Среда 01.11 16:00
Конференц-зал ИЦИГ

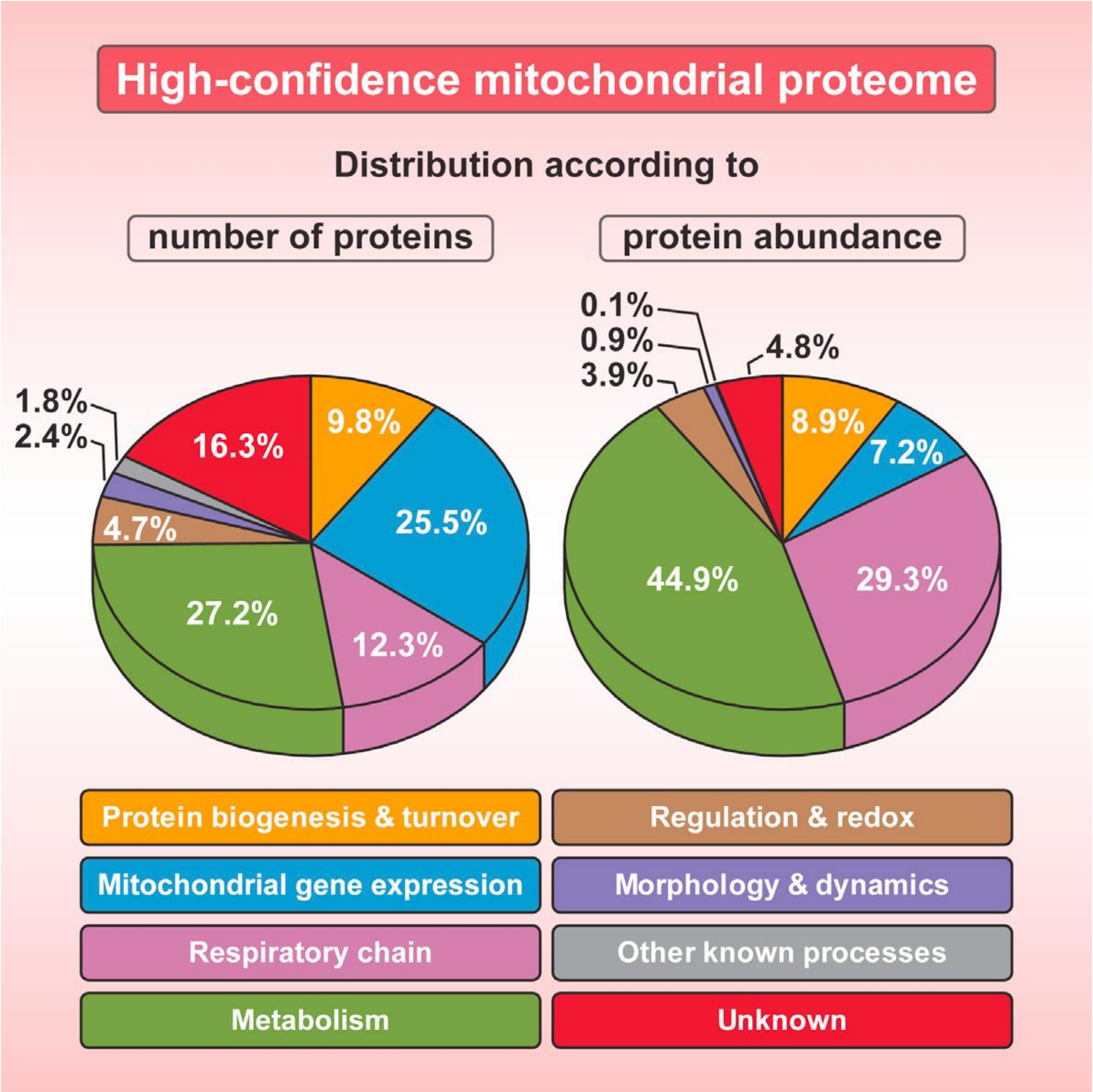
Михаил Тюменцев (ИЦИГ)

