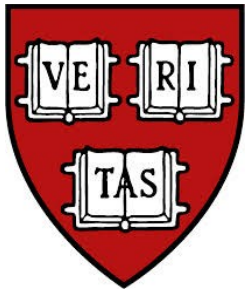
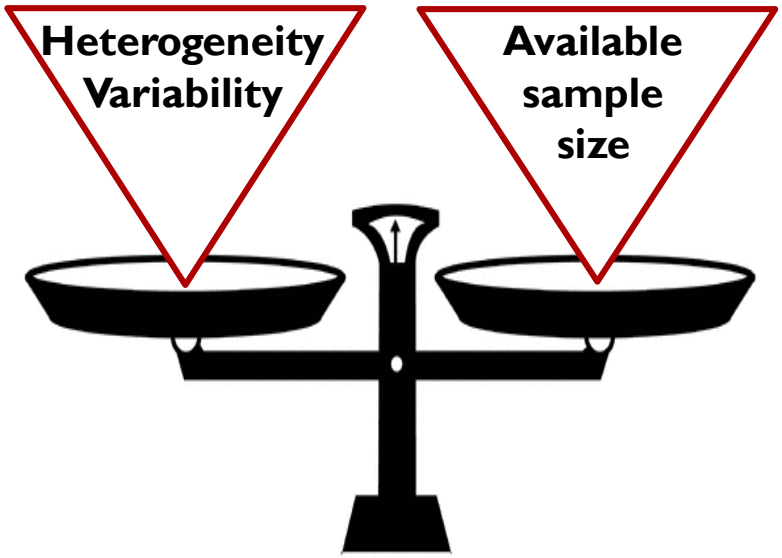


To clump or to split? That is the question.

Cases

- 8 mo female with jaundice and liver failure
- 3 yo male with developmental regression and seizures
- 15 yo female with migraines, severe constipation, fainting
- 24 yo male with speech and balance problems
- 30 yo female with enlarged heart and strokes
- 55 yo male with weakness, muscle pain, hearing loss
- 71 yo female with dementia, diabetes, jerking limbs

The Challenge !



Clump Patients?
- Target all mitochondrial diseases
- Target a clinical phenotype
  - → a specific symptom
  - → a specific organ
  - → a specific syndrome
- …..

Split Patients?
- Target a specific genotype
- Target a specific cellular pathway
- Target a specific biochemical defect
- Target a specific age group
- ….

The Challenge !

Clump Patients?

- Target all mitochondrial diseases (Master protocol)

What is a mitochondrial disease?

→ Primary mitochondrial disease
→ Secondary mitochondrial dysfunction

Mitochondrial disorders are one of the most complex and heterogeneous group of diseases:

- Affect all ages from birth to late-adulthood
- Range from monosymptomatic to multi-systemic diseases
- Hundreds of presentations

The Challenge !

Clump Patients?

- Target all mitochondrial diseases (Master protocol)

  → small numbers of patients with any given MD might preclude meaningful subgroup analyses

  → differences in outcomes between patients with different MD types could be missed

The Challenge !

Clump Patients?

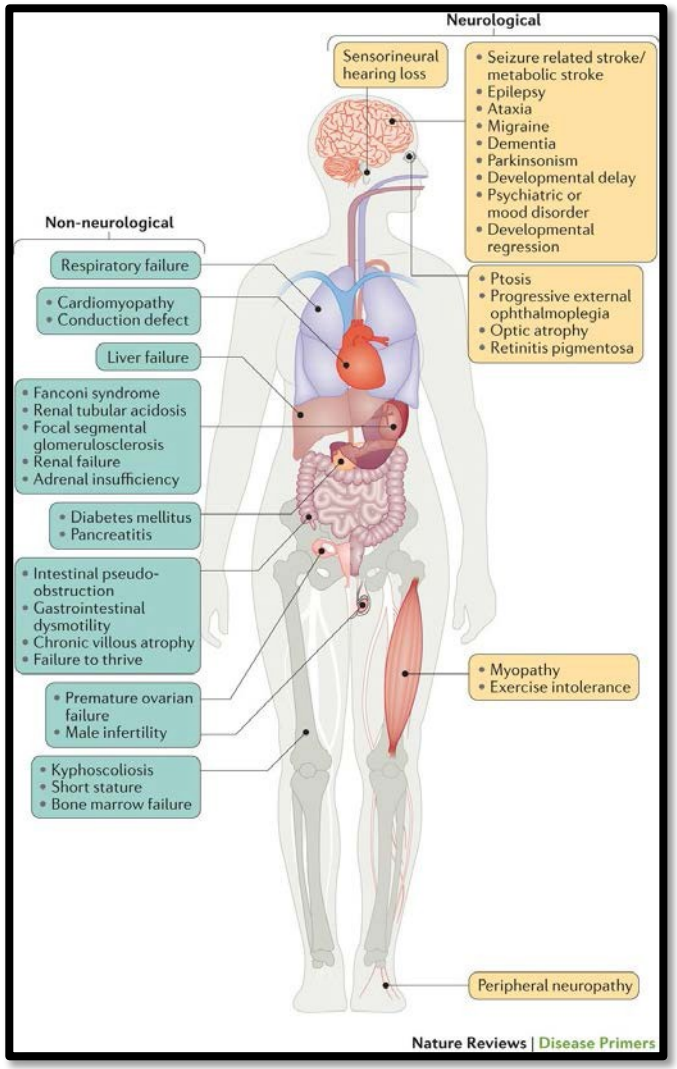
- Target all mitochondrial diseases
- Target a clinical phenotype

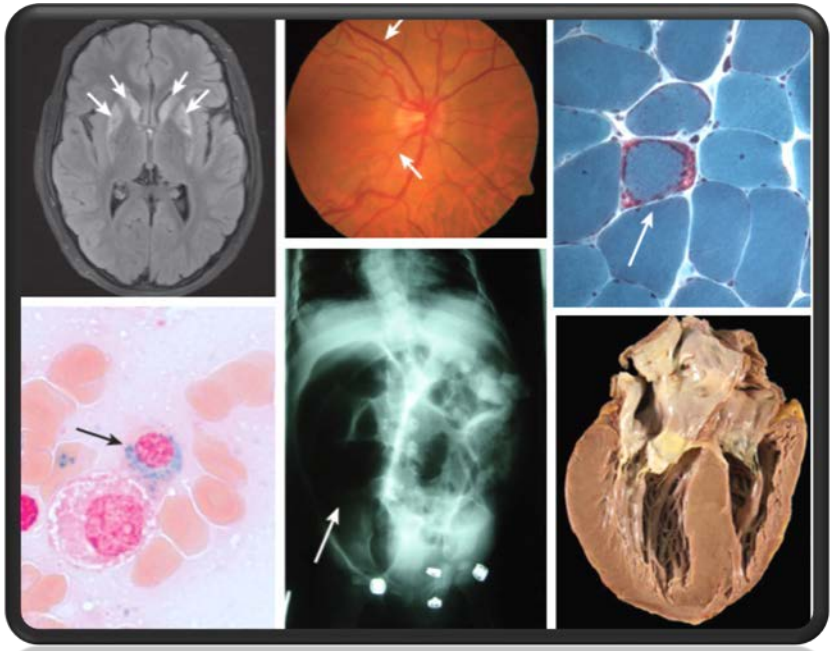
The Challenge !

Clump Patients?

- Target all mitochondrial diseases
- Target a clinical phenotype
  → a specific symptom

Mitochondrial disorders are one of the most complex and heterogeneous group of diseases:





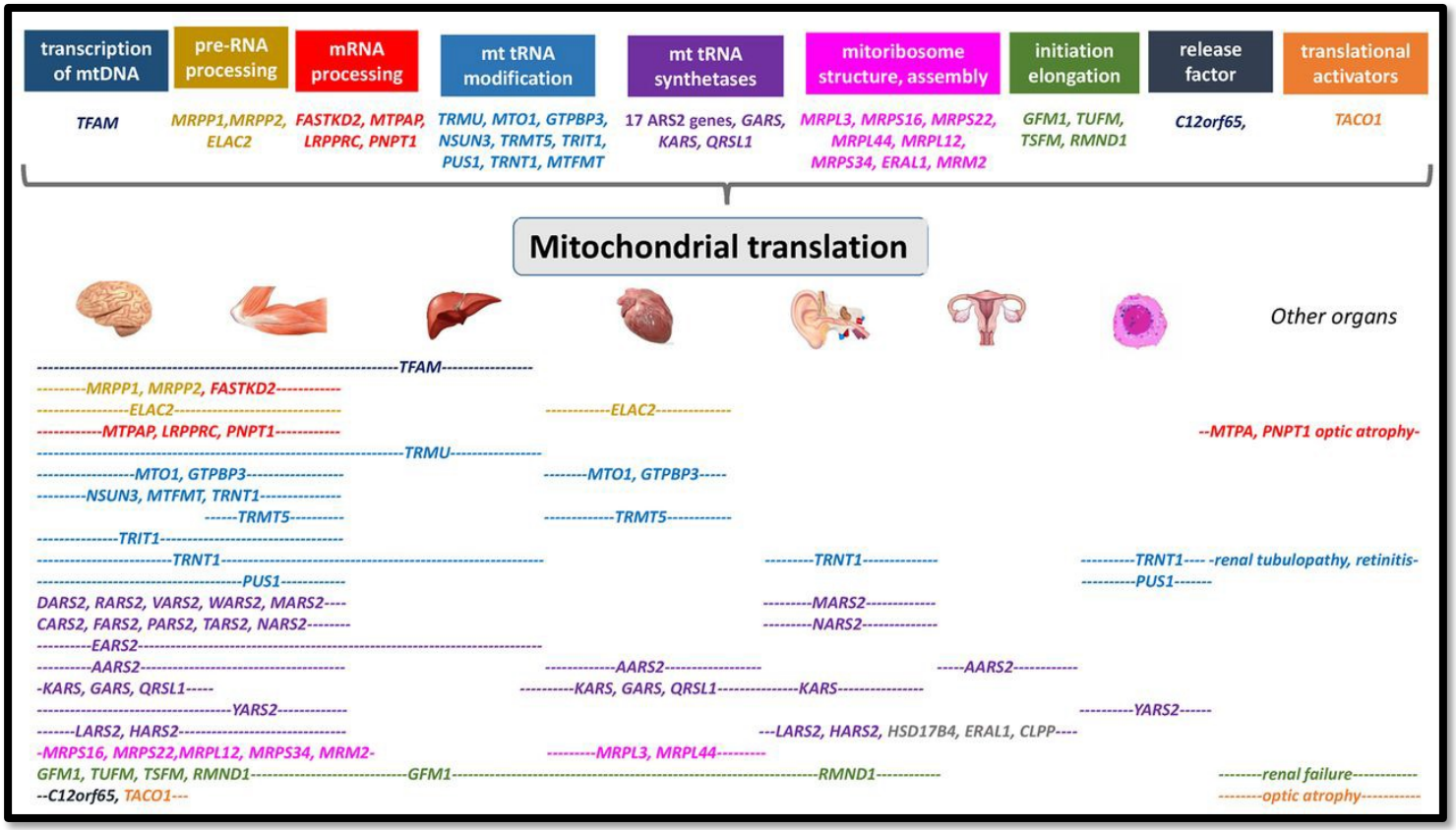
Vafai and Mootha, Nature 2012

The Challenge !

