mtDNA disease: recurrence risks & reproductive strategies

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overview

- mitochondrial disorders & oxidative phosforylation
  - what-where-how ?
- recurrence risks & appropriate genetic counseling
- future prospects & summary

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mitochondrial disorder (1) ?

- single organ or multisystem disease
- dysfunction of oxidative phosphorylation system (OXPHOS)
- clinically very heterogeneous condition, affecting patients
  - at any age (early in infancy or in late adulthood),
  - in any tissue or organ
  - mild or severe phenotype

mitochondrial disorder (2) ?

- often even fatal outcome
- incidence of mt cytopathies
  - 1/5.000 affected with mt disorder
  - >1/200 carriership in life births

: investigation in UK of 10 frequent mtDNA mutations

(Gorman 2015, Chinnery & Taylor in 2000 & 2008, Thornburn 2003)

mitochondrial disorder (2) ?

- no cure(s) yet
  - early phase trials and clinical studies are in progress
  - Idebenone is licensed in Europe for LHON
  - Taurine is licensed in Japan for Melas

- most therapy or treatment only supportive (ptosis, cardio, diabetes, epilepsy…)

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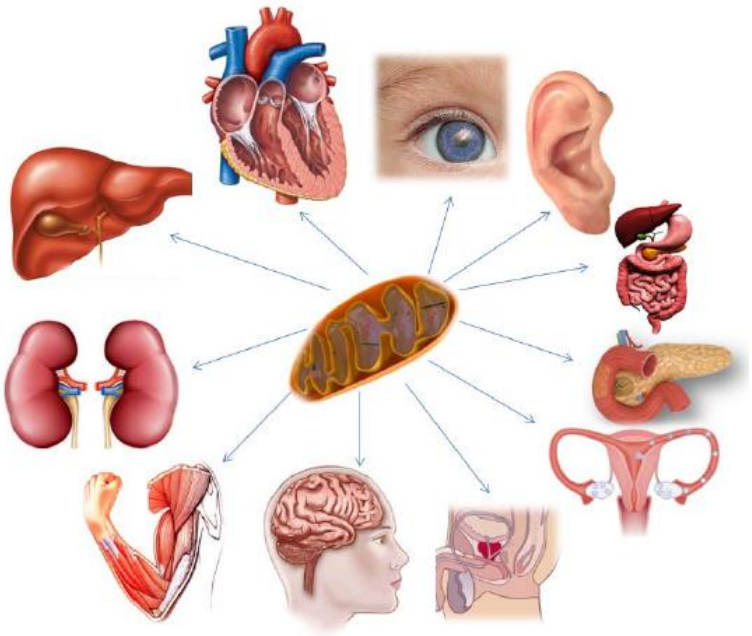
illustration of clinical diversity

might include, but not limited to

- migraine
- deafness
- blindness
- diabetes
- cardiac problems
- epilepsy
- seizures
- dysphagia
- ophthalmoplegia



- respiratory failure
- myopathy
- neuropathy
- gastrointestinal dysmotility
- liver failure
- bone marrow dysfunction
- …..

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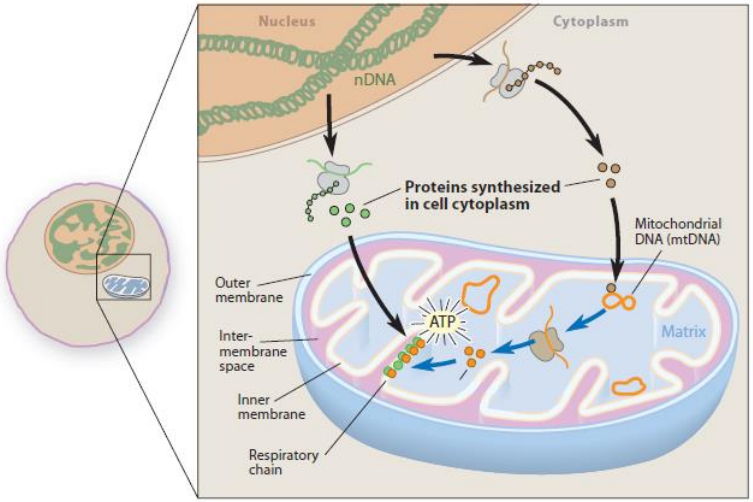
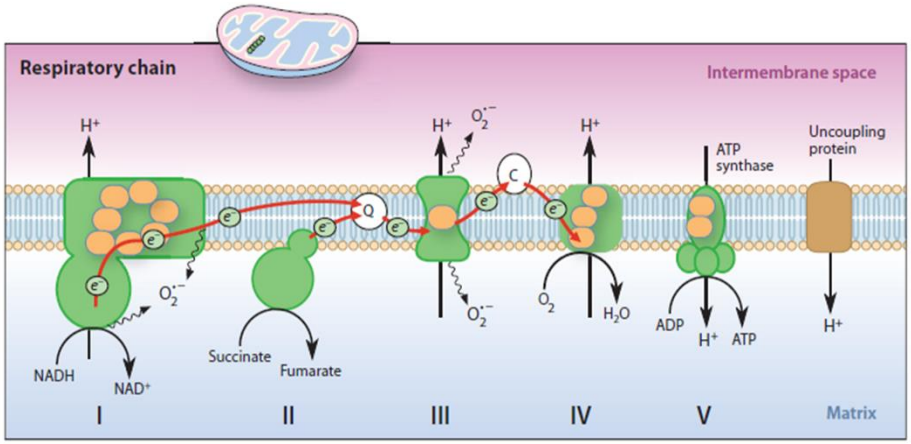
short overview OXPHOS pathway

largest generator of ATP





mitochondria harbour a small genome: **mtDNA**

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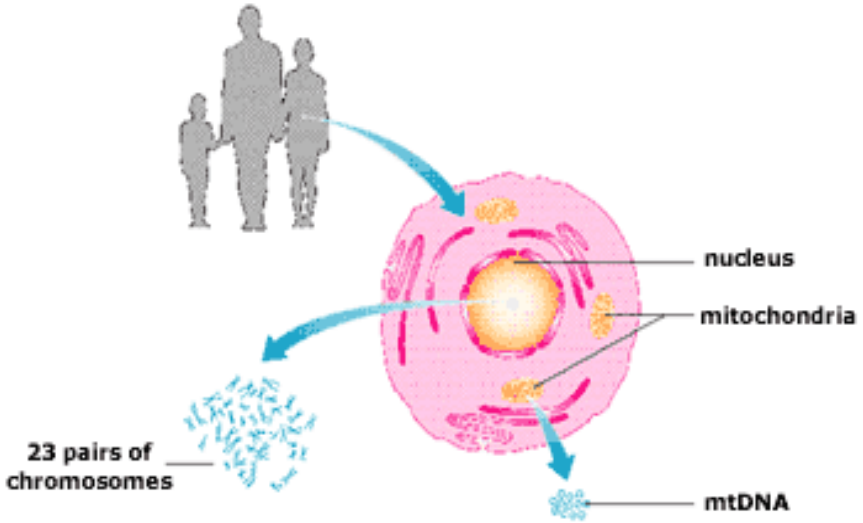
genetics of mt diseases (1)

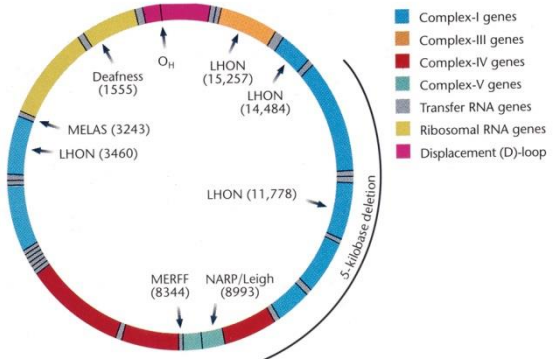
molecular causes of OXPHOS **problems** are **dual** :

- **nuclear DNA**: 3 10^9 bp

versus

- **mtDNA**: 16 569 bp
  - small double stranded molecule
  - only 37 genes
  - essential to OXPHOS





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genetics of mt diseases (2)

- recurrence risks of **mtDNA mutations**
  - ➢ **maternal inheritance**

- recurrence risk for nuclear encoded gene mutations ➢ Mendelian rules for dominant, recessive and X-linked inheritance

unique characteristics of mtDNA

- polyploid genome
- maternal inheritance
- homoplasmic/heteroplasmic
- treshold level
- random mitotic segregation
- high mutation rate (polymorf)
- bottleneck concept

polyploid : multicopy genome

- ⇔ nuclear genome
- multiple mtDNA copies/cell
- # dependent of cell type & energy demand

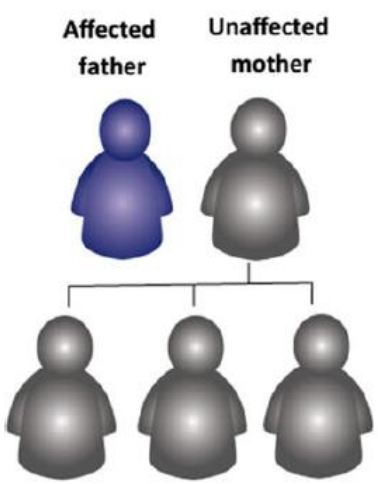
  e.g. sperm cell: ± 10-100 mtDNA molecules

  e.g. oocytes : ±1-3.10^5 mtDNA molecules

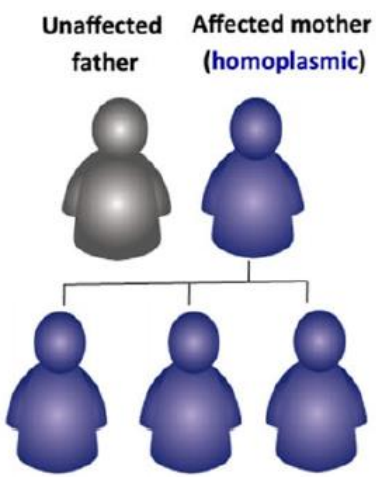
  average cell : ± 10^3-10^4 mtDNA molecules

strict maternal inheritance

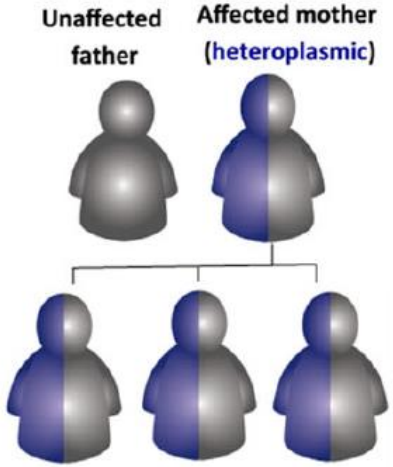
only maternal contribution from oocyte,
no paternal contribution from sperm cell



