A MITOCHONDRIAL ETIOLOGY OF COMPLEX DISEASES

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…

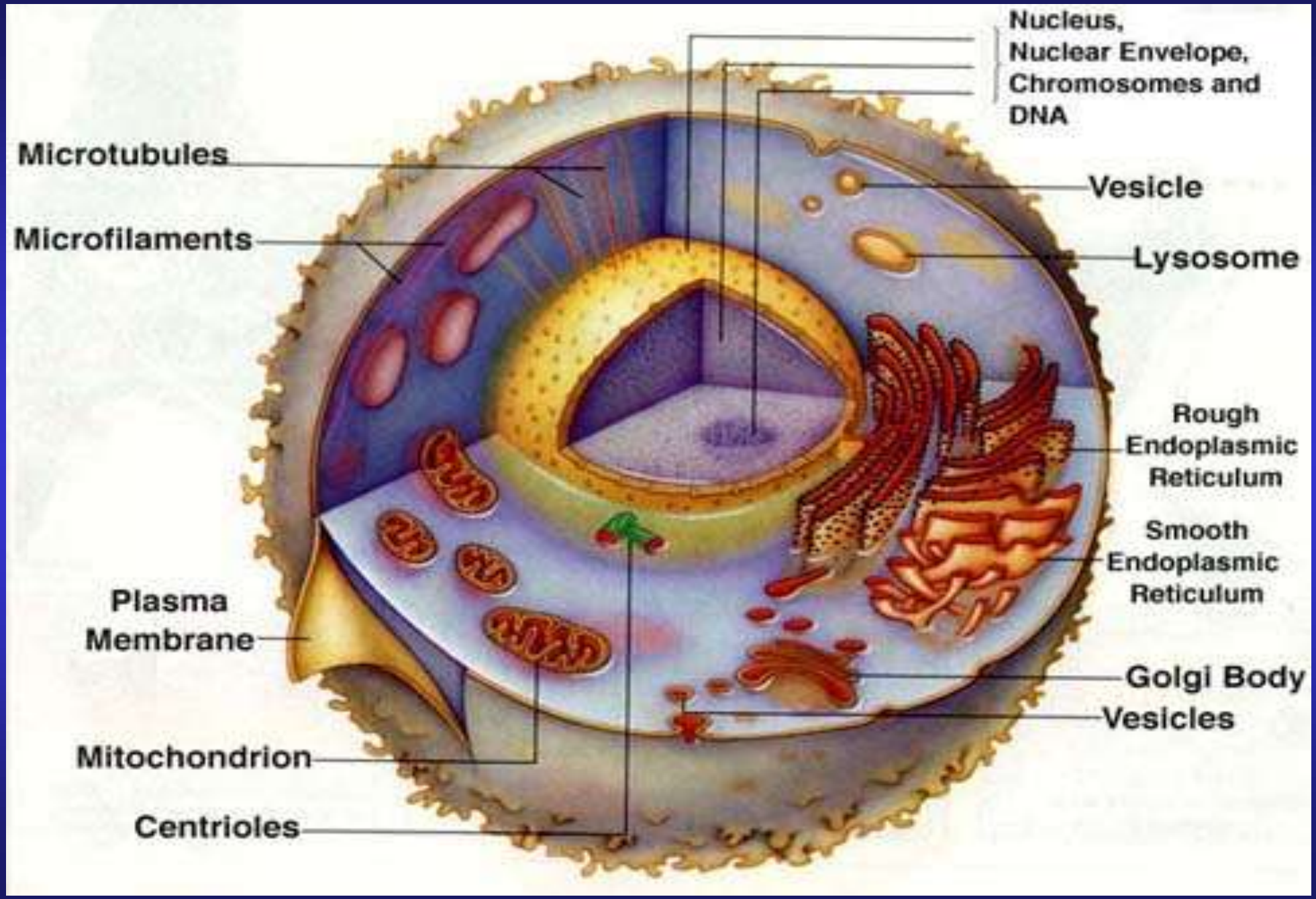
Cancer & Aging

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

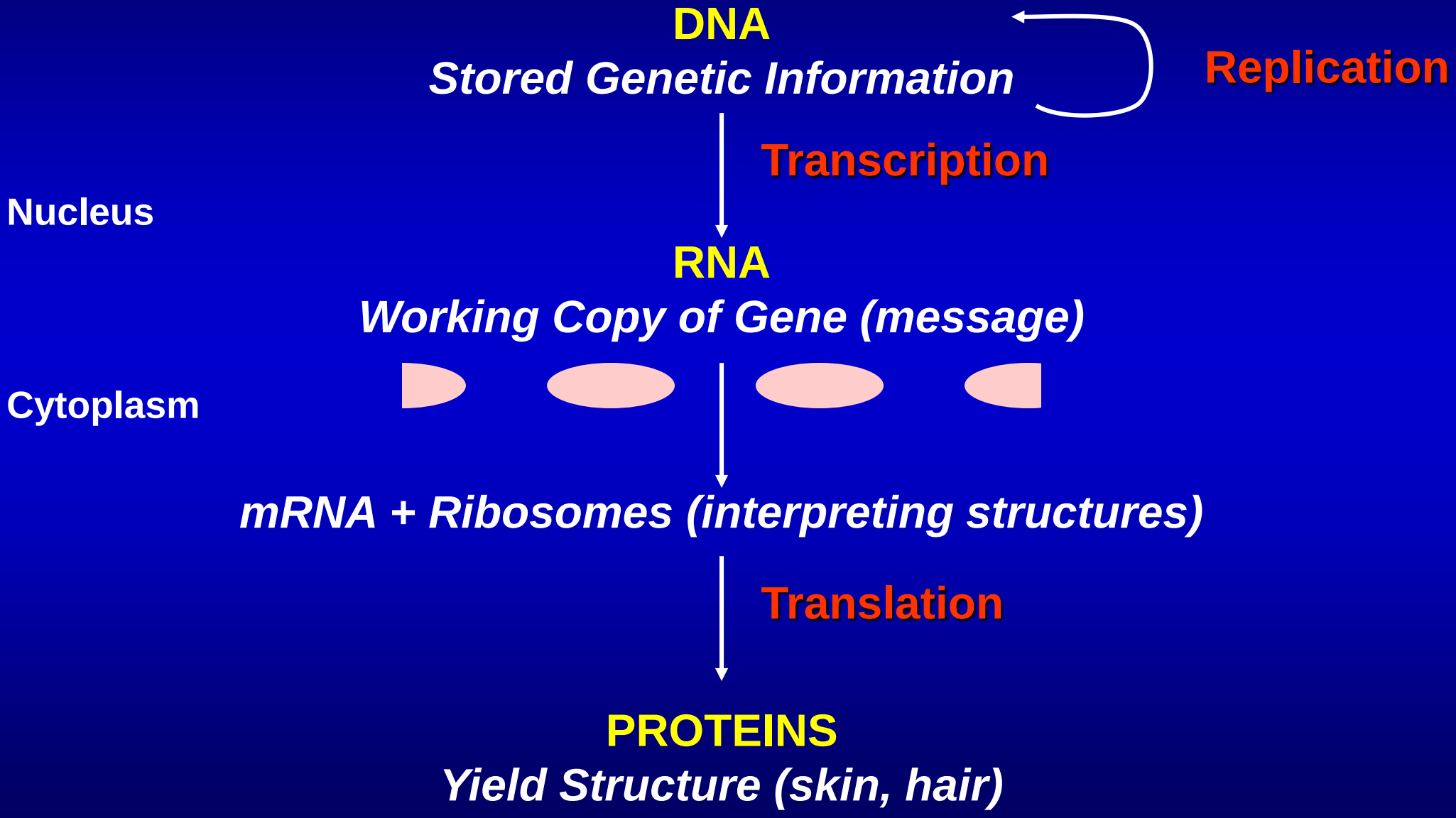
Life = Anatomy + Energetics + Information

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.


Nucleus,
Nuclear Envelope,
Chromosomes and
DNA
Microtubules
Microfilaments
Vesicle
Lysosome
Rough
Endoplasmic
Reticulum
Smooth
Endoplasmic
Reticulum
Plasma
Membrane
Golgi Body
Vesicles
Mitochondrion
Centrioles

Information Flow in The Cell



DNA Genetic Code Dictates Amino Acid Identity and Order

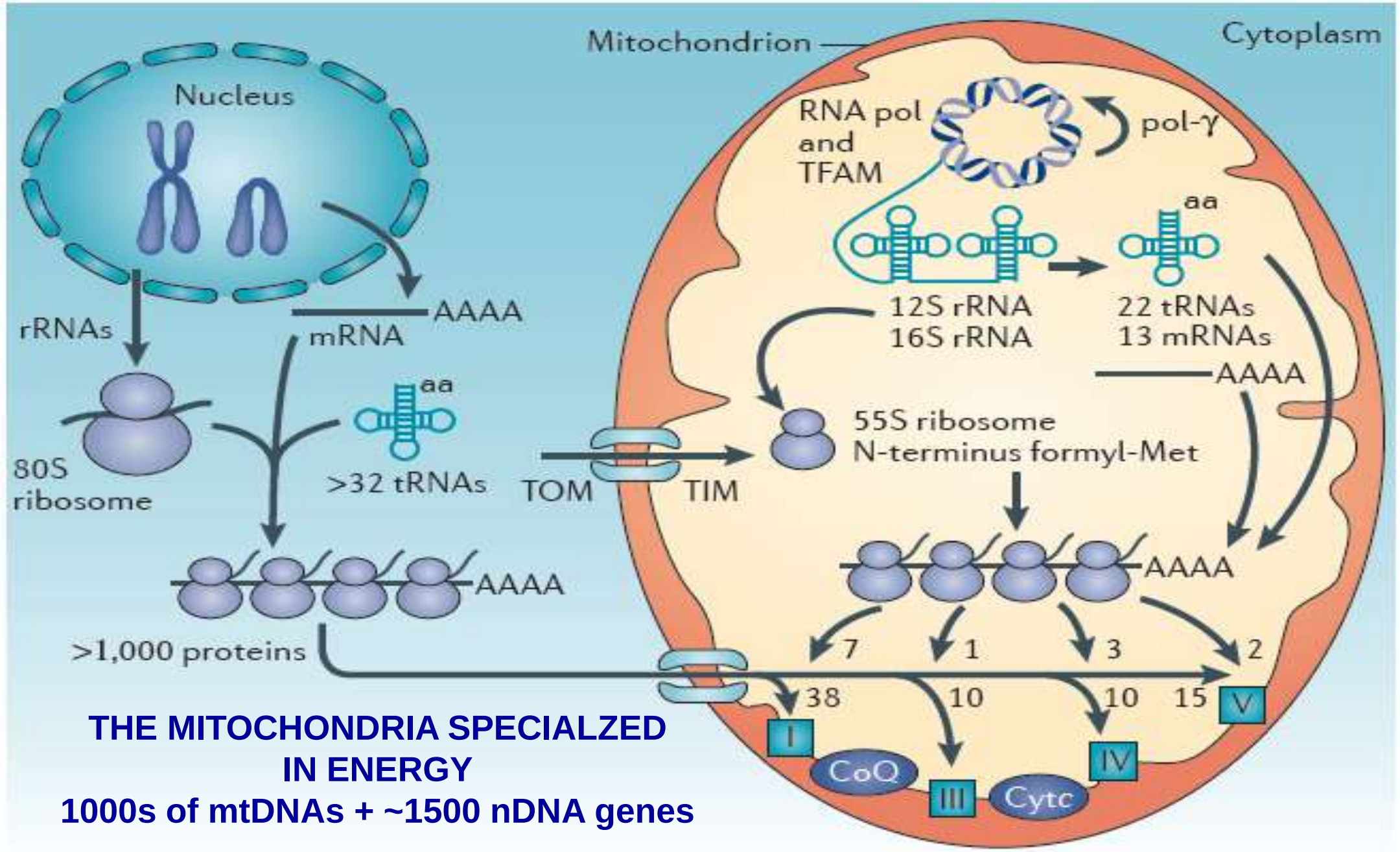
DNA Sequence Is the Genetic Code.

GCA AGA GAT AAT TGT . . .

. . . *Growing Protein Chain*

Y-GA 98-648

THE EUKARYOTIC CELL IS COMPOSED OF TWO ORGANISMS



THE MITOCHONDRIA SPECIALZED IN ENERGY

1000s of mtDNAs + ~1500 nDNA genes

MITOCHONDRIAL FUNCTION IS CENTRAL TO HEALTH

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

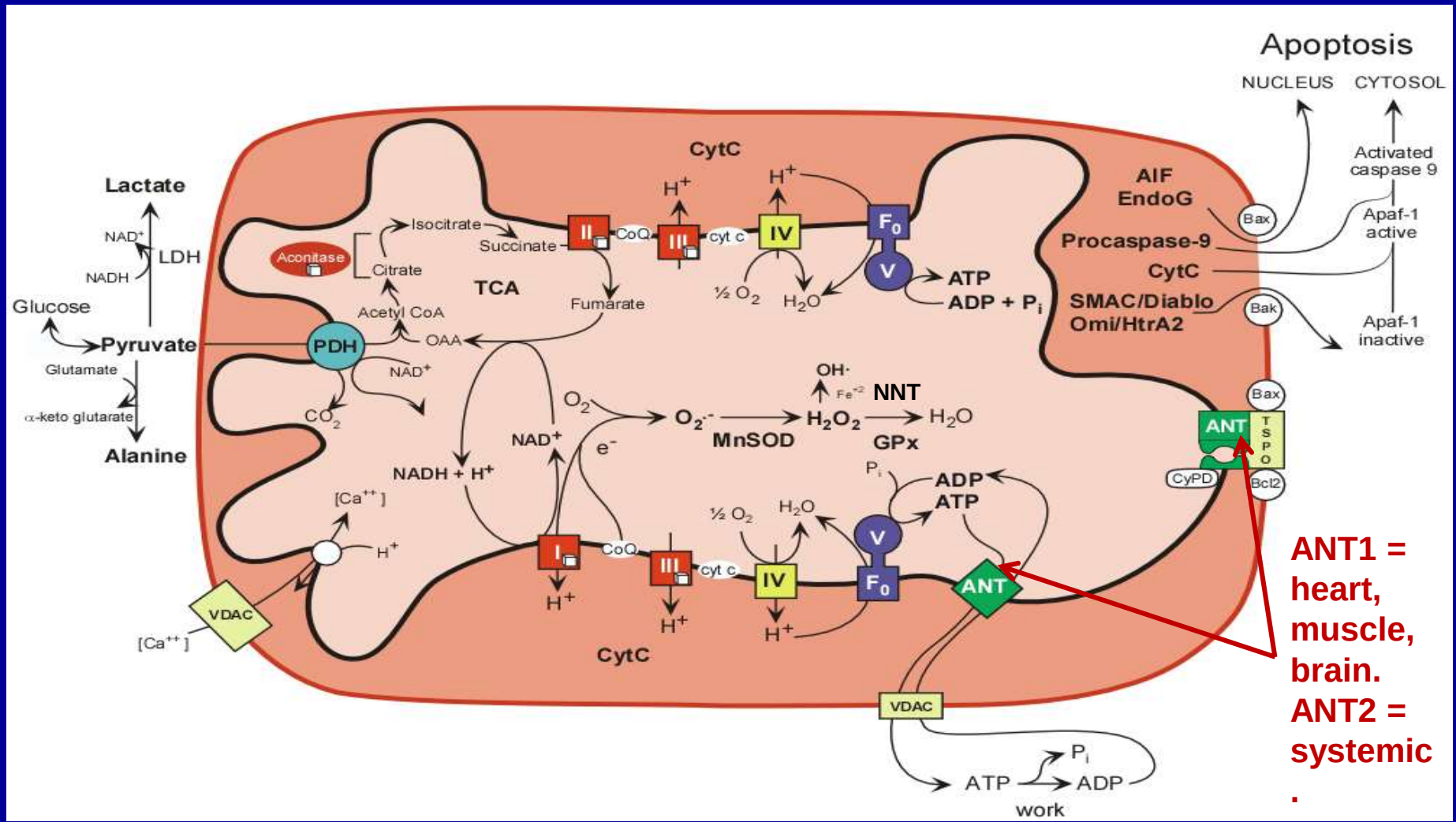
REDOX BALANCE: Thiol-Disulfide Regulation of Pathways and Transcription Factors.