Clump Patients?

- Target all mitochondrial diseases
- Target a clinical phenotype
  - → a specific symptom
  - → a specific organ

The different phenotypes



Essays Biochem. 2018;62(3):321–340. Published 2018 Jul 20.

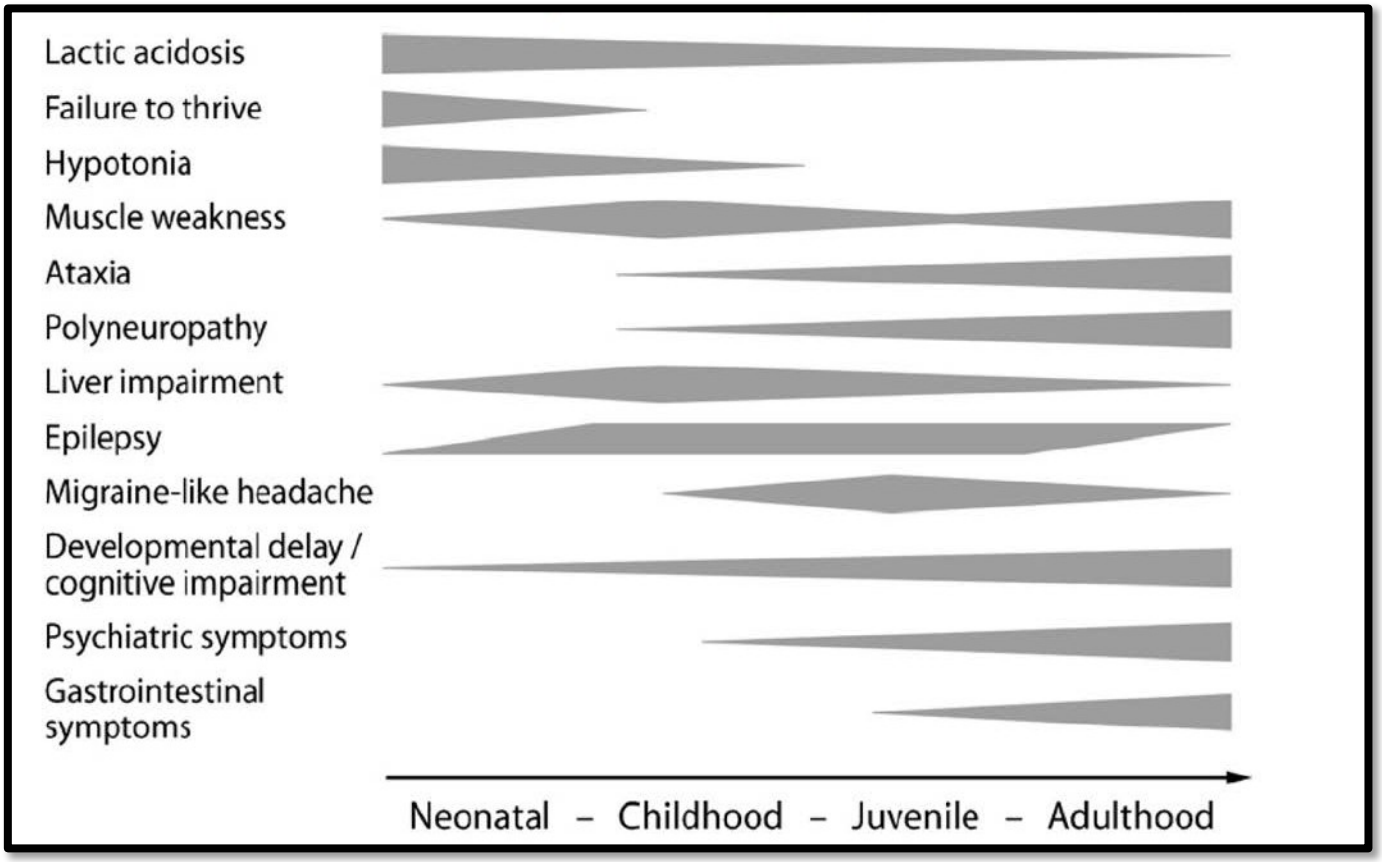
The Challenge !

Clump Patients?

- Target all mitochondrial diseases
- Target a clinical phenotype
  - → a specific symptom
  - → a specific organ
  - → a specific syndrome

The different phenotypes

The depletion syndrome



Suomalainen A Neuromuscular Disorders 20 (2010) 429-437

The different phenotypes

KSS
MERRF
MELAS

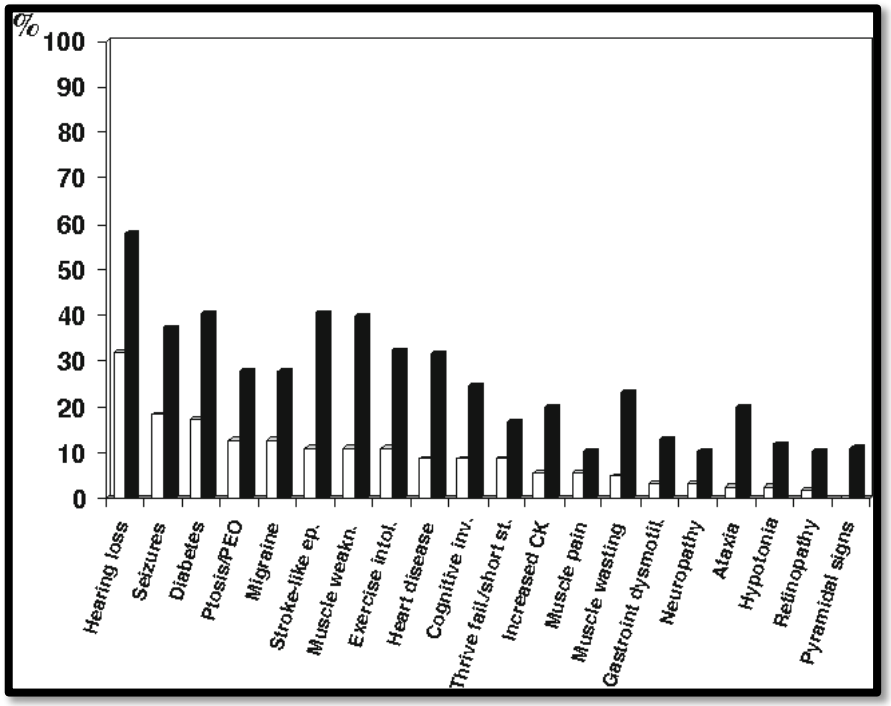
NARP
LHON

Leigh
CPEO

Tissue or Area	Symptom or Sign	Kearns–Sayre Syndrome	Myoclonus Epilepsy with Ragged-Red Fibers	Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes	Neuropathy, Ataxia, Retinitis Pigmentosa	Maternally Inherited Leigh Syndrome
Central nervous system	Seizures	–	+	+	+	+
	Ataxia	+	+	+	+	±
	Myoclonus	–	+	±	–	–
	Psychomotor retardation	–	–	–	–	+
	Psychomotor regression	+	±	+	–	–
	Hemiparesis or hemianopia	–	–	+	–	–
	Cortical blindness	–	–	+	–	–
	Migraine-like headache	–	–	+	–	–
	Dystonia	–	–	+	–	+
Peripheral nervous system	Peripheral neuropathy	±	±	±	+	–
Muscle	Weakness or exercise intolerance	+	+	+	+	+
	Ophthalmoplegia	+	–	–	–	–
	Ptosis	+	–	–	–	–
Eye	Pigmentary retinopathy	+	–	–	+	±
	Optic atrophy	–	–	–	±	±
Blood	Sideroblastic anemia	±	–	–	–	–
Endocrine	Diabetes mellitus	±	–	±	–	–
	Short stature	+	+	+	–	–
	Hypoparathyroidism	±	–	–	–	–
Heart	Conduction block	+	–	±	–	–
	Cardiomyopathy	±	–	±	–	±
Gastrointestine	Exocrine pancreatic dysfunction	±	–	–	–	–
Ear, nose, throat	Sensorineural hearing loss	–	+	+	±	–
Kidney	Fanconi's syndrome	±	–	±	–	–
Laboratory results	Lactic acidosis	+	+	+	–	±
	Ragged-red fibers on muscle biopsy	+	+	+	–	–
Inheritance	Maternal	–	+	+	+	+
	Sporadic	+	–	–	–	–

NEJM 2010. 354(10):1096-7

The different phenotypes



	Onset 23.4 ± 15.6 years[a] (%)	Last evaluation 36.0 ± 20.7 years (%)
Hearing loss	**39 (31.0)**	**73 (57.9)**
Generalized seizures	**23 (18.3)**	**47 (37.3)**
Diabetes	**22 (17.5)**	**51 (40.5)**
Ptosis/ophthalmoparesis	**16 (12.7)**	**35 (27.8)**
Migraine	**16 (12.7)**	**35 (27.8)**
Stroke-like episodes	**14 (11.1)**	**51 (40.5)**
Muscle weakness	**14 (11.1)**	**50 (39.7)**
Exercise intolerance	**14 (11.1)**	**41 (32.5)**
Heart disease	**11 (8.7)**	**40 (31.7)**
Cognitive involvement	**11 (8.7)**	**31 (24.6)**
Failure to thrive/short st.	11 (8.7)	21 (16.7)
Increased CK	7 (5.6)	25 (19.8)
Muscle pain	7 (5.6)	13 (10.3)
Muscle wasting	6 (4.8)	29 (23.0)
Vomiting	5 (4.0)	7 (5.6)
Gastrointestinal dysmotil.	4 (3.2)	16 (12.7)
Neuropathy	4 (3.2)	13 (10.3)
Ataxia	3 (2.4)	25 (19.8)
Hypotonia	3 (2.4)	15 (11.9)
Retinopathy	3 (1.8)	13 (10.3)
Myoclonus	3 (2.4)	8 (6.3)
Hypothyroidism	2 (1.6)	5 (4.0)
Psychiatric involvement	1 (0.8)	8 (6.3)
Optic neuropathy	1 (0.8)	6 (4.8)
Hypogonadism	1 (0.8)	5 (4.0)
Pyramidal signs	–	14 (11.1)
Respiratory impairment	–	6 (4.8)
Status epilepticus	–	5 (4.0)

Journal of Neurology 2013 (261):504-510

The Challenge !

Split Patients?