No affected children



All affected children (assuming complete penetrance)



Children may be affected or unaffected (depending on level of heteroplasmy, which can vary between children)

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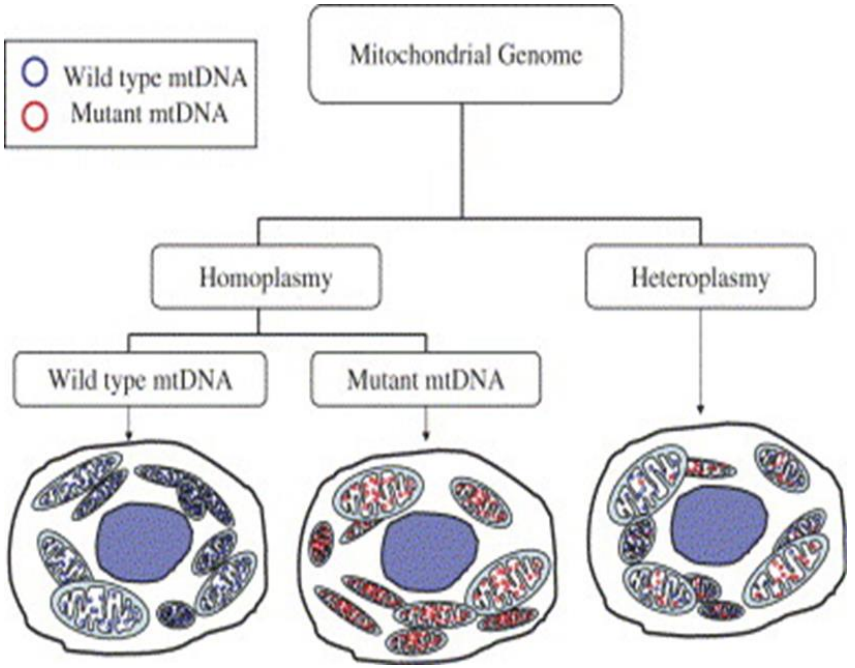
fate of father's mitochondria

- active elimination of sperm mtDNA in zygote
  - ubiquitinated & targeted for distruction
  - mitophagy

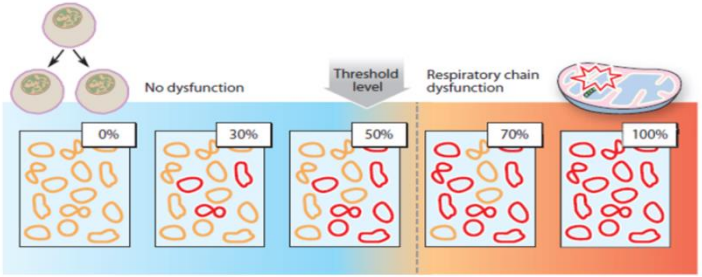
- paternal transmission
  - extremely rare & results probably from defect
    - Schwartz & Vissing 2002
    - Luo 2018

definition homo/heteroplasmy

- presence of **identical** mtDNA molecules or **WT** or **variant**
- presence of **different types** (sequence) of mtDNA molecules



Heteroplasmy can vary



- ≠ **tissues** in 1 individual
- ≠ **cells** of same tissue in 1 individual
- changes with **time** in 1 individual
- (strong) impact on cell fie >> **treshold**
  - dependant of **tissue/organ**
  - dependant of **age** of individual
  - dependant of **mutation**
  - dependant of **haplogroup**
- blood levels often << post-mitotic tissues

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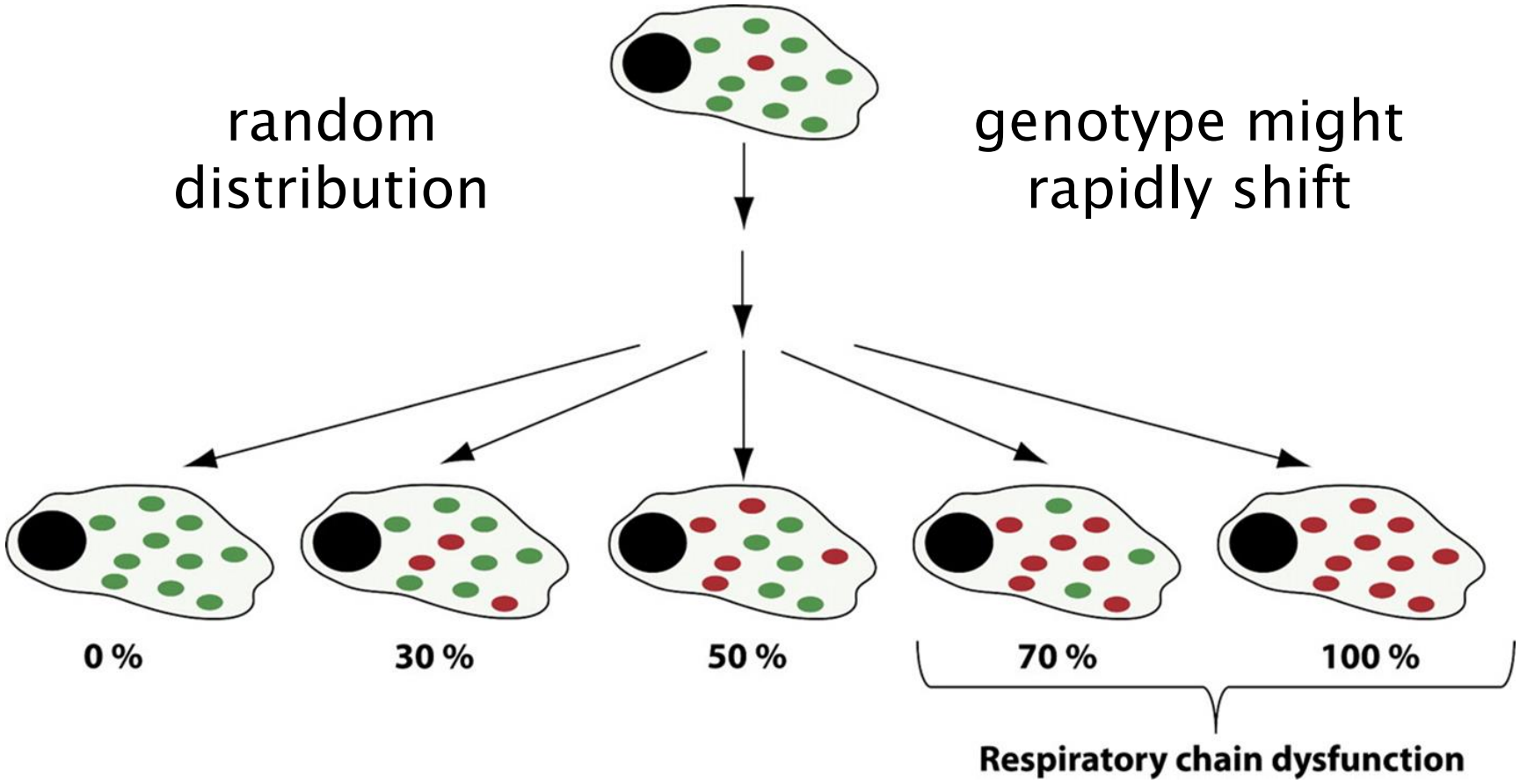
mitotic segregation of mtDNA



unique characteristics of mtDNA

- polyploid genome
- maternal inheritance
- homoplasmic/heteroplasmic
- treshold level
- random mitotic segregation
- high mutation rate (polymorf)
- genetic bottleneck concept

genetic bottleneck concept

- **transmission** across generations ➢ **no fit** with random genetic drift model
- **hypothesis** for rapid **shift** in **genotype** in successive generations
- exact mechanism in all details ?
  - ➢ 3 models were proposed

