Mitochondrial disease & Endocrine dysfunction

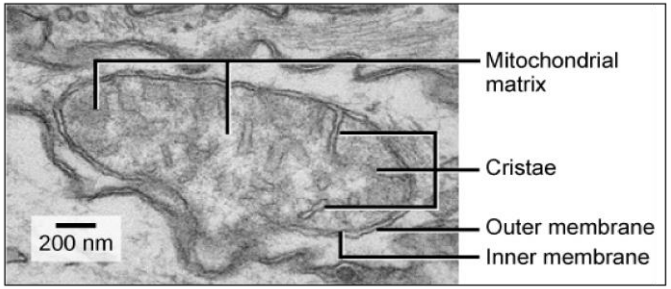
1

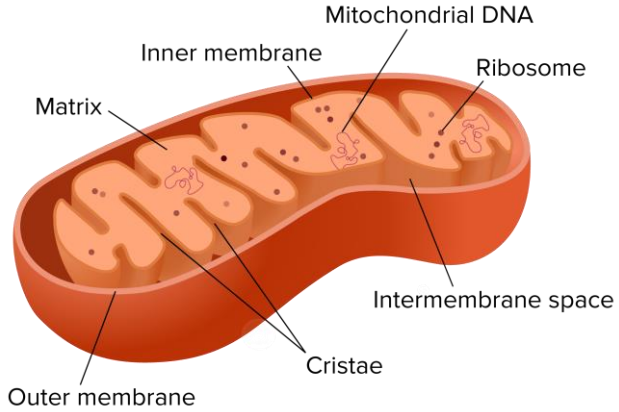
Mitochondrial disease

Mitochondria

- Present in all cells **except mature erythrocytes**
- Functions
  - **ATP production**
  - Intracellular Ca homeostasis
  - Reactive oxygen species (ROS) production
  - Apoptosis regulation
  - **Steroid hormone biosynthesis**

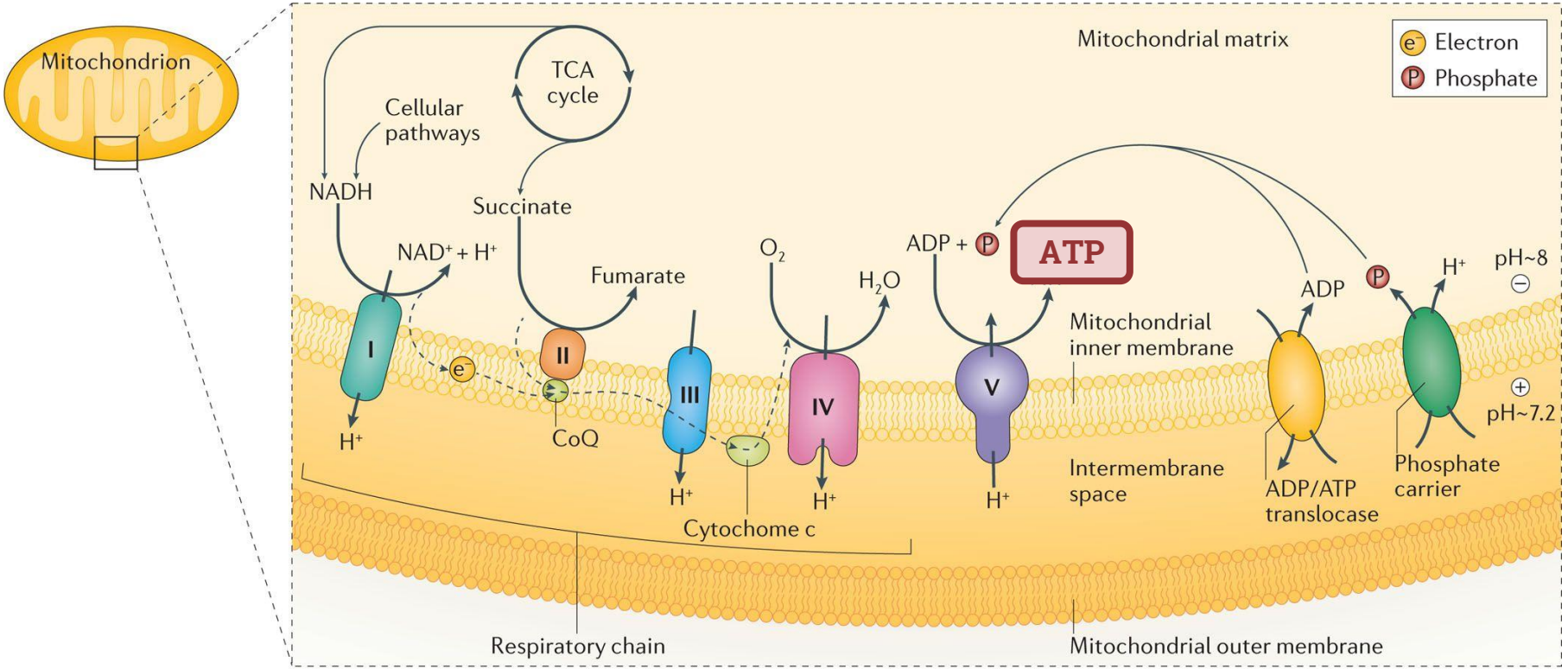
khanacademy.org





Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Oxidative phosphorylation

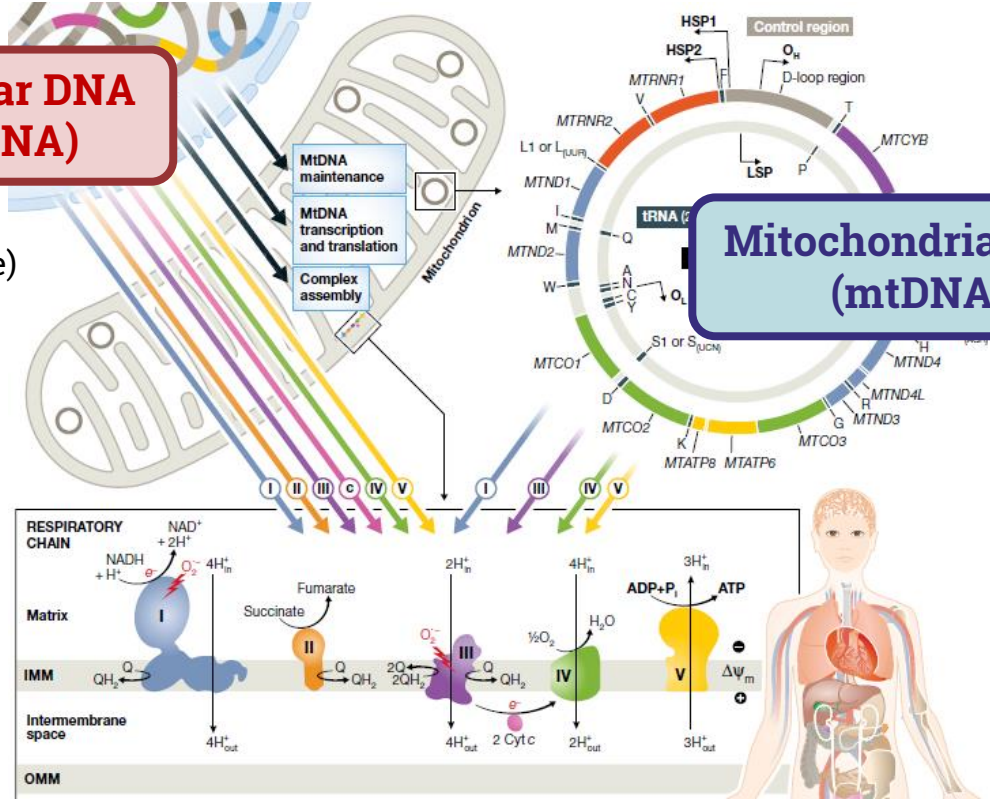


Nat Rev Dis Primers. 2016 Oct 20;2:16080.