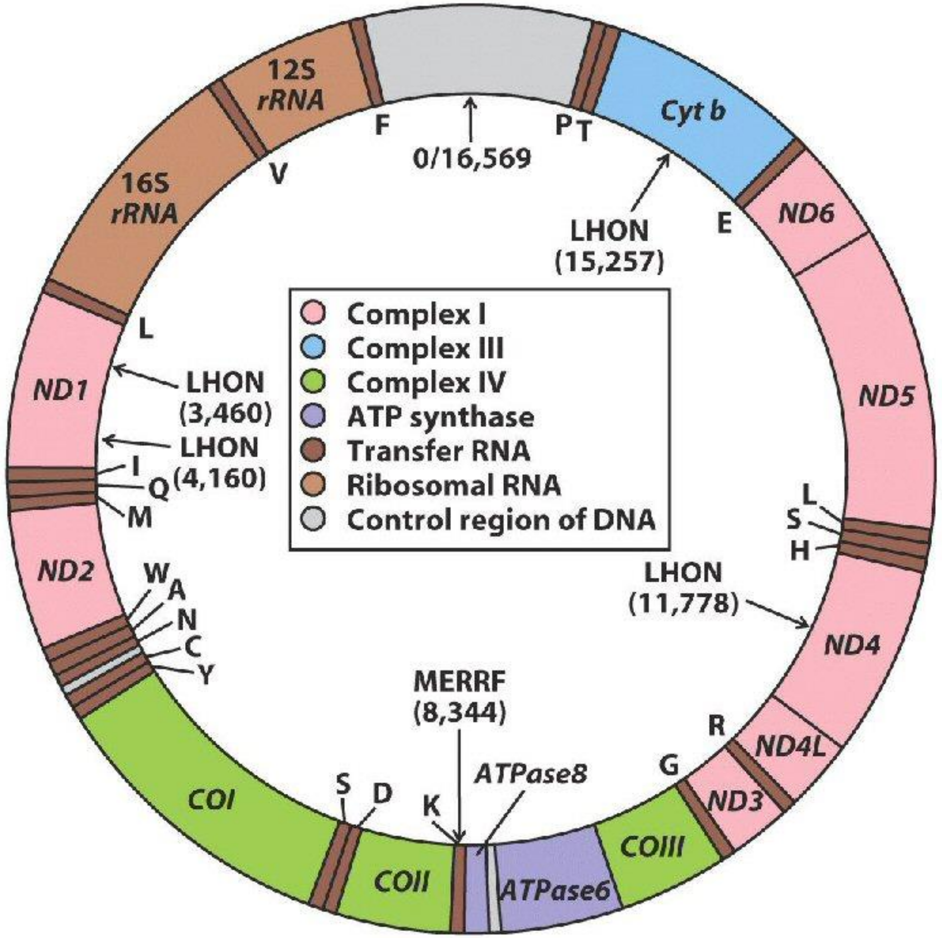
Митохондриальные болезни

Забудьте всё, чему учил вас Мендель

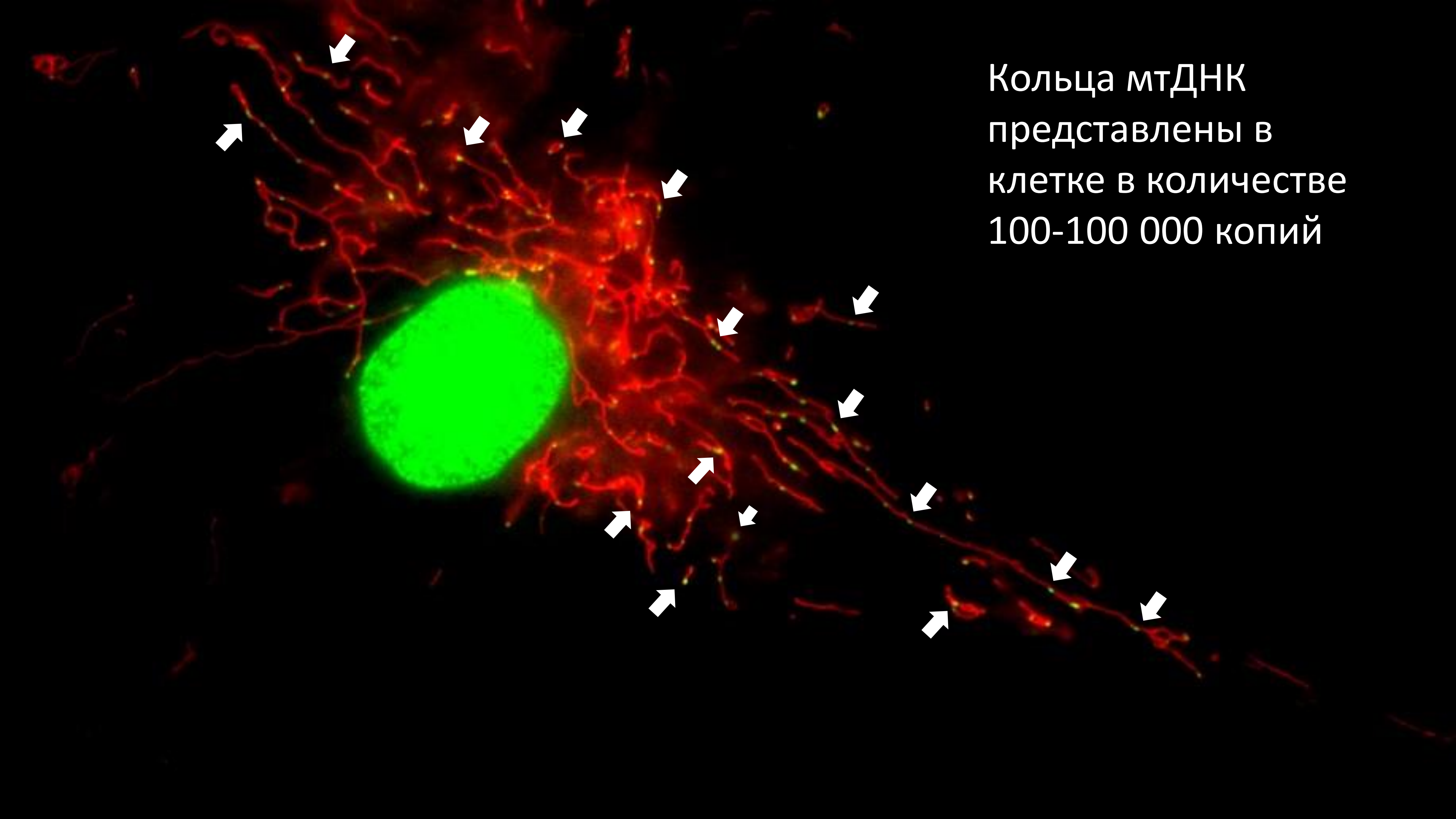
~1500 белков мт-протеома

37 (+2) гена мтДНК

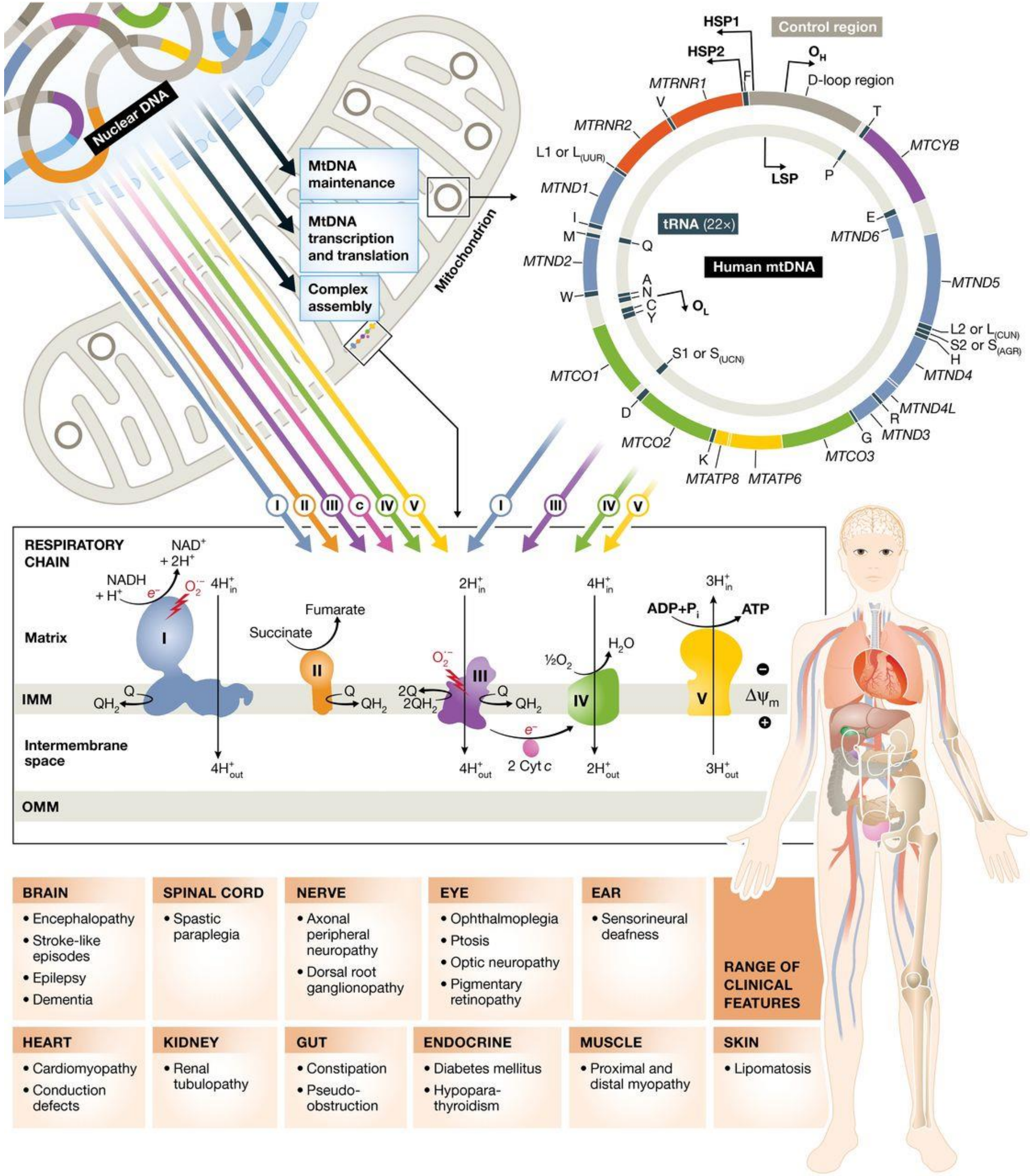




M Morgenstern - 2017

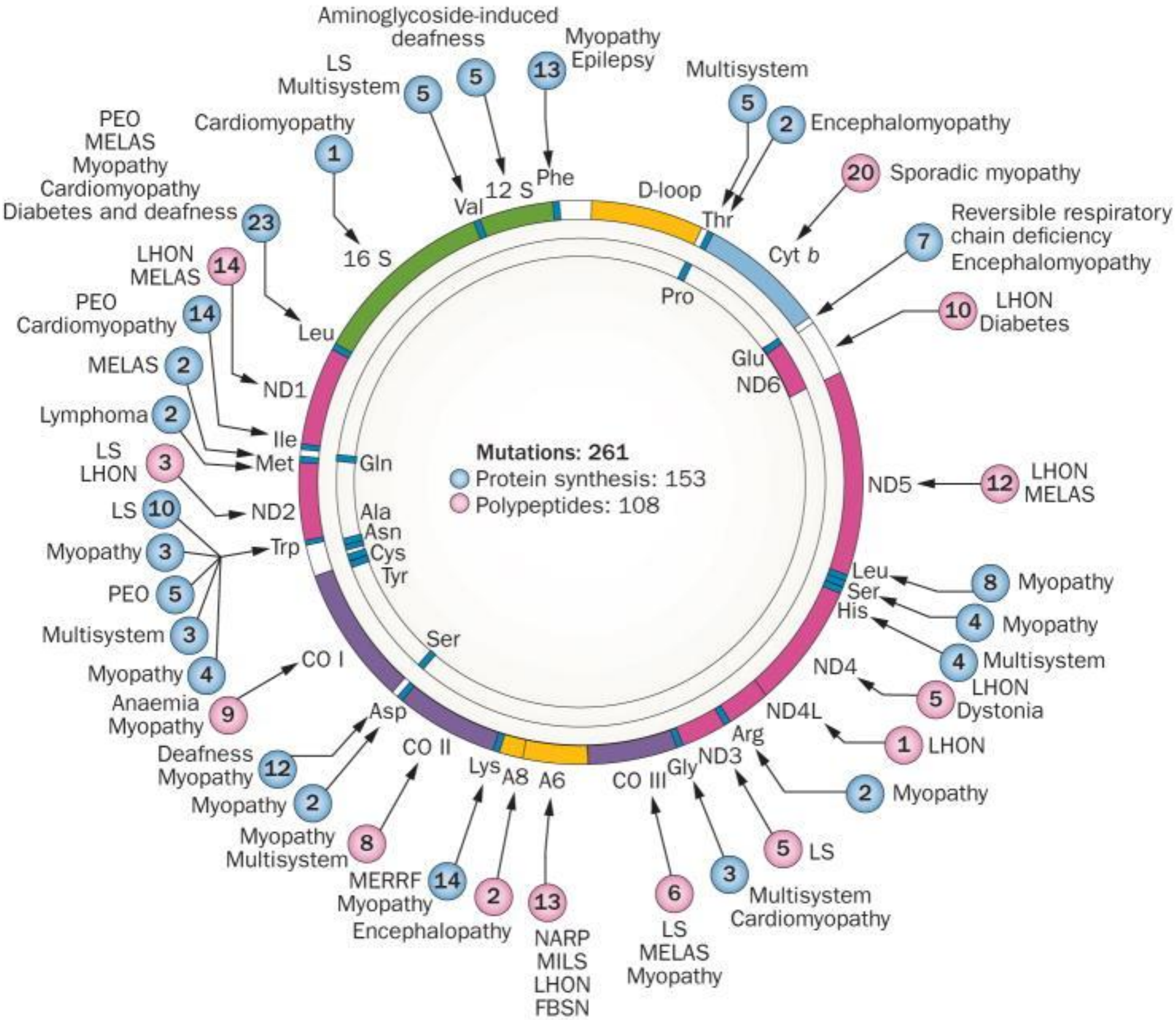


Кольца мтДНК
представлены в
клетке в количестве
100-100 000 копий



Некоторые самые распространенные типовые митохондриальные болезни

Name of Mitochondrial disease	Mutations
Chronic Progressive External Ophthalmoplegis (CPEO)	mt3243, polymerase gamma, twinkle, ANT
Leiber's Hereditary Optic Neuropathy (LHON)	mt11778, mt14459, mt3460
Mitochondrial Encephalopathy Lactic Acidosis and Stroke-like Episodes (MELAS)	mt3243, mt3271, mt3260
Myoclonic Epilepsy Raged Red Fibers (MERRF)	mt8844
Neurogenic Ataxia and Retinitis Pigmentosa (NARP)	mt8993
Myoneurogastrointestinal Encephalopathy (MNGIE)	thymidine phosphorylase
Leigh's syndrome	mt8993, SURF1, NDUFS1



Mutations: 261
Protein synthesis: 153
Polypeptides: 108
Aminoglycoside-induced deafness 5
Myopathy Epilepsy 13
LS Multisystem 5
Cardiomyopathy 1
PEO MELAS Myopathy Cardiomyopathy Diabetes and deafness 23
LHON MELAS 14
PEO Cardiomyopathy 14
MELAS 2
Lymphoma 2
LS LHON 3
LS 10
Myopathy 3
PEO 5
Multisystem 3
Myopathy 4
Anaemia Myopathy 9
Deafness Myopathy 12
Myopathy 2
Myopathy Multisystem 8
MERRF Myopathy 14
Encephalopathy 2
NARP MILS LHON FBSN 13
LS MELAS Myopathy 6
Multisystem Cardiomyopathy 3
LS 5
Myopathy 2
LHON 1
LHON Dystonia 5
Multisystem 4
Myopathy 4
Myopathy 8
LHON MELAS 12
LHON Diabetes 10
Reversible respiratory chain deficiency Encephalomyopathy 7
Sporadic myopathy 20
Encephalomyopathy 2
Multisystem 5
Val
12 S
Phe
D-loop
Thr
Cyt b
Pro
16 S
Leu
Glu
ND6
ND1
Ile
Met
Gln
ND2
Ala
Asn
Cys
Tyr
Trp
ND5
Leu
Ser
His
ND4
ND4L
Ser
CO I
Asp
CO II
Lys
A8
A6
CO III