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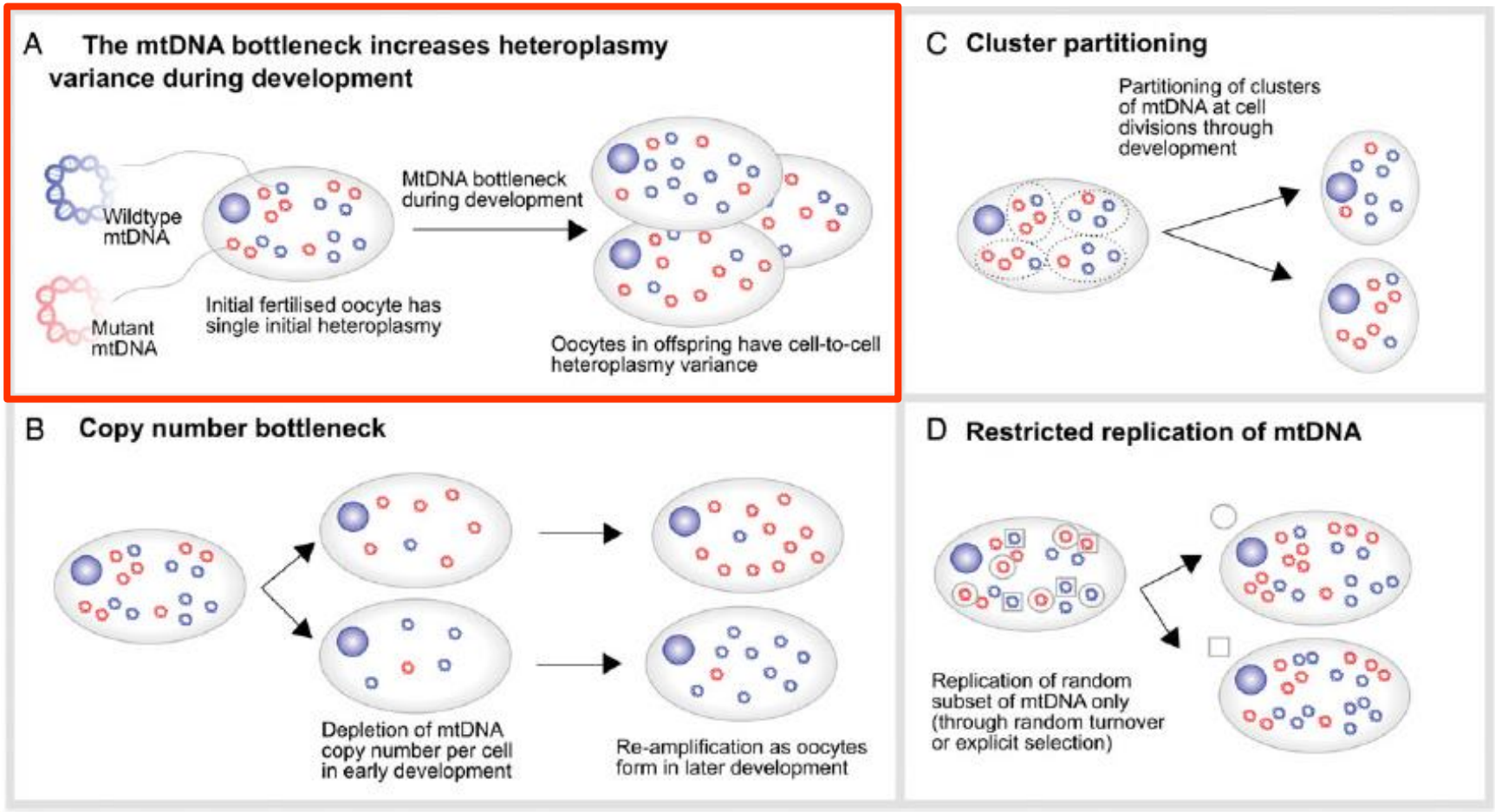
genetic bottleneck concept

- **hypothesis**:
  - Cree et al. 2008: ↓↓ in # mtDNAs in oocytes during early embryonic development
  - Cao et al. 2007: no ↓ in # mtDNAs in oocytes
    - random segregation of mtDNA clusters
  - Wai et al. 2008: no ↓ in # mtDNAs
    - replication of subset of mtDNAs

genetic bottleneck concept



Burgstaller 2015

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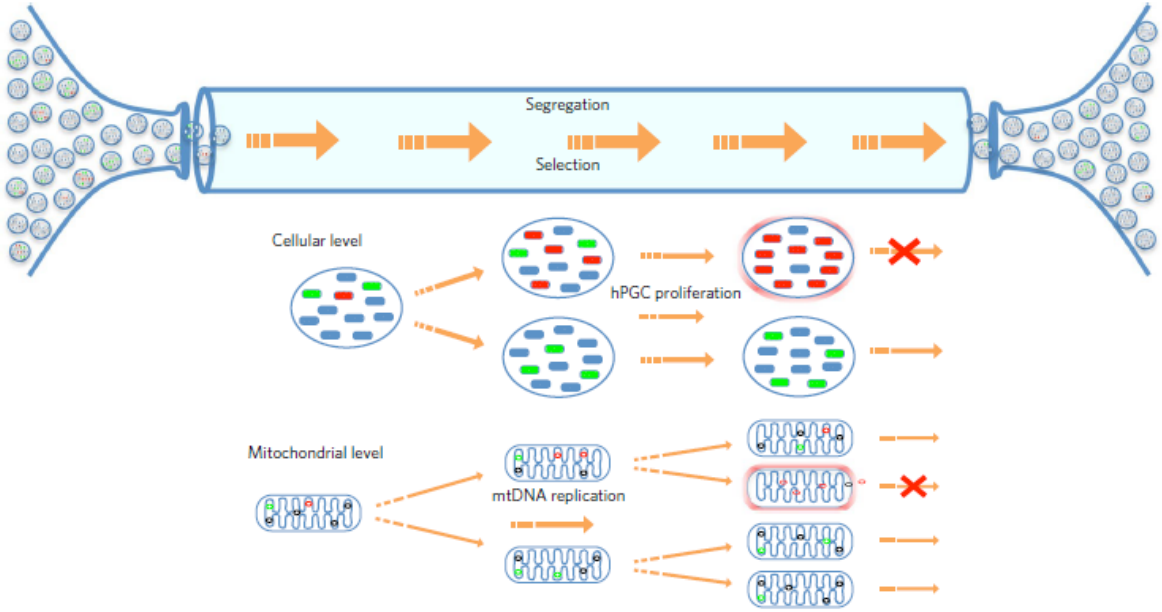
genetic bottleneck concept➢

Floros et al. 2018 : copy number bottleneck

- ➢ human embryos
- ➢ reduction ➢ 5 mtDNA molecules / mitochondrion



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mtDNA disease

defects of mtDNA

- **(large) rearrangements**
  - deletions
  - duplications
  - insertions
- **point mutations**
- scattered over the **whole genome**
  (protein coding and synthesizing genes)

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mtDNA disease

characteristics of mtDNA inheritance

&

no cure, limited therapy and no effective treatment

⇩

knowledge of **risk assessment** and prevention of transmission of disease

is **very important** for **counseling** of families & prevention of birth of an (other) affected child

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recurrence risk determination

5 ≠ situations

1. ***de novo*** mutations : single deletions
2. ***homoplasmic*** mutation : e.g. LHON
3. ***stable*** mutation + ***predictable*** outcome : e.g.m.8993T>G for narp/LS.
4. ***unstable*** mutation + ***unpredictable*** outcome : e.g.m.3243A>G melas
5. ***unknown*** outcome : any private/family-specific mutation

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de novo mutations

e.g. a large single mtDNA deletion

nearly always sporadic ? …<1% but …? ?

- systematic study of 226 families in 7 centers (Chinnery 2004)
- unaffected mothers ➢ very unlikely to have another affected child (no case)
- affected mothers ➢ 3/73 ➢ recurrence risk of ≈ 4%
- no influence of maternal age

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homoplasmic mutation

e.g. LHON

(**L**eber **H**ereditary **O**ptic **N**europathy)

- (sub)acute bilateral loss central vision
  - ➢ 15 - 35y (young adults)
- degeneration retinal ganglion cells
- incidence ➢ ≈12/100.000
- pathogenesis is unclear

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Leber Hereditary Optic Neuropathy

- 3 frequent pathogenic variants (m.11778G>A (*MTND4*), m.3460G>A (*MTND1*), or m.14484T>C (*MTND6*)) : ≈ 95% of cases
- majority patients **homoplasmic**
- strong gender bias ➢ 80% ♂ patients
- incomplete penetrance (in a family)
  - ➢ 50% of ♂ & (only) 10% ♀ affected

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Leber Hereditary Optic Neuropathy

(homoplasmic mutation)

- all offspring will be homoplasmic
  - PND or PGT is not useful

- incomplete penetrance
  - sex selection, an option ?
    - ♀ embryos/fetuses
    - still 10% residual risk

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criteria for ‘mitochondrial’ PND (1)

3. *stable* mutation + *predictable* outcome
4. *unstable* mutation + *unpredictable* outcome
5. *unknown* outcome

potential for **PND** ? ➢ **criteria** defined

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criteria for ‘mitochondrial’ PND (2)

- (i) close **correlation** between the level of mutant load and disease severity
- (ii) uniform **distribution** of mutant mtDNA in all tissues
- (iii) **no change** in mutant load with **time**

Poulton & Turnbull 2000

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questions for PND ?

is mutation load

- CV sample **representative** other villi ? all fetal tissue ?
- **idem** for amniotic cells ?
- **constant** during development, **now** (fetal) ?
- **constant** during development, **later** (adult) ?

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stable mutation + *predictable* outcome

e.g. **m.8993 T>G mutation**

- common in Leigh syndrome (>90% load)
- Narp (70-80% load)

  neuropathy, ataxia, retinitis pigmentosa (with muscle weakness, seizures, MR, …)
- 'rapid segregation' (only 1 generation)
- '*de novo*' families

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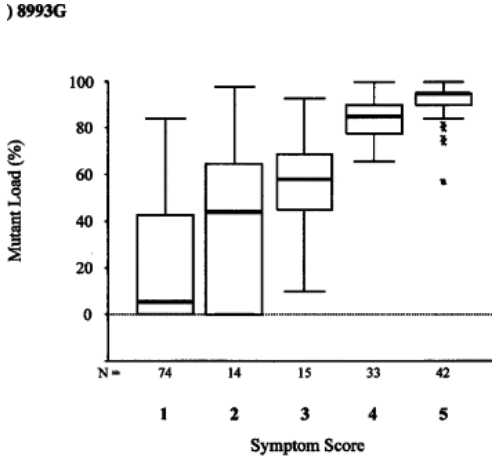
m.8993T>G mutation

check criteria ?

- tissue-dependent variation ↓
- age-dependent variation ↓
- genotype - phenotype correlation

excellent



White et al. 1999

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m.8993T>G mutation : PND ?