Mitochondrial genetics

Nuclear DNA (nDNA)

~1,500 nuclear genes
(7% of the nuclear exome)



Mitochondrial DNA (mtDNA)

37 gene; found in multiple copies within the mitochondrial matrix

EMBO Mol Med. 2015 Dec;7(12):1503-12.

Mitochondrial disease

- A group of **genetic disorders** characterized by **dysfunctional mitochondria**
- ~ **1:5000** of the population
- **Clinically heterogeneous**
  - wide range of clinical symptoms
  - occur at any age
- **Often progressive** with high morbidity and mortality

Nat Rev Dis Primers. 2016 Oct 20;2:16080.
EMBO Mol Med. 2015 Dec;7(12):1503-12.

Mitochondrial disease

- **Pathogenesis**

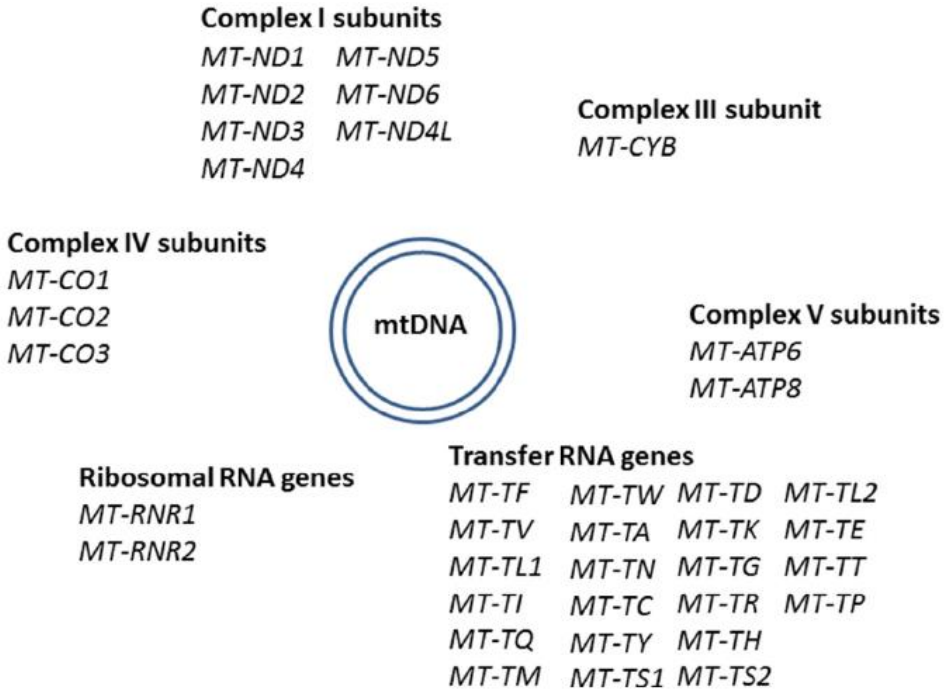
Genetic defects

- mtDNA
- nDNA

Have been found >250 monogenic defects

Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Mitochondrial DNA genes associated with mitochondrial disease



Arch Dis Child. 2017 Nov;102(11):1082-1090.

Nuclear DNA genes associated with mitochondrial disease

OXPHOS structural subunits

Complex I

NDUFS1 NDUFS2 NDUFS3 NDUFS4 NDUFS6 NDUFS7 NDUFS8 NDUFV1 NDUFV2 NDUFA1 NDUFA2 NDUFA9 NDUFA10 NDUFA11 NDUFA12 NDUFA13 NDUFB3 NDUFB9 NDUFB11

Complex II

SDHA SDHB SDHC SDHD

Complex III

UQCRB UQCRQ CYC1 UQCRC2

Complex IV

COX4I2 COX6A1 COX6B1 COX7B COX8A NDUFA4

Complex V

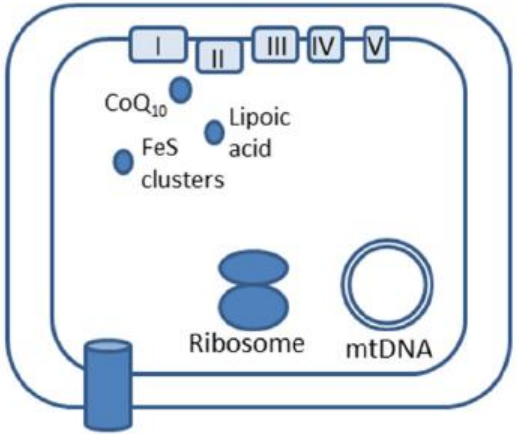
ATP5E ATP5A1

Membrane function, lipid metabolism, dynamics, import

TAZ AGK SERAC1 MFN2 OPA1 GDAP1 DNM1L MFF STAT2 YME1L AIFM1 TIMM8A TIMM50 DNAJC19 GFER SLC25A3 SLC25A4 SLC25A12 SLC25A13 SLC25A19 SLC25A22 SLC25A25 SLC25A26 SLC25A32 SLC25A40 SLC25A42 SLC25A46 MICU1 QIL1 MPC1

Inhibitors

ETHE1 HIBCH ECHS1 TXN2



Cofactor biosynthesis

PDSS1 PDSS2 COQ2 ADCK3 ADCK4 COQ4 COQ6 COQ7 COQ9 BOLA3 LIAS LIPT1 GLRX5 IBA57 ISCU ISCA2 FXN FDX1L NFU1 ABCB7 SFXN4 LYRM4 NFS1 TPK1 MECR FLAD1 NADK2 NAXE

Mitochondrial translation

ELAC2 PUS1 MTO1 TRMU GTPBP3 TRIT1 TRMT5 TRMT10C HSD17B10 NSUN3 TRNT1 PNPT1 MRPS7 MRPS16 MRPS22 MRPS23 MRPL3 MRPL12 MRPL44 GFM1 GFM2 TSFM TUFM AARS2 CARS2 DARS2 EARS2 FARS2 HARS2 IARS2 LARS2 MARS2 NARS2 PARS2 RARS2 SARS2 TARS2 VARS2 YARS2 QRSL1 GARS KARS MTFMT MTPAP LRPPRC TACO1 C12orf65 RMND1

OXPHOS assembly factors

Complex I

NDUFAF1 NDUFAF2 NDUFAF3 NDUFAF4 NDUFAF5 NDUFAF6 FOXRED1 ACAD9 NUBPL TMEM126B

Complex II

SDHAF1 SDHAF2

Complex III

BCS1L HCCS TTC19 UQCC2 LYRM7

Complex IV

SURF1 SCO1 SCO2 COX10 COX14 COX15 COX20 COA5 COA6 COA7 FASTKD2 PET100 CEP89

Complex V

ATPAF2 TMEM70

mtDNA maintenance

POLG POLG2 TWNK TYMP DGUOK TK2 RRM2B SUCLA2 SUCLG1 MPV17 FBXL4 DNA2 MGME1 ABAT RNASEH1 SAMHD1

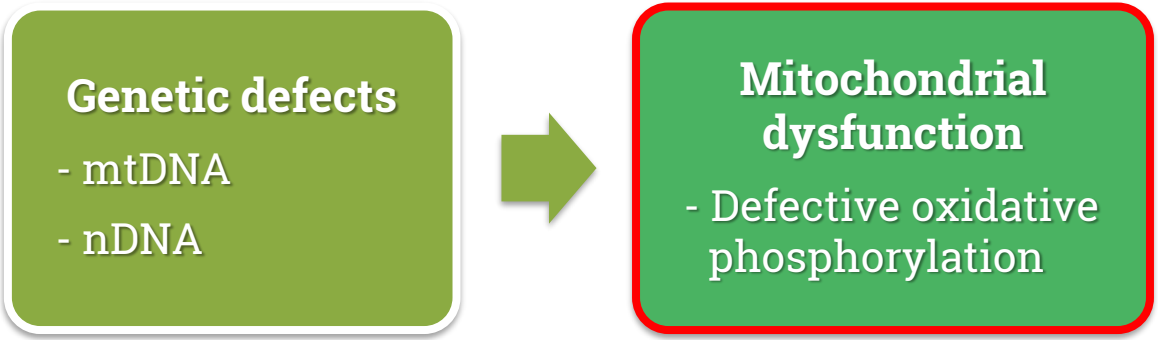
Others

TMEM126A SPG7 HSPD1 AFG3L2 TRAP1 DARS LARS NNT POP1 APOPT1 CLPB CLPP LONP1 CHCHD10 OPA3

Arch Dis Child. 2017 Nov;102(11):1082-1090.