Gly
ND3
Arg


a
b
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d
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REVIEWS

The clinical maze of mitochondrial neurology

Salvatore DiMauro, Eric A. Schon, Valerio Carelli and Michio Hirano

Abstract | Mitochondrial diseases involve the respiratory chain, which is under the dual control of nuclear and mitochondrial DNA (mtDNA). The complexity of mitochondrial genetics provides one explanation for the clinical heterogeneity of mitochondrial diseases, but our understanding of disease pathogenesis remains limited. Classification of Mendelian mitochondrial encephalomyopathies has been laborious, but whole-exome sequencing studies have revealed unexpected molecular aetiologies for both typical and atypical mitochondrial disease phenotypes. Mendelian mitochondrial defects can affect five components of mitochondrial biology: subunits of respiratory chain complexes (direct hits); mitochondrial assembly proteins; mtDNA translation; phospholipid composition of the inner mitochondrial membrane; or mitochondrial dynamics. A sixth category—defects of mtDNA maintenance—combines features of Mendelian and mitochondrial genetics. Genetic defects in mitochondrial dynamics are especially important in neurology as they cause optic atrophy, hereditary spastic paraplegia, and Charcot–Marie–Tooth disease. Therapy is inadequate and mostly palliative, but promising new avenues are being identified. Here, we review current knowledge on the genetics and pathogenesis of the six categories of mitochondrial disorders outlined above, focusing on their salient clinical manifestations and highlighting novel clinical entities. An outline of diagnostic clues for the various forms of mitochondrial disease, as well as potential therapeutic strategies, is also discussed.