- affected fetuses 8 wk & 11 wk & 12 wk
- variety of fetal tissues: placenta, brain, muscle, limb, lung, heart, spinal cord, liver, kidney investigated

results:

equal distribution of mutation load

&

comparable to chorionic villi

A.Harding

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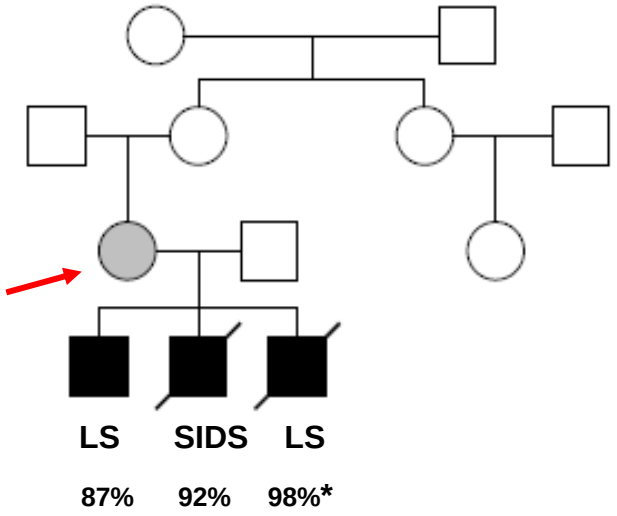
m.8993T>G mutation : oocytes ?

woman 50% m.8993T>G in leukocytes

study of oocytes

- total of 8 oocytes
  - 1 lost for analysis
  - 6 load >95%
  - 1 no mutation detected



Blok et al. 1997

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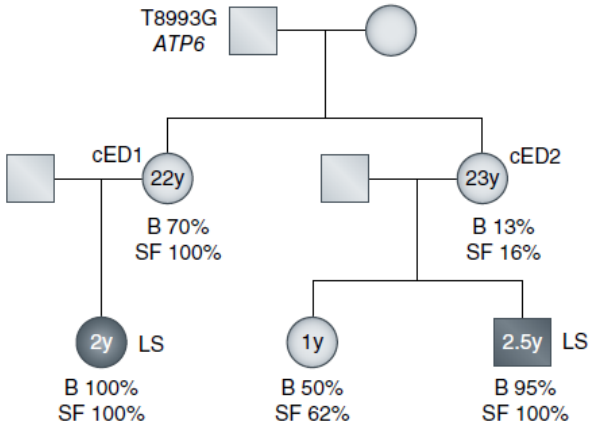
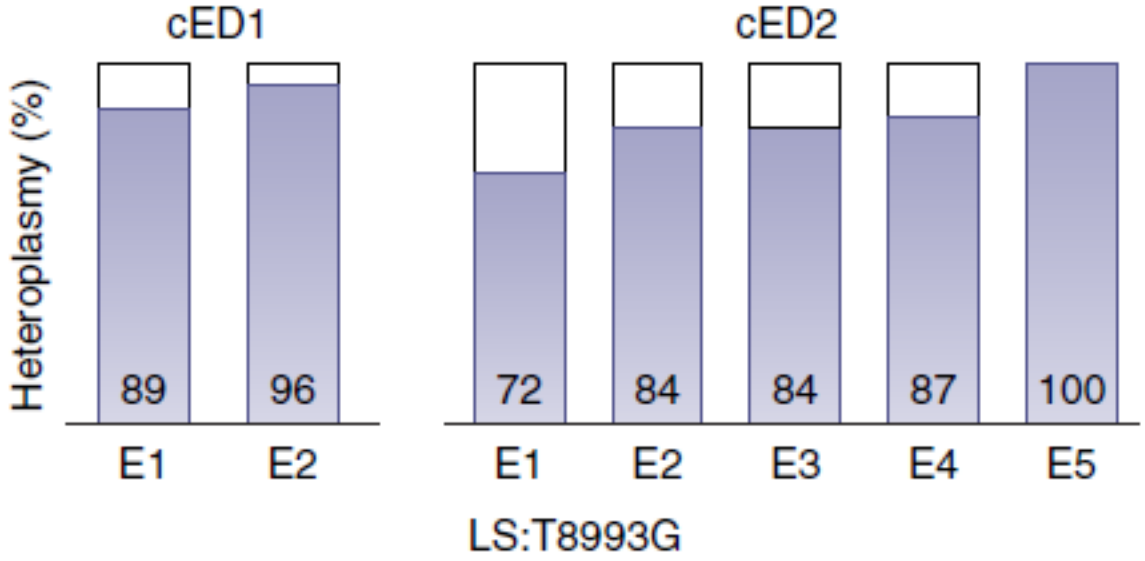
m.8993T>G mutation : oocytes ?



woman 1
B 70%

woman 2
B 13%



Kang et al. 2016

unstable mutation + *unpredictable*

e.g. classical m.3243A>G melas

check criteria ?

- **poor** geno - phenotype **correlation**
- mutation **load differs** among tissues
- mutation load **changes in time**

no good

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unstable mutation + *unpredictable*

'unpredictability' of **m.3243A>G** is illustrated:

- load changes in leukocytes over time
- load in oocytes
- load in placenta samples
- load in ≠ tissues of 1 fetus
- transmission: mother – child - siblings

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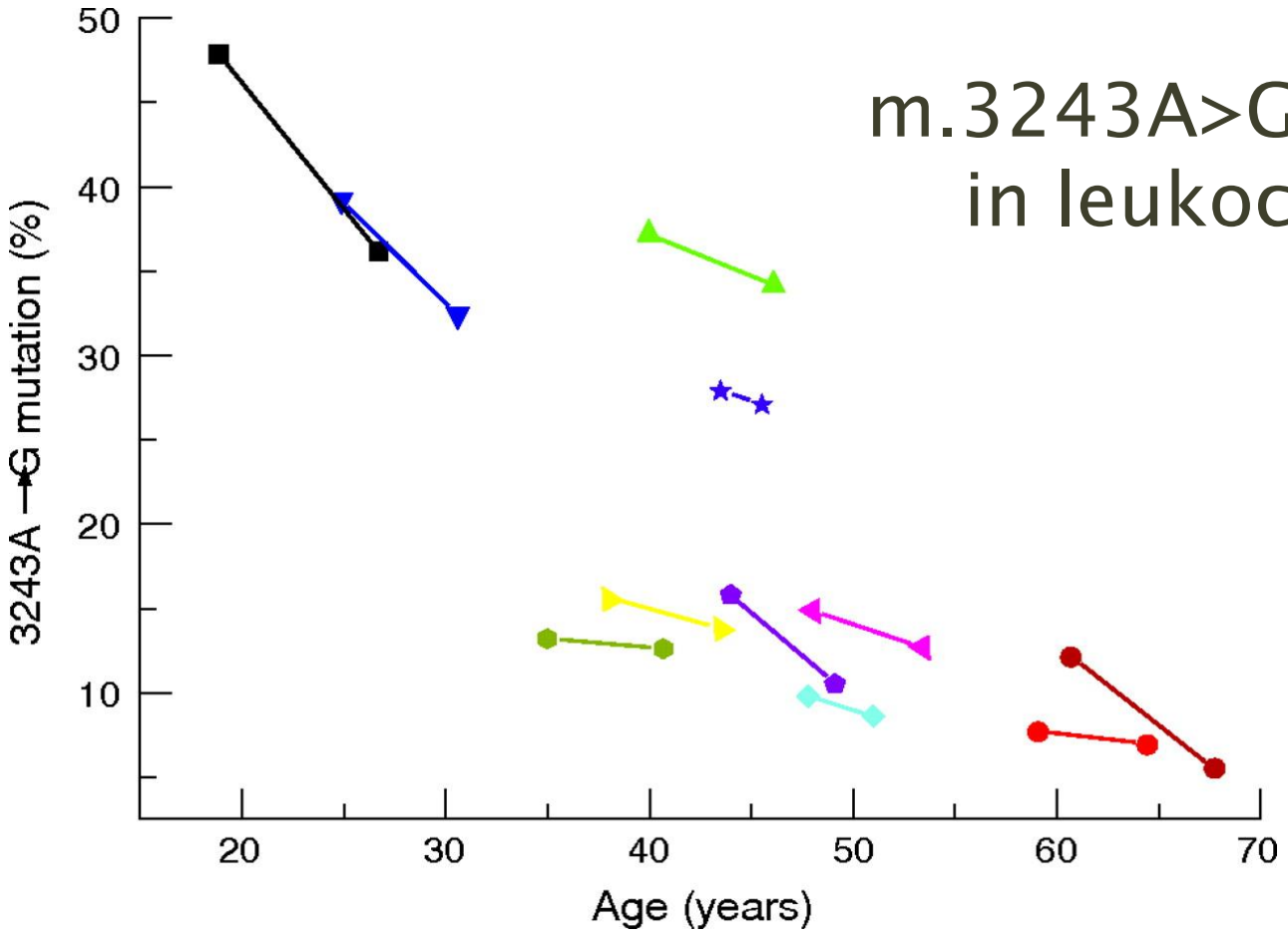
mutation load changes in time



m.3243A>G melas in leukocytes

Pyle et al. 2007

Langdahlet al. 2018

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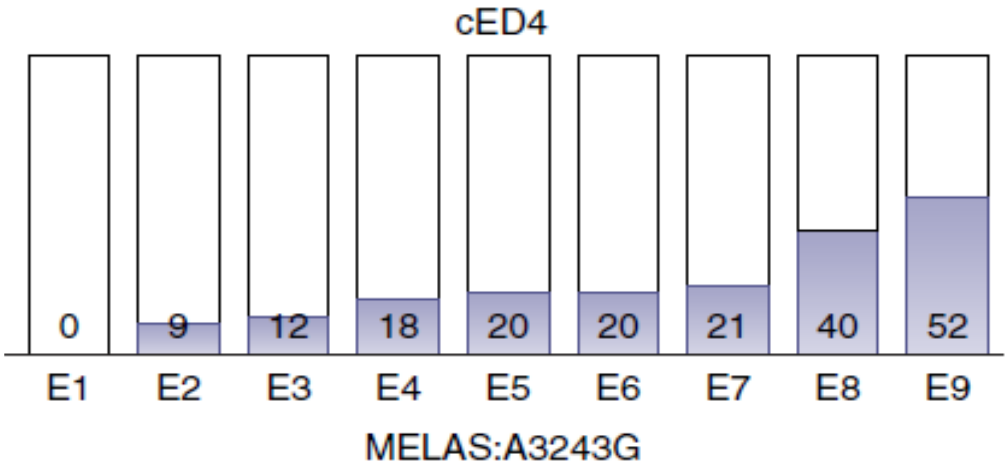
m.3243A>G melas : oocytes