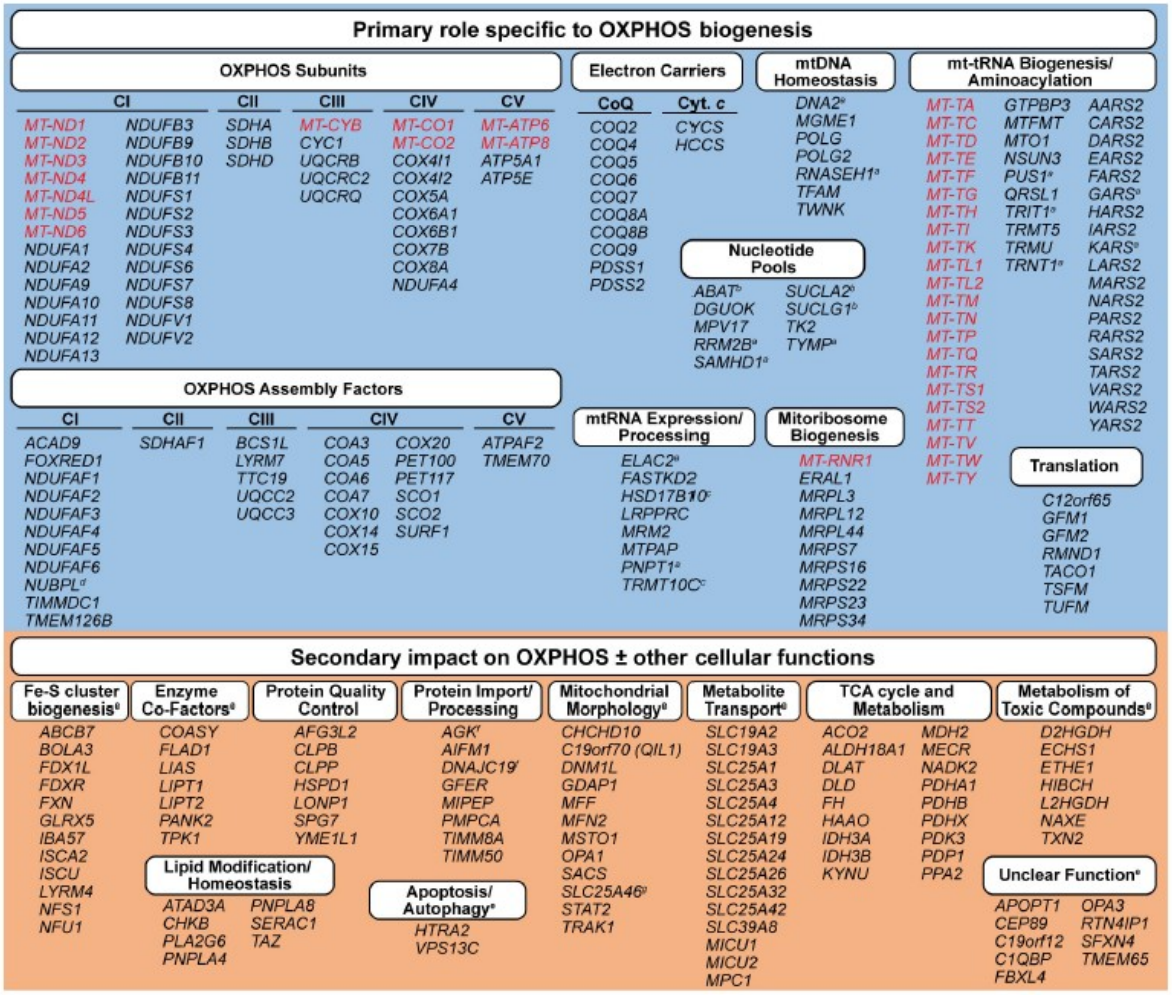
- Target a specific genotype

Mitochondrial disorders are one of the most complex and heterogeneous group of diseases:

- Caused by mutations in nDNA, mtDNA or both

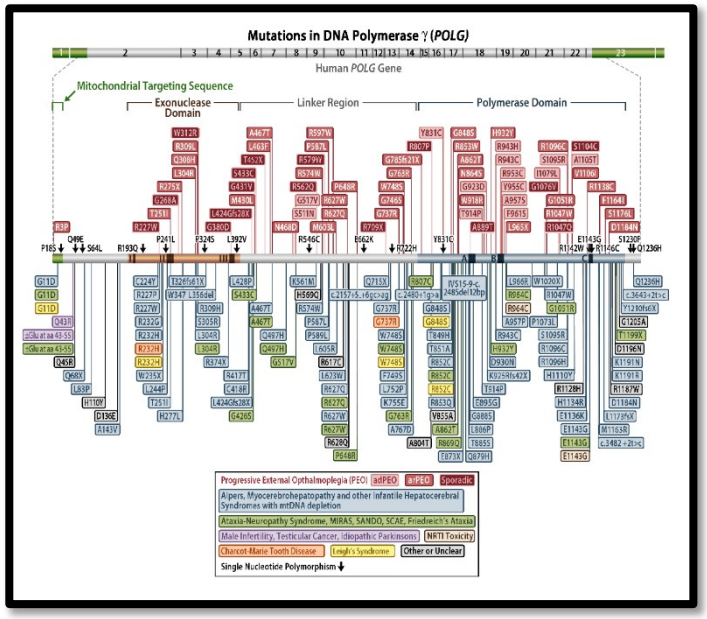
Complicated genotypes

nDNA (~350 genes)



The Journal of Biological Chemistry 294, 5386-5395.

Complicated genotypes



https://tools.niehs.nih.gov/polg/

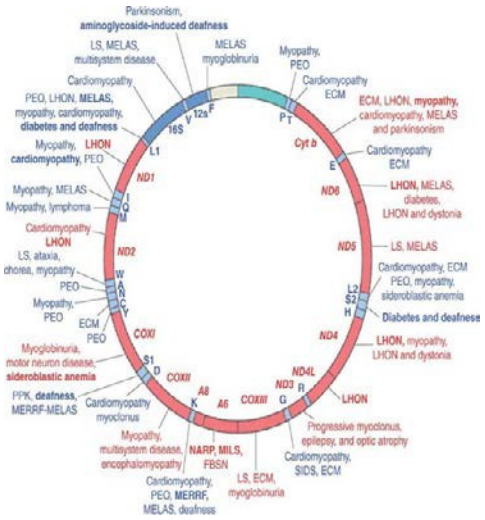
Alpers–Huttenlocher syndrome (AHS)	nDNA (*POLG*-related)	Intractable epilepsy, psychomotor regression and liver disease; might also include the clinical features of MCHS and MEMSA	55–57
Childhood myocerebrohepatopathy spectrum (MCHS)		Neuropathy, ataxia, hypotonia, myoclonus (spontaneous muscle contractions), choreoathetosis (the occurrence of involuntary jerky, writhing movements of muscles or muscle groups) and Parkinsonism, in addition to renal tubulopathy	
Ataxia neuropathy spectrum (ANS; previously referred to as mitochondrial recessive ataxia syndrome (MIRAS) and sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO))		Sensory axonal neuropathy with variable sensory and cerebellar ataxia	
Myoclonic epilepsy myopathy sensory ataxia (MEMSA; previously referred to as spinocerebellar ataxia with epilepsy (SCAE))		Epilepsy, PEO, seizures, dysarthria, dementia, spasticity and myopathy	
	POLG1, which encodes α-DNA polymerase subunit γ1	Ataxia, peripheral sensory neuronopathy, Parkinsonism, premature ovarian failure, psychiatric symptoms, MELAS syndrome and epilepsy	195
	POLG2, which encodes DNA polymerase subunit γ2	Ptosis and proximal myopathy, dystrophy, cerebellar ataxia and gastrointestinal symptoms	196

Gorman et al. Nature reviews primers 2016

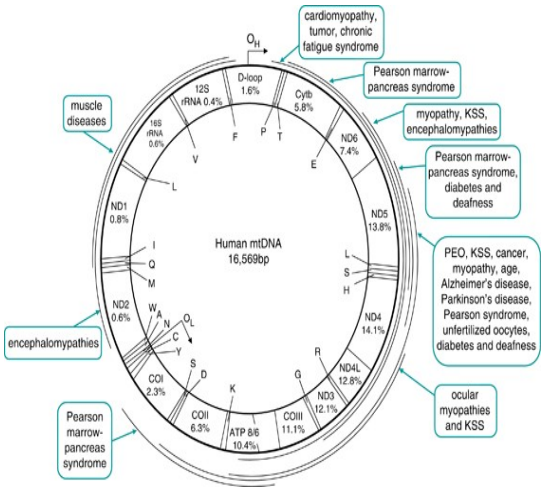
Complicated genotypes

mtDNA (16 569 bp and contains 37 genes)

