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Chapter 13

Mitochondrial genetic disorders

Lei Huang, Department of Medical Genetics
leihuang@shsmu.edu.cn

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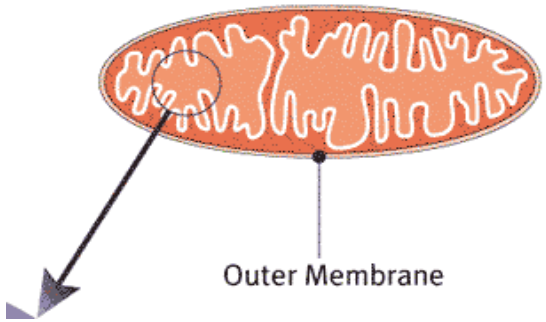
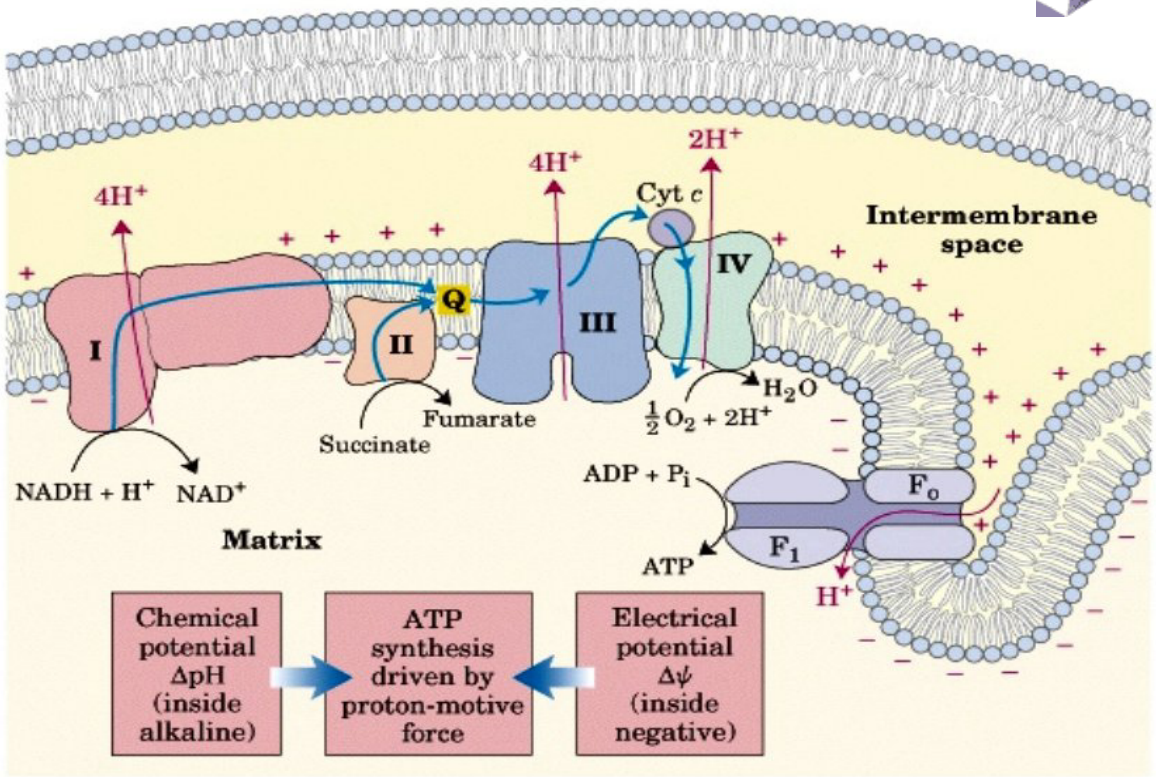
Outline

- Structure of human mitochondrial DNA (mtDNA)
- Characteristics of Mitochondrial Inheritance
- Mutations in mtDNA and Disease