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.

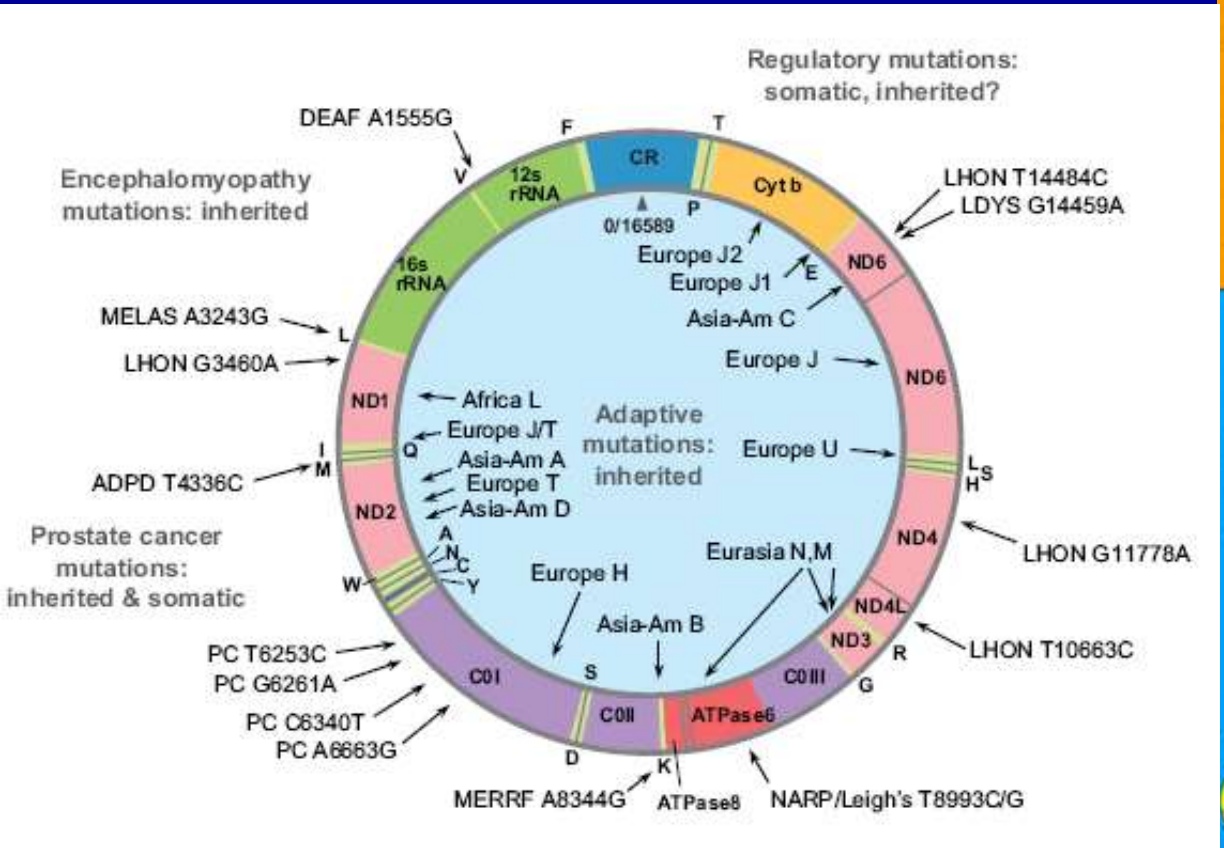


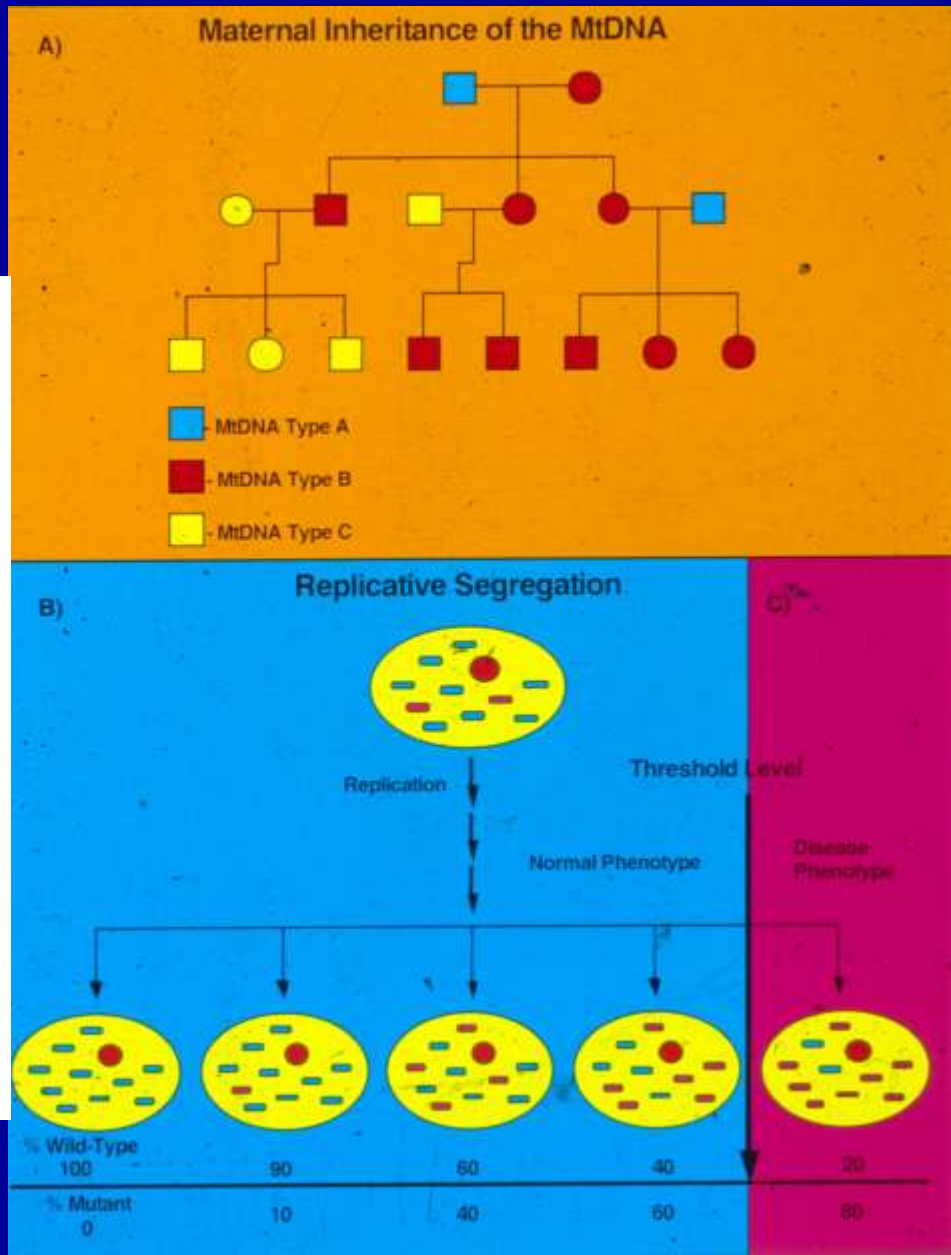
THE MITOCHONDRIAL GENOME IS DISTRIBUTED ACROSS THE nDNA & mtDNA

THE MITOCHONDRIAL GENOME:

~ 1500 nDNA Genes
Dispersed Across the Chromosomes

+ 37 mtDNA Genes



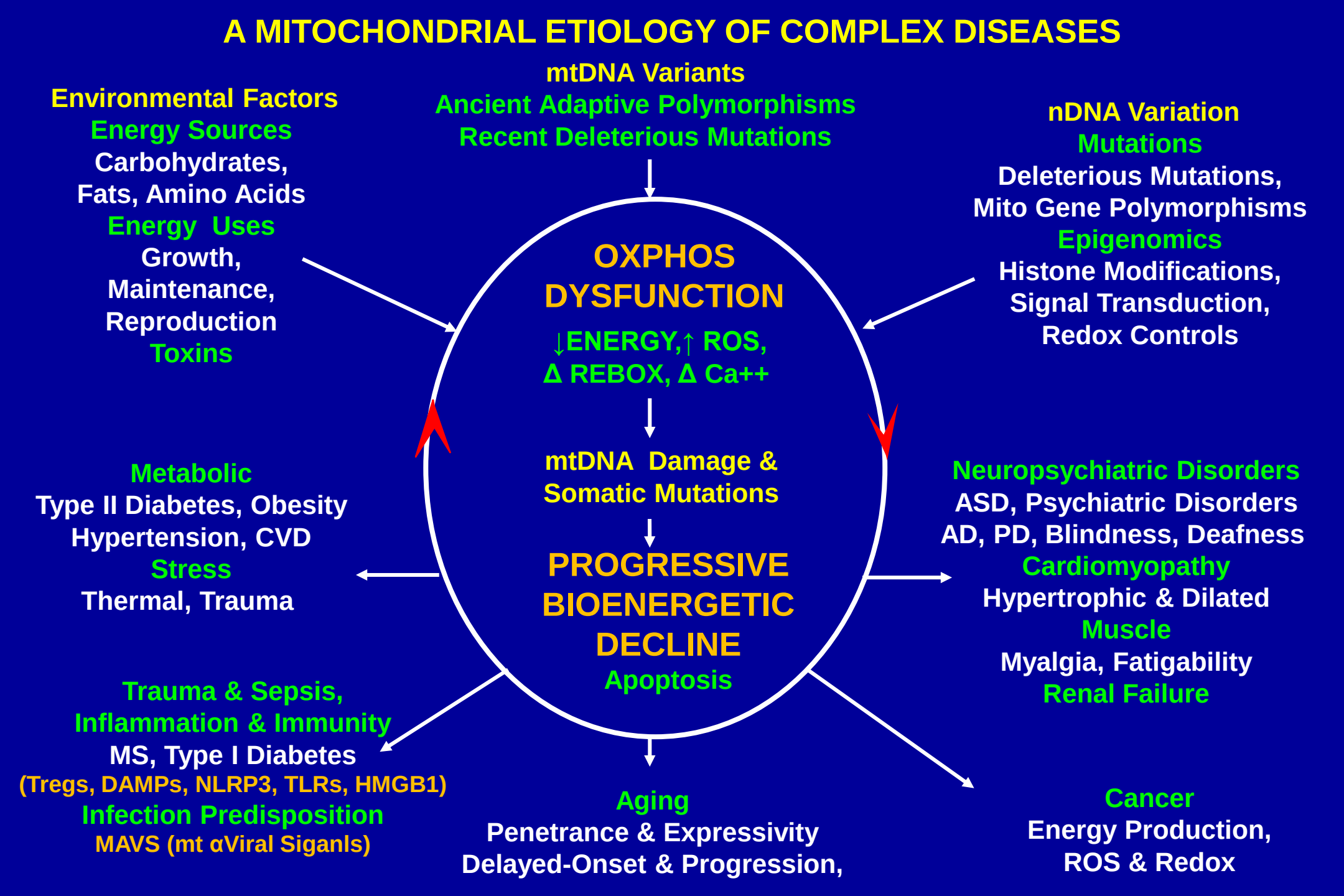


High Mutation Rate: ROS

THE BODY'S ANALTOMY IS DEFINED BY ENERGY
Origin of Tissue-Specific Disease

- **Energy Utilizing Tissues**:
  - **Brain**: High demand-Low reserve.
    ~2% body weight but uses ~20% of the O_2.
  - **Heart, Muscle, Renal, etc.**: Constant demand-High reserve.
- **Energy Storage Tissues**:
  - **WAT**: Energy storage for activities.
  - **BAT**: Energy storage for thermal regulation.
- **Energy Homeostasis Tissues**:
  - **Liver**: Glucose homeostasis.
- **Energy Sensing Tissues**:
  - **Purpose: Monitor & adapt to seasonal plant carbohydrates**
  - **Pancreatic β Cells**: Glucose abundant-Insulin signaling.
  - **Pancreatic α Cells**: Glucose limitation-Glucagon signaling.

