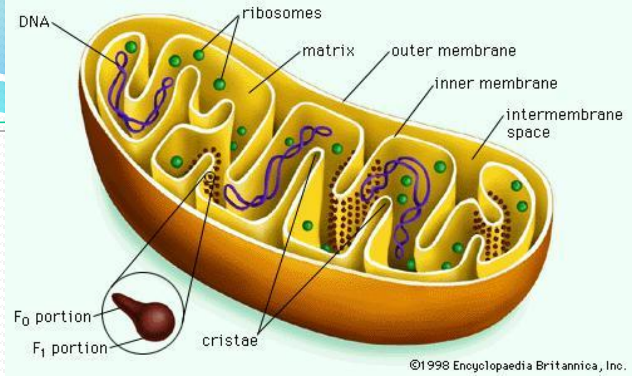
Biparental Inheritance Through Uniparental Transmission: The Doubly Uniparental Inheritance (DUI) of Mitochondrial DNA

Journal Club

21.01.15

Kairi Raime

Articles:

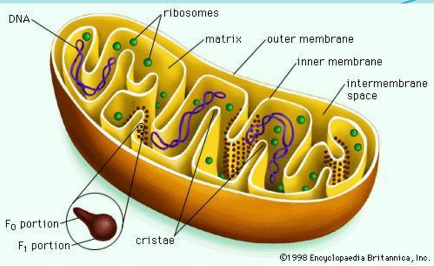


©1998 Encyclopaedia Britannica, Inc.

- Zeros, E. (2013). Biparental Inheritance Through Uniparental Transmission: The Doubly Inheritance (DUI) of Mitochondrial DNA. *Evolutionary Biology*, 40:1-31.

- Breton, S. *et al* (2014). A resourceful genome: updating the functional repertoire and evolutionary role of animal mitochondrial DNAs. *Trends in Genetics*, 30 (12): 555-564.

Inheritance of mt DNA



©1998 Encyclopaedia Britannica, Inc.

- **Biparental inheritance of nuclear genomes** is typically accompanied with **uniparental inheritance of cytoplasmic genomes**.
- mtDNA or plastid DNA **uniparental** transmission can be either **maternal** or **paternal**.
- **In animal kingdom strict maternal inheritance (SMI) of mtDNA is the rule** (except some accidental „leakages“ of paternal mtDNA) – all copies of mtDNA in each cell typically have identical DNA sequences, a situation known as **homoplasmy**.
- In species in which **biparental transmission** of mtDNA is common (e.g. several fungi), rapid reversion from heteroplasmy to homoplasmy is a rule.
- **Doubly uniparental inheritance (DUI)** – the only case of a stable mechanism of biparental transmission of a cytoplasmic genome.

Mitochondrial genomes of bivalves

- Quite large mitochondrial genomes (median 16 898 bp, maximum 46 985 bp).

- More noncoding DNA regions (URs) compared to analyzed Metazoa (average amount 11.2% vs. 6.6%, $P<0.001$).

- Have very variable primary sequence:
  - Very high mutation rate
  - an unusual mitochondrial inheritance system: **the doubly uniparental inheritance (DUI)** – carrying both **a maternally** (through the female line) **and a paternally** (through the male line) **transmitted mitochondrial genomes.**