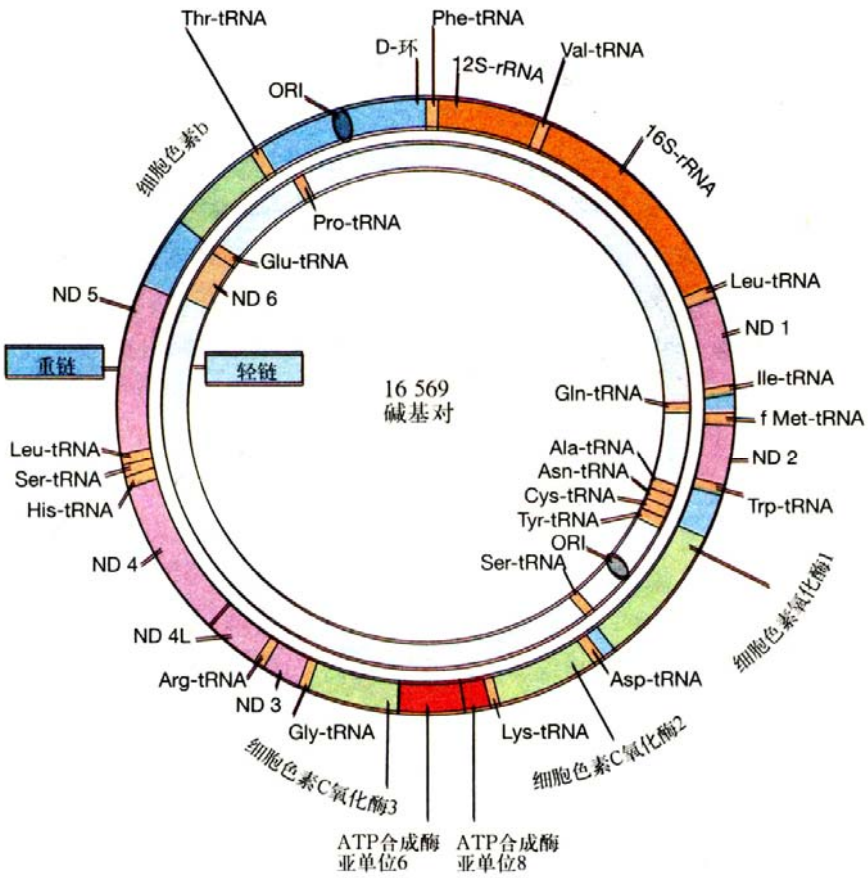
Mitochondrial





1894, discover Mit
1963, mtDNA
1987, mtDNA & Leber

Structure of human mitochondrial DNA (mtDNA)



人类线粒体基因组

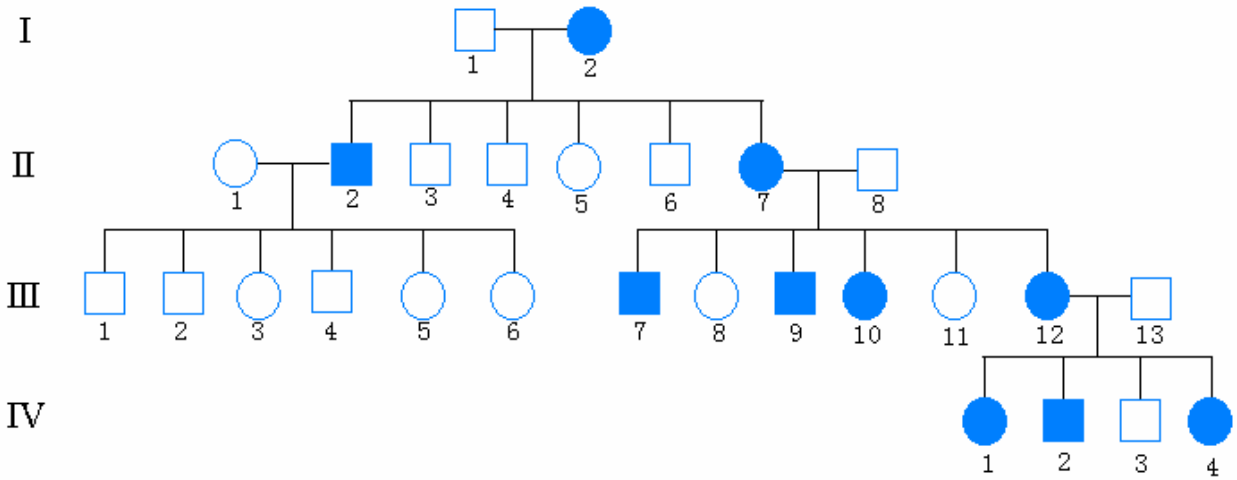
- No.25 chromosome or M chromosome
- Double strand (closed ring)

Heavy strand ; Light strand

- 16 569 bp ⟶ 37 genes
  - *13 genes enconding proteins involved respiratory chain*
  - *22 genes enconding tRNA*
  - *2 genes enconding rRNA*

Characteristics of Mitochondrial Inheritance

- **Replication: 半自主性复制**
- **Special Codon：UGA（Trp）**
- **Maternal inheritance（母系遗传）**
- **Replicative segregation（复制分离）：mtDNA distributed randomly between the two daughter cells**
- **Quantitative threshold （阈值效应）：Homoplasmy and heteroplasmy**
- **High mutation frequency: 20 times higher**