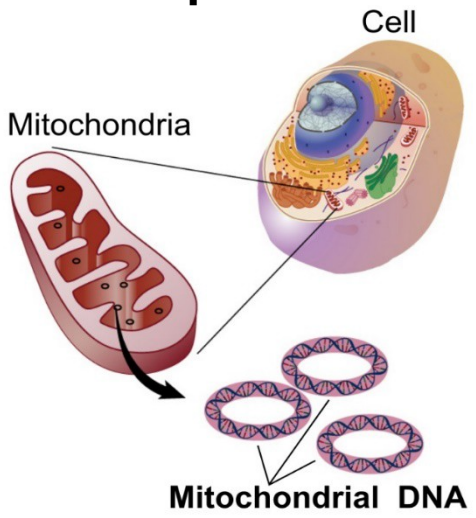
Point mutations



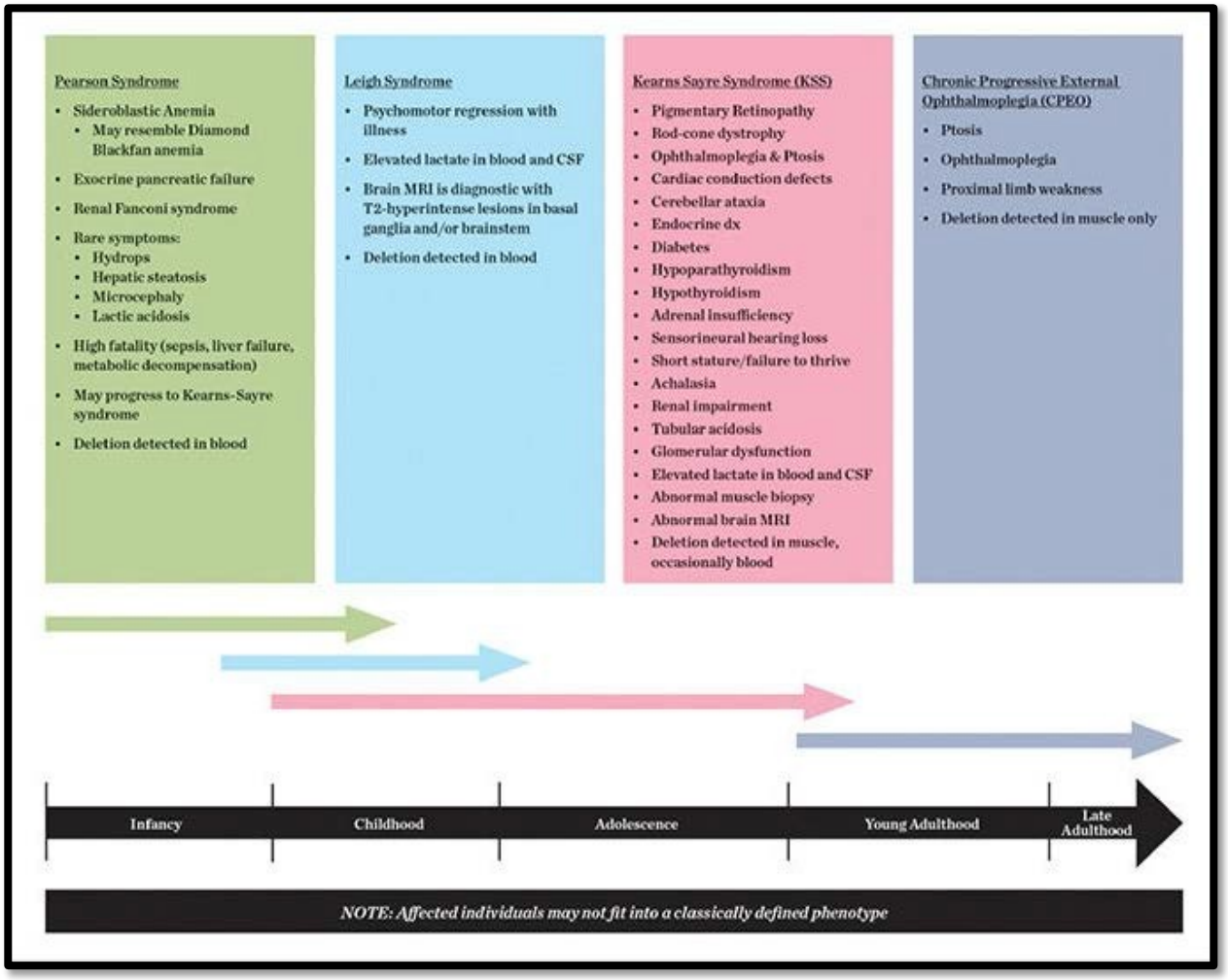
Deletions/Duplications



Depletion



Complicated genotypes

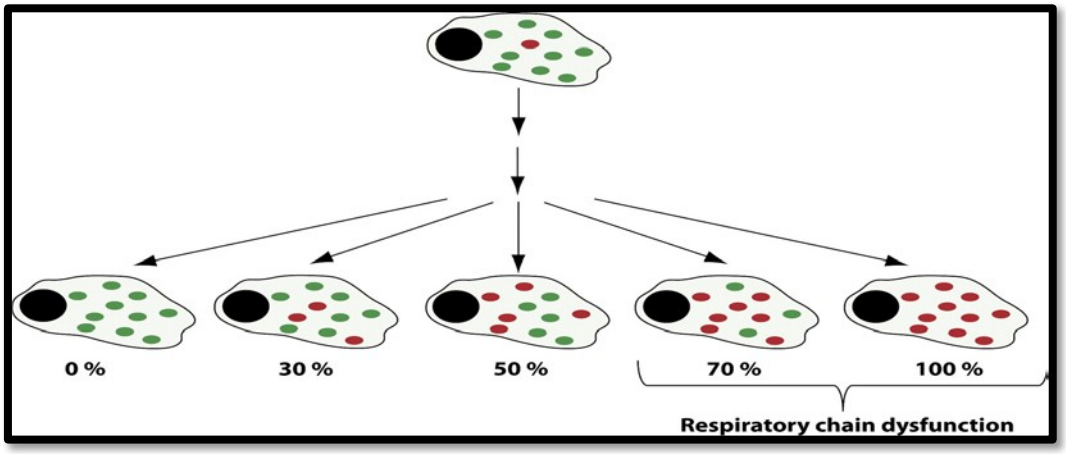


https://www.chop.edu/news

Complicated genotypes

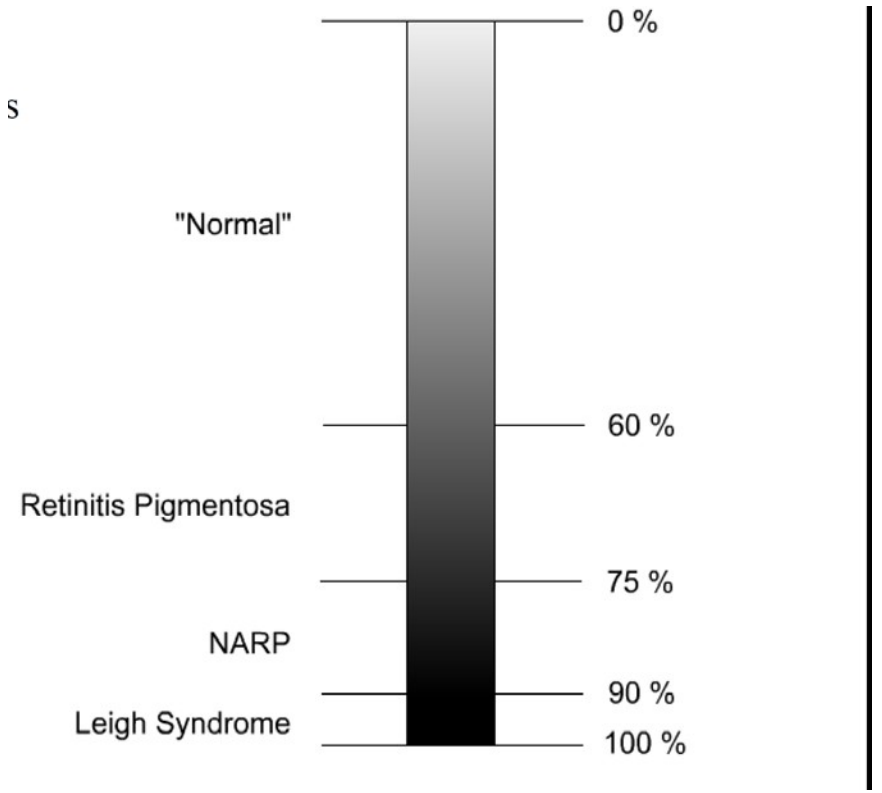
Mitochondrial DNA

- Heteroplasmy
- Random mitotic segregation
- Threshold expression



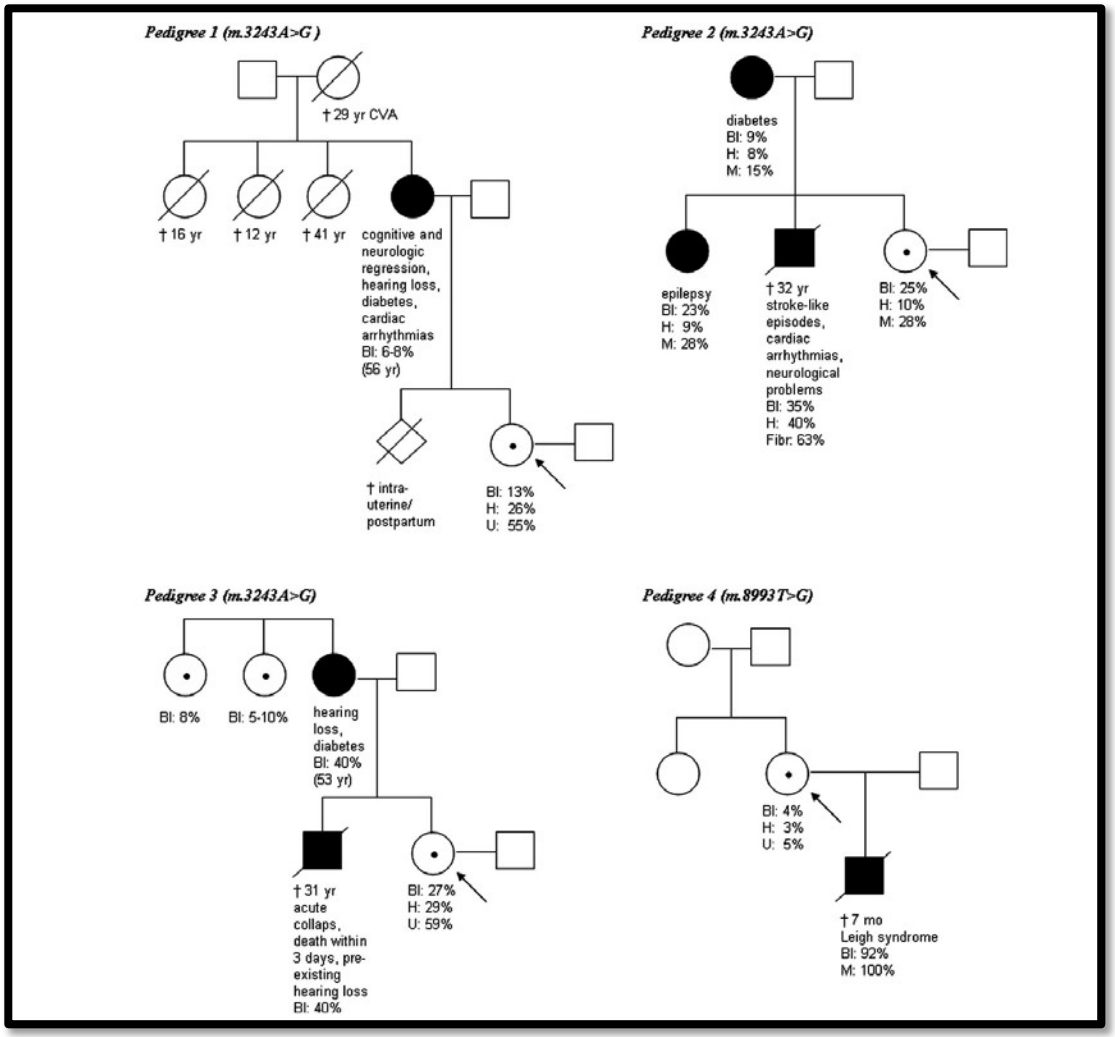
Complicated genotypes

Importance of tissue heteroplasmy:
m.T8993G mutant load



Carelli V et al. Arch Neurol 2002;59:264–70

Complicated genotypes



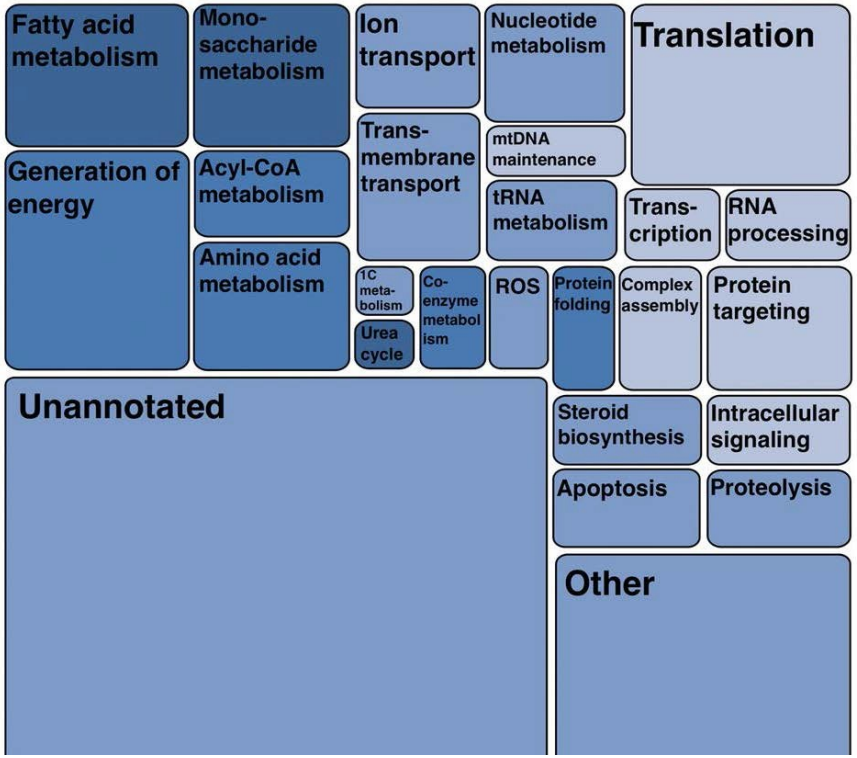
J Med Genet -2012-101172

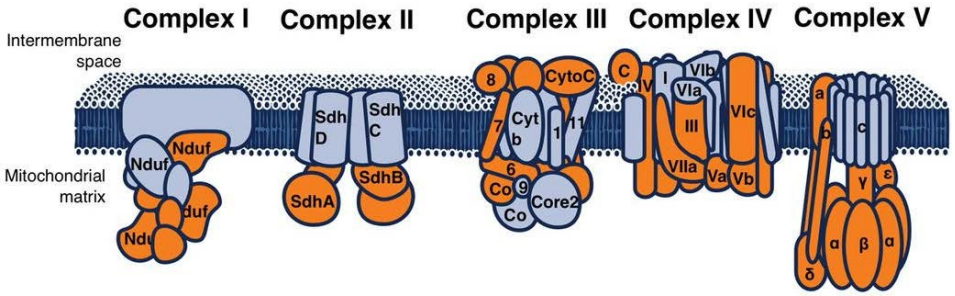
