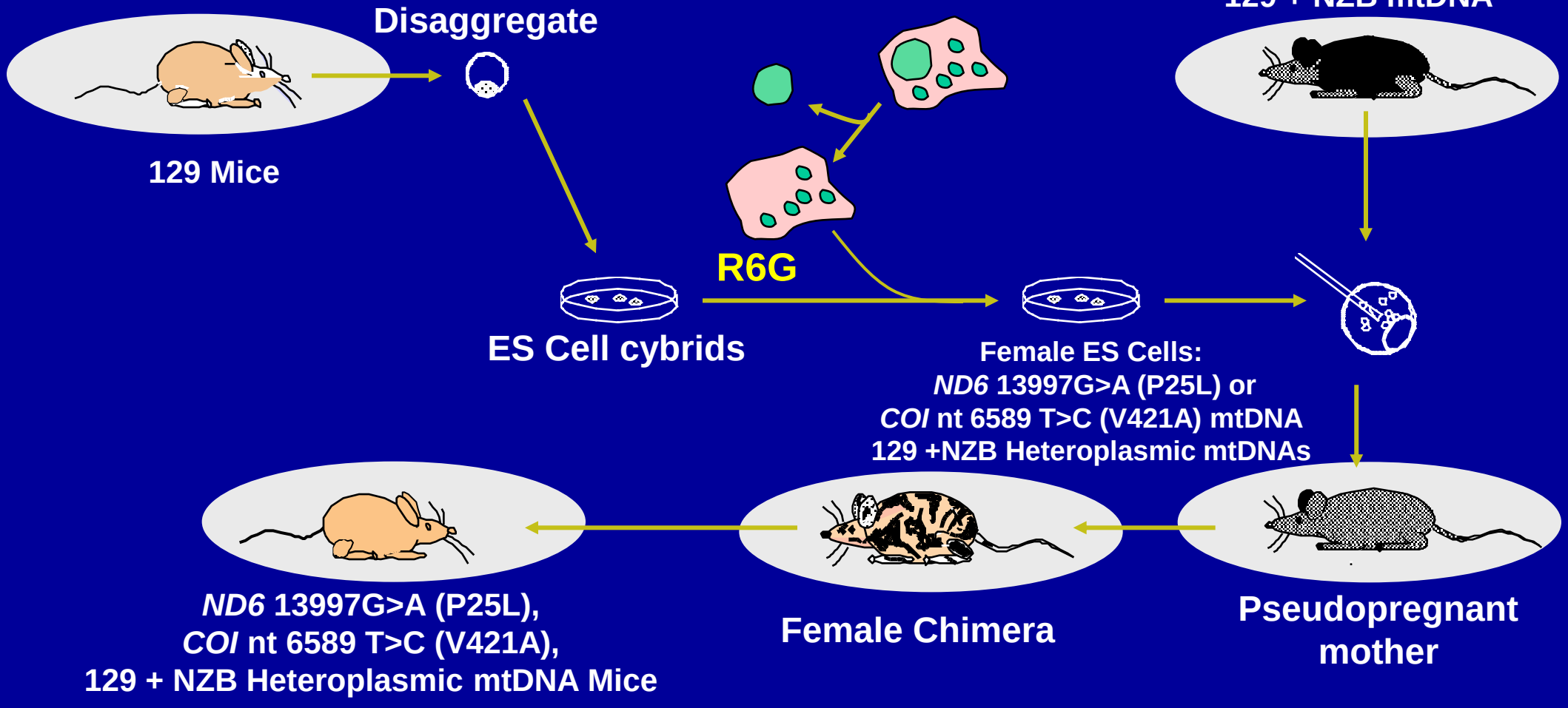
MOUSE MODELS OF mtDNA DISEASE:

ND6 = NEURODEGERATION

COI = CARDIOMYOPATHY & METABOLIC SYNDROME

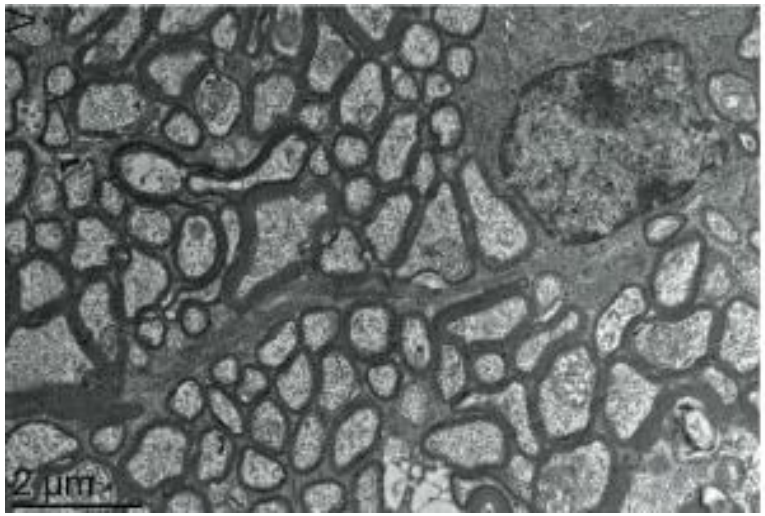
129 + NZB = NEUROPSYCHIATRIC DISEASE

Mouse *ND6* nt G13997A (P25L) = Human *ND6* G14600A (P25L),
COI nt 6589 T>C (V421A), &
129+NZB Heteroplasmy

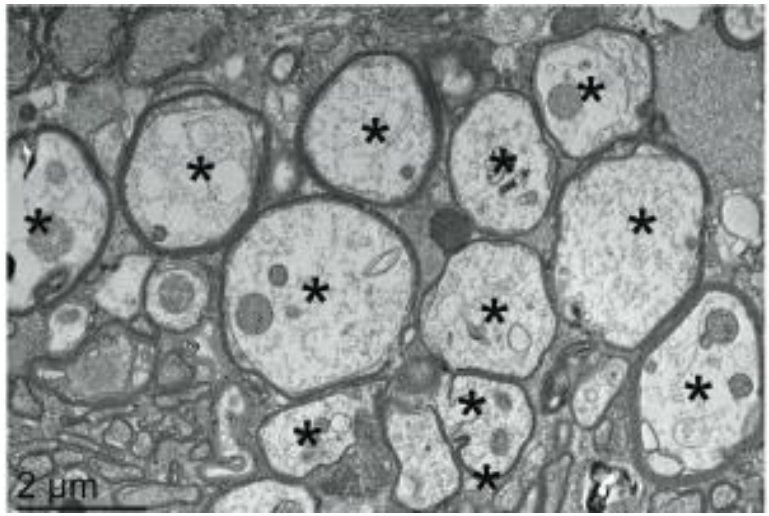


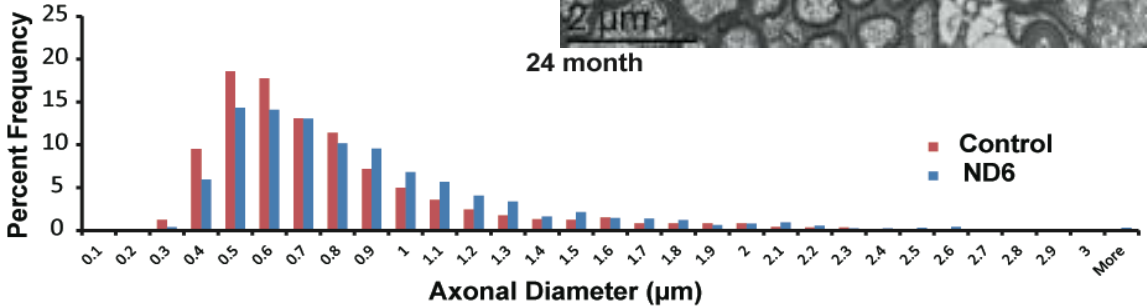
ND6 P25L mtDNA MOUSE EXHIBITS NEURODEGENERATIVE DISEASE