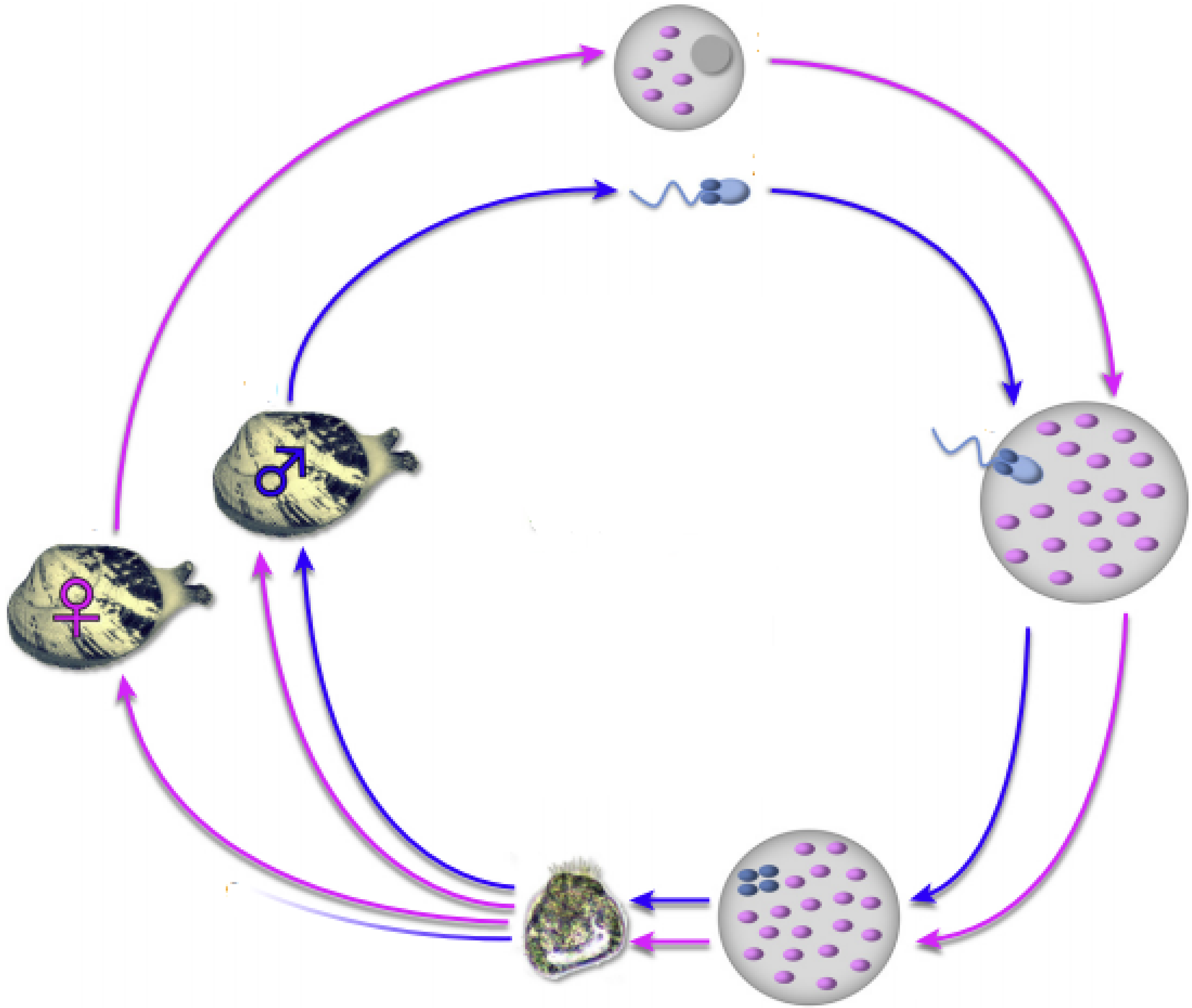
The phenomenon of DUI

- two distinct mitochondrial genomes that came to be known as **F (female inherited)** and **M (male inherited)** co-occur in the mtDNA pool of the species.

- **Egg** contain the **F genome** and **sperm** contains the **M**.

- After fertilization and during development:
  - **female** become **homoplasmic for F genome**,
  - **male** become **mtDNA mosaics (heteroplasmic)**:
    - **somatic tissues** are **dominated by the F genome**
    - **germ line** becomes homoplasmic for the **M genome**.

The doubly uniparental inheritance of mitochondria



Modified figure from Breton S.,et al (2014). A resourceful genome: updating the functional repertoire and evolutionary role of animal mitochondrial DNAs. Trends in Genetics, 30 (12: 555-564.

The bivalvian taxons with DUI of mt DNA

- Presently DUI is known to occur in about 40-50 molluscan bivalve species:

- Order **Mytiloida** – marine mussels:
  - Mytilus sp, Geukensia sp, Brachidontes sp, Musculista sp, etc.

- Order **Unionoida** – fresh-water mussels:
  - Pyganodon sp. Inversidens sp. Hyriopsis sp. Potamilus sp., etc.

- Order **Veneroida** – marine clams
  - Ruditapes sp. Acanthocardia sp., etc.

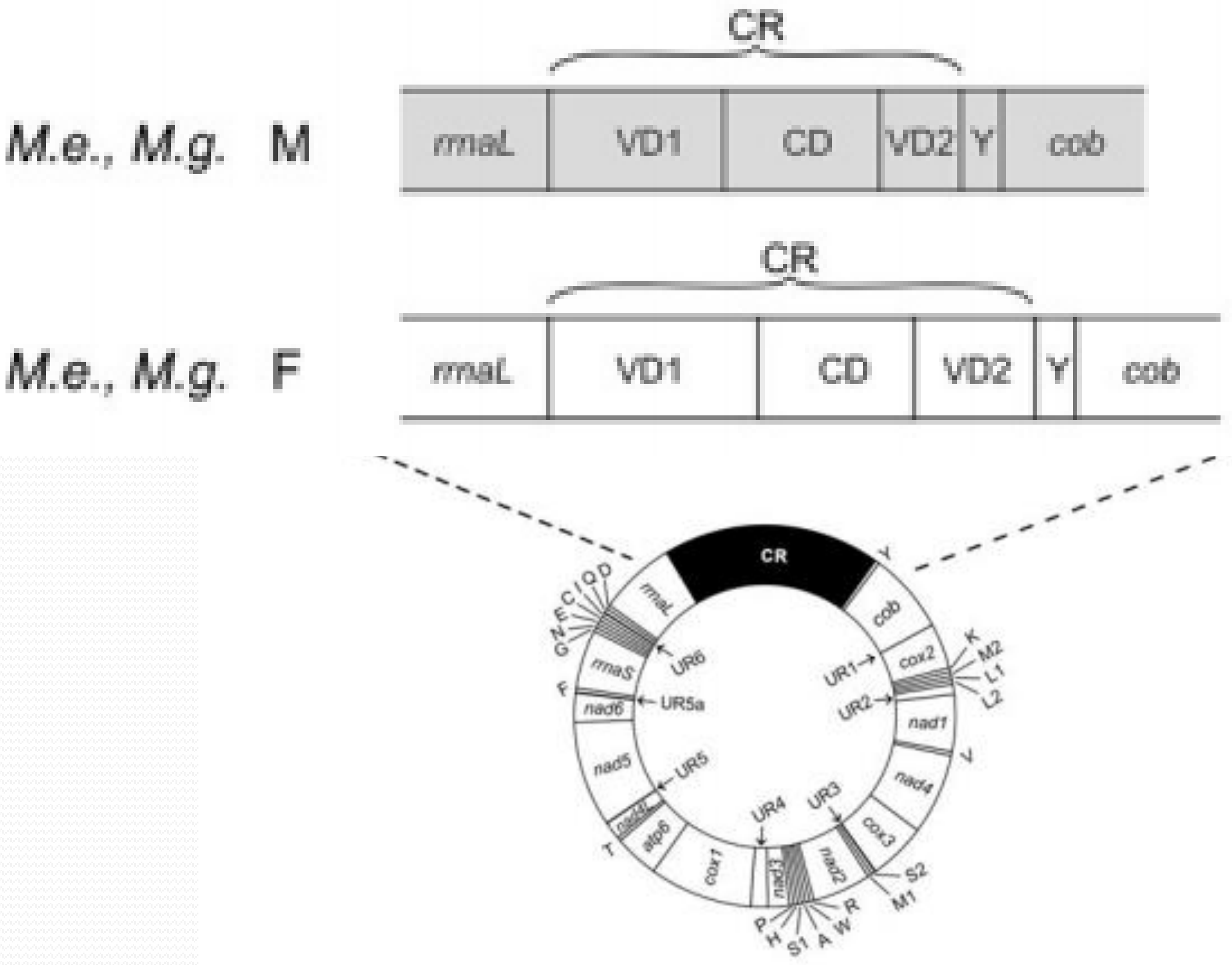
- **....** -> Not many fully sequenced mt genomes of mollusks yet, not determed if the sequenced genome is F or M type and not determined if species have DUI.