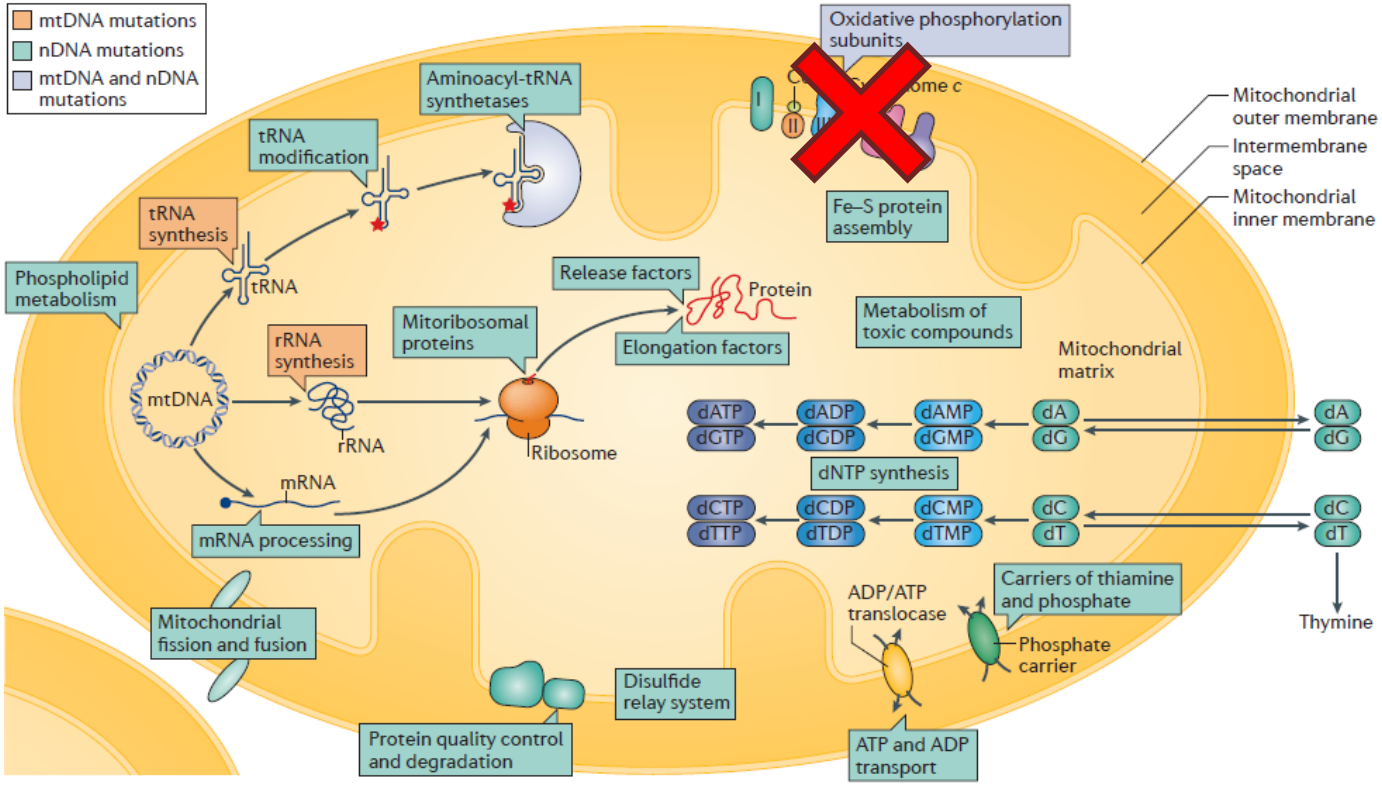
Mitochondrial disease

- **Pathogenesis**



Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Role of mDNA and nDNA in mitochondrial function



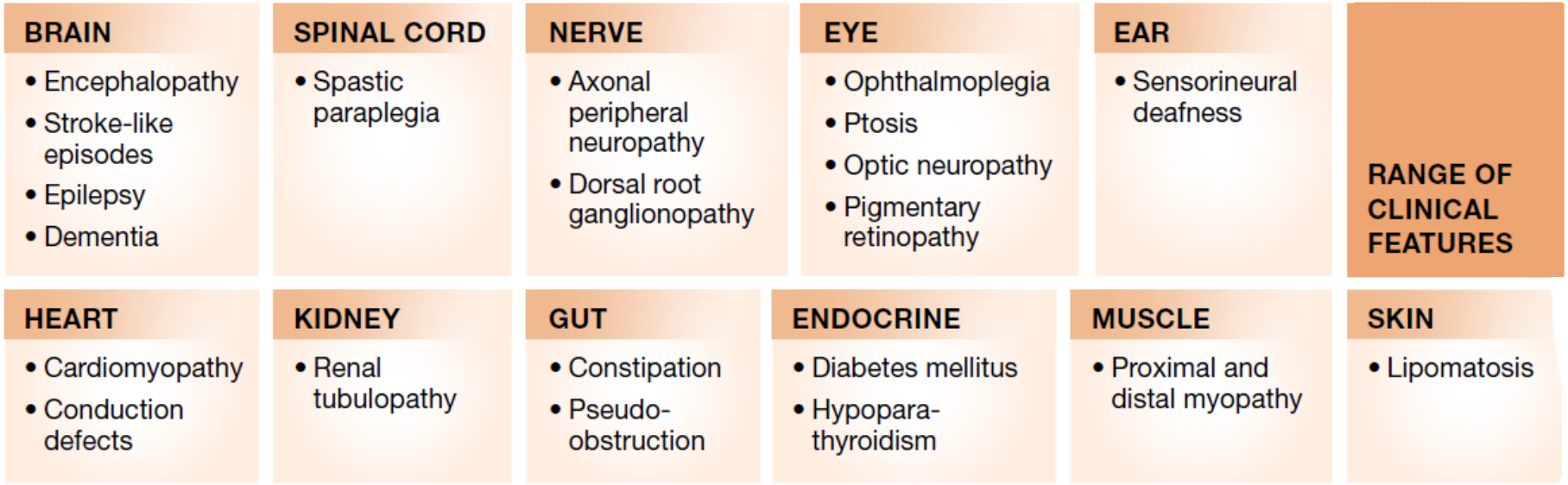
Nat Rev Dis Primers. 2016 Oct 20;2:16080.

Mitochondrial disease

- **Pathogenesis**

Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Clinical features of mitochondrial disease in adults



Affecting organs that are highly dependent on aerobic metabolism

EMBO Mol Med. 2015 Dec;7(12):1503-12.