SELECTIVE LOSS OF THIN FIBERS & SPARING OF THICK FIBERS, DEMYELINATION & ABNORMAL MITOCHONDRIA, INCREASED ROS PRODUCTION



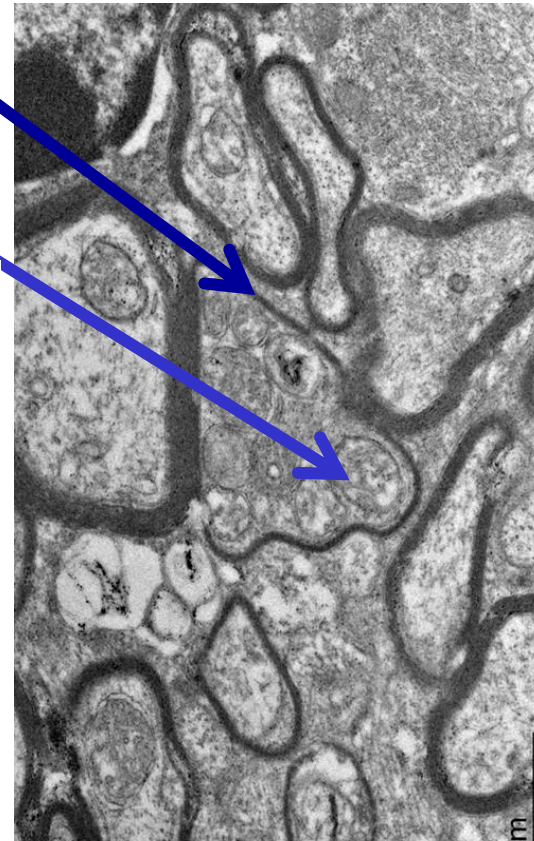
24 month

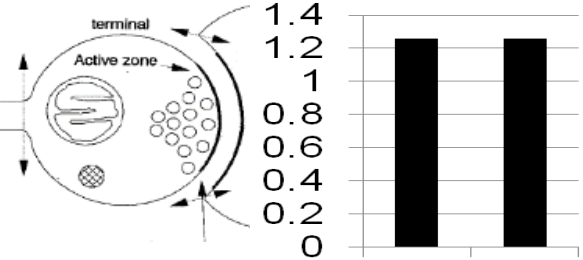


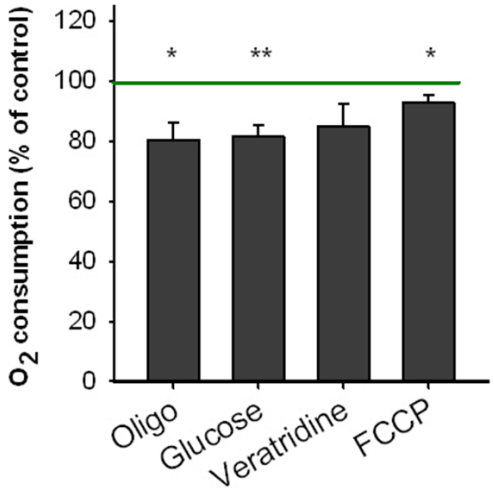


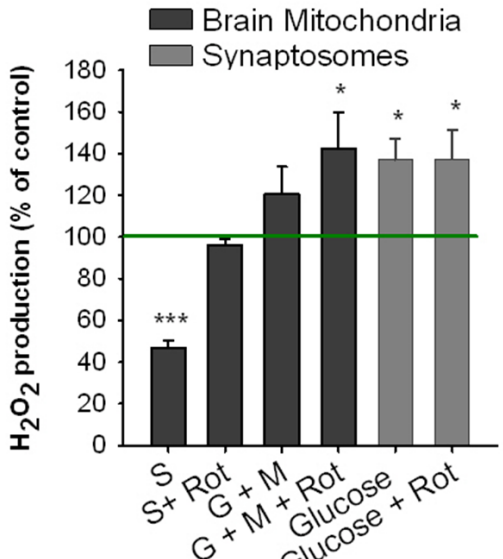
Demyelination

Abnormal Mitochondria





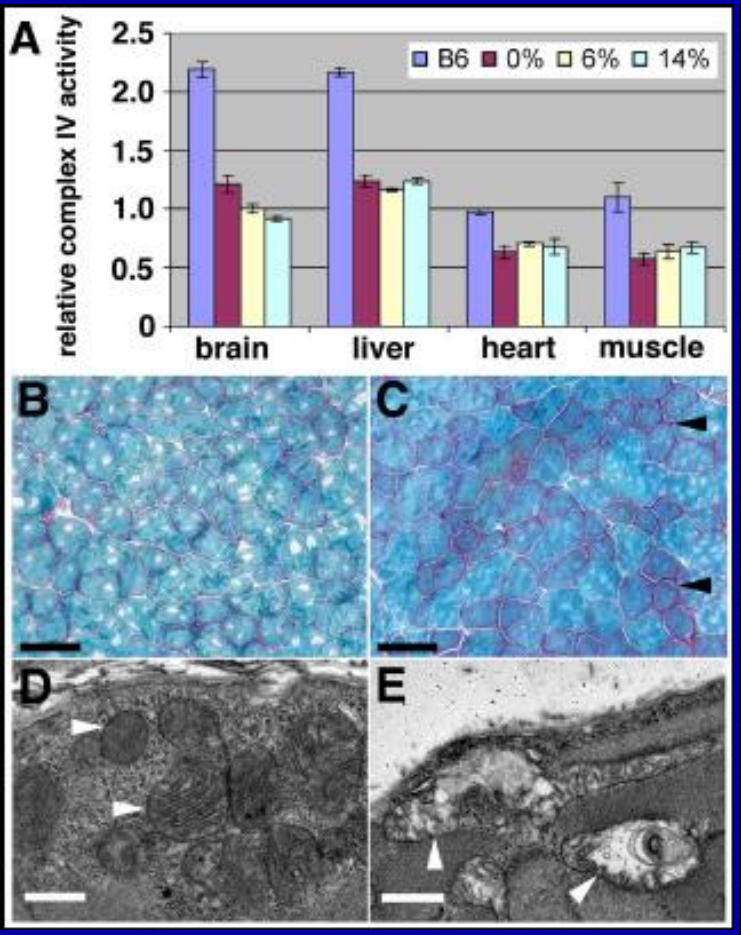




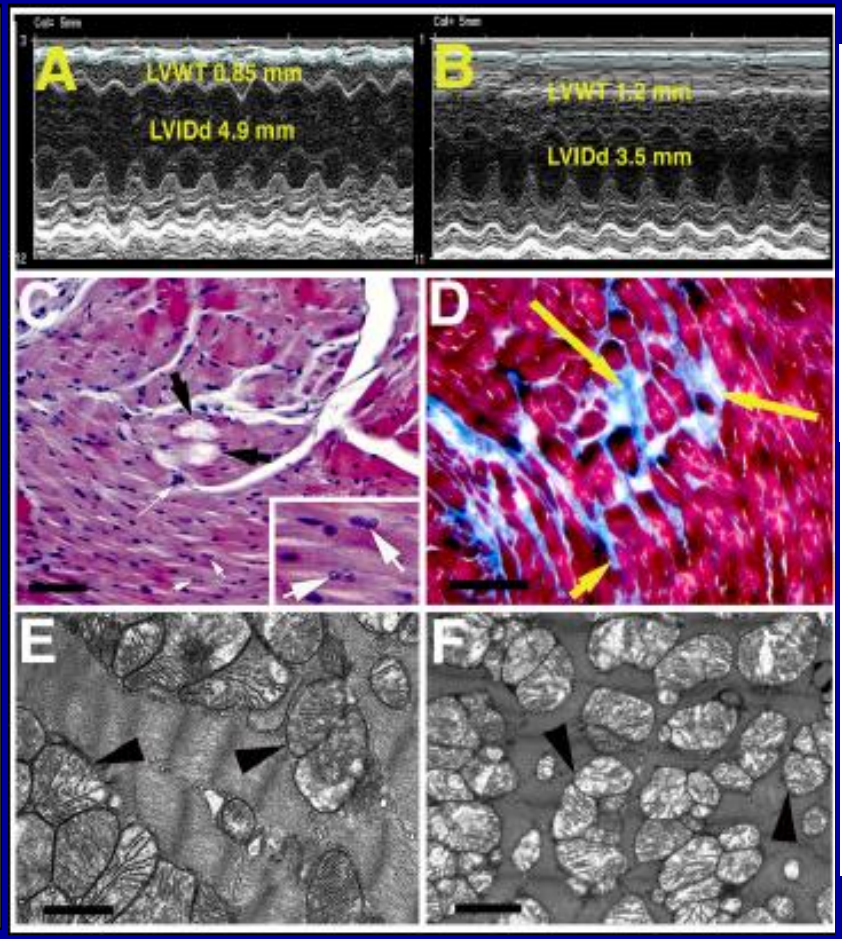
THE *COI* V421A mtDNA MOUSE EXHIBITS MYOPATHY, CARDIOMYOPATHY & METABOLIC SYNDROME

COI (6589T>C, V421A) MISSENSE MUTATION

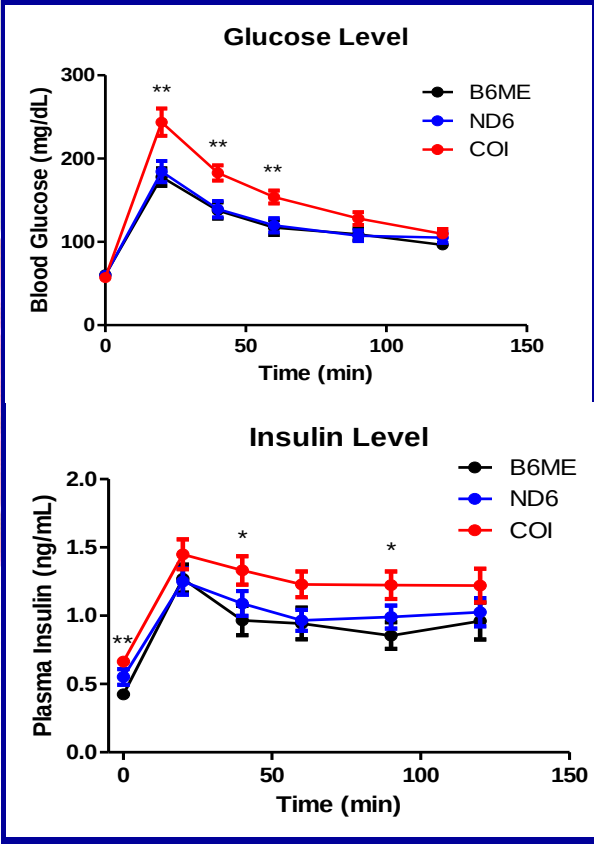
Mitochondrial Myopathy



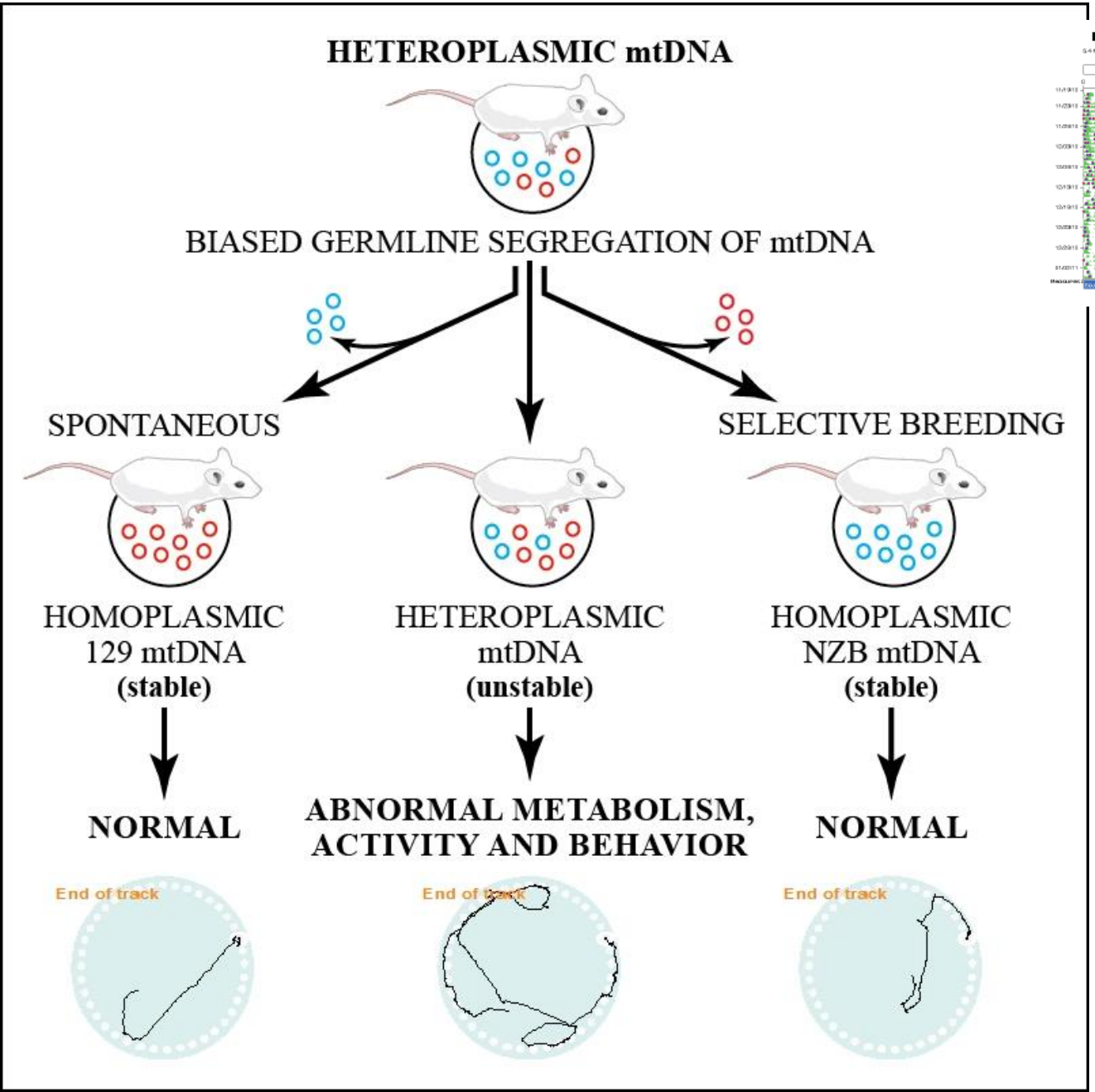
Mitochondrial Cardiomyopathy

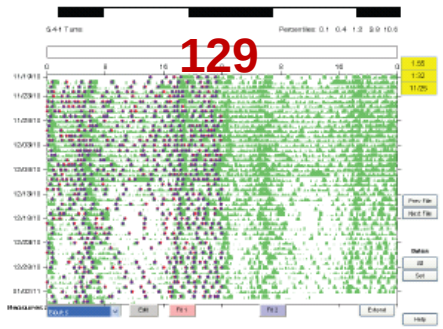


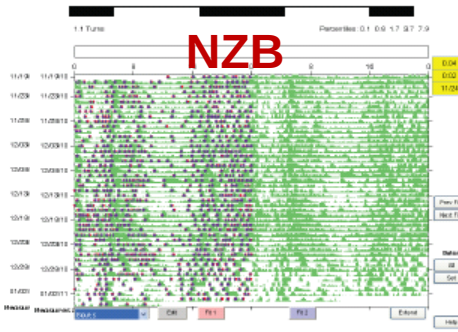
Glucose Intolerance & Insulin Resistance