The extent of variation between F and M genomes (in species of family *Mytilidae)*

- **„core“ region** of mt genome – the same gene order and size, all proteins and RNA genes are coded in one and same strand, but highly divergent in primary sequence (22 – 39%)
- **CR (LUR)** of mt genome (houses the elements that control the replication and transcription of molecule) –
  - **„conserved domain“ (CD**) – the least diverged part in the two genomes - differing by less than 2%
  - **„the first variable domain“** (VD1, upstream to CD, more than half of CR) – the most diverged part - differs by more than 50%)
  - **„the second variable domain“** (VD2, downstream from CD, the smallest part) – differs by about 24%.

- Large differences between species from different genera but from the same family - an indication that the mitochondrial genomes of DUI species undergo much more drastic changes and at a much faster rate than the genomes of species with standard maternal mtDNA inheritance.

Mitochondrial F and M genomes of *Mytilus edulis* and *Mytilus galloprovincialis*



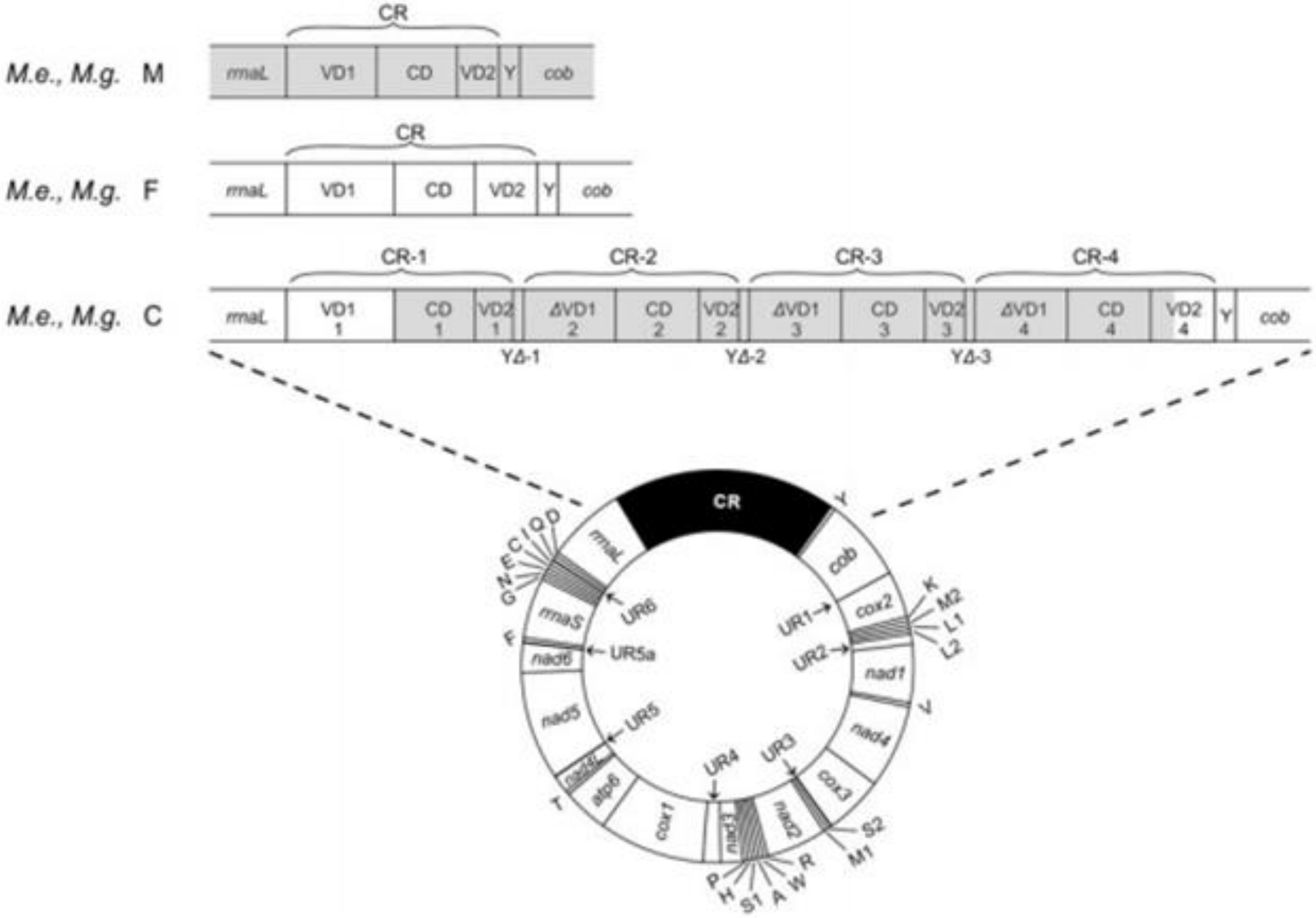
The role of the differences between F and M genomes – the relation with transmission mode?