The Challenge !

Split Patients?

- Target a specific genotype
- Target a specific cellular pathway

Mitochondrial disorders are one of the most complex and heterogeneous group of diseases:

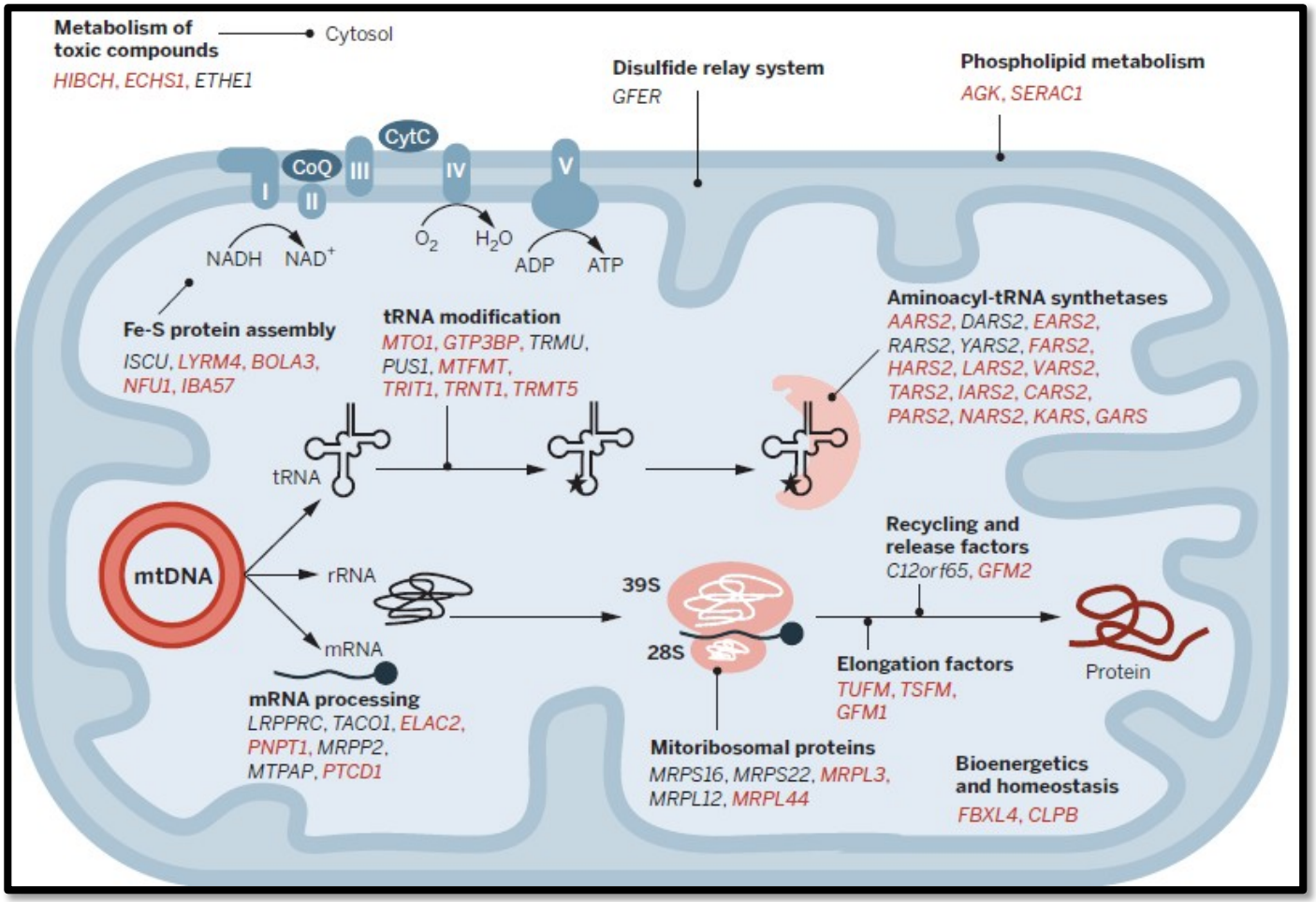




Essays In BiochemistryMay 25, 2012,5223-35;

Mitochondrial disorders are one of the most complex and heterogeneous group of diseases:

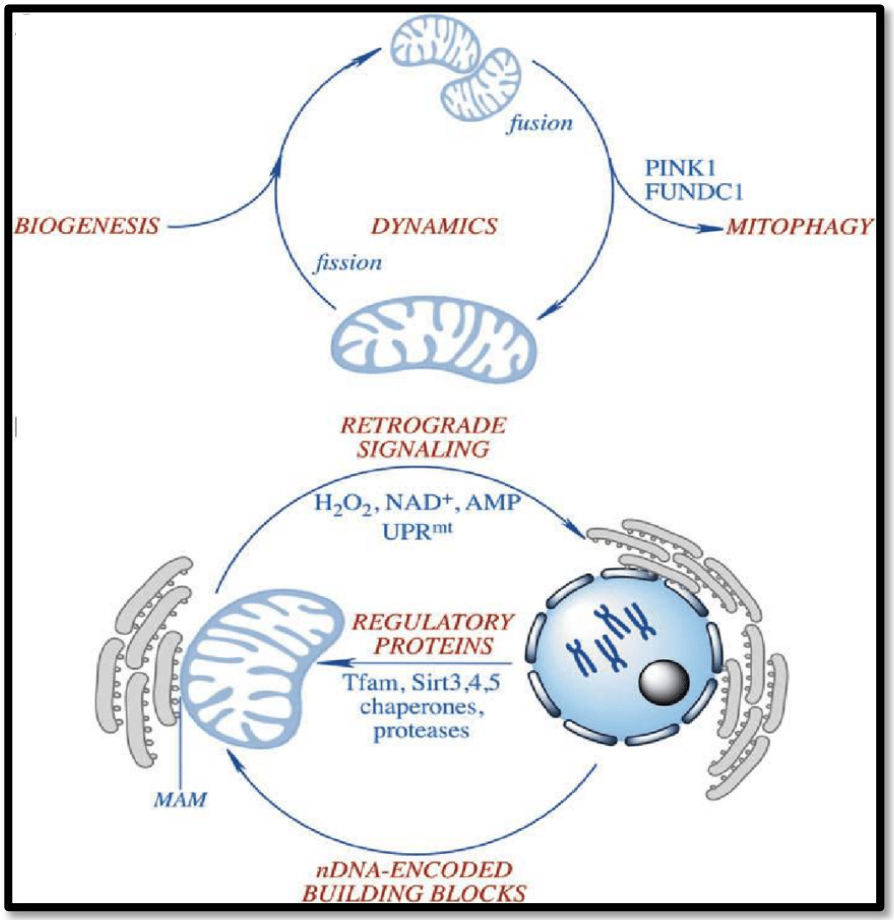
Mitochondrial maintenance and translation



Science, VOL 349 ISSUE 6255

Mitochondrial disorders are one of the most complex and heterogeneous group of diseases:

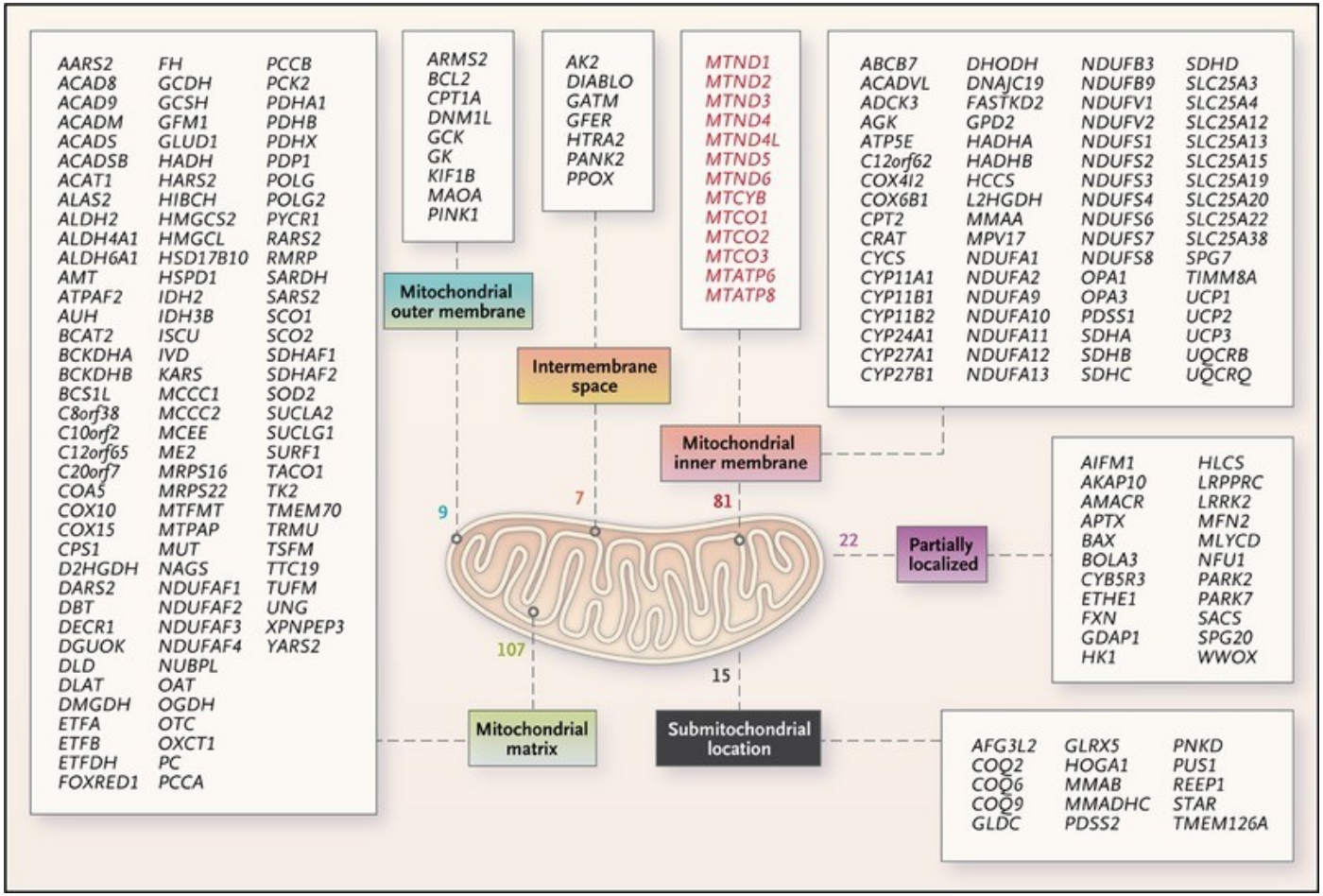
Mitochondrial dynamic



Antioxidants & redox signaling. 22. 10.1089/ars.2014.6200.