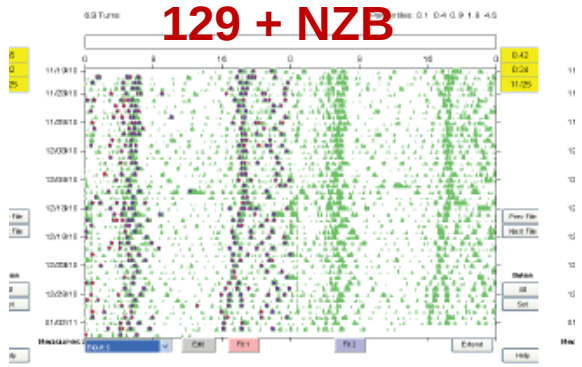


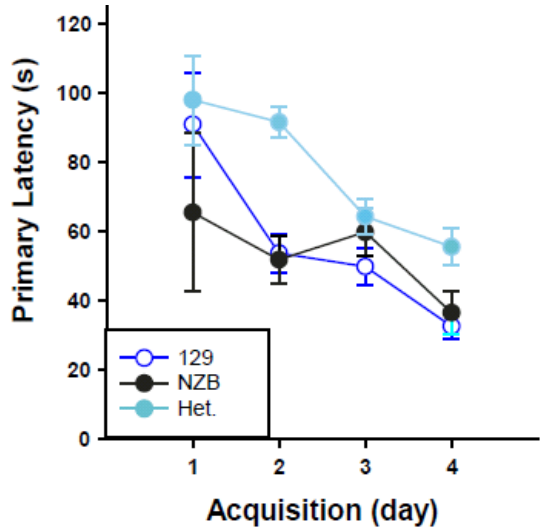
129-NZB mtDNA HETEROPLASMIC MICE ARE DEPRESSED & HAVE LONG TERM MEMORY DEFICITS







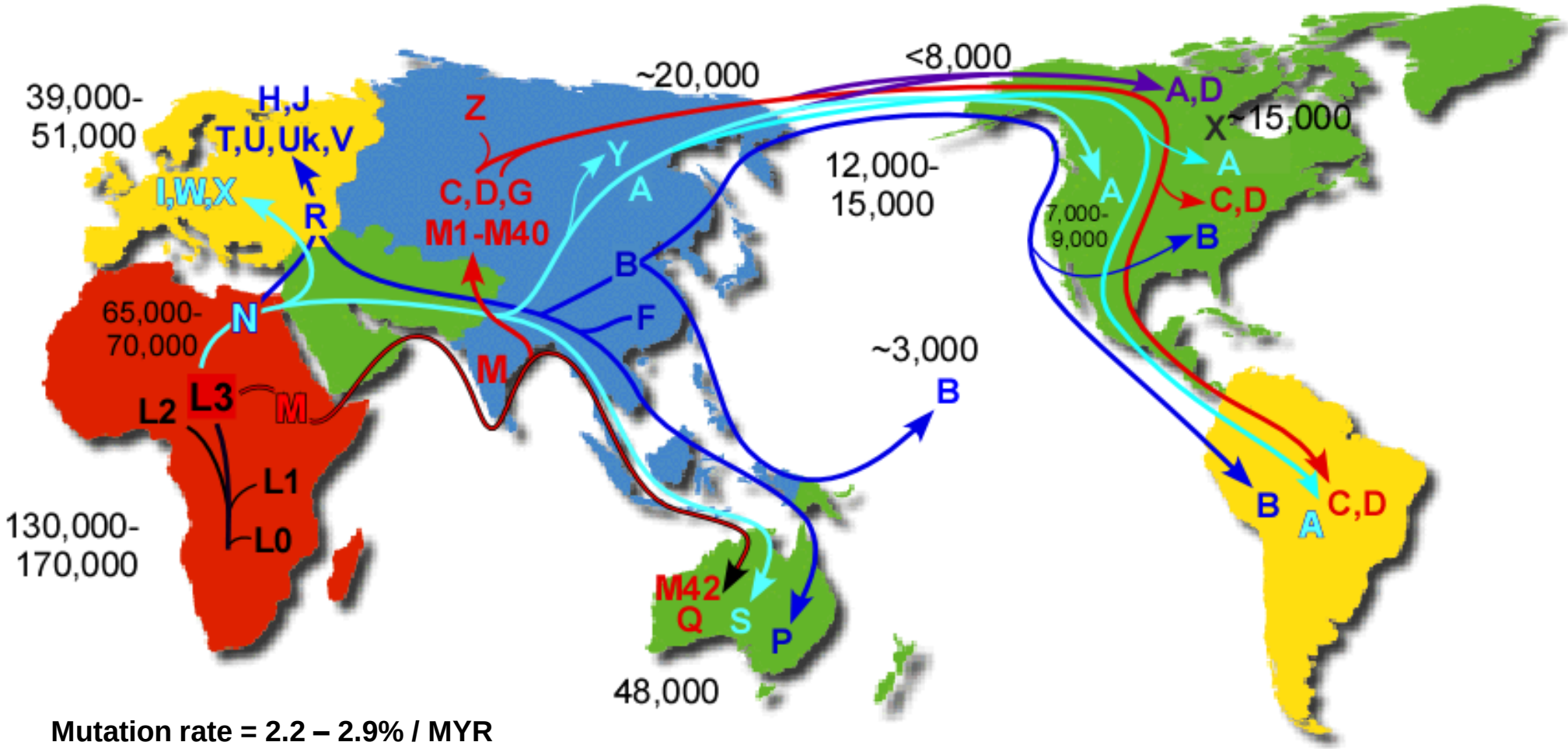




ANCIENT mtDNA VARIANTS PREDISPOSE TO COMMON DISEASES

mtDNA VARIATION CORRELATES WITH THE GEOGRAPHIC LOCATIONS OF INDIGENOUS PEOPLES.

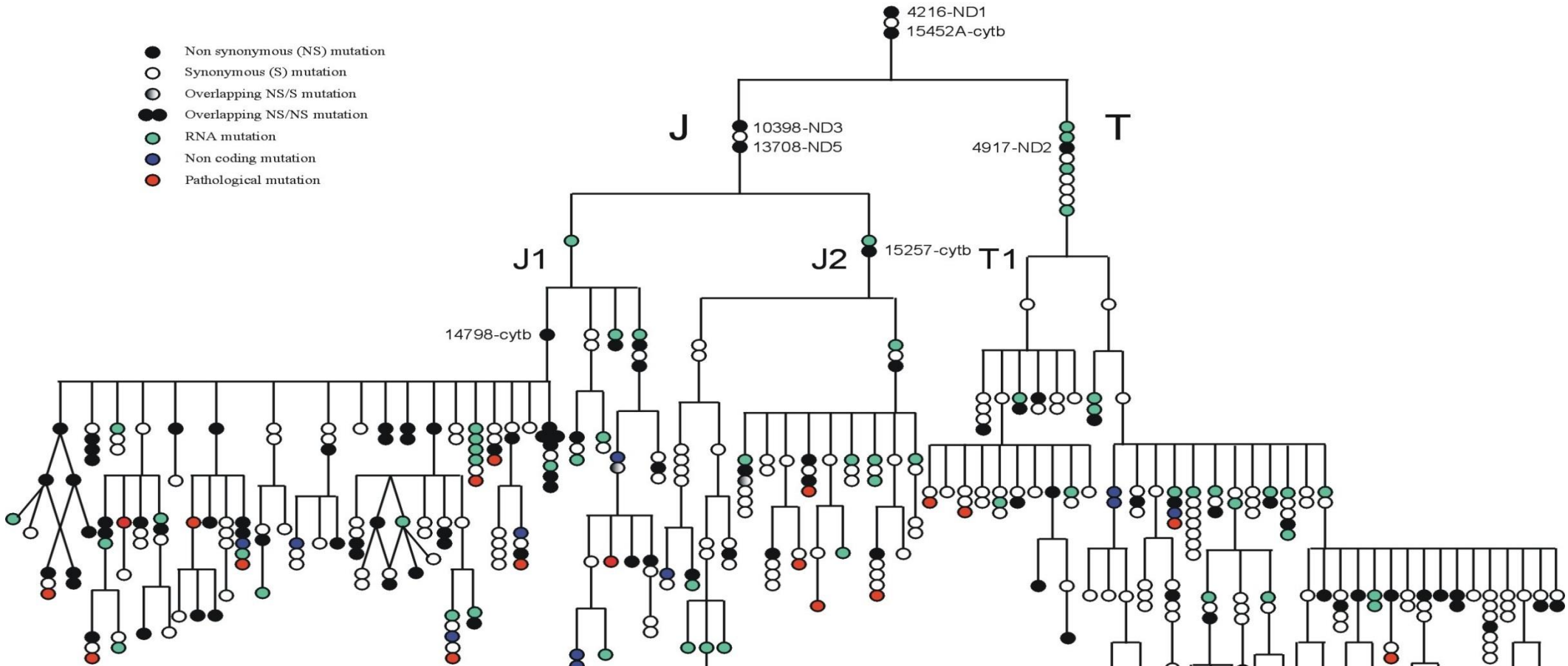
Groups of Related mtDNA Haplotypes (Haplogroups) were Founded by Adaptive Variants that Permitted Migration into New Environments.



Mutation rate = 2.2 – 2.9% / MYR
Time estimates are YBP.

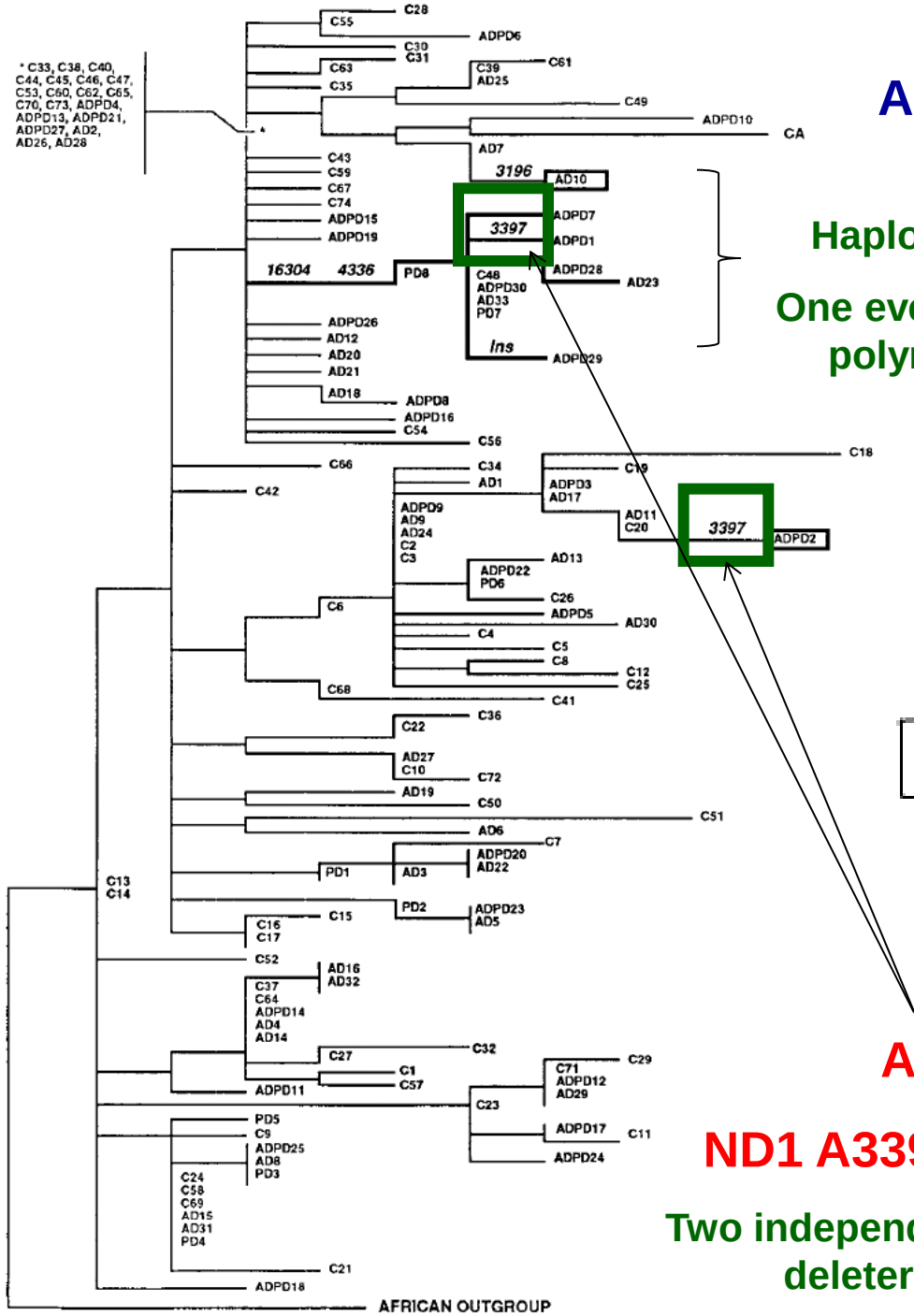
NODAL SUBSTITUTIONS ALTERING CONSERVED AMINO ACIDS INITIATE EACH mtDNA HAPLOGROUP

EUROPEAN HAPLOGROUPS T & J



Hplgr	Gene	npΔ	CI %	Funct
T	ND2	4917A	90	?
J1	Cytb	14798C	79	Qi
J2	Cytb	15257A	95	Qo