- F and M genomes of DUI species harbor functional **open reading frames (ORFs)** that do not correspond to any known mtDNA gene (ORFans) – F-ORF (maintained > 13-200 Mya) and M-ORF
- **F-ORFs** are located **in the VD1 of CR** (highly divergent among species and are apparently absent from the M genomes.
- These ORFs produce a protein –
  - **F-ORF** product is present in female gonads and absent from male gonads (In ovarian tissue the putative protein of the F-ORF is found in the nucleus and in the cytoplasm (most likely in the mitochondria) of eggs)
  - **M-ORF** product is present in male gonads and absent from female gonads

- The existence of two different protein products, each coded by a different gender-specific genome is not enough to prove a role of this product in DUI.
- Hermaphroditic species have lost DUI and have extensive mutations in F-ORF gene of their female-type mtDNAs.

„Masculinized“ mitochondrial genomes (C genomes) in Mytilids

- An mtDNA genome may reverse the function and transmission route (from F to M) - mediated through **recombination** that produces CRs with F-type and M-type parts
- **masculinization** involves the exchange of sequences only at the **CR**, not in other parts of the F genome. But not every F-like genome with mosaic CR need to be a masculinized genome.
- **„Masculinized“ genomes** originated from F genomes that invaded the male gonad, assumed the role of the M genome and became onwards sperm-transmitted
- The **core part** of masculinized genomes (coding sequences) is almost identical to the core of the standard (maternally inherited) F genome but **control regions** (CR) varied in length and also in composition: they were F/R mosaics (containing parts from typical F and typical M genome).
- Such „DUI breakdowns“ have been observed in hybrids between *Mytilius* species.
- The existence of M-specific and/or F-specific mtDNA sequences that possibly determine the genome`s transmission route does not implify that these sequences are also involved in sex determination.