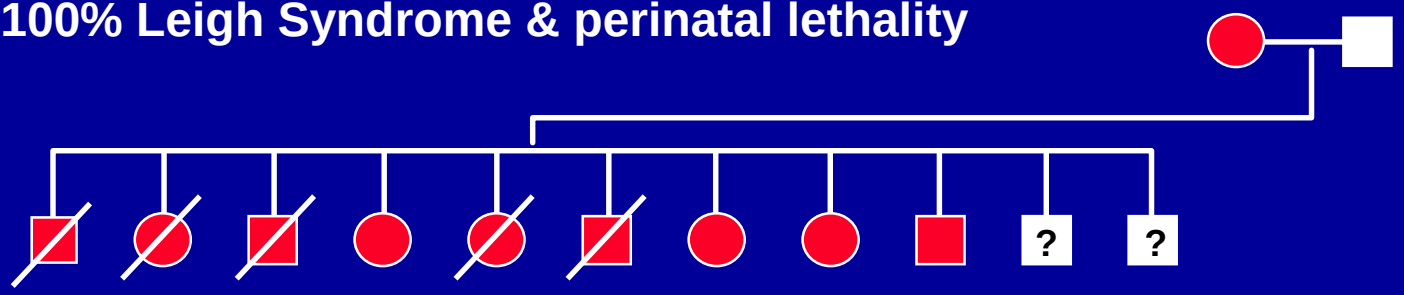
A MITOCHONDRIAL ETIOLOGY OF COMPLEX DISEASES



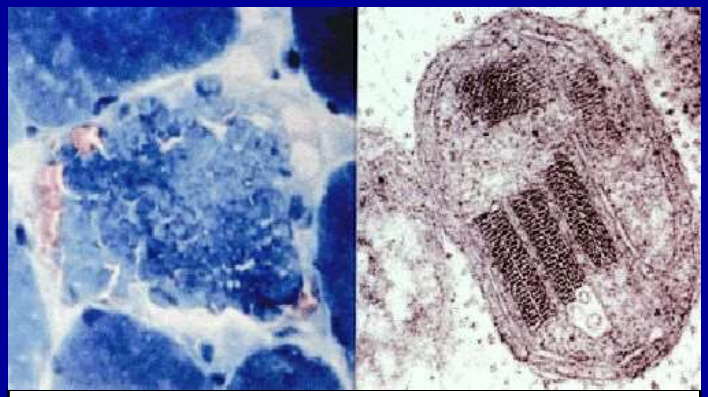
mtDNA GENE MUTATIONS GIVE VARIABLE PHENOTYPES

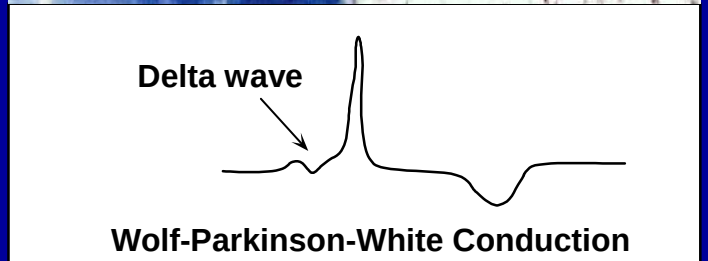
THE SAME mtDNA $tRNA^{Leu(UUR)}$ np A3243G MUTATION CAUSES DIFFERENT DISEASES

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



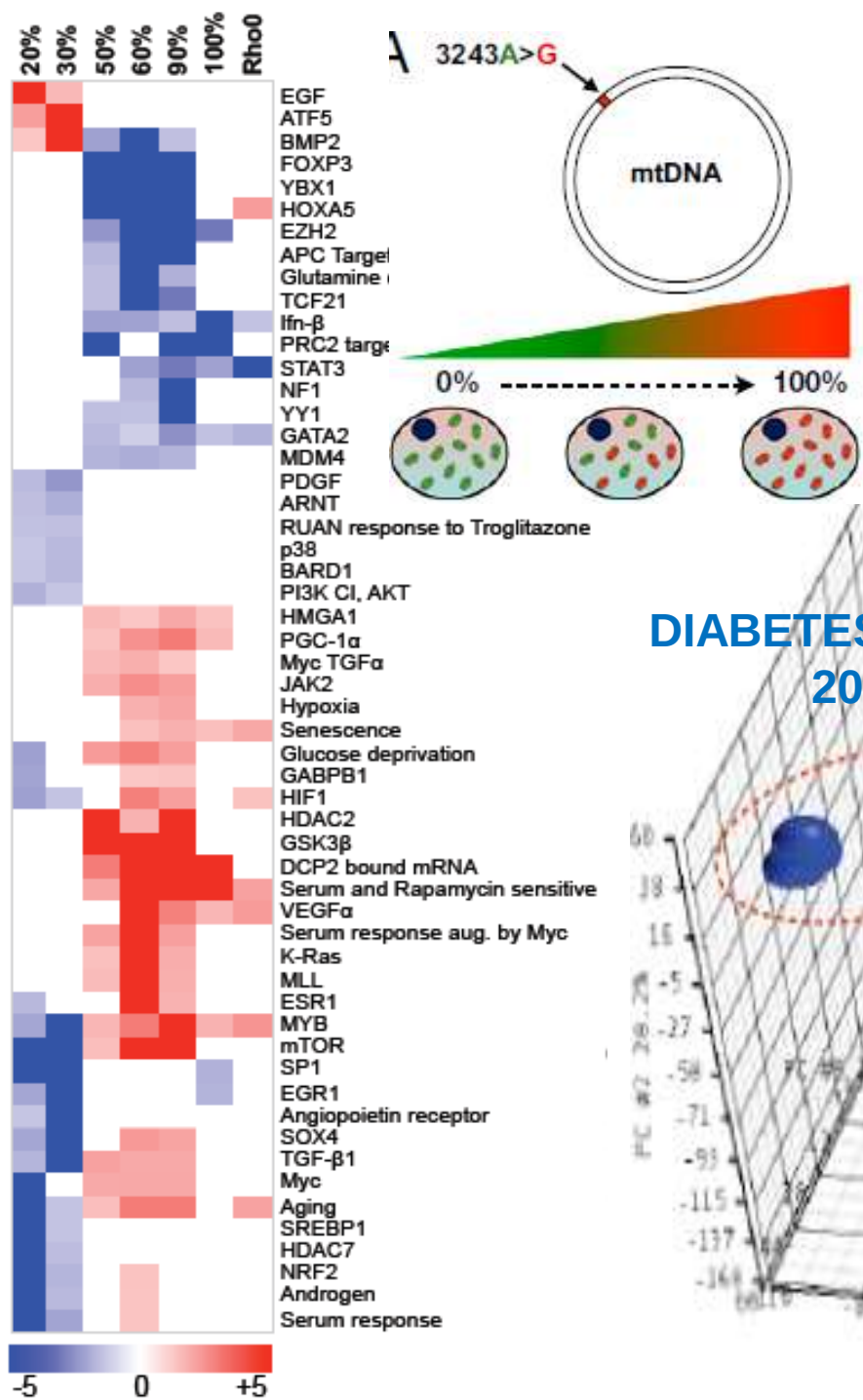
Lactic Acidosis	+	+	+	+	+	+	+	+	+	?	?	+	-
Growth Retardation	+	+	+	+	+	+	+	+	+	?	?	+	-
Dementia	+	+	+	+	+	+							
Stroke-Like Episodes	+	+	+	+	-								
Hypertrophic Cardiomyopathy	+	+	+	+	+	+							
Conduction Abnormalities	+	+		+	+	+							





Wolf-Parkinson-White Conduction

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



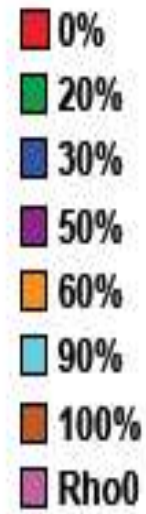
LEIGH SYNDROME &
PERINATAL LETHALITY
100%

NEUODEGENERATION
50-90%

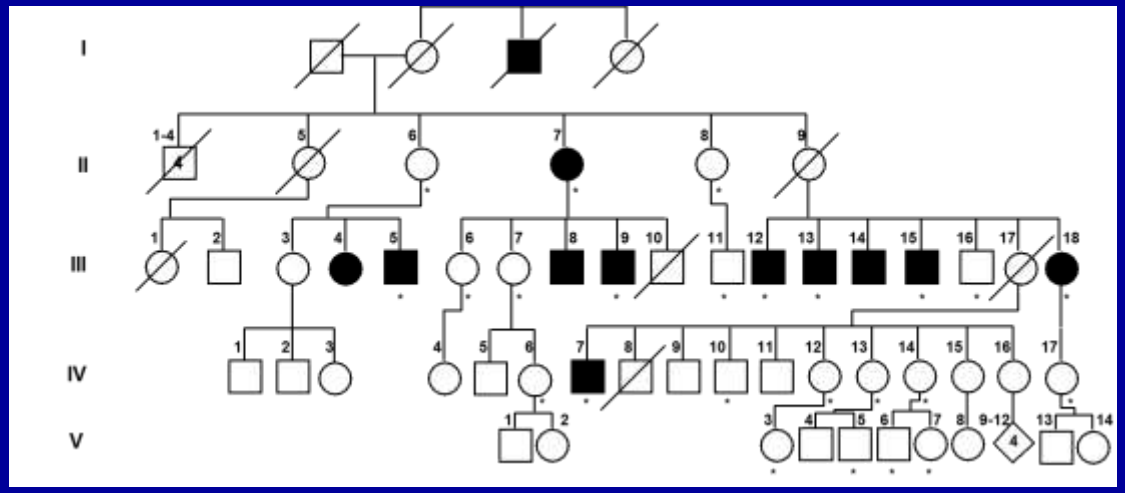
DIABETES & AUTISM
20-30%

NORMAL
0%

ρ^o



LEBER HEREDITARY OPTIC NEUROPATHY MATERNAL INHERITANCE, MALE BIAS, & BACKGROUND REGULATION OF EXPRESSIVITY



MATERNALLY INHERITED OPTIC NEUROPATHY, VARIABLE PENETRANCE, & 4:1 MALE BIAS

mtDNA *ND4* np 11778 G>A
arginine 340 to histidine

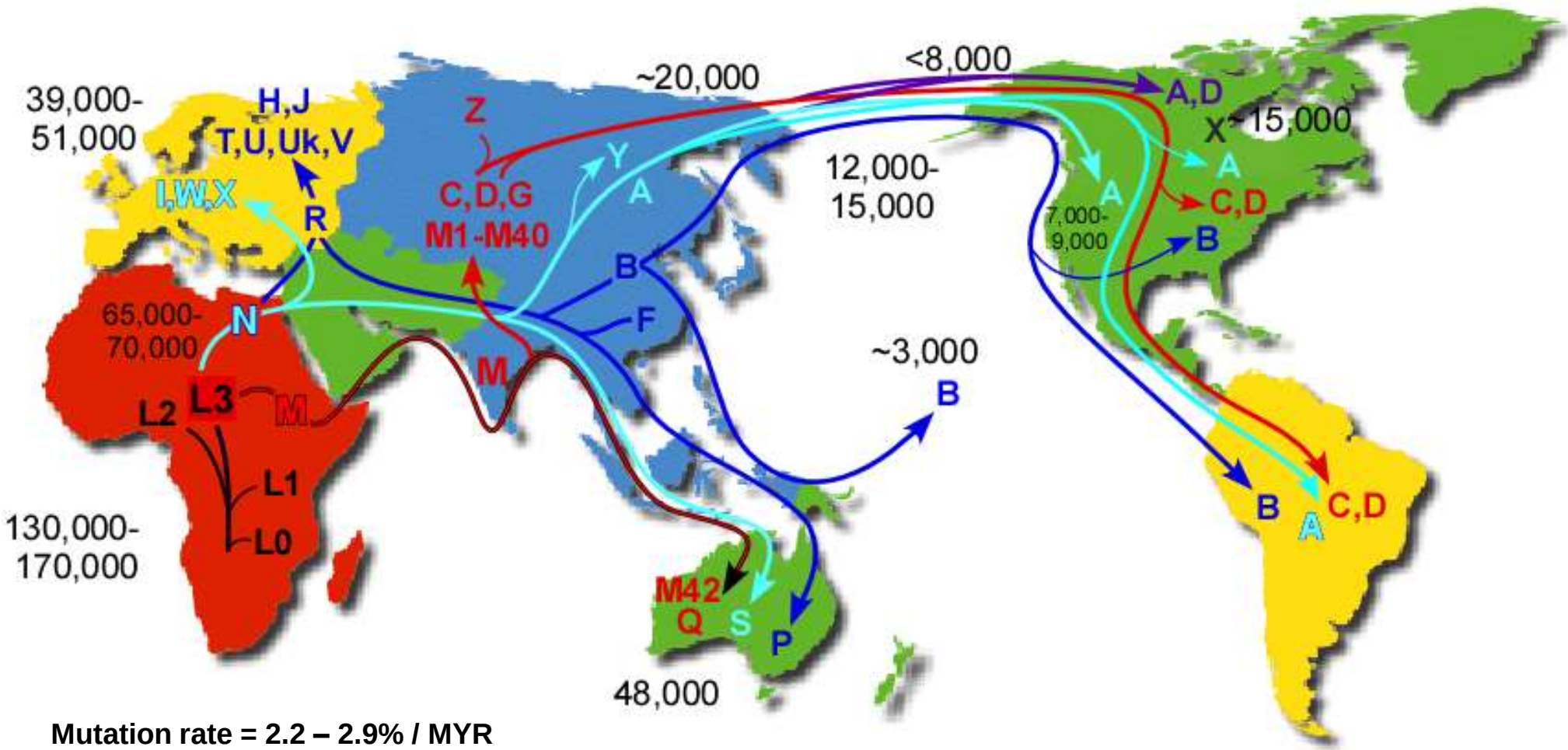
Penetrance of Milder Mutations exacerbated by Haplogroup J or *ND1* T3394C (Y30H)

Mutation	Gene	~ % Patients	Complex I Defect	AA Cons	% Hplgr J	*ND1* 3394C
3460A	ND1	15	Severe	Moderate	~10	-
11778A	ND4	50	Moderate	Moderate	29	+
14484C	ND6	15	Mild	Low	79	+

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.



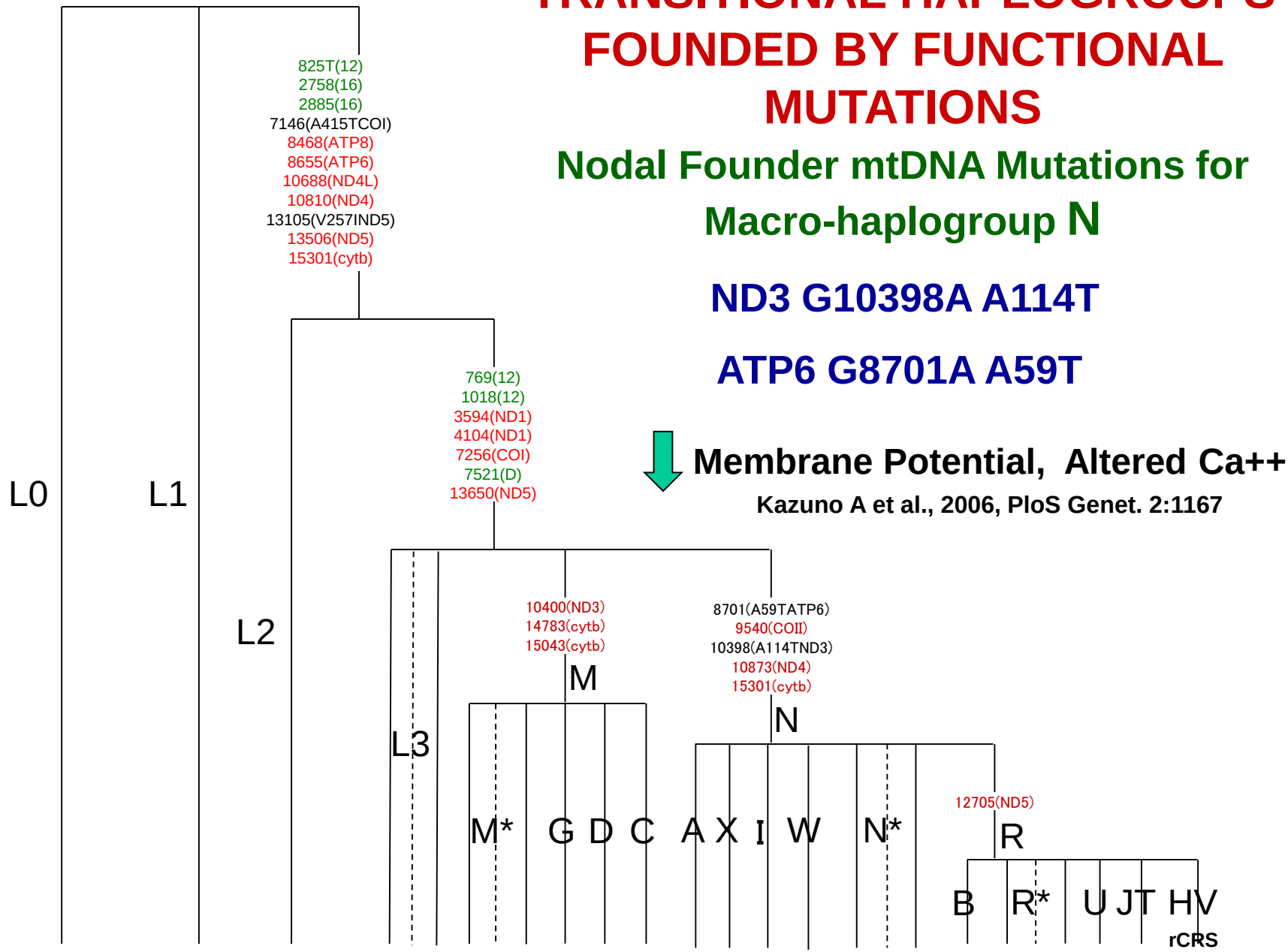
Mutation rate = 2.2 – 2.9% / MYR
Time estimates are YBP.