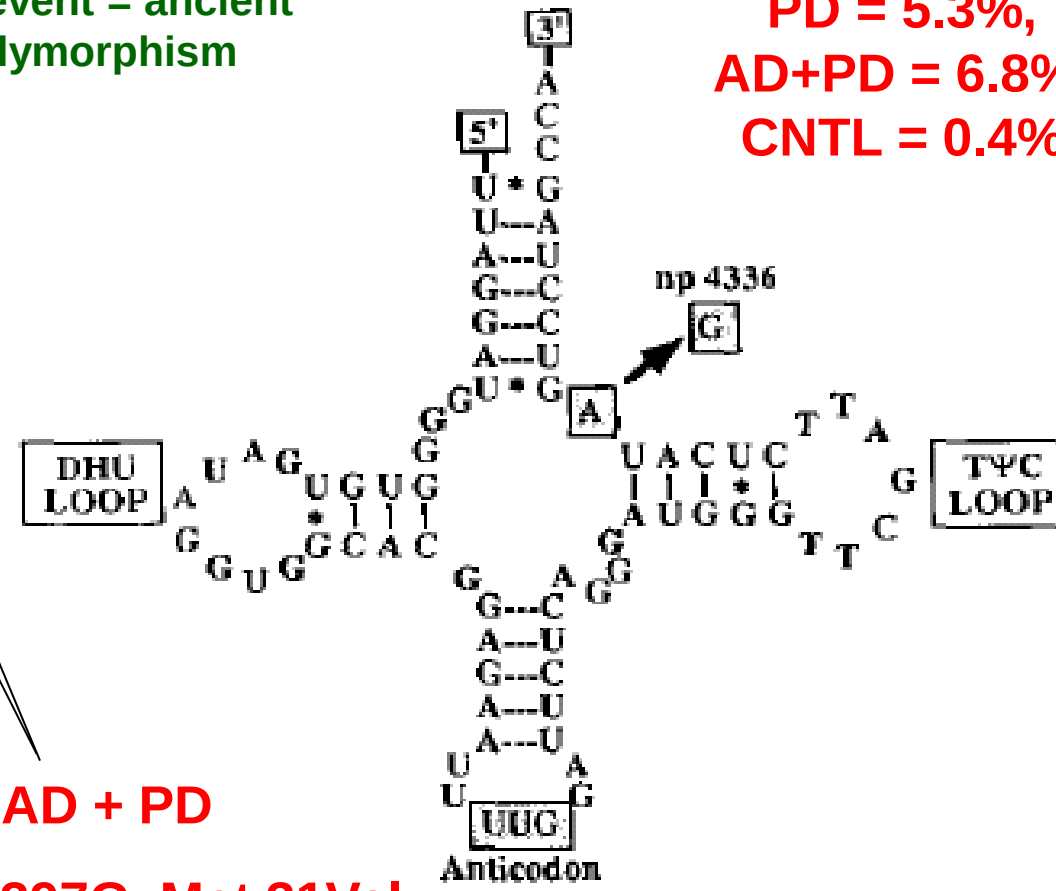
EUROPEAN ASSOCIATION OF tRNA^{Gln} A4336G & *ND1* (M31V) WITH ALZHEIMER & PARKINSON DISEASE



Haplogroup H5a

One event = ancient polymorphism

AD = 3.3%,
PD = 5.3%,
AD+PD = 6.8%,
CNTL = 0.4%



AD + PD

ND1 A3397G Met 31Val

Two independent events = recent deleterious mutation

GENOMICS 17, 171–184 (1993)

ASSOCIATION BETWEEN mtDNA HAPLOGROUPS AND AUTISM SPECTRUM DISORDER RELATIVE TO HAPLOGROUP RO

Illumina 550 GWAS data set. Generalized Linear Modeling Analysis

Results with GEE Solution for the AGRE Family mtDNA SNPs Relative to R0 (H-HV-V)

Continent Co-Variant	Haplogroup	Odds Ratio	95% Confidence Interval	P-Value	Benjamini-Hochberg Correction
Europeans	I	2.12	1.26-3.55	0.004	0.04
	J	2.18	1.59-3.00	<0.001	<0.001
	K	1.76	1.31-2.36	<0.001	0.002
	T	1.79	1.30-2.46	0.003	0.004
	U	1.98	1.45-2.71	<0.001	<0.001
	W	1.41	0.81-2.45	0.22	0.89
	X-O	2.00	1.23-3.25	0.005	0.04
Asians-N Amer	A	1.83	1.32-2.53	<0.001	0.004
	M	1.55	1.16-2.06	0.003	0.03
	N+	2.02	1.19-3.42	0.009	0.06
Africans	L	1.01	0.63-1.61	0.98	0.98
Gender (Male)		3.93	3.3-4.67	<0.001	<0.001

(N_{ALL}=4041, N_{ASD}=1624, 933 families with 1-12 members) (reference haplogroup = HHV+, N_{ALL}=1792, N_{ASD}=712)

Covariates: haplogroups, sex.

ASSOCIATIONS BETWEEN mtDNA HAPLOGROUPS & COMMON DISEASES

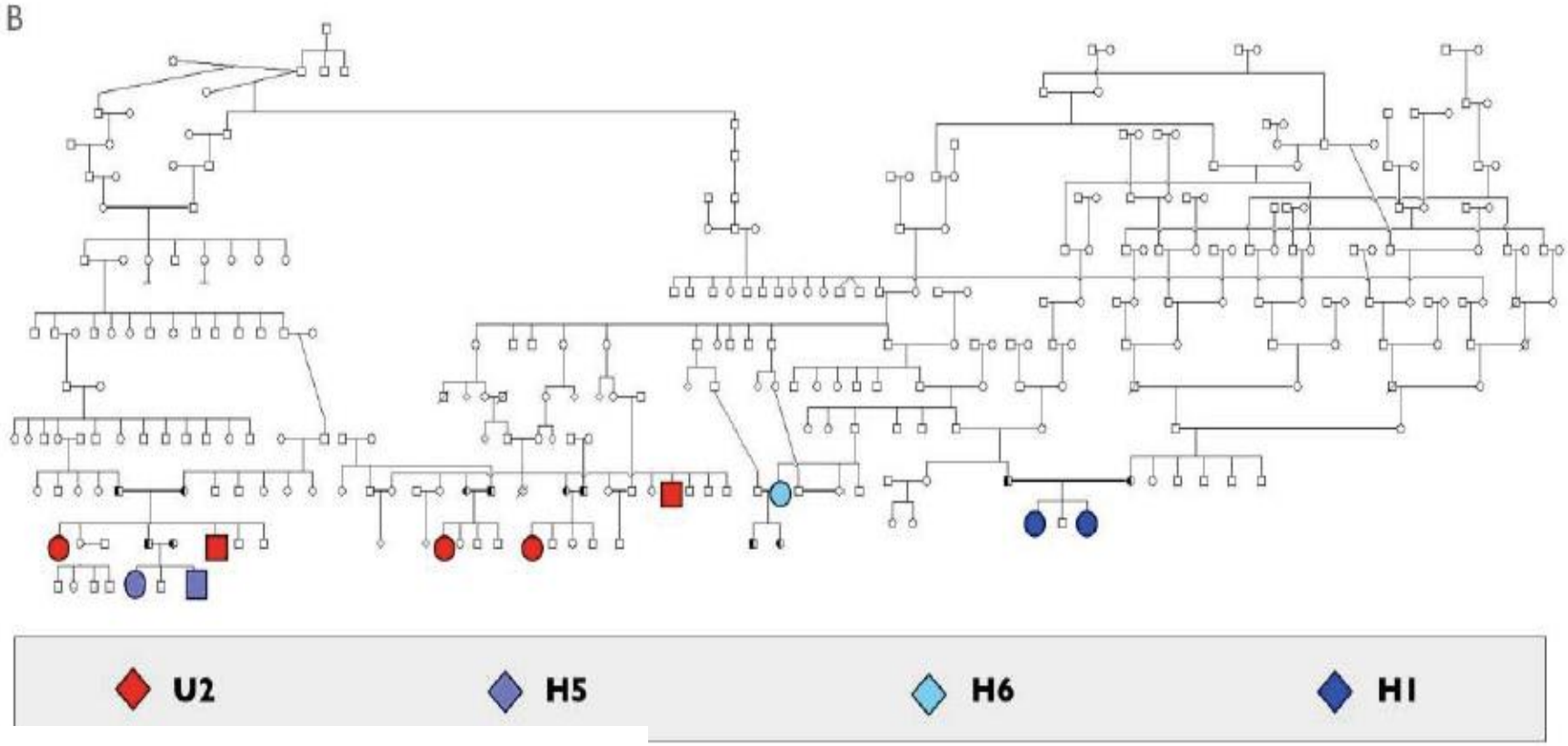
H > J = T > U (U* > U4 = U5a1 > Uk)

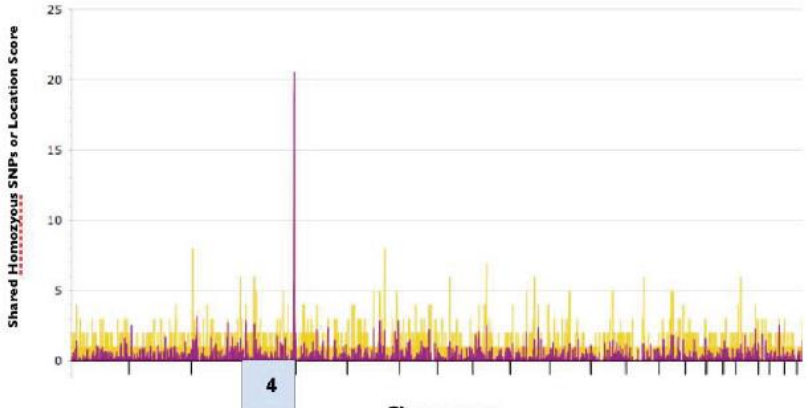
- **NEURODEGENERATIVE DISEASES**
  - Autism
  - Alzheimer Disease
  - Parkinson Disease
  - Macular Degeneration
  - Familial Amyloidosis with Polyneuropathy
  - Migraine
  - Psychiatric Disorders
- **NEUROLOGICAL DISEASES**
  - Stoke
- **METABOLIC DISEASES**
  - Diabetes
  - Cardiovascular Disease
  - Metabolic Syndrome
- **INFLAMMATORY & INFECTIOUS DISEASES**
  - Sepsis
  - IgE Levels
  - Asthma
  - AIDS progression
  - Anti-AIDS HAAT* Lipodystrophy
  - Osteoarthritis
- **ALTITUDE ADAPTATION** (M, *ND1* 3394T>C Y30H)
- **CANCERS**
- **AGING**
- **ATHLETIC PERFORMANCE** (L0>L3>N>H>J-U-T)

* HAAT- highly active anti-retroviral therapy

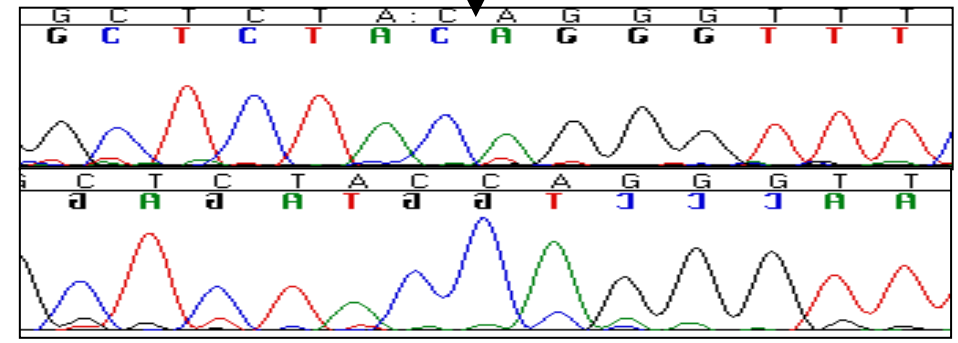
NUCLEAR MITOCHONDRIAL GENE MUTATIONS AND DISEASE:

ANT1 FRAMESHIFT MUTATION ASSOCIATED WITH HUMAN AUTOSOMAL RECESSIVE MYOPATHY AND CARDIOMYOPATHY

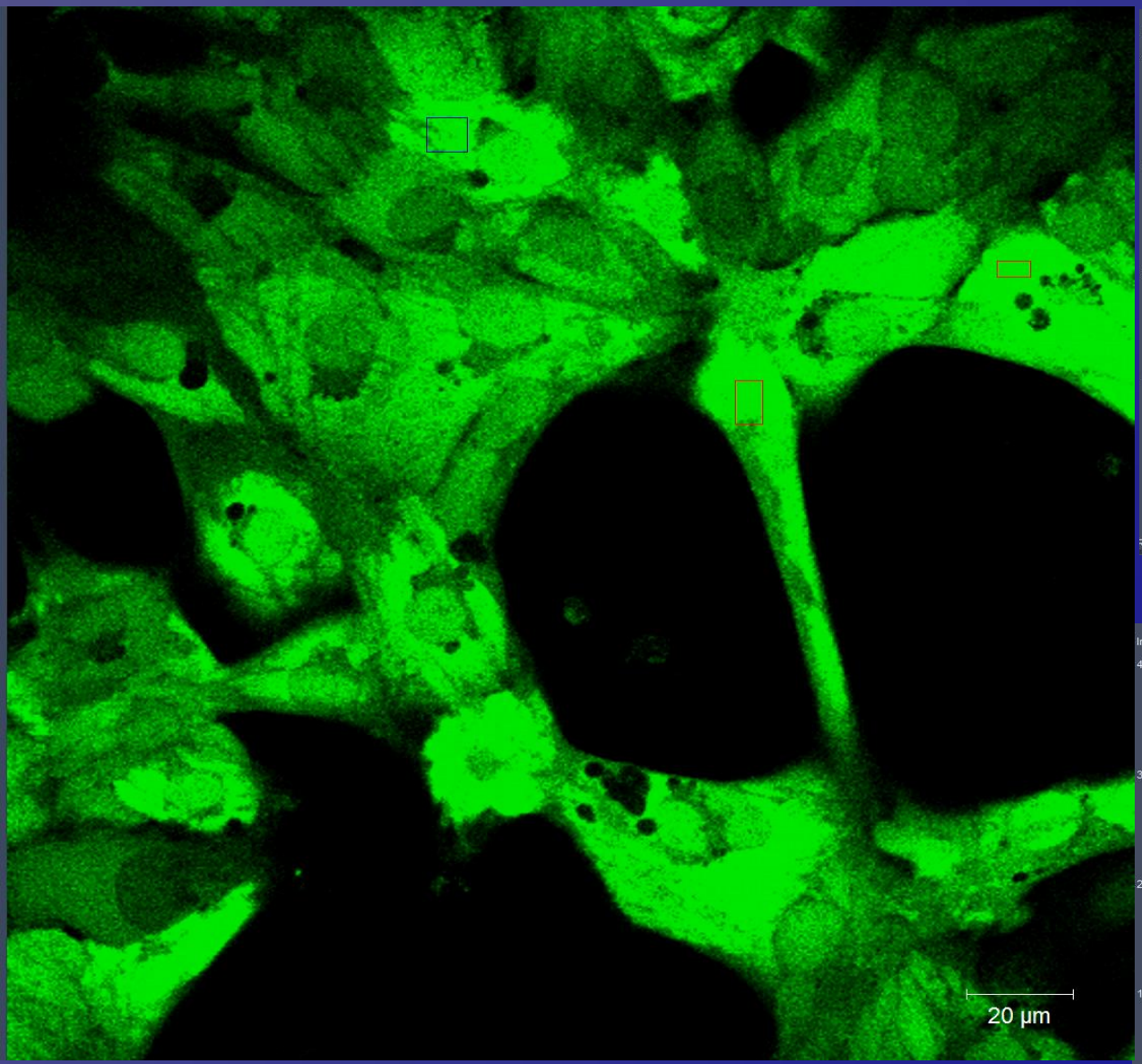




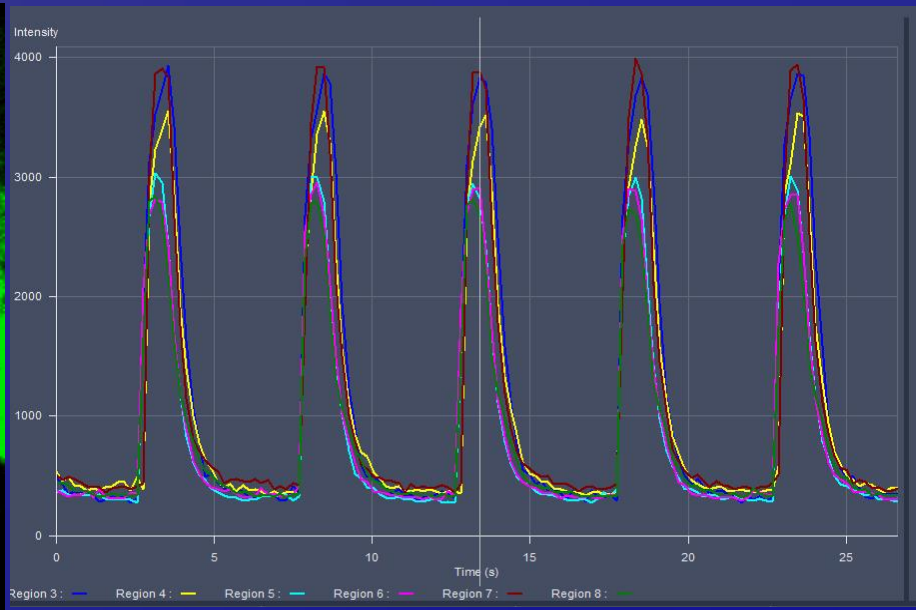
c.523delC, p.Q175RfsX38



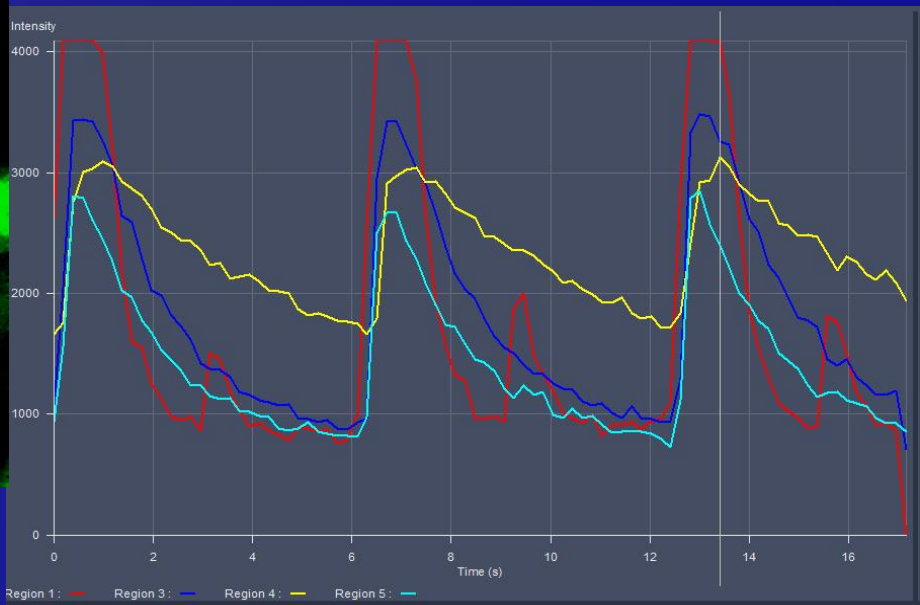
IPSC-DERIVED ANT-/- CARDIOMYOCYTES HAVE DYSRHYTHMIC CONTRACTIONS



ANT+/+

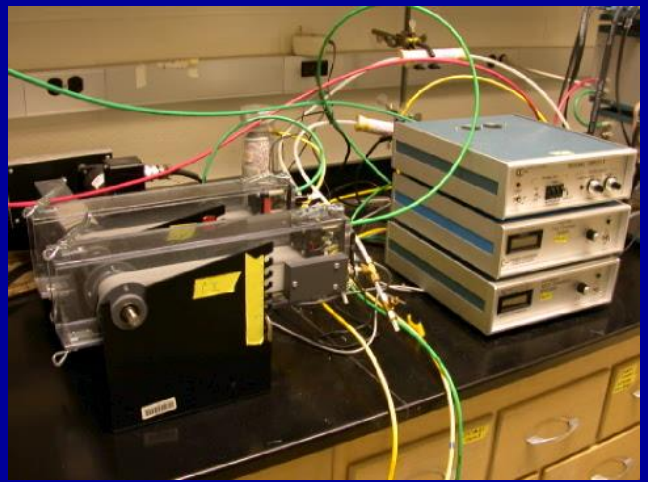


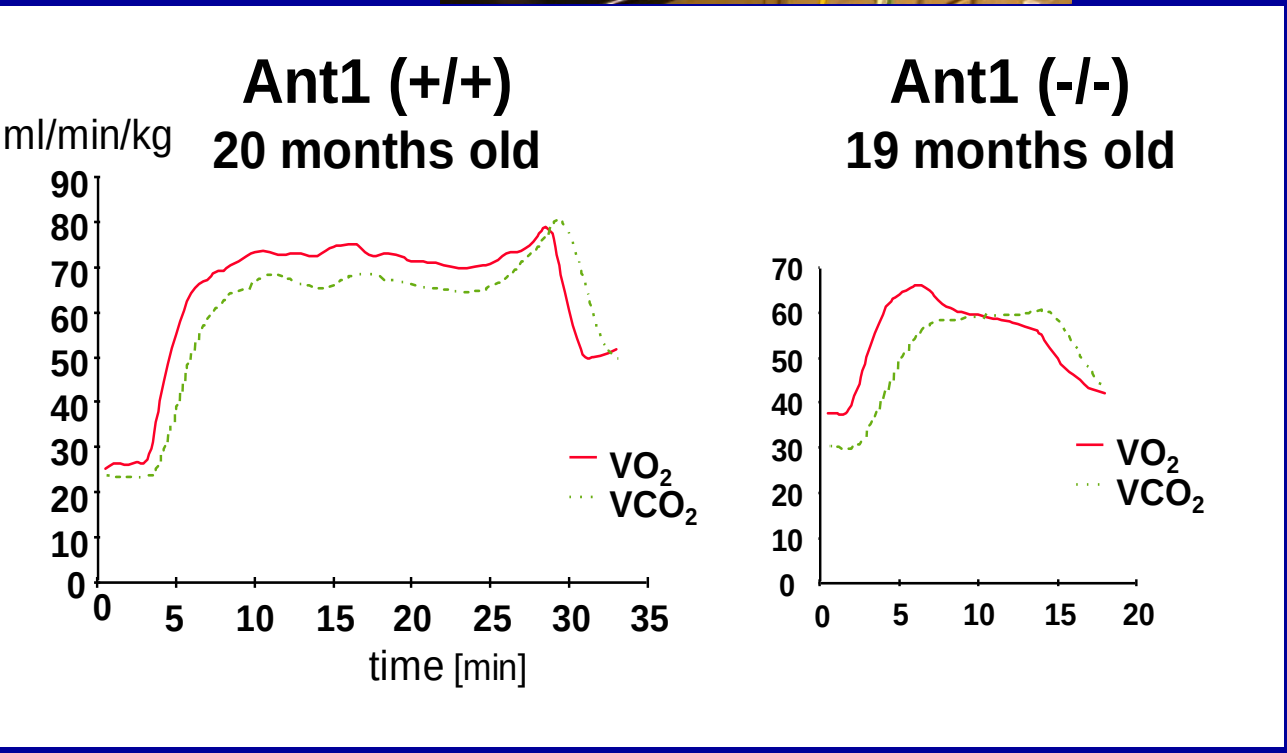
ANT1-/-

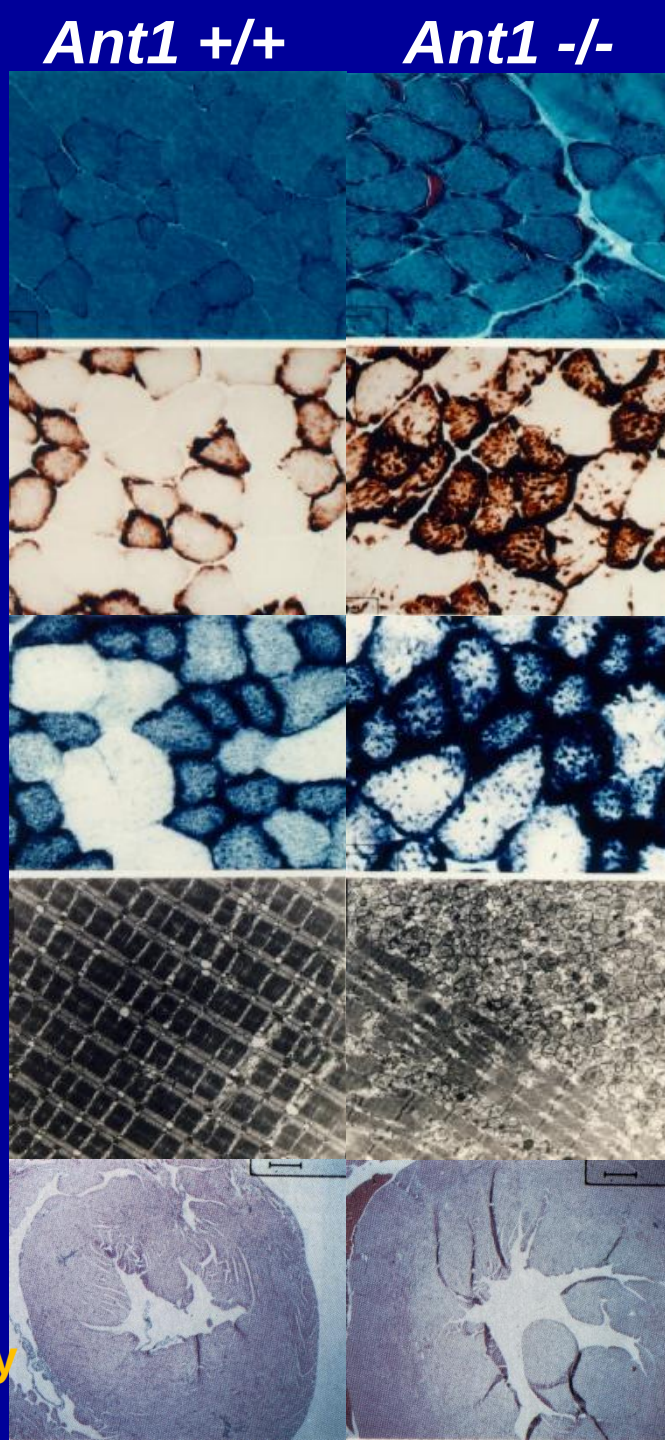


Ant-/- MOUSE HAS MYOPATHY & CARDIOMYOPATHY

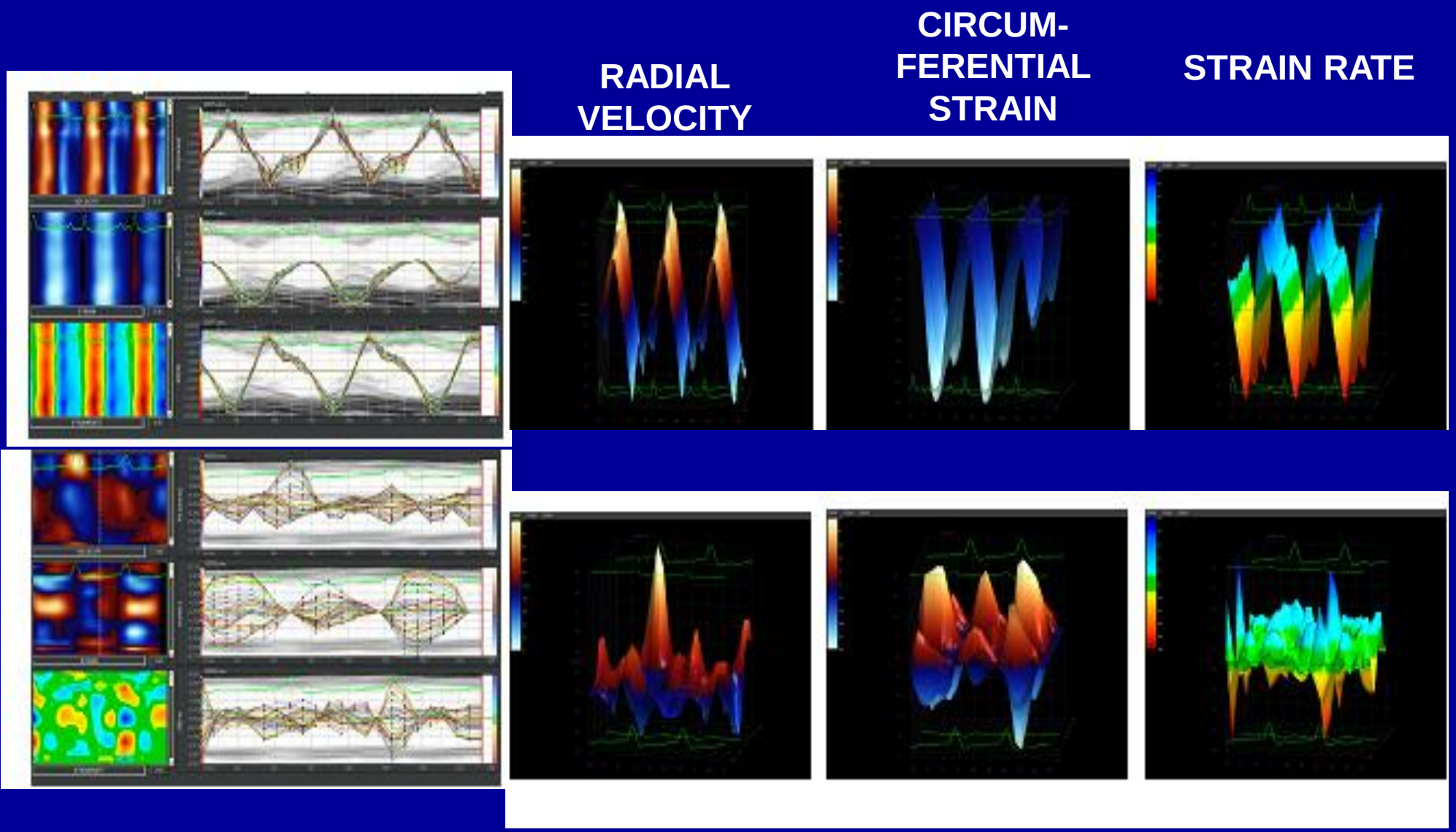
Mouserciser





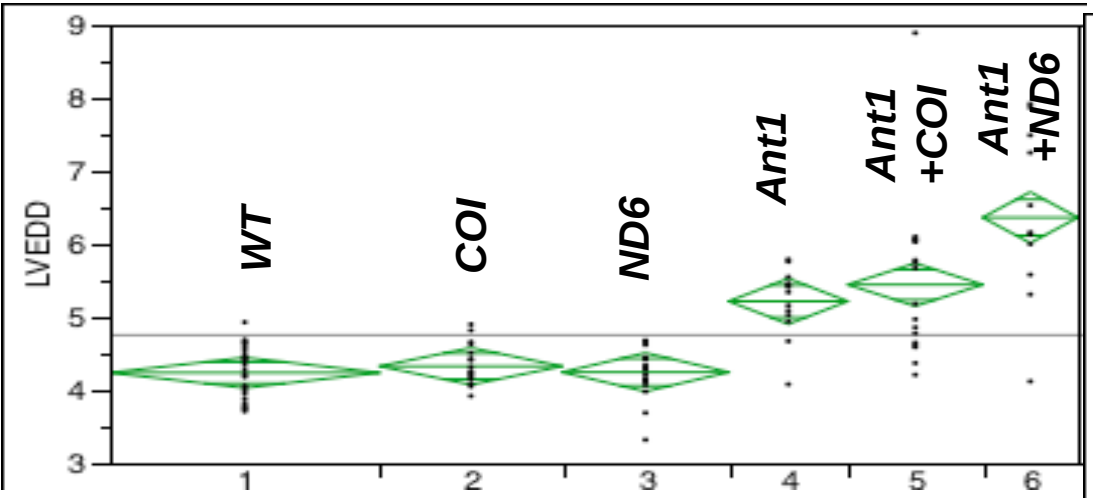


MOUSE Ant1 -/- HEARTS EXHIBIT DYSRHYTHMIC MYOCARDIAL MECHANICS: ECHOCARDIOGRAM VELOCITY VECTOR IMAGING