•**The maternal inheritance : reflects the fact that sperm mitochondria are generally eliminated from the embryo, so that mtDNA is almost always inherited entirely from the mother.**

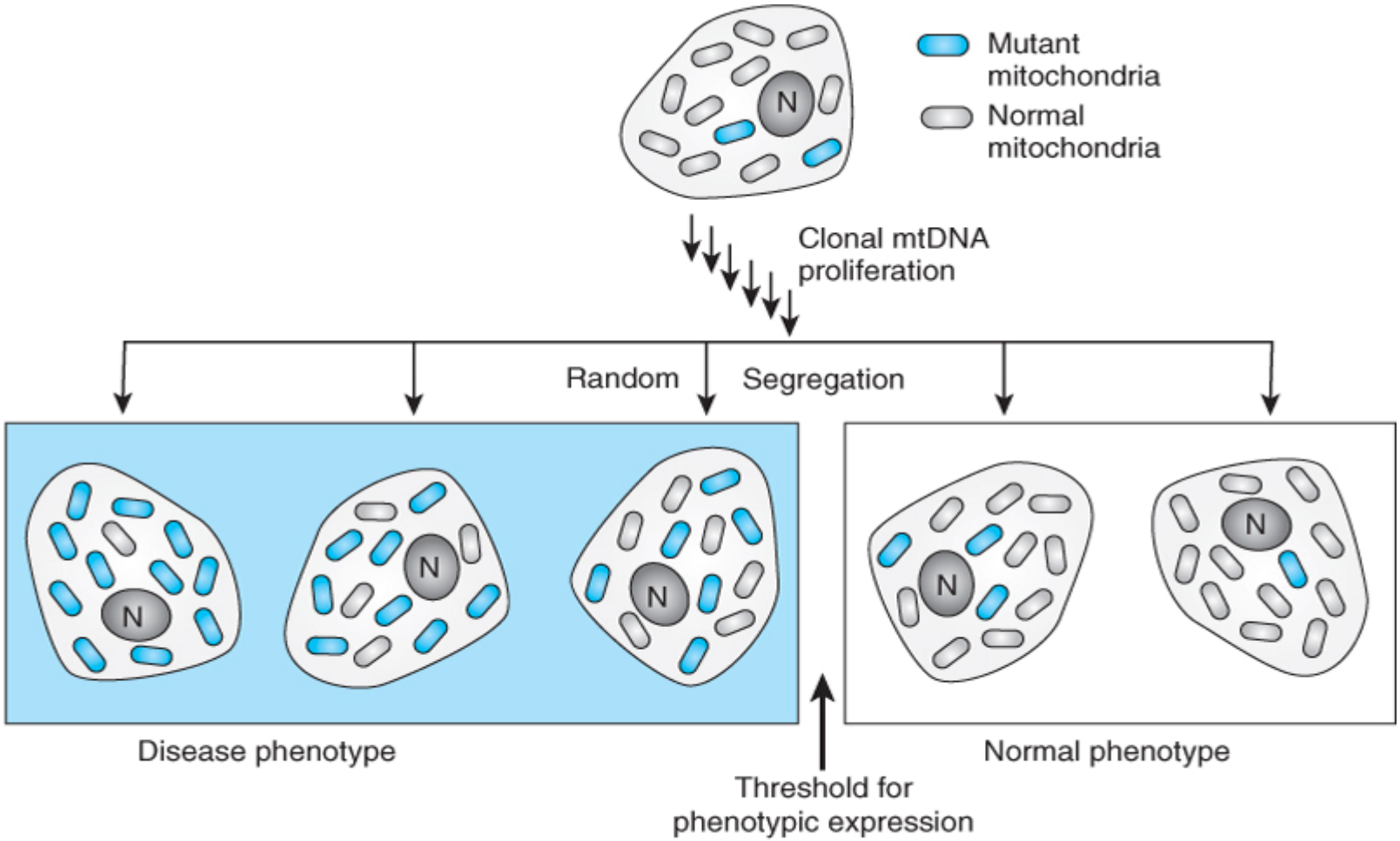
Mitochondrial genetic bottleneck (遗传瓶颈)

Oocyte	→	Mature oocyte	→	Early development
100000 mt		10~ 100 mt		100000 mt

- Within the maturity of the oocyte, the amount of mitochondria decreased rapidly, from 100,000 to less than 100, this is "**genetic bottleneck**".
- It can decrease the probability of disease-carrying mother to transmit the mutant gene to their offspring.