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Alpers syndrome
Leigh disease
MELAS
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CPEO
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LHON
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KSS
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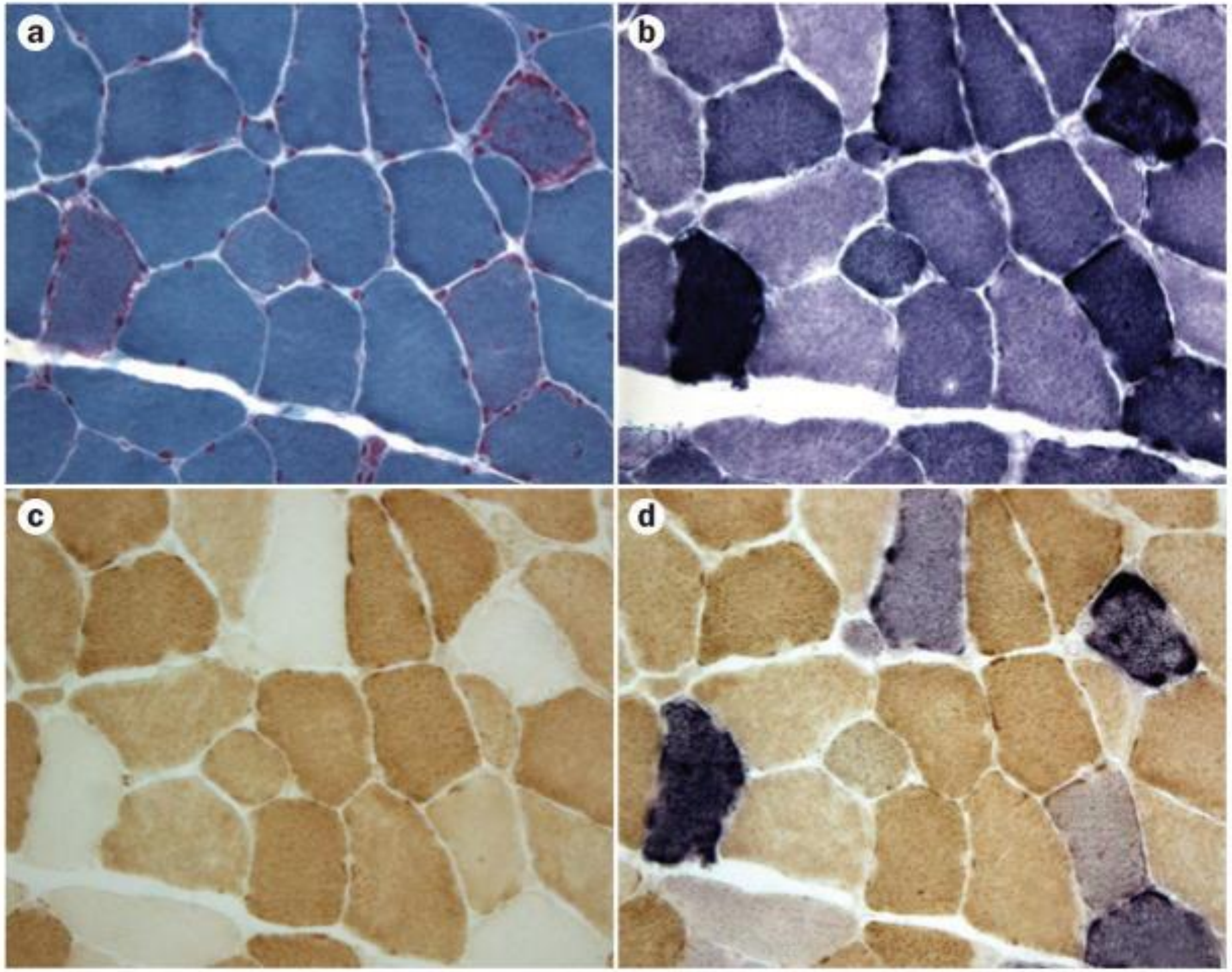


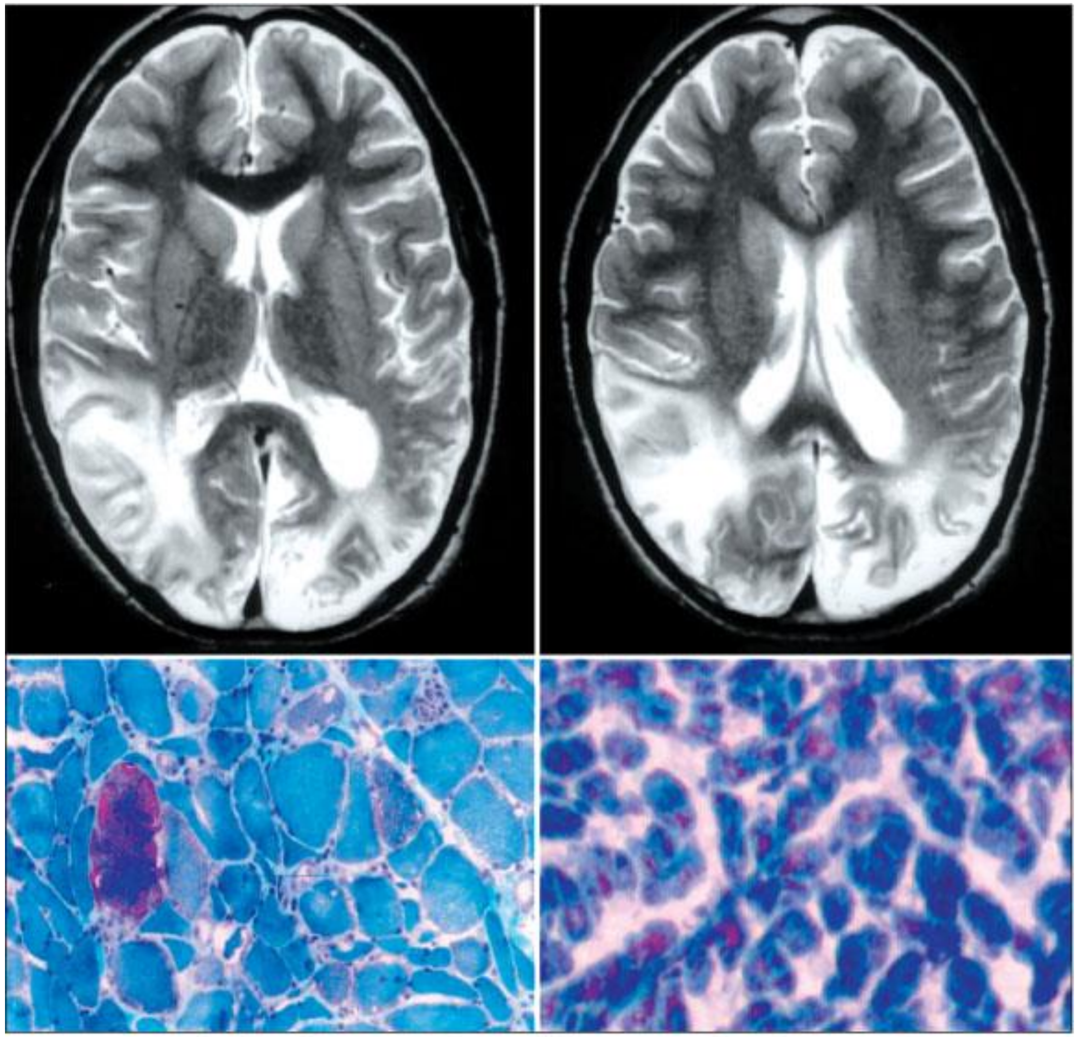
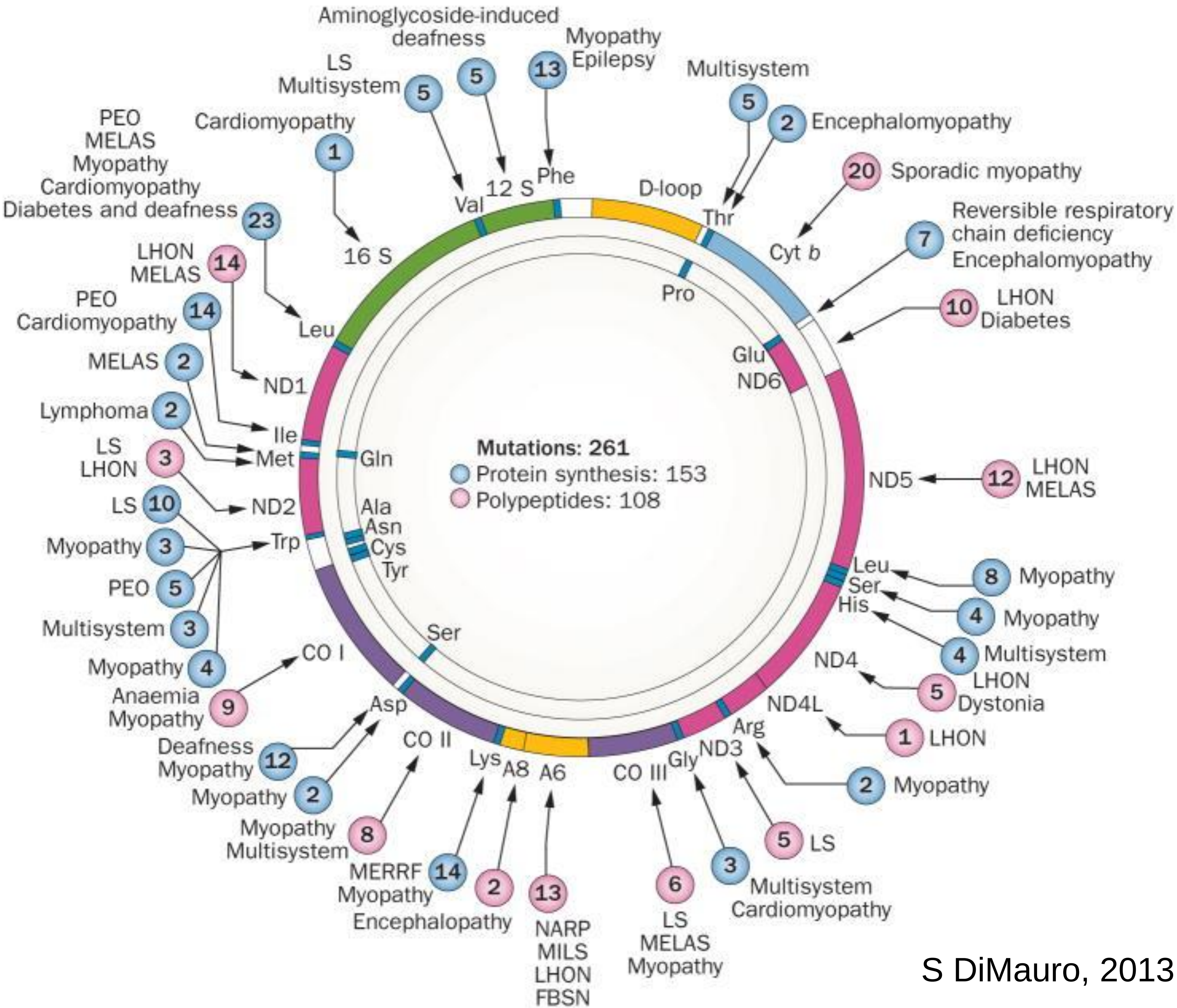