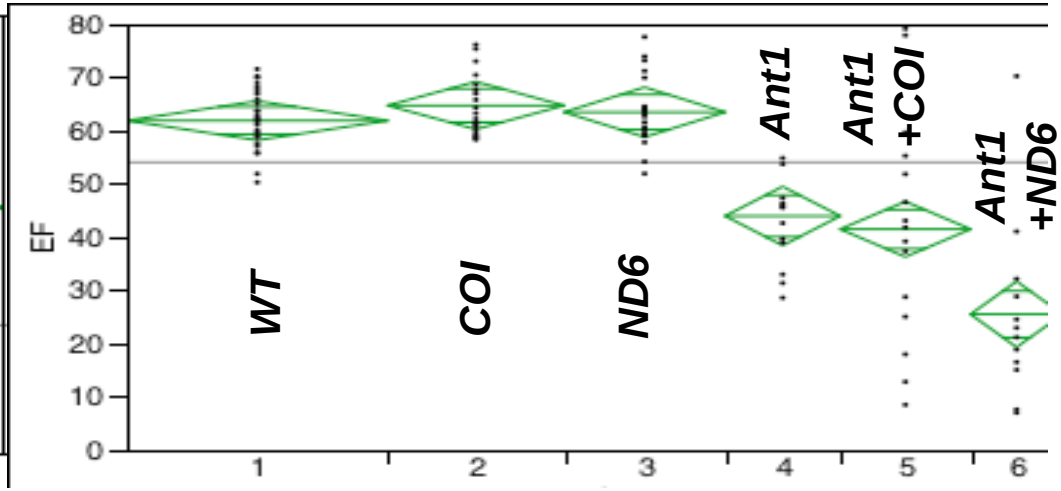


MOUSE mtDNA *COI* & *ND6* MUTATIONS AUGMENT *Ant1-/-* CARDIOMYOPATHY

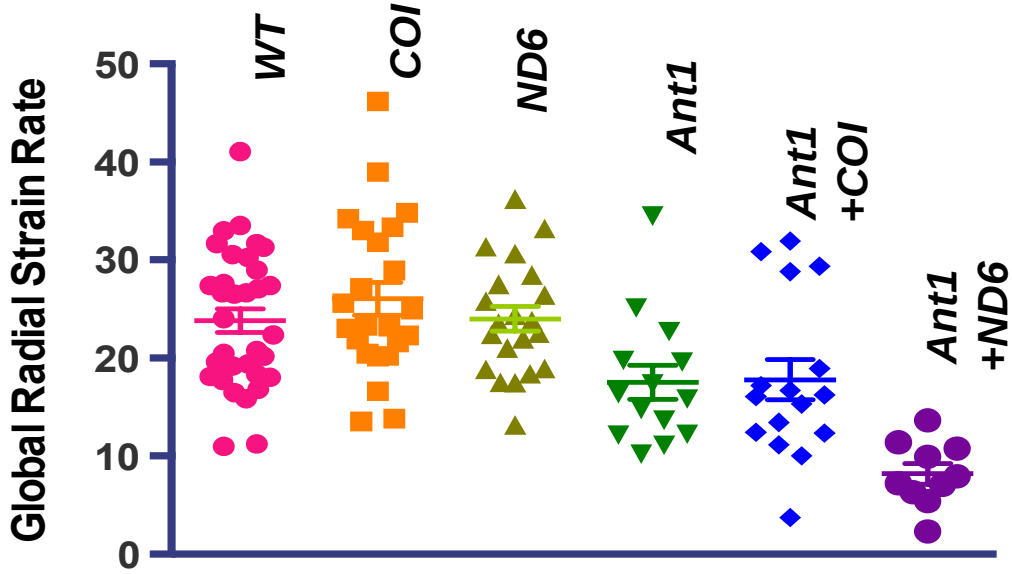
M Mode: LV Diastolic Diameter



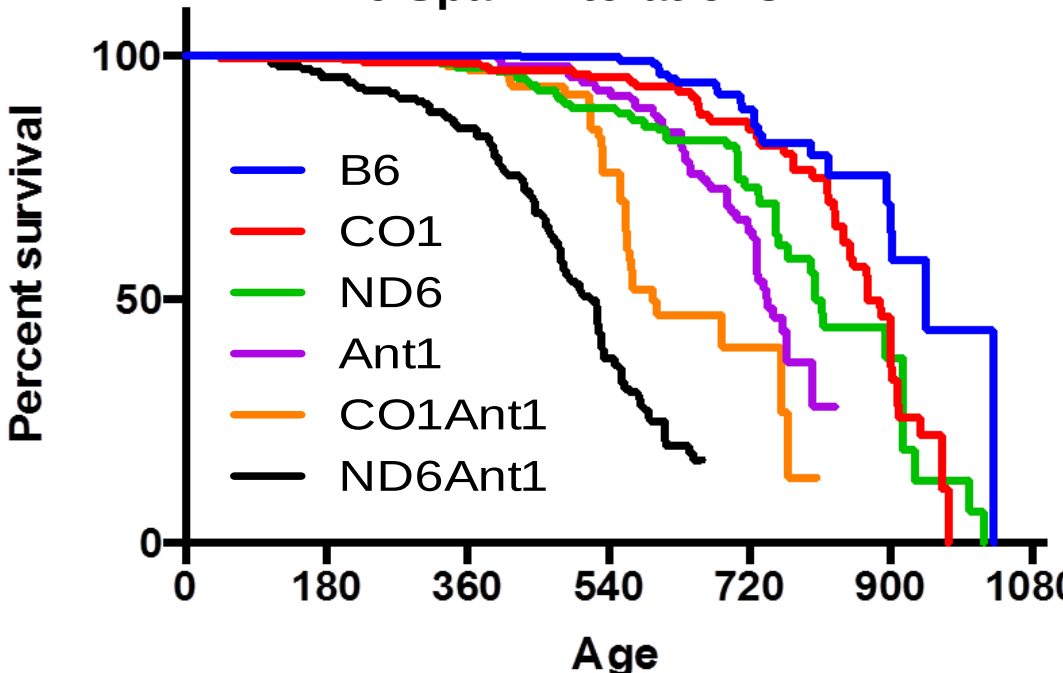
M Mode: LV Ejection Fraction



Radial Strain

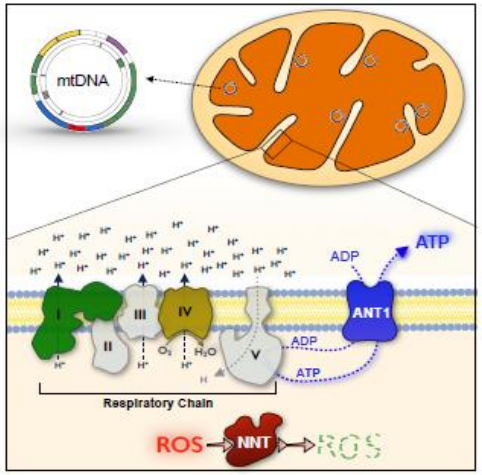


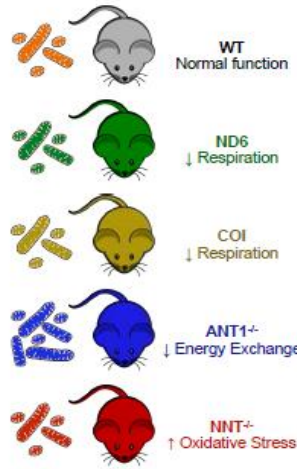
Life Span Alterations

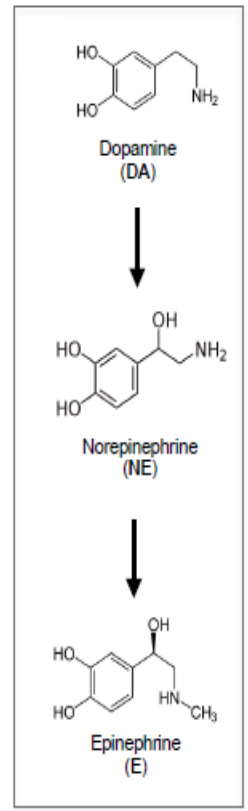


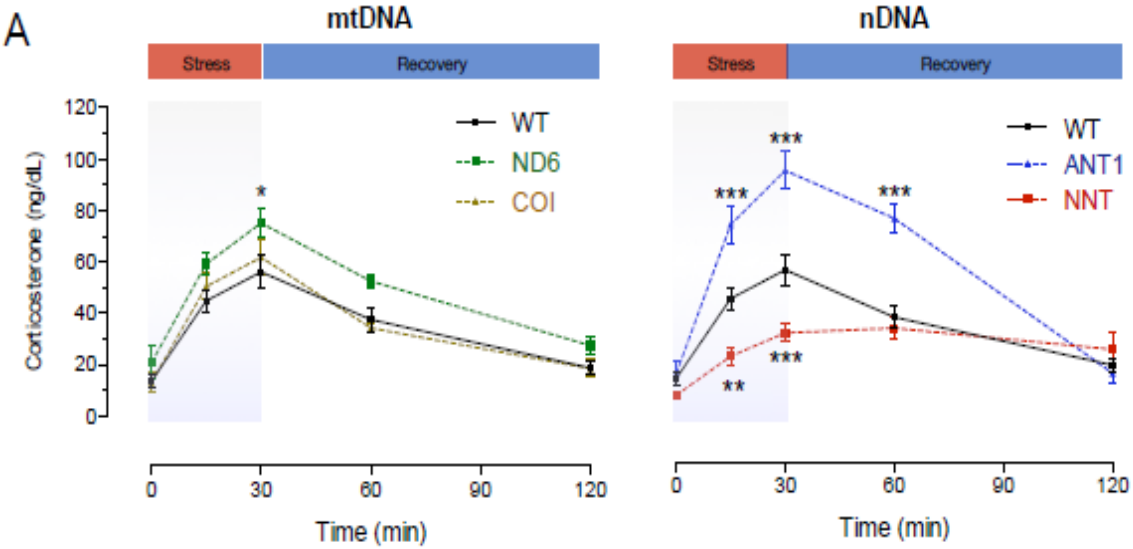
MITOCHONDRIAL ALTERATIONS MODULATE NEUROENDOCRINE RESPONSES TO ACUTE STRESS

Modulation of Corticosterone: the Hypothalamic-Pituitary-Adrenal (HPA) axis

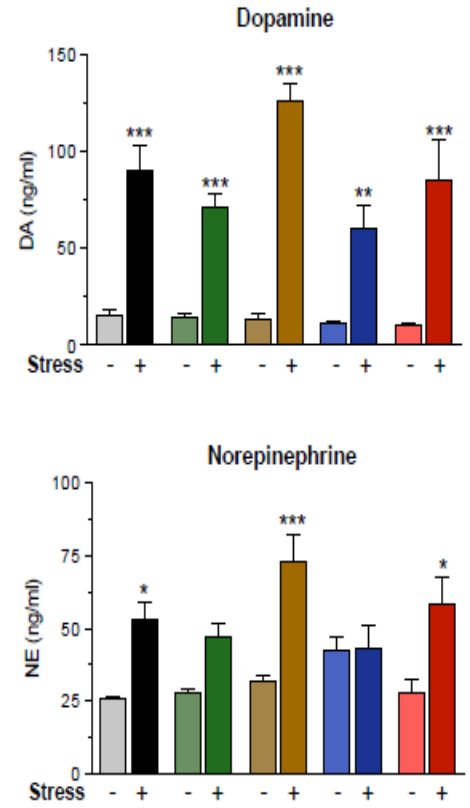








Modulation Catecholamines: of the Sympathetic-Medullary Axis