TRANSITIONAL HAPLOGROUPS FOUNDED BY FUNCTIONAL MUTATIONS

Nodal Founder mtDNA Mutations for Macro-haplogroup N

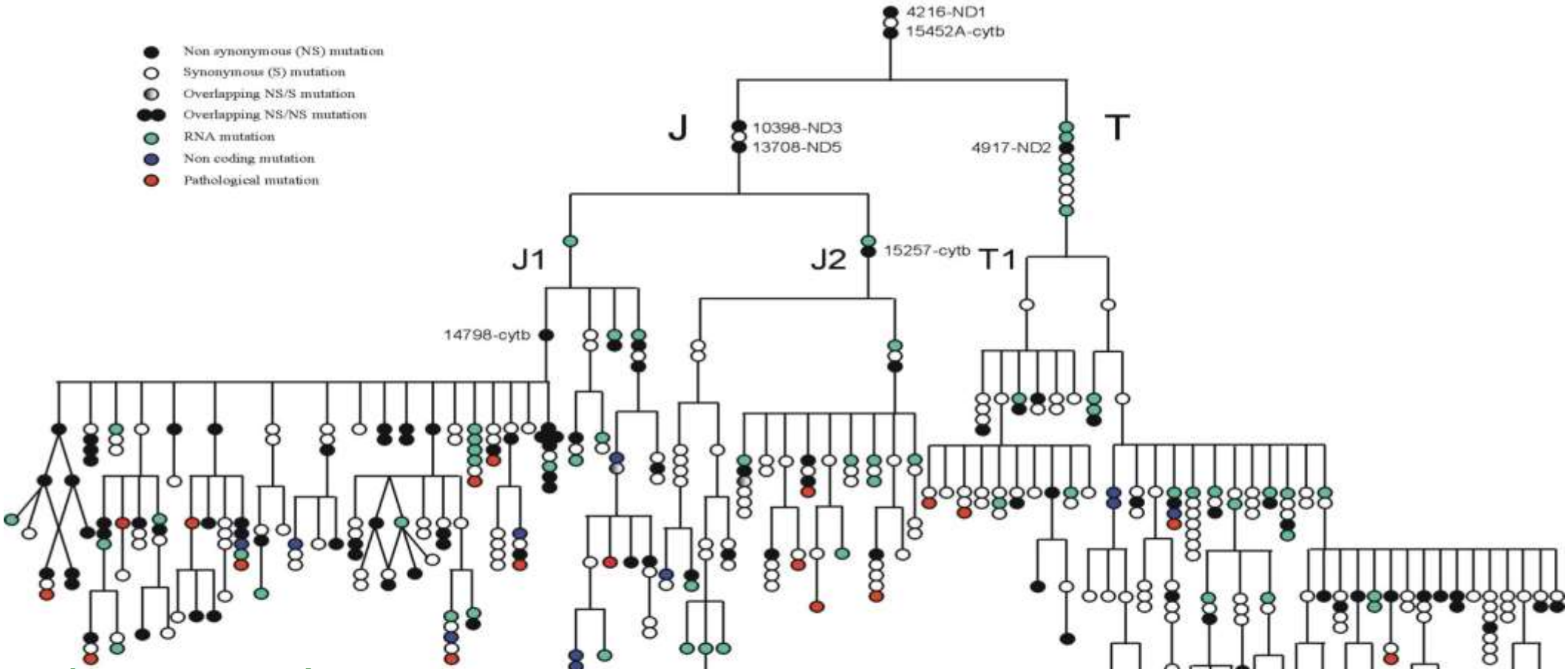
ND3 G10398A A114T

ATP6 G8701A A59T



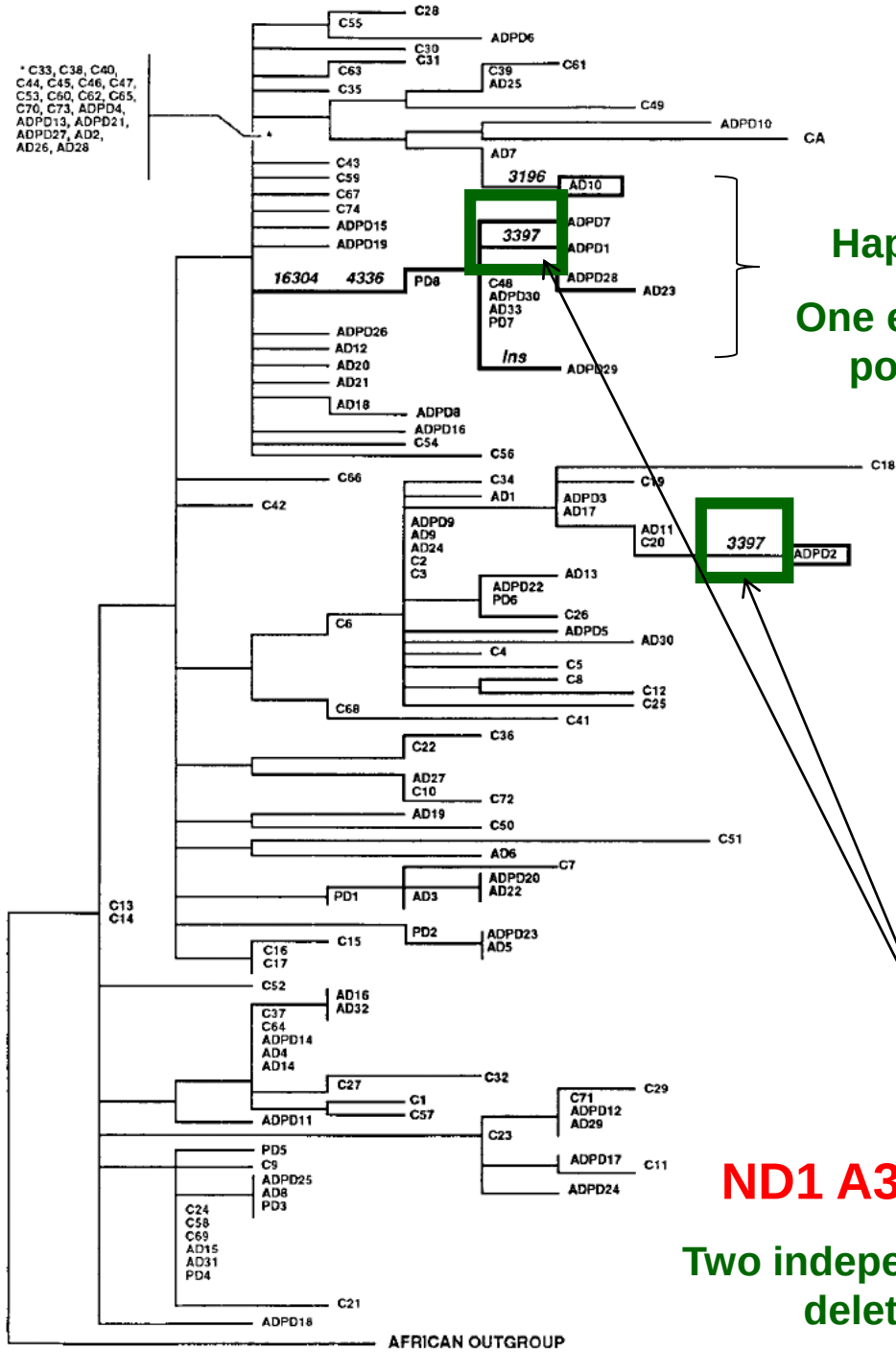
NODAL SUBSTITUTIONS ALTERING CONSERVED AMINO ACIDS INITIATE EACH mtDNA HAPLOGROUP

EUROPEAN HAPLOGROUPS T & J



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

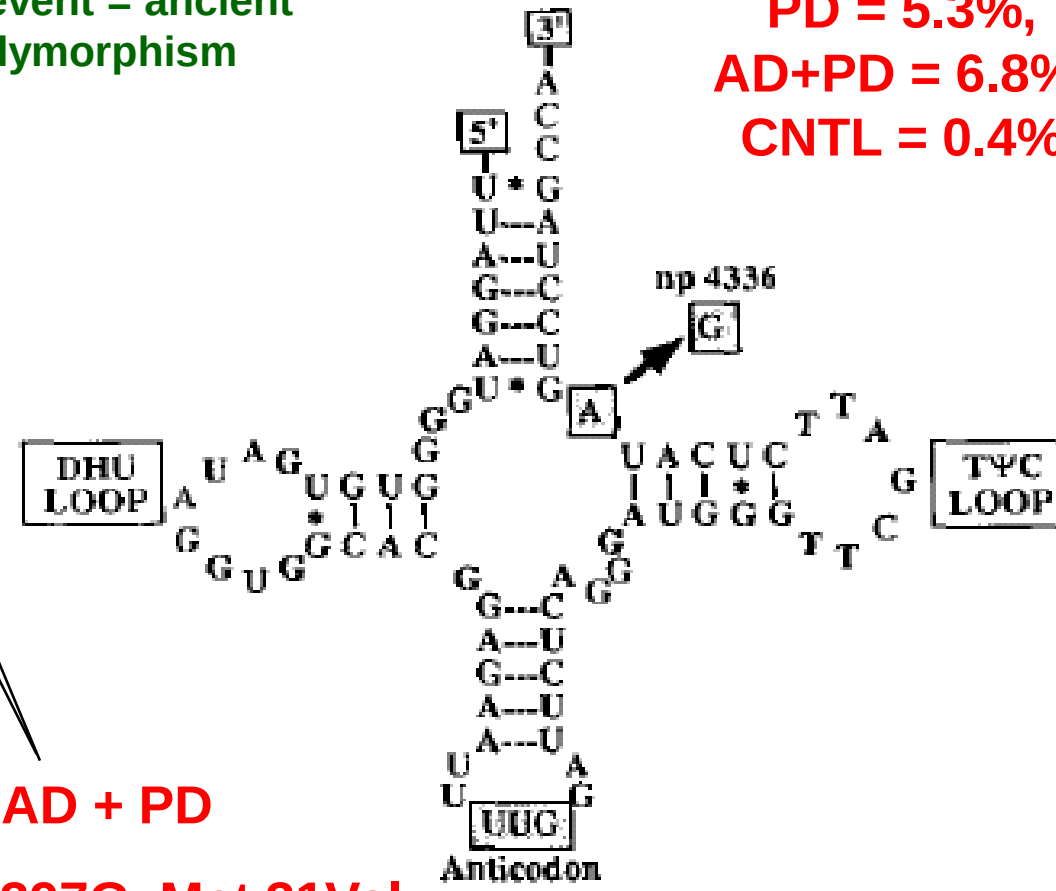
EUROPEAN ASSOCIATION OF tRNA^{Gln} A4336G & *ND1* (M31V) WITH ALZHEIMER & PARKINSON DISEASE



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

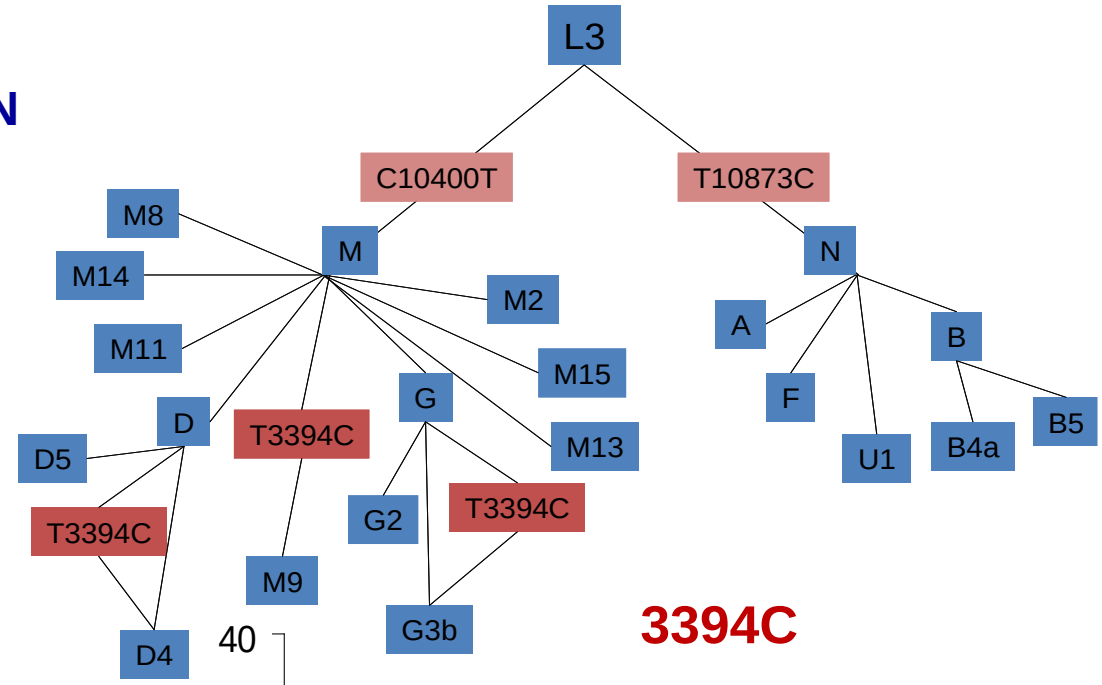
GENOMICS 17, 171–184 (1993)