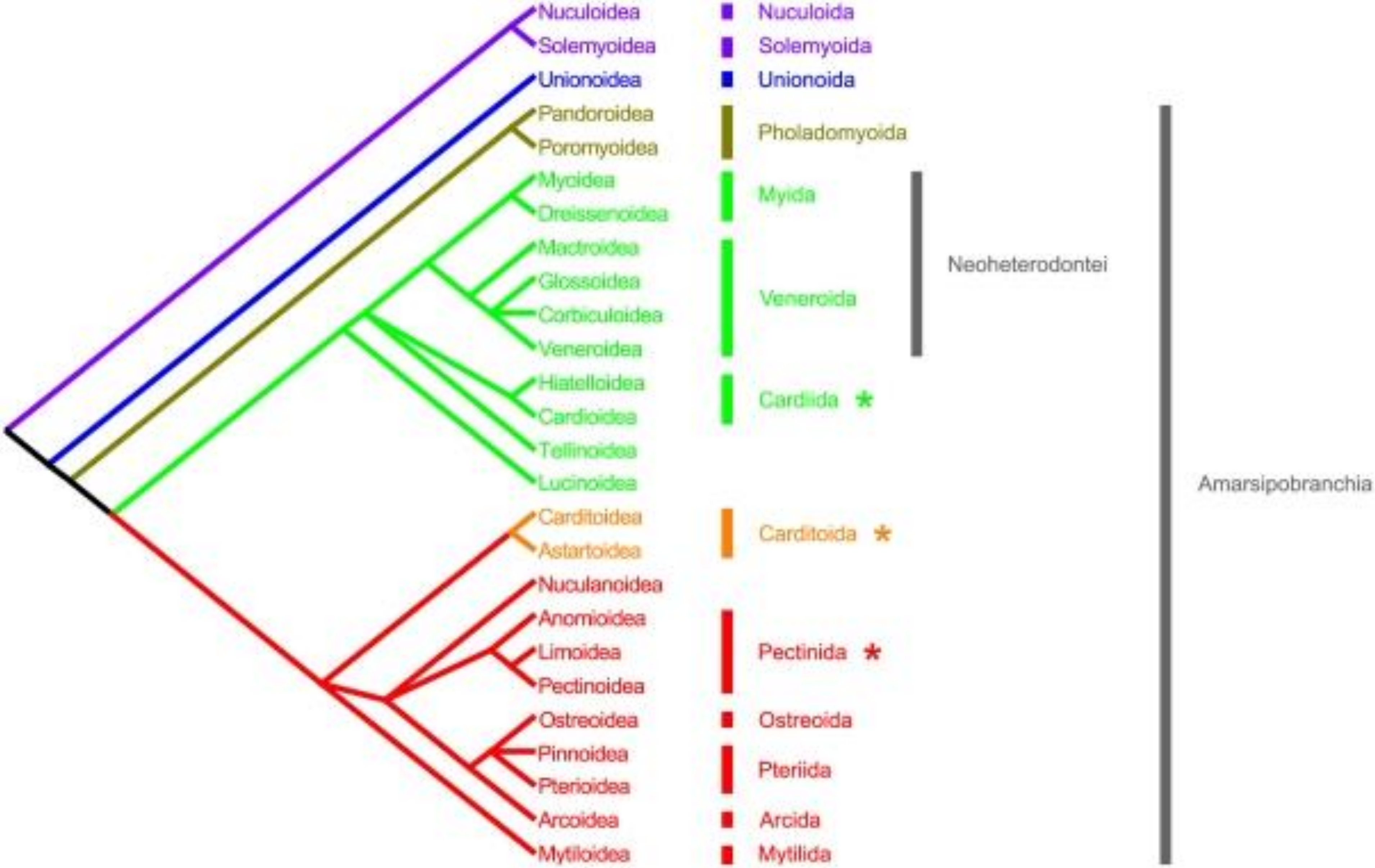

M.e., M.g. M
CR
rrnaL
VD1
CD
VD2
Y
cob
M.e., M.g. F
CR
rrnaL
VD1
CD
VD2
Y
cob
M.e., M.g. C
CR-1
CR-2
CR-3
CR-4
rrnaL
VD1 1
CD 1
VD2 1
ΔVD1 2
CD 2
VD2 2
ΔVD1 3
CD 3
VD2 3
ΔVD1 4
CD 4
VD2 4
Y
cob
YΔ-1
YΔ-2
YΔ-3
CR
Y
cob
K
M2
L1
L2
cox2
UR1
UR2
nad1
V
nad4
UR3
cox3
S2
M1
R
W
A
S1
H
P
nad2
nad3
UR4
cox1
atp6
nad4L
T
nad5
UR5
nad6
UR5a
F
rrnaS
UR6
G
N
Z
E
C
I
Q
D
rrnaL

The origin of DUI

- Presently DUI is known to occur in about 50 species of bivalvian mollusks (from different branches of phylogenetic tree of Bivalves)
- One hypothesis: **DUI has a single origin, its age is older than 400 million years, subsequent loss from a number of taxa.**
- Hermaphrodite species do not have DUI (?)