Mitochondrial disease

- **Mode of inheritance**

mtDNA mutations

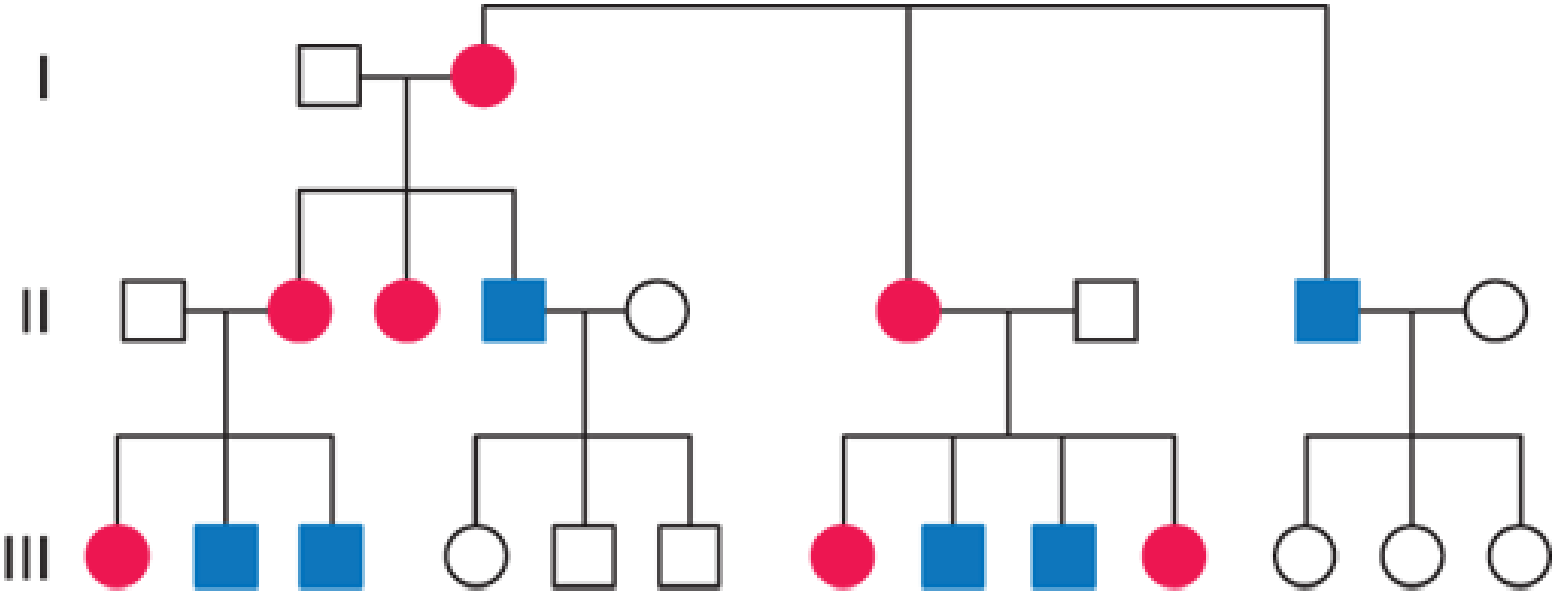
- Maternally inherited
- Sporadic

nDNA mutations

- Autosomal recessive (most frequent)
- Autosomal dominant
- X-linked

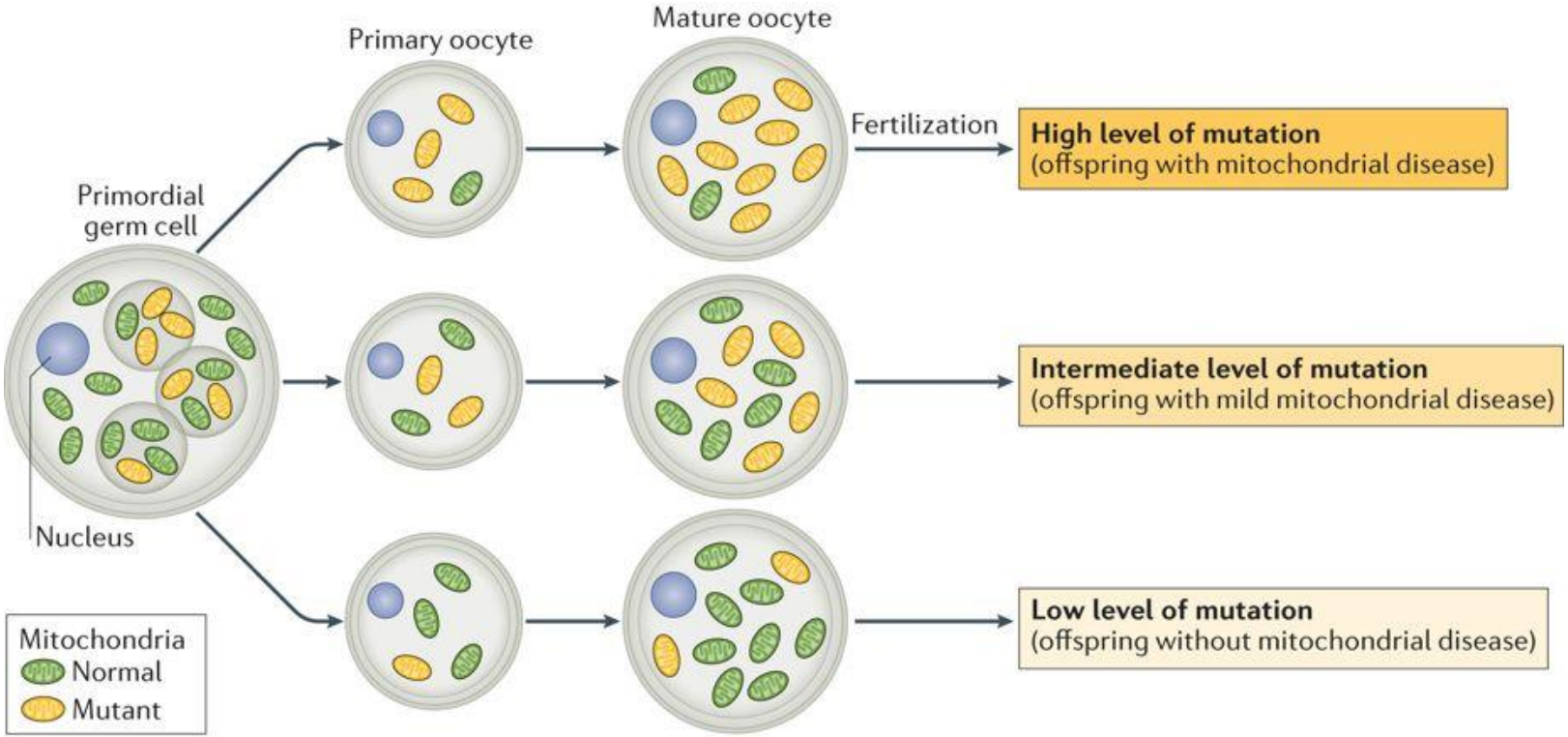
Nat Rev Dis Primers. 2016 Oct 20;2:16080.

Maternal inheritance of mitochondrial DNA



Harrison's Principles of Internal Medicine, 20th Edition

Heteroplasmy



Nat Rev Dis Primers. 2016 Oct 20;2:16080.

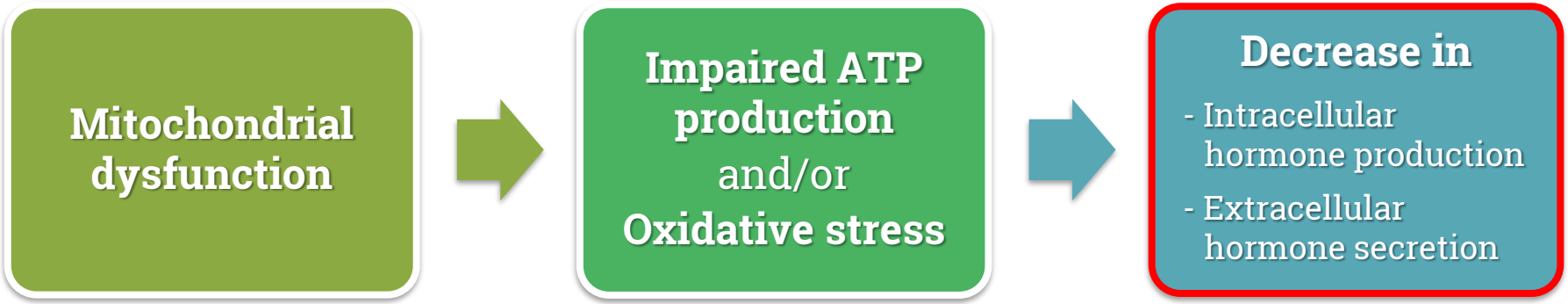
2

Endocrine dysfunction

in mitochondrial diseases

Endocrine dysfunction
in mitochondrial diseases

- **All steroid hormones** are synthesized within mitochondria



Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Endocrine dysfunction
in mitochondrial diseases