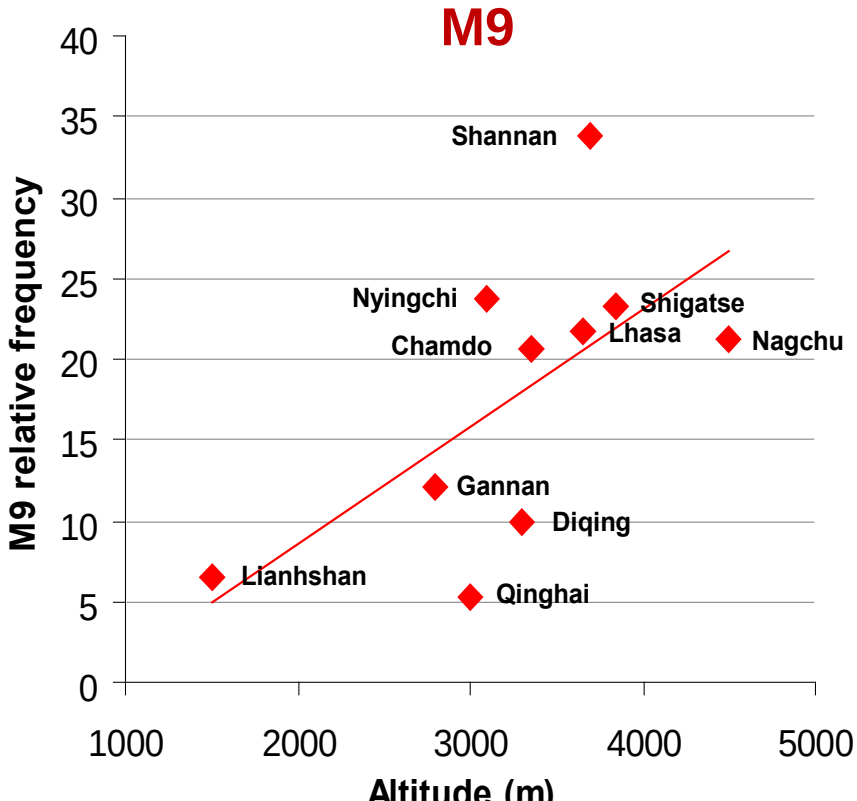
ADAPTATIVE SELECTION

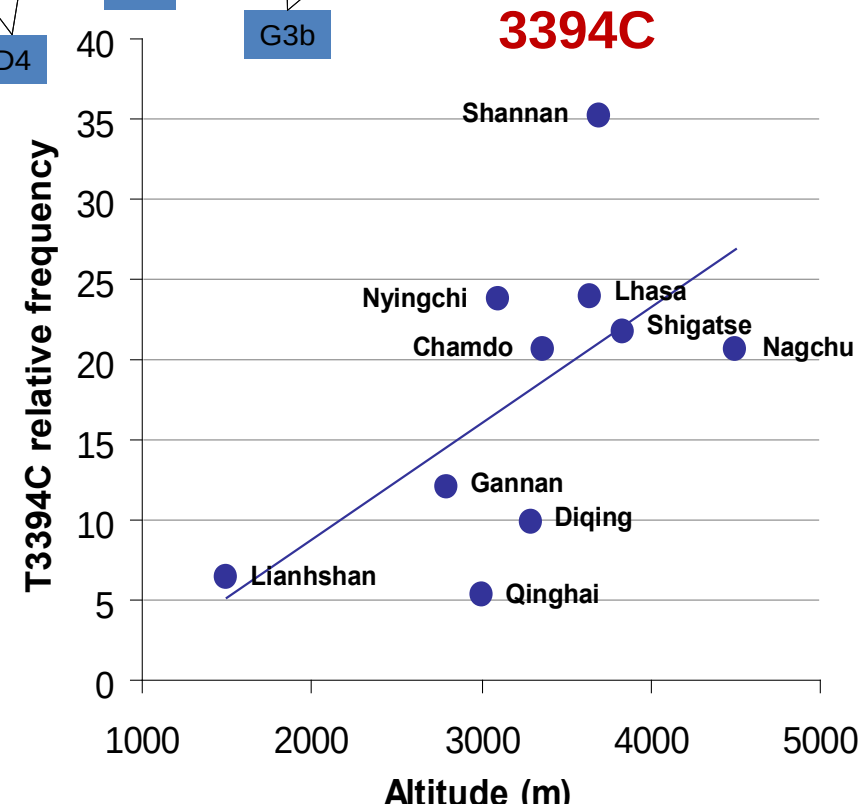
mtDNA AMINO ACID SUBSTITUTIONS CAN BE POSITIVE OR NEGATIVE DEPENDING ON CONTEXT

M [*ND3* 10398G (114A)] IS ENRICHED IN TIBET &

[*ND1* 3394C (30H)] IS PATHOGENIC ON N BUT ADAPTIVE ON M IN TIBETANS

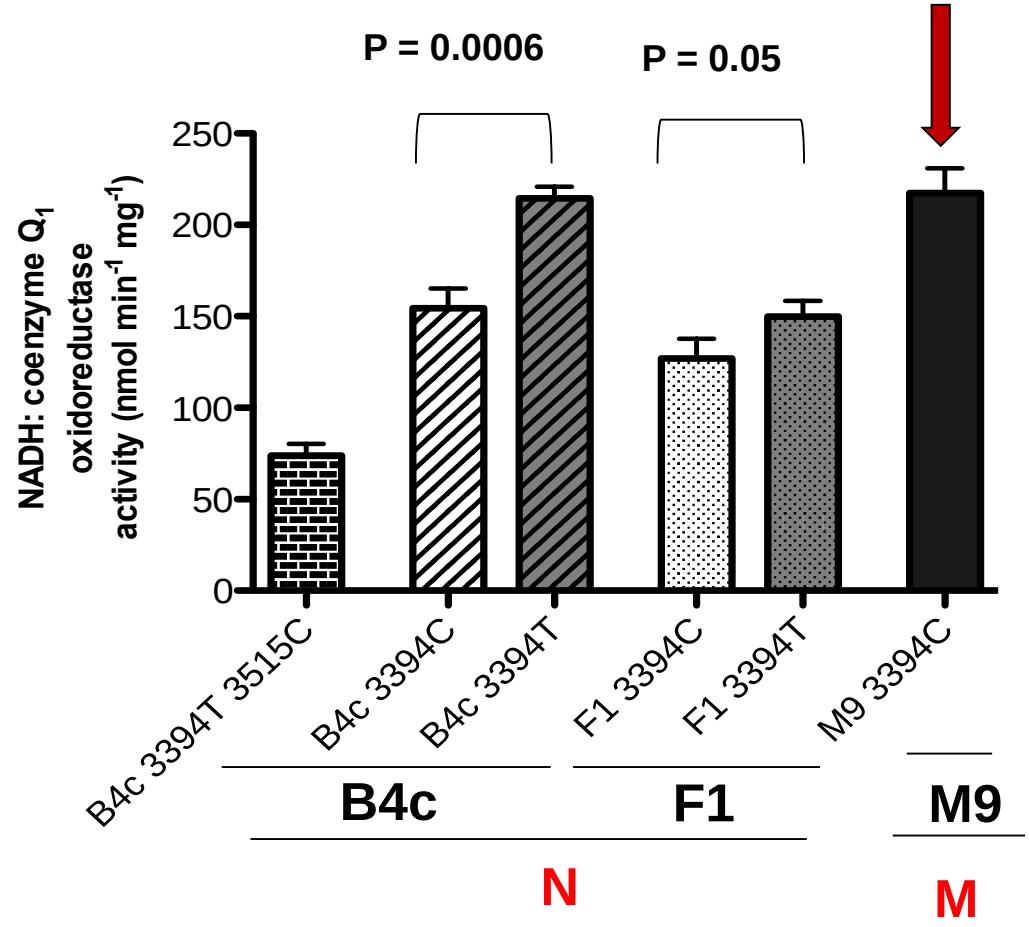






THE ND1 3394C (30H) MUTATION CAUSES A COMPLEX I DEFICIENCY ON N HAPLOGROUPS B4 & F1, BUT IS DOES NOT IMPAIR COMPLEX I ON M HAPLOTYPE M9

COMPLEX I SPECIFIC ACTIVITY



Blood Platelets X 143B (TK-) ρo → + BrdU, - uridine → Cybrids

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

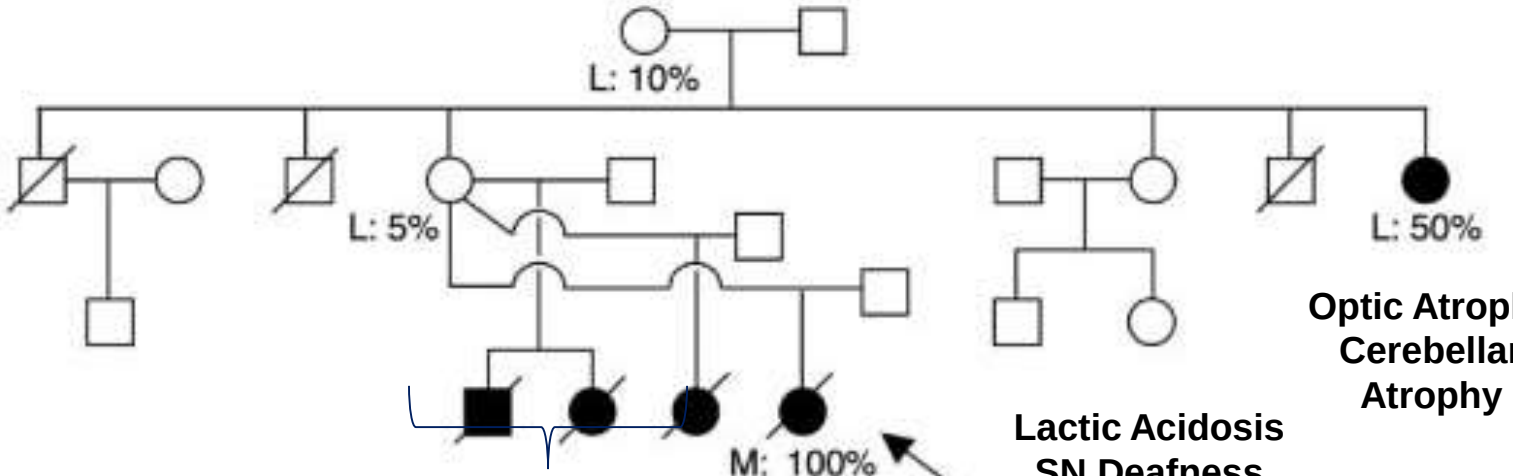
H > J = T > U (U* > U4 = U5a1 > Uk)

- **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
- **AGING**
- **CANCERS**
- **ATHLETIC PERFORMANCE (L0>L3>N>H>J-U-T)**

* HAAT- highly active anti-retroviral therapy

HETEROPLASMIC mtDNA MUTATIONS SEGREGATE RAPIDLY

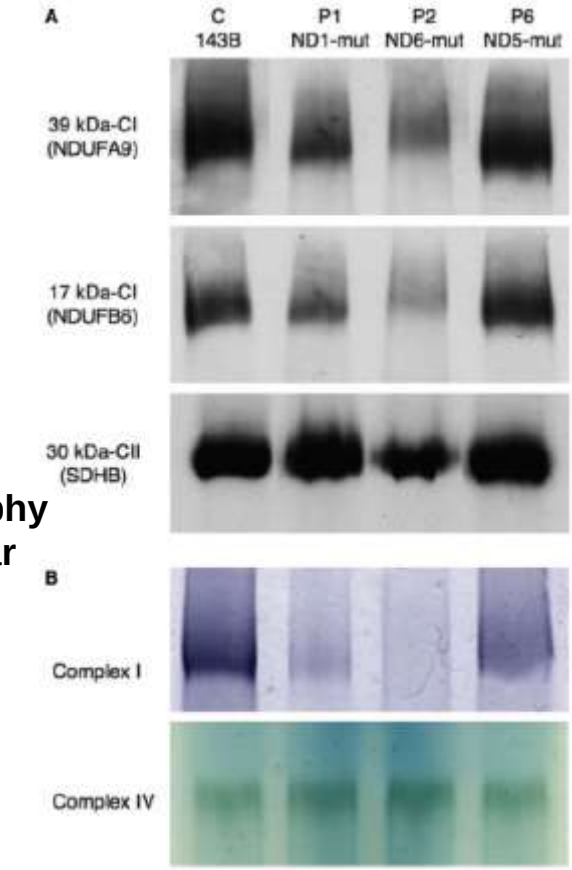
A HUMAN HETEROPLASMIC mtDNA *ND6* G14600A P25L MUTATION SEGREGATES TO GIVE VARIOUS PHENOTYPES

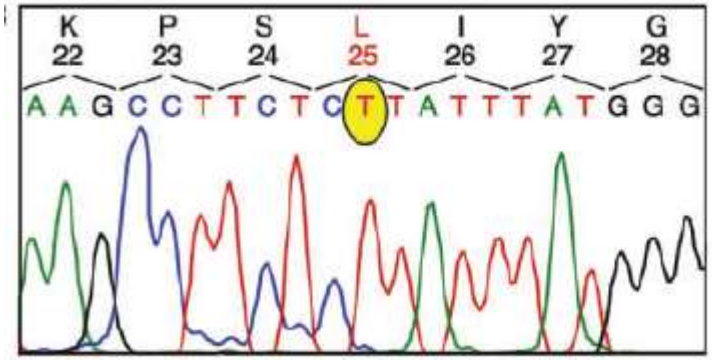


Leigh Syndrome

Lactic Acidosis
SN Deafness
Epileptic Seizures
Metabolic Failure
Muscle Myopathy
Cerebral atrophy
Death

Optic Atrophy
Cerebellar
Atrophy





ND6 Gene: 14600G>A

P25L

Human	15	GFVGFSSKPS PIYGGLVLIVS	35
Bovine	16	GFVGFSSKPS PIYGGLGLIVS	36
Pig	16	GFVGFSSKPS PIYGGLGLIVS	36
Rat	15	GCLGLALKPS PIYGGFGLIVS	35
Mouse	15	GCLGLALKPS PIYGGLGLIVS	35
Xenopus	15	GLVAVASNPS PFYAALGLVLA	35
Zebrafish	15	GMIA IASNPA PYFAAFGLVVV	35

Malfatti –Zevani *Brain* (2007), **130**, 1894–1904

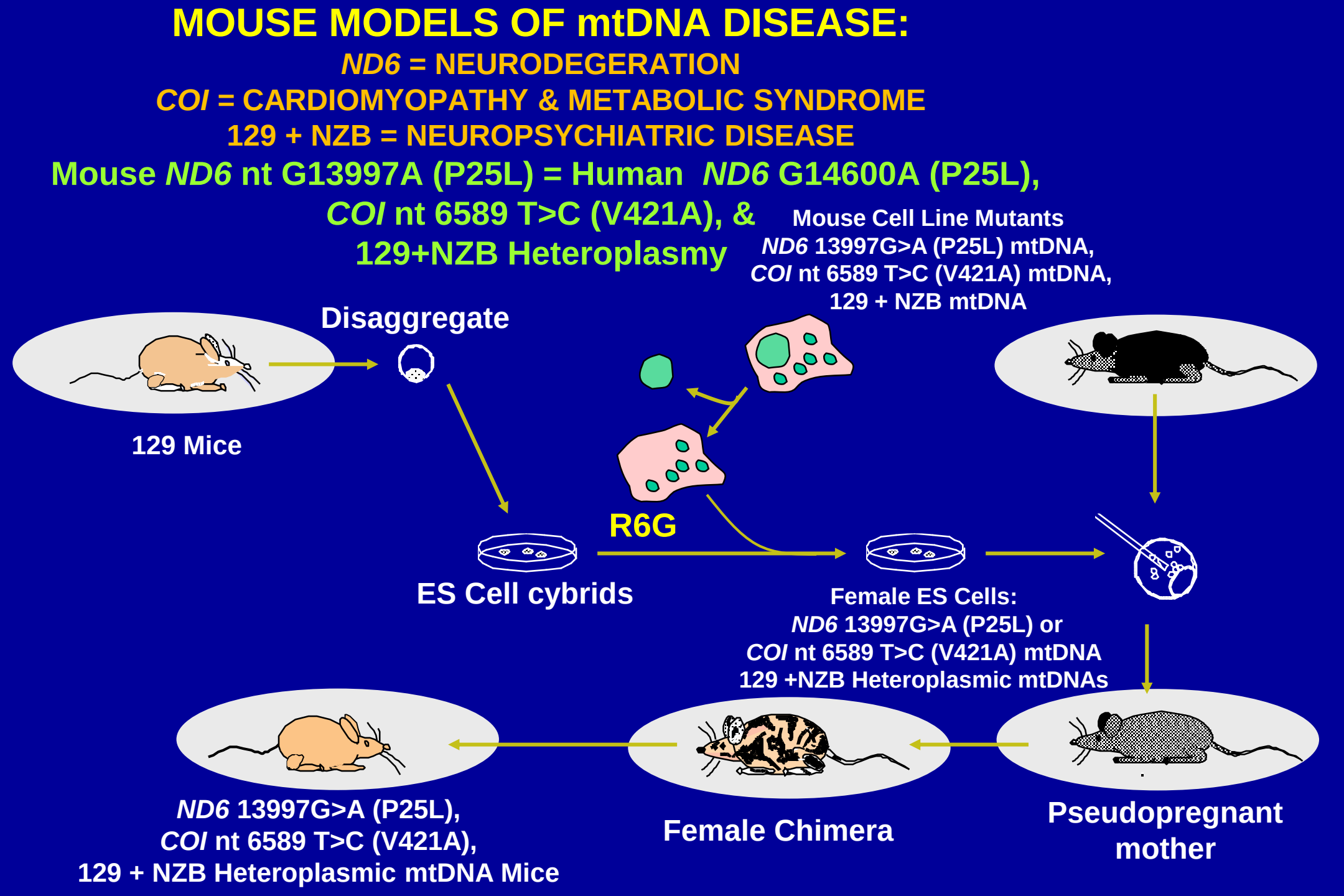
MOUSE MODELS OF mtDNA DISEASE:

ND6 = NEURODEGERATION

COI = CARDIOMYOPATHY & METABOLIC SYNDROME

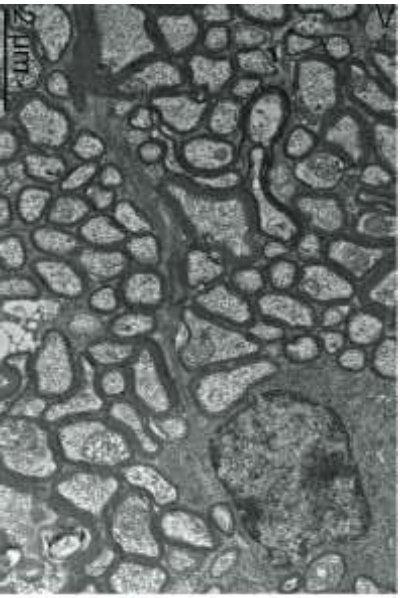
129 + NZB = NEUROPSYCHIATRIC DISEASE

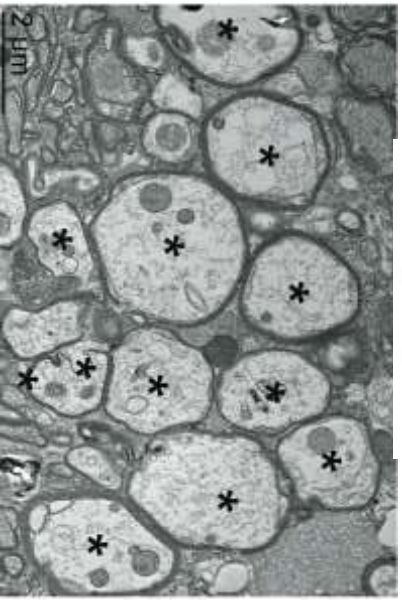
Mouse *ND6* nt G13997A (P25L) = Human *ND6* G14600A (P25L),
COI nt 6589 T>C (V421A), &
129+NZB Heteroplasmy



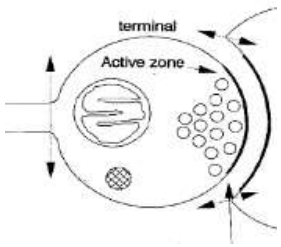
THE mtDNA *ND6* P25L MUTATION RESULTS IN ELEVATED REACTIVE SPECIED (ROS) PRODUCITON AND NEUROLOGICAL DISEASE

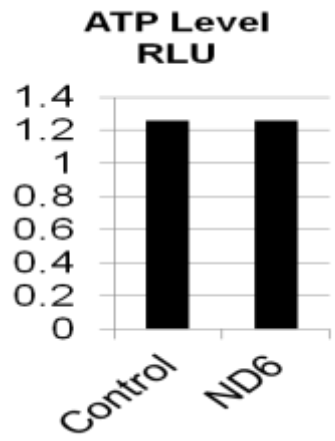
NEURONAL DEGENERATION

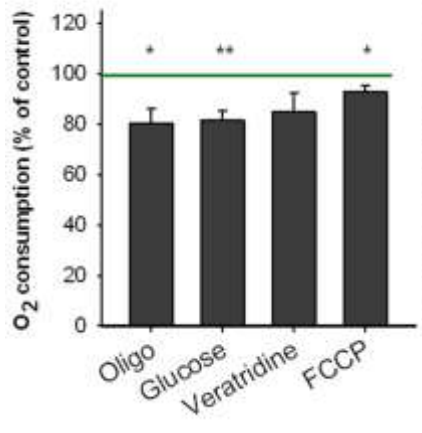


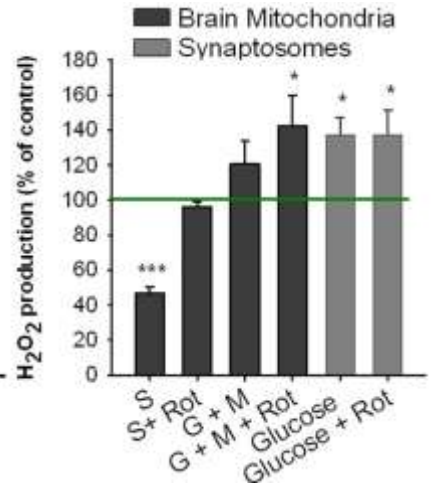


INCREASED ROS PRODUCTION, NORMAL ATP

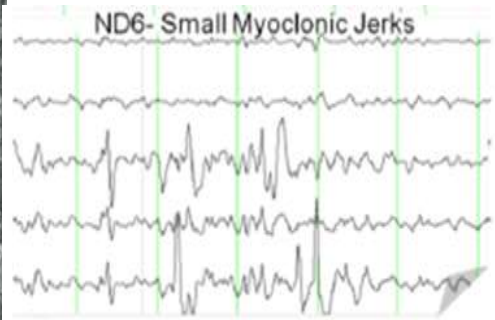


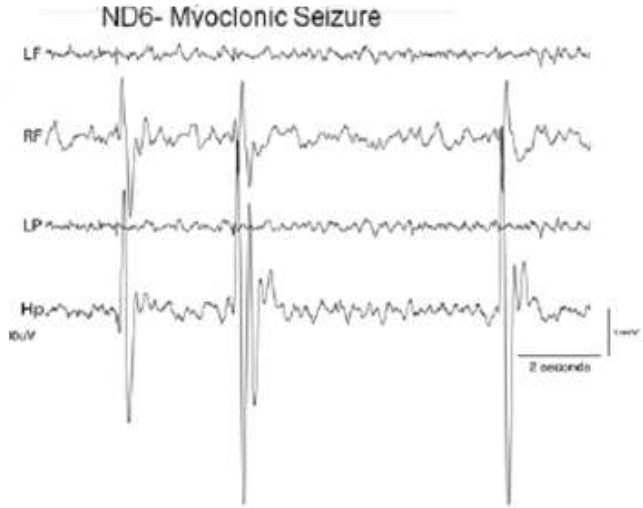


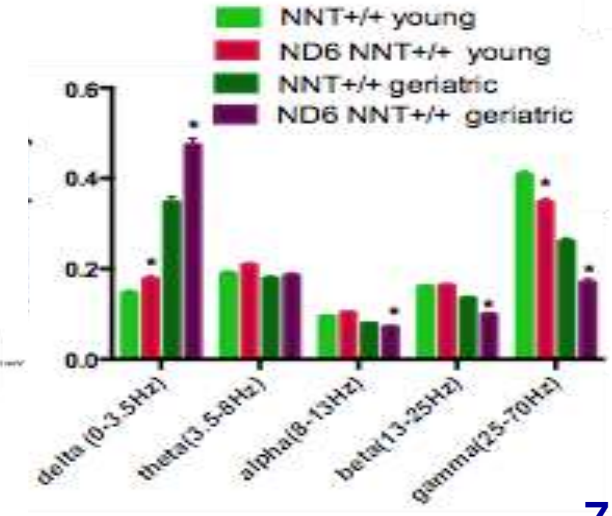




ALTERED EEGs



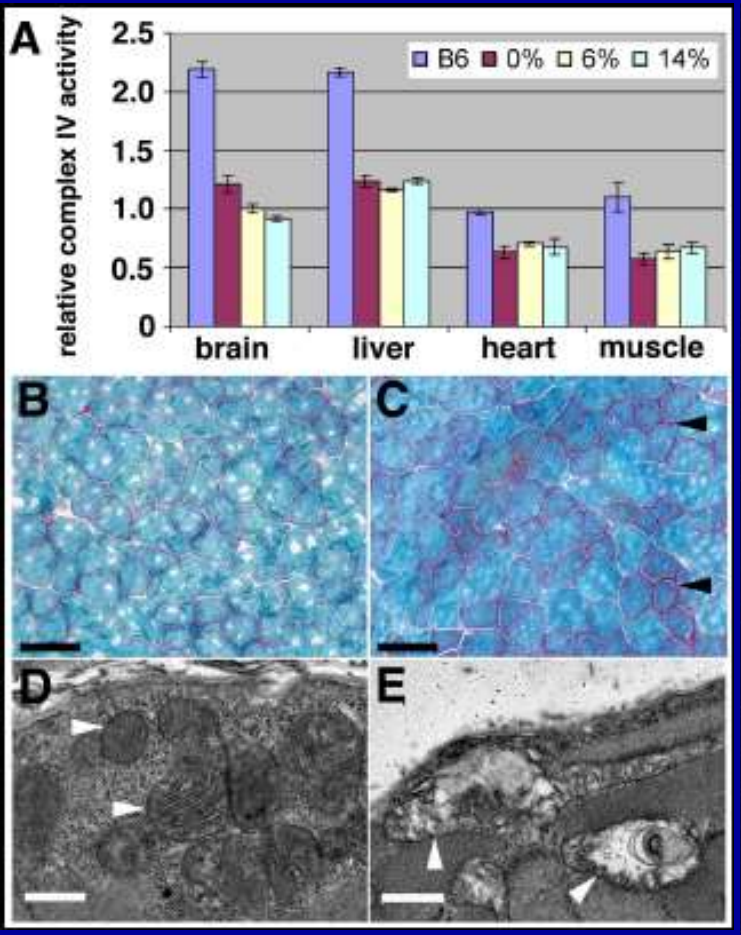




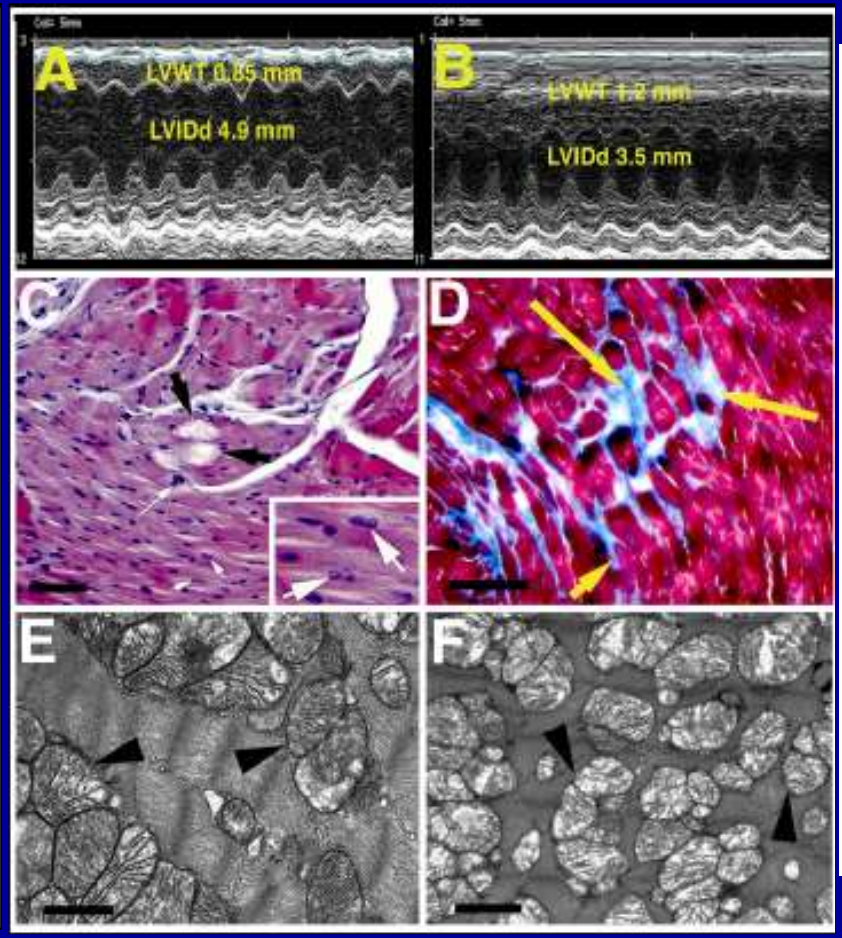
THE *COI* V421A mtDNA MOUSE EXHIBITS MYOPATHY, CARDIOMYOPATHY & METABOLIC SYNDROME