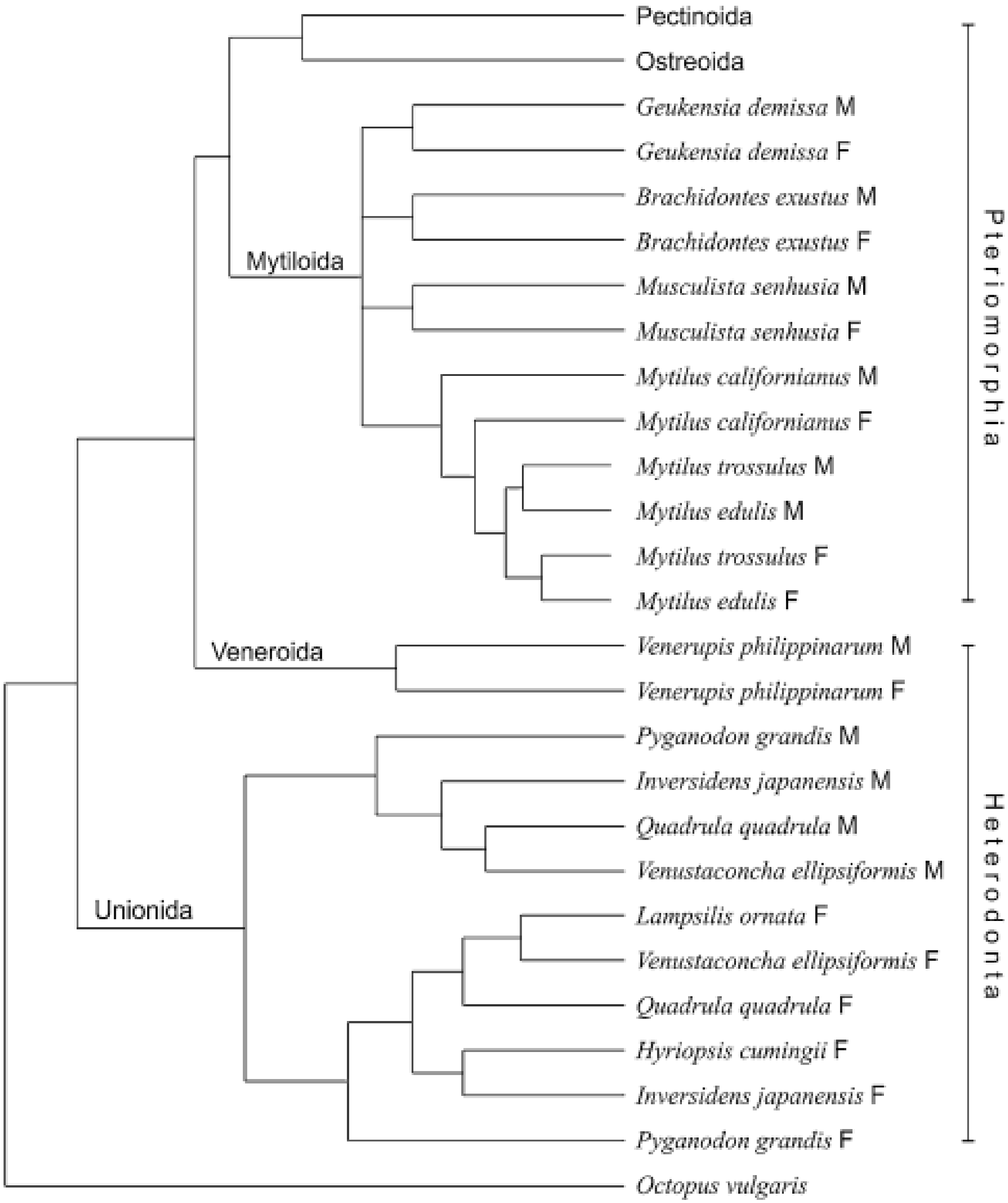
- Difficulties in determing DUI and its origin:
  - ➢ The high divergence between F and M genomes often does not allow the same pairs of primers to amplify from both genomes -> the detection of DUI is prone to false negatives
  - ➢ The complexities in mtDNA transmission, potential masculinization events and the limited carefully screened taxa make difficult to … the phylogenetic pattern of the presence of DUI.

Bivalvian mollusks:



Plazzi et al (2011) **A Molecular Phylogeny of Bivalve Mollusks: Ancient Radiations and Divergences as Revealed by Mitochondrial Genes .** PLoS One. 2011; 6(11): e27147.

Fig. 2 Phylogenetic relationship of mitochondrial genomes from five super-families of bivalvian mollusks. The tree is based on complete coding sequences, except for *Geukensia demissa*, *Brachidontes exustus* and *Musculista senhusia* for which partial sequences were used. This is one of the reasons the affiliation of the four mytilid genera cannot be delineated. No DUI has been reported in Pectinoida and Ostreoida. In unionids the clustering is gender-joining (the F and M genomes form two separate clusters). In mytilids it is taxon-joining (genomes from the same taxon cluster together) at the genus level. Within the genus Mytilus, the pattern is mixed-type for the three species and gender-joining for the pair *M. edulis/M. trossulus*. The pattern is taxon-joining at the level of super-families



Sex-Ratio Bias

- Might be common feature of species with DUI (observed in *Mytilus sp* and venerid *Ruditapes sp*)
- In the majority of crosses there is a strong dam-dependent and sire-independent sex-ratio bias.
  - „**Female-biased**“ mothers produced daughters either exclusively or in high ratio
  - „**Male-biased**“ mothers produced an excess of sons
  - „**Unbiased**“ mothers produced both sexes in an about equal ratio.
- The sex-ratio bias is **mother-depended** (**determined by the mother's nuclear genotype**) and not under maternal mtDNA) and not affected by other factors (such as the age of mother).
- Daughters did not always have the same bias as the mother.