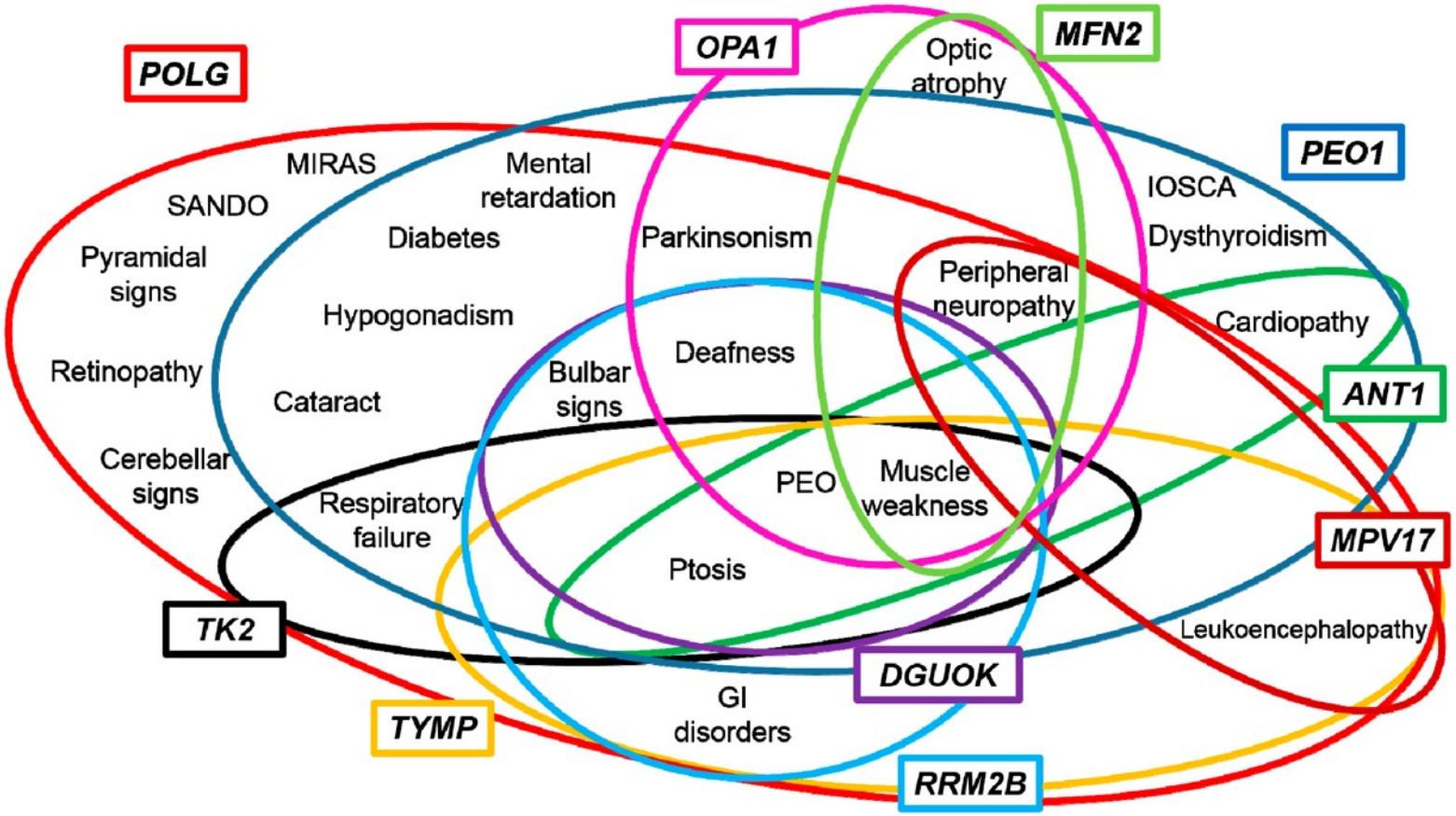
Mitochondrial disorders are one of the most complex and heterogeneous group of diseases:

Mitochondrial protein localization



N Engl J Med 2012; 366:1132-1141

Mitochondrial disorders are one of the most complex and heterogeneous group of diseases:



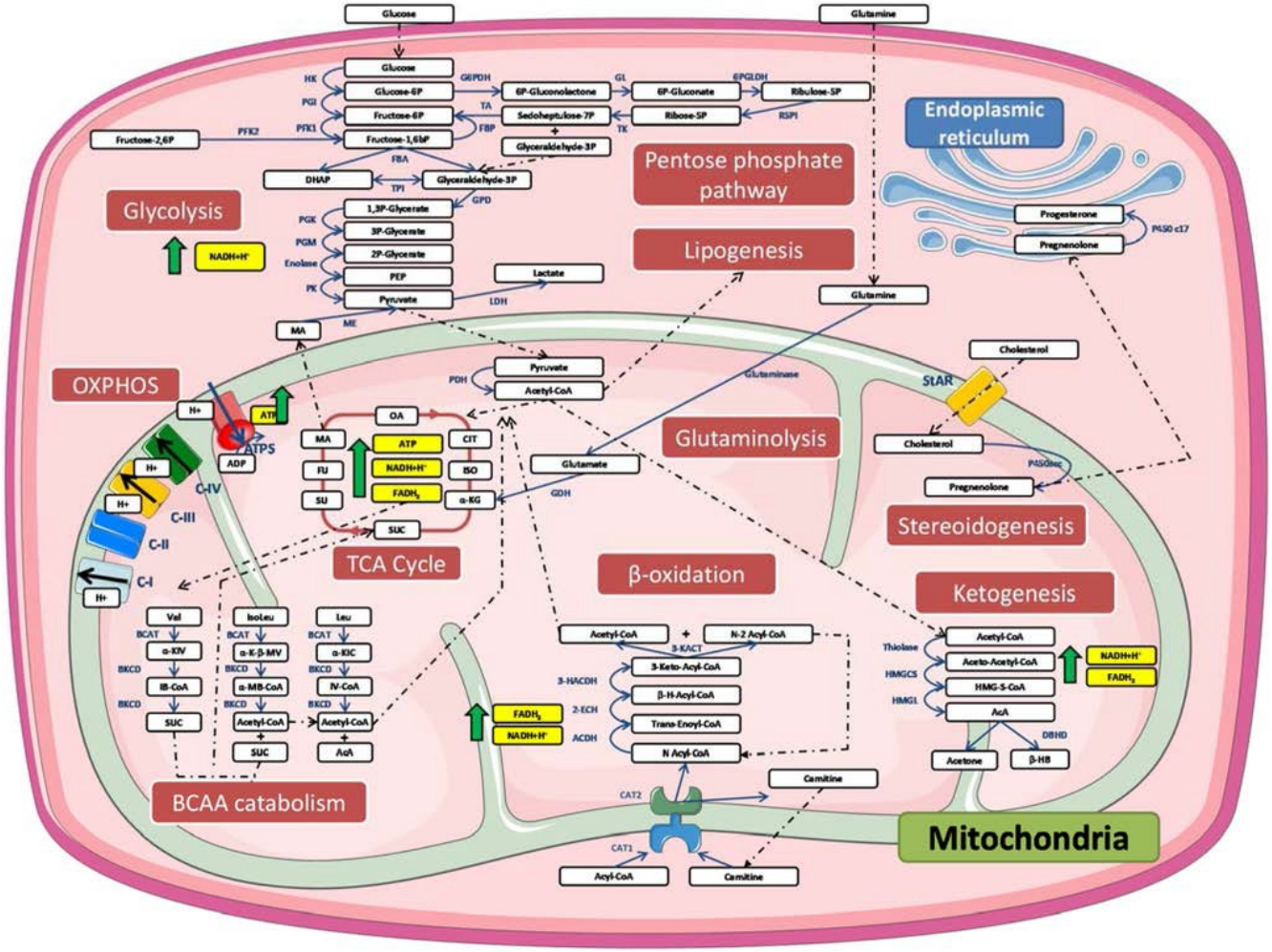
Int. J. Mol. Sci. **2015**, *16*(8), 18054-18076

The Challenge !

Split Patients?