- **Homoplasmy (纯质)**：指一种组织或细胞中的线粒体的基因完全相同，即全为突变基因或全为野生型的细胞或组织。

- **Heteroplasmy (杂质)**：指一种组织或细胞中的线粒体的基因一部分为突变型，一部分为野生型。



Quantitative threshold (阈值效应)

- **The mutant mtDNA in heteroplasmy will only lead to onset of the disease when it significantly with a quantitative threshold .**

  突变的mtDNA的数量超过一定限度时，会出现临床症状。（阈值）

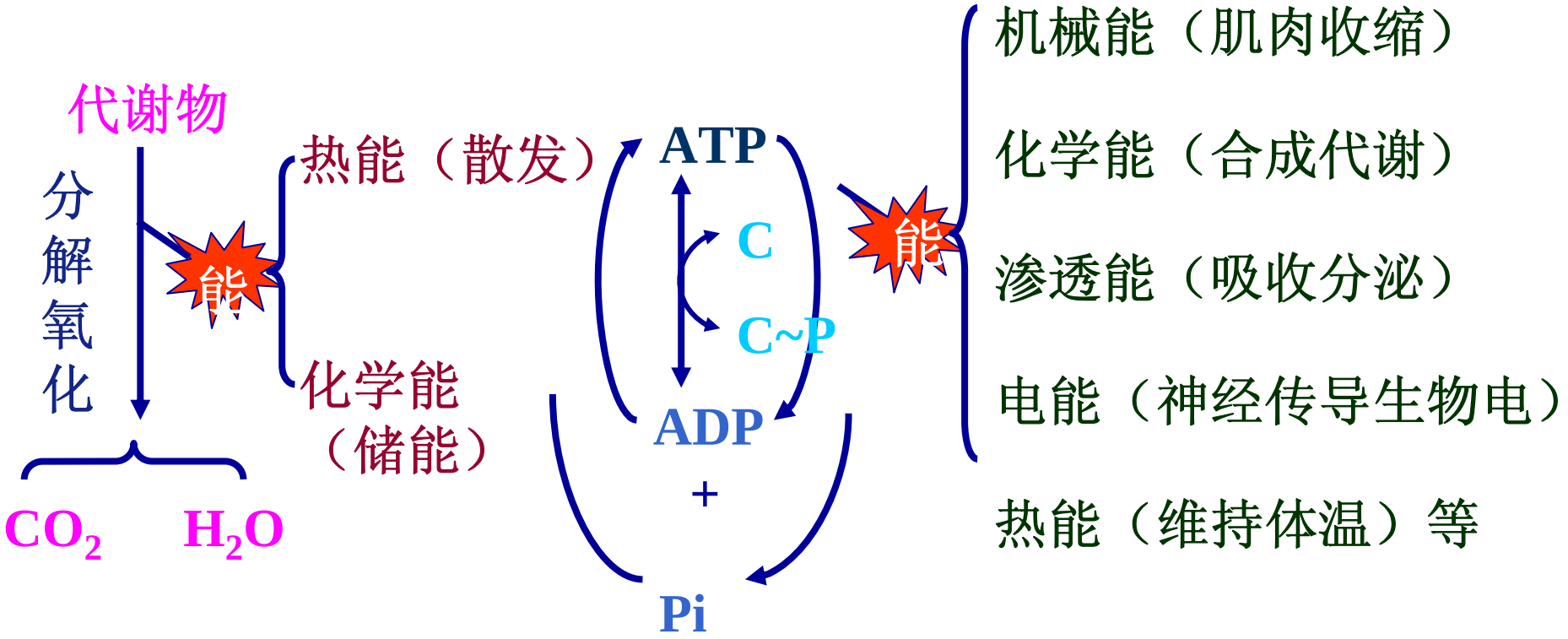
- **The severity of the disease associated with a mtDNA mutation will depend on the relative proportion of normal and mutant mtDNA in the cells of a particular tissue**