ANT1 MITOCHONDRIAL DYFUNCTION IMPAIRS INTERNEURON MIGRATION

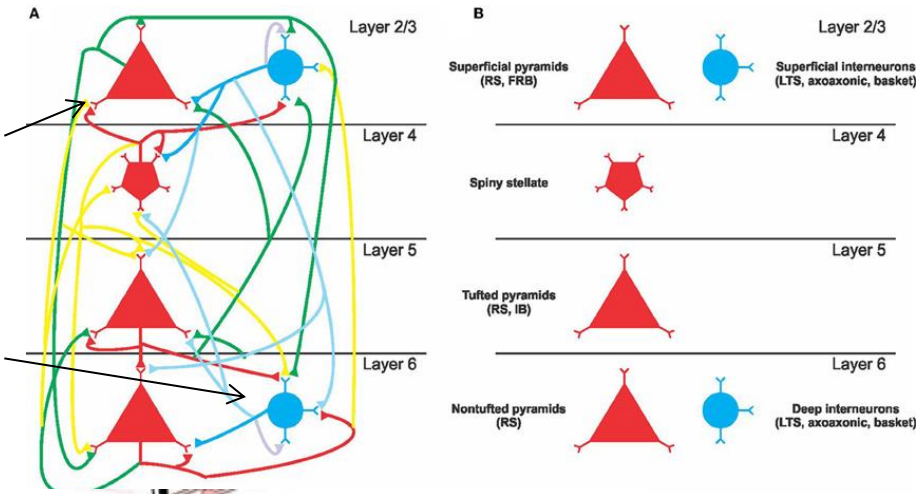
Partial Mitochondrial Defects Inhibit Tangential Inhibitory Interneuron Migration but not Radial Excitatory Neuron Migration

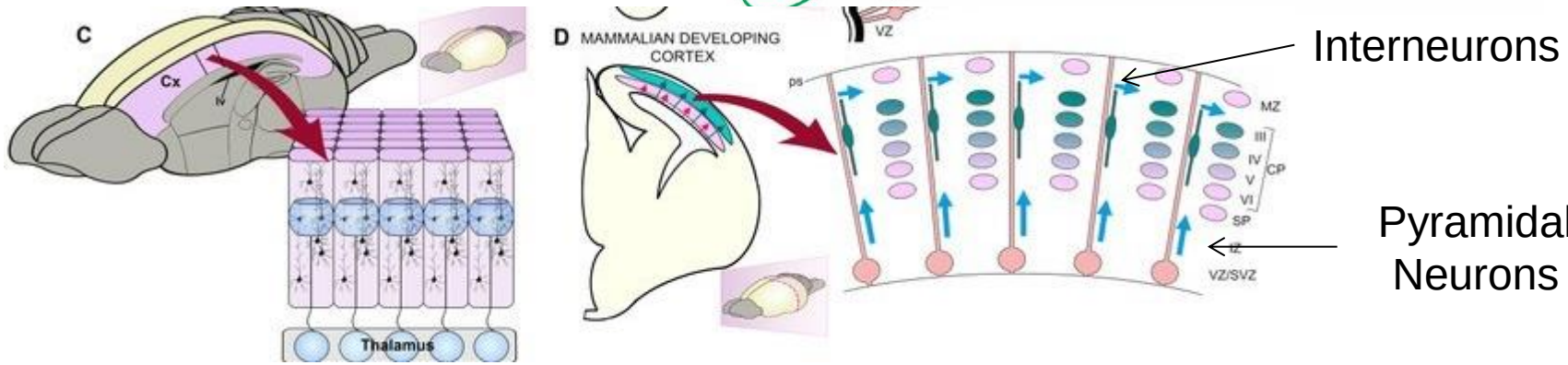
Cortical Function Requires Excitatory Glutamateric-Inhibitory GABAergic Neuronal Balance

Excitation-Inhibition Imbalance May Cause Epilepsy, ADHD, Autism, Manic-Depressive Disorder, etc.

Pyramidal Neurons

Interneurons

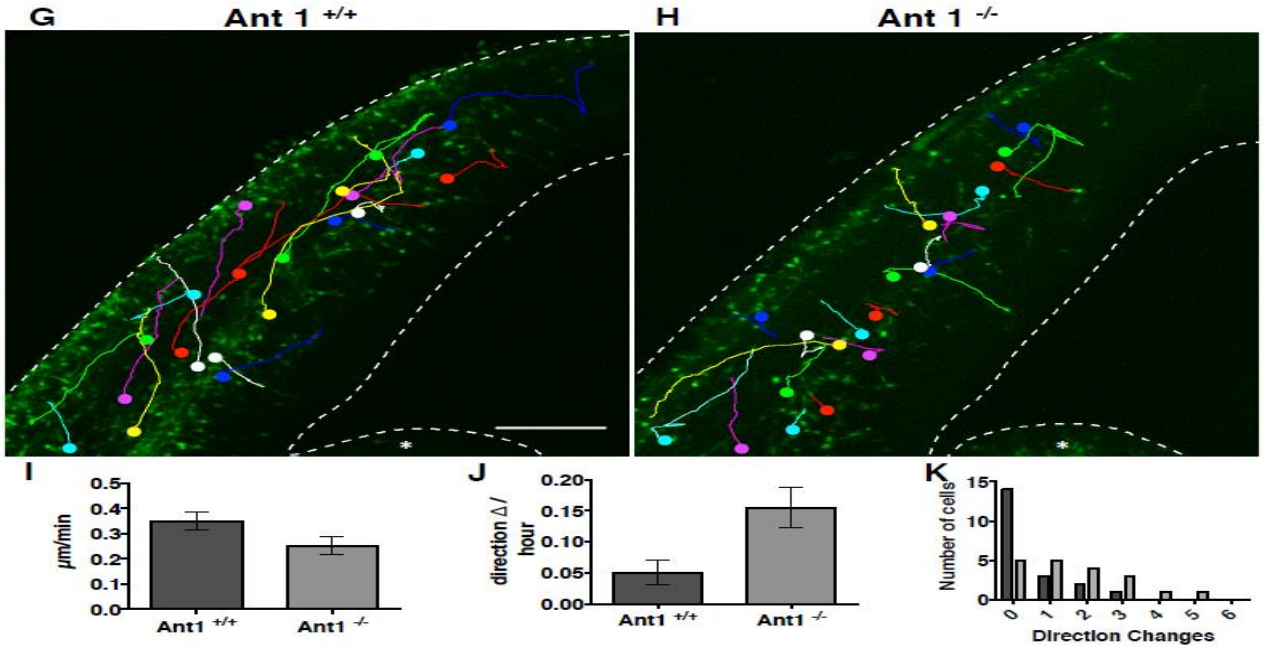




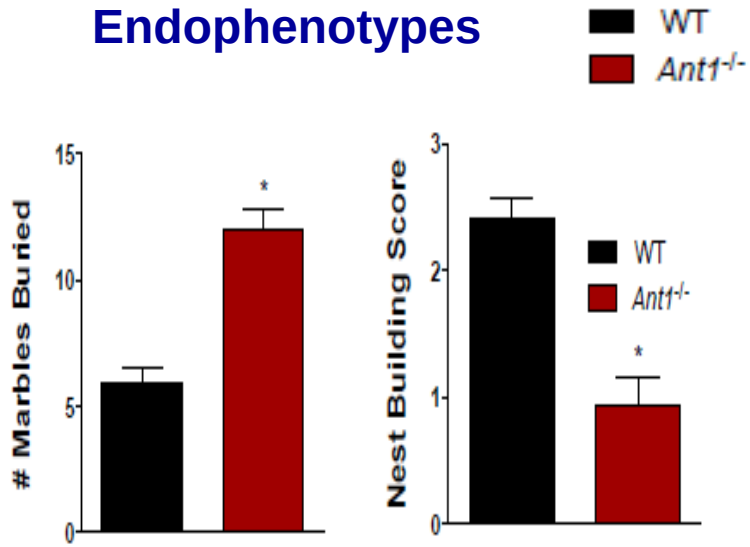
Excitatory Glutamateric Neurons Migrate Radially while the Inhibitory GABAergic Interneurons Migrate Tangentially from the Medial Ganglionic Eminence (MGE).