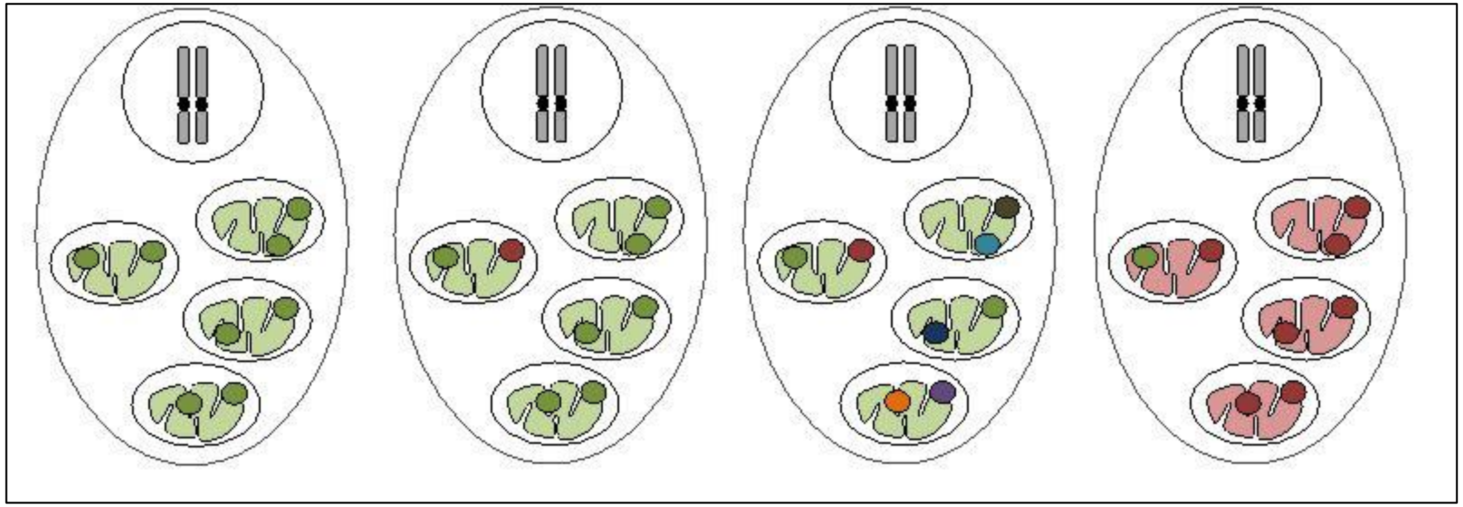
Fig 1. Top. T2-weighted MRI from Patient 3 (Group 2) shows increased signal in temporal cortex, occipital cortex and white matter bilaterally. Bottom. Postmortem findings in the same patient. Ragged red fibers (arrows) are present in diaphragm muscle (left) and heart muscle(right) stained by modified Gomori.