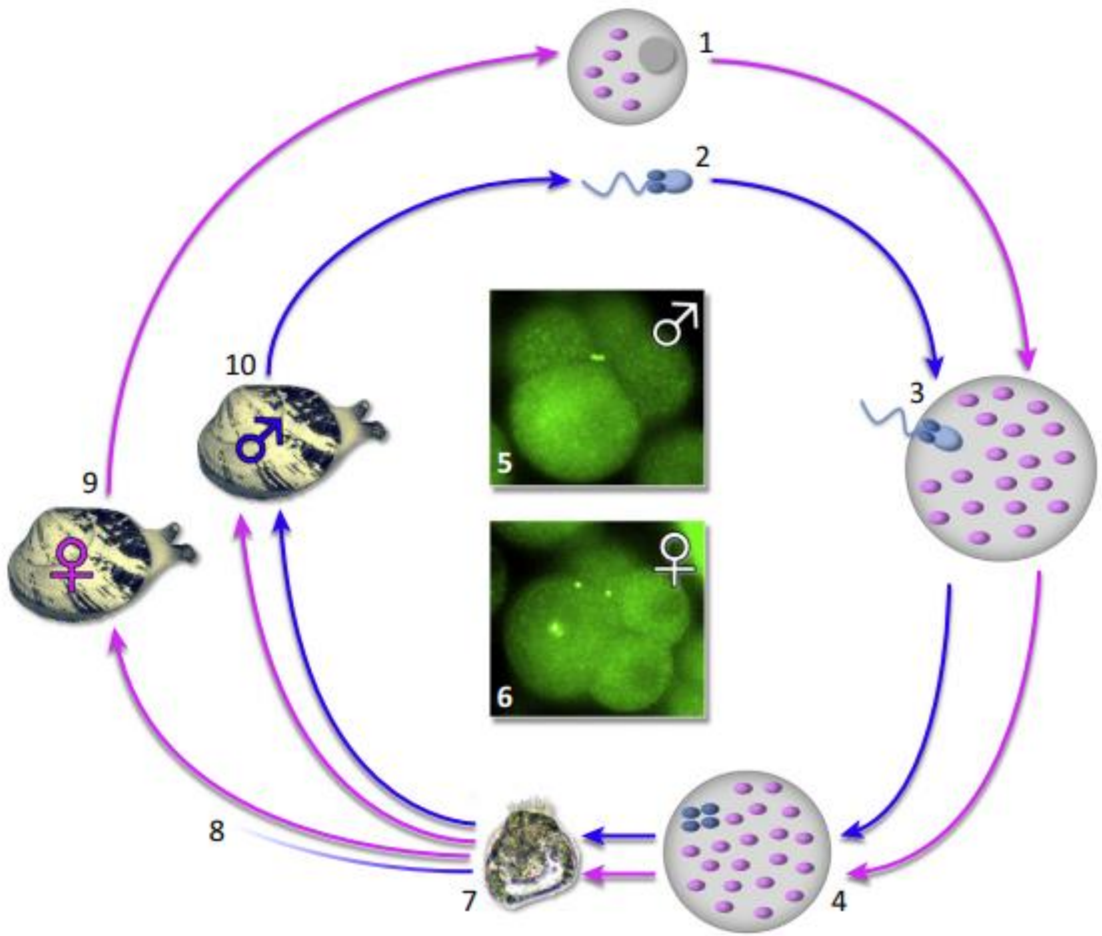
Sperm mitochondria behavior in newly formed zygotes

- The paternal mtDNA is a small minority in the newly formed zygote (4-5 vs tens of thousands of mitochondrias of fully developsed egg) but becomes the dominant and most likely the exclusive mitochondrial genome of the sperm of male embryos

- In DUI species sperm mitochondria enter the egg and there is no active mechanism for their elimination. Sperm mitochondria persist and remain, apparently undivided, in both male and female embryos for several cell divisions.
- The sperm mitochondria follow two distinct patterns:
  - The „**aggregate pattern**“ – predominant in embryos from mothers that produce mostly sons. At two-cell or four-cell stage all sperm mitochondria were found in one cell (the cell D -> germ cells)
  - The „**dispersed pattern**“ – predominant in embryos from mothers that produced mostly or almost exclusively daughters.

- In DUI species there is a tight link between the aggregate pattern and maleness but it is not a part of the mechanism of sex development.
- The aggregate pattern was not observed in oyster *Crassostrea gigas* (not DUI species)