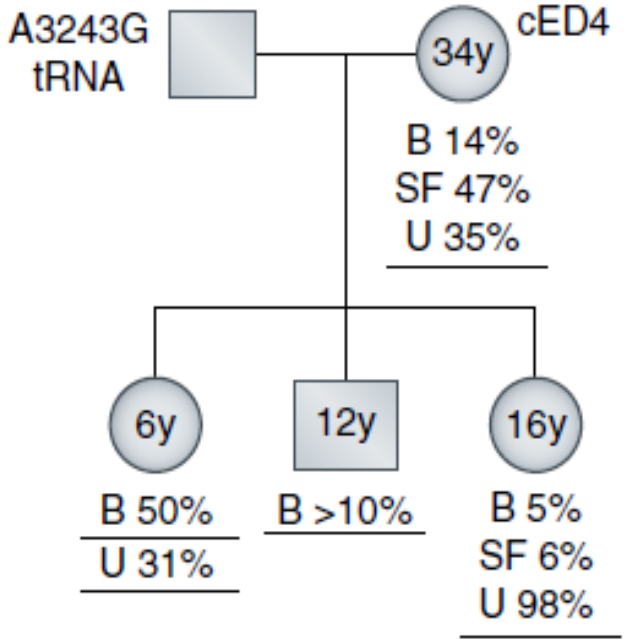
34y old woman

B 14%

U 35%

➢ 9 oocytes investigated





Kang et al. 2016

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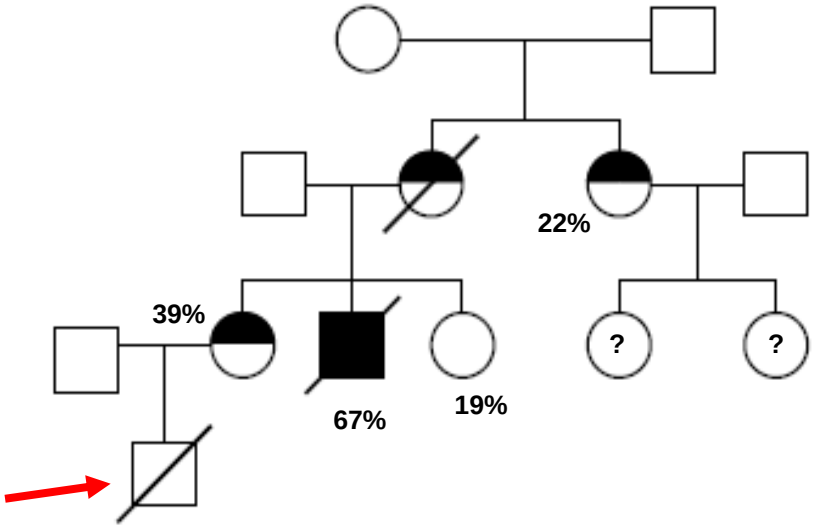
m.3243A>G melas : fetus

fibroblasts: 51%
brain: 52%
optic nerve: 51%
heart: 54%
muscle: 55%
gut: 53%
liver: 52%
kidney: 56%
placenta: 55%
tissue ≈ : 53%

stillborn fetus 24w



Matthews et al. 1994

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inheritance m.3243A>G mutation

study of de Laat et al. 2012
analysis of urinary epithelial cells

- 56 **mother-child** relations
  - 3 subgroups (0-5%; 5-25%; 25-50%)
- 63 **intersibling** relations
  - 5 subgroups (0-5%; 5-25%; 25-50%; 50-75%; 75-100%)

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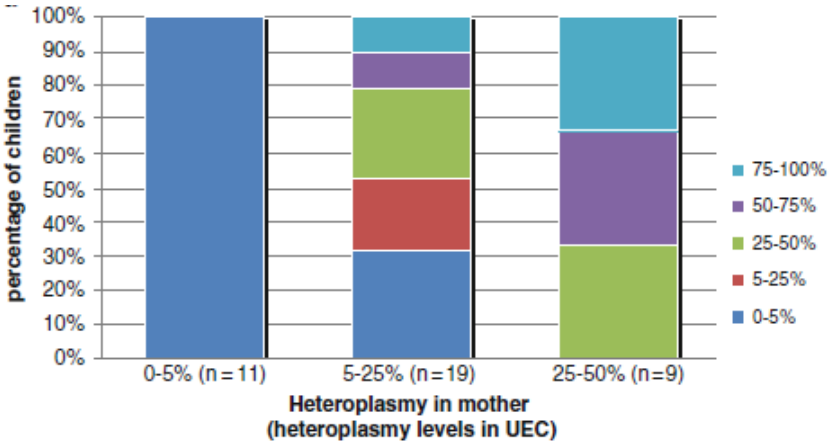
transmission between **mother-child**

- heteroplasmy <5%
  - ➢ no detectable transmission
- heteroplasmy 5-25%
  - ➢ no detectable transmission in 30% offspring
- heteroplasmy >25%
  - ➢ transmission to all offspring



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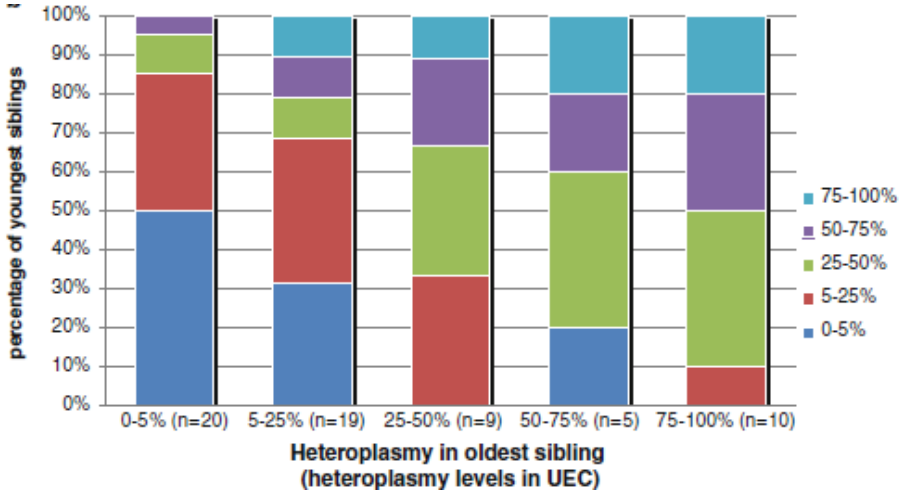
transmission between **siblings**

- in oldest sibling no detectable level >5%
  - < 5% for 50% of youngest sibling
- in oldest sibling level >50%
  - most siblings affected



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unknown outcome : 'private' mutation

- unique/rare mutations : few families
- no (or little) specific information
- genotype - phenotype correlation ?
- treshold level ?
- identify potential healthy offspring ?

➢ **insufficient data for conclusion**

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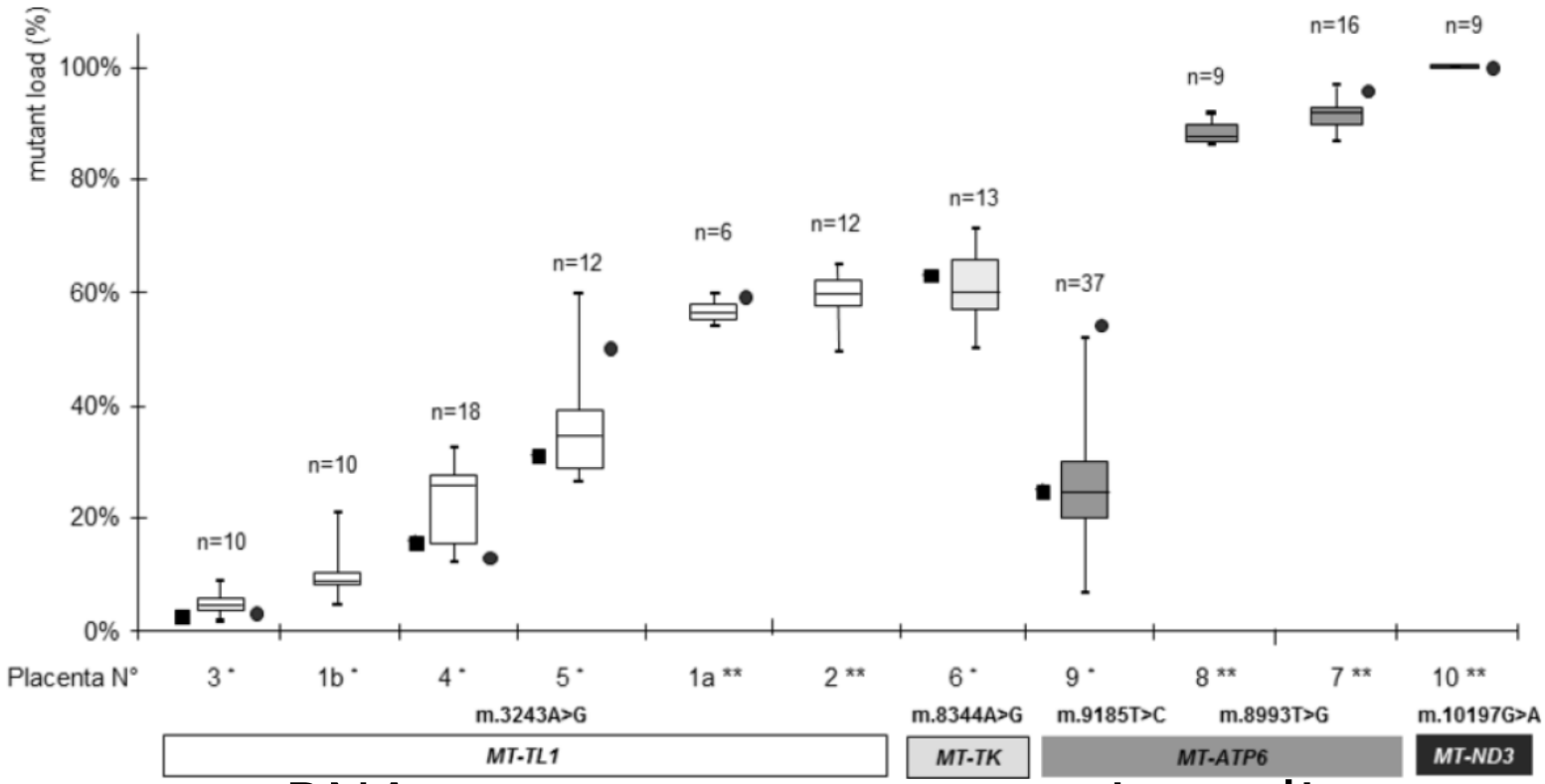
placenta: Vachin 2017