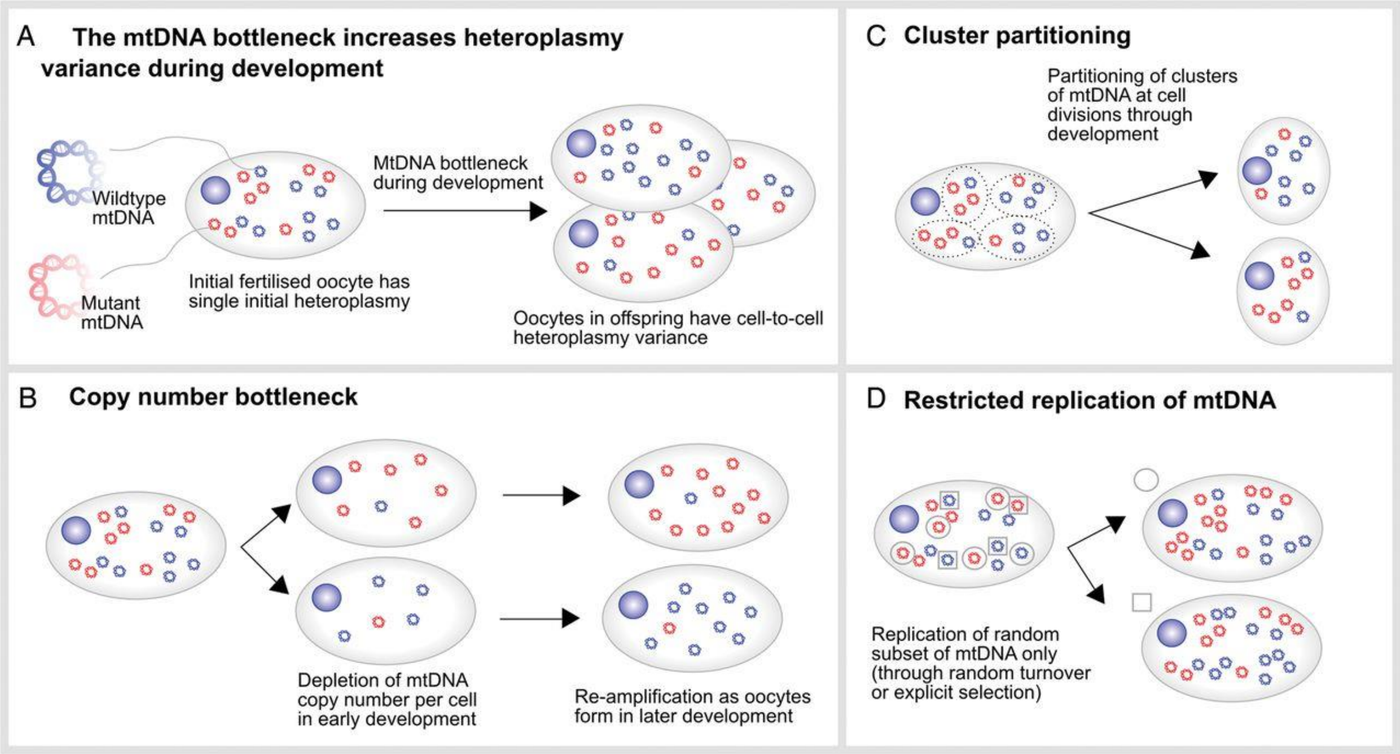
AB Conforto, 2007



S DiMauro, 2013

Гомо- и гетероплазмия





JP Burgstaller - 2014

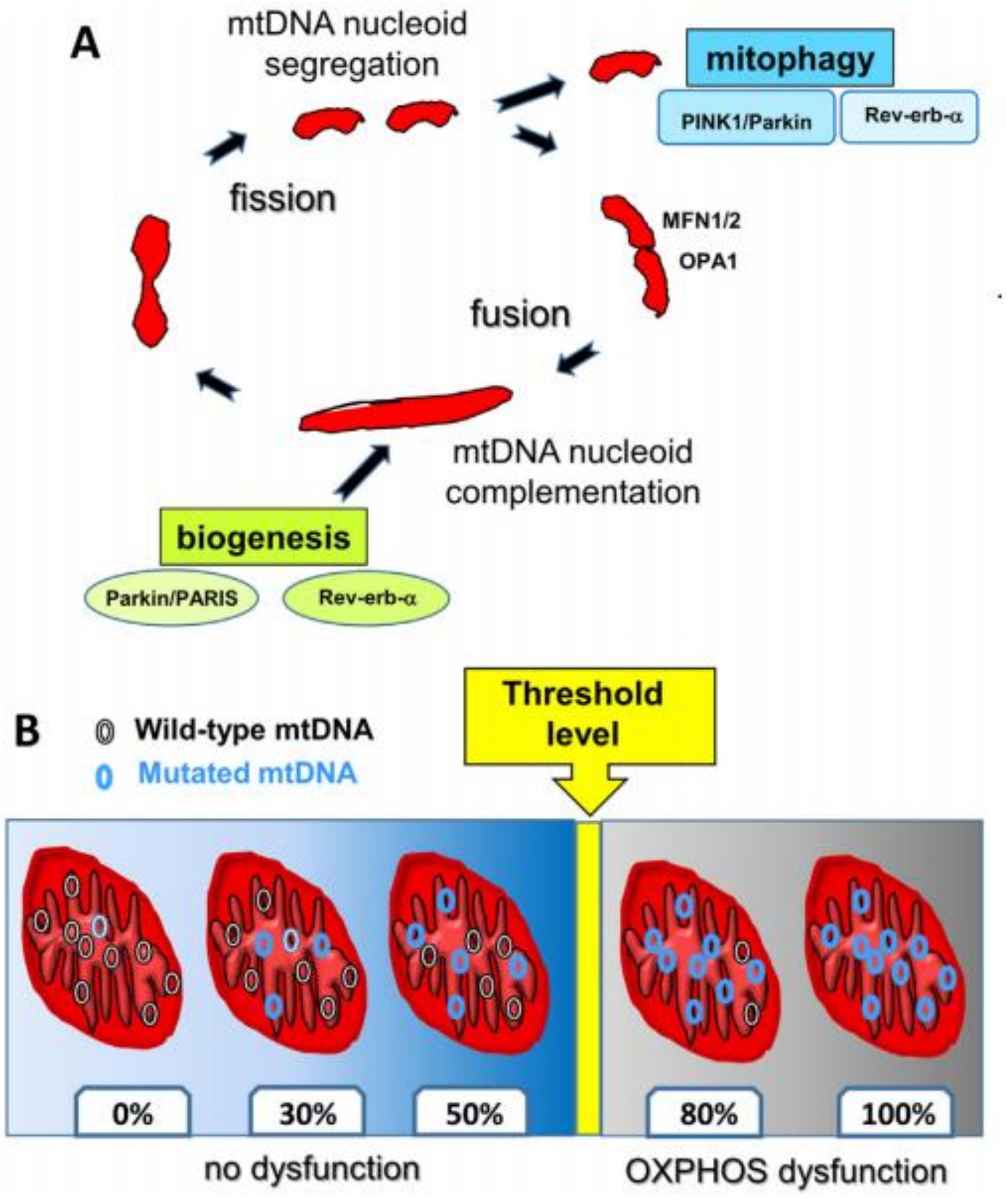
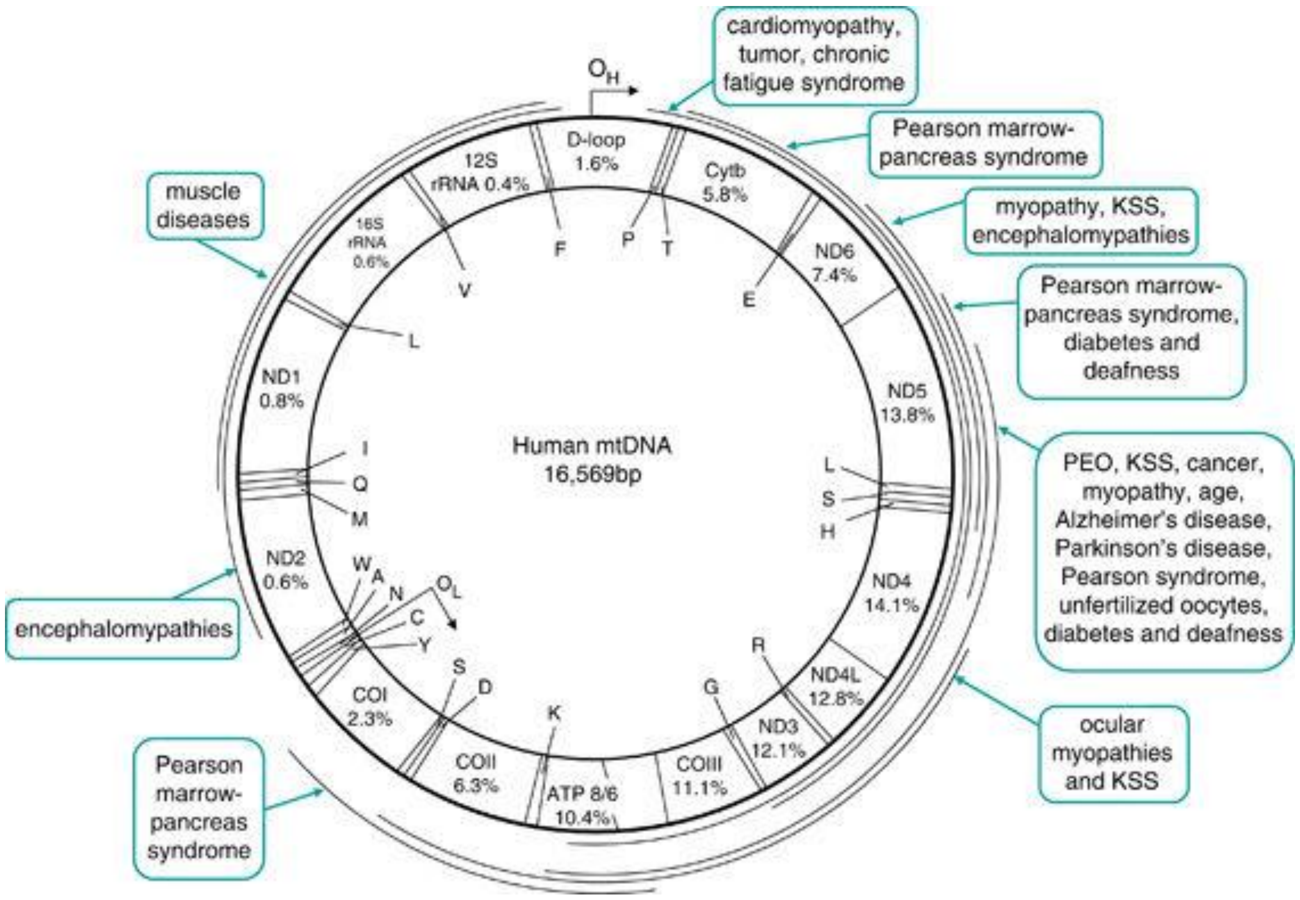


Fig. 1. Mitochondrial homeostasis and mechanisms involved in clonal expansion of mutated mtDNA molecules.