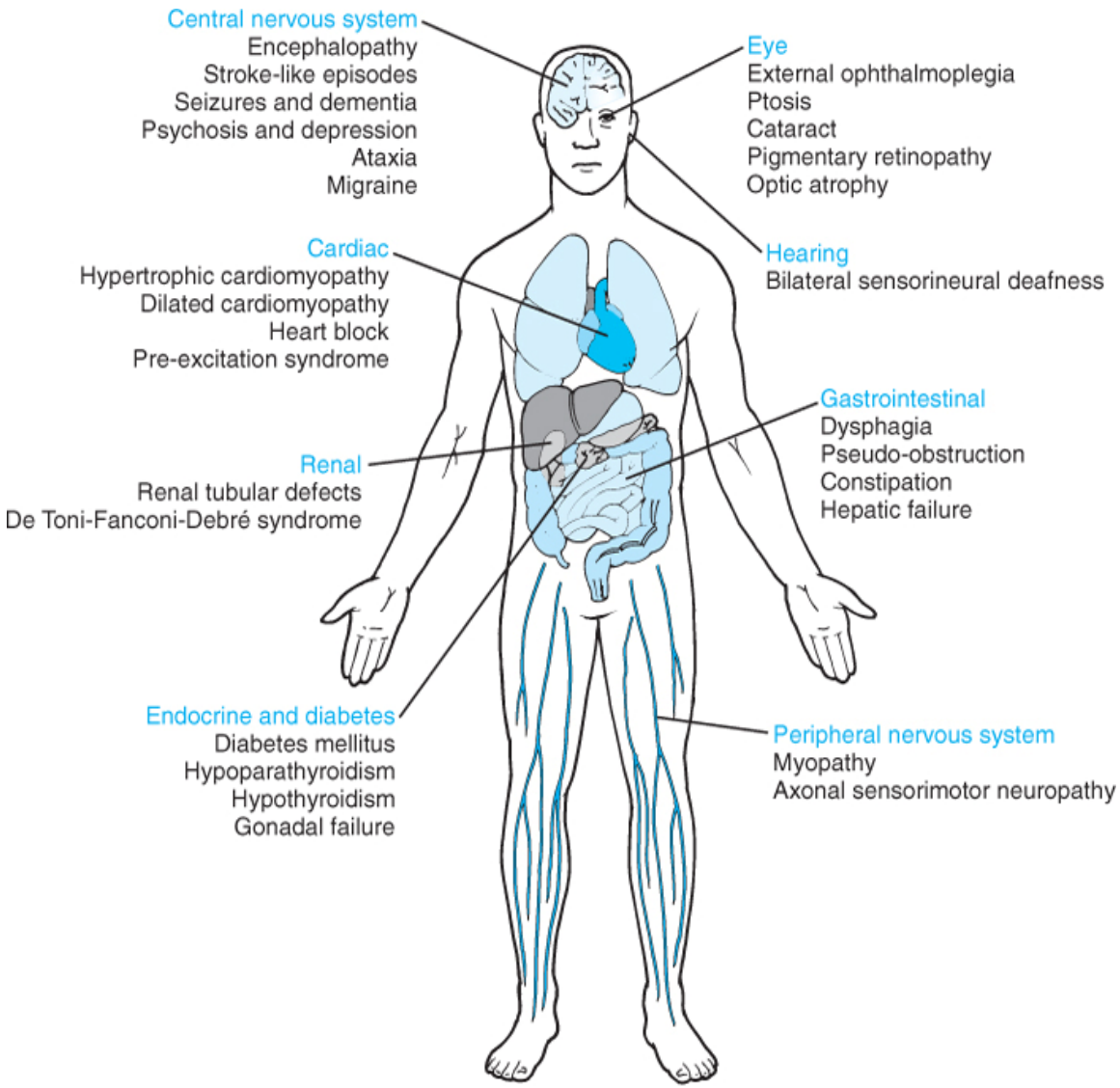
  突变mtDNA所占比例与临床症状的表现程度相关。

Compare with nuclear DNA (nDNA)

	nDNA	mt DNA
Location	nucleus	cytoplasm
Structure	double strand(linear)	double strand(closed ring)
Number of bp	3.1×10^9	16 569
Number of genes	30,000-35,000	37
Copy of genes	single	multiple
Intervening sequence	yes	no
Frequency of mutation	low	high

ATP的生成和利用


代谢物
分解氧化
CO_2 H_2O
能
热能（散发）
化学能（储能）
ATP
C
C~P
ADP
+
Pi
能
机械能（肌肉收缩）
化学能（合成代谢）
渗透能（吸收分泌）
电能（神经传导生物电）
热能（维持体温）等