- **Most frequently** in syndromes associated with **large-scale mitochondrial DNA rearrangements**
  - mtDNA deletion syndromes
  - mtDNA point mutations affecting tRNA genes
- Endocrine abnormalities **+ Multisystemic disease**
- **Can be the presenting feature** of mitochondrial diseases (can precede neurological symptomatology)

Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Mitochondrial diseases that endocrine dysfunction is commonly described

Mitochondrial syndromes	Clinical phenotype	Associated gene defects	Inheritance
Kearns–Sayre syndrome (KSS)	Progressive external ophthalmoplegia, retinitis pigmentosa, cardiomyopathy, heart block	mtDNA deletion	Usually sporadic
Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)	Stroke-like episodes < 40 years, seizures, migraine, cognitive decline, lactic acidosis, childhood onset muscle weakness	*MT-TL1* (m.32423A>G in 80% of patients) and other mtDNA point mutations	Maternal
Maternally inherited diabetes and deafness (MIDD)	Diabetes mellitus, deafness	*MT-TL1* (m.3243A>G)	Maternal
Pearson syndrome	Sideroblastic anemia, pancytopenia, exocrine pancreatic dysfunction	mtDNA deletion	Usually sporadic
Perrault syndrome	Premature ovarian failure, sensorineural hearing loss	*C10orf2, CLPP, HARS2, LARS2*	AR

Adapted from : Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Mitochondrial diseases that endocrine dysfunction is uncommonly described (1)

Mitochondrial syndromes	Clinical phenotype	Associated gene defects	Inheritance
Alpers–Huttenlocher	Infantile onset of developmental delay or regression, intractable epilepsy, with or without liver failure	*POLG, FARS2, NARS2, PARS2*	AR
Leber hereditary optic neuropathy	Optic neuropathy	mtDNA point mutations (most commonly m.11778G>A, m.3460G>A and m.14484T>C)	Maternal
Leigh syndrome	Subacute relapsing encephalopathy of infantile onset	>75 genes	Maternal, AR, X-linked
mtDNA depletion syndromes	Hepatocerebral, myopathic and encephalopathic variants	*POLG, DGUOK, MPV17, C10orf2, TK2, SUCLA2, SUCLG1, RRM2B, FBXL4, MGME1*	AR
Myoclonic epilepsy myopathy sensory ataxia (MEMSA)	Myopathy, seizures, cerebellar ataxia	*POLG*	AR
Myoclonic epilepsy with ragged-red fibres (MERRF)	Myoclonus, seizures, cerebellar ataxia, myopathy	*MT-TK* (m.8344A>G) and other mtDNA point mutations, *POLG*	Maternal, AR

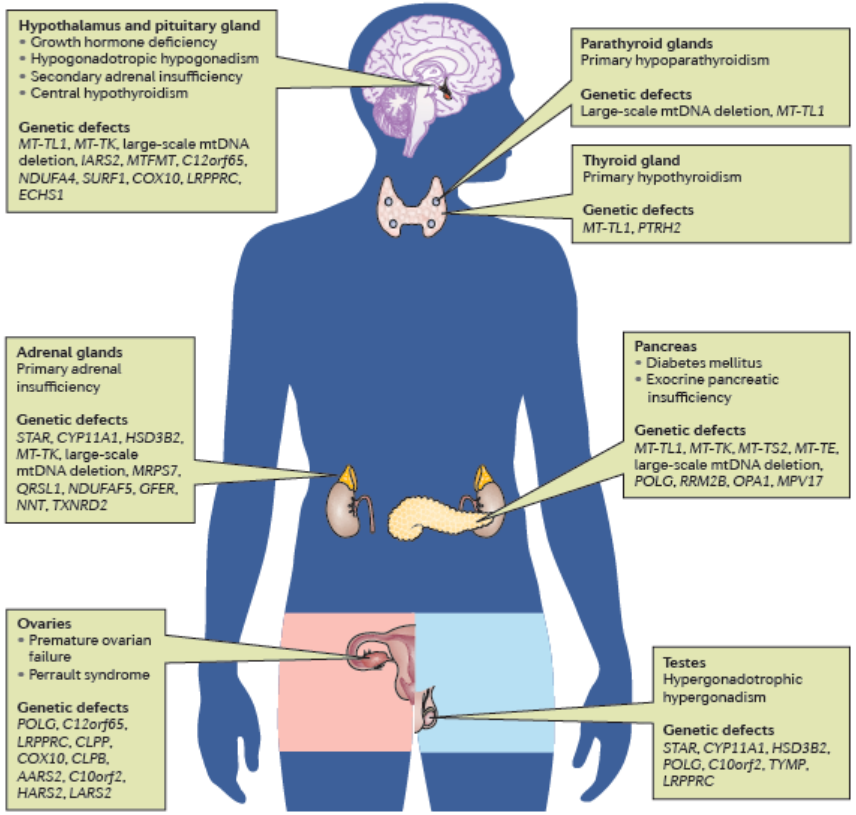
Adapted from : Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Mitochondrial diseases that endocrine dysfunction is uncommonly described (2)

Mitochondrial syndromes	Clinical phenotype	Associated gene defects	Inheritance
Mitochondrial neurogastrointestinal encephalopathy (MNGIE)	Progressive gastrointestinal dysmotility, ophthalmoplegia, leukoencephalopathy, peripheral neuropathy	*TYMP* (similar symptoms might occur with *POLG, RRM2B, MT-TL1 or MT-TV* mutations)	AR, maternal
Neurogenic weakness with ataxia and retinitis pigmentosa (NARP)	Late childhood or adult onset peripheral neuropathy, ataxia, retinopathy	*MT-ATP6* (most commonly m.8993T>G/C)	Maternal
Progressive external ophthalmoplegia (PEO)	Progressive external ophthalmoplegia with or without skeletal myopathy	mtDNA deletions or mtDNA mutations *(POLG, C10orf2, RRM2B, SLC25A4)*	Sporadic, maternal, AD
Sensory ataxia, neuropathy, dysarthria, ophthalmoparesis (SANDO)	Ataxia, peripheral neuropathy, eye movement disorders, epilepsy, cognitive impairment, psychiatric symptoms, involuntary movements (part of ataxia neuropathy spectrum)	*POLG, C10orf2, OPA1*	AR