11 placentas investigated



tRNA gene protein coding genes

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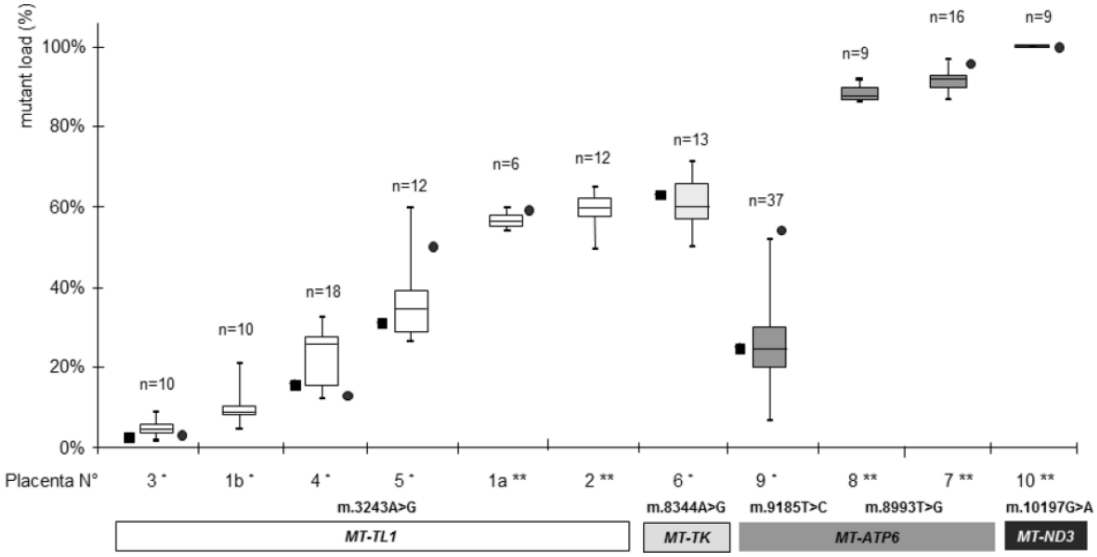
placenta: Vachin 2017

- 11 placentas investigated
  - 6 full term / 5 12-18 weeks gestation

- multiple samples (n=1 - 37) / placenta
  - 1 placenta homoplasmic (MT-ND3 gene)
  - 6/10: intraplacental variation limited to ≈ 10%
  - 4/10: large intraplacental variation
    - up to 55% in 1 case

placenta: Vachin 2017



- 1 placenta homoplasmic (MT-ND3 gene)
- 6/10: intraplacental variation limited to ≈ 10%
- 4/10: large intraplacental variation
  - up to 55% in 1 case

CV sample not (always) appropriate tissue for PND

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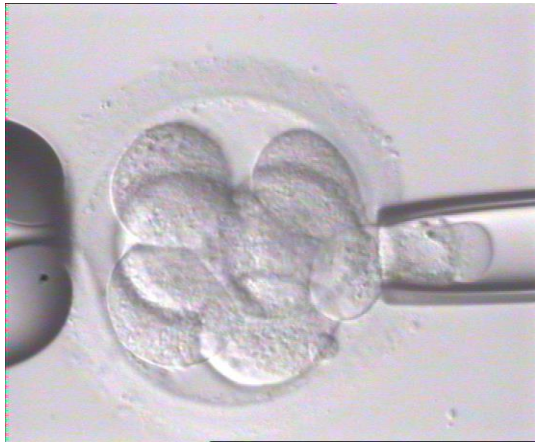
What about ART ?

PGT OR MRT

Preimplantation Genetic Test ?

solution ?



aim ?

- selection of ‘healthy’ or ‘low risk’ embryos to reduce the risk of mt disorder

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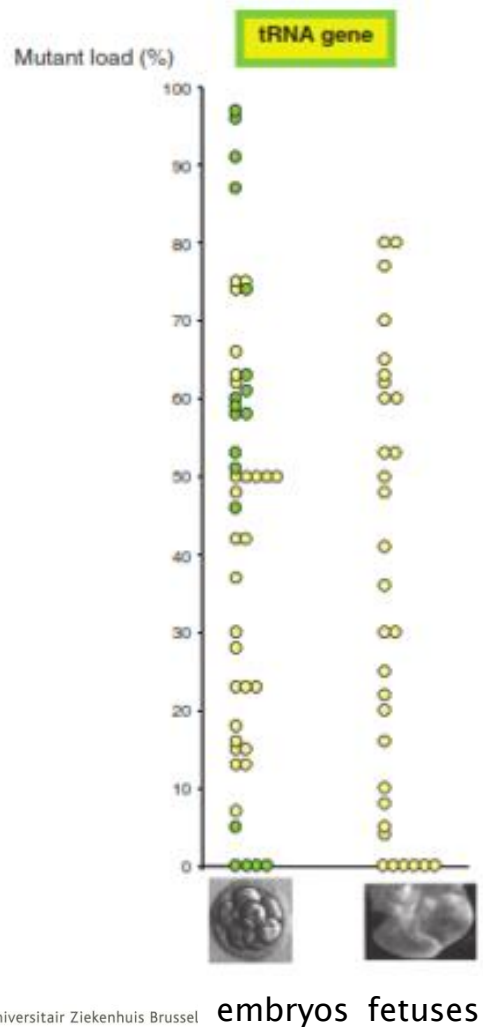
PGT procedure questions ?

- are results of 1 or 2 blastomers / blastocyst representative for embryo ?
- which embryos are suitable for transfer ?
  - save cut off point ?
  - criteria ?
- results of one family representative for the mutation in general ?

mtDNA load in PGT embryos & fetuses

Steffann 2015



tRNA genes

- widely, random distribution of loads
- also intermediate levels

yellow: m.3243A>G
green: m.8344A>G

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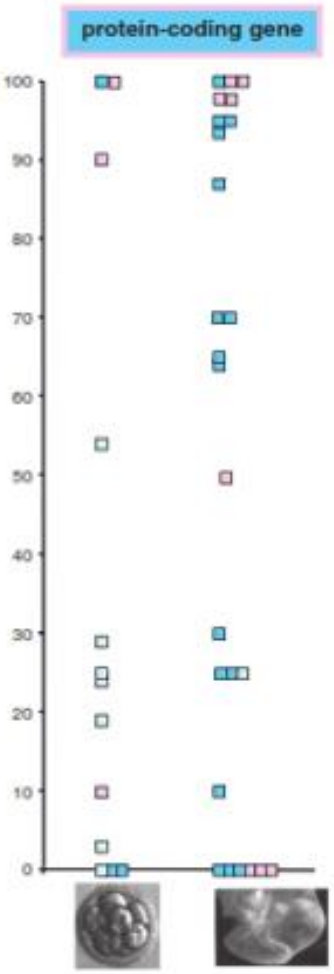
mtDNA load in PGT embryos & fetuses

Steffann 2015



protein coding genes

- more skewed loads
- ≥ 70%
  ≤ 30%
  with some exceptions

light blue: m.9185T>C
dark blue: 8993T>G/C
pink: others

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Preimplantation Genetic Test Baby

- PGT m.3243A>G embryo
- trophoblast heteroplasmy: 12%
- buccal cells
  - → 30 days: 15%
  - → fist year: stable
- 6 weeks
  - → blood: 42%
  - → urine: 55%

Blastocyst preimplantation genetic diagnosis (PGD) of a mitochondrial DNA disorder

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Limitations of Preimplantation Genetic Diagnosis for Mitochondrial DNA Diseases

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a clinically affected baby

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Preimplantation Genetic Test Baby

mutation burden @ biopsy does not always correspond with the one @ birth

Table 2 Mutation levels in live births following PGD for mitochondrial disease

Mutation	At biopsy	At birth	Comments
m.8993T > G	0% & 0%	0%	First report. Two embryos transferred
m.8993T > G	2.5%	4%	3–5% cord blood & placenta; buccal cells 5% at age 4½ years
m.3243A > G	5% & 13%	5%	Two embryos transferred; 15 ± 5% placenta, 5 ± 1% cord blood
m.3243A > G	12%	15%	47% blood, 52% urine at 1½m; 46 & 42% at 18m
m.8993T > G	0%	0%	'Healthy son', no further details
m.8344A > G	53% & 59%	63%	Two embryos transferred; no further details
m.3243A > G	0%	0%	Male; measured in cord blood, urine, saliva
m.36[b]G > A	2%	7%	Female, measured buccal and urine cells
m.83[b]A > G	48%	Not available	Male; <60% generally asymptomatic
m.130[b]T > C	1%	0%	Male; undetectable in blood, buccal and urine cells
m.101[b]*T* > C	1%	1–2%	Male; cord blood

[b] characters hidden to respect confidentiality

Greenfield et al. 2017

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other options ? in (near) future ?