COI (6589T>C, V421A) MISSENSE MUTATION

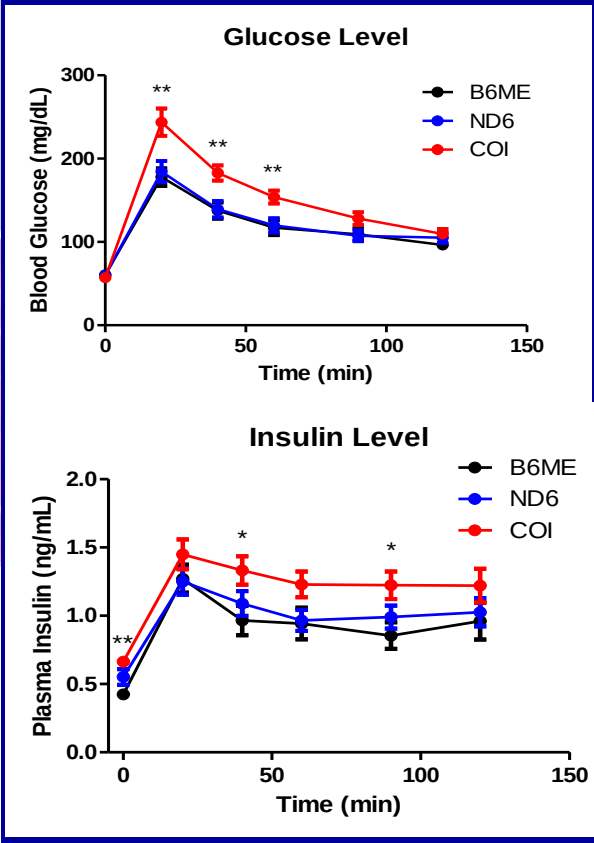
Mitochondrial Myopathy



Mitochondrial Cardiomyopathy

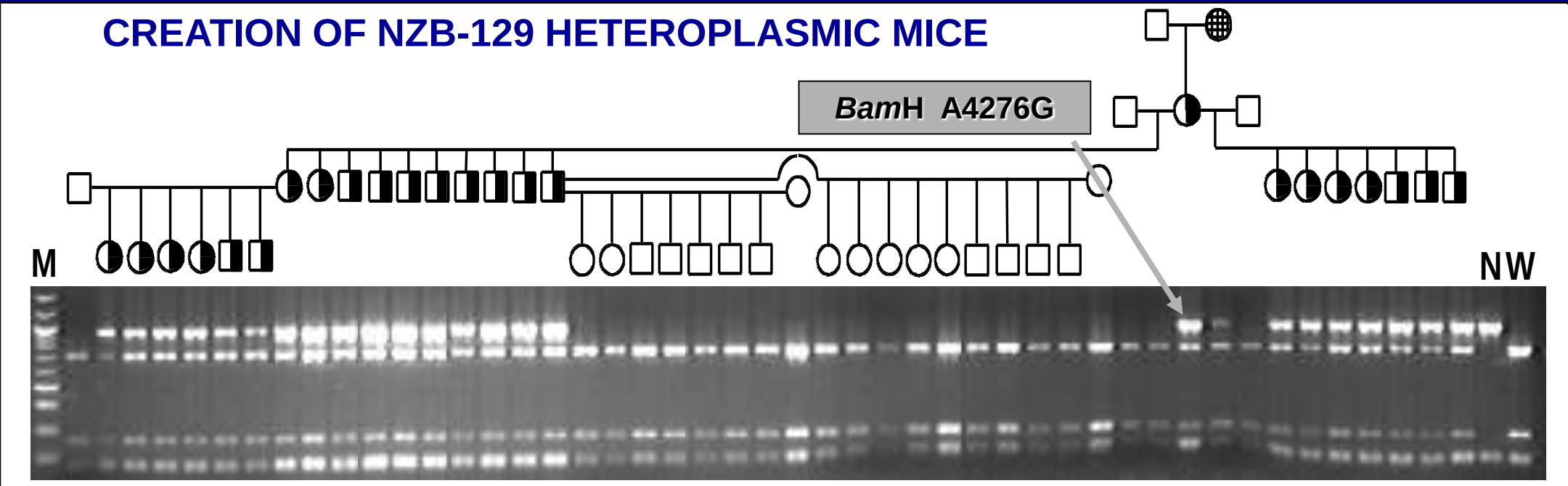


Glucose Intolerance & Insulin Resistance

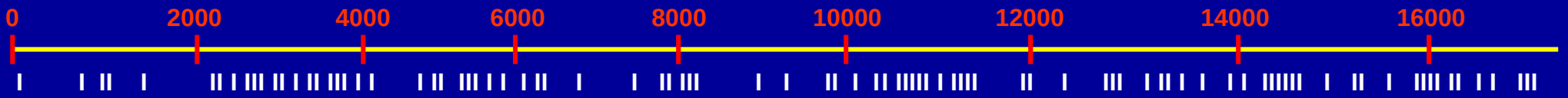


MATERNAL TRANSMISSION OF NORMAL mtDNA HETERPLASMY

CREATION OF NZB-129 HETEROPLASMIC MICE



91 “129” vs “NZB” mtDNAs differences: 15 aaΔ +5 tRNA +7 rRNA + 11 CR

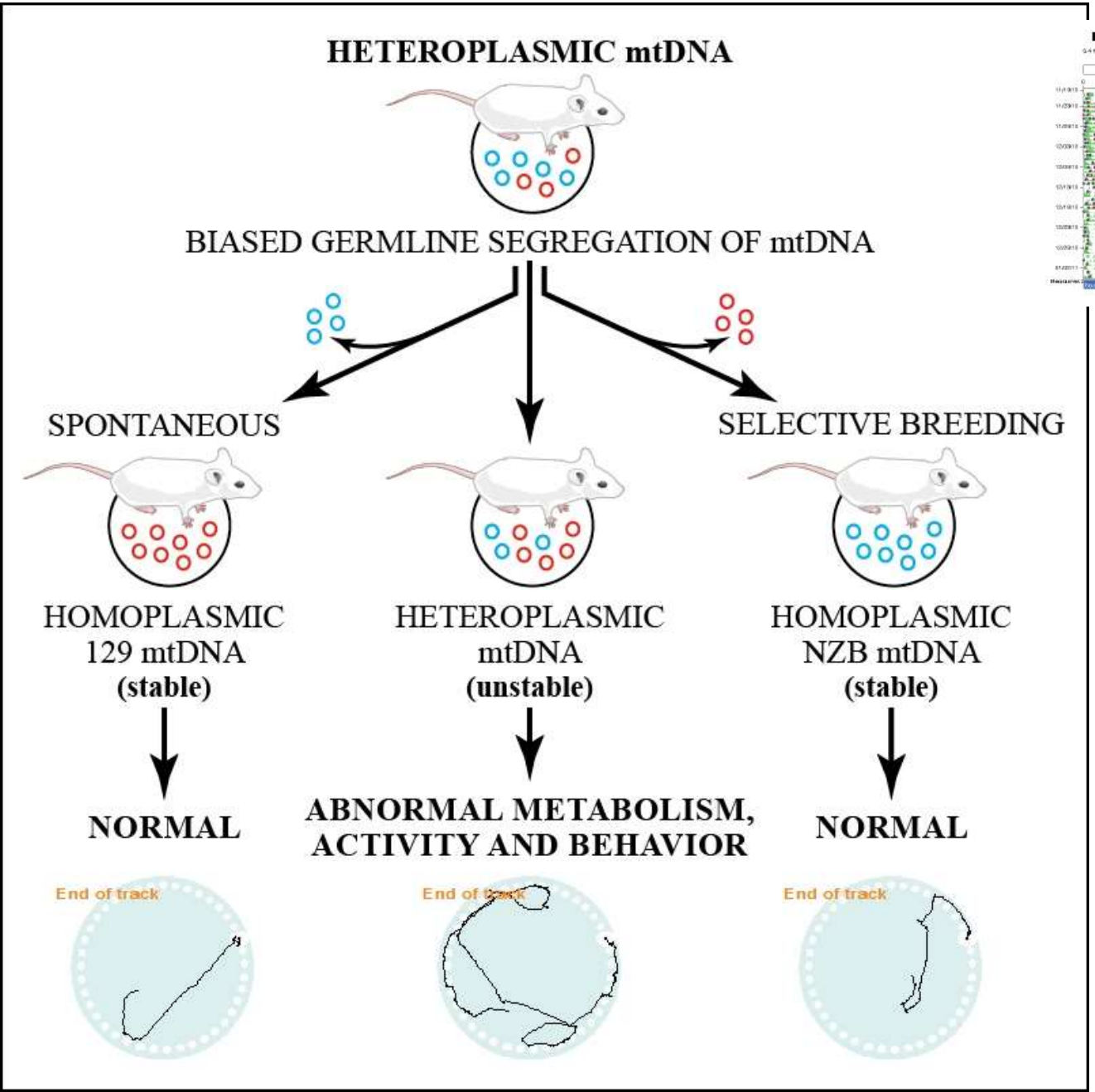


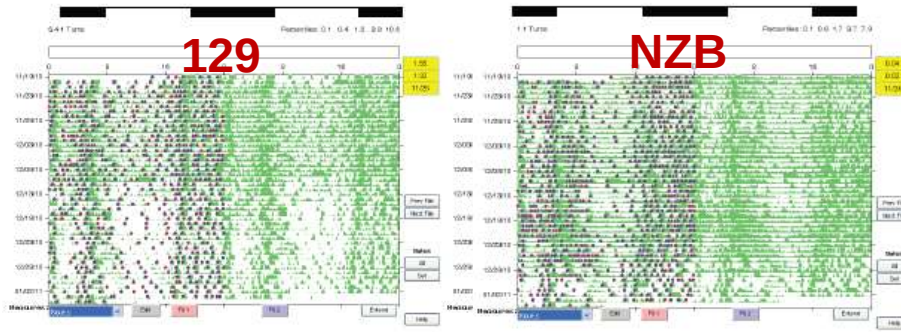
Backcrossed 20 generations onto C57BL/6L nDNA.

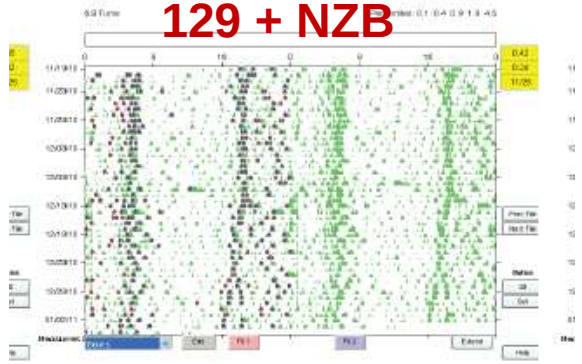
Permitted nZB-129 mtDNAs to segregate.

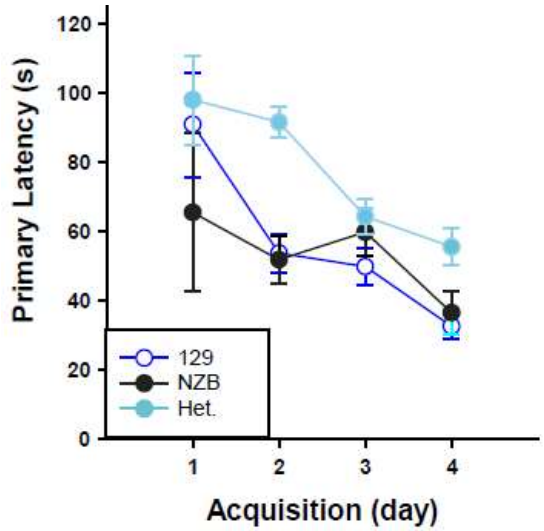
Correlated mtDNA NZB-129 genotypes with behavior.