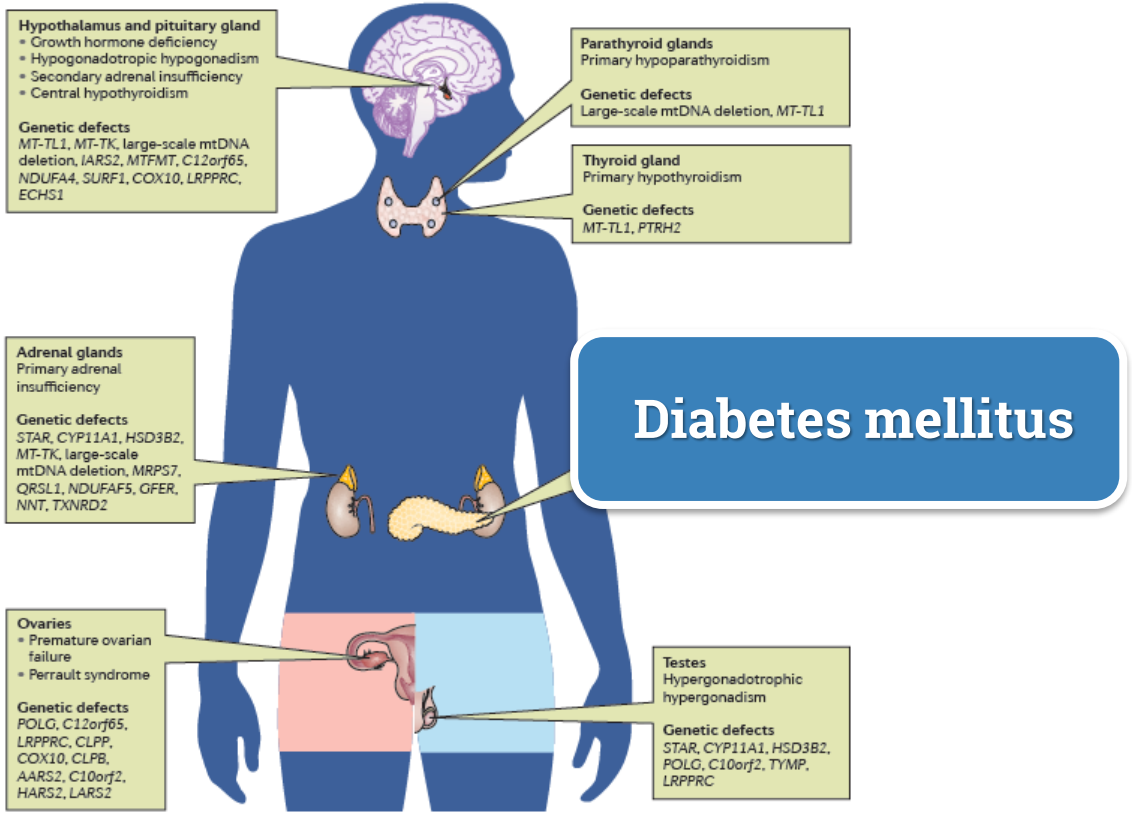
Adapted from : Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Endocrine dysfunction in mitochondrial disease



Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Endocrine dysfunction in mitochondrial disease



Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Diabetes mellitus

- **Well recognized**
- **Present insidiously at any age**
  - Early-onset mtDNA deletion (Pearson syndrome)

    neonatal period up to 21 months
  - m.3243A>G mutation (MIDD)

    11-68 years (average 38 years)
  - Other mutations

    40-56 years

Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Diabetes mellitus

- **Combined insulin deficiency** and **insulin resistance**
  - Clinical symptoms of type 1 or type 2 diabetes
  - **High risk of progression to insulin dependency** (ranging 4.2-10 years after diagnosis)
- **Pancreatic exocrine insufficiency** : Pearson syndrome
- **Treatment**
  - Drug of choice : **sulfonylurea, insulin**
  - **Avoid** : metformin, pioglitazone (worsen lactic acidosis)

Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

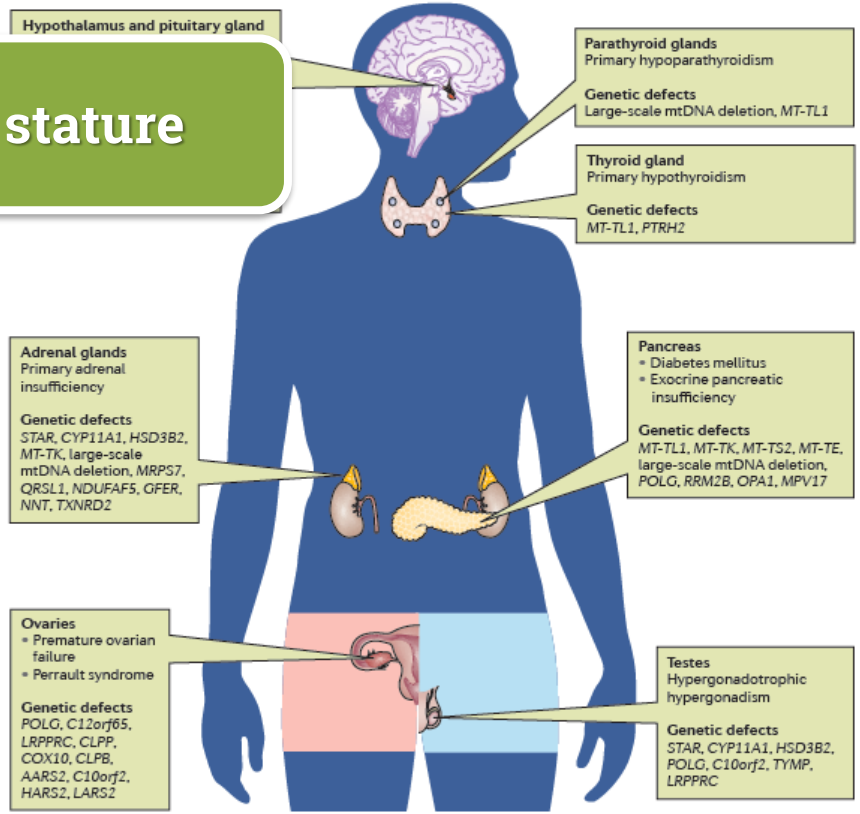
Gene defects associated with endocrine manifestations in mitochondrial disease

Endocrine manifestation	Gene defects	Inheritance mode	Molecular mechanism
Diabetes mellitus	*MT-TL1, MT-TK, MT-TS2, MT-TE*	Maternal	Impaired translation
	Large-scale mtDNA deletion	Sporadic	Impaired translation
	POLG, RRM2B, OPA1, MPV17	Autosomal dominant or Autosomal recessive	Impaired mtDNA maintenance

Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Endocrine dysfunction in mitochondrial disease

Short stature



Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Short stature

- **Common**
  - MELAS: 60% in juvenile-onset, 29% in adult-onset
  - KSS: 38-63%
- **Cause**
  - **Growth hormone deficiency**
  - **Unknown**
- **Low BMI**

Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Short stature

- **Treatment : GH therapy (in GHD)**
  - **Variable efficacy**
  - **Used with caution**

    Few reports of hypotonia, loss of language and memory, cerebellar ataxia, and pyramidal signs after 3 months of treatment → improved with discontinuation of the therapy

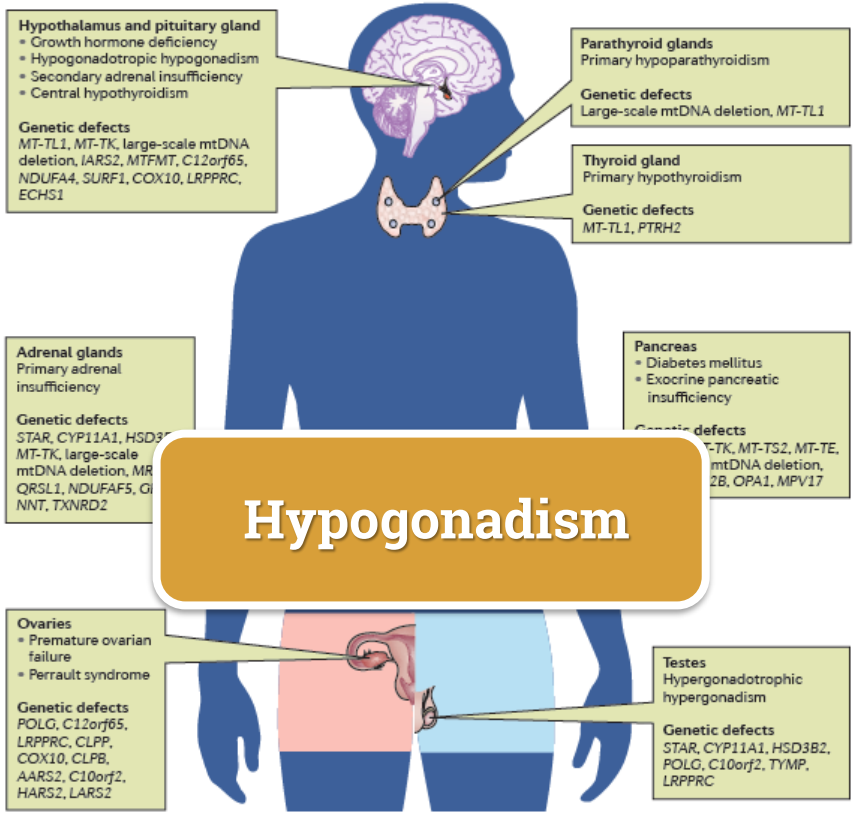
Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Gene defects associated with endocrine manifestations in mitochondrial disease