- **cytoplasmic transfer ?**

  was used to improve ART outcome in late ’90s
  - some children with chromosomal abnormalities (T21) & birth defects
  - some children with donor mtDNA
  - but, made a comeback with autologous transfer, recently

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mitochondrial replacement therapy ?

MRT, replacement of nuclear genome of the affected woman with that of a donor woman

- applied ***before*** **fertilisation**
  - GVT (**g**erminal **v**esicle **t**ransfer)
  - PBT (**p**olar **b**ody **t**ransfer)
  - MST (**m**aternal **s**pindle **t**ransfer)

- applied ***after*** **fertilisation**
  - PNT (**pron**uclear **t**ransfer)

Herbert & Turnbull et al. 2018

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MRT possible @ 2 different stages

study of

- proof of principle demonstrated
- safety
- efficacy

➢ for different strategies & different teams in pilot studies

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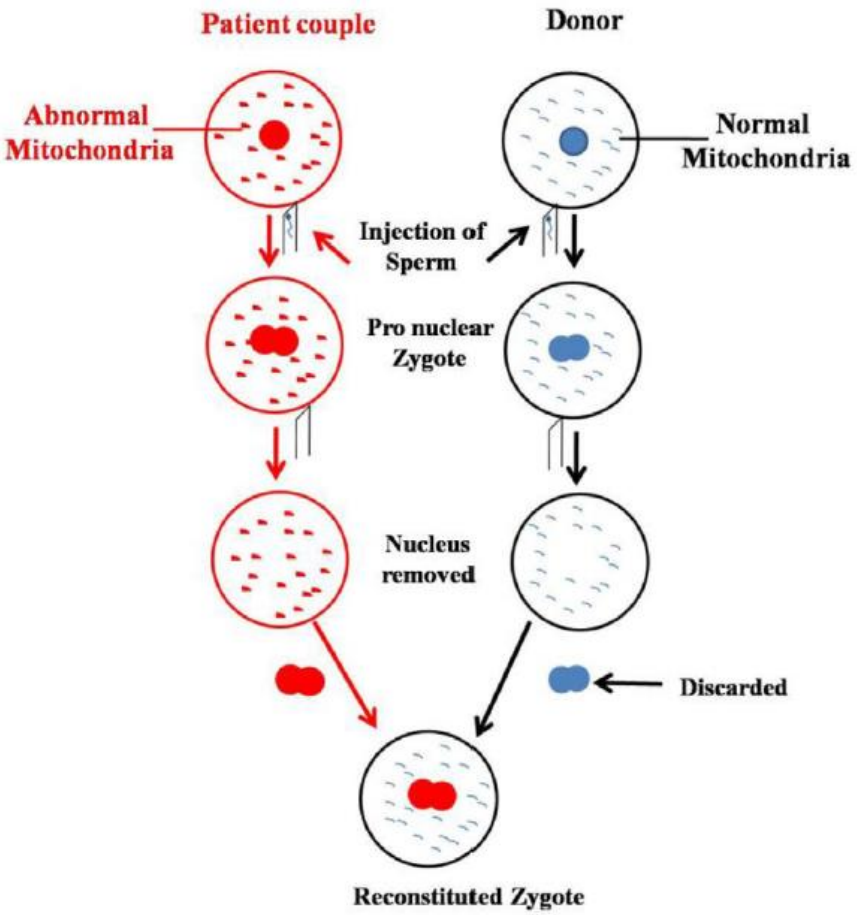
pronuclear transfer



limited hu mtDNA transfer:

- in some carry-over (0,01 – 2%) in 4/9 embryos not detectable

Craven 2010

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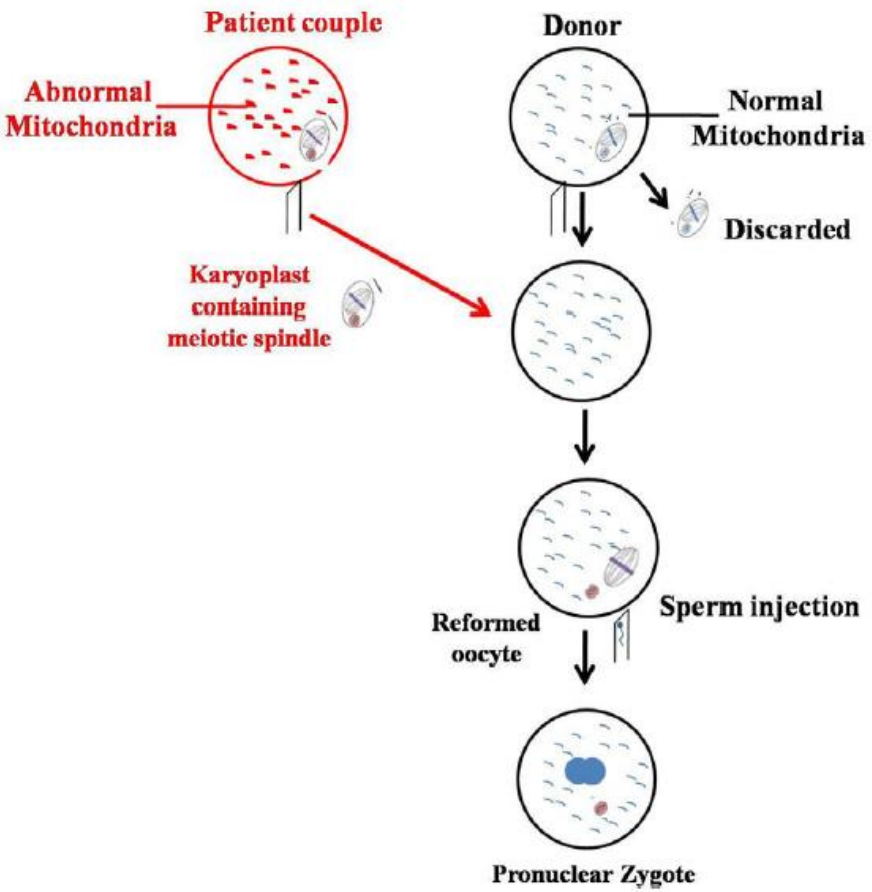
metafase II spindle transfer



limited hu mtDNA transfer:

- in some carry-over ≤ 2.0%

Tachibana 2013

mitochondrial replacement therapy ?

uncertainties of post therapy

- << amounts mtDNA carry over
- haplogroup differences

- nuclear – mtDNA interaction
  - haplogroup matching needed ?
- mtDNA – mtDNA interaction
  - possible detrimental effect ?
- mtDNA segregation
  - genetic drift & mtDNA reversion ?

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mitochondrial replacement therapy ?

uncertainties under debate

- nuclear compatibility needed (nuclear – mt interaction) ?
  - haplogroup matching needed ?
- << amounts mtDNA carry over ?
  - limiting co-transfer ➢ a technical challenge
  - genetic drift & mtDNA reversion ?

Herbert & Turnbull et al. 2018

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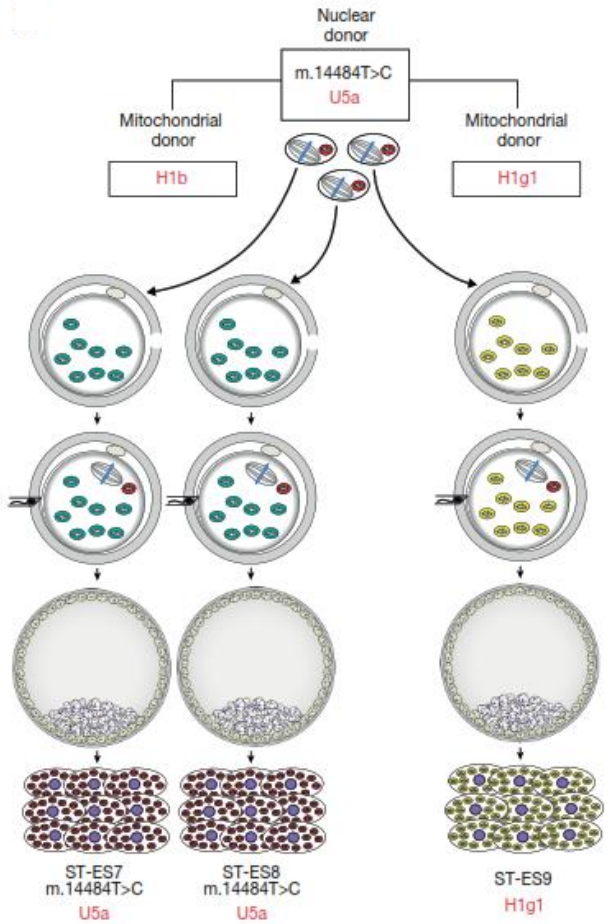
mitochondrial replacement therapy ?

- 3 ES cell lines derived from MRT embryo
- in vitro reversion ➢ original pathogenic LHON mtDNA mutation m.14484T>C
  - no haplogroup matching
  - needed ?
  - (other) cause ?
  - in vivo ?



Hudson 2019

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mitochondrial replacement therapy ?