Carelli V., 2015

Митохондриальные делеции



T Chen - 2011

TABLE I. Clinical Features of Mitochondrial Diseases Associated With mtDNA Mutations

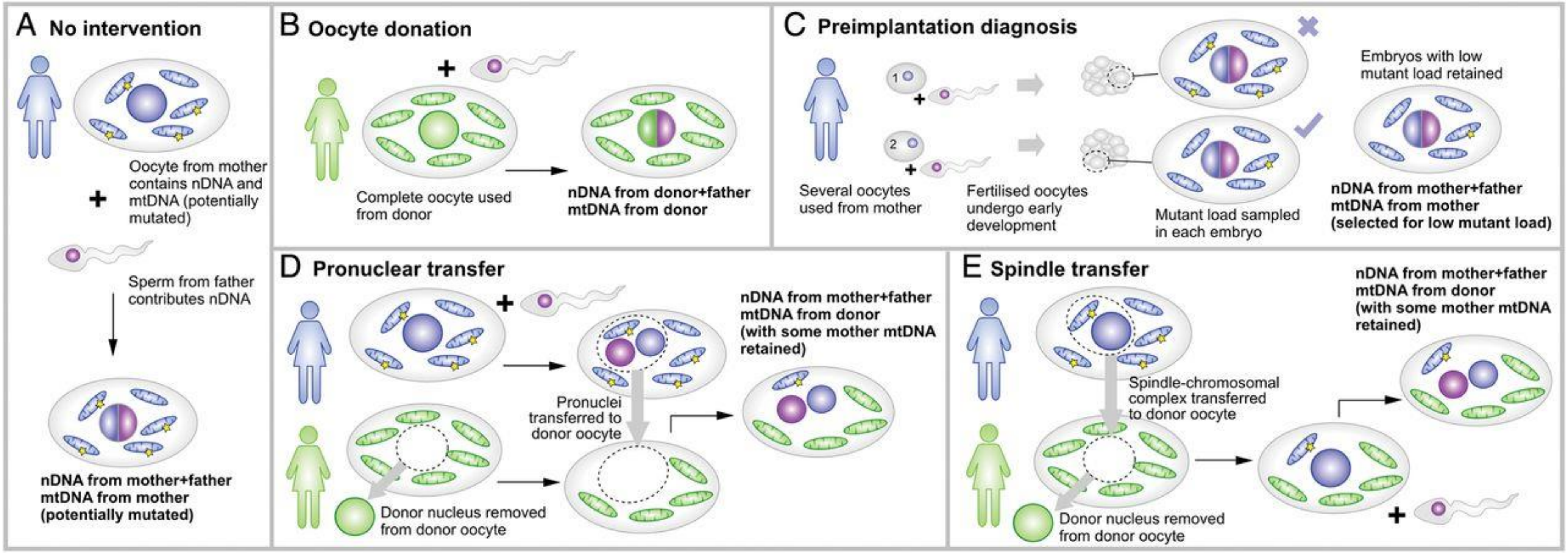
		Δ-mtDNA		tRNA		ATPase	
Tissue	Symptom/sigm	KSS	Pearson	MERRF	MELAS	NARP	MILS
CNS	Seizures	−	−	+	+	−	+
	Ataxia	+	−	+	+	+	±
	Myoclonus	−	−	+	±	−	−
	Psychomotor retardation	−	−	−	−	−	+
	Psychomotor regression	+	−	±	+	−	−
	Hemiparesis/hemianopia	−	−	−	+	−	−
	Cortical blindness	−	−	−	+	−	−
	Migraine-like headaches	−	−	−	+	−	−
	Dystonia	−	−	−	+	−	+
PNS	Peripheral neuropathy	±	−	±	±	+	−
Muscle	Weakness/exercise intolerance	+	−	+	+	+	+
	Opthalmoplegia	+	±	−	−	−	−
	Ptosis	+	−	−	−	−	−
Eye	Pigmentary retinopathy	+	−	−	−	+	+
	Optic atrophy	−	−	−	−	±	±
	Cataracts	−	−	−	−	−	−
Blood	Sideroblastic anemia	±	+	−	−	−	−
Endocrine	Diabeted mellitus	±	−	−	±	−	−
	Short stature	+	−	+	+	−	−
	Hypoparathyroidism	±	−	−	−	−	−
Heart	Conduction block	+	−	−	±	−	−
	Cardiomyopathy	±	−	−	±	−	±
GI	Exocine pancreatic dysfunction	±	+	−	−	−	−
	Intestinsl pseudo-obstruction	−	−	−	−	−	−
ENT	Sensorineural hearing loss	−	−	+	+	±	−
Kidney	Fanconi syndrome	±	±	−	±	−	−
Laboratory	Lactic acidosis	+	+	+	+	−	±
	Muscle biopsy:RRF	+	±	+	+	−	−
Inheritance	Maternal	−	−	+	+	+	+
	Sporadic	+	+	−	−	−	−

Why should defects of one and the same metabolic pathway all cause such a bewildering variety of symptoms and signs?

S DiMauro, 2013

Перспективы лечения?

Генетическая консультация и донорство митохондрий



JP Burgstaller - 2014

Редактирование генома?

Research Article

Efficient Mitochondrial Genome Editing by CRISPR/Cas9

Areum Jo,[1] Sangwoo Ham,[1] Gum Hwa Lee,[2] Yun-Il Lee,[3] SangSeong Kim,[4] Yun-Song Lee,[1] Joo-Ho Shin,[1] and Yunjong Lee[1]

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Received 25 May 2015; Revised 30 July 2015; Accepted 6 August 2015

ИМПОРТ НУКЛЕАЗЫ CAS9 В МИТОХОНДРИИ

К.Е. Орищенко [1,2], Ю.К. Софронова [2], Е.Г. Чупахин [2], Е.А. Лунев [2], И.О. Мазунин [2]
[1] ФГБНУ «Федеральный исследовательский центр Институт цитологии и генетики СО РАН», Новосибирск, Россия
[2] Балтийский федеральный университет им. И. Канта, Калининград, Россия

Delivery Cas9 into mitochondria

K.E. Orishchenko [1,2], J.K. Sofronova [2], E.G. Chupakhin [2], E.A. Lunev [2], I.O. Mazunin [2]
[1] Federal Research Center Institute of Cytology and Genetics, the Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russia
[2] I. Kant Baltic Federal University, Kaliningrad, Russia

ARTICLE

Selective Elimination of Mitochondrial Mutations in the Germline by Genome Editing

Pradeep Reddy[14], Alejandro Ocampo[14], Keiichiro Suzuki, Jinping Luo, Sandra R. Bacman, Sion L. Williams, Atsushi Sugawara, Daiji Okamura, Yuji Tsunekawa, Jun Wu, David Lam, Xiong Xiong, Nuria Montserrat, Concepcion Rodriguez Esteban, Guang-Hui Liu, Ignacio Sancho-Martinez, Dolors Manau, Salva Civico, Francesc Cardellach, Maria del Mar O'Callaghan, Jaime Campistol, Huimin Zhao, Josep M. Campistol, Carlos T. Moraes, Juan Carlos Izpisua Belmonte