- Target a specific genotype
- Target a specific cellular pathway
- Target a specific biochemical defect

Mitochondrial disorders are one of the most complex and heterogeneous group of diseases:



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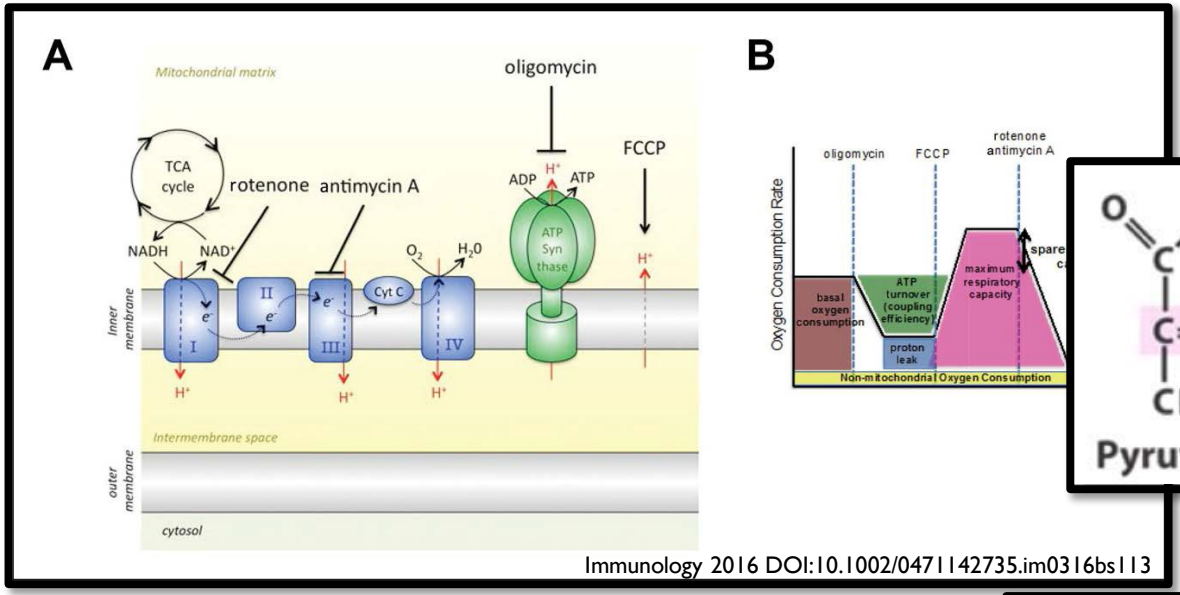
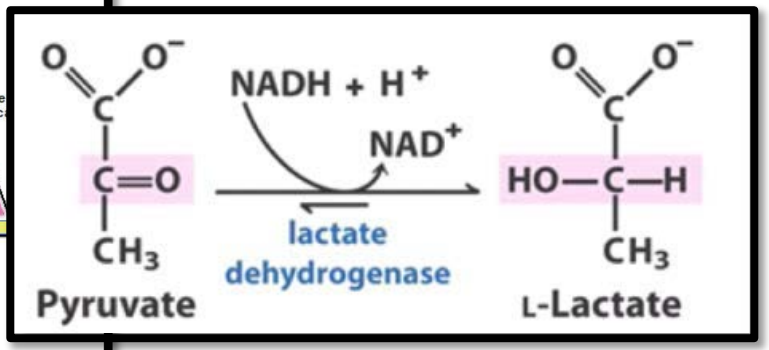
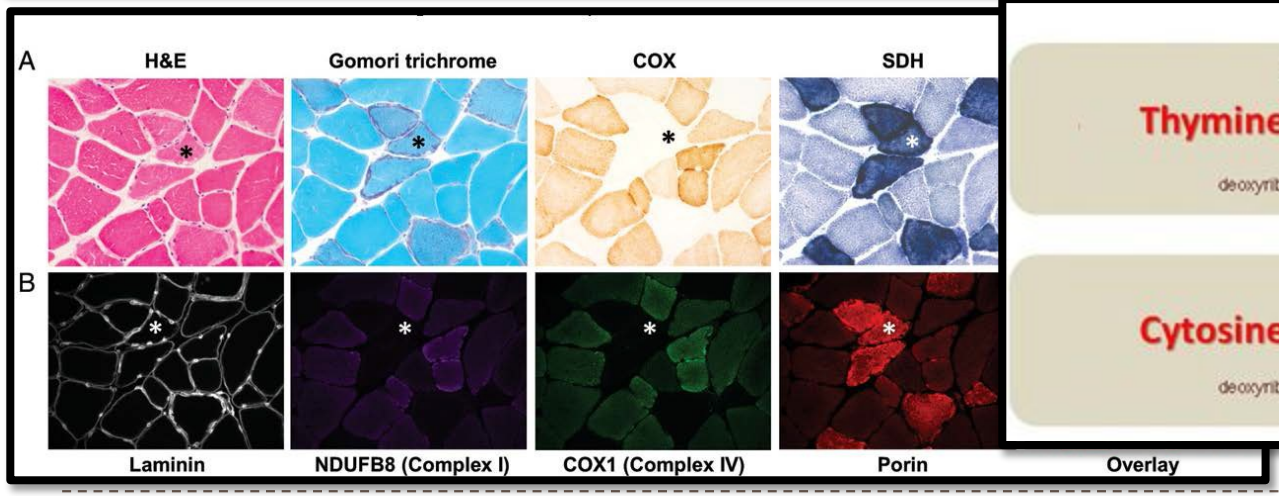
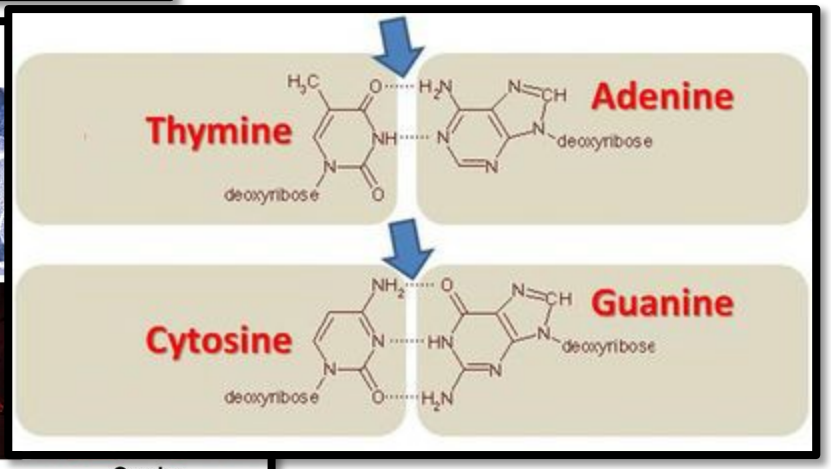




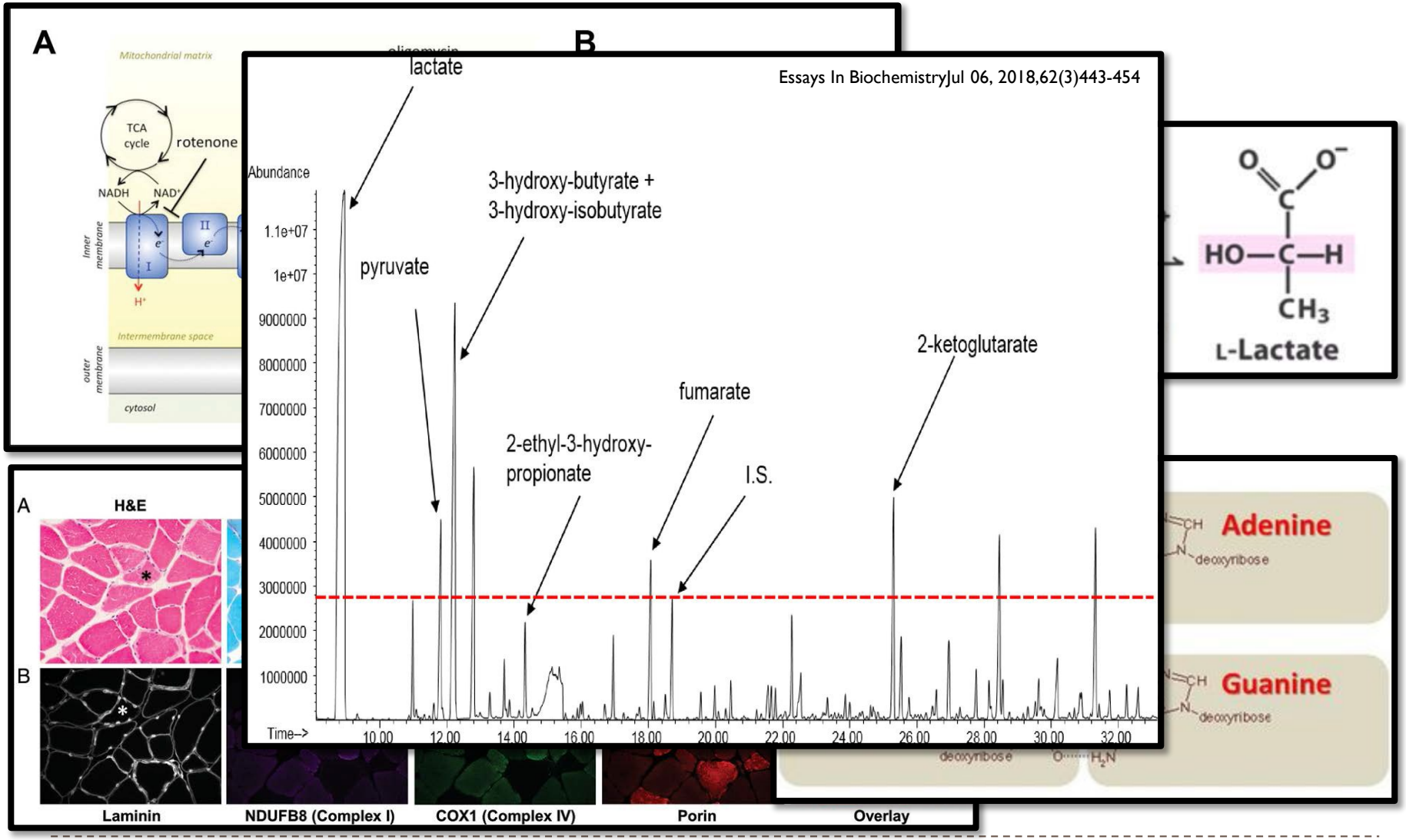
Immunology 2016 DOI:10.1002/0471142735.im0316bs113





•The Journal of pathology 2017 DOI:10.1002/path.4809

Mitochondrial disorders are one of the most complex and heterogeneous group of diseases:



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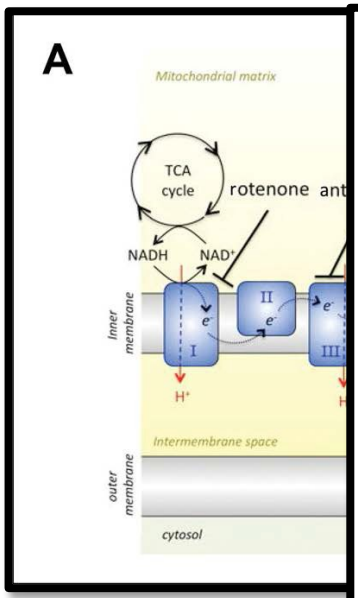
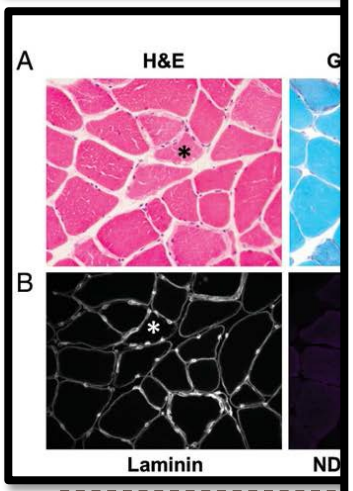
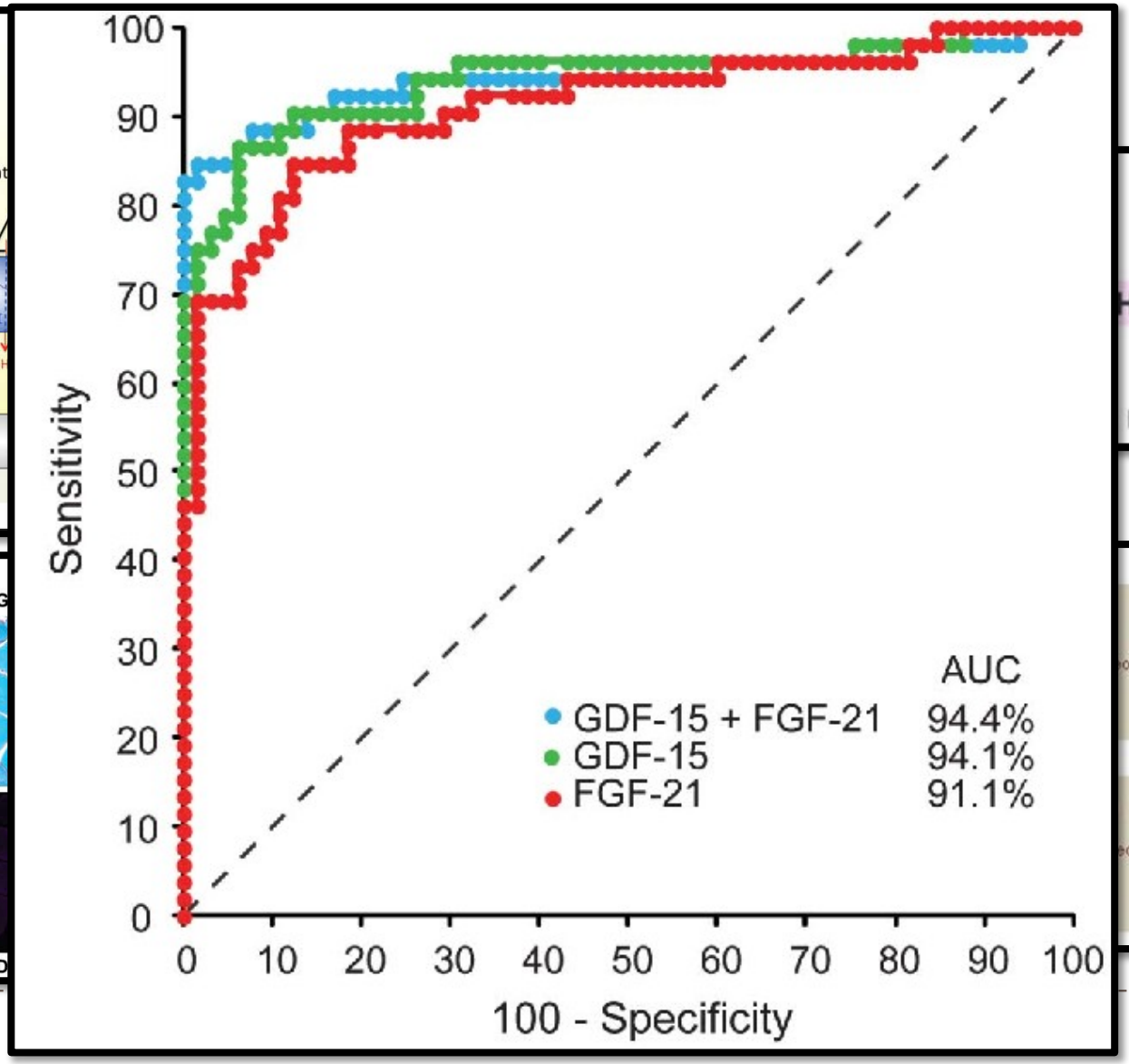
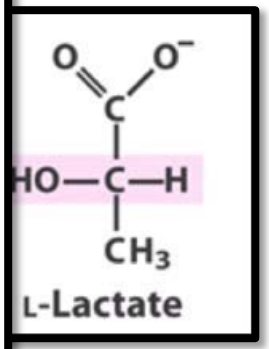








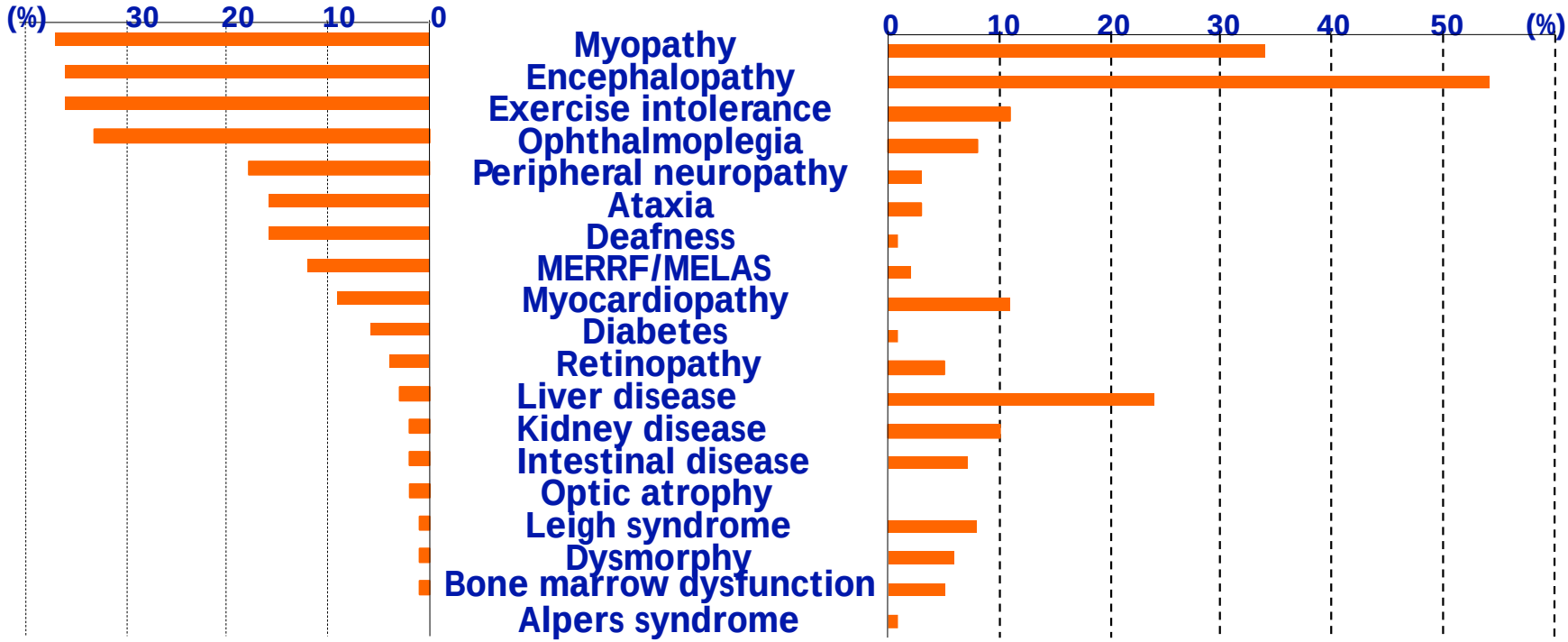
Neurology 2016 DOI:10.1212/wnl.0000000000002705

The Challenge !

Split Patients?

- Target a specific genotype
- Target a specific cellular pathway
- Target a specific biochemical defect
- Target a specific age group

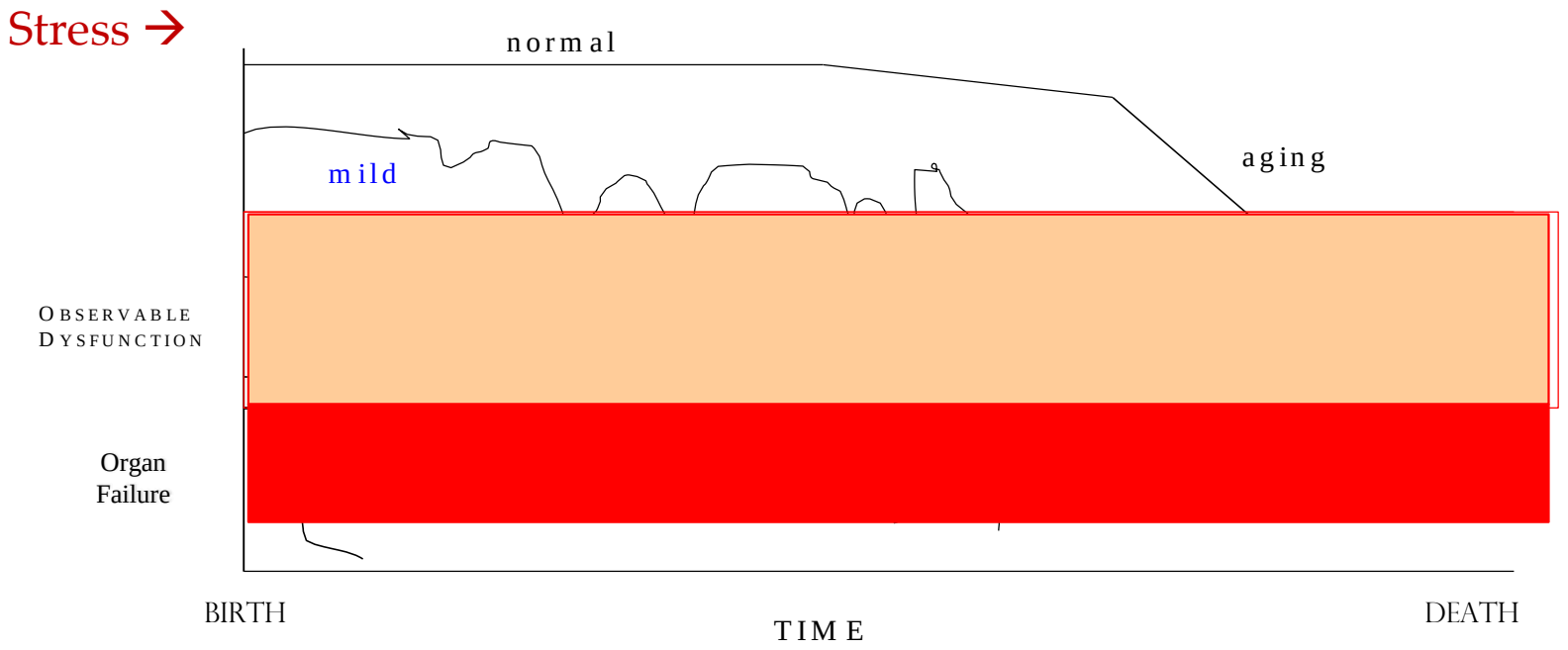
Mitochondrial disorders are one of the most complex and heterogeneous group of diseases:



SIMD/NAMA :Courtesy of Dr A Lombes Hopital La SalpétrièreUniversité Paris VI

Other considerations

Episodic, progressive Phenotype



The Challenge !

- Considerable heterogeneity
- No clear genotype-phenotype correlations

  - Is there consensus among clinical experts?
  - Uncertainties about the correct diagnosis in non-expert settings
  - Is there diagnostic consistency across centers?

- Clumping vs. splitting?

How to select the right trial patient population?

One size does not fit all

- Stable or highly variable condition?
- Life limiting or symptom control?
- Short or long-term endpoints?

How to select the right trial patient population?

One size does not fit all

Selection will need to be tailored by:

- Drug mechanism of action
- Therapeutic effects
- Off target effects
- Outcome measure
- Availability of natural history data
- Trial design
- Patient input

How to adequately power studies
Overcome recruitment problems

Thank you

akaraa@mgh.Harvard.edu