Endocrine manifestation	Gene defects	Inheritance mode	Molecular mechanism
Short stature and growth hormone insufficiency	*MT-TL1, MT-TK*	Maternal	Impaired translation
	Large-scale mtDNA deletion	Sporadic	Impaired translation
	IARS2, MTFMT, C12orf65	Autosomal recessive	Impaired translation
	NDUFA4, SURF1, COX10, LRPPRC	Autosomal recessive	Impaired complex IV
	ECHS1	Autosomal recessive	Oxidative stress

Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Endocrine dysfunction in mitochondrial disease



Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Hypogonadism

- **Various mitochondrial disorders**
  - **Hypogonadotropic** hypogonadism
    e.g., MELAS, MERRF, KSS
  - **Hypergonadotropic** hypogonadism
    e.g., Perrault syndrome, MNGIE, Leigh syndrome
- **Presentations**
  - **Primary or secondary amenorrhea**
  - **Delayed pubertal onset**
  - **Infertility**

Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Gene defects associated with endocrine manifestations in mitochondrial disease

Endocrine manifestation	Gene defects	Inheritance mode	Molecular mechanism
Hypogonadotropic hypogonadism	*MT-TL1*, *MT-TK*	Maternal	Impaired translation
	Large-scale mtDNA deletion	Sporadic	Impaired translation
	TYMP	Autosomal recessive	Impaired mtDNA maintenance
Hypergonadotropic hypogonadism	*STAR*, *CYP11A1*, *HSD3B2*	Autosomal recessive	Impaired mitochondrial steroidogenesis
testes	*C10orf2*, *POLG*, *TYMP*	Autosomal recessive	Impaired mtDNA maintenance
	LRPPRC, *MRPS7*, *AARS2*	Autosomal recessive	Impaired translation

Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

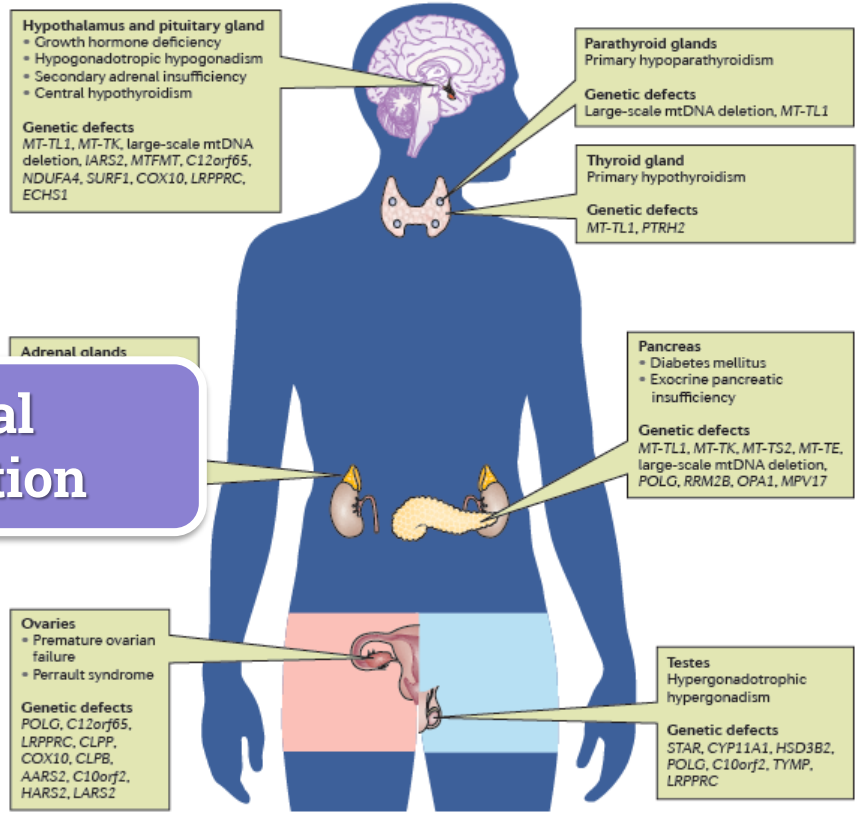
Gene defects associated with endocrine manifestations in mitochondrial disease

Endocrine manifestation	Gene defects	Inheritance mode	Molecular mechanism
Premature ovarian failure or premature menopause	*POLG*	Autosomal dominant or Autosomal recessive	Impaired mtDNA maintenance
	C12orf65, *LRPPRC*	Autosomal recessive	Impaired translation
	COX10	Autosomal recessive	Impaired complex IV assembly
	CLPB	Autosomal recessive	Impaired mitochondrial quality control
Perrault syndrome (ovarian dysgenesis and sensorineural hearing loss)	*C10orf2*	Autosomal recessive	Impaired mtDNA maintenance
	HARS2, *LARS2*	Autosomal recessive	Impaired translation
	CLPP	Autosomal recessive	Impaired mitochondrial quality control

Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Endocrine dysfunction in mitochondrial disease

Adrenal dysfunction



Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Adrenal dysfunction

- **Primary adrenal insufficiency**
  e.g., mtDNA deletion e.g., KSS, Pearson syndrome
- **Secondary adrenal insufficiency (rarely)**
  one report in a patient with MERRF
- **Presentation** : **only glucocorticoid deficiency**
- **Age at onset** : ranging from 7 months to 32 years

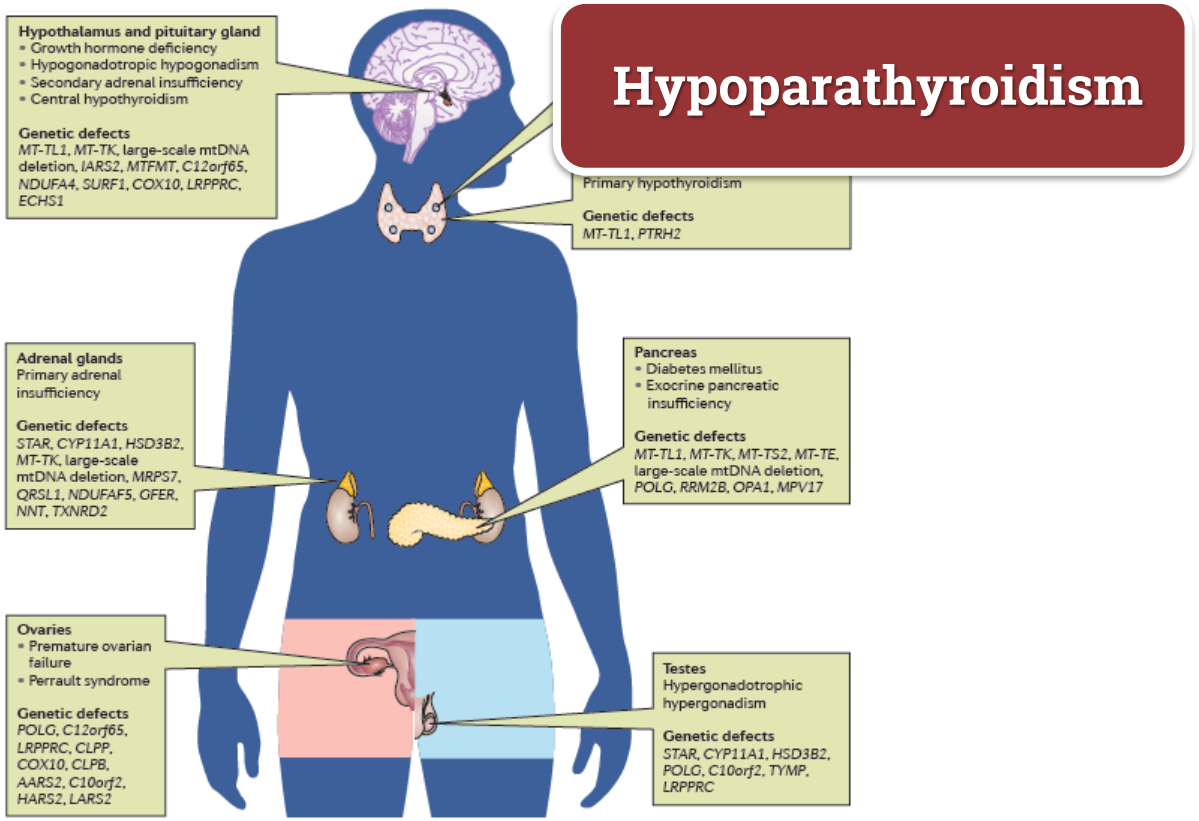
Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Gene defects associated with endocrine manifestations in mitochondrial disease