[14] Co-first author

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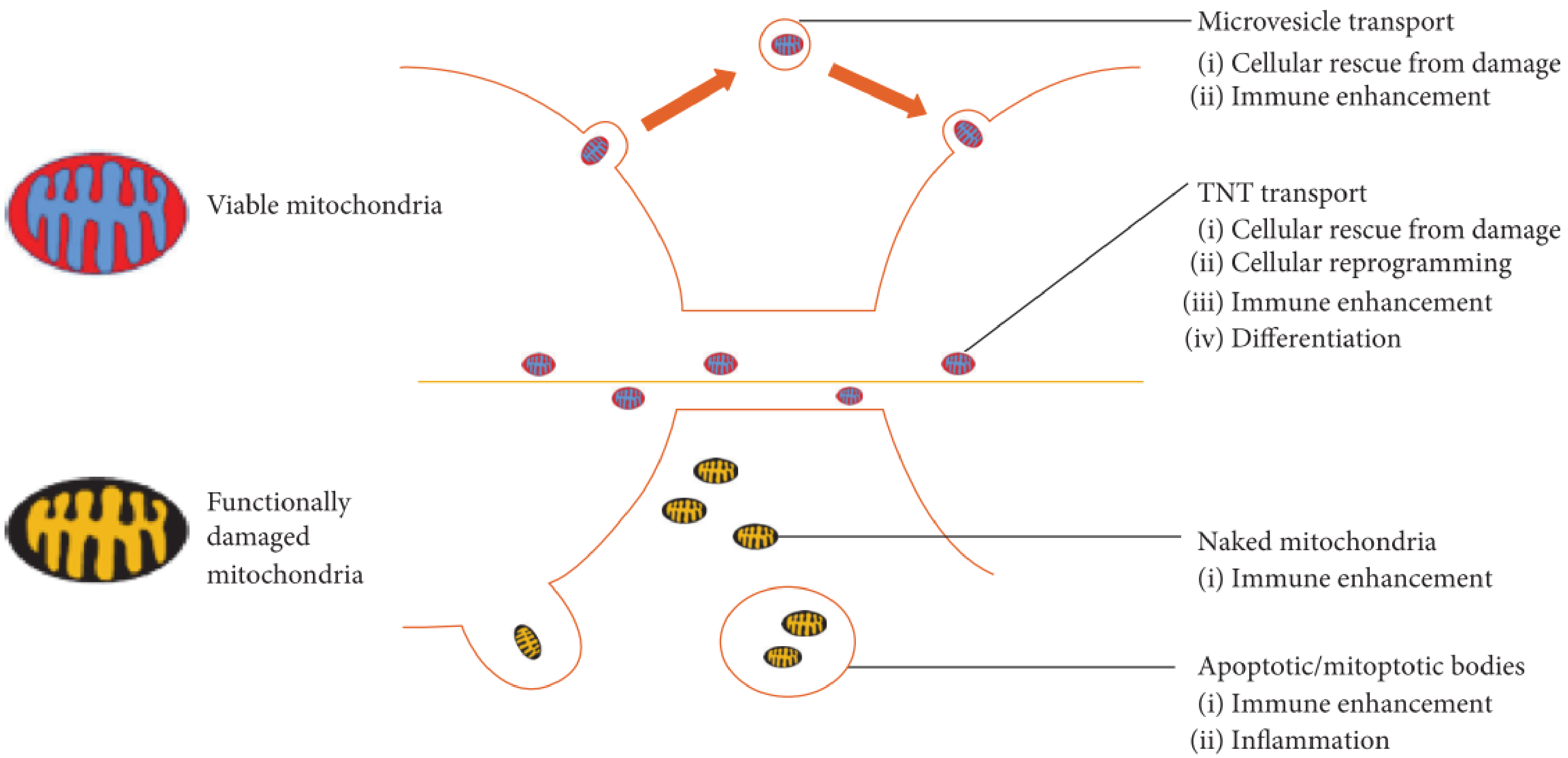
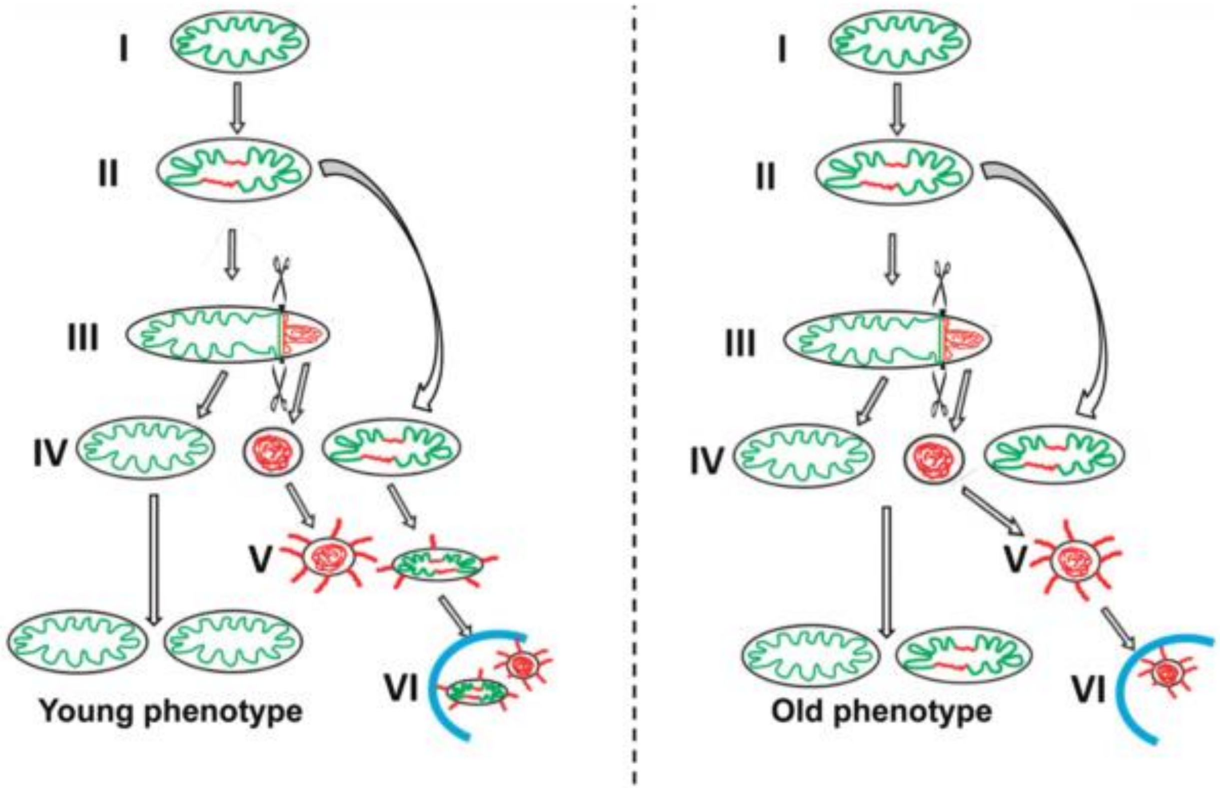
Пересадка?



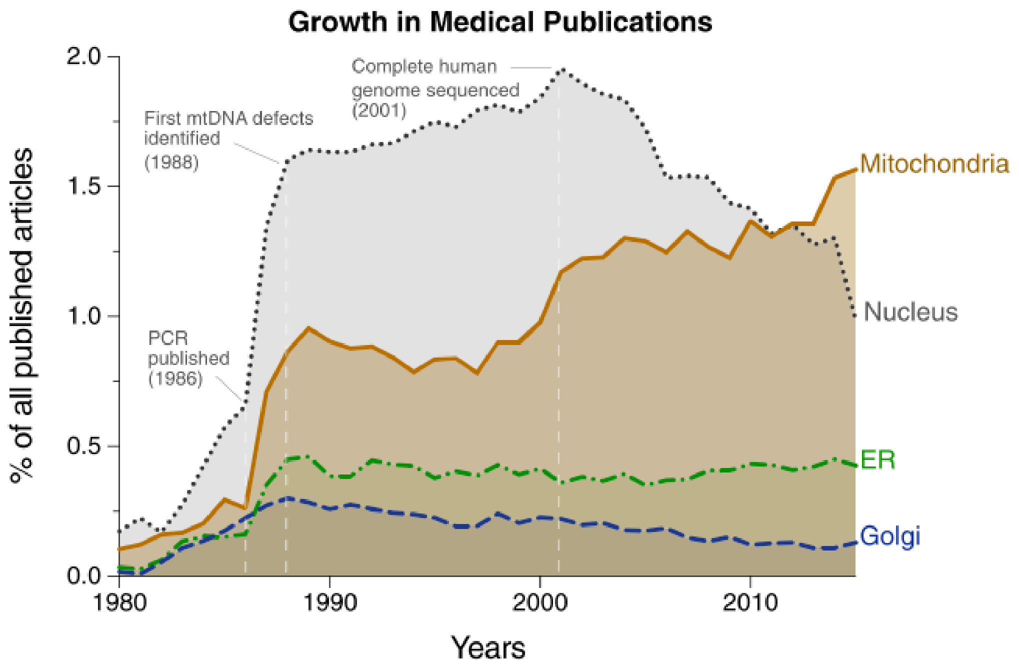
A Caicedo, 2017

Сдвиг гетероплазмии?

Контроль качества митохондрий



DB Zorov - 2016



M Picard - 2016

Благодарю за внимание

Благодарю за внимание