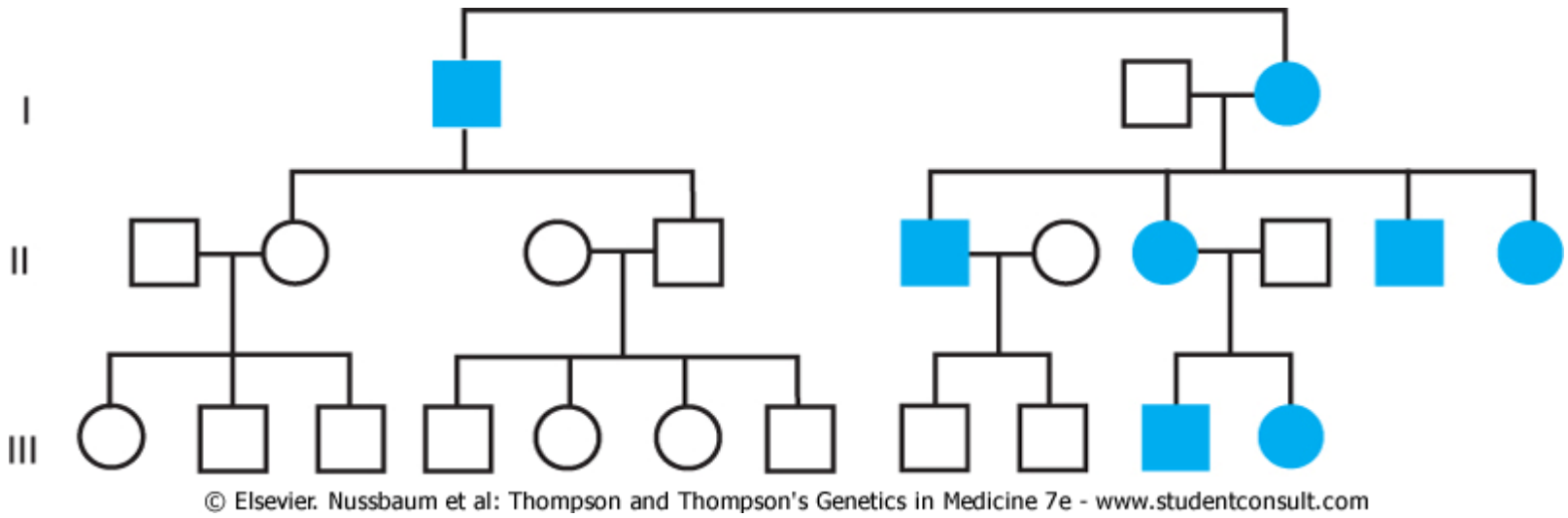
高需能组织敏感：

脑、骨骼肌、心脏、肝、肾、眼、耳、胃肠等

痴呆、耳聋、失明、肌病、心肌病、贫血、糖尿病等

Mutations in mtDNA and Disease

1. Leber hereditary optic neuropathy (LHON, Leber 遗传性视神经病)



Mutations in mtDNA and Disease

1. Leber hereditary optic neuropathy (LHON, Leber 遗传性视神经病)

Major clinic features:

① **Rapid loss of vision in the central visual field as a result of optic nerve death;**

② **Vision loss typically begins in the third decade of life and is usually irreversible;**

③ **More males than females (6M:1F) are affected .**

Leber hereditary optic neuropathy

- **Nine Mito gene disorders are involved in**

  (ND1, ND2, CO1, ATP6, CO3, ND4, ND5, ND6, CYTB)

- **LHON is heterogeneous, it can be caused by different mutations，90% harbor:**

  MTND1*LHON3460A

  MTND4*LHON11778A，50-75%

  MTND6*LHON14484C.

- **Homoplasmic.**

2. Mitochondrial encephalomyopathy, lactic acidosis,and stroke-like episodes (MELAS, 线粒体肌病脑病伴乳酸酸中毒及中风样发作综合征)

Major clinic features:

- **Stroke-like episodes**（复发性休克）
- **Encephalomyopathy**（肌病，肌阵挛，共济失调）
- **Lactic acidosis**（丙酮酸代谢障碍 → 乳酸酸中毒）
- **Sensorineural hearing loss**（感觉神经性听觉丧失）
- **Dementia**（痴呆）

Mitochondrial encephalomyopathy, lactic acidosis,and stroke-like episodes (MELAS)

- **Mutation of $tRNA^{leu/Val}$ gene causes MELAS;**
- **MELAS is heterogeneous, it can be caused by different mutations:**

