THE INHERITANCE OF MITOCHONDRIAL HETEROPLASMY

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INTRODUCTION

The mammalian mitochondrial genome (mtDNA) is a small double-stranded molecule that is exclusively transmitted down the maternal line. The existence of a mixture of mutant and wild-type mtDNA within the same organism is called heteroplasmy and, although not necessarily, this event can be associated with pathogenic effects. However, the exact mechanism of inheritance that controls the amount of mutant mtDNA that is going to be transmitted from a mother to her offspring is still unknown. Therefore, understanding the biological basis of this uncertainty is one of the principal challenges facing scientists in the field of mitochondrial genetics. In this review the main goal is to shed light on the factors responsible for inheritance through the different theories about when and how the mitochondrial genetic bottleneck is produced and whether selection, random drift or both are influencing in the segregation patterns.

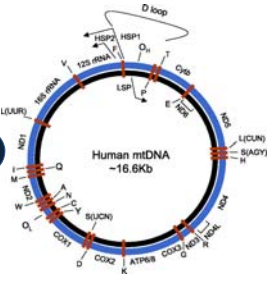
THE HUMAN MITOCHONDRIAL GENOME

High copy number

Lack of recombination

Maternal inheritance

High mutation rate



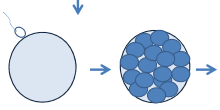
HETEROPLASMY

→Different types of mtDNA within the same organism.
→More frequent in control region.
→ 62,37% population.
→50-85% of affectation to cause phenotypic effect.
→ Different rates among tissues and offspring.

POINT | **LENGTH**

INHERITANCE

Sporadic



Non-random segregation

Maternal

Non proliferative tissues

Proliferative tissues

HETEROPLASMY

Expansion and accumulation of somatic mutations

Aging

Neurodegenerative diseases

HETEROPLASMY

Deleterious mutations will be lost through replication

RANDOM INTRACELLUAR GENETIC DRIFT

GENETIC BOTTLENECK

EARLY OOGENESIS

Human Ovum 200,000 mtDNAs

Fertilized oocyte

Early embryonic development

Rapid zygotic divisions

No mtDNA replication

Primordial germ cells

100 mtDNAs/cell

10 mtDNAs

PGC migrate to the ovary and a subpopulation of diploid cells (oogonia) are formed by mitotic divisions.

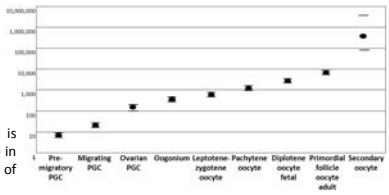
Mitochondrial DNA multiplication

PHYSICAL BOTTLENECK

No differences were observed when heteroplasmy was measured in primary oocytes and mature oocytes from adult mice.

RANDOM DRIFT

Variance in primary oocyte is sufficient to explain variance in mtDNA frequencies in adults of next generation



NUMBER OF SEGREGATING UNITS

$$Vn = p0(1-p0)\,[1-(1-1/N)^{gn}]$$

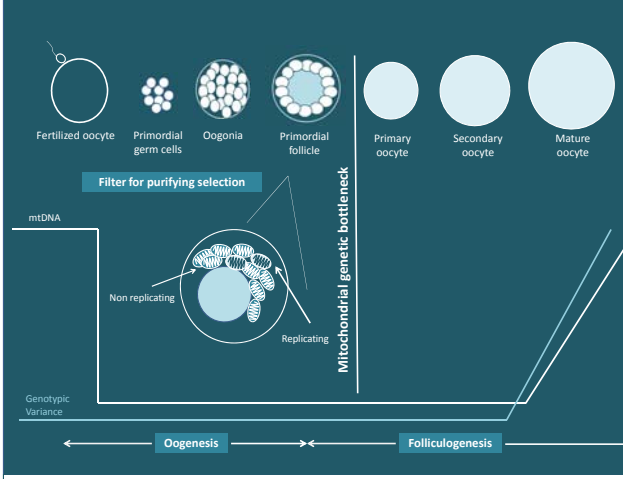
Variance in *n*th generation | Initial frequency | Cell divisions in germline

N ≈ 200

GENETIC BOTTLENECK

Very small number of mtDNAs, or even a single one, serve as templates for replication to populate the oocytes from which mtDNA is transmitted to the offspring.

POSTNATAL FOLLICULOGENESIS



SELECTION

RAPID SEGREGATION (2-3 generations) → Heteroplasmy ↔ Homoplasmy

Pathogenic mutations → Small pedigrees

PURIFYING SELECTION

- Lost from maternal line
- Severity prevents further transmission

Nucleoids: mtDNAs replicate as a unit

Physical bottleneck + Selective pressure

DRIFT + SELECTION

Selection at different levels of organization

Initial proportions of mtDNA variants in the mother

Moment in which mutation arises

Bottleneck: Before | During | After

Position of mutated mitochondria

Peripheral

Perinuclear

Nuclear genetic background

RANDOM DRIFT

Random genetic drift is the main mechanism of segregation acting in the female germ line

- Explains the different proportions of heteroplasmy among the offspring
- Neutral and polymorphic variants

Mutant mtDNA escapes from selection → RANDOM SEGREGATION

DISCUSSION

✓More than 100 different types of pathological mutations in mtDNA have been described but heteroplasmy itself can appear equally in healthy individuals. Only rates over 50-80% will show phenotypic affectation.

✓ There are different levels of heteroplasmy among tissues produced by somatic mutations that describe a non-randomly pattern of inheritance. This is influenced by selection at the level of organism associated with the phenotypic affectation.

✓The inheritance of heteroplasmy can be explained by the bottleneck theory. A physical reduction of units in the early oogenesis is evident but the bottleneck responsible for the genetic variance occurs during folliculogenesis, when mutations that escape from purifying selection in early oogenesis are rapidly segregated and exposed to selection at the level of organism.

✓ 200 is the approximate number of segregating units which are going to contribute to next generation's genetic variance.

✓In the transmission of heteroplasmy it is evident the action of random drift although selection acts over pathogenic mutations. Below the threshold of 80% affectation mutations would be invisible to selection and would segregate randomly.

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