ANT1 INHIBITION DISORIENTS INTERNEURONAL MIGRATION CREATING AN EXCITATION-INHIBITION IMBALANCE AND AUTISM ENDOPHENOTYPES

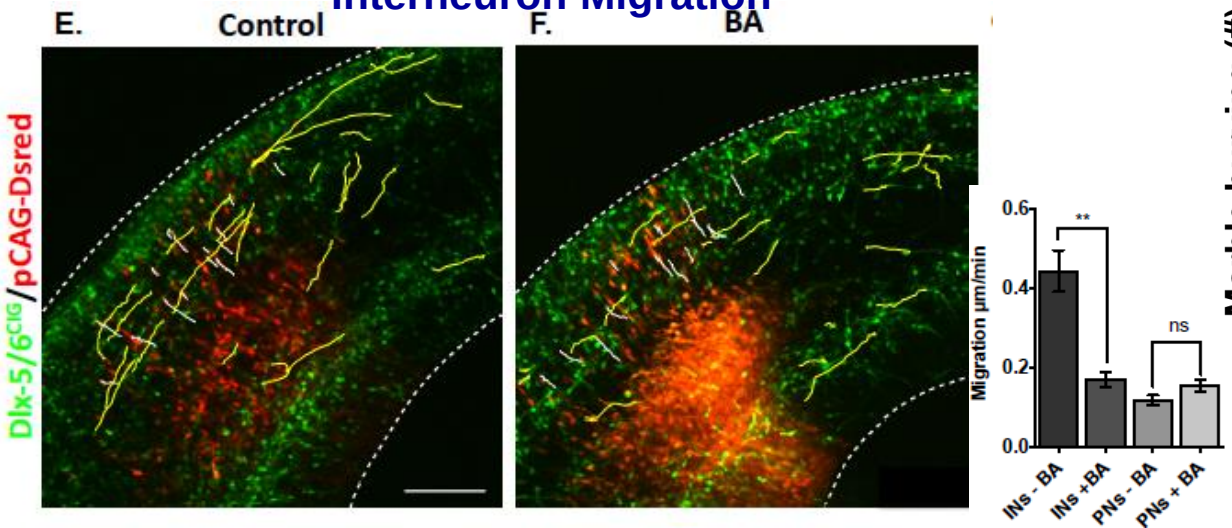
ANT1$^{-/-}$ Inactivation Disorients Interneuron Migration

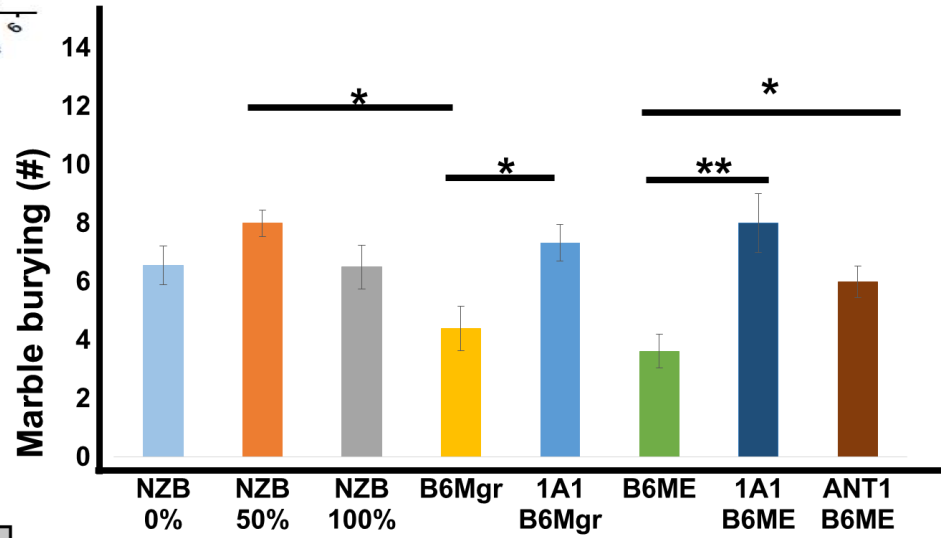


Ant1-Defect Caused ASD Endophenotypes

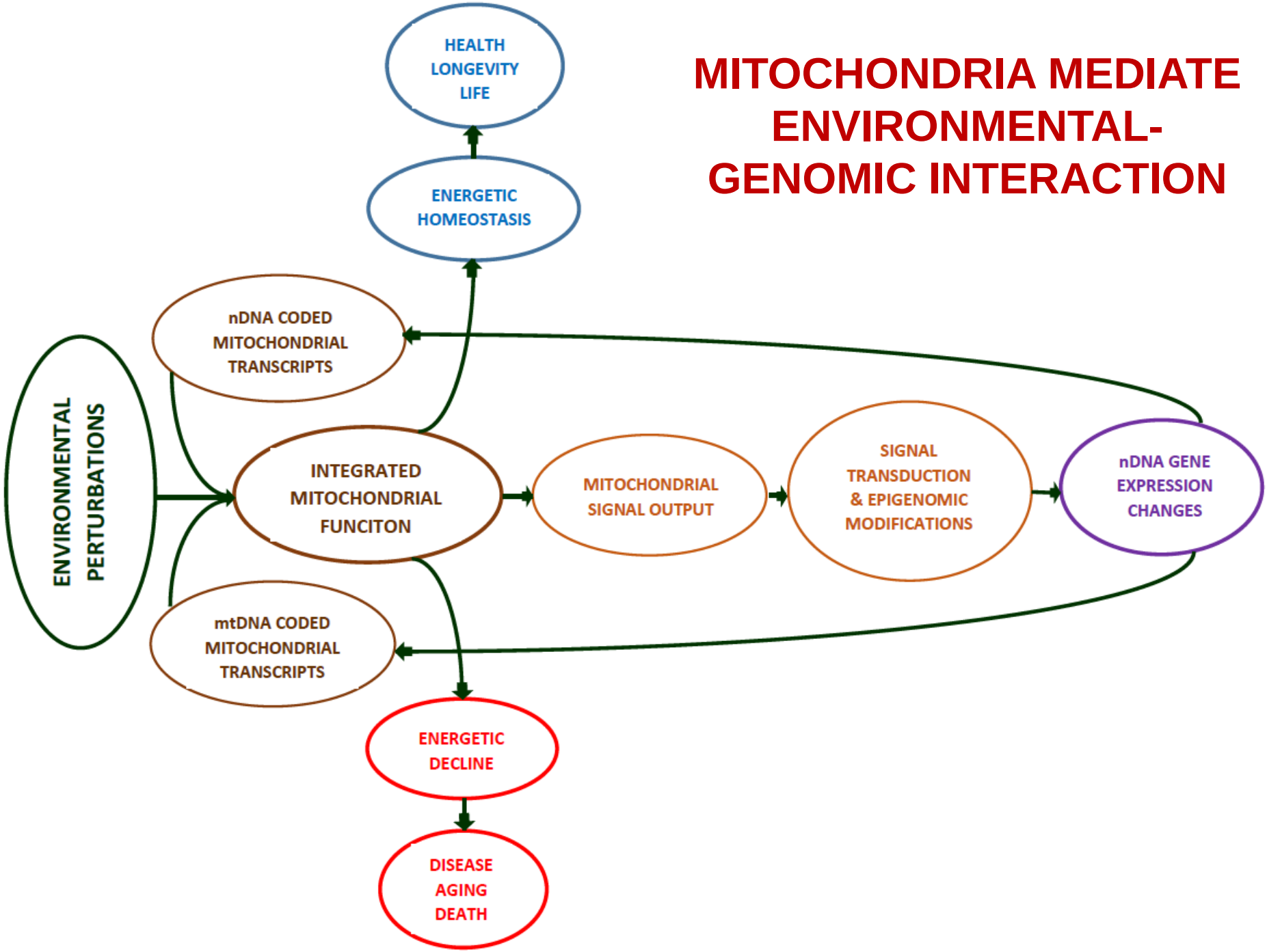


ANT1 Inhibitor Bongkrekic Acic (BA) Disorients Interneuron Migration





MITOCHONDRIA MEDIATE ENVIRONMENTAL-GENOMIC INTERACTION

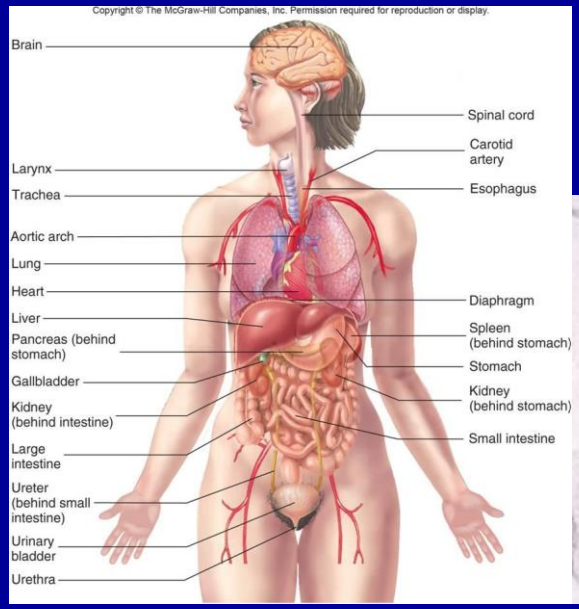


MITOCHONDRIA: OUR ORIGINS-OUR DISEASES

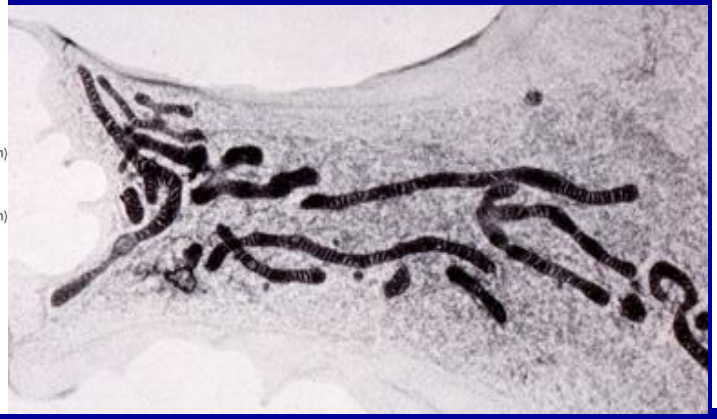
MITOCHONDRIA AS QI

Center for Mitochondrial and Epigenomic Medicine, CHOP, University of Pennsylvania
DC Wallace Institute for Mitochondrial & Epigenomic Information Sciences
Xi'an Jiaotong University

WEST-STRUCTURE (ANATOMY)



SYNTHESIS MITOCHONDRIAL BIOENERGETICS & GENETICS



EAST-VITAL FORCE (ENERGY-QI)

Mitochondria = Energy & Qi = Vital Force.

Hypothesis: Bioenergetic dysfunction is the "cause" of the common diseases.

East: 5000 years of observational medicine, Phytochemicals, Tai Qi, Acupuncture

Eastern Therapeutics may act through Mitochondrial Biology & Biophysics

ENERGY IS LIFE

CMEM, CHOP
MAMMAG, UCI
MEM, Emory
Alessia Angelin
Dimitra Chalkia
Olga Derbeneva
Weiwei Fan
Taosheng Huang
Kierstin keller
Ryan Lin
Masha Lvova
Grant MacGregor
Meagan McManus
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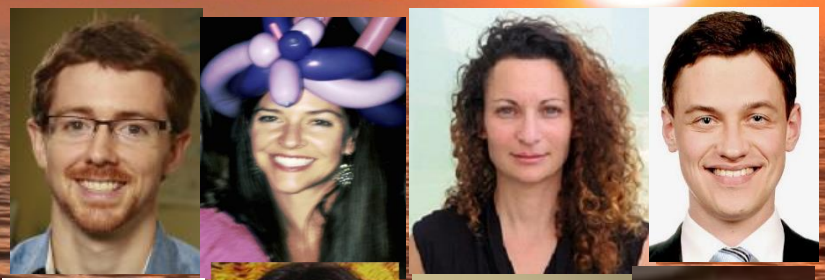
Mark Sharpley
Larry Singh
Jesus Tintos
Katrina Waymire
Tal Yardeni



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DNA BioTech, S Africa
Antonlle Olckers
Novosibirsk, Russia
Rem Sukernik

NIH, Autism Speaks, Simons Foundation

Thank You