  MTTL1*MELAS 3243 A →G

  MTTV*MELAS ; MTCO3

- **Heteroplasmic（*MTTL1*MELAS 3243 A →G*）**

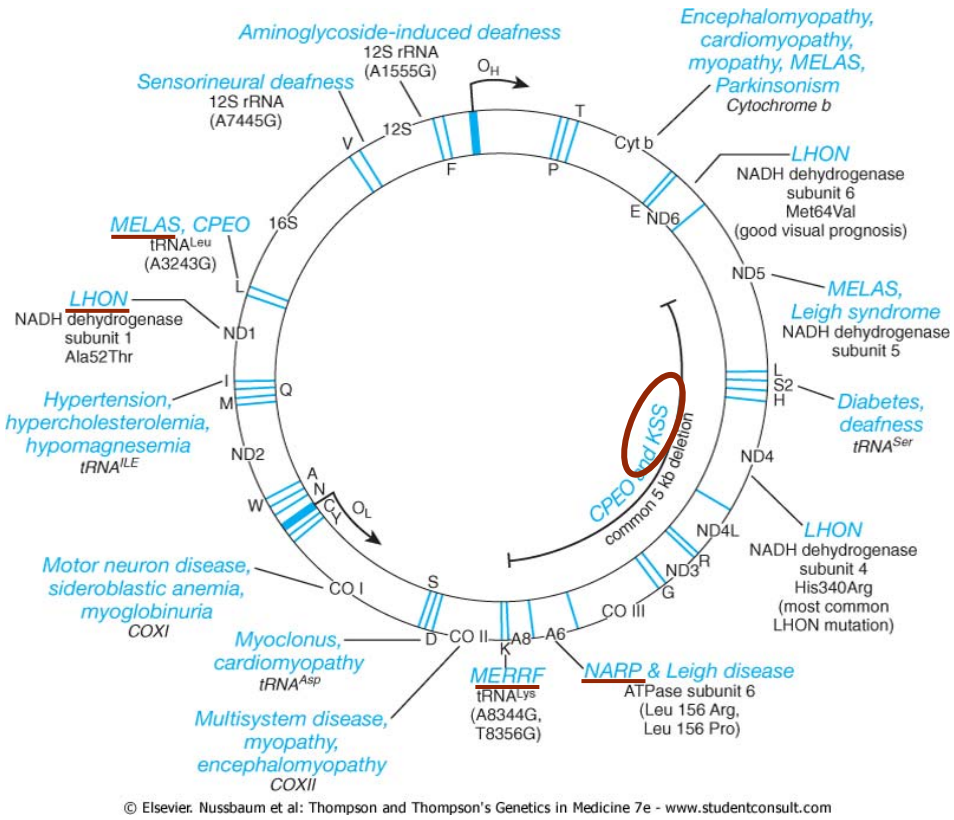
  Mutaion ≥90%:复发性休克,共济失调,痴呆

  Mutaion 40%-50%: 慢性进行性眼外肌麻痹, 肌病， 耳聋

Representative Examples of Disorders due to Mutations in Mitochondrial DNA and Their Inheritance

Disease	Phenotypes-Largely Neurological	Most Frequent Mutation in mtDNA Molecule	Homoplasmy vs. Heteroplasmy	Inheritan
Leber hereditary optic neuropathy (LHON)（Leber 遗传性视神经病	Rapid onset of blindness in young adult life due to optic nerve atrophy; some recovery of vision, depending on the mutation Strong sex bias: ~50% of male carriers have visual loss vs. ~10% of females	Substitution 1178A>G in the ND4 subunit of complex I of theelectron transport chain; this mutation, with two others, accounts for more than 90% of cases; 14459T>A, in the ND1 subunit, is the most severe mutation, with less sex bias	Largely homoplasmic	Maternal
NARP（神经病伴共济失调和视网膜色素变性）	Neuropathy, ataxia, retinitis pigmentosa; developmental delay, mental retardation, lactic acidemia	Point mutations in the ATPase subunit 6 gene	Heteroplasmic	Maternal
Leigh syndrome	Early-onset progressive neurodegeneration with hypotonia, developmental delay, optic atrophy, and respiratory abnormalities	Point mutations in the ATPase subunit 6 gene	Heteroplasmic	Maternal
MELAS （线粒体肌病脑病伴乳酸酸中毒及中风样发作综合征）	Myopathy, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; may present only as diabetes mellitus and deafness	Point mutations in $tRNA^{leu(UUR)}$, a mutation hotspot, most commonly 3243A>G	Heteroplasmic	Maternal
MERRF（肌阵挛性癫痫伴碎红纤维病）	Myoclonic epilepsy with ragged-red muscle fibers, myopathy, ataxia, sensorineural deafness, dementia	Point mutations in $tRNA^{lys}$, most commonly 8344A>G	Heteroplasmic	Maternal
Deafness	Progressive sensorineural deafness, often induced by aminoglycoside antibiotics; nonsyndromic sensorineural deafness	1555A>G mutation in the 12S rRNA gene 7445A>G mutation in the 12S rRNA gene	Homoplasmic Homoplasmic	Maternal Maternal
Chronic progressive external ophthalmoplegia (CPEO) （慢性进行性眼外肌麻痹）	Progressive atrophy of extraocular muscles, ptosis	The common MELAS point mutation in $tRNA^{leu(UUR)}$; large deletions similar to KSS	Heteroplasmic	Maternal with point mutations, sporadic with deletions
Pearson syndrome	Pancreatic insufficiency, pancytopenia, lactic acidosis, KSS in second decade	Large deletions	Heteroplasmic	Generally sporadic, due to somatic mutations
Kearns-Sayre syndrome (KSS)（慢性进行性外眼肌麻痹）	Progressive myopathy, progressive external ophthalmoplegia of early onset, cardiomyopathy, heart block, ptosis, retinal pigmentation, ataxia, diabetes	The ~5 kb large deletion	Heteroplasmic	Generally sporadic, due to somatic mutations