The doubly uniparental inheritance of mitochondria

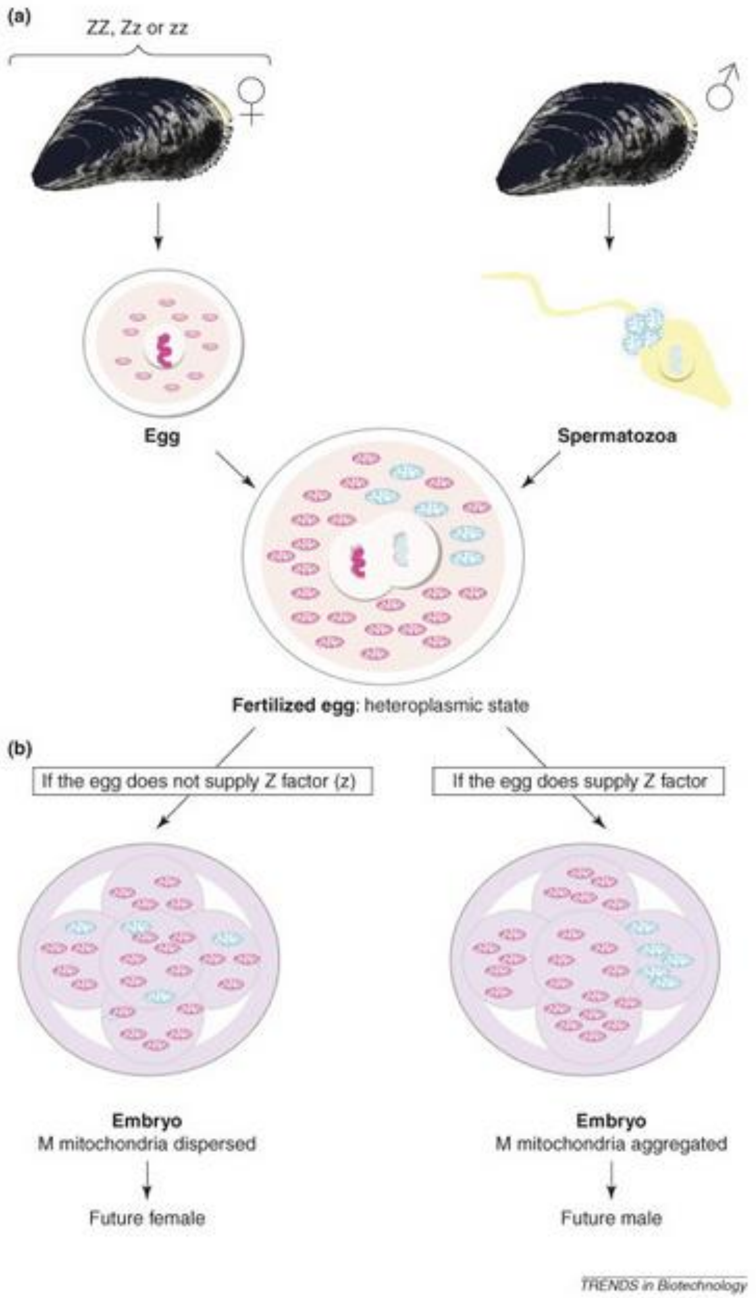


1. Eggs are homoplasmic for F mitochondria
2. Sperm is homoplasmic for M mitochondria
3. The spermatozoon carries M into the egg
4. Zygotes are heteroplasmic
5. Sperm mitochondria are aggregated in males
6. Sperm mitochondria are dispersed in females
7. Embryos continue development
8. M is often lost in adult females
9. Adult females transmit only F with eggs
10. Adult males transmit only M with spermatozoa

Zygotes, developing embryos, and adult males are heteroplasmic for F and M

TRENDS in Genetics

Breton S.,et al (2014). A resourceful genome: updating the functional repertoire and evolutionary role of animal mitochondrial DNAs. Trends in Genetics, 30 (12: 555-564.



Breton et al (2007) The unusual system of doubly uniparental inheritance of mtDNA: isn't one enough? Trends in Genetics.

Distribution of F and M genomes in female and male tissues

- The erratic **presence of the M genome in female somatic tissues** is in accord with the random segregation of sperm mitochondria in the early blastomeres of female embryos.
- But nearly **universal presence of M in male somatic tissues**? – needs more inevestigation
- The presence of the **M genome (as a minority) in the egg** - is not a serious issue - egg mitochondria do not participate in the aggregate that is formed in male embyos but there is a possibility of heteroplasmy of third or even higher degree for female or male somatic tissues.
- In the ***Ruditapes*** species there is a **mechanism that actively excludes the paternal genome** from the female germ line. No evidence for such mechanism in *Mytilus*.
- Investigations of the presence of **F genome in male gonads** are complicated (contamination of gamete preparations from somatic tissues, PCR failure, not detected masculinized F genome)
- It appears nearly certan that **the sperm does not contain the maternal genome** in DUI species.

Expression of F and M genomes in female and male tissues

- **F genome** was expressed in **all female and male tissues.**
- The expression of **M genome** in somatic tissues of either sex was erratic, if at all.
- The only unambiguous instance of M genome expression was in **male gonads, in spermatogenic cells (spermatogonia, spermatocytes)** where expression of F genome was not detected.
- Expression of M was also weak or absent in spermatids and spermatozoa
- **The male germ line may not become fully homoplasmic for the M genome until spermatogenesis or that the line depends on nursing somatic cells up until this stage – there is a small window of expression of M genome.**
- **F genome is the one that fuels all somatic tissues of both sexes, the female germ line and to a large, but not exclusive degree, the male germ line.**
- The expression patterns of F and M genomes of mitochondria may be different in different DUI taxons (e.g. mytilids and unionids).

Rate of evolution and selection of the two genomes

- The **M genome evolves faster than the F** at all coding sequences (rRNA, tRNA, synonymous sites and non-synonymous sites of protein genes), but difference in the rate of accumulation of substitutions is higher for **non-synonymous sites**.
- The **selection is more stringent on the F genome** because this genome is called to perform the standard mtDNA's role more often and under a wider variety of conditions than the M.
- F genome fuels all tissues of females and the somatic tissues of males but the M is performing this role only in the male germ line at a certain stage of gamete development.
- **M genome is under more relaxed selection** that allowes amino acid substitutions to float in the population for longer periods of time and eventually be fixed in one or the other species.
- An alternative scenario would be that **M** has **a function in sperm and/or spermatogenesis:** sex and reproduction-related genes evolve rapidly.

- F genome of DUI species evolves faster than the typical maternally inherited animal mtDNA (?)

Conclusions

- Most likely the DUI machinery was assembled and established in the common ancestor of Autolamellibranchia and, possibly, of all bivalvian molluscs (about 400 million years ago).
- Apparently it has been lost since then in a number of lineages at various taxonomic levels (reversal of transmission route – one explanation of loss of DUI)
- The sequence of mt genomes of bivalvian molluscs are very variable (because of high mutation rate and because of DUI)
- There is no good prior reason why DUI must be restricted within bivalvian molluscs.
- Our knowledge of animal mtDNAs is still incomplete and strongly biased towards vertebrates.
- mtDNA-encoded proteins are not limited to a role in energy metabolism.

Thanks for listening!