Endocrine manifestation	Gene defects	Inheritance mode	Molecular mechanism
Adrenal insufficiency	*STAR*, *CYP11A1*, *HSD3B2*	Autosomal recessive	Impaired mitochondrial steroidogenesis
	Large-scale mtDNA deletion	Sporadic	Impaired translation
	MT-TK	Maternal	Impaired translation
	MRPS7, *QRSL1*	Autosomal recessive	Impaired translation
	NDUFAF5	Autosomal recessive	Impaired complex I assembly
	GFER	Autosomal recessive	Impaired mitochondrial import
	NNT, *TXNRD2*	Autosomal recessive	Oxidative stress

Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Endocrine dysfunction in mitochondrial disease



Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Hypoparathyroidism

- **Uncommon**
- **Reported in patients with**
  - KSS : 6-9%
  - MIDD (m.3243A>G mutation in *MT-TL1*) : 1 report
- **Presentation** : Hypocalcemic tetany
- **Age of onset** : 6-13 years
- **Associated with severe multisystem disease** and often seen **in combination with other endocrinopathies**

Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Hypoparathyroidism

- **Renal tubulopathy (more common)**
  - Urinary loss of Ca, K, and Mg
  - KSS and other mitochondrial disorders

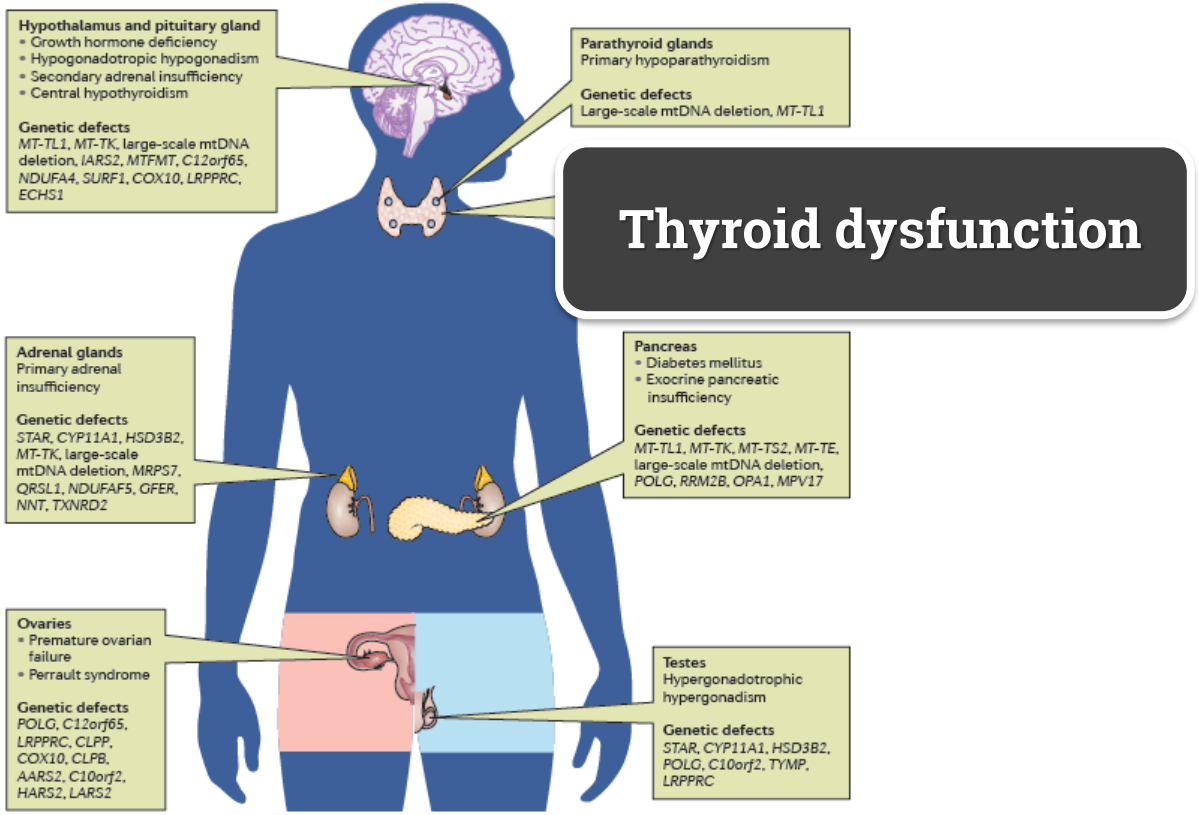
Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Gene defects associated with endocrine manifestations in mitochondrial disease

Endocrine manifestation	Gene defects	Inheritance mode	Molecular mechanism
Hypoparathyroidism	Large-scale mtDNA deletion	Sporadic	Impaired translation
	MT-TL1	Maternal	Impaired translation

Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Endocrine dysfunction in mitochondrial disease



Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Thyroid dysfunction

- **Infrequently reported**
  - Heterogeneous group of patients e.g., late-onset CPEO, mtDNA deletions (e.g., KSS), nuclear-encoded mitochondrial defects
- **Inadequate data**
  - Unknown causal relationship between mitochondrial disease and thyroid dysfunction

Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Thyroid dysfunction

- **Types of thyroid dysfunction**
  - Compensated hypothyroidism
  - Multinodular goiter
  - Congenital thyroid malformation
  - Papillary carcinoma
  - Central hypothyroidism (in a patient with MELAS)

Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Gene defects associated with endocrine manifestations in mitochondrial disease

Endocrine manifestation	Gene defects	Inheritance mode	Molecular mechanism
Hypothyroidism	*MT-TL1*	Maternal	Impaired translation
	PTRH2	Autosomal recessive	Impaired translation

Nat Rev Endocrinol. 2017 Feb;13(2):92-104.

Take home message : Short stature in KSS

- Common
- Can be the presenting feature of the syndrome
- GH therapy
  - In a patient with GH deficiency
  - Variable efficacy
  - Cautiously used
- Always looking for other associated conditions

References

1. Gorman GS, Chinnery PF, DiMauro S, et.al. Mitochondrial diseases. Nat Rev Dis Primers. 2016 Oct 20;2:16080.
2. Chow J, Rahman J, Achermann JC, et.al. Mitochondrial disease and endocrine dysfunction. Nat Rev Endocrinol. 2017 Feb;13(2):92-104.
3. Chinnery PF. Mitochondrial disease in adults: what's old and what's new? EMBO Mol Med. 2015 Dec;7(12):1503-12.
4. Davison JE, Rahman S. Recognition, investigation and management of mitochondrial disease. Arch Dis Child. 2017 Nov;102(11):1082-1090.

Thank you