Mutations in mtDNA and Disease



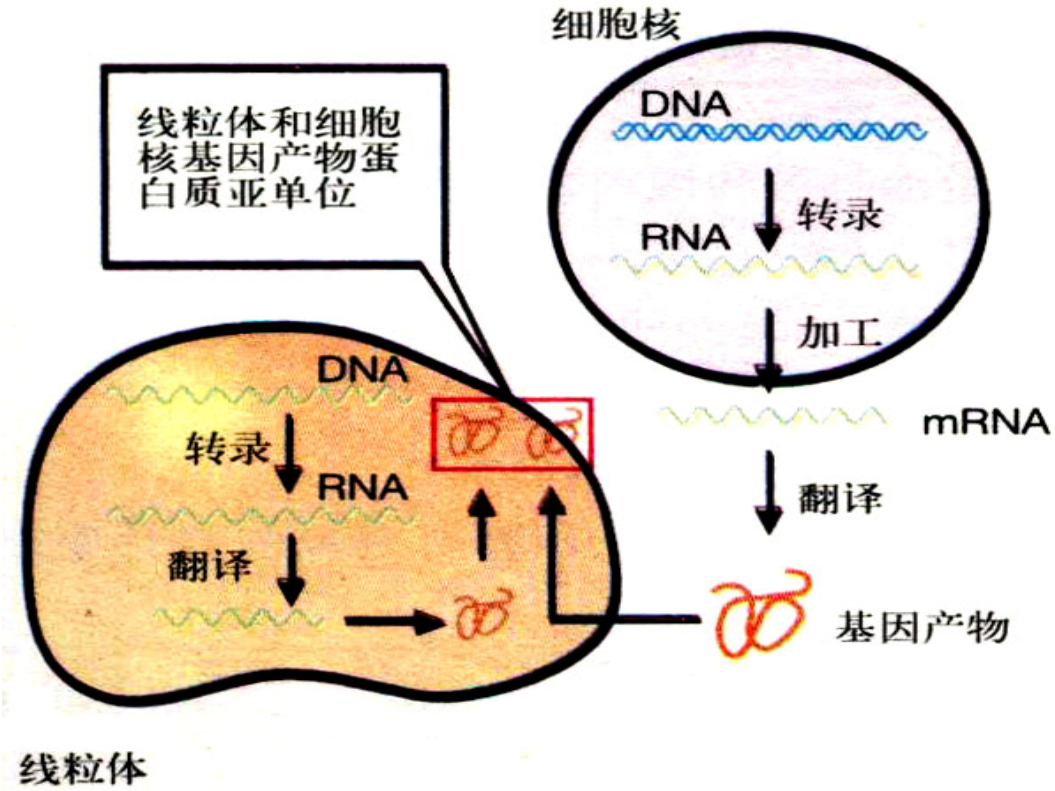
mtDNA Mutations

- Point mutation
  - *Missense mutations in oxidative phosphorylation protein*
  - *point mutations in tRNA or rRNA genes*
- Rearrangement
  - *Deletion and insertion*
- Copy number mutation

Characteristics of Mitochondrial Disorder

- Maternal inheritance;
- Quantitative threshold of mutant mtDNA in the onset of mitochondrial genetic disorders;
- Multiple energy-required system are affected;
- Asymptomatic carrier of mutant mtDNA.

Interaction between the mitochondrial and nuclear genomes



线粒体和核内基因组之间的协同作用

- 1500 mitochondrial proteins;
- 74 polypeptides of the oxidative phosphorylation complex;
- 200 factors required for the maintenance and expression of mtDNA or for the assembly of oxidative phosphorylation protein complexes.

Interaction between the mitochondrial and nuclear genomes

Mutations in many of these nuclear genes can also lead to disorders with the phenotypic characteristics of mtDNA diseases, but of course the patterns of inheritance are those typically seen with nuclear genome mutations.

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