- 2015 : licenced by UK parliament
- 2016 : HFEA agreemant on case-by-case basis
- 2017 : HFE licenced a fertility clinic
  - ➢ clincal trials have started

- US : rider in section 734 of US Consolidated Appropriations Act, 2018
  - ➢ FDA ban on clinical trails of MRT

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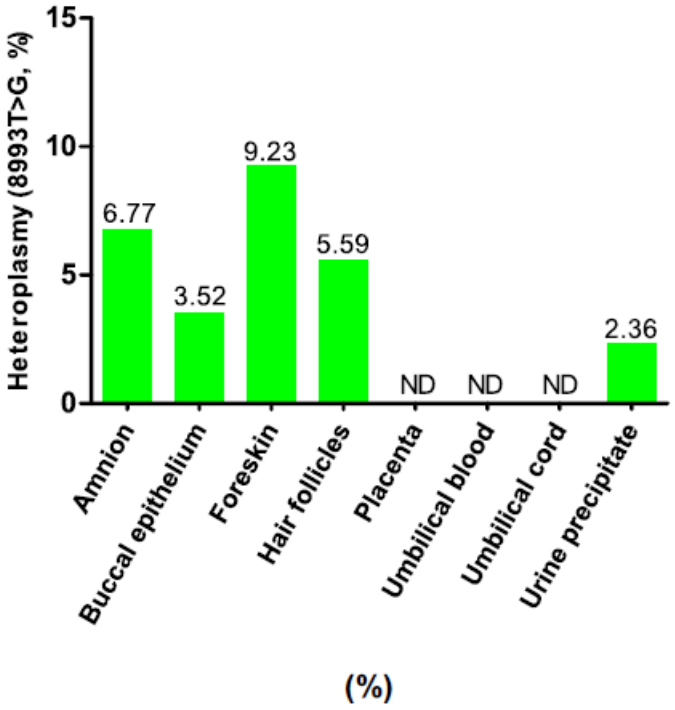
a human baby was born

- a ‘spindle transfer baby’ is already born in Mexico
- m.8993T>G
  - 5,9% heteroplasmy blastocyst stage
  - 2,36 to 9,23% in various tissues at birth



Zhang et al. 2017

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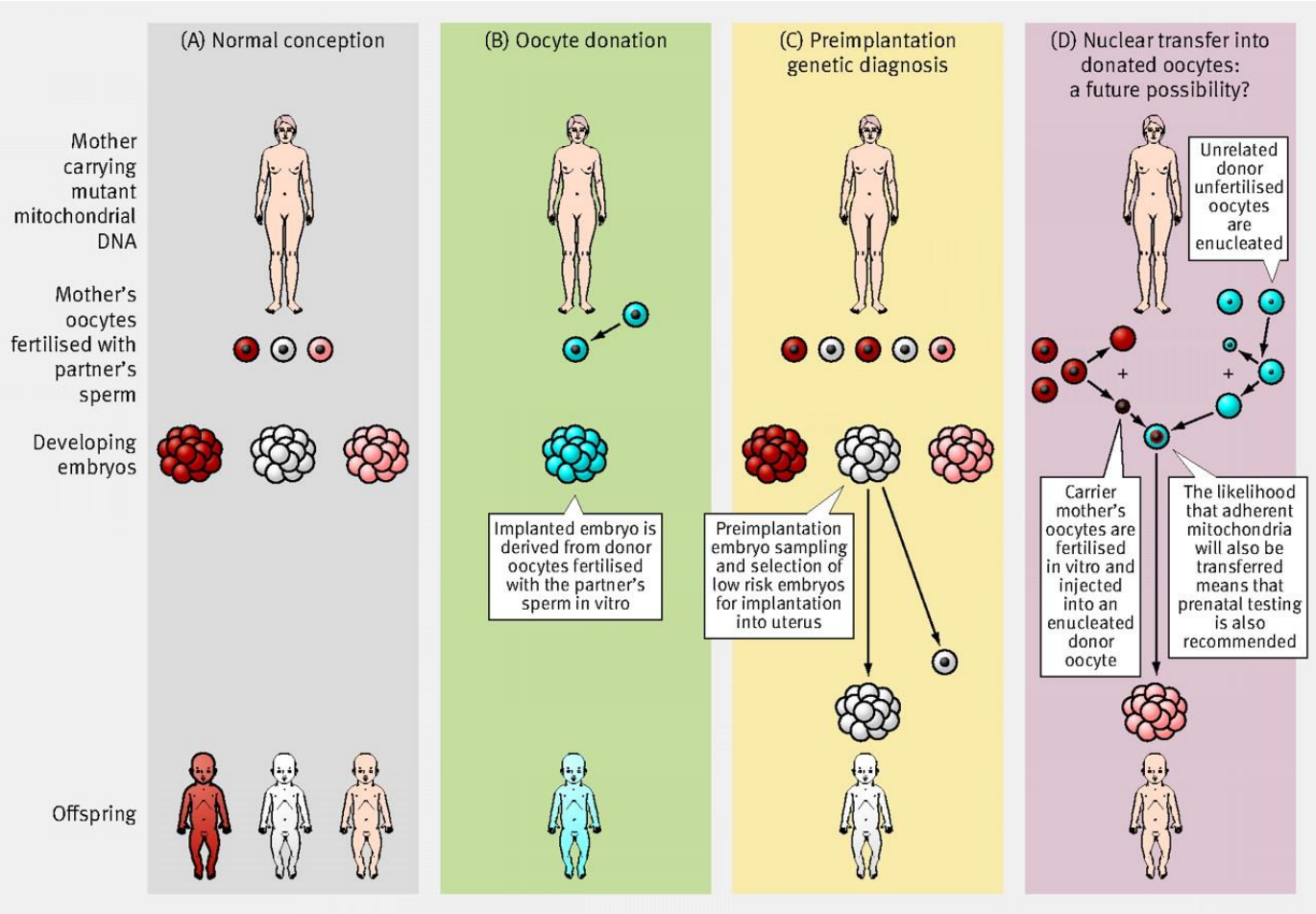
transmitting mtDNA disease



option of oocyte or embryo donation which avoids all riks

key points (1) summary

- mtDNA disorders are frequent in humans
- many different factors interfere in final risk determination

  (heteroplasmy & bottleneck)
- reliable predictions are limited
- counseling is difficult
- PND can be an option

key points (2) summary

- PGT can be an alternative
- analysis of oocytes might be directive
- interpretation of test results &
  'grey zone' could be a problem
- oocyte or embryo donation could be considered
- MRT is still experimental but might be a promising track in a near future

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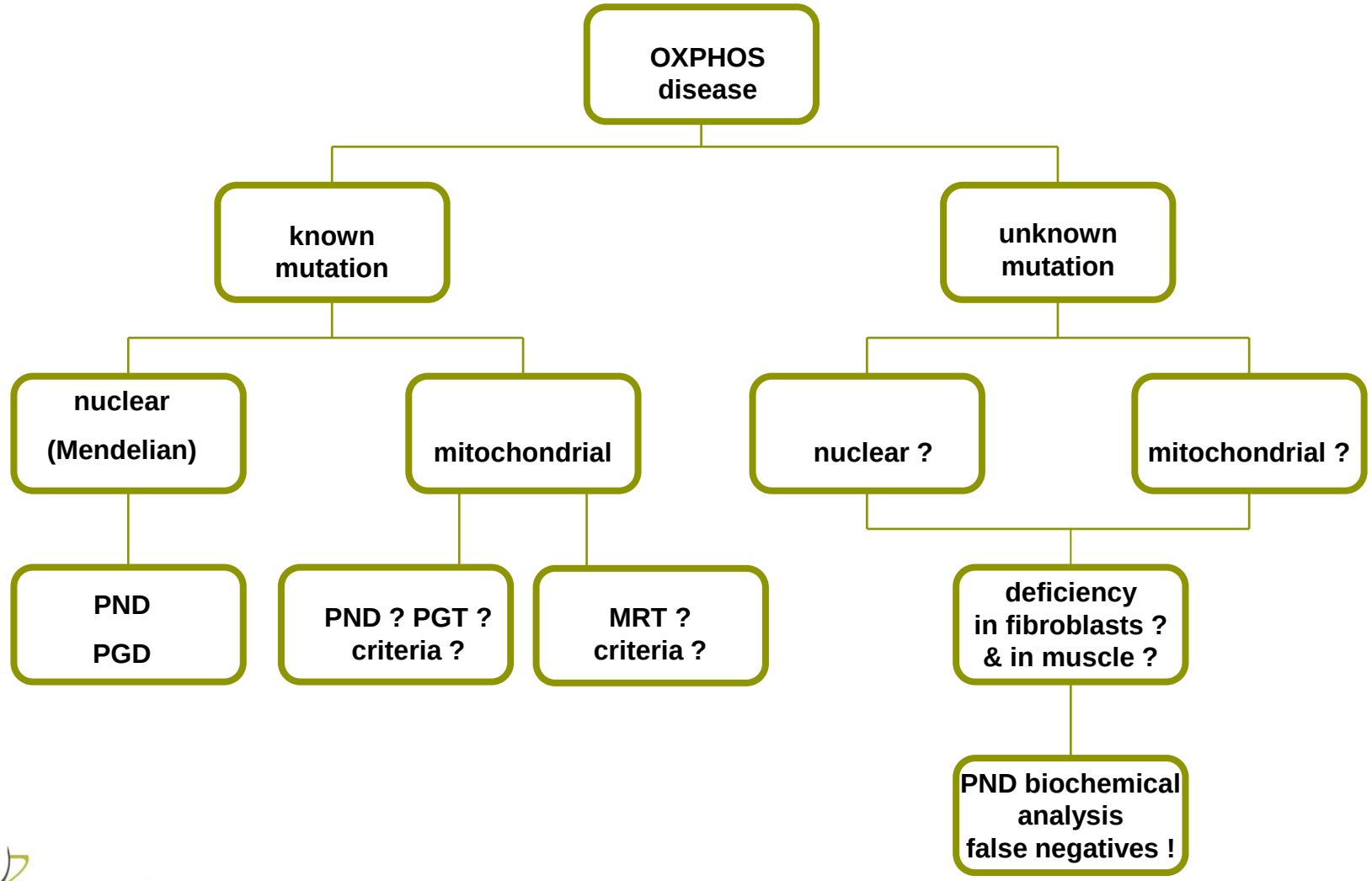
key points (3) counseling overview



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THE END
THANK YOU

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