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



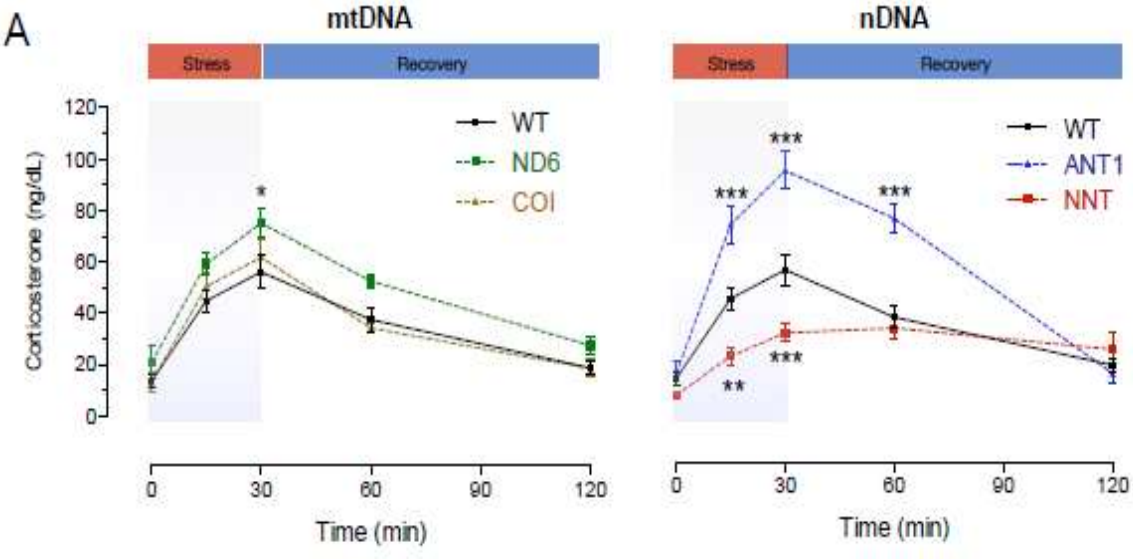


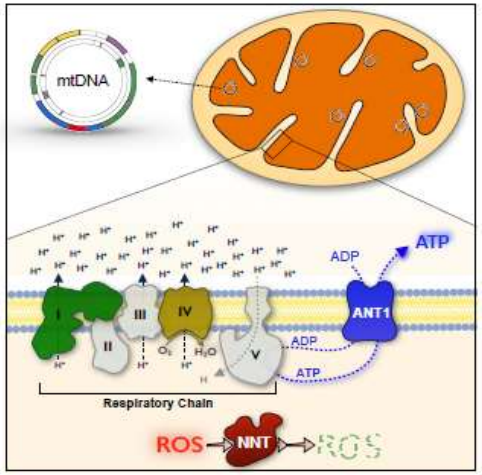


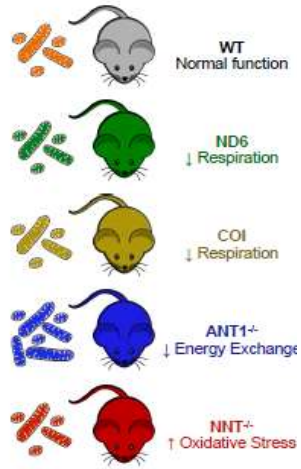


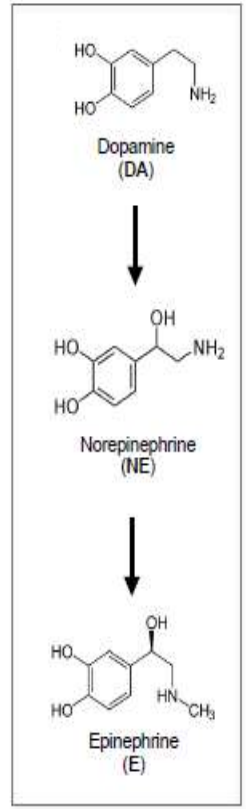
MITOCHONDRIAL ALTERATIONS MODULATE NEUROENDOCRINE RESPONSES TO ACUTE STRESS

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

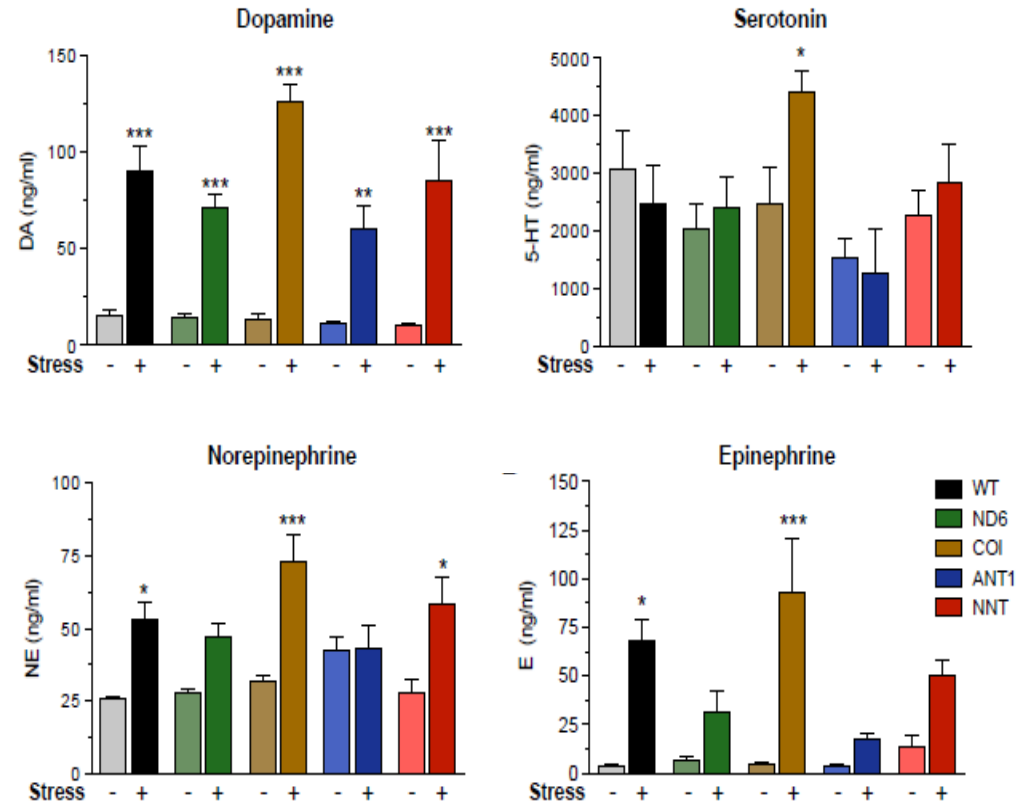








Modulation Catecholamines: of the Sympathetic-Medullary Axis



ANT1 MITOCHONDRIAL DYFUNCTION IMPAIRS INTERNEURON MIGRATION

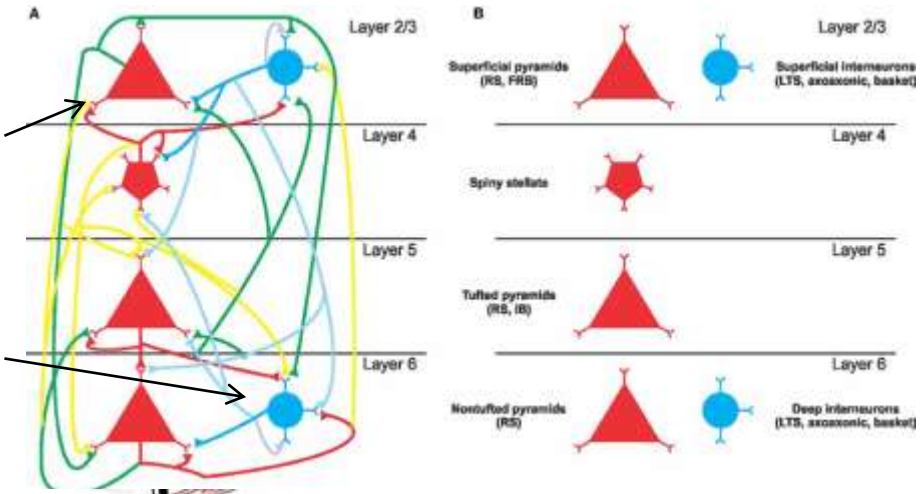
Partial Mitochondrial Defects Inhibit Tangential Inhibitory Interneuron Migration but not Radial Excitatory Neuron Migration

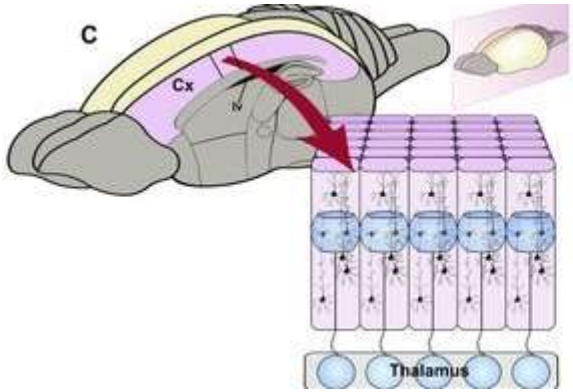
Cortical Function Requires Excitatory Glutamateric-Inhibitory GABAergic Neuronal Balance

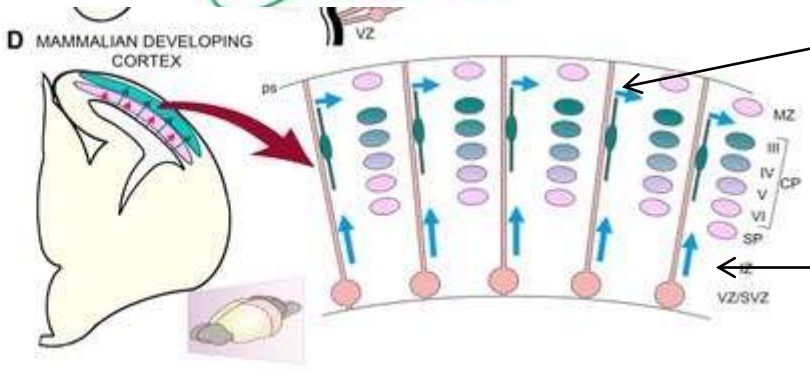
Excitation-Inhibition Imbalance May Cause Epilepsy, ADHD, Autism, Manic-Depressive Disorder, etc.

Pyramidal Neurons

Interneurons







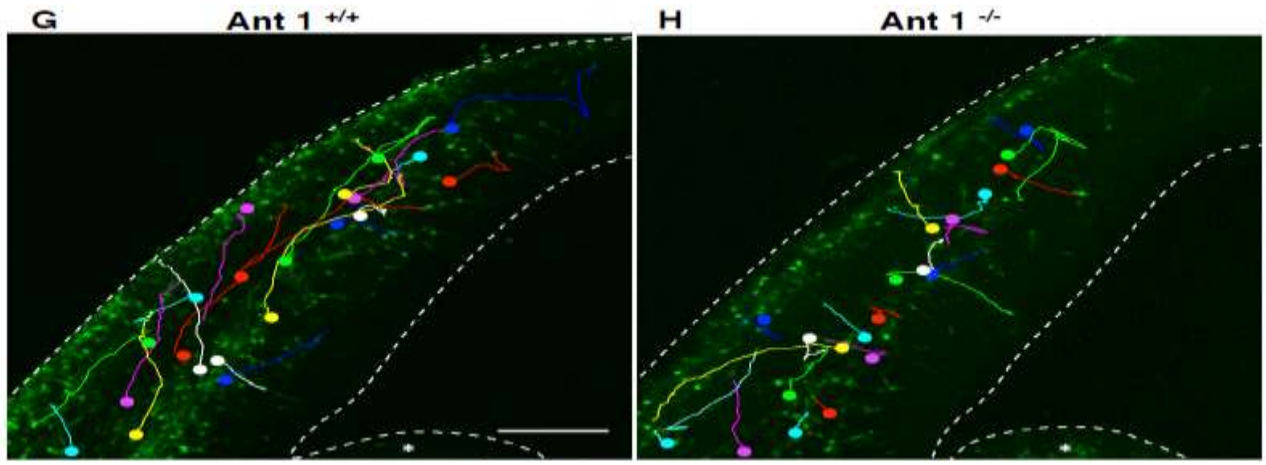
Interneurons

Pyramidal Neurons

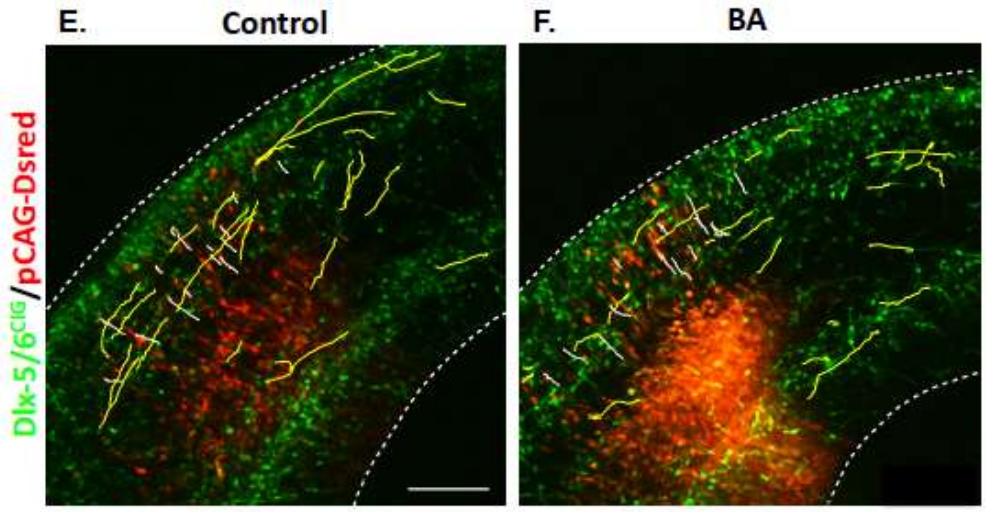
Excitatory Glutamateric Neurons Migrate Radially while the Inhibitory GABAergic Interneurons Migrate Tangentially from the Medial Ganglionic Eminence (MGE).

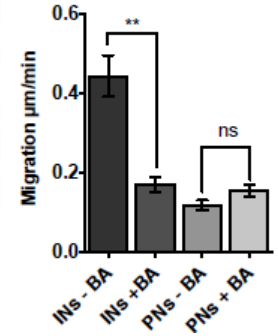
ANT1$^{-/-}$ IMPAIRS INTERNEURONAL MIGRATION = EXCITATION-INHIBITION IMBALANCE
ANT1-ND6-NNT DEFICIENCY YIELDS AUTISM ENDOPHENOTYPES

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

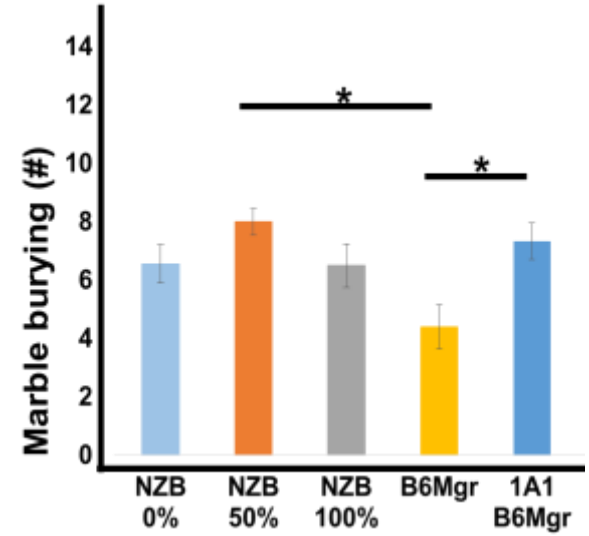


ANT1 Inhibitor Bongkrekic Acic (BA) Disorients Interneuron Migration

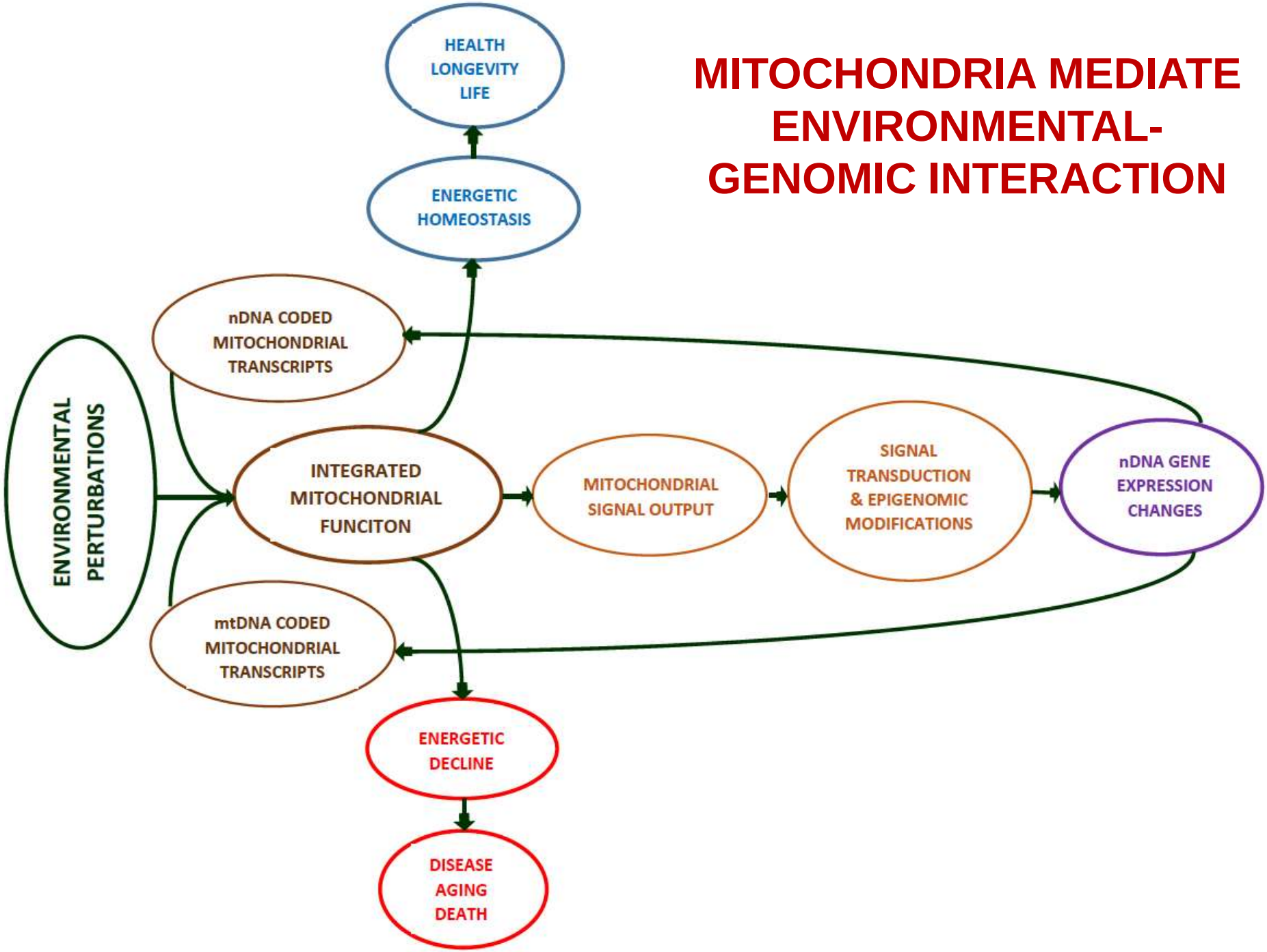




Social Interactions



MITOCHONDRIA MEDIATE ENVIRONMENTAL-GENOMIC INTERACTION



ENERGY IS LIFE

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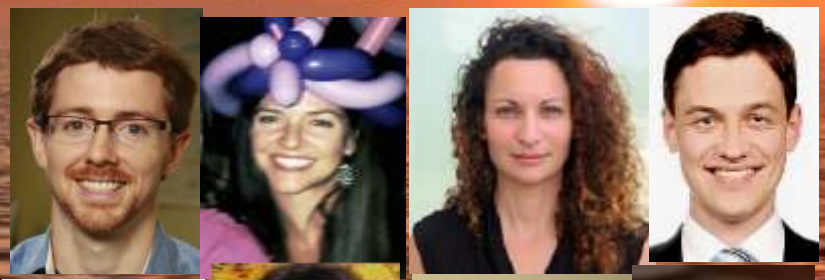

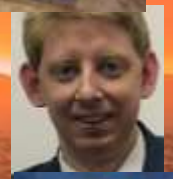

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